Bidentate Phosphine Ligand Impacts on Previously Inaccessible 5-Membered N-Heteroaryne Formation and Functionalization

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Arynes, bidentate phosphines, N-heterocycles

ABSTRACT: 5-Membered N-heteroarynes have long been considered synthetically inaccessible; however, we recently reported the use of a bisphosphine-ligated nickel center to stabilize and enable the formation of these otherwise unobtainable intermediates. Motivated by this success, we were compelled to study the role of the ancillary phosphine in aryne formation and reactivity. Herein, a set of four bidentate phosphine ligands with altered phosphine substituents and backbone length are interrogated for their competence as ancillary ligands for 5-membered N-heteroaryne formation. We determined that ligands with phenyl phosphine substituents or linker lengths longer than three carbons were unsuitable for this purpose, while ligands having alkyl phosphine substituents and one, two, or three carbon linkers allowed for successful aryne formation. Reactivity studies using 2-PyZnBr as a nucleophilic coupling partner revealed intriguing regioselectivity enhancement (up to >20:1 r.r.) when utilizing ligands with altered linker lengths. We hypothesize that regioselectivity can be traced back to structural differences between these Ni-aryne complexes, as evidenced by crystallographic characterization.

Nitrogen containing heterocycles are essential elements of medicinally relevant molecules as well as agrochemicals and materials.[1–4] To this end, N-heterocyclic arynes are important synthons for highly-decorated N-heteroarenes. While many indolynes and pyridynes with the aryne bond in the six-membered ring have been used in the synthesis of natural products,[5–7] the universal use of the heteroaryne synthon is limited due to the inaccessibility of 5-membered N-heteroarynes. Paton, Garg, and Houk have elegantly demonstrated the reason for this inaccessibility using a computational workflow to predict the synthetic utility of N-heterocyclic arynes (**Figure 1A**).[8]

Our group was interested in leveraging metals to overcome this inaccessibility as the σ-donation and π-back donation between the aryne and the metal alleviates the strain associated with the triple bond through elongating it.[9,10] We recently disclosed access to the first inaccessible aryne, Ni-bound 7-aza-2,3-indolyne (**Figure 1B**).[11] This complex had remarkable reactivity in that it readily reacts with electrophiles, nucleophiles, and enophiles.[12,13] This ambiphilic reactivity opens up a wide variety of substituents at the 2 and 3 positions of 7-azaindole. Excellent regioselectivity was observed with most coupling partners (C(sp3) and C(sp) hybridized organometallic nucleophiles, alkyl halides, aldehydes, and iodoniums). This is in alignment with the Ni–C1 and Ni–C2 bond lengths being inequivalent, meaning one site is electronically differentiated from the other.[14] Interestingly, with C(sp2) nucleophiles such as 2-PyZnBr, poor regioselectivity was observed.

With these observations, we hypothesized that changing the identity of the bidentate phosphine ligand could impact both reactivity and selectivity. The donor ability of the phosphine ligand is governed in part by the geometry and orbital overlap of the metal and phosphine ligand.[15] Thus, altering the geometry by increasing or decreasing the linker length of the ligand may
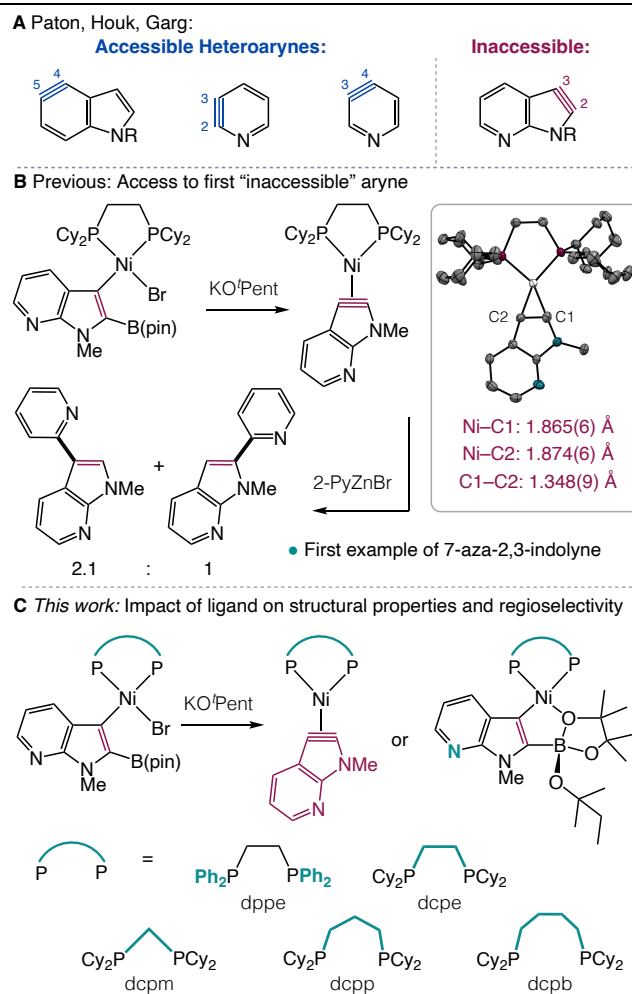

Figure 1. A) Heteroaryne inaccessibility, B) Previous work demonstrating first access to previously inaccessible 7-aza-2,3-indolyne, C) Examination of ligand effects on aryne formation, properties, and regioselectivity upon reaction

allow its donor ability to be finely tuned. These interactions consequently impact the amount of back donation into the aryne bond.[16] Similarly, the non-linker substituents on the phosphine impact the donation and proximity of the phosphine to the metal which in turn also effects the amount of electron density that can be back donated to the aryne.[17] Regioselective addition could also be impacted by these two phenomenon by changing the Ni–C bond lengths.[18] Herein we report a systematic study to understand the importance of these factors for aryne formation or borate byproduct formation.
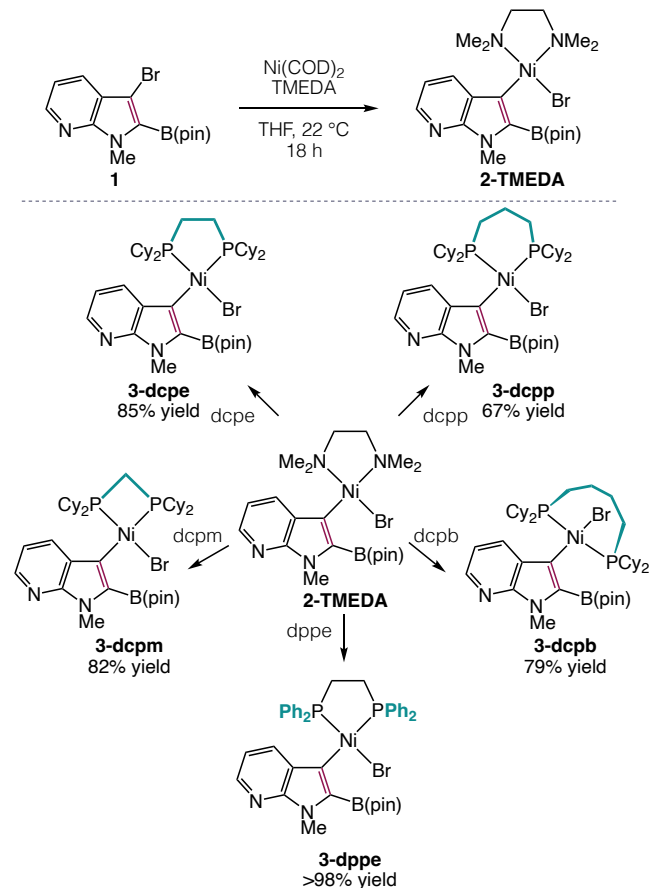

Figure 2. Ligand exchange from TMEDA ligated σ-aryl complex, see SI for full experimental details

We initiated this study by synthesizing a variety of bidentate phosphine ligated σ-aryl complexes via ligand exchange from the corresponding N,N,N',N'-tetramethylethylenediamine (TMEDA) ligated complex **2-TMEDA** (**Figure 2**). Our previous work utilized a triphenylphosphine ligated σ-aryl complex for ligand exchange,[11] however, we discovered that oxidative addition and ligand exchange were cleaner and more efficient using the TMEDA ligand.[19,20] We successfully synthesized the previously-studied 7-azaindole complex bearing a 1,2-bis(dicyclohexylphosphino)ethane (dcpe) ligand (**3-dcpe**) in 85% yield using this method. We then altered the phosphorus substituents to phenyl rings using a ethylenebis(diphenylphosphine) (dppe) ligand to synthesize complex **3-dppe** in >98% yield. Next, we synthesized complexes with cyclohexyl substituents but varied linker length. Complex **3-dcpm** bearing a bis(dicyclohexylphosphino)methane (dcpm) ligand was synthesized in 82% yield. The 1,3-bis(dicyclohexylphosphino)propane (dcpp) ligated complex **3-dcpp** was produced in 67% yield, and the 1,3-bid(dicyclohexylphosphino)butane (dcpb) ligated complex **3-dcpb** was produced in 79% yield.

We next attempted transmetallation of each of these σ-aryl species with the intent of forming the corresponding aryne complex. We hypothesized that complexes with less donating phosphine substituents, as in complex **3-dppe**, would lead to lessened backdonation in the subsequent aryne **4-dppe** and a shorter C1-C2 bond distance. Upon activation using potassium tert-pentoxide (KO^tPent), we instead observed the formation of an intriguing borate species **6-dppe**, with transfer of a ligand phenyl group to the nickel center (**Figure 3**). Monitoring transmetallation by ³¹P{¹H} NMR spectroscopy revealed the initial formation of the expected borate species **5-dppe** which converts into **6-dppe** over time. We hypothesize that the structure of this intermediate borate species **5-dppe** is similar to the putative intermediate proposed in our previous study.[11] The conversion of **5-dppe** into **6-dppe** may be mediated through a phosphonium salt formation followed by oxidative addition into the P⁺-Ph bond. We believe this deleterious pathway is more prevalent with phenyl ligand substituents due to their smaller steric profile which enables closer proximity to the metal center for nucleophilic attack and phosphonium salt formation. Additionally, the electron withdrawing nature of the phenyl substituents make the following oxidative addition more facile leading to irreversible formation of **6-dppe**. Overall, we ascertained that phenyl substituents on the phosphine ligand were unsuitable for aryne formation.
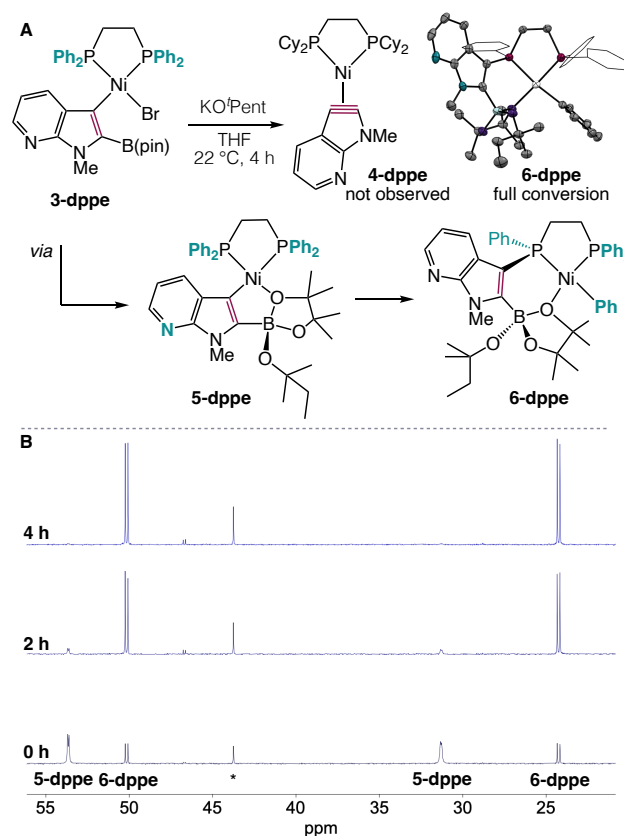

Figure 3. A) Transmetallation attempts with dppe ligand, B) reaction monitoring with ³¹P{¹H} NMR spectroscopy over 4 h; *Ni(dppe)₂

Having observed the detrimental effects of phenyl phosphine substituents we returned to cyclohexyl substituents and turned our attention to the linker length of the bidentate ligand. We began this study by subjecting dcpm-ligated complex **3-dcpm** to transmetallation conditions with KO^tPent as activator (**Figure 4**). This led to an intractable mixture of three 7-azaindole species as determined by ¹H NMR in a 1:1:1 ratio. The presence
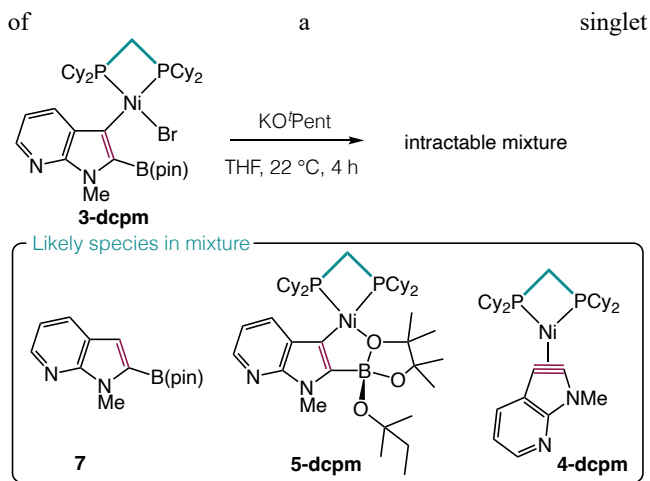
of a singlet

Figure 4. Transmetallation attempts with dcpm ligand

in the aromatic region of the ^{1}H NMR spectrum indicates that one of these species is protonated at the C1 or C2 position. The ^{31}P{^{1}H} NMR spectrum revealed two sharp doublets in addition to two broad signals. This suggests that only two of the three azaindole species are bound to a Ni(dcpm) center. The ^{11}B NMR contained two signals at 21.3 ppm and 5.1 ppm. The 5.1 ppm signal is similar to those we have observed for previous borate species, while the 21.3 signal is more similar to the shift of the boron signal of the borylaryl bromide aryne precursors or a byproduct of transmetallation [^{t}PentO–B(pin)].[11] All of these data suggest that the mixture of products contains one non-metallated azaindole with a B(pin) substituent which is hypothesized to be **7**, and two metallated azaindoles, only one of which is a borate species **5-dcpm**. ESI-MS analysis of this mixture suggested the potential for one of these species to be the aryne complex **4-dcpm**, however, we were unable to crystallize any of the three products so this could not be confirmed by X-ray crystallography.
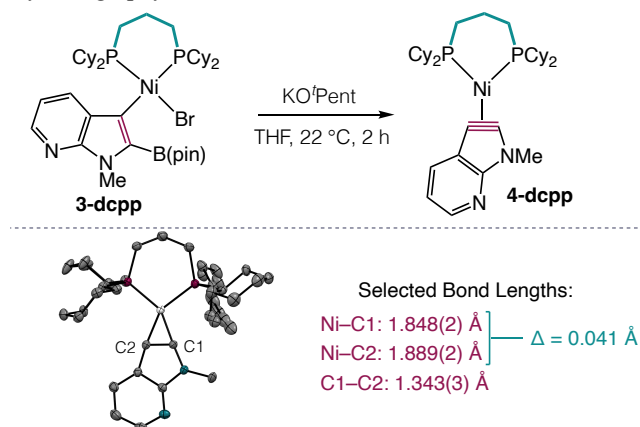

Figure 5. Transmetallation with dcpp ligand, Δ = (Ni–C2) - (Ni–C1)

We continued the study utilizing longer ligand linker lengths (**Figure 5**). Excitingly, complex **3-dcpp** proceeded successfully to the corresponding aryne complex **4-dcpp** in >98% yield upon addition of KO^{t}Pent. Crystallographic analysis revealed a C1–C2 bond length of 1.343(3) Å, which is slightly shorter than the previously studied dcpe-ligated analogue: **4-dcpe** (1.348(9) Å).[11] The Ni-C1 vs Ni-C2 distances are also altered in **4-dcpp** as compared to **4-dcpe**. Ni-C2 remains as the longer Ni-aryne distance at 1.889(2) Å versus the Ni-C1 distance of 1.848(2) Å, however, these values are much more disparate than **4-dcpe** (Δ = 0.041 and 0.009 Å, respectively). Excitingly, this indicates

that the geometry and orbital overlap of the bidentate phosphine can impact the electronics and degree of backdonation in these aryne complexes.

Finally, we attempted transmetallation on **3-dcpb** using KO^{t}Pent (**Figure 6**). The reaction was allowed to proceed for 18 hours, however full conversion of **3-dcpb** was not observed even after this longer reaction time. It should be noted that complex **3-dcpb** appears to have fluxional geometry indicated by broad signals in the ^{1}H and ^{13}C NMR spectra. The major species is hypothesized to have tetrahedral geometry or *trans* substitution of the phosphorus atoms at the nickel center. This hypothesis is based on the ^{31}P{^{1}H}NMR spectrum which contains a major broad singlet, indicating symmetry of the phosphorus atoms. Based on our previous work we believe sigma aryl complexes with *trans* geometry (and presumably tetrahedral geometry) are inefficient at transmetallation/aryne formation. Nonetheless, we did observe a set of sharp doublets in the ^{31}P{^{1}H} NMR spectrum in addition to σ-aryl **6** and various decomposition signals. The ^{11}B NMR spectrum reveals 2 signals at 22.4 and 21.3 ppm. These are similar in shift to the byproduct of transmetallation [^{t}PentO–B(pin)] which suggests that transmetallation may have occurred;[11] however, due to poor conversion and the intractable mixture we rule out dcpb as a competent ligand to cleanly form an aryne complex.
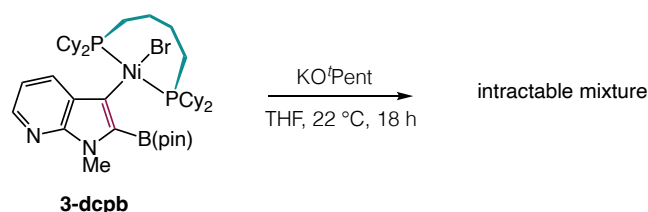

Figure 6. Transmetallation attempts with dcpb ligand

We next wanted to explore reactivity and/or regioselectivity differences between the variously ligated aryne species (**Figure 7**). We hypothesized that **4-dcpp** would react more regioselectively than the **4-dcpe** due to the greater disparity between Ni-C1 and Ni-C2 distances. We thus subjected aryne both complexes, **4-dcpe** and **4-dcpp**, to 1 equivalent of 2-pyridylzinc bromide. Here we observed a 54% combined NMR yield and 3.5:1 regioisomeric ratio (r.r.) of products **8** and **8'** using **4-dcpe** and a 51% combined NMR yield and 5.4:1 r.r. using **4-dcpp** (**Figure 7A**). The regioselectivity differences between these two complexes suggest that the Ni-aryne distances play a role in the regioselectivity of these Ni-bound arynes. This is in keeping with previous regioselectivity studies of six-membered arynes from our group.[18]

Although we were unable to isolate aryne complex **4-dcpm** from the transmetallation of **3-dcpm,** we were curious if we could trap an aryne functionalization product if activation was performed in the presence of an aryne coupling partner. We thus subjected complex **3-dcpm** to two equivalents of 2-PyZnBr, to be used for both B(pin) activation and nucleophilic functionalization of the aryne (**Figure 7B**). Excitingly, we observed 49% combined NMR yield and >20:1 r.r., along with 32% NMR yield of the debrominated aryne precursor **7** as a byproduct. This markedly enhanced regioselectivity suggests that the structure of **4-dcpm** is even more distorted than that of **4-dcpp**. Additionally, the demonstrated ability to perform an *in situ* aryne formation and functionalization beginning from a relatively stable σ-aryl complex is equally compelling as it renders 5-

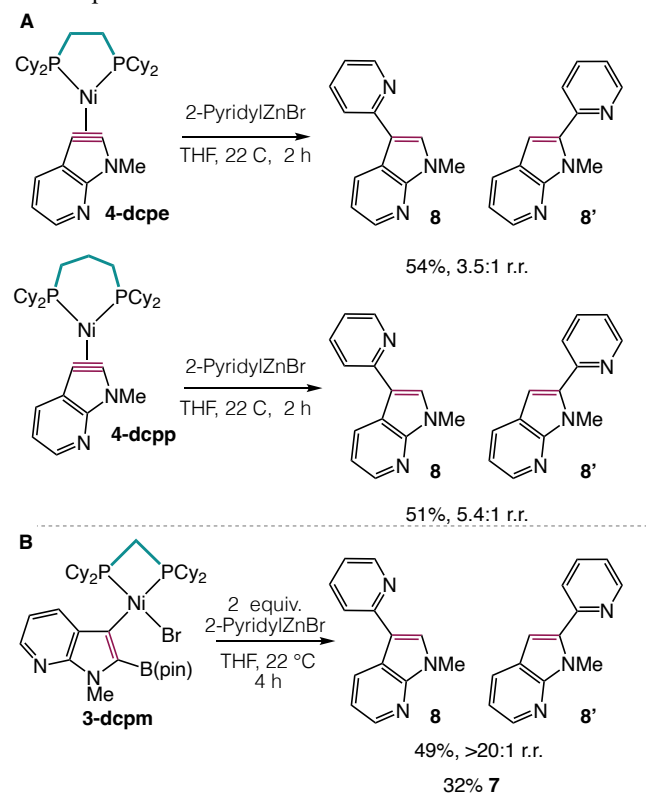membered N-heteroaryne methodology more amenable to the benchtop or Schlenk line.

Figure 7. A) Reactivity studies with isolated aryne complexes, B) Reactivity studies with *in situ* activated **3-dcpm**

In summary, we have explored the effects of phosphine substituents and linker length on the success of aryne formation as well as the reactivity and regioselectivity of corresponding Ni-aryne complexes. Through these studies we have discovered that ligands with phenyl phosphine substituents and/or backbones greater than three carbons long are generally unsuitable for aryne generation. In contrast, Ni-aryne complexes can be successfully generated and isolated using two and three carbon linker ligands (**4-dcpe** and **4-dcpp**). These complexes were found to be structurally disparate, owing to regioselectivity differences upon reaction with 2-PyZnBr. Finally, while a Ni-aryne complex bearing a one carbon linker ligand (**4-dcpm**) could not be isolated, we have performed compelling in situ aryne trapping reactions which proceed with excellent regioselectivity. We anticipate that this systematic ligand exploration will inform future studies regarding the formation and reactivity of 5-membered heteroarynes and will allow for the successful formation and functionalization of a larger breadth of heteroarynes.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization (PDF)

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

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Author Contributions

All authors have given approval to the final version of the manuscript.

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phosphine donor, R

R₂P   PR₂
   Ni
   NMe
   N

carbon linker length, n

n = 2, **R** = Ph   **n** = 3, **R** = Cy