Expanding Access to Previously Inaccessible 5-Membered N-Heteroarynes

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ABSTRACT: We previously reported the synthesis of an inaccessible 7-aza-2,3-indolyne through stabilizing interactions with nickel. This was achieved via intramolecular Suzuki coupling (i.e. oxidative addition and transmetallation) with *ortho*-borylaryl bromide derivatives of 7-azaindole. Herein, we sought to use this same strategy to expand the scope of previously inaccessible five-membered heteroarynes. Five new classes of heteroarynes derived from indole, pyrrolopyrimidine, and the remaining isomers of azaindole were accessed. Transmetallation studies show that aryne formation depends on the electronics of the heteroarene. A borate complex of 4-azaindole was isolated and characterized via NMR spectroscopy and crystallographically. This heterocycle could be promoted to undergo transmetallation through the installation of an electron-donating substituent. Each class of heterocycles require a unique synthetic strategy. Thus, to demonstrate the utility of heteroarynes as a general synthon, a one-pot difunctionalization was achieved across these classes of heterocycles using the newly accessible heteroaryne complexes.

N-Heteroaromatic compounds are ubiquitous in biologically active molecules.[1,2] They are the cores of many commercially available pharmaceuticals and agrochemicals.[3] Due to their critical importance and challenging syntheses, a multitude of reactions for the synthesis of heterocycles have been developed but the downside of these methods is that they generally apply to individual heterocycles rather than classes.[4] An exception to these more singly-focused strategies could be a more universal synthon used in the synthesis of heterocyclic compounds: an aryne.[5–7] Arynes–a triple bond within an aromatic ring–are attractive synthons due to their ability to undergo a difunctionalization in a single step and ability to be applied to a variety of 6-membered (hetero)arenes. Despite the attractiveness as functional groups, 5-membered N-heterocyclic arynes such as 2,3-indolyne are considered inaccessible due to the large amount of strain associated with a triple bond in a 5-membered ring.[8] Gribble attempted the synthesis of 2,3-indolyne through a lithiation/elimination strategy starting from an *ortho*-dibromo precursor that is common in 6-membered aryne formation (**Figure 1A**).[9] The product of the trapped aryne was not observed. Instead, the reaction can be quenched with D_2O which shows deuteration at the 2 position and the C–Br bond still intact. Various other elimination strategies with better leaving groups, thermal activation, or TMS activation have been attempted to no avail.[5,10,11] Paton, Houk, and Garg explained this phenomenon computationally and concluded that 5-membered N-heteroarynes are inaccessible (**Figure 1B**).[8]

Our group hypothesized that 5-membered inaccessible arynes could be accessed using a metal to relieve the strain associated with a triple bond in a 5-membered ring through metal-ligand interactions such as σ-donation and π-back donation (**Figure 1C**).[12–14] Using these fundamental principles of organometallic chemistry, access to a Ni-bound 7-aza-2,3-indolyne was achieved for the first time.[15] A crystal structure revealed that Ni-bound 7-aza-2,3-indolyne had a significantly elongated aryne bond compared to the calculated value but was still shorter than a typical arene double bond. This demonstrates that

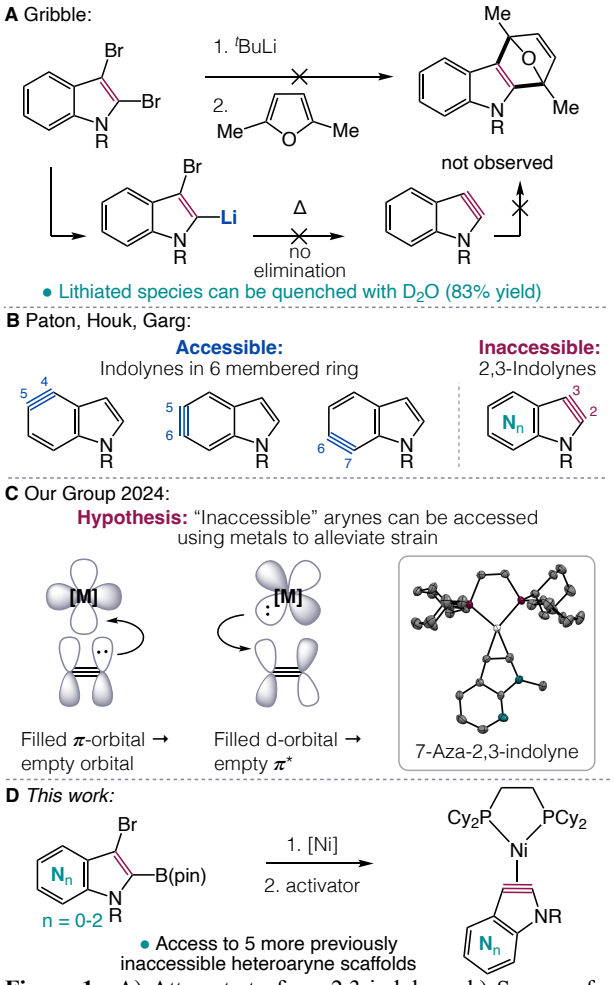

Figure 1. A) Attempts to form 2,3-indolyne, b) Survey of heteroaryne accessibility, C) Accessing aryne of 7-aza-2,3-indolyne through alleviation of strain through metal binding, D) This work: expanding scope to other heteroaryne scaffolds

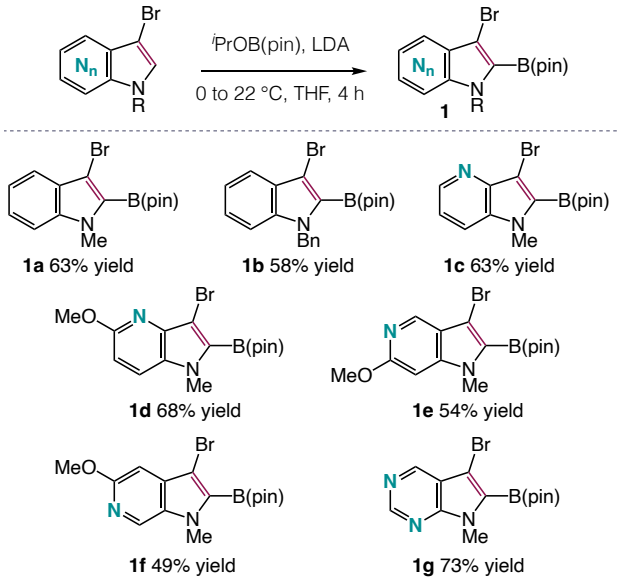

Figure 2. Synthesis of heteroaryne precursors

a large amount of π-back donation is necessary to access 5-membered N-heterocyclic arynes.[16] This complex displayed remarkable ambiphilic reactivity as compared to the typical nucleophilic character of Ni-bound benzyne, further demonstrating the unique electronic structure of 5-membered N-heteroarynes.[17,18]

We hypothesized that this newly accessible functional group could be extended to other classes of 5-membered N-heterocyclic arynes. This would help to make 5-membered N-heteroarynes a more universal synthon, aiding in the synthesis of libraries of biologically active molecules. Herein we report 5 new classes of N-heteroarynes that have never been accessed before to our knowledge. Interestingly, aryne formation occurs at different rates and yields depending on the heterocycle identity. The electronics of the aryne clearly play an important role as electronically activating groups can be used to tune reactivity. Solid state structural studies reveal that the aryne bond length changes with heterocycle identity as well. Finally, difunctionalization reactions also reveal differences in aryne structure depending on the heterocycle as different regioselectivities are observed.[19–21]

N-heteroarynes were accessed from *ortho*-borylaryl bromide precursors.[22,23] These molecules undergo oxidative addition followed by an intramolecular transmetallation to form Ni-bound arynes. These *ortho*-borylaryl bromide precursors were synthesized from commercially available starting materials. Some of these starting materials had to be brominated using N-Bromo succinimide (**1a**, **1b**), methyl protected using methyl iodide (**1c**, **1f**), or both (**1d**, **1e**) to form 3-bromo-N-methyl azaindoles. These arenes were then subjected to lithium diisopropylamide (LDA)–promoted borylation with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2- dioxaborolane [^{i}PrOB(pin)] in THF to form the desired aryne precursors in moderate to good yields (49% - 73%) (**Figure 2**).

The methoxy substituted precursors were prepared to aid in solubility. Pyrrolo[2,3-*d*]pyrimidine precursor (**1g**) was observed to be unstable on silica gel as it undergoes protodeborylation during column chromatography in silica. Therefore the reaction was monitored for complete conversion, and the unreacted ^{i}PrO-B(pin) was removed by washing with hexane to give the desired precursor molecule in 73% yield.

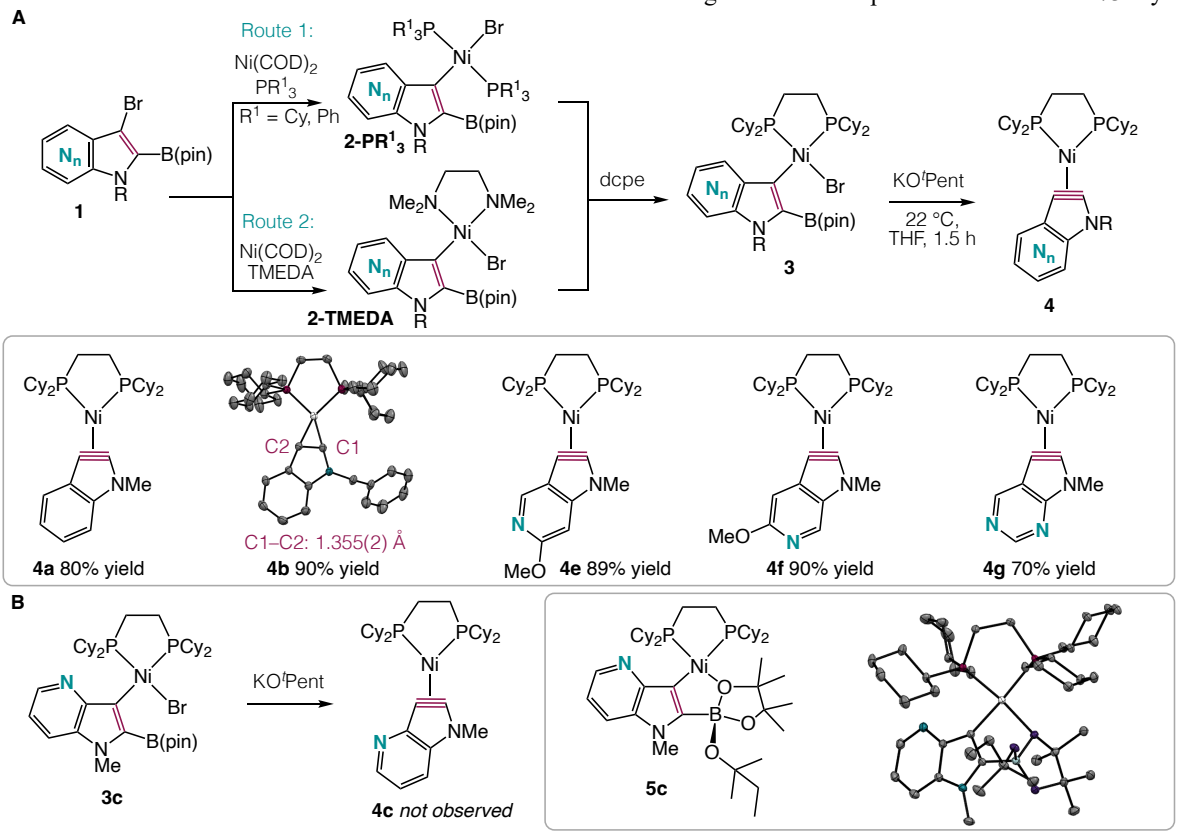

Figure 3. A) Synthesis of heteroaryne complexes through multiple routes, B) Borate formation with 4-azaindole

Previously, in order to make inaccessible aryne complexes, a three step procedure was employed which involved: oxidative addition of the *ortho*-boryl bromides (**1**) at Ni, ligand exchange with 1,2-bis[dicyclohexylphosphino]ethane (dcpe) and transmetallation.[15,22] However, the oxidative addition step was typically low yielding therefore we developed improved routes. A total of three methods were utilized to achieve oxidative addition. The first, which we previously reported, involves oxidative addition of **1** with $Ni(COD)_2$ in the presence of PPh_3. This method was used to prepare **2a-PPh$_3$**, **2e-PPh$_3$**, and **2g-PPh$_3$** in 43-56% yield. A second method was developed using N,N,N',N'-tetramethylethylenediamine (TMEDA), in place of PPh_3, which was generally the highest yielding method to achieve oxidative addition.[24,25] This method was used to prepare the pink complexes **2b-d-TMEDA** in 79-95% yield. Oxidative addition of **1f** was possible with PPh_3 and TMEDA, but the resulting complexes either decomposed in solution or had poor solubility, respectively, which hindered their characterization. Therefore, a third method was developed using PCy_3 instead of PPh_3 to prepare **2f-PCy$_3$** in 41% yield.

Ligand exchange from **2-PR$_3$** and **2-TMEDA** with dcpe resulted in the corresponding yellow dcpe σ-aryl complexes **3** in 64-91% yield. Activation of **3a,b,e-g** with KO^{t}Pent results in transmetallation to form the corresponding arynes **4a,b,e-g** which were isolated in 70-90% yield. Single crystals of complex **4b** suitable for X-ray diffraction were grown from a THF solution with pentane vapor diffusion. Interestingly, the C1-C2 aryne bond in **4b** is 1.355(2) Å which is longer than the bond length of our previously report N-Bn 7-azaindole analogue of **4**

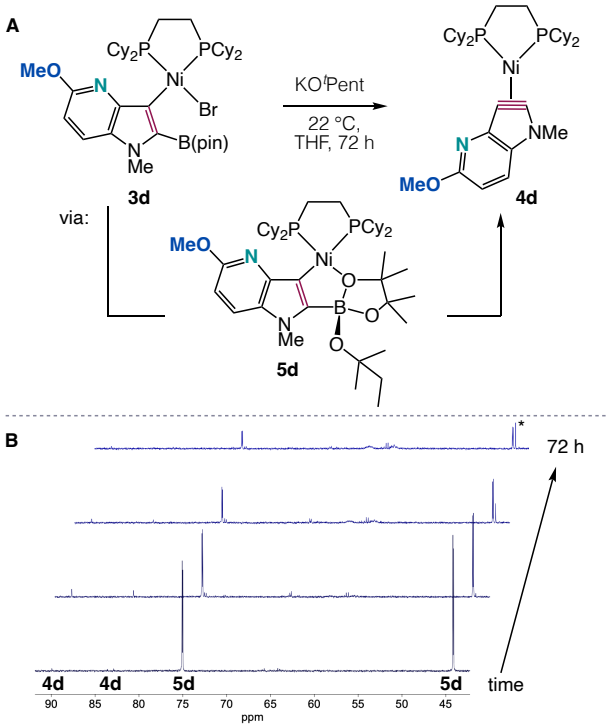

Figure 4. A) Use of electronically activating group to enable aryne formation, B) $^{31}P\{^1H\}$ NMR spectroscopy monitoring, *$(dcpe)_2Ni$

that has a C1-C2 aryne bond of 1.348(3) Å. This demonstrates that the degree of backdonation from the metal to the aryne depends on the identity of the heterocycle.

Attempted transmetallation of **3c** to generate the corresponding aryne **4c** resulted instead in the formation of a borate complex, **5c** (**Figure 3B**). In C_6D_6, the $^{31}P\{^1H\}$ NMR spectrum of this complex shows two doublets at 72.91 and 45.23 ppm with a $^2J_{PP}$ coupling of 12.9 Hz, and the ^{11}B NMR spectrum shows a broad singlet at 8.18 ppm. This is spectroscopically similar to the recently reported proposed transient borate intermediate observed for the transmetallation of the 5-CF_3 7-azaindole analog of **3**. This analog has $^{31}P\{^1H\}$ NMR signals at 66.5 and 47.6 ppm ($^2J_{PP}$ 19.6 Hz) and an ^{11}B NMR signal at 10.4 ppm in THF-d_8. Unlike the 5-CF_3 7-azaindole analogue which eventually converted to the aryne and therefore the borate structure could not be definitively assigned, excitingly complex **5c** was isolated in 75% yield and single crystals suitable for X-ray diffraction were grown from a THF solution layered with pentane that was stored at -35°C. The structure shows that the complex has maintained its square planar geometry. This borate complex results from activation of B(pin) in **3c** with $^-$O^{t}Pent and subsequent KBr salt elimination. The resulting vacant coordination site at Ni is occupied by coordination from a pinacol oxygen, which contrasts with the proposed structures from Thomas and Denmark which have the activator coordinated to the metal.[26–30] Monitoring **5c** in solution shows that this complex is stable and that subsequent transmetallation to form the corresponding aryne does not occur, even over a period of 3 days.

In our previous report, the CF_3 substituted 7-azaindolyne took two hours to fully convert to the aryne but the OMe substituted 7-azaindolyne was fully converted in ten minutes. Therefore, we hypothesized that we could overcome this issue of borate formation by electronically biasing 4-azaindole to undergo transmetallation through the installation of a methoxy group. Doing so would render the heterocycle more electron-rich and a stronger nucleophile for transmetallation. Thus, complex **3d** was prepared which contains an OMe group in the 5-position of 4-azaindole. Activation of **3d** with KO^{t}Pent also results in the initial formation of the corresponding borate complex, **5d** (**Figure 4A**). The $^{31}P\{^1H\}$ NMR spectrum (**Figure 4B**) of this reaction mixture shows the borate complex **5d** as a set of doublets at 75.04 and 44.15 ppm ($^2J_{PP}$ = 12.9 Hz) and the ^{11}B NMR spectrum shows a broad singlet at 8.04 ppm, consistent with complex **5c** (see supporting information). However, in contrast to **5c**, **5d** slowly undergoes transmetallation to form the aryne **4d**, which is observed at 89.94 and 82.88 ppm ($^2J_{PP}$ = 4.5 Hz) in the $^{31}P\{^1H\}$ NMR spectrum. This aryne is not stable and decomposes before full conversion of **5d** occurs. Interestingly, a borate intermediate is also observed in the transmetallation of **3f** (see supporting information). However, this complex undergoes transmetallation to completion and faster (~5 h) than **3d**. Together, these results suggests that the electronic nature of the heterocycles and the position of N in the six-membered ring impacts transmetallation to form the corresponding arynes.

With various N-heteroarynes in hand, we sought to develop their utility as a universal synthon for decorated heterocycles. Strategies have been developed to target specific heteroarenes, however there is a lack of a general approach to making an array of heteroarenes. This is a substantial problem for discovery chemists who seek to determine structure-function relationships of lead candidates via scaffold hopping – a strategy in which iterative structural changes are made to lead candidates to optimize traits such as efficacy, specificity, absorption, and lifetime.[31–33] Often the strategies for introducing one heterocycle, for example a pyrrolopyrimidine, are vastly different than strategies for introducing another, such as indole, meaning a unique synthetic strategy is often required for each structural change to the lead candidate.[4] Therefore, often in the process of making,

testing, and designing a new target the rate determining step is the synthesis.[34] Alternatively, heteroaryne chemistry represents a promising intermediate to target in scaffold swapping campaigns as they would represent a more universal synthon. Thus, the same synthetic strategy would apply across various classes of heterocycles.

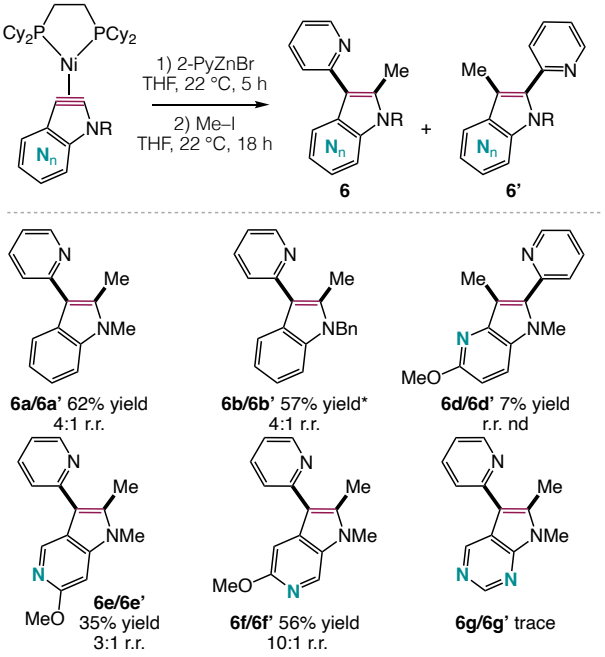

Figure 5. Difunctionalizations and comparisons of regioisomeric ratios (r.r.) depending on substrate identity, major regioisomer shown. Only the major regioisomers are depicted, and r.r.'s are of functionalization at C2:C1. Unless noted all yields are combined isolated yield of both regioisomers. *Yield calculated by ^{1}H NMR spectroscopy with CH_2Br_2 internal standard after 48 h. See supporting information for full experimental details.

Therefore, we aimed to demonstrate the utility of the newly accessible N-heteroarynes by developing a difunctionalization to achieve a scaffold hop between various classes of heterocycles. While metal-aryne complexes are typically regarded as nucleophilic, our past studies showed 5-membered N-heteroaryne complexes demonstrate ambiphilic reactivity – meaning they react as both electrophiles and nucleophiles. Therefore, the electrophilic reactivity of free arynes appears to be maintained in the metal-bound complexes. A one-pot difunctionalization was developed in which a nucleophilic insertion was achieved with 2-pyridylZnBr followed by an electrophilic coupling with iodomethane (**Figure 5**).[35] This strategy was found to translate to difunctionalized indoles (**6a/a'** and **6b/b'**) and various isomers of azaindole products (**6d/d'** and **6f/f'**). In most cases, the major regioisomer observed resulted from nucleophilic insertion at the 3-position, however the degree of regioselectivity varied across arynes from 3:1 up to 10:1 r.r. This demonstrates that the structural features of the heteroarynes dictate the observed regioselectivity.

Aryne complex **4d** could not be isolated, however it was still able to be applied to the same reaction. After complete conversion of pre-transmetallation complex **3d** to activated borate **5d**, 2-pyridylZnBr was added to trap the aryne generated in situ. After the 18 hours, iodomethane was added. The difunctionalized product **6d'** was isolated in a low 7% yield due to poor conversion to aryne.

The difunctionalization strategy did not apply to pyrrolo[2,3-*d*]pyrimidine **6g/6g'**. Upon addition of the nucleophile, complete conversion of aryne complex **4g** was observed when monitoring the reaction by ^{31}P{^{1}H} NMR spectroscopy. However, upon analysis of the reaction mixture after aqueous workup, only a small peak corresponding to the difunctionalized product was observed by GC-MS but was unable to be isolated due to low yield. Due to the additional heteroatoms in the arene, it is possible bridging oligomers are formed in which an N-atom of the arene coordinated to a Ni center.[36] Therefore, we hypothesize the mass balance for reactions with aryne **4g** largely goes to Ni-complex oligomer formation rather than the desired reactivity.

In conclusion, we have expanded the scope of now accessible N-heterocyclic arynes to include other classes of azaindoles, indoles, and pyrrolopyrimidines. This has greatly expanded the synthetic utility of this previously inaccessible functional group which will allow libraries of N-heteroaromatics to be quickly built up with a common set of coupling partners. Additionally, the propensity for aryne formation was explored and found to be dependent on the electronics of the N-heterocycle. Future work includes ligand and activator design to eliminate the substrate dependence on aryne formation.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization (PDF)
Crystal structures can be found in the CCDC #2362705-2362709

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Author Contributions

All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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Notes

A provisional patent has been filed on this work by the University of Minnesota.

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