

Nickel-Bound 5-Membered N-Heterocyclic Arynes: Access to Previously “Inaccessible” 7-Aza-2,3-indolynes

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Abstract: N-Heteroaromatics are key elements of life-saving pharmaceuticals, potent agrochemicals, and vital materials. N-Heteroarynes provide a scaffold to build these essential molecules but are underutilized because 5-membered N-heteroarynes have been computed to be inaccessible to synthetic chemists due to the strain of a triple bond in a 5-membered ring. Using principles of metal-ligand interactions that are foundational to organometallic chemistry, herein is reported the first access to a previously inaccessible 5-membered N-heteroaryne. A series of 1,2-bis(dicyclohexylphosphino)ethane nickel 7-azaindol-2,3-yne complexes are synthesized and characterized crystallographically and spectroscopically. In order to showcase the synthetic potential, a difunctionalization of N-methyl-7-azaindol-2,3-yne to form two new C-C bonds is performed. By overcoming a 120-year old limitation, we have unlocked a new synthon for the synthesis of difunctionalized N-heteroaromatics for transformative synthesis.

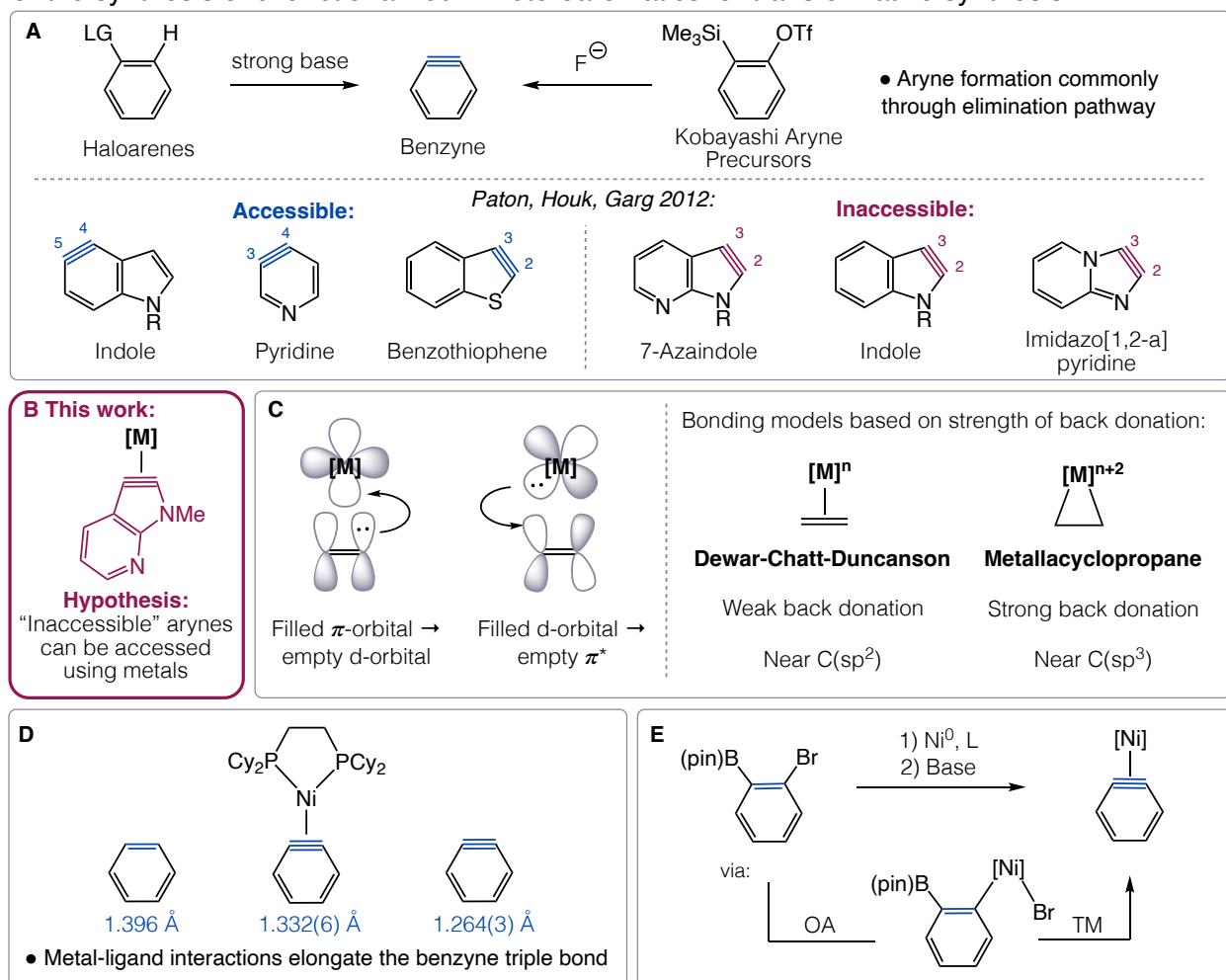


Fig. 1. Synthesis and accessibility of aryne and orbital interactions of metal- π ligands. (A) Formation and accessibility of aryne through elimination, (B) Hypothesis of this work, (C) Metal- π ligand interactions, (D) Comparison of computed and crystallographic bond lengths of benzene and benzyne, (E) Formation of Ni-benzyne; OTf = trifluoromethanesulfonate; LG = leaving group; M = metal; L = ligand, pin = pinacol, OA = oxidative addition; TM = transmetalation.

Heteroaromatic compounds are essential building blocks for pharmaceuticals, agrochemicals, and materials (1–4). N-Heteroarynes—an aromatic system containing a triple bond and an N atom—are attractive synthons particularly due to their ability to undergo a difunctionalization in a single step (5, 6). For example, a variety of 6-membered heteroarynes such as 3,4-pyridyne and 4,5-indolyne have been used as key intermediates in the synthesis of natural products (7–10). Despite its widespread use in the synthesis of natural products, aryne methodology is afflicted with major challenges related to the scope of arynes that can be formed.

Typical methods to access arynes involve formation of an anion followed by expulsion of a good leaving group to generate the triple bond through an elimination reaction (**Fig. 1A**). Formation of the anion generally requires a harsh base to deprotonate a haloarene for elimination (11, 12). Alternatively, Kobayashi silylaryl triflate precursors have been developed and are widely used (5). These aryne precursors can be activated under mild conditions using a fluoride activator and eliminate through a similar mechanism.

Based on these elimination pathways, a computational model was developed by Paton, Houk, and Garg to determine the accessibility of arynes for use in synthesis (**Fig. 1A**) (13). The model delineates between accessible arynes that can be formed and inaccessible arynes that cannot be formed by using the heat of dehydrogenation as a metric. This model predicts that heteroarynes such as 3,4-pyridyne or 4,5-indolyne can be accessed when the aryne being formed is in a 6-membered ring. These predictions were confirmed experimentally by Garg and coworkers (14). 5-Membered heteroarynes have been invoked as intermediates for over 120 years but their intermediacy has been contested (4, 15). Based on the computational model, the only 5-membered heteroarynes predicted to be accessible contain sulfur; this is due to strain relief provided by the size of the S atom and long C–S bond length (13). However, there has been limited success in the formation of free arynes and one publication exists on metal-bound S-containing arynes (16–18). This computational model also predicts that 5-membered N-heteroarynes are “inaccessible”; meaning they cannot be formed via an elimination mechanism due to the strain associated with forming a triple bond within a 5-membered ring (**Fig. 1A**). This represents a significant limitation of aryne chemistry as functionalized 5-membered N-heterocycles are abundant in pharmaceutically relevant compounds and agrochemicals (1–3). Due to the utility of aryne chemistry and the ubiquity of N-heteroaromatics in drug molecules, agrochemicals, and materials, we sought to overcome the limitation of 5-membered N-heterocyclic arynes being “inaccessible.”

We hypothesized that transition metal complexes can be used to alleviate strain through metal back-bonding as well as ligand donation and allow access to “inaccessible” heteroarynes (**Fig. 1B**). When unsaturated C-based ligands bind to metal centers, there are multiple bonding interactions to consider: 1) the donation of electrons from the filled π -orbital of the C–C unsaturated bond into the empty metal d-orbital and 2) the back-donation of a filled metal d-orbital to the empty π^* orbital of the C–C unsaturated bond (**Fig. 1C**). Both interactions change the bond order of the unsaturated bond. This phenomenon is well-studied for alkenes and depending on the identity and oxidation state of the metal center, these interactions are described by the Dewar-Chatt-Duncanson model or the metallacyclopropane model (**Fig. 1C**) (19).

When an aryne is bound to a transition metal, the bond length of the triple bond is elongated through similar bonding interactions to those described above. The crystal structure of 1,2-bis(dicyclohexylphosphino)ethane (dcpe) Ni-benzynes shows the length of the triple bond (1.332(6) Å) is longer than the calculated value in free benzyne (1.264(3) Å), but shorter than a double bond in benzene (1.396 Å) (**Fig. 1D**) (20, 21). Although benzyne is not considered “inaccessible,” this example demonstrates that the triple bond of an aryne is elongated through metal binding. While other methods exist to synthesize metal bound arynes, Wenger and coworkers developed an *ortho*-borylaryl bromide precursor that can be used to synthesize the Ni-benzynes complex under mild conditions (**Fig. 1E**) (22). While mechanisms have been proposed that involve aryne precursors that generate an aryne through an elimination reaction followed by

capture of an aryne by a metal, borylaryl bromides can be used to definitively generate metal-bound arynes by an inner sphere oxidative addition followed by intramolecular transmetalation (23). This differing mechanism for metal aryne formation opens up the opportunity to address limitations of “inaccessible” N-heteroarynes because it does not involve a problematic elimination step. While other metal-bound aryne examples exist, to date, no complexes of “inaccessible” N-heteroarynes are known. Therefore we set out to use these borylaryl bromide precursors en route to the synthesis of “inaccessible” arynes.

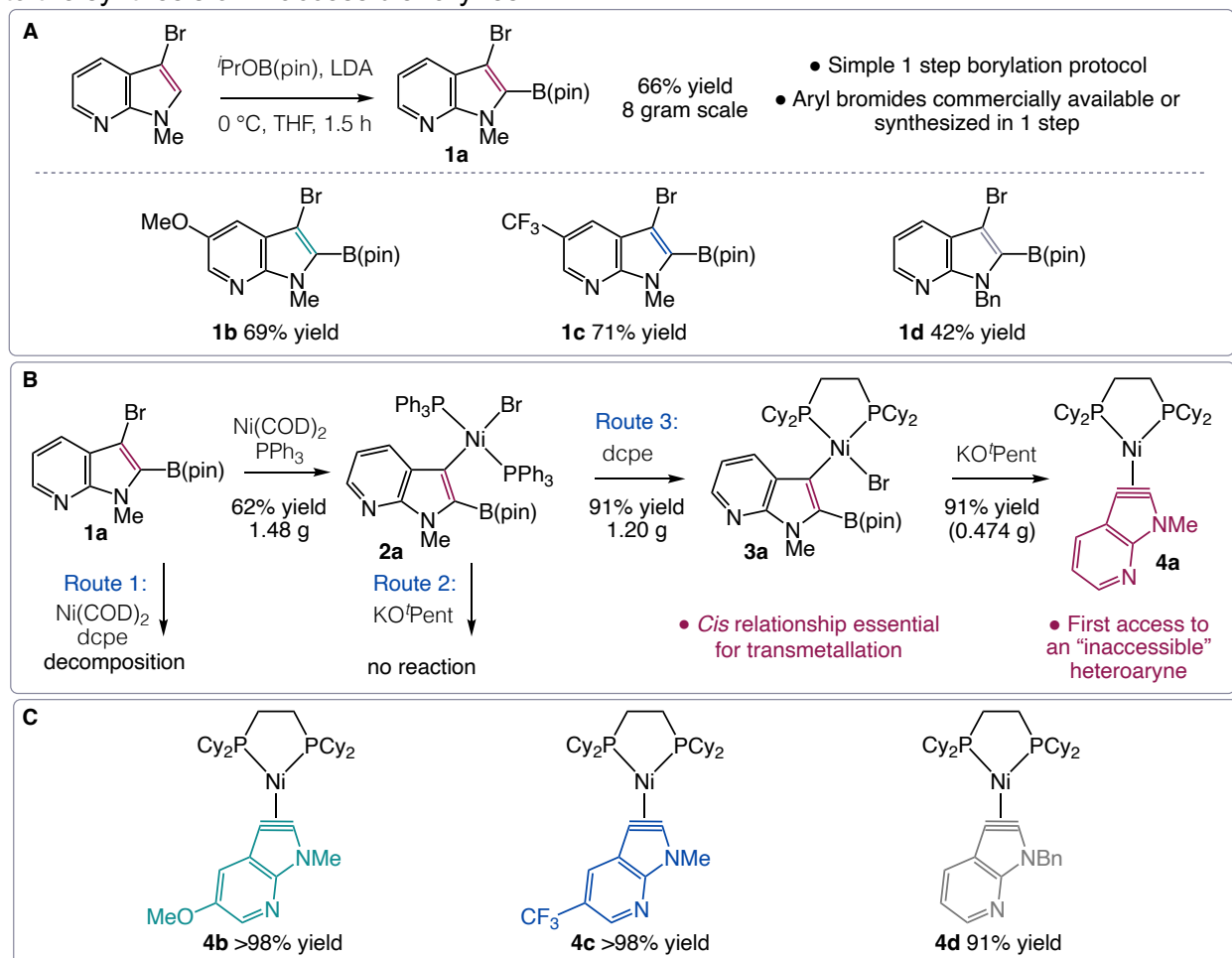


Fig. 2. Synthetic access to “inaccessible” 7-azaindolyne. (A) Synthesis of heteroaryne precursors, (B) Development of route to Ni-bound 7-azaindolyne complex, see SI for full reaction conditions (C) Electronically and sterically differentiated Ni-bound 7-azaindolyne complexes; LDA = lithium diisopropylamide; THF = tetrahydrofuran; Bn = benzyl; dcpe = 1,2-bis(dicyclohexylphosphino)ethane; COD = 1,5-cyclooctadiene; O^tPent = *tert*-pentoxide.

We targeted 7-azaindole because it is the most common azaindole core due to its hinge H-bonding abilities (24–26). A one-pot route to 7-azaindole *o*-borylaryl bromide precursor **1a** was developed from commercially available aryl bromide starting materials (Fig. 2A). This route involves an LDA-promoted borylation using ^tPrOB(pin), which avoids going through a highly unstable boronic acid intermediate (Fig. 2A) (16, 27). Model aryne precursor **1a** was scaled up to an 8 gram scale using this method. In order to vary the electronics, 5-OMe- (**1b**) and 5-CF₃-7-azaindole (**1c**) precursors were synthesized. Additionally, Bn protected 7-azaindole precursor **1d** was made in order to study the impact of the N-substituent.

With “inaccessible” 7-azaindole aryne precursors **1a-d** in hand, the first example of the synthesis of an “inaccessible” aryne was developed (Fig. 2B). Initial attempts at direct oxidative addition of the Ni(COD)₂ with dcpe and **1a** did not yield the desired σ -aryl complex **3a** (route 1). Therefore, the use of a less electron-rich monodentate ligand was necessary when using

Ni(COD)₂. Compound **1a** underwent oxidative addition with Ni(COD)₂ and 2 equivalents of PPh₃ to generate an isolable σ -aryl complex **2a**. The PPh₃ ligands in **2a** are in a *trans* relationship to each other, which prevents transmetalation and results in no reaction upon addition of an activator (route 2). This PPh₃ complex **2a** subsequently underwent ligand exchange with a more stabilizing bidentate phosphine ligand, dcpe, to generate the desired σ -aryl complex **3a** (route 3). The bidentate ligand forces a *cis* geometry of the arene and bromide ligands. Subsequently, the addition of potassium *tert*-pentoxide as a soluble activator promoted intramolecular transmetalation, resulting in the formation of the desired Ni-bound 7-azaindolyne complex **4a**. This complex was characterized by X-ray crystallography, ¹H, ¹³C{¹H} and ³¹P{¹H} NMR

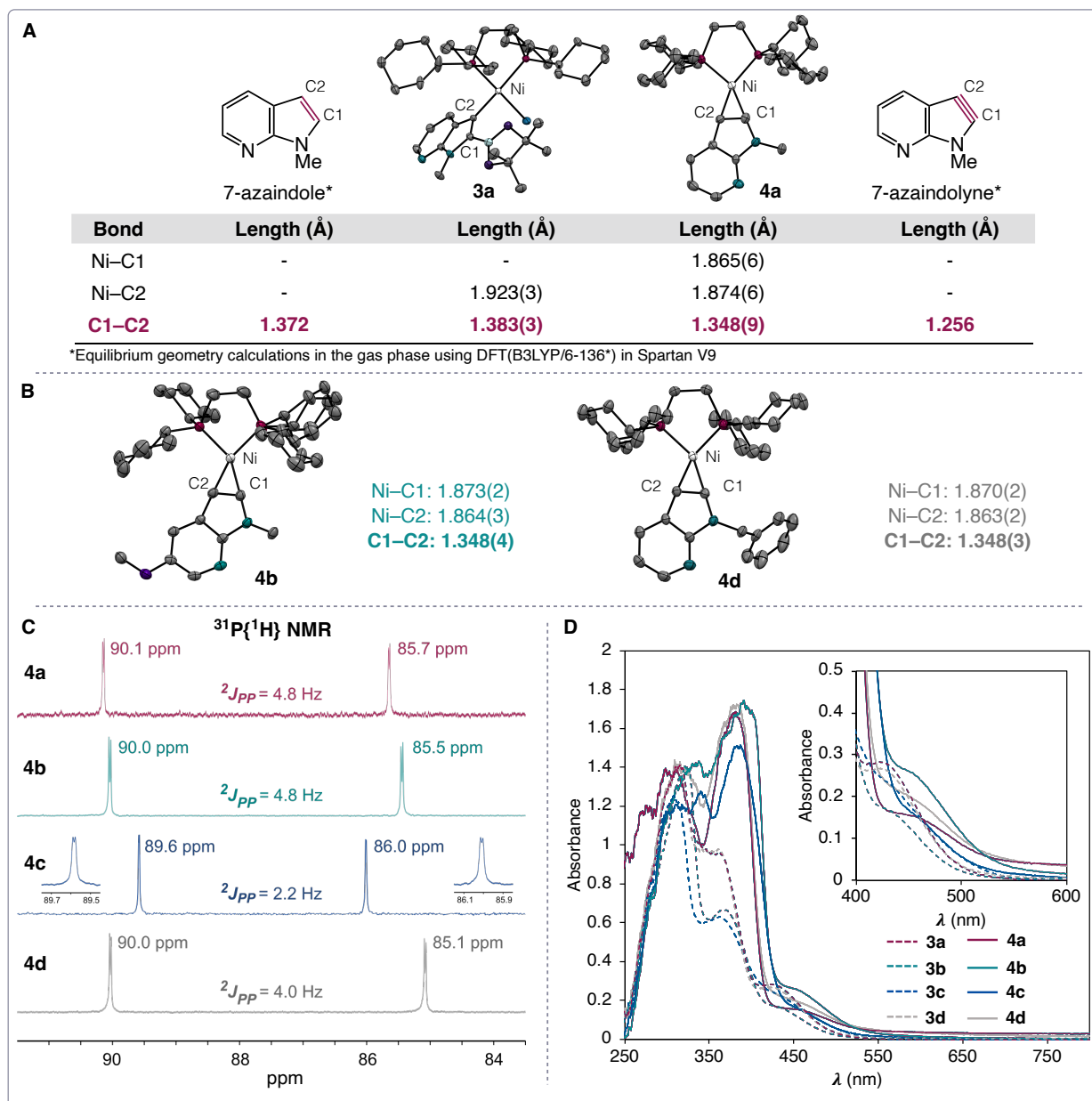


Fig. 3. Structural and spectroscopic characterization. (A) Comparison of computed and crystallographic bond lengths of 7-azaindole and 7-azaindolyne, (B) Crystallographic comparison of electronically and sterically differentiated Ni-bound 7-azaindolyne complexes, (C) ³¹P{¹H} NMR spectra of **4a-d** in THF-d₈, (D) UV-vis spectra of **3a-d** compared to **4a-d**, 0.2 mM in THF; ppm = parts per million, Hz = hertz; NMR = nuclear magnetic resonance.

spectroscopy, and UV-vis spectroscopy. This is the first example of access to an “inaccessible” 5-membered N-heterocyclic aryne.

In order to confirm our hypothesis that metal-bound “inaccessible” arynes can be formed through strain relief due to metal back-bonding, the crystal structures of **3a** and **4a** were compared to calculated structures of 7-azaindole and 7-azaindolyne (**Fig. 3A**). Compounds **3a** and **4a** were crystallized from layering CH_2Cl_2 with pentane or from a solution of THF with pentane vapor diffusion, respectively. The 7-azaindole and 7-azaindolyne structures (**pg. 96**) were calculated using equilibrium geometry calculations developed by Paton, Houk, and Garg (13). The C1 and C2 bond lengths were compared across 7-azaindole, **3a**, **4a**, and 7-azaindolyne. As was hypothesized, the C1–C2 aryne bond exhibits elongation in the metal-bound structure **4a** (1.348(9) Å) compared to the calculated bond length of the triple bond of 7-azaindolyne (1.256 Å). The C1–C2 bond of **4a** is still shorter than the calculated bond length of the double bond in 7-azaindole (1.372 Å) or of the σ -aryl complex **3a** (1.383(3) Å). This demonstrates the aryne character of **4a**. The C1–C2 bond of **4a** is also elongated compared to the previously reported accessible dpce-Ni benzothiohyne structure (average: 1.332(7) Å), indicating that more back-donation is necessary to form “inaccessible” arynes (16). The distance from the Ni center to the C1 terminus of the aryne bond of **4a** (1.865(6) Å) is shorter than the Ni–C2 distance (1.874(6) Å) by 0.009 Å demonstrating a slight difference in donation of the ancillary ligands and back-donation to the two aryne carbons in **4a**.

Surprisingly the C1–C2 aryne bond length is the same across structures **4a**, **4b**, and **4d** (**Fig. 3B**) which vary electronically and sterically. However, the Ni–C distances change. In **4a**, the longer Ni–C distance is Ni–C2 whereas in **4b** and **4d** the longer Ni–C distance is Ni–C1. Multiple attempts to crystallize **4c** did not result in X-ray quality single crystals. However, this slight difference in electronics of the whole series of **4a-d** can be observed in the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra.

The chemical shift and coupling constants in $^{31}\text{P}\{^1\text{H}\}$ NMR spectroscopy can be an indication of donation of the phosphine donors (28, 29). Regarding chemical shift, complexes **4a-d** (peaks in the 90–85 ppm range) are far more electron deshielded than the dcpe-Ni complex of benzyne which has a chemical shift of 78.4 ppm (**Fig. 3C**) (20). Interestingly, in complexes of dcpe Ni 6-membered arynes with unsymmetric substitution (*m*-Me, *m*-CO₂Me, *m*-CF₃), the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra generally show one singlet, indicating both phosphines are in a nearly identical chemical environment, despite the benzyne substitution (30). The only case where the phosphine resonances separate out is with a *m*-OMe substituent but this only separates the singlets by 0.6 ppm and no coupling constant is reported (30). This is in contrast to the 5-membered heteroaryne complexes which all appear as two distinct doublets, indicating the two P donors are chemically inequivalent. The most downfield ^{31}P shift (90.1 to 89.6 ppm, P trans to C1) only changes by 0.5 ppm across all 4 arynes **4a-d** and the upfield peak (86.0 to 85.1 ppm, P trans to C2) experiences a nearly 1 ppm shift difference, indicating a stronger change in the donation of the upfield P donor (31). Both signals are downfield from those reported for the accessible dcpe Ni-benzothiohyne which appear at 87.7 and 83.5 ppm, indicating the increased phosphine donation to the Ni and resulting back-donation to the aryne in **4a-d**. The $^2J_{\text{PP}}$ coupling constant is an indication of σ -donation of a phosphine to the Ni center (28). Interestingly, the $^2J_{\text{PP}}$ coupling constants have very little change (4.0 to 4.8 Hz range) between **4a**, **4b**, and **4d**. In contrast, the CF₃ substituted aryne **4c** has a $^2J_{\text{PP}}$ of 2.2 Hz coupling constant indicating a large difference in electronic structure as compared to **4a**, **4b**, and **4d**. This smaller coupling constant is due to the electron-deficient CF₃ aryne withdrawing more electron density from the phosphine donors. The $^2J_{\text{PP}}$ coupling constants (average of 7.1 Hz) of the accessible dcpe Ni-benzothiohyne complex are much larger, indicating a difference in the phosphine σ -donation into an accessible aryne versus an “inaccessible” aryne, which requires more strain relief. This is in agreement with the crystallographic analysis *vide supra*.

The $^{13}\text{C}\{^1\text{H}\}$ NMR shifts of the two aryne carbons also indicate how electronically unique these 5-membered N-heterocyclic arynes are (**figs. S53, S56, S59, S64**). The C1 and C2 signals are doublets of doublets due to coupling to both chemically inequivalent P donors. Across the series of 4 complexes **4a-d**, C1 has a resonance range of 170.6-166.0 ppm and C2 ranges from 120.7-119.9 ppm as confirmed by 2D NMR spectroscopy (**fig. S66-70**). This is in contrast to the $^{13}\text{C}\{^1\text{H}\}$ NMR shift reported for dcpe Ni-benzynes which appears at 146 ppm and the dcpe Ni-benzothiophyne complex where the C1 and C2 share nearly identical chemical shifts of 154.9 and 152.6 ppm, respectively (16, 20). Again this indicates the remarkable differences between metal complexes of accessible and “inaccessible” arynes.

Very little is known about the electronic structure of metal-aryne complexes as it relates to UV-vis spectroscopy. Therefore the σ -aryl complexes **3a-d** were compared to the aryne complexes **4a-d** and distinct spectra occur for each (**Fig. 3D**). Ligand based π - π transitions (250-350 nm) are observed in all the spectra. The peaks assigned to the d-d transitions (400-500 nm, $\epsilon \approx 700$ -1300 $\text{M}^{-1}\text{cm}^{-1}$) red shift slightly in the aryne compared to the σ -aryl complexes. The most notable feature of the aryne spectra of **4a-d** versus σ -aryl spectra of **3a-d** is the appearance of a strong MLCT band (λ_{max} range = 385-400 nm) in **4a-d** which is assigned to metal back-donation to the aryne.

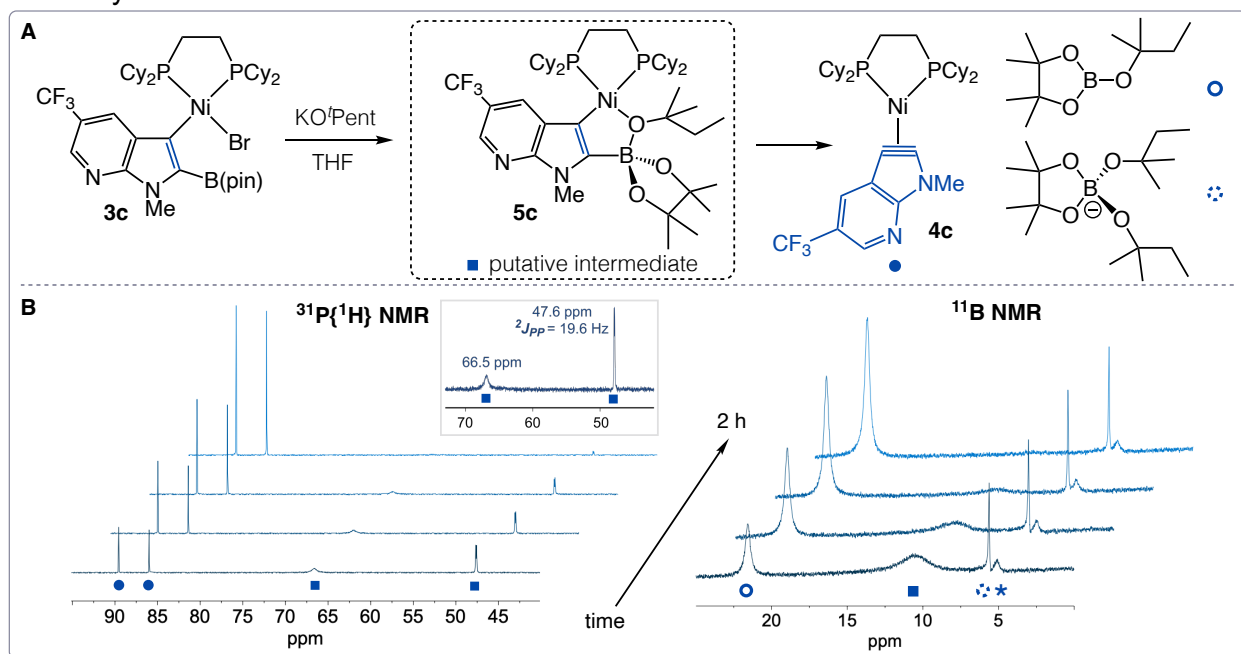


Fig. 4. Studies of the transmetalation step during aryne formation. (A) Proposed pathway for transmetalation through an activated borate intermediate, (B) Reaction monitoring through $^{31}\text{P}\{^1\text{H}\}$ and ^{11}B NMR spectroscopy in THF. * = unidentified borate species.

The transformation of **3c** to **4c** was slow enough to observe an alkoxide activated intermediate **5c** prior to transmetalation (**Fig. 4A**). The reaction was monitored by $^{31}\text{P}\{^1\text{H}\}$ and ^{11}B NMR spectroscopy over a 2 hour period (**Fig. 4B**). The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showed a small amount of aryne formation within the time it took to collect the initial spectrum. Two additional resonances were observed – a broad peak at 66.5 ppm and a sharp doublet at 47.6 ppm with a $^2J_{\text{PP}}$ value of 19.6 Hz. Over time these two additional resonances, which are always in a 1:1 ratio, disappeared and the aryne signals grew in. The ^{11}B NMR also showed the $^t\text{PentO}-\text{B}(\text{pin})$ product of transmetalation as well as the $[(^t\text{PentO})_2-\text{B}(\text{pin})]^-$ borate byproduct at the first time point. An additional broad resonance was also observed in the borate region at 10.4 ppm. This shift and broad peak is consistent with a structure that Denmark and coworkers were able to observe of an activated borate prior to transmetalation (32–34). As with the $^{31}\text{P}\{^1\text{H}\}$ NMR spectra, this broad

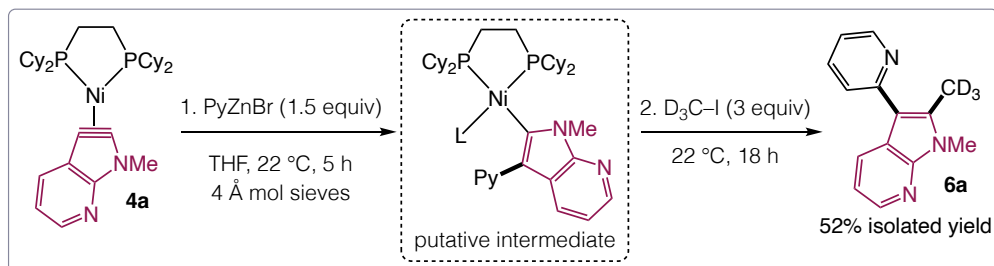


Fig. 5. Reactivity of 7-azaindolyne. One pot difunctionalization through two C–C bond formations; Py = pyridine; mol = molecular.

evidence and precedent by Denmark, we propose the activated borate species with a bound alkoxide **5c**. The Ni-bound alkoxide could alternatively be one of the oxygens on the pinacol, leading to a mixture of structures and a broad $^{31}\text{P}\{^1\text{H}\}$ resonance for the phosphine *trans* to that position. This would represent observation of an activated pre-transmetallation complex at room temperature.

With the aryne complexes in hand, we aimed to demonstrate the synthetic utility of Ni-bound 7-azaindolyne as a synthon of heterocyclic compounds. A one-pot multicomponent difunctionalization was achieved which highlights the use of isotopically labeled atoms. Upon the addition of PyZnBr, complex **4a** underwent 1,2-insertion to give a resulting σ -aryl intermediate which resulted in a second functionalization upon the addition of CD_3I to give **6a** as the single regioisomer of the difunctionalized product in 52% isolated yield. This result shows the promising utility of “inaccessible” N-heteroarynes as synthons.

The first ever purported aryne was later contested and deemed “inaccessible.” Despite this, for over 120 years this class of highly elusive intermediates has been sought after by chemists. Our studies experimentally affirm access to an “inaccessible” aryne for the first time. We provide definitive evidence of the existence of 7-azaindolyne through synthetic, crystallographic, and spectroscopic studies. The broad impact of a new functional group for 5-membered N-heteroaromatics provides a myriad of opportunities due to its potential as a synthon for heterocycle difunctionalization.

Acknowledgements:

We thank Dr. Thomas Smith for help with NMR experiments and Victor Young Jr. and Alex Lovstedt for help with crystallography. We thank the Wayne Gladfelter lab for access to UV-vis instrumentation and the Thomas Hoyer lab for access to IR instrumentation. We thank Sofie Hokanson for help with the collection of the crystal structure of **3a**.

Funding:

The University of Minnesota is acknowledged for startup funds. We also acknowledge the NIH R35GM146957 for funds. A provisional patent application has been filed on this work. JNH is supported by an NSF Graduate Research Fellowship (#2237827) and a Jane B. Spence Excellence Fellowship. EEP is supported by Newman and Lillian Bortnick Excellence Fellowship and a UMN Doctoral Dissertation Fellowship. SSK is supported by the Graham N. Gleysteen Award. CCR is grateful for an Amgen Young Investigator award. Instrumentation for the UMN Chemistry NMR facility was supported from a grant through the National Institutes of Health (NIH) (S10OD011952). Mass spectrometry analysis was performed at the UMN Department of Chemistry Mass Spectrometry Laboratory (MSL), supported by OVPR, CSE, and the Department of Chemistry at UMN, as well as the NSF (CHE-1336940). X-ray diffraction experiments were

resonance at 10.4 ppm in the ^{11}B NMR spectra disappears over time in proportion to growth of the byproduct of transmetalation. With this

performed with a diffractometer purchased through a grant from NSF/MRI (1229400) and the University of Minnesota.

Notes: JNH, RGB, and EEP are co-first authors

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