

Ligand-Controlled Regioinduction in a PHOX-Ni Aryne Complex

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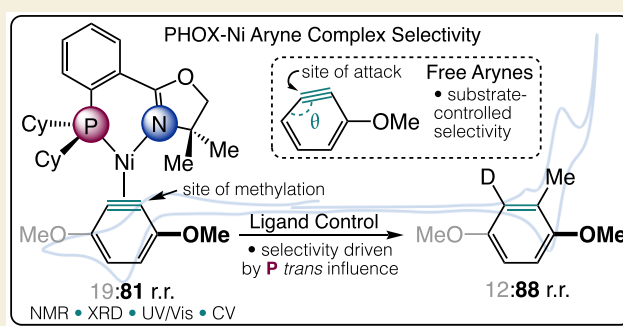
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ABSTRACT: Phosphinooxazoline (PHOX) ligands have been used to control the regio- and enantioselectivity in a wide variety of metal-catalyzed reactions. Despite their widespread use, PHOX ligands have never been studied in metal-aryne complexes. Herein we report the first example of a PHOX-Ni aryne complex. As demonstrated in other systems, the differentiated P versus N donors and different steric environments of the unsymmetric ligand are able to induce regiocontrol. A 81:19 mixture of *o*-methoxy substituted aryne complexes is observed. Single-crystal X-ray crystallographic analysis, UV/vis spectroscopy, and cyclic voltammetry are used to gain further insight into the molecular and electronic structure of these complexes. Lastly, a methylation/deuteration sequence shows retention of the PHOX ligand-induced regiocontrol in the difunctionalized products and that the regioselectivity of these difunctionalizations is due to the *trans* influence of the P donor.

KEYWORDS: Nickel, PHOX ligands, regioselectivity, arynes, methylation



Phosphinooxazoline (PHOX) ligands have been used to control regioselectivity in allylic substitution and other reactions (Figure 1A).^{1–4} The differentiated sterics of the phosphine versus oxazoline govern substrate binding when a substrate is unsymmetrical, for example, in a monosubstituted allyl group. Numerous structural studies have been carried out in order to explore these unique structures. Crystal structures reveal that the *trans* influence of the P versus N donor impact the site of nucleophilic attack.^{5,6} This is due to the lengthening and weakening of the M–C bond that is *trans* to the P donor. These studies have led to the design of substituted PHOX and other C₁-symmetric ligands in order to improve selectivity in reactions involving a PHOX-M substrate intermediate such as alkene or imine hydrogenation.^{7–12}

Metal-bound aryne complexes are an isolable counterpart to free aryne intermediates. Unlike in metal-free aryne methodology, very few examples exist of unsymmetrically substituted metal-bound arynes and nothing is understood about how regioselectivity is governed or if it can be induced through ligand design.^{13–15} For example, Hosoya and co-workers report a rare example of a methoxy-substituted Ni-aryne complex supported by PEt₃.¹⁶ We are unaware that any unsymmetrical ligand systems have been reported to date in isolated metal-aryne complexes. We hypothesized that, by leveraging the PHOX ligand properties that have been established in allylic substitution, regioinduction could be observed in metal-aryne complexes (Figure 1B). Our group

recently reported the first example of monodentate ligands controlling regioselectivity in metal-catalyzed annulations involving metal-aryne intermediates.¹⁷ Thus, this study can be used to design regioselective metal-catalyzed reactions using bidentate PHOX ligands.

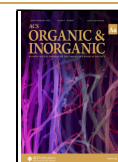
Metal aryne complexes using unsymmetric bidentate ligands such as PHOX have not been previously reported. Therefore, a synthetic route toward these complexes was developed (Figure 2). Methoxy-substituted *o*-borylaryl triflate **1** was treated with Ni(COD)₂ and 2.2 equiv of PPh₃ at room temperature for 1.5 h. In order to stabilize the resulting σ -aryl complex **2**, LiBr was added to replace the triflate.¹⁶ Square planar complex **2** was obtained in 76% isolated yield and structurally characterized via XRD (SI Figure S11). The ³¹P{¹H} NMR spectrum of **2** shows a single resonance, indicating the *trans* relationship between the phosphines. Complex **2** then underwent ligand exchange with CyPHOX to access σ -aryl complex **3**. However, this complex was unable to be observed by ³¹P{¹H} NMR spectroscopy or isolated. In the crystal structures for the

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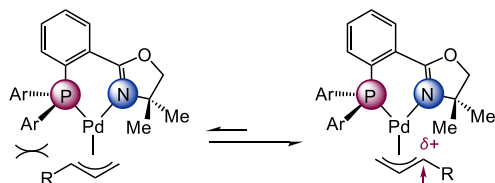
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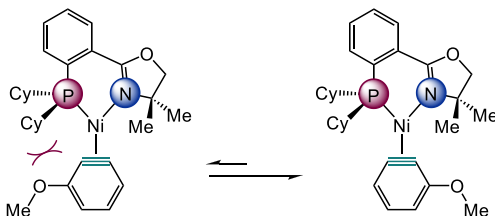


A. Ligand-controlled regioselectivity in metal-bound allyl groups



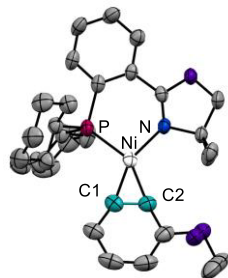
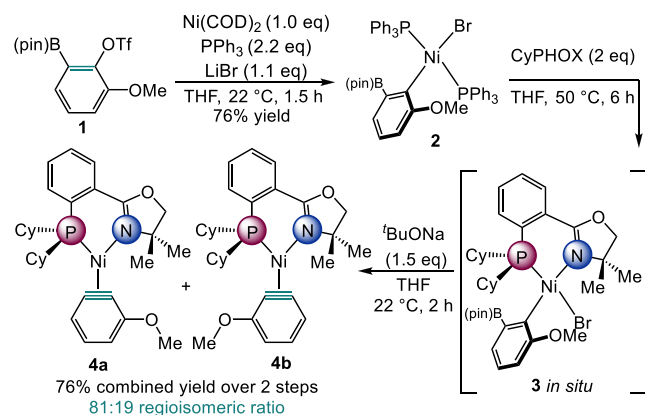
- Allyl group binds to avoid steric interaction with phosphine ligand
- Addition at position trans to P to give site selectivity

B. Ligand-controlled regioselectivity in metal-bound arynes (This work)



- Aryne binds preferentially to avoid steric interaction with phosphine ligand
- Characterized through crystallography, CV, UV-vis, and NMR spectroscopy

Figure 1. (A) Insight into ligand-controlled binding of allyl groups with phosphino-oxazoline (PHOX) ligands. (B) This work: Use of PHOX ligands to control binding of an aryne.



Bond	Bond Length (Å)
Ni–C1	1.862
Ni–C2	1.881
Ni–P	2.175
Ni–N	1.932
C1–C2	1.316

Figure 2. Synthesis and crystal structure of the first PHOX-Ni-aryne complex. One molecule in the unit cell is shown; bond lengths are an average of the bond lengths in both molecules in the unit cell.

reported *dcpe*-Ni *o*-borylated σ -aryls, significant steric interactions between the *dcpe* and the B(pin) group can be seen, which are likely the cause of the instability of complex 3. Thus, 2 was taken forward to an *in situ* ligand exchange-transmetalation sequence. During the ligand exchange, ^tBuONa was added as an activator to promote transmetalation and cleanly generate the *o*-methoxybenzyne complexes 4a and 4b in a combined yield of 76% over 2 steps. Direct oxidative addition of 1 with CyPHOX did not yield desired complex 3. Previous attempts to synthesize σ -aryls with tertiary bidentate

ligands such as dicyclohexylphosphinoethane (*dcpe*) have also been shown to be problematic, highlighting the need for a ligand exchange step.¹⁸

As hypothesized, the CyPHOX ligand induced a regioisomeric ratio of products, favoring the methoxy substituent on the same side as the oxazoline side of the ligand in a 81:19 regioisomeric ratio (*rr*), as determined by ³¹P{¹H} NMR spectroscopy. Interestingly, 2 distinct ³¹P NMR resonances are present in the spectrum, 1 for each regioisomer. This matches with the ¹H NMR signals, which show 2 distinct regioisomers with sharp signals. Because there is no coalescence at room temperature, we hypothesized that there could potentially be little equilibration between regioisomers. Interestingly, a 2D ³¹P{¹H}–³¹P{¹H} NOESY experiment was conducted, which showed some exchange peaks between the two regioisomers on the 2.5 s mixing time scale (Figure S9).

Crystals of complexes 4a were grown in a mixture of benzene and pentane at –35 °C. The crystal structure (Figure 2) revealed insight into the dynamic behavior of these complexes. The arynes C–C bond was determined to be 1.316 Å as an average of the 2 molecules in the unit cell, which is shorter than previously reported late transition metal aryne complexes such as the (*dcpe*)-Ni benzyne, which has a bond length of 1.332(6) Å.^{19,20} When compared to the calculated bond length for benzyne at 1.240 Å, the triple bond of the Ni-bound aryne is significantly elongated.²¹ The P–Ni–C1 and N–Ni–C2 bond angles of 106.3° and 114.8° suggest a pseudotrigonal planar geometry. The unit cell contained 2 molecules of the major regioisomer; however, the minor regioisomer was also observed as rotational disorder, which could not be modeled. Interestingly, the aryne carbons show an internal angle difference of 5.4°, compared to the free *o*-methoxybenzyne calculated angle difference of 15°.¹³ In this case, the position *ortho* to the methoxy substituent, C2, has the smaller internal angle, which is the opposite of what is observed in the parent free *o*-methoxybenzyne and the aryne distortion model. This position is also *trans* to the phosphine donor, and its strong *trans* influence compared to the oxazoline donor is evidenced by the longer Ni–C2 bond vs Ni–C1 (1.881 vs 1.862 Å, respectively).

To probe the electronic properties of complex 4, cyclic voltammetry experiments were conducted in 0.1 M [ⁿPr₄N][BAR^F₄] electrolyte solutions (Ar^F = 3,5-bis(trifluoromethyl)phenyl) and internally referenced to the [FeCp₂]⁺⁰ redox couple. Figure 3 displays the full window cyclic voltammogram (CV) and the scan rate dependence studies on the observed reduction. Complex 4 exhibits a one-electron irreversible oxidation event at *E*_{pa} = –0.38 V. Interestingly, 4 displays an electrochemically quasi-reversible (see SI Figure S14 and Table S5) reduction at *E*_{pc} = –2.67 V, followed by an oxidation event at *E*_{pa} = –2.61 V. Additional CV experiments were conducted on CyPHOX (see SI Figure S15) to determine if any events were ligand-based, where two ligand oxidation events were observed far beyond the oxidation event at *E*_{pa} = –0.38 V.

A (*dcpe*)Ni(COD) complex, where COD = 1,5-cyclooctadiene, was observed to have both Ni(0/I) and Ni(I/II) events at –0.95 and –0.78 V (vs FeCp₂)⁺⁰, respectively, in [ⁿBu₄N]PF₆ THF solutions; however, due to the difference in electrolyte and ligand electronic environment, direct comparisons are difficult to establish.²² Due to the absence of multiple strong, electron rich donors (only one Cy₂P donor) and the expected strong metal π -backdonation into the aryne bond, the

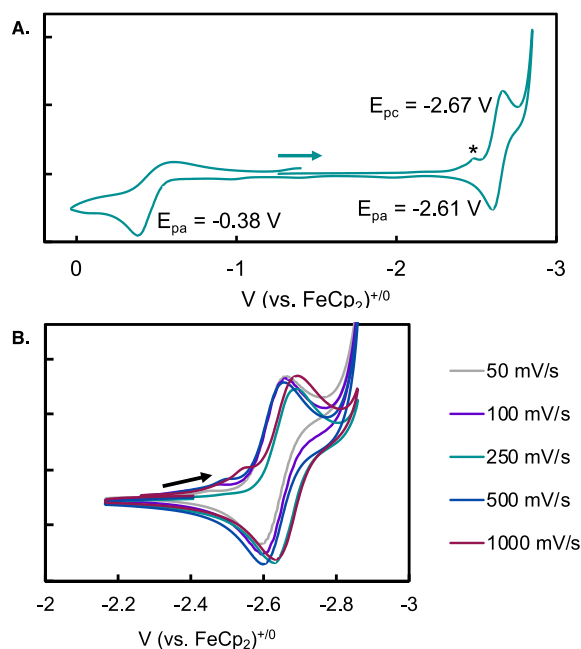


Figure 3. CVs of **4** display (a) full electrochemical window events at 100 mV/s and (b) scan rate dependence studies on the reduction event with normalized peak currents. CVs collected in 0.1 M [${}^{\text{Pr}}\text{Pr}_4\text{N}$][BARF_4] electrolyte solutions in THF under Ar. *Minor impurity.

Ni center is significantly electron deficient compared to most Ni–phosphine complexes. As a result, the harsher oxidation event at $E_{\text{pa}} = -0.38$ V is proposed to be a Ni-based oxidation event. While unfortunate that little comparison can be drawn to complex **4**, this highlights the first electrochemical study on a metal-bound aryne complex. Current investigations to identify the reduced species are underway.

Complex **4** resembles a deep raspberry red color in both noncoordinating and coordinating solvents. Three primary charge transfer bands were observed in 0.3 mM THF solutions of **4** (Figure 4). Transitions I and II at both 329 nm ($\epsilon = 1176$ $\text{M}^{-1} \text{cm}^{-1}$) and 365 nm ($\epsilon = 857$ $\text{M}^{-1} \text{cm}^{-1}$), respectively, are consistent with ligand-based transitions (see SI Figure S17). Transition III occurs at 503 nm ($\epsilon = 457$ $\text{M}^{-1} \text{cm}^{-1}$), which is proposed to be a weak metal-to-ligand charge transfer (MLCT) band. The identity and effects that the –OMe

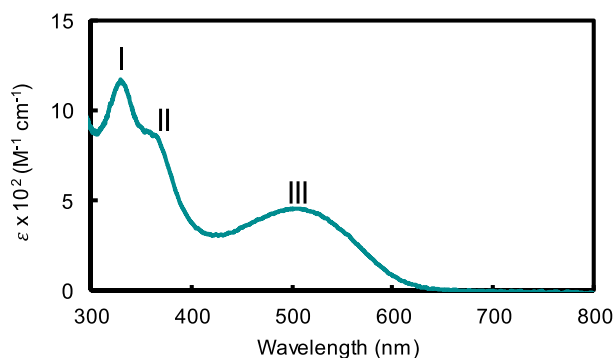


Figure 4. UV–vis spectrum of complex **4** in THF at 298 K.

group imposes on this charge transfer band are currently being explored.

In order to gain preliminary insight into reactivity and whether the regioisomeric ratio of complexes resulted in a similar regioisomeric ratio of products, methylation followed by deuteration was performed (Figure 5). A deuteration over a

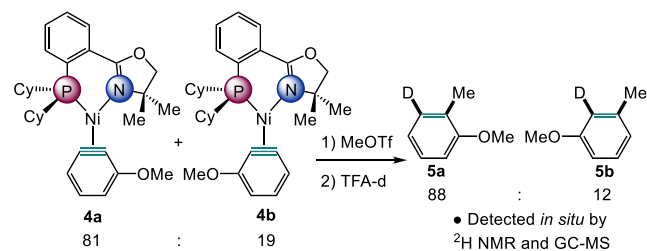


Figure 5. Preliminary reactivity of Me/D coupling partners.

protonation was selected due to the desirability of the products and the ease of detection *in situ*. The products were detected by ${}^2\text{H}$ NMR spectroscopy in an 88:12 ratio, and the ratio and product identity were further verified by GC-MS (see the SI). The yield was low due to the instability of the Ni–aryl product formed after methylation prior to deuteration and was unable to be quantified. Despite this, the ratios in the ${}^2\text{H}$ NMR spectrum and GC-MS were insightful and provide a preliminary understanding that the ligand is providing regiocontrol of functionalization as compared to symmetric ligand systems.¹⁶ Due to the absence of any Ni(I/II) redox processes in the CV, no observed d–d transitions in the UV–vis spectrum, observed bond metrics, and the diamagnetic nature of the complex, complex **4** is proposed to react similarly to a low-valent Ni complex. The reactivity of **4a** and **4b** with an electrophile is consistent with the nucleophilic nature of these complexes.

In summary, we report the first example of an aryne complex with an unsymmetrical bidentate PHOX ligand. In order to study the effect of the PHOX ligand, we chose an *o*-methoxy aryne as a model system. As hypothesized, the impact of the different steric and electronic effects of the phosphine versus oxazoline donor generates a regioisomeric mixture of complexes, favoring the methoxy in the position ortho to the aryne C that is *trans* to phosphine. The first CV studies of an aryne complex are also reported and demonstrate that there is significant π -backdonation into the aryne bond, leaving the metal electron deficient. Finally, preliminary reactivity studies demonstrate that the ligand can control the regioselectivity in the product.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study is available in the published article and Supporting Information.

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscorginorgau.3c00046>.

Experimental details and characterization (PDF)

Accession Codes

CCDC 2292397 and 2301325 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by

emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. CRediT: **Alexander Umanzor** conceptualization, data curation, formal analysis, investigation, methodology, writing-original draft, writing-review & editing; **Nicholas A Garcia** data curation, formal analysis, investigation, methodology, writing-original draft, writing-review & editing; **Courtney C. Roberts** conceptualization, formal analysis, funding acquisition, project administration, resources, supervision, writing-original draft, writing-review & editing.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

Cy, cyclohexyl; PHOX, phosphinoxazoline; COD, cyclooctadiene

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