

# **Nickel-Mediated Carbon-Heteroatom Bond Formation and Efforts Towards High-Oxidation State Nickel Complexes**

by

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## ABSTRACT

### **Nickel-Mediated Carbon-Heteroatom Bond Formation and Efforts Towards High-Oxidation State Nickel Complexes**

by

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The formation of carbon-heteroatom bonds via reductive elimination from late transition metals is a topic that has recently garnered great interest in the field of organometallic chemistry. The Sanford lab has done a great deal of research in this field, especially with regards to palladium and platinum. Given the high cost and relative rarity of these metals, investigations were extended to nickel.

$\text{Ni}(\text{phpy})_2$  (phpy = 2-phenylpyridine) was the initial target due to the success of the analogous  $\text{Pd}^{\text{II}}(\text{phpy})_2$  complex at supporting isolable high oxidation state  $\text{Pd}^{\text{IV}}$  complexes. The Ni synthesis was accomplished using a metal-assisted deprotonation to install the second phpy ligand onto the metal, following an oxidative addition into the C–Br bond of 2-(2-bromophenyl)pyridine.

$\text{Ni}^{\text{II}}(\text{phpy})_2$  was reacted with a wide variety of electrophilic oxidants. In all cases, reductive elimination of the C–C homocoupling of the ligands was the major

organic product, making further elucidation and identification of the intermediates difficult. The reaction also proceeded too quickly to detect either Ni<sup>III</sup> or Ni<sup>IV</sup> species spectroscopically, even at low temperatures. Interestingly, however, there were low yields of products resulting from C–X bond reductive elimination.

Van Koten's isolation of an organometallic Ni<sup>III</sup> complex with a nickel-carbon bond and multiple bromide ligands provided an initial point of investigation into the reductive elimination of C–X bonds directly from an isolable Ni<sup>III</sup> organometallic complex. Under forcing conditions desired product was observed in 33% yield.

Ni(phpy)(Pic)(Br) (Pic = 2-methylpyridine) was reacted with various brominating reagents, which resulted in our desired C–X reductive elimination product (2-(2-bromophenyl)pyridine) being generated in high yields with minimal competing C–C bond formation. Mechanistic investigations suggested that this transformation was possibly taking place via a transient high oxidation state intermediate.

A number of strategies to stabilize a high oxidation state organometallic Ni complex were pursued, including using perhalogenated aryl ligands, trifluoromethyl ligands, and tridentate chelating ligands. Unfortunately, the desired scaffolds were not isolated.

# Chapter 1

## Introduction and Background

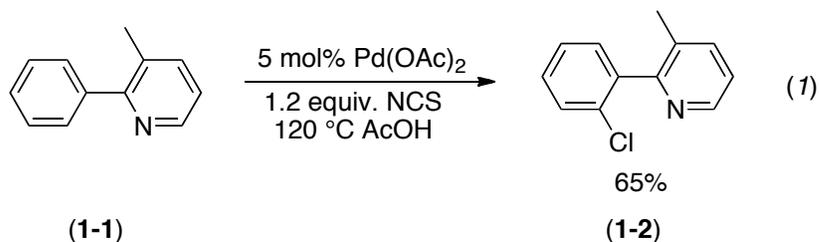
### 1.1 Carbon–Heteroatom Bond Formation

The formation of carbon–heteroatom (C–X) bonds is a fundamentally important facet of organic chemistry. One method for the installation of such bonds is via C–X bond-forming reductive elimination from a metal center. Recently, reductive elimination from late transition metals has been widely investigated in diverse reactions involving C–H functionalization,<sup>1</sup> cross coupling,<sup>2</sup> or alkene functionalization.<sup>3</sup> Research into the fundamental nature of these bond-forming processes may result in new modes of reactivity and enhanced scope or synthetic utility. As such, the group 10 triad has been an area of intense study by our lab and others, with the majority of the research focusing on Pd and Pt.<sup>4,5</sup>

### 1.2 Palladium Catalyzed C–X Bond Formation in the Sanford Group

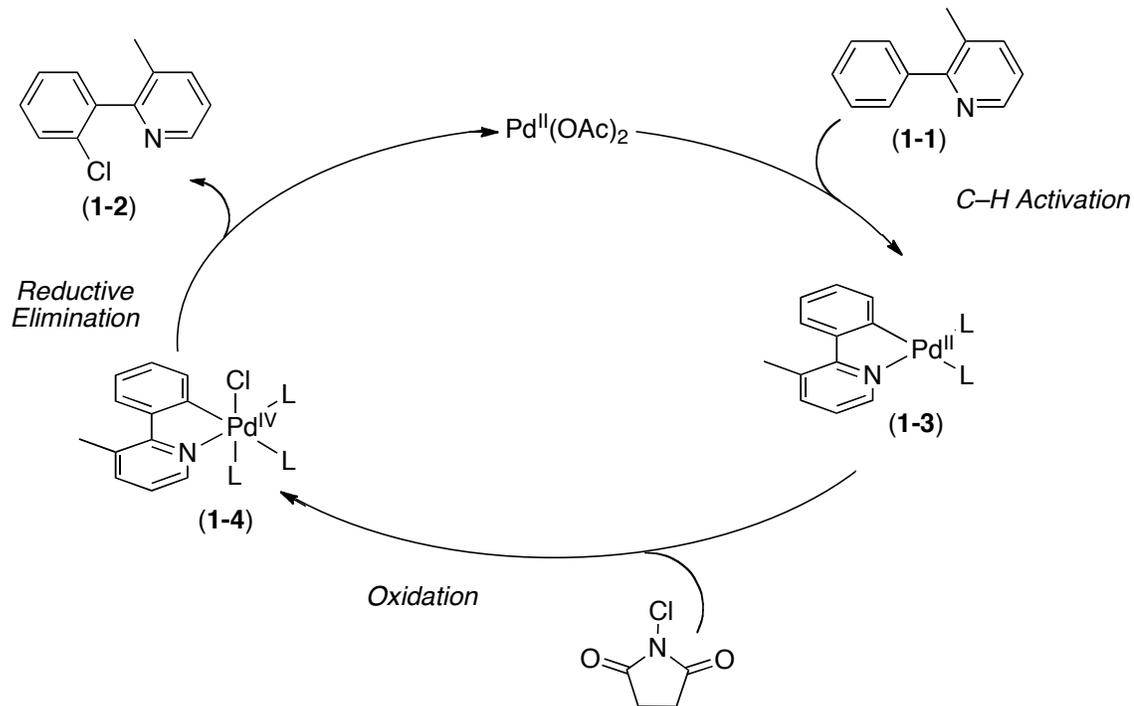
Much of the research in the Sanford group has focused on directed Pd-catalyzed C–H activation and oxidative functionalization of organic substrates. Using this chemistry, a number of different functional groups have been introduced to a wide variety

of substrates. A specific example of this chemistry is the regioselective installation of Cl to a 3-methyl-2-phenylpyridine substrate (**1-1**) using Pd(OAc)<sub>2</sub> as the catalyst and *N*-chlorosuccinimide (NCS) as the functionalizing oxidant (eq 1).<sup>6</sup>

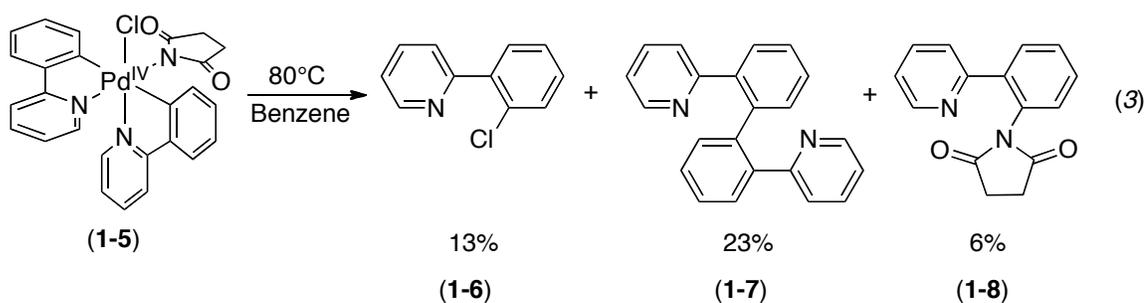
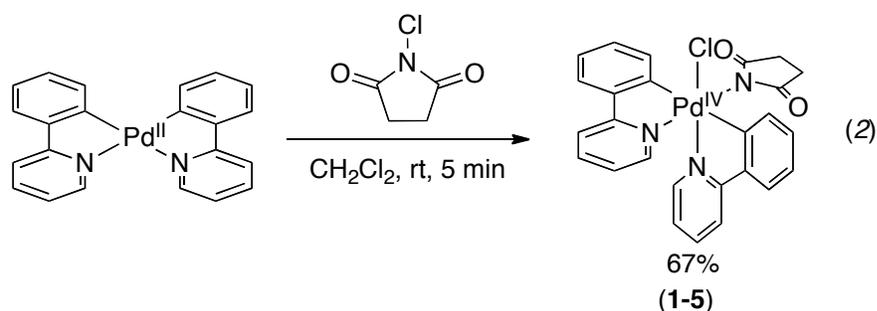


The first step of the proposed mechanism for this reaction is electrophilic C–H activation of the *ortho* C–H bond on the phenyl ring of **1-1** by [Pd<sup>II</sup>]. This regioselectivity is dictated by the directing ability of the pyridine by coordination to Pd. The second step is the oxidation of cyclometallated species **1-3** by NCS to Pd<sup>IV</sup>. Finally, Pd<sup>IV</sup> species **1-4** decomposes back to the more stable Pd<sup>II</sup> oxidation state via a two-electron C–Cl bond-forming reductive elimination, resulting in the functionalized product **1-2** and regenerating the Pd<sup>II</sup> catalyst, which can reenter the catalytic cycle (Figure. 1).

**Figure 1.1** – Pd-catalyzed C–H activation and Functionalization



One of the key features of the proposed mechanistic cycle is the relatively unusual Pd<sup>IV</sup> species (**1-4**). Until recently, such high oxidation state Pd species were rare and not frequently proposed. In an effort to provide evidence for the intermediacy of Pd<sup>IV</sup>, our group was able to synthesize and isolate stable organometallic Pd<sup>IV</sup> complexes, such as [Pd(phpy)<sub>2</sub>(Suc)(Cl)] (**1-5**) (phpy = 2-phenylpyridine, suc = succinimide, eq. 2).<sup>7</sup> While this complex is stable at room temperature, it readily undergoes thermally-induced reductive elimination to form the products of C–Cl, C–C, and C–N bond formation (eq. 3), suggesting that Pd<sup>IV</sup> could be an operative species in the catalytic transformation. Our group synthesized a number of other complexes to study thermally-induced reductive elimination to form a variety of bonds (*e.g.* C–O,<sup>8</sup> C–C,<sup>8</sup> C–F,<sup>9</sup> C–CF<sub>3</sub><sup>10</sup>).



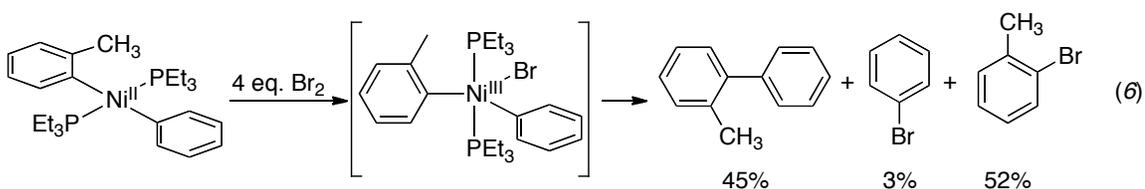
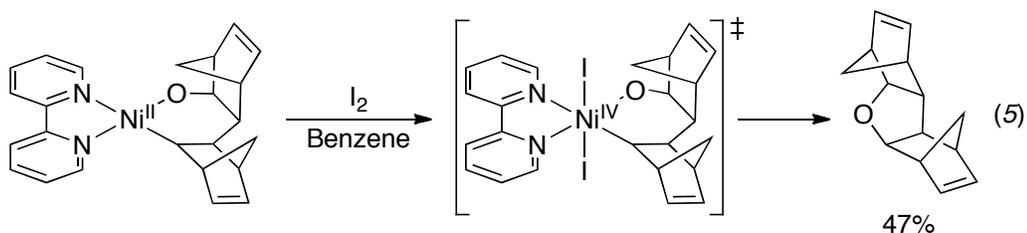
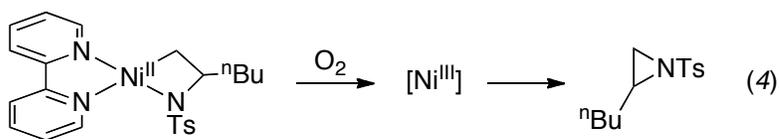
While Pd has proven to be effective at mediating these transformations, we sought to investigate the possibility of a cheaper alternative. As such, we turned our attention to Ni. Since Ni is in the same group of periodic table as Pd, we hypothesized that it might be able to undergo similar modes of reactivity. A cost comparison for all three group 10 metals suggests that Ni could provide a substantial cost reduction to the desired transformations, compared to Pd (Table 1.1).<sup>11</sup>

**Table 1.1** – Prices of Anhydrous MCl<sub>2</sub> Group 10 Salts

Entry	MCl <sub>2</sub> Salt	Cost (USD/mole)
1	Ni	70
2	Pd	8160
3	Pt	40160

### 1.3 Nickel-Mediated C–X Bond Forming Reactions

Though relatively rare, several examples of stoichiometric oxidatively induced reductive elimination at Ni to afford C–X bonds have been demonstrated. For example, Hillhouse and coworkers have used  $O_2$  to induce C–N bond formation<sup>12</sup> (eq. 4) and  $I_2$  to induce C–O bond formation<sup>13</sup> (eq. 5) from cyclometallated  $Ni^{II}$  complexes. Similarly, Muller and coworkers have reported C–Br bond formation from  $Ni^{II}$  biaryl complexes induced by  $Br_2$  (eq. 6).<sup>14</sup> A number of other examples have been reported by these authors and others.<sup>15</sup> Importantly, high oxidation state  $Ni^{III}$  and  $Ni^{IV}$  species are proposed as the operative intermediates in each of these transformations.

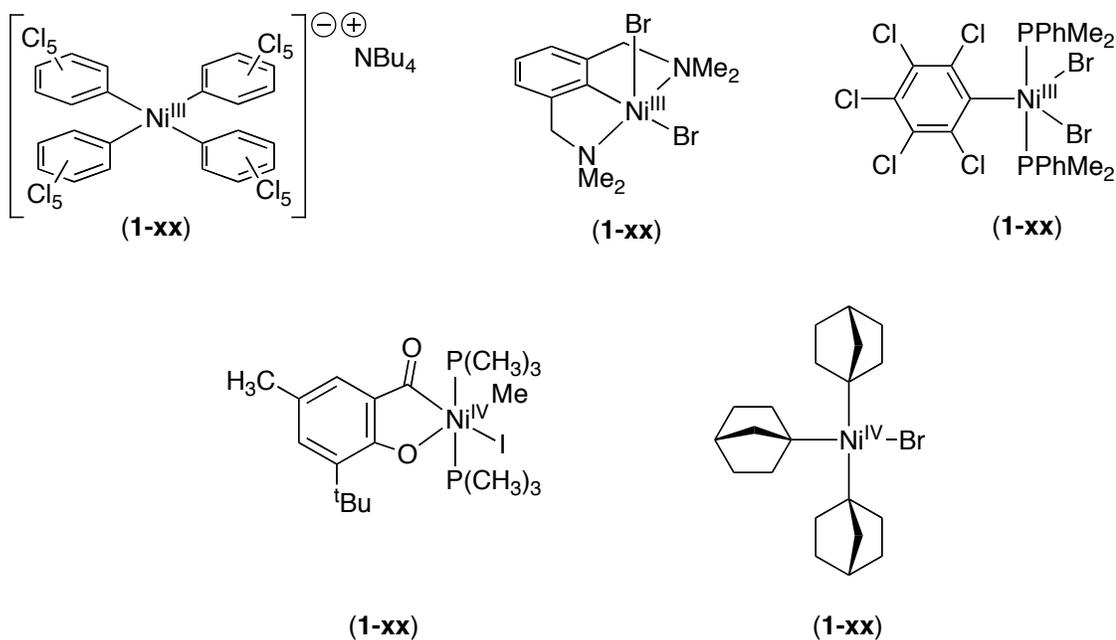


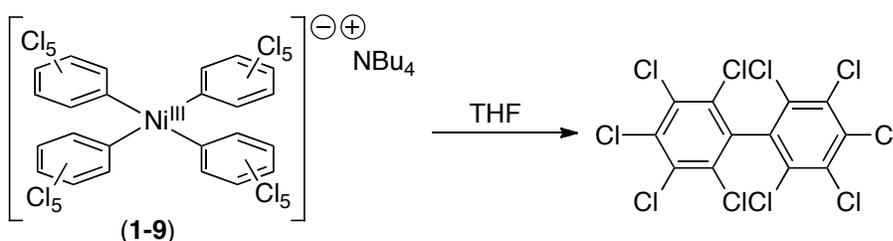
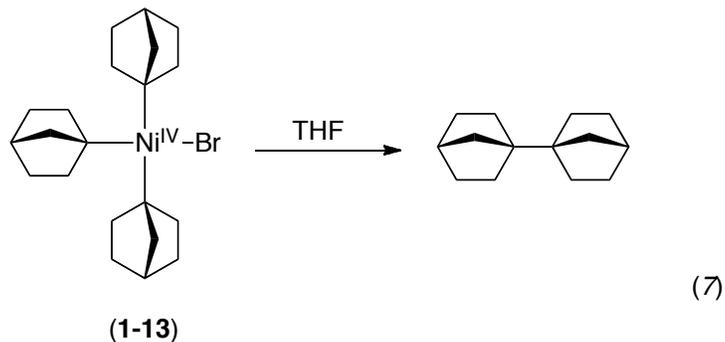
These reports suggest that Ni might be capable of modes of reactivity analogous to the high oxidation state Pd<sup>IV</sup> chemistry described previously. Our goal, therefore, was to design a high oxidation state Ni<sup>III</sup> or Ni<sup>IV</sup> complex that could be used to study C–X bond reductive elimination.

## 1.4 High Oxidation State Ni Complexes

Such Ni<sup>III</sup> or Ni<sup>IV</sup> complexes are exceedingly rare, but there are limited examples in the literature (Figure 1.2).<sup>16,17</sup> Complexes **1-9** and **1-13** were especially interesting because both are reported to undergo thermally induced reductive elimination to form C–C coupled products (eq. 7). While no examples of analogous C–X bond-forming reductive elimination have been reported, this precedent suggests that similar high oxidation state complexes could be used to study C–X bond formation.

**Figure 1.2** – Examples of High Oxidation State Ni Complexes





<sup>1</sup> (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2181.

<sup>2</sup> Hartwig, J. F. *Nature* **2008**, *455*, 314.

<sup>3</sup> (a) Muniz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (b) Muller, T. E.; Hultzsch, K. C.; Yuss, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

<sup>4</sup> Pd examples: (a) Alsters, P. L.; Engel, P. F.; Hogerheide, M. P.; Copijn, M.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1831. (b) Canty, A. J.; Jin, H.; Skelton, B. W.; White, A. H. *Inorg. Chem.* **1998**, *37*, 3975. (c) Yamamoto, Y.; Kuwabara, S.; Matsuo, S.; Ohno, T.; Nishiyama, H.; Itoh, K. *Organometallics* **2004**, *23*, 3898. (d) Kaspri, A. W.; Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *Inorg. Chem.* **2008**, *47*, 5. (e) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050. (f) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (g) Furuya, T.; Benitez, D.; Tkatchouk, E.; Strom, A. E.; Tang, P.; Goddard, W. A., III; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793.

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<sup>6</sup> Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.

<sup>7</sup> Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

<sup>8</sup> Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

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- <sup>9</sup> Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796
- <sup>10</sup> Ball, N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878.
- <sup>11</sup> Prices were calculated based on Strem Chemical's Catalog No. 23 for 2010-2012.
- <sup>12</sup> Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.
- <sup>13</sup> Koo, K.; Hillhouse, G. L. *Organometallics*, **1998**, *17*, 2924.
- <sup>14</sup> Coronas, J. M.; Muller, G.; Rocamora, M. *J. Organomet. Chem.* **1986**, *301*, 227.
- <sup>15</sup> (a) Matsunaga, P. T.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075. (b) Koo, K.; Hillhouse, G. L.; Rheingold, A. L. *Organometallics* **1995**, *14*, 456. (c) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421. (d) Ceder, R. M.; Granell, J.; Muller, G.; Font-Bardfa, M.; Solans, X. *Organometallics* **1996**, *15*, 4618.
- <sup>16</sup> Ni<sup>III</sup> examples: (a) Oguro, K.; Wada, M.; Sonoda, N. *J. Organomet. Chem.* **1979**, *165*, C10. (b) Grove, D. M.; van Koten, G.; Zoet, R.; Murrall, N. W.; Welch, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 1379. (c) Grove, D. M.; van Koten, G.; Mul, P.; Zoet, R.; van der Linden, J. G. M.; Legters, J.; Schmitz, J. E. J.; Murrall, N. W.; Welch, A. J. *Inorg. Chem.* **1988**, *27*, 2466. (d) Alonso, P.; Falvello, L. R.; Fornies, J.; Martin, A.; Menjon, B.; Rodriguez, G. *Chem. Commun.* **1997**, 503. (e) Xiao, Z.; Patrick, B. O.; Dolphin, D. *Inorg. Chem.* **2003**, *42*, 8125. (f) Alonso, P. J.; Arauzo, A. B.; Garcia-Monforte, M. A.; Martin, A.; Menjon, B.; Rillo, C.; Tomas, M. *Chem. Eur. J.* **2009**, *15*, 11020.
- <sup>17</sup> Ni<sup>IV</sup> examples: (a) Klein, H.-F.; Bickelhaupt, A.; Jung, T.; Cordier, G. *Organometallics* **1994**, *13*, 2557. (b) Klein, H.-F.; Bickelhaupt, A.; Lemke, M.; Sun, H.; Brand, A.; Jung, T.; Rohr, C.; Florke, U.; Haupt, H.-J. *Organometallics* **1997**, *16*, 668. (c) Dimitrov, V.; Linden, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2631. (d) Carnes, M.; Buccella, D.; Chen, J. Y.-C.; Ramirez, A. P.; Turro, N. J.; Nuckolls, C.; Steigerwald, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 290.

## Chapter 2

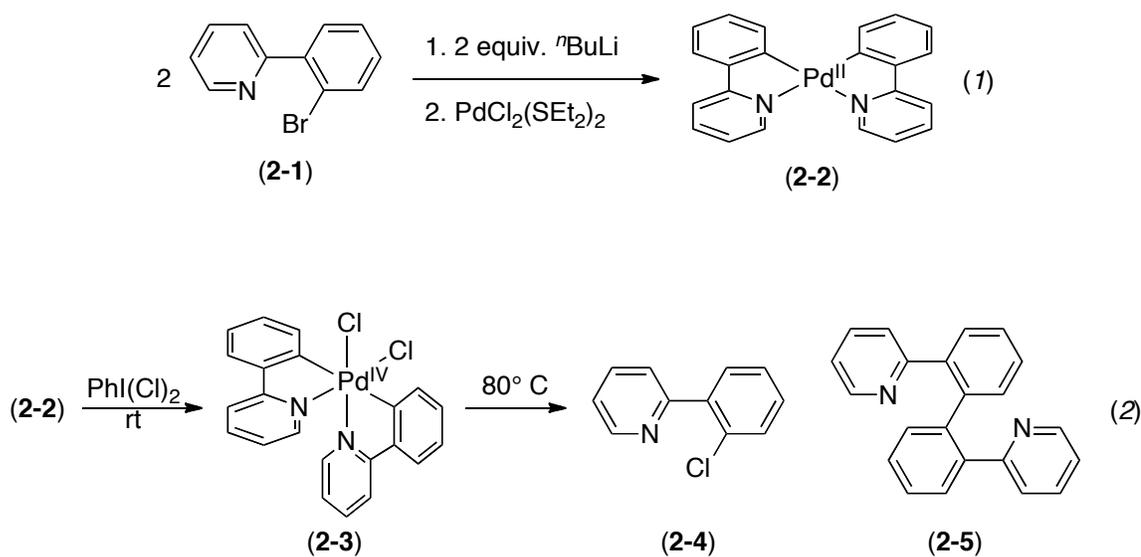
# Synthesis of Ni<sup>II</sup>(2-phenylpyridine)<sub>2</sub> and Attempts Toward High Oxidation State Complexes

### 2.1 Introduction

The Sanford group has been particularly interested in carbon–halogen bond formation at high oxidation state group 10 metal centers, with the bulk of the research focusing on Pd and Pt.<sup>1,2,3,4</sup> Investigation of analogous Ni complexes would potentially provide a great deal of insight into the possibility of using Ni as an alternative to the more expensive group 10 metals. Additionally, there have been proposals that high oxidation state Ni species are involved in the formation of C–X,<sup>5</sup> C–N,<sup>6</sup> C–O,<sup>7</sup> C–S,<sup>8</sup> and C–C<sup>9</sup> bonds. Since the formation of these types of bonds is a key aspect of our research with Pd and Pt, it seems natural to extend that investigation to Ni. We sought, therefore, to design a ligand scaffold that had the potential to stabilize high oxidation state Ni organometallic complexes.<sup>10,11</sup>

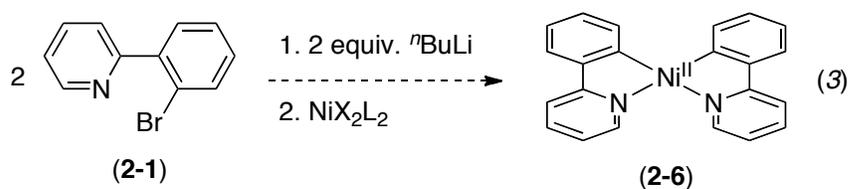
While such Ni complexes are exceedingly rare, we were inspired by work that had been done in our lab with bis-cyclometallated Pd<sup>II</sup> complex, Pd<sup>II</sup>(Phpy)<sub>2</sub>, (**2-2**), which was shown to react with strong oxidants [e.g., PhI(Cl)<sub>2</sub>, *N*-chlorosuccinimide (NCS),

PhI(OAc)<sub>2</sub>, and Br<sub>2</sub>] to afford unusually stable high oxidation state Pd<sup>IV</sup> complexes like **2-3** (eq. 2).<sup>1a,b,d</sup> These compounds are isolable at room temperature, but they undergo reductive elimination reactions at elevated temperatures (40–80 °C) to generate the products of carbon–halogen (**2-4**) and carbon–carbon (**2-5**) bond-forming reductive elimination. By analogy, we hypothesized that this ligand arrangement may also serve as an appropriate scaffold to stabilize the high oxidation state Ni complexes that could then be isolated.

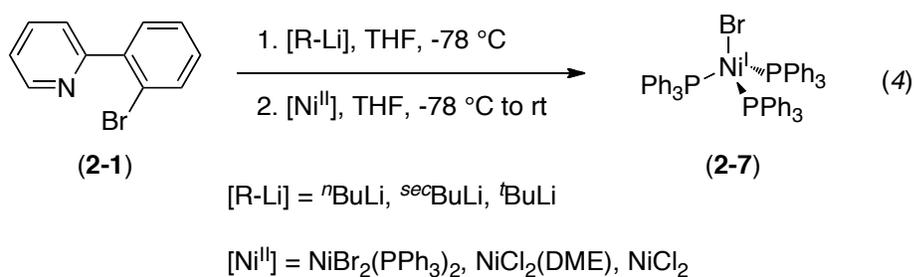


## 2.2 Synthesizing Ni<sup>II</sup>(phpy)<sub>2</sub>

Our first attempts toward the synthesis of Ni<sup>II</sup>(phpy)<sub>2</sub> (**2-6**) (eq. 3) were directly inspired by the synthesis of the analogous Pd<sup>II</sup> complex **2-2**, which is prepared by reacting PdCl<sub>2</sub>(SEt<sub>2</sub>)<sub>2</sub> with 2 equiv of *ortho*-lithiated 2-phenylpyridine (Li-phpy) (eq. 1).

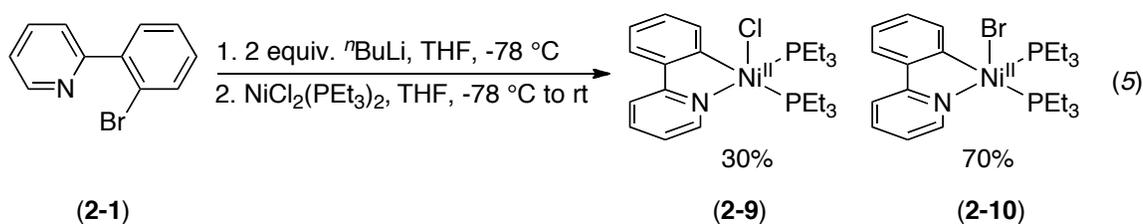


With this precedent in mind, we investigated the reaction of  $\text{Ni}^{\text{II}}$  dihalide salts (e.g.  $\text{NiBr}_2(\text{PPh}_3)_2$ ,  $\text{NiCl}_2(\text{DME})_2$ , and  $\text{NiCl}_2$ ) with 2 equiv of Li-phy at  $-78\text{ }^\circ\text{C}$  in  $\text{Et}_2\text{O}$  and THF.<sup>12</sup> However, in all cases, intractable mixtures of  $\text{Ni}^0$  and paramagnetic inorganic products were obtained. Dr. Paul Zinn isolated a large amount of  $\text{Ni}^{\text{I}}\text{Br}(\text{PPh}_3)_3$  (**2-7**) from the reaction with  $\text{NiBr}_2(\text{PPh}_3)_2$  (eq. 4) and confirmed the identity via X-ray crystal structure. This suggests that reduction of the  $\text{Ni}^{\text{II}}$  metal center by the lithium reagents outcompetes the desired transmetalation of the ligand to the metal.<sup>13</sup> In an effort to avoid this undesired side-reaction, we investigated the use of milder transmetallating reagents based on both magnesium and zinc. Unfortunately, these approaches resulted in either no reaction or decomposition into complex mixtures of products.



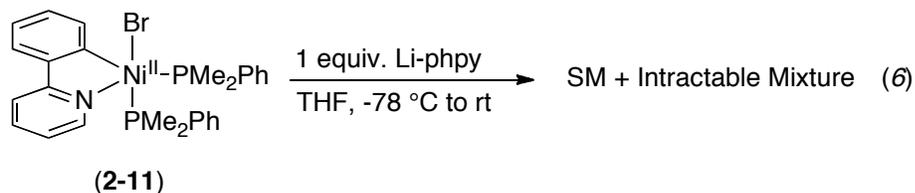
Since reduction appeared to be problematic, we investigated starting materials with more electron-donating ligands, reasoning that the increased electron density on the metal center would make it less susceptible to the competing reduction side reactions. To

that end, we used  $\text{NiCl}_2(\text{PEt}_3)_2$  (**2-8**) as a starting material (eq. 5). Analysis of the crude reaction mixture by  $^1\text{H}$  NMR spectroscopy revealed downfield peaks that appeared to be consistent with a cyclometallated species. Crystallization from pentanes produced co-crystals of general structure  $(\text{phpy})\text{Ni}^{\text{II}}(\text{PEt}_3)_2(\text{X})$  where  $\text{X} = \text{Cl}$  (**2-9**) and  $\text{Br}$  (**2-10**), respectively. Both appeared to be stable up to  $70^\circ\text{C}$  in benzene without any equilibration or isomerization. This suggested that the reduction could potentially be circumvented by the use of electron-rich ligands, but it also seemed that those same ligands might be too strongly coordinating to permit the second cyclometallation to take place.

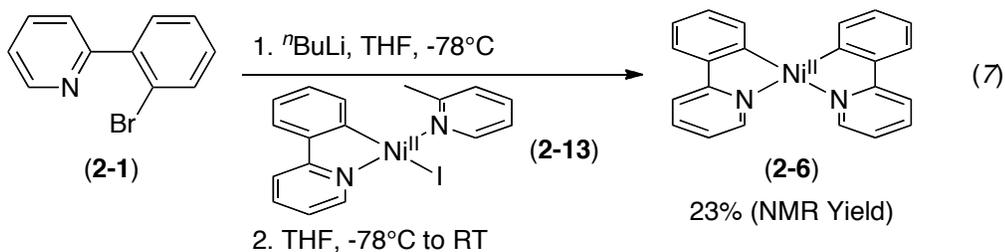


The fact that **2-9** and **2-10** seemed to be stable in the presence of Li-*phpy* suggested a new route towards the synthesis of **2-6**. We reasoned that if we could start with one *phpy* cyclometallated at the  $\text{Ni}^{\text{II}}$  metal center, we might be able to use ligands that are more easily displaced to facilitate complexation of the second *phpy*. In conjunction with Dr. Paul Zinn,  $(\text{phpy})\text{Ni}^{\text{II}}(\text{PMe}_2\text{Ph})_2(\text{Br})$  (**2-11**) was synthesized to test this hypothesis. Complex **2-11** contains a  $\text{PMe}_2\text{Ph}$  ligand, which has a slightly smaller cone angle ( $122^\circ$ ) than  $\text{PEt}_3$  ( $132^\circ$ ).<sup>14</sup> However, a comparison of the CO stretching frequencies of  $\text{Ni}(\text{CO})_3\text{L}$  complexes for  $\text{PMe}_2\text{Ph}$  ( $2065.3 \text{ cm}^{-1}$ ) and  $\text{PEt}_3$  ( $2061.7 \text{ cm}^{-1}$ ) demonstrates that  $\text{PMe}_2\text{Ph}$  ligand is slightly less electron donating, so we hypothesized that it might be easier to displace.<sup>15</sup> Unfortunately, the reaction of **2-11** with 1 equiv of

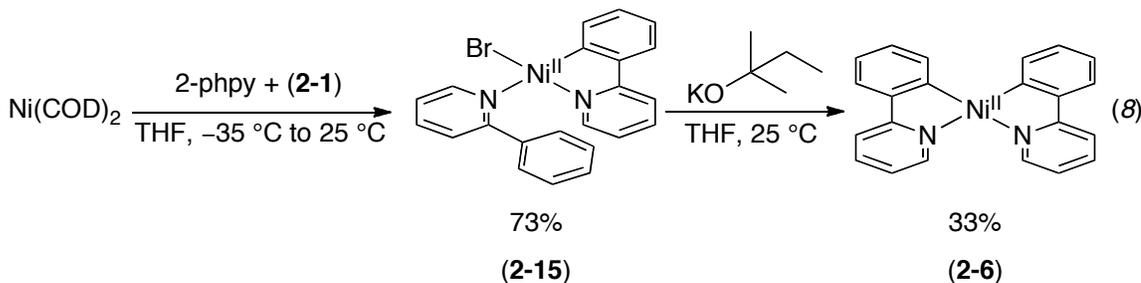
Li-phpy afforded a mixture of unidentifiable species along with some recovered starting material as observed by  $^1\text{H}$  and  $^{31}\text{P}$  NMR (**2-11**) (eq. 6).



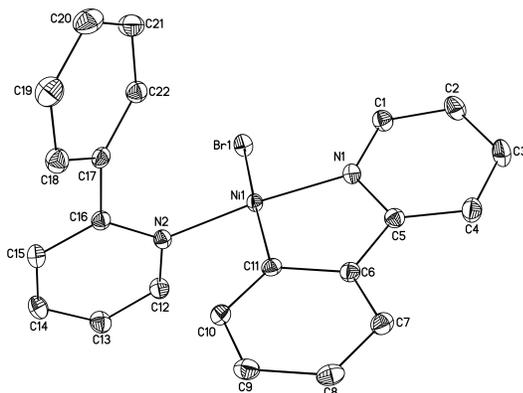
Since the phosphine ligands proved challenging to displace, we next decided to try using pyridine-based ligands. We started with the mono-cyclometallated  $\text{Ni}^{\text{II}}$  complex  $(\text{phpy})\text{Ni}^{\text{II}}(\text{pic})(\text{I})$  (**2-12**), which was generated via the oxidative addition of  $\text{Ni}(\text{COD})_2$  into the C–I bond of 2-(2-iodophenyl)pyridine (**2-13**) in the presence of 2-methylpyridine. With one cyclometallated ligand already on the metal center, we reacted complex **2-12** with 1 equiv of Li-phpy. Gratifyingly,  $^1\text{H}$  NMR spectroscopic analysis of the crude reaction mixture showed a 23% yield of the desired product **2-6** (eq. 7). However, separation of this material from other byproducts proved challenging, and **2-6** could not be isolated in pure form from this reaction. These results indicated that we needed to find a way to circumvent the use of lithium reagents in these reactions.



A recent report by Wolczanski demonstrated the formation of **2-6** via *ortho*-deprotonation of the coordinated 2-phenylpyridine ligand of  $[(\text{phpy})\text{Ni}^{\text{II}}(\text{phpy-H})_2]^+$  and  $(\text{phpy})\text{Ni}^{\text{II}}(\text{Br})(\text{phpy-H})$  (**2-14**).<sup>16</sup> On the basis of this precedent, we synthesized **2-15** via the oxidative addition of  $\text{Ni}(\text{COD})_2$  into the C–Br bond of 2-(2-bromophenyl)pyridine (**2-1**) in the presence of 2-ppy. This product was isolated and characterized by Dr. Paul Zinn. An X-ray crystal structure of this complex (Figure 2.1) revealed that the *ortho* hydrogen of the phenyl ring of the coordinated 2-ppy is only 2.704 Å away from the metal center. According to literature precedent, this corresponds to a pre-agostic interaction distance,<sup>17</sup> placing the hydrogen atom close enough to the metal center to potentially form an agostic interaction between the C–H bond and the metal center. We were pleased to find that addition of an external base (potassium *t*-amylate) as a solution in THF resulted in deprotonation at this site and afforded the desired product **2-6** (eq. 8). Given the relatively close proximity of the *ortho* hydrogen to the metal center, we propose that the metal coordinates to the C–H bond and assists in this deprotonation event. While both potassium *t*-amylate and potassium *t*-butoxide effected the desired deprotonation, the potassium *t*-amylate was utilized due to its greater solubility in THF, which facilitated addition of this reagent to the reactions.



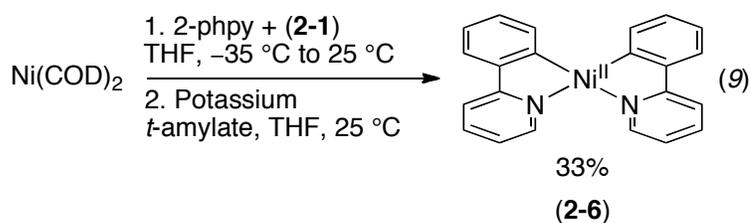
**Figure 2.1** – ORTEP View of [Ni<sup>II</sup>(phpy)(phpy-H)(Br)], **2-15**



**Table 2.1** – Selected Bond Lengths (Å) and Angles (°) for **2-15**

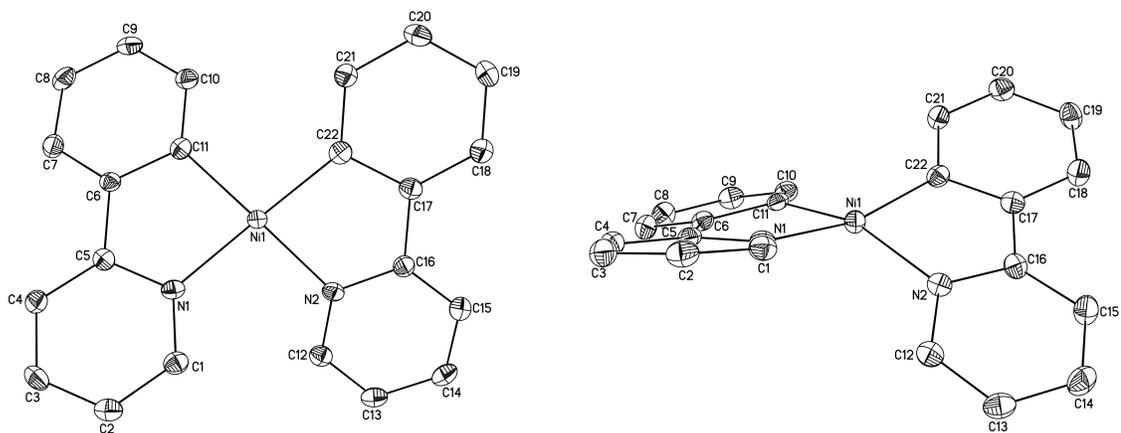
Ni(1)-Br(1)	2.4054(3)	C(11)-Ni(1)-N(1)	84.44(6)
Ni(1)-N(1)	1.9131(12)	N(1)-Ni(1)-Br(1)	94.82(4)
Ni(1)-N(2)	1.9004(12)	Br(1)-Ni(1)-N(2)	89.21(4)
Ni(1)-C(11)	1.9005(14)	N(2)-Ni(1)-C(11)	84.44(6)

We next targeted a one-pot synthesis of **2-6** via the formation and *in situ* deprotonation of **2-15**. Gratifyingly, treatment of Ni(COD)<sub>2</sub> with **2-1** in the presence of 1 equiv of 2-phenylpyridine followed by the addition of potassium *t*-amylate resulted in formation of the desired product. Filtration of the crude reaction through a Celite plug followed by precipitation from benzene or acetone with pentanes or hexanes provided clean samples of **2-6** in modest yield (33% over two steps), but in a highly reproducible fashion (eq. 9). Slow crystallization from benzene with pentanes provided X-ray quality crystals and a crystal structure was obtained (**Figure 2-2**).



Unlike an analogous Pt structure [Pt(bzq)<sub>2</sub>, bzq = 7,8-benzoquinoline, **2-16**], which is an approximately square planar structure with a maximum dihedral angle of 16.2°,<sup>18</sup> **2-16** has a rather distorted square planar geometry with the 2-phenylpyridine rings being twisted out of plane by 26.8° from each other. We attribute this in part to the difference in atomic radius for Ni (63 pm) compared to Pt (74 pm). The smaller atomic radius likely forces the ligands into a more congested environment. As discussed below, this structural change appears to have significant implications for the reactivity of **2-6**.

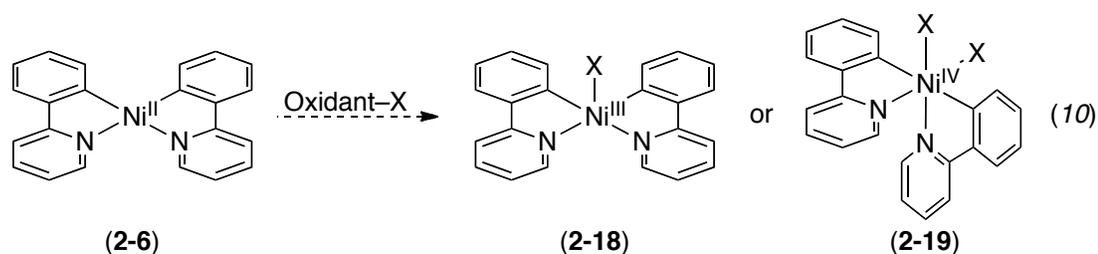
**Figure 2.2** – ORTEP View of [Ni<sup>II</sup>(ppy)<sub>2</sub>], **2-6**



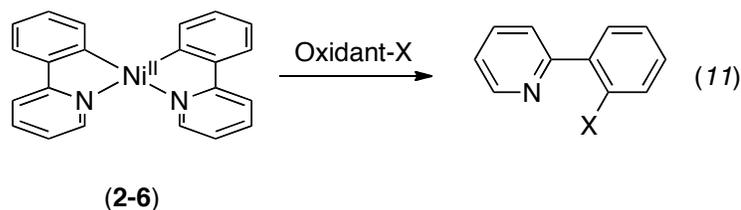
**Table 2.2** – Selected Bond Lengths (Å) and Angles (°) for [Ni<sup>II</sup>(phpy)<sub>2</sub>], **2-6**

Ni(1)-C(11)	1.901(2)	C(11)-Ni(1)-C(22)	99.42(9)
Ni(1)-C(22)	1.893(2)	C(22)-Ni(1)-N(2)	84.73(8)
Ni(1)-N(2)	1.9576(18)	N(2)-Ni(1)-N(1)	98.18(7)
Ni(1)-N(1)	1.9477(18)	N(1)-Ni(1)-C(11)	84.37(8)

### 2.3 General Reaction Plan



With complex **2-6** in hand, our goal was to expose it to a variety of oxidants that had been used to access high oxidation state Ni, Pd, and Pt. However, as discussed in detail in section 2.5, our initial screens revealed that we were not generating stable high oxidation state complexes. Instead, we observed a series of organic products that were functionalized at the site of the Ni–C bond (eq. 11), presumably via reductive elimination from a transient high oxidation state Ni intermediate. Before we could systematically analyze these reactions, we had to first determine the most effective workup to account for all of the organic products that were produced.



## 2.4 Designing a Work-Up

When **2-6** (along with other analogous complexes yet to be discussed) was reacted with a variety of oxidants, we discovered that there was a number of challenges had to be addressed before we could accurately and reproducibly determine the yields of the organic products resulting from these reactions. The three key challenges were: (1) halogenated products can potentially oligomerize on the GC if the injection port or column are contaminated with metals, resulting in artificially lower yields, (2) the inorganic byproducts are paramagnetic, making NMR analysis difficult, and (3) the products that resulted from the reductive elimination have pyridine groups that can coordinate to the metal byproducts, causing product loss if the metal is filtered out of the reaction.

The initial workup (Workup A) simply consisted of filtering the reaction through a plug of Celite to remove the insoluble inorganic byproducts and then flushing the plug with pyridine to displace any coordinated organic products. The filtrate was then concentrated, a standard (nonadecane) was added, and the reaction was analyzed on the GC. The brightly colored filtrate made it was quite clear that the pyridine was not just displacing the organic products, but was also transporting the metal through the plug, which was then being injected onto the GC, exacerbating any problems that would be caused by the cleanliness of the injection port or the column.

In an effort to better remove the metal byproducts and prevent them from passing through the Celite, we next tried filtering the reaction through a layer of polyvinylpyridine (PVP) over the plug of Celite (Workup B<sub>1</sub>). Unfortunately, the very brightly colored filtrate and the irreproducibility of the product yields and distribution

suggested there was not enough interaction between the inorganic byproducts and the layer of PVP to sufficiently displace the coordinated organic products. As such, we next explored adding the PVP directly to the crude reaction mixture and stirring for 1 h. The reaction was then filtered through a Celite plug, the filtrate was concentrated, the standard was added, and the reaction was analyzed by GC (Workup B<sub>2</sub>).

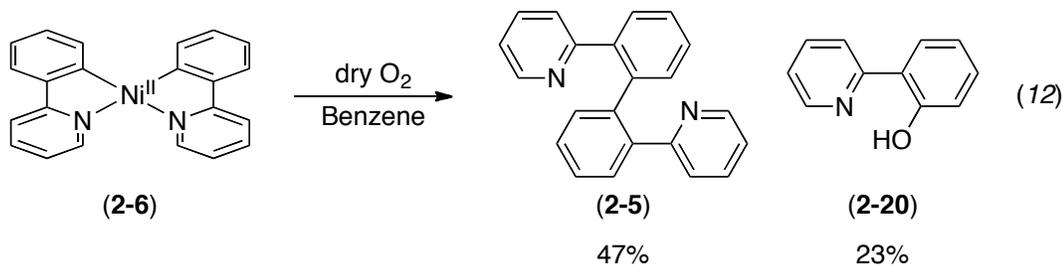
While this approach seemed to provide reproducible data for the short-term, the data was not reproducible when identical reactions were run weeks apart. This led to the concern that the products were still reacting on the GC to an extent that varied based on how much and in what manner the instruments had been used. To avoid these pitfalls, we decided to switch to an NMR method of analysis for these reactions. However, when we examined the reactions by <sup>1</sup>H NMR post-workup B<sub>2</sub> the signal broadening made it clear that there was still an unacceptably high amount of paramagnetic metal in the samples. This made identification of the organic products difficult and accurate integration for the determination of yields impossible.

Fortunately, we determined that an acceptable amount of the Ni byproducts could be removed via extraction with a chelating reagent like sodium citrate. By removing the reaction solvent, taking up the remaining material in either methylene chloride or ethyl acetate, extracting the mixtures with a 1.0 M solution of sodium citrate, and then collecting and concentrating the organic layer, we were able to generate samples that were appropriate for <sup>1</sup>H NMR analysis (Workup C<sub>1</sub>). There was a minor issue with excess oxidant reacting with the electron-rich NMR standard (1,3,5-trimethoxybenzene), but that was easily addressed via an extraction with saturated sodium thiosulfate to quench any unreacted oxidant (Workup C<sub>2</sub>). This workup allowed us to obtain reliably reproducible

data for all of our oxidatively-induced reductive elimination reactions involving the 2-phenylpyridine ligand set and was the primary workup used to obtain publication-quality data.<sup>19</sup> Data obtained using one of the older workups, primarily B<sub>2</sub>, will be noted as such throughout this thesis.

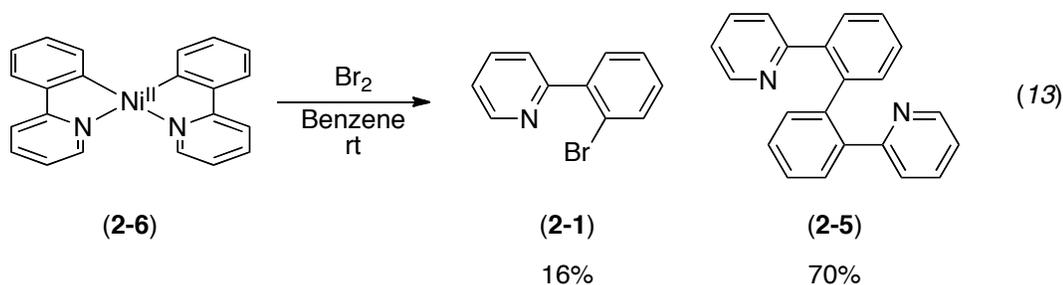
## 2.5 Stability and Reactivity of Ni<sup>II</sup>(2-ppy)<sub>2</sub>

Complex **2-6** is a brick-red solid that shows no signs of decomposition after 1 month at -35 °C in a N<sub>2</sub>-filled drybox. This bis-cyclometalated Ni<sup>II</sup> adduct is also stable in benzene or acetone solution for at least 24 h at room temperature under N<sub>2</sub>. It decomposes instantly upon exposure to HCl in MeOH (6 M), changing from a deep red solution to clear yellow. <sup>1</sup>H NMR analysis suggests that this is due to rapid protonolysis of the Ni-C bonds. It is stable for a limited amount of time (<12 h) in solutions of halogenated solvents (CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub>) and in wet solvents. However, exposure of a benzene solution of **2-6** to dry O<sub>2</sub> under otherwise identical conditions resulted in a rapid color change from red to yellow-brown in less than a minute, accompanied by the formation of pppy homocoupled dimer (**2-5**, 47 ± 3% yield) and the phenol product (**2-20**, 23 ± 2% yield) (eq. 12). This result demonstrates that **2-6** is highly susceptible to oxidatively-induced C-C and C-heteroatom bond-forming reactions.

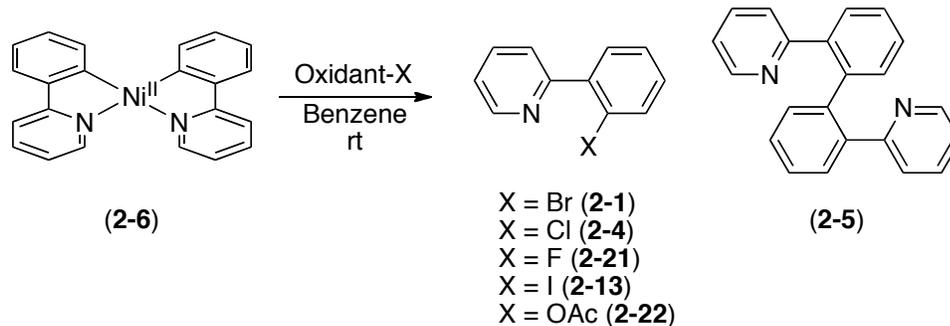


Previous analogous reactions have suggested that Ni participate in aerobic oxygenation reactions via high oxidation state peroxo and oxo intermediates to generate aldehydes, ketones, and epoxides.<sup>20</sup> There are also several examples of macrocyclic, square planar Ni<sup>II</sup> complexes that can cleave O<sub>2</sub>, resulting in hydroxylation of either the coordinated macrocycle<sup>21</sup> or of an external substrate.<sup>22</sup> In both cases, the hydroxylation was proposed to proceed via a Ni<sup>III</sup> peroxo intermediate. In the latter example, this proposal is supported by comparison to electrochemically-generated Ni<sup>III</sup>, which displays similar spectroscopic and electrochemical behavior, strongly suggesting that O<sub>2</sub> is capable of oxidizing Ni<sup>II</sup> to Ni<sup>III</sup>.

Treatment of a benzene solution of **2-6** with Br<sub>2</sub> resulted in a color change from red to dark brown within seconds at room temperature. Analysis of the organic products revealed the formation of **2-5** (70%) along with significant amounts (16%) of the halogenated C–Br coupled product Phpy–Br (**2-1**) (eq. 13). As summarized in **Table 2.3**, a variety of other electrophilic functionalizing reagents reacted with **2-6** in a similar fashion to Br<sub>2</sub>. In all of these cases, C–C bond formation to generate **2-5** predominated over any other coupling reaction. The brominating reagents Br<sub>2</sub>, NBS, and CuBr<sub>2</sub> provided the highest (although still modest) yields of C–halogen coupled Phpy–Br (**2-1**) (2-16%) along with **2-5** as the major organic product (entries 1–3).



**Table 2.3** – Reaction of **2-6** with Electrophilic Halogenating Reagents (Workup C<sub>2</sub>)



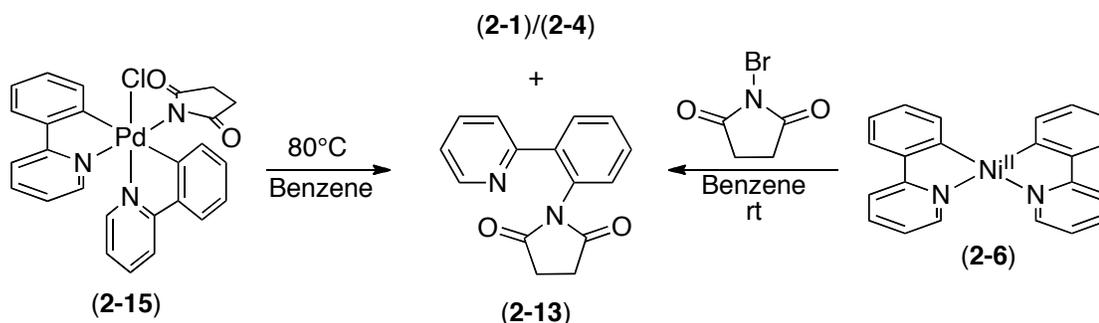
Entry	Oxidant	Yield C–X <sup>a</sup>	Yield C–C ( <b>2-5</b> ) <sup>a</sup>
1	Br <sub>2</sub>	16 ± 3%	70 ± 4%
2	NBS <sup>b</sup>	10 ± 2%	53 ± 2%
3	CuBr <sub>2</sub>	2 ± 1%	59 ± 5%
4	PhICl <sub>2</sub>	3 ± 1%	69 ± 3%
5	NCS	nd <sup>c</sup>	68 ± 3%
6	CuCl <sub>2</sub>	nd <sup>c</sup>	79 ± 3%
7	NFTPT <sup>d</sup>	nd <sup>c</sup>	58 ± 3%
8	CH <sub>3</sub> I <sup>e</sup>	nd <sup>c</sup>	40 ± 4%
9	C <sub>4</sub> F <sub>9</sub> I	nd <sup>c</sup>	48 ± 3%
10	NIS	15%	79 ± 2%
11	I <sub>2</sub>	nd <sup>c</sup>	37 ± 5%
12	PhI(OAc) <sub>2</sub>	22 ± 2%	58 ± 1%
13	XeF <sub>2</sub>	nd <sup>c</sup>	nd <sup>c</sup>

<sup>a</sup>Yields determined by <sup>1</sup>H NMR spectroscopy based on an average of 2 runs. <sup>b</sup>The C–N coupled product **2-23** was also formed in 7 ± 2% yield (see Table 2). <sup>c</sup>nd = not detected. <sup>d</sup>N-fluoro-2,4,6-trimethylpyridinium triflate. <sup>e</sup>The C–CH<sub>3</sub> product **2-24** was also formed in 25 ± 4% yield.

The reaction of **2-6** with NBS was particularly notable because it afforded C–N coupled product **2-23** (7%) along with **2-1** (10%) and **2-5** (53%) (Table 1, entry 2). Interestingly, thermolysis of the high oxidation state Pd complex Pd<sup>IV</sup>(phpy)<sub>2</sub>(Cl)(succinimide) (**2-23**) in benzene afforded a similar distribution of C–N,

C–X, and C–C products (Table 2.4, entry 2).<sup>1b</sup> This result suggests the possibility that the Ni reaction may proceed via a similar high oxidation state M<sup>IV</sup> intermediate. However, other pathways for oxidatively induced C–Br/C–N/C–C bond-formation at Ni, including the formation of a Ni<sup>III</sup> species<sup>23</sup> and/or Ni–C bond homolysis/free radical based coupling processes, are also potential routes to these products.

**Table 2.4** – Comparison of Reaction of **2-6**/NBS to Reductive Elimination from **2-23**



Entry	Reaction	Yield C–X (2-1)/(2-4)	Yield C–N (2-13)	Yield C–C (2-5)
1 <sup>a</sup>	<b>2-6</b> /NBS	10 ± 3%	7 ± 3%	53 ± 4%
2 <sup>b</sup>	<b>2-15</b>	13%	6%	23%

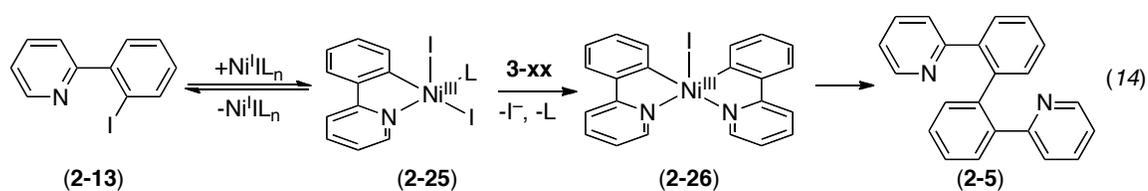
<sup>a</sup>Yields determined by <sup>1</sup>H NMR spectroscopy based on an average of 2 runs. <sup>b</sup>Data from ref. <sup>1b</sup>

There appears to be no clear trend regarding which oxidants resulted in no functionalized products other than **2-5**, but several of them had rather interesting results nonetheless. The reaction of XeF<sub>2</sub> (Table 2.3, entry 13) was the most unusual. When **2-6** and XeF<sub>2</sub> were combined in the solid state in the glovebox, they immediately exploded with a flash of visible flame. The resulting black ash was taken up in benzene and filtered through Celite. The resulting filtrate was analyzed by <sup>19</sup>F and <sup>1</sup>H NMR spectroscopy, but

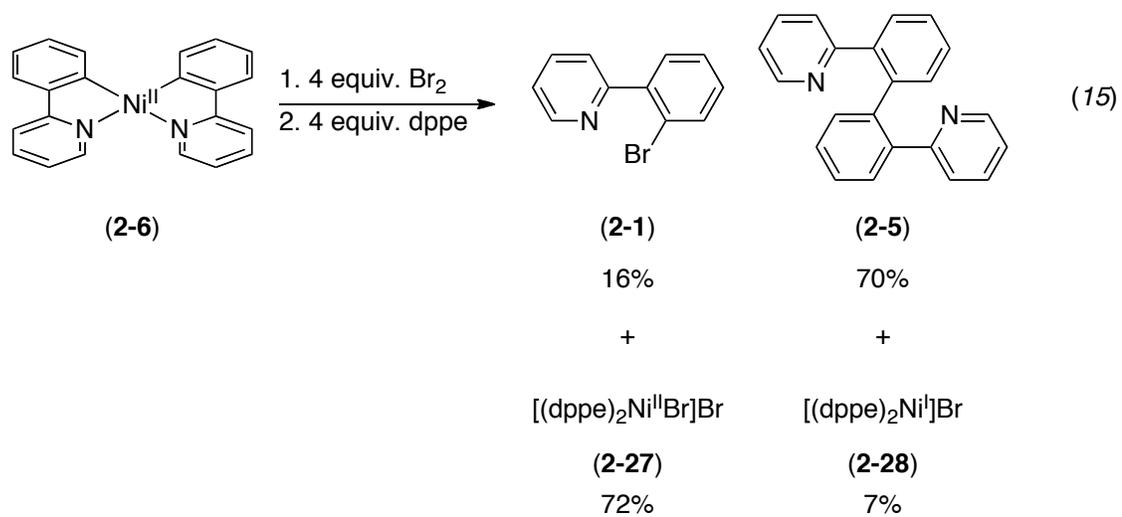
no organic products were observed. Unusually, when both components were pre-solvated and then mixed, there was no reaction whatsoever.

The iodinating oxidants were also rather interesting. The methyl iodide (Table 2.1, entry 8) result was interesting because the methylated product (**2-24**) completely outcompetes any C–I reductive elimination product (**2-13**). In fact, only NIS (Table 2.3, entry 10) had a detectable yield (15%) of the C–I product (**2-13**). It is possible, however, that the absence of **2-13** is the result of it undergoing a side reaction after it has been formed. We have seen that **2-13** is extremely susceptible to side reactions that result in homocoupling of the 2-phenylpyridine and subsequent generation of **2-5**. For example, injecting a purified authentic sample of **2-13** onto the GC results in substantial amounts of **2-5** being generated.

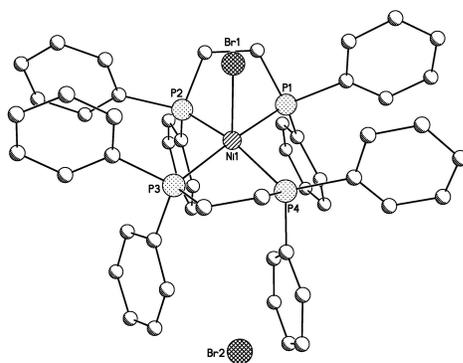
Such a side reaction could take place under our reaction conditions and would potentially be mediated by the presence of low-valent Ni byproducts (eq. 14). The low-valent Ni<sup>I</sup> byproducts resulting from reductive elimination from Ni<sup>III</sup> could potentially reinsert into the C–I bond of **2-13**, forming **2-25**. If this species was present in high enough concentrations or had a long enough lifetime, it could potentially transmetallate with the starting material, forming **2-26**. This species could, of course, now reductively eliminate a C–C bond to form dimer **2-5**. Such a pathway could potentially convert any **2-13** that was formed into **2-5**. This pathway would suggest that the nature of the inorganic byproducts of the initial reductive elimination is an important factor in the product distribution. This led us to investigate the nature of these inorganic species.



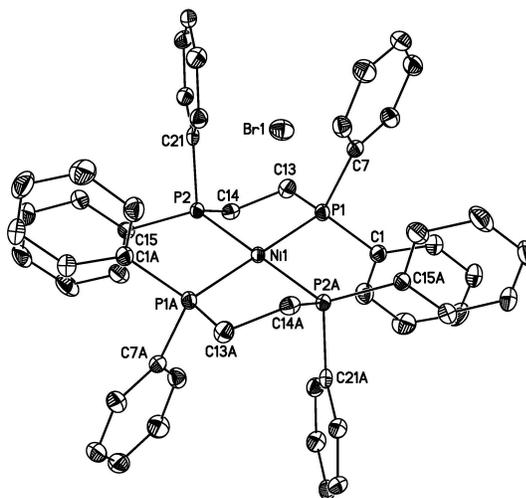
Attempts to directly characterize the inorganic byproducts of these oxidatively-induced reductive elimination reactions were complicated by the low crystallinity and paramagnetic nature of these Ni species. However, the addition of 4 equiv of diphenylphosphinoethane (dppe) to the crude reaction mixture resulting from the reaction of **2-6** with Br<sub>2</sub> formed the diamagnetic Ni<sup>II</sup> species, [(dppe)<sub>2</sub>Ni<sup>II</sup>Br]Br (**2-27**), in 72% yield as determined by <sup>31</sup>P NMR spectroscopy (eq. 15). The identity was confirmed by a preliminary crystal structure. The paramagnetic Ni<sup>I</sup> species [Ni<sup>I</sup>(dppe)<sub>2</sub>]Br (**2-28**) was also formed as a minor side product of this reaction (7% isolated yield of yellow crystals) and was characterized by X-ray crystallography. On the basis of these results, we propose that the initial inorganic products of reductive elimination are Ni<sup>I</sup> species that are coordinated to arylpyridines **2-1** and **2-5**. The excess oxidant in the reaction then oxidizes the majority of these Ni<sup>I</sup> species up to the more stable Ni<sup>II</sup> species that forms the majority of the observed inorganic products.



**Figure 2.3** – Preliminary crystal structure of [Ni<sup>II</sup>(dppe)<sub>2</sub>Br]Br, **2-27**



**Figure 2.4** – ORTEP View of  $[\text{Ni}^{\text{I}}(\text{dppe})_2]\text{Br}$ , **2-28**



**Table 2.5** – Selected Bond Lengths (Å) and Angles (°) for  $[\text{Ni}^{\text{I}}(\text{dppe})_2]\text{Br}$ , **2-28**

Ni(1)-P(1)	2.2447(7)	P(1)-Ni(1)-P(2)	83.65(3)
Ni(1)-P(1A)	2.2447(7)	P(1)-Ni(1)-P(2A)	96.35(3)
Ni(1)-P(2)	2.2367(7)	P(2A)-Ni(1)-P(1A)	83.65(3)
Ni(1)-P(2A)	2.2367(7)	P(1A)-Ni(1)-P(2)	96.35(3)

## 2.6 The Pursuit of High Oxidation State Intermediates

We attempted to observe and identify intermediates in the reaction of **2-6** with  $\text{Br}_2$  via  $^1\text{H}$  NMR spectroscopy. A solution of **2-6** in toluene- $d_8$  was frozen in a screw-cap NMR tube with liquid nitrogen. A solution of  $\text{Br}_2$  in toluene- $d_8$  was added via syringe and frozen as a second layer. The frozen sample was placed in the NMR instrument at  $-80$  °C, and spectra were obtained as the sample was warmed in  $10$  °C increments. Locking and shimming on the sample was challenging and the lowest temperature spectra contained little more than a very large, broad peak in the 1-3 ppm range. No clearly identifiable peaks appeared as the sample was warmed in  $10$  °C increments. There were, however, several broad resonances that were visible around 6-8 ppm when the sample

warmed to -50 °C. These seemed like they could potentially be the result of paramagnetic intermediates. Expansion of the acquisition window did not reveal any additional peaks outside of the normal range of a  $^1\text{H}$  NMR spectrum. These peaks changed very little as the sample was heated to 30 °C.

We further investigated the possibility of paramagnetic intermediates by analyzing the reaction by EPR. The EPR instrument is not capable of variable temperature analysis, so solutions of **2-6** and  $\text{Br}_2$  in benzene were combined in an EPR tube and immediately frozen with liquid nitrogen. Unfortunately, if there were any paramagnetic intermediates present, they were transient and present in concentrations that were too low for us to observe.

## 2.7 Conclusions

Unlike analogous Pd systems, no high oxidation state Ni intermediates were detected in the oxidatively-induced reductive elimination of C–X bonds from  $\text{Ni}^{\text{III}}(\text{phpy})_2$  by either  $^1\text{H}$  NMR or EPR. We interpret this as being a result of the transient nature of the proposed intermediates. Additionally, the Ni-bound phpy ligands appear to be more susceptible to oxidatively-induced C–C homocoupling in comparison to their Pd analogues. These features make it difficult to draw definitive conclusions about the mechanism of C–X bond formation at Ni in these systems. This clearly indicates that the stabilization/isolation of high oxidation state Ni intermediates in carbon-heteroatom bond-forming processes will require supporting ligands that are not susceptible to competing C–C coupling.<sup>10,11</sup> We were very gratified, however, to see that the formation of a variety of interesting carbon-heteroatom products were obtained via these Ni-

mediated reactions and we were inspired to try and design a system that would allow for the generation of these types of products without the competing C–C coupling side products.

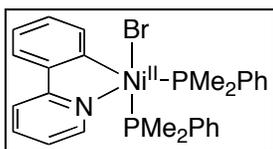
## 2.8 Experimental Procedures

**General Considerations.** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for  $^1\text{H}$ ; 125.70 MHz for  $^{13}\text{C}$ ) and a Varian Inova 400 (399.96 MHz for  $^1\text{H}$ ; 100.57 MHz for  $^{13}\text{C}$ ; 376.34 MHz for  $^{19}\text{F}$ ).  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br).

**Materials and Methods.** Tetrahydrofuran, pentanes, and methylene chloride were purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. Benzene was distilled from sodium, pyridine was distilled from  $\text{CaH}_2$ , and acetone was distilled from anhydrous calcium sulfate. 2-(2-Bromophenyl)pyridine (**2-1**) was synthesized according to a literature procedure,<sup>24</sup> while 2-(2-iodophenyl)pyridine was prepared by lithium halogen exchange on **2-1** followed by a quench with  $\text{I}_2$ , using a modification of a literature procedure.<sup>25</sup>  $\text{Ni}(\text{COD})_2$  (Strem) was stored in a glovebox at  $-35\text{ }^\circ\text{C}$ .  $\text{Ni}(\text{Phpy})(\text{Pic})(\text{I})$  was prepared via reaction of  $\text{Ni}(\text{COD})_2$  with Phpy–I and picoline via a modification of a literature procedure.<sup>19a</sup>  $\text{PhICl}_2$  was prepared via a modification of a literature procedure<sup>26</sup>

and was stored at  $-35\text{ }^{\circ}\text{C}$  in a glovebox. NBS and NCS (Acros) were recrystallized from boiling water and benzene respectively, dried under vacuum overnight, and stored in a glovebox. NIS (Acros) and  $\text{PhI}(\text{OAc})_2$  (AK Scientific, Inc.) were dried under vacuum overnight and stored in a  $\text{N}_2$ -filled glovebox. 1-Fluoro-2,4,6-trimethylpyridinium triflate (Acros) and potassium *tert*-amylate was dried under vacuum overnight and stored in the glovebox.  $\text{CuBr}_2$  (General Chemical Company) and  $\text{CuCl}_2$  (Acros) were dried under vacuum at  $100\text{ }^{\circ}\text{C}$  overnight and stored in a glovebox.  $\text{Br}_2$  (Aldrich),  $\text{I}_2$  (sublimed, Acros), and *n*-BuLi (Acros) were used without further purification. MeI (Sigma Aldrich) was stored in a freezer ( $-35\text{ }^{\circ}\text{C}$ ) and used without further purification.  $\text{C}_4\text{F}_9\text{I}$  (Acros) was stored in a refrigerator and used without further purification.  $\text{XeF}_2$  (Matrix) was stored in a freezer ( $-35\text{ }^{\circ}\text{C}$ ) in  $\text{N}_2$ -filled glovebox and used without further purification.

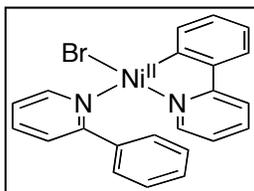
Gas chromatography was performed on a Shimadzu GC-17A equipped with a Restek Rtx®-5 column (15 m, 0.25 mm ID, 0.25 m df) and a flame ionization detector. The reported yields in all oxidation reactions represent the average of at least two independent trials. Authentic samples of each of the oxidation products **2-4**,<sup>14</sup> **2-1**,<sup>14</sup> **2-21**,<sup>27</sup> **2-5**,<sup>28</sup> **2-20**,<sup>29,30,31</sup> and **2-23**<sup>32</sup> were prepared using literature methods.



**Bis-(dimethylphenylphosphine)(2-(2'-Pyridyl)phenyl) Nickel (II) Bromide (2-11).** From Dr. Paul Zinn. All in Schlenk flasks

under  $\text{N}_2$ , a solution of 2-1 (0.125 g, 0.534 mmol) and dimethylphenylphosphine (0.148 g, 1.07 mmol) in THF (4 ml) was transferred dropwise over  $\sim 5$  min via cannula to a suspension of  $\text{Ni}(\text{COD})_2$  (0.147 g, 0.534 mmol) in THF (4 mL) that has been cooled to -

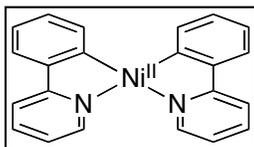
78 °C. The transfer and washings were completed with 2 x 2mL THF. The reaction mixture immediately became a brighter yellow somewhat homogeneous. Within 10 minutes of removing it from the cooling bath, the reaction mixture turned deep red and completely homogeneous. The resulting mixture was stirred at room temperature for 1 h. The solvent was removed via vacuum and the resulting dark, oily residue was washed with pentane and filtered to obtain a maroon powder. This solid was dried under vacuum (197 mg, 65%). This complex is stable in benzene for at least 24 h at room temperature, but will eventually decompose in CH<sub>2</sub>Cl<sub>2</sub> at room temperature within 24 h.



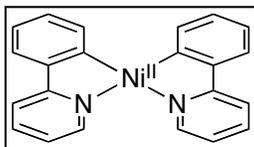
**(2-phenylpyridine)(2-(2'-pyridyl)phenyl) Nickel (II) Bromide (2-**

**15).** From Dr. Paul Zinn. This complex was prepared using the same procedure as stated for [(phpy)Ni(PMe<sub>2</sub>Ph)<sub>2</sub>(Br)] using 2-1

(0.166 g, 0.709 mmol), 2-phenylpyridine (0.110 g, 0.709 mmol), and Ni(COD)<sub>2</sub> (0.195 g, 0.709 mmol) with the following observations. About 15 minutes after the cooling bath was removed, the reaction began to turn a bright orange-yellow, which eventually became homogeneous. After about 15 more minutes, the reaction mixture became orange and a yellow-brown solid precipitated. The reaction was allowed to stir for another 30 minutes at room temperature. The entire time from removing the cooling bath to removing the solvent was 1 h. Isolation was the same as for [(phpy)Ni(PMe<sub>2</sub>Ph)<sub>2</sub>(Br)], resulting in an orange solid (232 mg, 73%). For better purity, this compound should be dissolved in benzene and filtered to separate some insoluble impurities that seem to be responsible for broadening the NMR signals. The pure product can then be obtained after removing the solvent via vacuum.

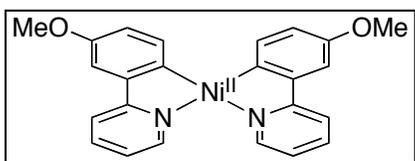


**bis-(2-(2'-pyridyl)phenyl) Nickel(II) – Two Steps (2-6).** Under  $N_2$ , 2-(2-Bromophenyl)pyridine (0.041 g, 0.18 mmol, 1.05 equiv) was dissolved in THF (5 mL) in a dry 25 mL Schlenk flask, and this mixture was cooled to  $-78\text{ }^\circ\text{C}$ . *n*-BuLi (0.07 mL of a 2.5 M solution in hexanes, 0.18 mmol, 1.05 equiv) was added via syringe, which resulted in an immediate color change from colorless to bright yellow. This mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 10 min. It was then transferred via cannula to a cold ( $-78\text{ }^\circ\text{C}$ ) solution of Ni(phpy)(pic)(I) (0.075 g, 0.17 mmol, 1.00 equiv) in THF (5 mL), resulting in a rapid color change from yellow to blood red. This mixture was stirred for 15 min at  $-78\text{ }^\circ\text{C}$  and then allowed to warm to rt over 1 h. The solvent was removed under vacuum, the resulting oily solid was dissolved in benzene (15 mL) and filtered through Celite, and the solvent was removed under vacuum to afford a dark yellow/black oily solid. This crude material was dissolved in acetone- $d_6$ , an internal standard (1,3,5-trimethoxybenzene) was added, and the mixture was analyzed by  $^1\text{H}$  NMR spectroscopy, which showed that **2-6** was formed in 23% yield.



**bis-(2-(2'-pyridyl)phenyl) Nickel(II) – one step (2-6).** In a glovebox, Ni(COD) $_2$  (0.250 g, 0.91 mmol, 1.00 equiv) was dissolved in THF (5 mL) in a dry 20 mL scintillation vial. In a second 4 mL vial, 2-phenylpyridine (0.143 g, 0.92 mmol, 1.01 equiv) and 2-(2-bromophenyl)pyridine (0.215 g, 0.92 mmol, 1.01 equiv) were also dissolved in THF (2 mL). Both vials were cooled to  $-35\text{ }^\circ\text{C}$ , and then the ligand solution was added to the

Ni(COD)<sub>2</sub> solution. The resulting yellow-brown mixture was stirred for 10 min at rt. A solution of potassium *tert*-amylate (0.117 g, 0.92 mmol, 1.02 equiv) in THF (4 mL) was then added, which resulted in an immediate color change to blood red. The mixture was stirred for an additional 10 min, and then the solvent was removed under vacuum. The resulting red solids were dissolved in dry benzene (15 mL) and filtered through a pad of Celite. Pentanes (100 mL) was added to the red filtrate, and this solution was cooled at –35 °C overnight. The resulting precipitate was collected and dried under vacuum to afford **2-6** as a brick red solid (112 mg, 33% yield). The <sup>1</sup>H and <sup>13</sup>C NMR data for **2-6** matched that reported in the literature.<sup>10</sup>



**bis-(2-(2'-pyridyl)-5-methoxyphenyl) Nickel (II) (2-29)**. From Dr. Paul Zinn. Using the same procedure as **2-6** with 2-(2-bromo-5-methoxyphenyl)pyridine (**2-30**)

(0.170 g, 0.642 mmol, 1.00 equiv), 2-(3-methoxyphenyl)pyridine (**2-31**) (0.119 g, 0.642 mmol, 1.00 equiv), Ni(COD)<sub>2</sub> (0.177 g, 0.642 mmol, 1.00 equiv), and potassium *t*-amylate (0.083 g, 0.66 mmol, 1.03 equiv) with 12 total mLs of THF. The same observations were found. After crystallization, maroon crystals were obtained and dried via vacuum, (93 mg, 34% yield).

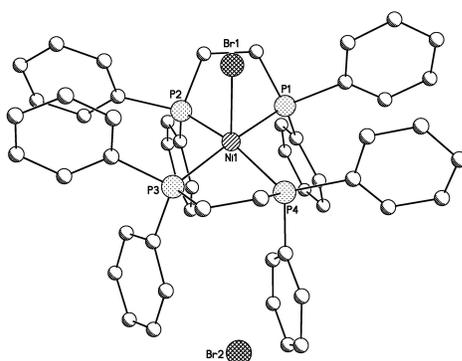
**Reaction of 2-6 with O<sub>2</sub>**. In a glovebox, complex **2-6** (4.8 mg, 0.013 mmol, 1.0 equiv) was dissolved in benzene (1 mL) in a J-Young NMR tube. The sample was removed from the glove box, degassed via three freeze-pump-thaw cycles, and then filled with 1 atm of dry O<sub>2</sub>. The sample was shaken vigorously, which resulted in a color change from deep

red to yellow brown. The resulting mixture was then allowed to stand at room temperature overnight. The solvent was removed under vacuum, the solid residue was taken up in EtOAc (10 mL). Several drops of HCl were added and then the organic layer was neutralized with saturated sodium bicarbonate. The EtOAc layer was then washed with 1.0 *M* aqueous sodium citrate (2 x 20 mL) and saturated aqueous sodium thiosulfate (1 x 20 mL). The organic layer was collected and concentrated under vacuum, an internal standard (1,3,5-trimethoxybenzene) was added, and the reaction was analyzed by <sup>1</sup>H NMR spectroscopy.

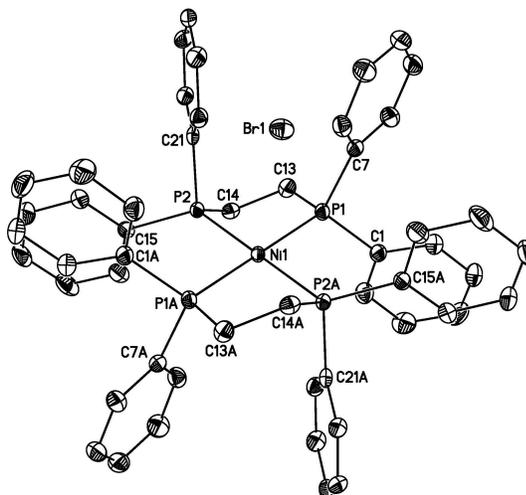
**Reaction of 2-6 with Br<sub>2</sub> (Identification of Organic Products).** In a glovebox, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) was dissolved in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar and sealed with a Teflon-lined cap fitted with a rubber septum. The vial was removed from the glove box, and Br<sub>2</sub> (0.104 mmol, 4.0 equiv) was added via syringe. The reaction mixture was stirred at room temperature overnight. The solvent was then removed under vacuum, the resulting material was taken up in EtOAc (10 mL), and the EtOAc solution was washed with 1.0 *M* aqueous sodium citrate (2 x 20 mL) and saturated aqueous sodium thiosulfate (1 x 20 mL). The organic layer was collected and concentrated under vacuum, an internal standard (1,3,5-trimethoxybenzene) was added, and the reaction was analyzed by <sup>1</sup>H NMR spectroscopy.

**Reaction of 2-6 with Br<sub>2</sub> (Identification of Inorganic Products).** In a glove box, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) was dissolved in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar and sealed with a Teflon-lined cap

fitted with a rubber septum. The vial was removed from the glove box, and the oxidant (0.104 mmol, 4.0 equiv) was added via syringe. The reaction mixture was stirred at rt overnight. The solvent was then removed under vacuum, the resulting material was dissolved in MeOH (1 mL), and a solution of 1,2-bis(diphenylphosphino)ethane (dppe) (41.4 mg, 0.104 mmol, 4 equiv in 1 mL of toluene) was added, immediately turning the solution a deep purple-red. The reaction was allowed to stir at rt overnight. The solvent was then removed under vacuum, an internal standard (triphenylphosphine oxide) was added, and the reaction was analyzed by  $^{31}\text{P}$  NMR spectroscopy. The inorganic products were then crystallized from  $\text{CHCl}_3$ /petroleum ether to afford a mixture of purple crystals (complex **2-27**, 19.1 mg, 72% isolated yield) and yellow crystals (complex **2-28**, 1.6 mg, 7% isolated yield). The crystals were manually separated and dried under vacuum to obtain isolated yields of each complex. In addition, each complex was characterized by single crystal X-ray crystallography. The X-ray analysis of **2-27** yielded a preliminary structure (suitable for determining composition and stoichiometry), and further refinement was not pursued.



**Figure 2.3** – Preliminary crystal structure of  $[\text{Ni}^{\text{II}}(\text{dppe})_2\text{Br}]\text{Br}$ , **2-27**



**Figure 2.4** – ORTEP View of  $[\text{Ni}^{\text{I}}(\text{dppe})_2]\text{Br}$ , **2-88**

**Reaction of 2-6 with  $\text{PhI}(\text{Cl})_2$ , NCS,  $\text{CuCl}_2$ , NBS,  $\text{CuBr}_2$ , NIS,  $\text{PhI}(\text{OAc})_2$  and 1-Fluoro-2,4,6-trimethylpyridinium Triflate.** In a glove box, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) and oxidant (0.104 mmol, 4.0 equiv) were suspended in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar, sealed with a Teflon lined cap, and the reaction mixture was stirred at rt overnight. The vial was removed from the dry box, and the solvent was removed under vacuum. The resulting material was taken up in EtOAc (10 mL), and the EtOAc solution was washed with 1.0 M aqueous sodium citrate (2 x 20 mL) and saturated aqueous sodium thiosulfate (1 x 20 mL). The organic layer was then collected and concentrated under vacuum, an internal standard (1,3,5-trimethoxybenzene) was added, and the reaction was analyzed by  $^1\text{H}$  NMR spectroscopy.

**Reaction of 2-6 with MeI and  $\text{C}_4\text{F}_9\text{I}$ .** In a glovebox, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) was dissolved in benzene (2 mL) in a 4 mL vial. The vial was equipped with a

magnetic stir bar and sealed with a Teflon-lined cap fitted with a rubber septum. The vial was removed from the glove box, and oxidant (0.104 mmol, 4.0 equiv) was added via syringe. The reaction mixture was stirred at room temperature overnight. The solvent was then removed under vacuum, the resulting material was taken up in EtOAc (10 mL), and the EtOAc solution was washed with 1.0 M aqueous sodium citrate (2 x 20 mL) and saturated aqueous sodium thiosulfate (1 x 20 mL). The organic layer was collected and concentrated under vacuum, an internal standard (1,3,5-trimethoxybenzene) was added, and the reaction was analyzed by  $^1\text{H}$  NMR spectroscopy.

**Reaction of 2-6 with  $\text{XeF}_2$  (Solid Addition).** In a glovebox, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) was weighed into a 4 mL vial. An unknown amount of  $\text{XeF}_2$  was added. When the  $\text{XeF}_2$  touched **2-6**, there was an immediate explosion that was audible through the window of the glovebox as a loud pop, accompanied by a visible flash of flame ejecting out of the top of the vial. Much of the solid material was ejected in the form of black ash, but some black solid material remained in the vial. This material was suspended in benzene and filtered through Celite. The solvent was removed from the resulting clear filtrate and analyzed by  $^{19}\text{F}$  and  $^1\text{H}$  NMR, but no identifiable products were detected.

**Reaction of 2-6 with  $\text{XeF}_2$  (Liquid Addition).** In a glovebox, complex **2-6** (9.5 mg, 0.026 mmol, 1.0 equiv) was weighed into a 4 mL vial equipped with a magnetic stir bar and dissolved in 1.0 mL of benzene.  $\text{XeF}_2$  (17.6 mg, 0.104 mmol, 4.0 equiv) was weighed into a separate 4 mL vial and dissolved in 1.0 mL of benzene. Each vial was shaken for

~1 minute until the solids were completely dissolved. The XeF<sub>2</sub> solution was then added to the solution of **2-6** via pipette and the resulting solution was allowed to stir overnight. The next morning the solvent was removed from the reaction and it was analyzed by <sup>1</sup>H and <sup>19</sup>F NMR. There was no trace of any fluorinated Ni or organic products in the <sup>19</sup>F NMR and the only identifiable peaks in the <sup>1</sup>H NMR corresponded to the starting complex **2-6**, so it seems that there was no reaction.

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- <sup>13</sup> For example, the use of Ni<sup>II</sup>Br<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the Ni<sup>II</sup> starting material produced Ni<sup>I</sup>Br(PPh<sub>3</sub>)<sub>3</sub> as the major inorganic product (characterized by EPR spectroscopy and X-ray crystallography). For a similar observation, see ref. 8.
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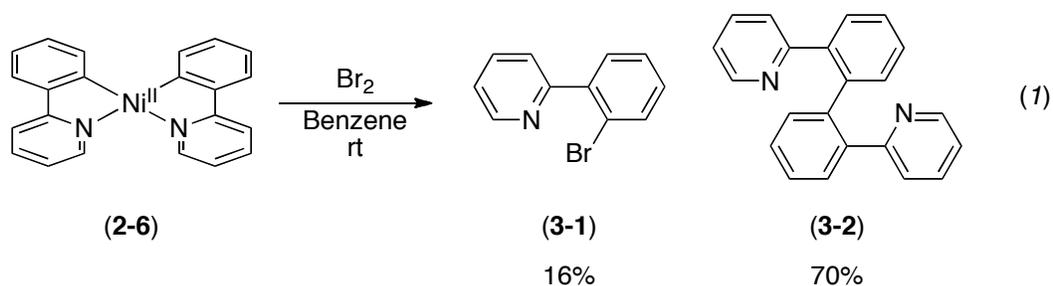
<sup>32</sup> Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

## Chapter 3

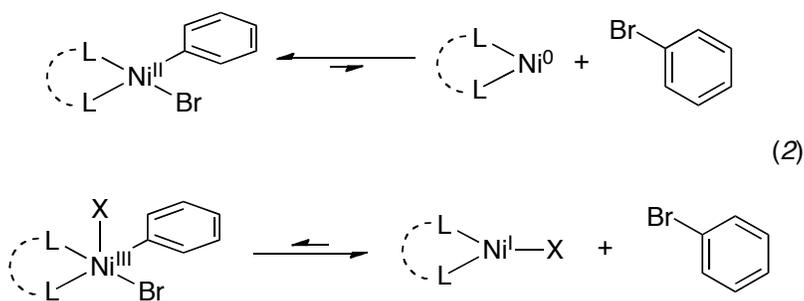
### Synthesis and Reactivity of Ni<sup>II</sup>(phenylpyridine)(Pic)(Br)

#### 3.1 Introduction

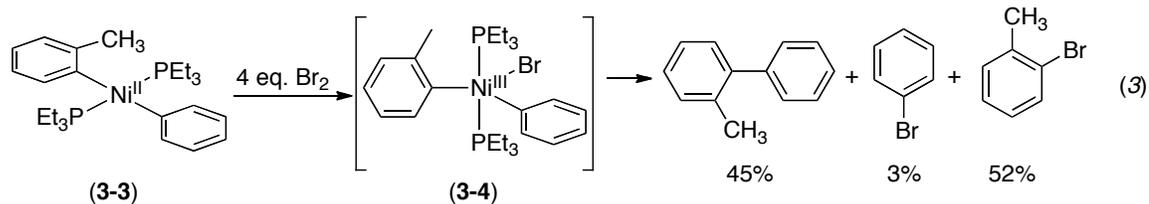
The Ni<sup>II</sup>(phpy)<sub>2</sub> (phpy = 2-phenylpyridine) complex (**2-6**) described in Chapter 2 proved to be unsuitable for isolating high oxidation state Ni complexes. However, upon exposure of **2-6** to various oxidants, functionalized organic products were observed. To our delight, complex **2-6** afforded products that were suggestive of C–Br (**3-1**) reductive elimination from a high oxidation state Ni complex. While C–X products were formed in moderate yields, the competing C–C homocoupling product (**3-2**) accounted for the majority of the recovered organic material (eq. 1). This prompted us to design a system that would minimize **3-2** and produce the C–X coupled product **3-1** in high yields. Additionally, the new system might allow for mechanistic investigation of carbon-halogen bond formation from a high oxidation state Ni species.



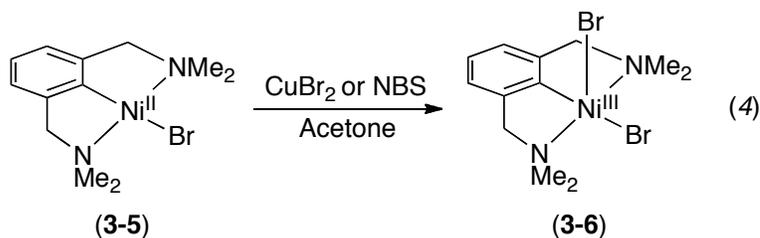
In general,  $\text{Ni}^{\text{II}}(\text{Ar})(\text{X})$  complexes can be accessed by oxidative addition of  $\text{Ar-X}$  to a  $\text{Ni}^0$  precursor.<sup>1</sup> The equilibrium for this reaction typically lies heavily to the left, favoring the oxidative addition product  $\text{Ni}^{\text{II}}(\text{Ar})(\text{X})$  (eq. 2). However, isolated reports have suggested that higher oxidation state Ni complexes may mediate C–X bond-forming reactions, which agrees with our previously proposed mechanism (Chapter 2).<sup>1d</sup>



For example, Muller has shown that treatment of  $(\text{PR}_3)_2\text{Ni}^{\text{II}}(\text{Ar})(\text{Ar}')$  (**3-3**) with  $\text{Br}_2$  affords  $\text{Ar-Br}$  products in yields ranging from 28 to 93%.<sup>2</sup> He also reports side reactions leading to biaryl C–C coupled products and oxidation of the phosphine ligands (eq. 3). A mechanism involving one-electron oxidation of the organonickel complex to  $\text{Ni}^{\text{III}}$  (**3-4**) was proposed. We concluded that these factors made this system unsuitable for detailed investigation.

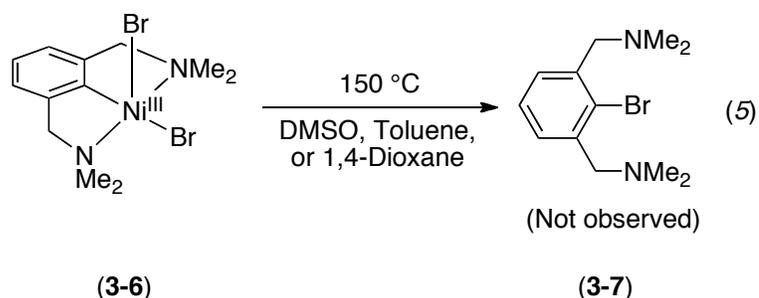


Beautiful work by van Koten has shown Ni<sup>II</sup> pincer complex **3-5** can be oxidized with CuBr<sub>2</sub> or *N*-bromosuccinimide (NBS) to afford the organometallic Ni<sup>III</sup> dibromide complex **3-6** (eq 4).<sup>3</sup> Further reactivity of this Ni<sup>III</sup> species, including any reductive elimination pathways, was not described. As such, we determined that this was an attractive starting point for our investigations of C-X bond formation at high oxidation state Ni.

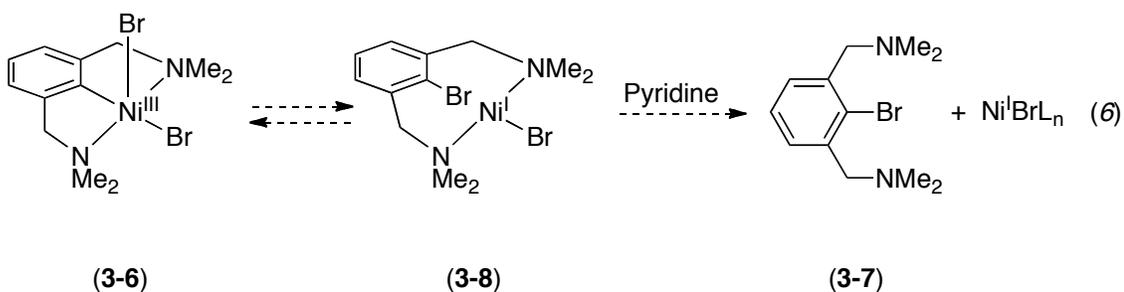


### 3.2 C–X Bond Reductive Elimination Directly From a Ni<sup>III</sup> complex

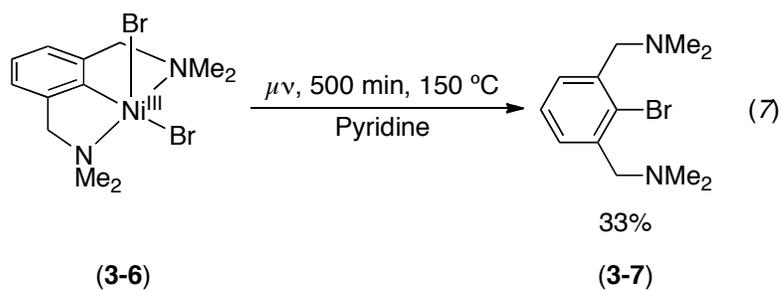
Complex **3-6** was synthesized according to the literature procedure.<sup>3</sup> We then investigated the feasibility of thermally induced C–Br bond-forming reductive elimination from this species. However, when **3-6** was heated to 150 °C for 12 h in toluene, dioxane, or DMSO, none of the Ar–Br product **3-7** was observed (eq. 5).



This apparent lack of reactivity could be due to rapid reinsertion of Ni<sup>I</sup> into the Ar–Br bond (eq. 6). Such reinsertion is expected to be relatively facile in this system, since the chelating pincer ligand can coordinate to the Ni<sup>I</sup> byproduct. As a result, the Ar–Br bond would remain in close proximity to the Ni center. As shown in eq. 6, an additive that could displace the chelating ligand from the Ni<sup>I</sup> byproduct (*e.g.*, pyridine) would potentially prevent this.



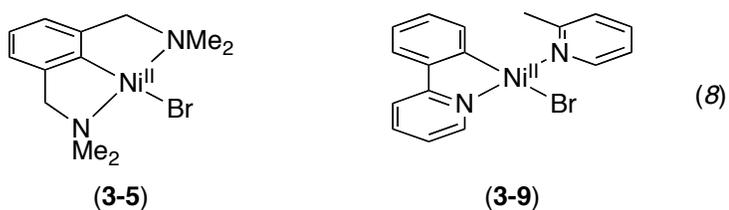
Gratifyingly, heating **3-6** at 150 °C for 8 h in pyridine resulted in the formation of the desired C–Br reductive elimination product **3-7** in 16 ± 3% yield as determined by GC analysis. The yield of **3-7** could be improved to 33 ± 3% by heating the reaction using microwave irradiation ( $\mu\nu$ , 500 min, 150 °C) (eq. 7). To our knowledge, this is the first example of carbon–halogen bond formation from an isolable Ni<sup>III</sup> species.



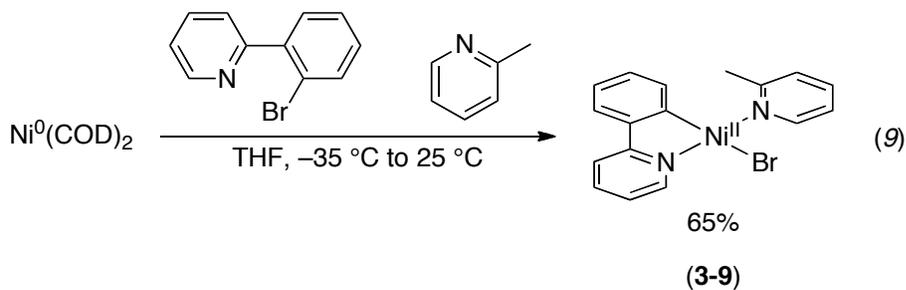
Despite the success of these initial experiments, this system has several limitations. Most significantly, the requirement for elevated temperatures (150 °C) makes direct spectroscopic observation of the reaction difficult. In addition, the yield of **3-7** remained less than 50% despite screening a variety of solvents (toluene, dioxane, DMSO), additives (bromobenzene, bipyridine, ethylenediamine tetraacetic acid,  $\text{CuBr}_2$ , NBS, and tri-*o*-tolylphosphine), and microwave conditions in an effort to optimize the reaction. Additionally, the tridentate pincer ligand differs significantly from most substrates of interest for potential catalytic applications. Therefore, we sought to design a system that maintained the same ligand coordination sphere, but was more conformationally flexible.

To this end, we targeted the synthesis of  $\text{Ni}^{\text{II}}(\text{phpy})(\text{Br})(\text{pic})^{12}$  (**3-9**) (pic = 2-methylpyridine) in order to study its reactivity with electrophilic brominating reagents. This complex has a  $(\text{N})_2(\text{Ar})(\text{Br})$  ligand set that is analogous to complex **3-5**, but is composed of a pair of monodentate ligands and one bidentate ligand rather than one monodentate ligand and the more rigid tridentate ligand (eq. 8). 2-Phenylpyridine is also more labile and catalytically relevant than the tridentate ligand.<sup>4</sup> We continued to use pyridine-based supporting ligands because they are stable in the presence of the oxidants

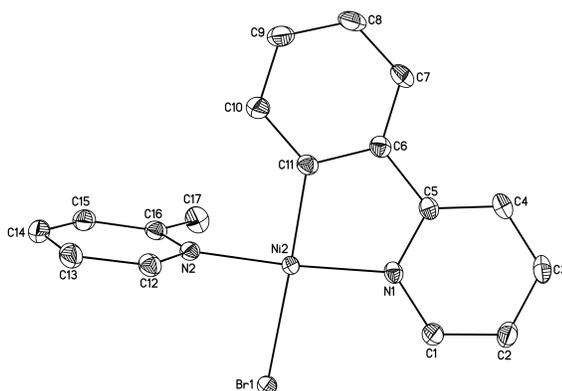
that we were interested in ( $\text{Br}_2$ , NBS, and  $\text{CuBr}_2$ ). 2-Methylpyridine was selected as the pyridine-based supporting ligand because steric bulk in the *ortho* position has been shown to prevent decomposition in analogous complexes.<sup>5</sup>



Synthesis of the desired complex (3-9) was achieved by reacting 3-1 with  $\text{Ni}(\text{COD})_2$  in the presence of 2-methylpyridine. Following workup and crystallization, 3-9 was isolated in 65% yield (eq. 9). This complex was fully characterized by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, elemental analysis, and X-ray crystallography (Figure 3.1).



**Figure 3.1** – ORTEP View of  $[\text{Ni}^{\text{II}}(\text{phpy})(\text{Pic})(\text{Br})]$  (**3-9**)

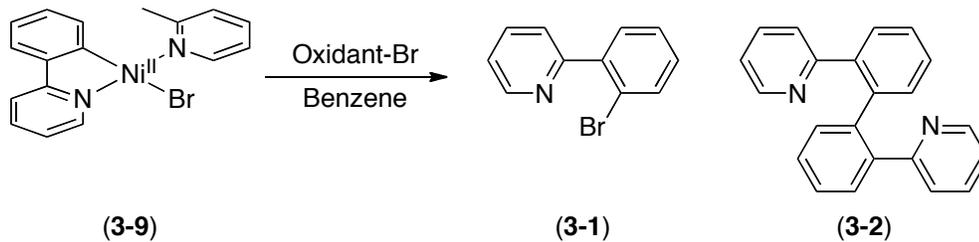


**Table 3.1** – Selected Bond Lengths (Å) and Angles (°) for **3-9**

Ni(2)-C(11)	1.8944(15)	C(11)-Ni(2)-N(1)	84.36(6)
Ni(2)-N(1)	1.9168(13)	N(1)-Ni(2)-Br(1)	97.27(4)
Ni(2)-Br(1)	2.4035(3)	Br(1)-Ni(2)-N(2)	87.54(4)
Ni(2)-N(2)	1.8894(13)	N(2)-Ni(2)-C(11)	91.19(6)

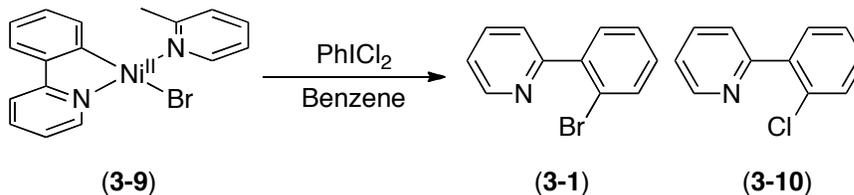
### 3.3 C–X Bond Reductive Elimination From $\text{Ni}^{\text{II}}(\text{phpy})(\text{Pic})(\text{Br})$

Solutions of **3-9** in benzene were reacted with a variety of brominating oxidants overnight at room temperature before being worked up using procedure B<sub>2</sub> (Table 3.1). Both Br<sub>2</sub> and NBS reacted with **3-9** to afford C–Br coupled product **3-1** in 67-61% yield. In contrast, CuBr<sub>2</sub> afforded only 12% of the desired product. Due to this result, we initially hypothesized that the CuBr<sub>2</sub>-induced transformation be proceeding through a different mechanism than the reaction with Br<sub>2</sub> or NBS. Unfortunately, even in our best example (Table 3.2, entry 2), we accounted for less than 80% of our organic products.

**Table 3.2** – Reaction of **3-9** with Brominating Oxidants (Workup B<sub>2</sub>)

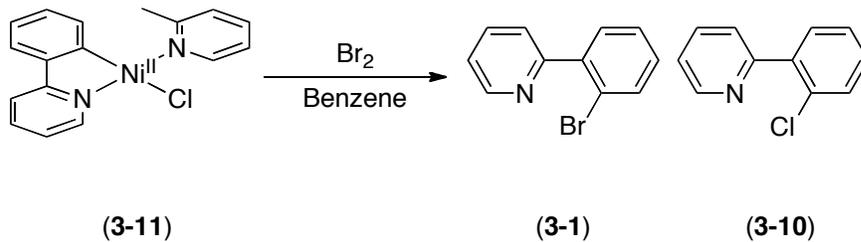
Entry	Oxidant	C-Br (GC Yield)	C-C (GC Yield)
1	Br <sub>2</sub>	61 ± 13%	9 ± 7%
2	NBS	67 ± 15%	12 ± 7%
3	CuBr <sub>2</sub>	12 ± 9%	7 ± 5%

At this point, we sought to investigate the origin of the halogen that was incorporated into the organic product. In the previous example, it was impossible to determine if the bromine atom that was incorporated into **3-1** originated from the oxidant or the starting complex, **3-9**. Therefore, we designed an experiment wherein the halogen being delivered by the oxidant was different than the halogen that originated on the starting Ni<sup>II</sup> complex. Thus, we examined the reaction of **3-9** with PhICl<sub>2</sub> (Table 3.2). We saw substantial (17-53%) yield of the brominated product, **3-1**, demonstrating incorporation of the halogen on the metal into the organic products. While there was no clear trend in the relative yields of the two products, in all cases substantial amounts of both halogenated products were observed.

**Table 3.3** – Reaction of **3-9** with PhICl<sub>2</sub> (Workup B<sub>2</sub>)<sup>6</sup>

Entry	Solvent	C-Cl (Yield)	C-Br (Yield)
1	Benzene	53 ± 4%	25 ± 3%
2	THF	27 ± 12%	53 ± 10%
3	CH <sub>2</sub> Cl <sub>2</sub>	30 ± 8%	43 ± 11%
4	Pyridine	62 ± 10%	17 ± 12%

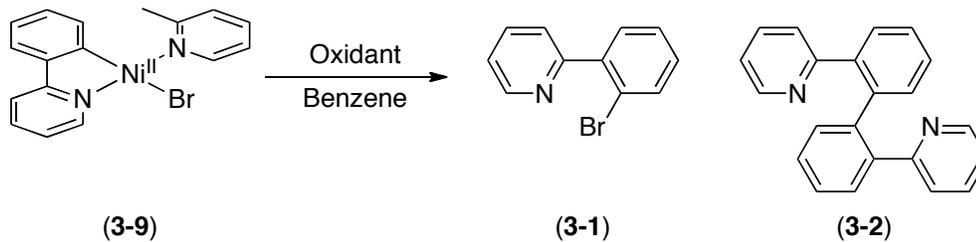
We also investigated the reaction of the analogous chloride complex (**3-11**) with Br<sub>2</sub> (Table 3.4). In contrast to the reaction of **3-9** with PhICl<sub>2</sub>, we observed much lower yield of the product that incorporated the halogen from the metal, **3-10**, in the mixture of organic products (3-18%). Product **3-10** was not observed in benzene or THF, but, interestingly, we still obtained the highest yields of **3-10** in pyridine. In all cases, however, the incorporation of the halogen derived from the oxidant was observed in the highest yields (55-86%). Taken together, all of these examples (Table 3.3 and 3.4) suggest that the reactive intermediate in these transformations likely involves both the halogen from the metal and the oxidant.

**Table 3.4** – Reaction of **3-11** with Br<sub>2</sub> (Workup B<sub>2</sub>)

Entry	Solvent	C-Cl (Yield)	C-Br (Yield)
1	Benzene	<sup>a</sup> nd	77 ± 11%
2	THF	<sup>a</sup> nd	62 ± 10%
3	CH <sub>2</sub> Cl <sub>2</sub>	3 ± 1%	86 ± 16%
4	Pyridine	18 ± 9%	55 ± 11%

<sup>a</sup>nd = not detected

We also investigated the reactivity of **3-9** with ceric ammonium nitrate [(NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub>], ferrocenium tetrafluoroborate [FeCp<sub>2</sub>(BF<sub>4</sub>)], and benzoquinone in benzene. The common feature of all of these oxidants is that can act as outer sphere oxidants that are incapable of transferring a halide. Observation of halogenated organic product **3-1** must, therefore, be the result of the incorporation of the halide originating from **3-9**. As shown in Table 3.5, all three oxidants promoted the transformation to generate **3-1**, albeit in modest (13-25%) yields. Substantial amounts (44-50%) of the C-C coupled product, **3-2**, were also observed. The origin of this product will be discussed at length in due course.

**Table 3.5** – Reaction of **3-9** with Non-Functionalizing Oxidants (Workup C<sub>2</sub>)

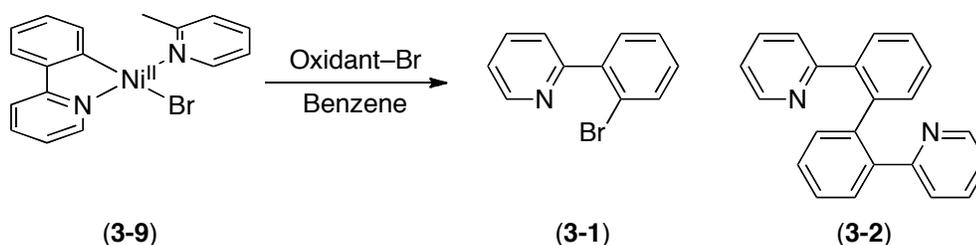
Entry	Oxidant	C–Br (Yield)	C–C (Yield)
1	(NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>	25 ± 3%	50 ± 2%
2	FeCp <sub>2</sub> (BF <sub>4</sub> )	19 ± 3%	44 ± 2%
3	Benzoquinone	13 ± 2%	50 ± 3%

At this point we discovered that there was an unacceptable amount of variability in product yields when reactions were repeated several weeks apart. We hypothesized that Workup B<sub>2</sub> was not removing a sufficient amount of the metal byproducts and that product coordination to these inorganic species was the source of the yield variation. Furthermore, such coordination would be even more pronounced with a superstoichiometric metal oxidant such as CuBr<sub>2</sub>, potentially accounting for the substantially lower yields observed in that reaction. Thus, we developed Workup C<sub>2</sub>. See Chapter 2.4 for a more extensive discussion of the various workups.

Once the procedure for Workup C<sub>2</sub> was established, we reexamined the reaction of **3-9** with a number of brominating oxidants (Table 3.6). We were excited to see that not only were the yields more reproducible, but we were also able to account for more of the mass balance of organic material in these reactions. In all cases, we can account for more than 80% of the organic material. The increase in yield of the reaction with CuBr<sub>2</sub> (Table 3.6, entry 3) was especially notable. This was the only reaction that used a metal-based oxidant. It seems likely, therefore, that product loss with the old workups was due to product coordination to the superstoichiometric copper salts. The yield of this reaction

is now similar to the reactions with NBS and Br<sub>2</sub>, making it far less likely that CuBr<sub>2</sub> is operating by a fundamentally different mechanism. The reaction with Br<sub>2</sub> (Table 3.6, entry 1) was most exciting because the desired halogenated product was the only major organic product detected in high yield, making this system a rare example of a nickel-mediated C–X bond formation without substantial competing side reactions.

**Table 3.6** – Oxidation of **3-9** with Brominating Oxidants (Workup C<sub>2</sub>)

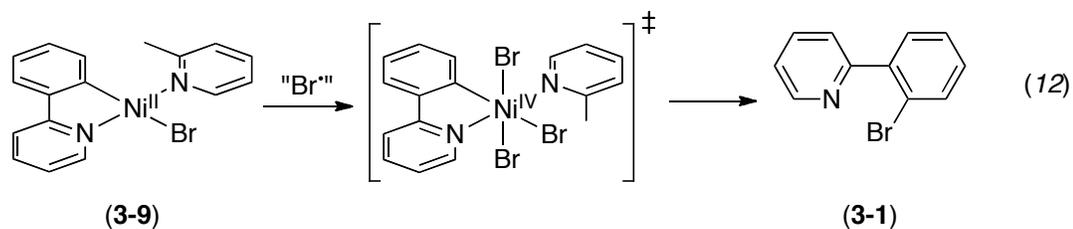
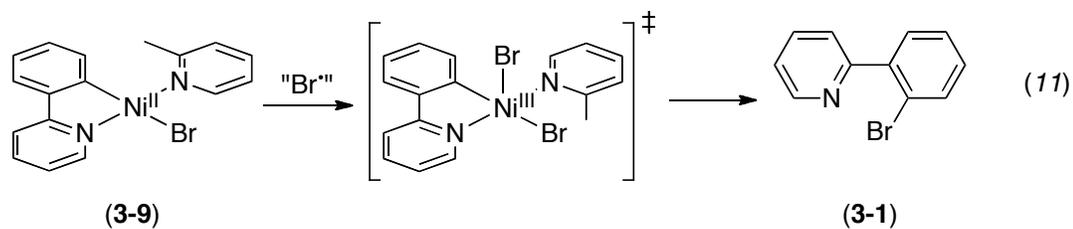
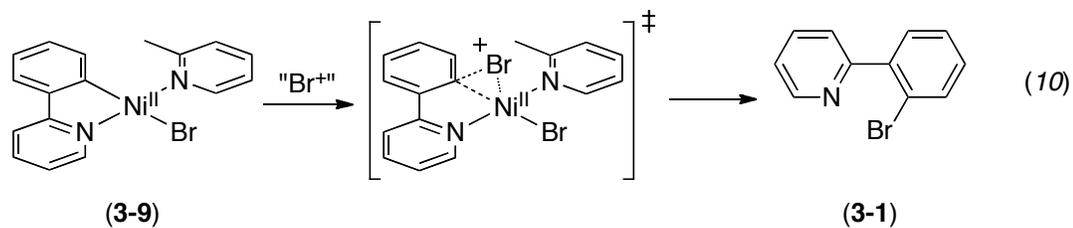


Entry	Oxidant	3-6 (Yield)	3-7 (Yield)
1	Br <sub>2</sub>	89 ± 2%	6 ± 3%
2	NBS <sup>a</sup>	67 ± 3%	12 ± 3%
3	CuBr <sub>2</sub>	79 ± 5%	4 ± 3%

<sup>a</sup>The C–N product (**3-12**) was also observed in 7% yield.

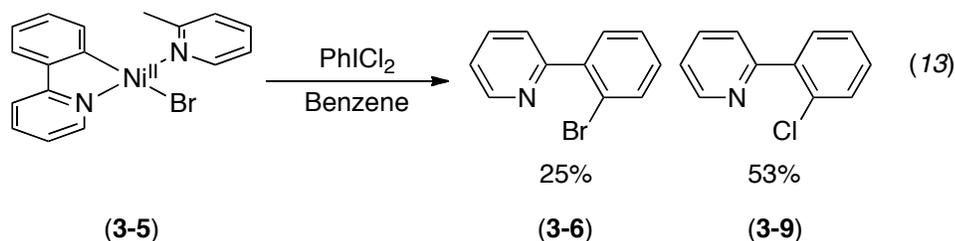
### 3.4 Mechanistic Investigation of C–X and C–C Bond Formation

With these observations in hand, we turned our investigation towards the potential mechanism of this transformation. Several mechanisms could be proposed to account for the observed reactivity of Ni<sup>II</sup>(phpy)(Pic)(Br) with these oxidants: 1) direct electrophilic cleavage of the Ni–C bond (eq. 10), 2) oxidation of the Ni<sup>II</sup> complex to a reactive and unstable Ni<sup>III</sup> intermediate followed by C–X bond-forming reductive elimination (eq. 11) or 3) oxidation to a Ni<sup>IV</sup> intermediate, followed by C–X coupling (eq. 12).



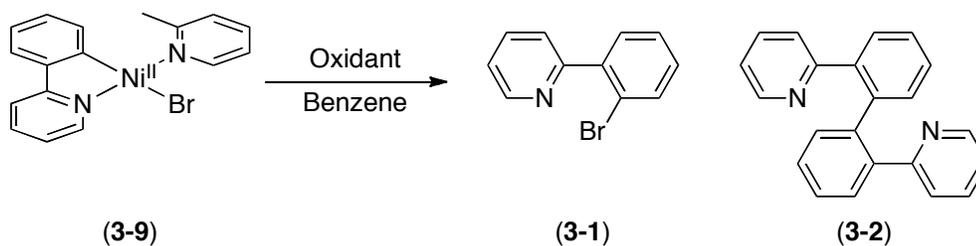
A direct electrophilic cleavage of the C–Ni bond (eq. 10) would not involve a change in metal oxidation state. Instead, only the halogen from the oxidant should be observed in the organic products. Thus, if an electrophilic mechanism were operative, only C–Cl products should be observed when  $\text{PhICl}_2$  is used and, likewise, only C–Br products should be observed when  $\text{Br}_2$  is used. When we performed experiments with competing halogens, however, (Table 3.3 and 3.4), in almost all cases we saw the incorporation of both the halogen from the metal and the halogen from the oxidant in the mixture of organic products (eq. 13).<sup>7</sup> This reactivity strongly suggests that electrophilic

cleavage is not the only mechanism for functionalization and suggests that a high oxidation state species containing both halogens may also be present.



Additionally, when outer sphere oxidants were used, we still observed the formation of **3-1** with a concomitant increase in the formation of **3-2**. Since the generation of **3-1** must be the result of incorporation of the bromide ligand from the metal, these results strongly suggest the presence of a high oxidation state intermediate that decomposes via a C–X bond-forming reductive elimination.

**Table 3.7** – Reaction of **3-9** with Non-Functionalizing Oxidants (Workup C<sub>2</sub>)

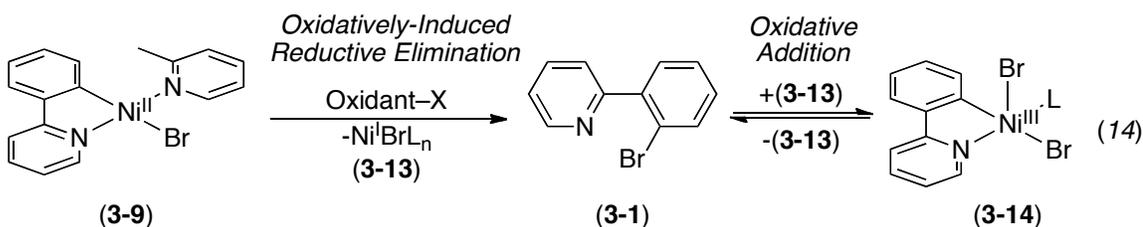


Entry	Oxidant	C–Br (Yield)	C–C (Yield)
1	(NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>	25 ± 3%	50 ± 3%
2	FeCp <sub>2</sub> (BF <sub>4</sub> )	19 ± 3%	44 ± 4%
3	benzoquinone	13 ± 3%	50 ± 3%

Having determined that electrophilic bond cleavage was likely not the sole operative mechanism, we sought further insight into the mechanism of the reaction by

investigating the origin of C–C product **3-2**. While this product was expected in our previous work with  $\text{Ni}^{\text{II}}(\text{phpy})_2$ , we were surprised to observe it in the reactions of **3-9**, given that there was only one 2-phenylpyridine ligand on the starting complex. We hypothesized that **3-2** was the result of the brominated organic product **3-1** undergoing further reactions after it formed and that this side reaction may provide insight into the nature of the reactive intermediate that is operative in this transformation.

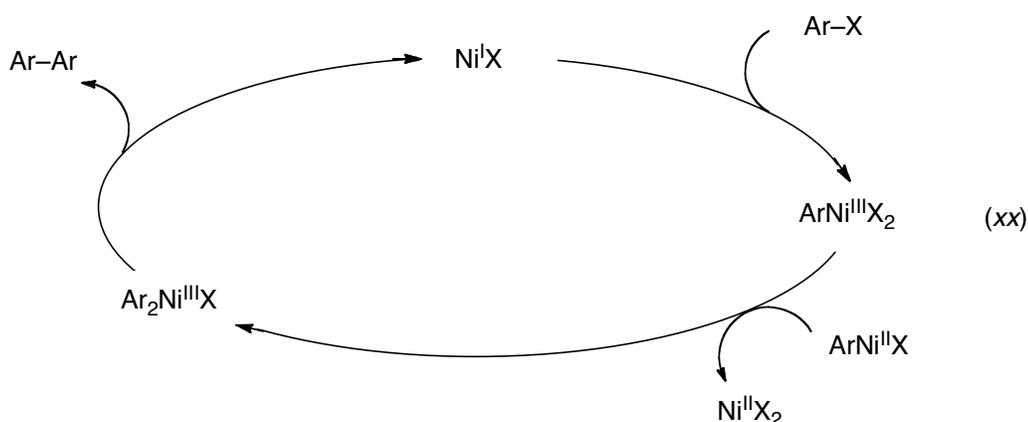
If, for example,  $\text{Ni}^{\text{I}}\text{BrL}_n$  (**3-13**), the byproduct of oxidatively-induced reductive elimination from  $\text{Ni}^{\text{III}}$ , rapidly reinserted into the C–Br bond of the organic product (**3-1**), it would generate a new  $\text{Ni}^{\text{III}}$  species (**3-14**) (eq. 14). The pyridine ligand of **3-1** could facilitate reinsertion by coordinating to the  $\text{Ni}^{\text{I}}$  byproduct. This  $\text{Ni}^{\text{III}}$  species could be present in high enough concentrations or have a long enough lifespan to undergo another reaction besides reductive elimination.



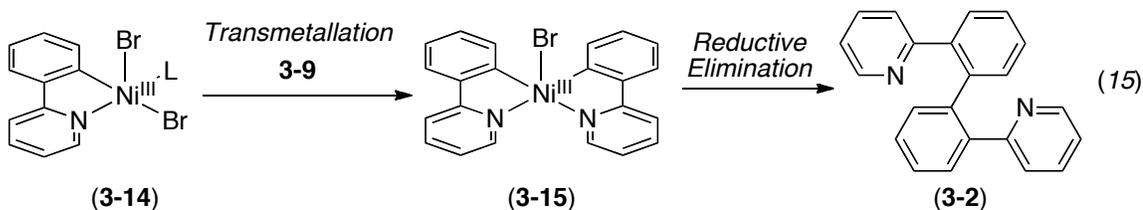
One potential pathway is transmetalation of 2-phenylpyridine from an equivalent of **3-9** to generate a bis- $\text{phpy}$   $\text{Ni}^{\text{III}}$  species (**3-15**), which could undergo C–C bond-forming reductive elimination to afford **3-2** (eq. 15). Our earlier work with  $\text{Ni}^{\text{II}}(\text{phpy})_2$ , demonstrated the instability of species **3-15** towards C–C bond-forming reductive elimination. Additionally, this type of mechanism is similar to the mechanism that Kochi proposed for Ni-mediated formation of biaryls from aryl halides (Figure 3.2).<sup>8</sup> Excess

oxidant likely helps to suppress this pathway by oxidizing the reactive Ni<sup>I</sup> species (**3-13**) to a Ni<sup>II</sup> species that is unable to insert into the C–X bond of the halogenated products.

**Figure 3.2** – Kochi Mechanism for Biaryl Coupling

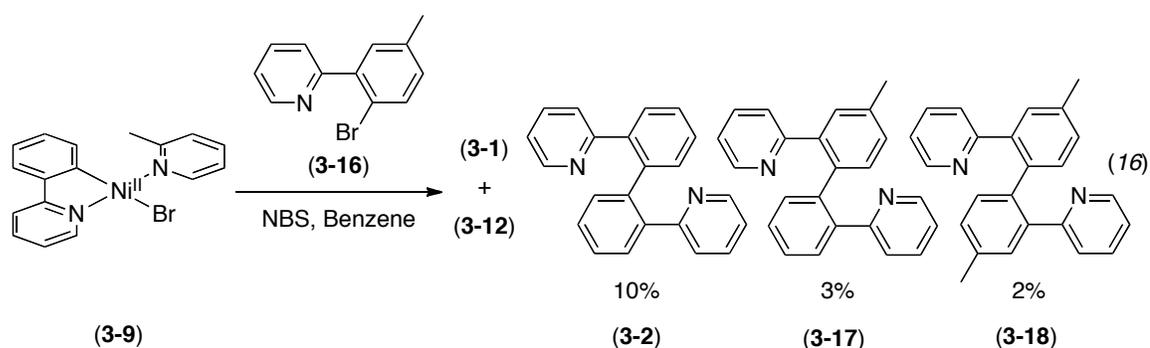


One of the key aspects of this mechanism is that it suggests the presence of Ni<sup>I</sup>, which would be formed by the reductive elimination from Ni<sup>III</sup>. In contrast, a reductive elimination from Ni<sup>IV</sup> would result in Ni<sup>II</sup>, which would not readily insert into a C–X bond.

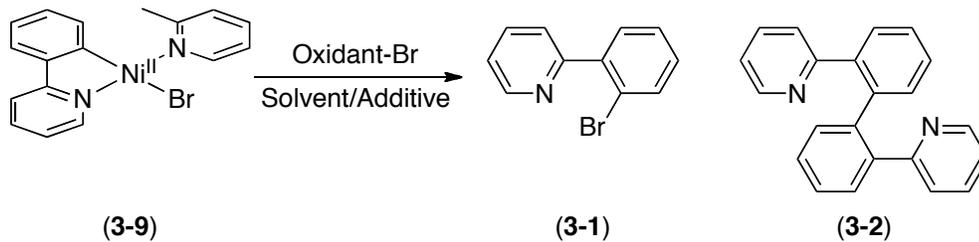


To test our proposed mechanism for C–C bond formation, we designed a crossover study to determine whether the halogenated product reinserts at the Ni<sup>I</sup> metal center. We first synthesized a methylated analogue of **3-6** (**3-16**) and then prepared a 1:1

mixture of **3-16** and **3-9** in benzene. The mixture was subjected to an oxidant (NBS) at room temperature overnight and the crude reaction was worked up using Workup B<sub>2</sub> before being analyzed by GC (eq. 6). We were excited to see incorporation of **3-16** into the mixture of products (**3-2**, **3-17**, and **3-18**)<sup>9</sup> resulting from C–C reductive elimination, validating our hypothesis that the halogenated product can reinsert at Ni<sup>I</sup> following reductive elimination.



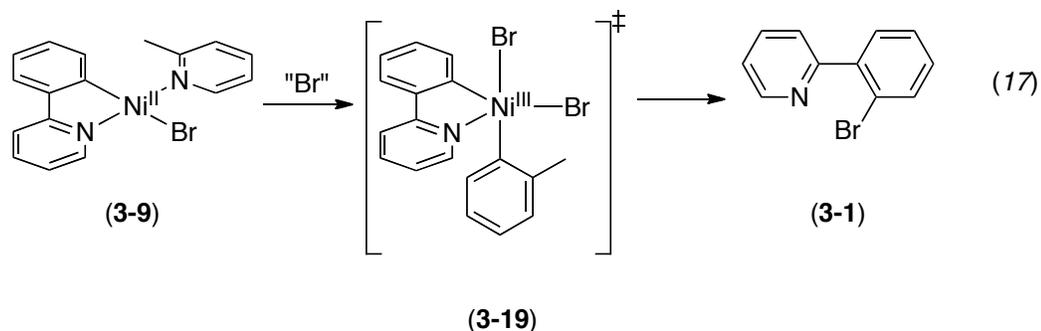
The key step of this proposed mechanism is the transmetallation that generates **3-15**. Such a transformation would require the loss of two ligands (Br<sup>-</sup> and L) from **3-14**. We thus hypothesized that the addition of an excess of one or both of these ligands would reduce the ability of the ligands to dissociate from the metal and thereby suppress the formation of **3-15** and the subsequent formation of **3-2**. Addition of 1 equiv of NBu<sub>4</sub>Br suppressed the formation of **3-2** to <5% (Table 3.8, entry 1 and 2). Gratifyingly, running the reaction in pyridine also suppressed the formation of **3-2** to <5% (Table 3.8, entry 3 and 4). These results are consistent with transmetallation between **3-9** and a transient Ni<sup>III</sup> intermediate being an operative mechanism.

**Table 3.8** – Effect of Additives on the Yield of **3-2** (Workup B<sub>2</sub>)

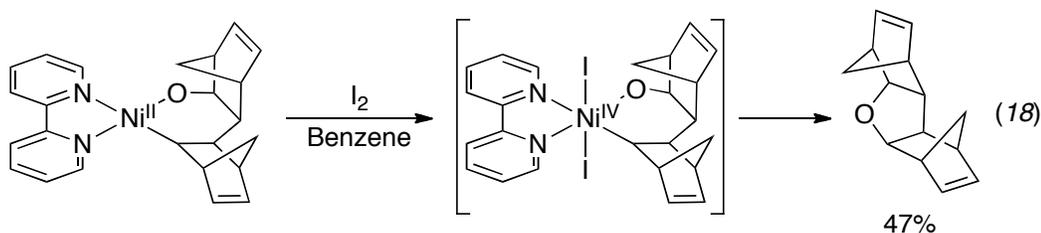
Entry	Oxidant	Solvent/Additive	C-Br (Yield)	C-C (Yield)
1	Br <sub>2</sub>	Benzene/Bu <sub>4</sub> NBr	64 ± 10%	<sup>a</sup> nd
2	NBS	Benzene/Bu <sub>4</sub> NBr	72 ± 14%	3 ± 8%
3	Br <sub>2</sub>	Pyridine	63 ± 8%	4 ± 2%
4	NBS	Pyridine	59 ± 12%	4 ± 2%

<sup>a</sup>nd = not detected

This Ni<sup>III</sup> mechanism is further supported by other evidence from these reactions. Our work with van Koten's isolable Ni<sup>III</sup> complex (**3-6**) demonstrated that C-Br bond formation is viable at Ni<sup>III</sup>. Both CuBr<sub>2</sub><sup>10</sup> and NBS<sup>3</sup> have been used to access Ni<sup>III</sup> complexes that have Ni<sup>III</sup>(Ar)(Br)<sub>2</sub> ligand arrangements, which are similar to the type of intermediate (**3-19**) that we propose to be operative in these transformations. Kochi has also proposed Ni<sup>III</sup> intermediates in the Ni-mediated formation of biaryls from aryl halides that are very similar to the intermediate (**3-15**) that we propose in the formation of the C-C coupled product (**3-2**). The current evidence, therefore, suggests that these reactions proceed through Ni<sup>III</sup> intermediate (eq. 17).

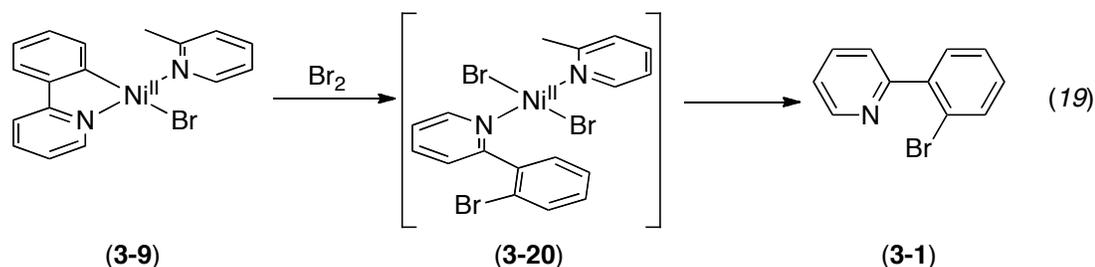


In the absence of direct observation of the intermediates, we cannot completely discount the possibility of a  $\text{Ni}^{\text{IV}}$  intermediate.  $\text{Br}_2$  can react as a two-electron oxidant.<sup>11</sup> Likewise, succinimide-based oxidants like NCS have been shown to oxidize the  $\text{Pd}^{\text{II}}$  analogue of **2-6** to  $\text{Pd}^{\text{IV}}$  via addition across the N–Cl bond and such a mechanism could be operative at  $\text{Ni}^{\text{II}}$ .<sup>12</sup> Finally, one-electron oxidation by  $\text{CuBr}_2$  to  $\text{Ni}^{\text{III}}$ , followed by disproportionation could result in a  $\text{Ni}^{\text{IV}}$  species that could undergo reductive elimination.<sup>13</sup>  $\text{Ni}^{\text{IV}}$  is not typically proposed as an intermediate in catalytic transformations, but Hillhouse has proposed it as an intermediate in stoichiometric reactions of cyclometallated Ni complexes with  $\text{I}_2$  (eq. 18).<sup>14</sup> There are also several examples of isolable  $\text{Ni}^{\text{IV}}$  complexes that can be accessed with careful selection of the ligands and oxidant.<sup>15</sup> While this mechanistic possibility cannot be definitively eliminated, we still feel that the balance of the evidence supports the  $\text{Ni}^{\text{III}}$  mechanism.



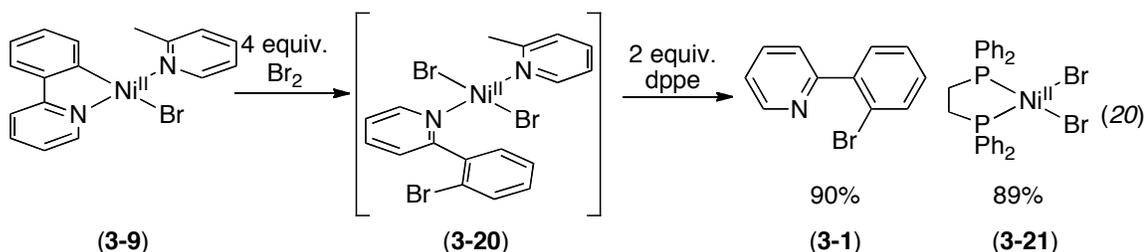
### 3.5 Identification of Inorganic Products

In the reaction of **3-9** with Br<sub>2</sub> (Table 3.9, Entry 1), we can now account for 95% of the organic products. We next investigated the nature of the inorganic byproducts generated in this reaction. Examination of the crude reaction by <sup>1</sup>H NMR spectroscopy showed very broad resonances that could be evidence of paramagnetic Ni species. These proved to be challenging to characterize. We theorized that these species were Ni<sup>II</sup>Br<sub>2</sub> salts that were ligated by the pyridine groups in the organic products and the picoline – Ni<sup>II</sup>Br<sub>2</sub>L<sub>2</sub> (**3-20**) (eq. 19).



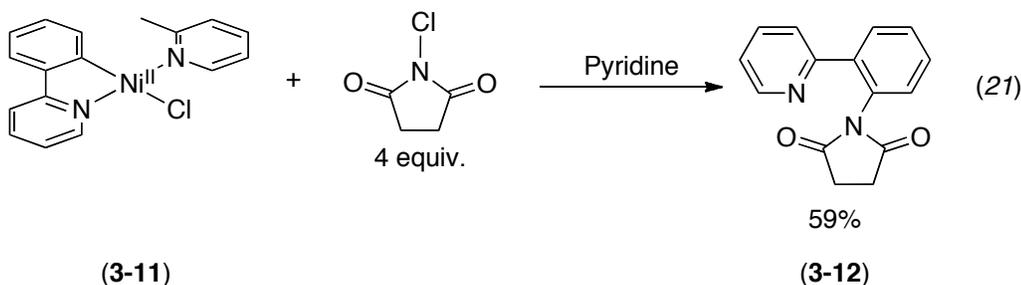
Ni<sup>II</sup> is a d<sup>8</sup> metal and can frequently take on a high-spin tetrahedral configuration that has two unpaired electrons, rendering it paramagnetic. However, the addition of strongly electron donating bidentate ligands like *bis*-diphenylphosphinoethane (dppe), can change the configuration to a low-spin, square planar geometry.<sup>16</sup> Therefore, solvent was removed from the crude reaction of **3-9** and Br<sub>2</sub> and the resulting material was dissolved in methanol before adding two equivalents of dppe. This procedure rapidly generated the desired [NiBr<sub>2</sub>(dppe)] (**3-21**) adduct. Addition of two internal standards (triphenylphosphine oxide and 1,3,5-trimethoxybenzene) and analysis by <sup>31</sup>P NMR and

$^1\text{H}$  NMR spectroscopy showed formation of **3-21** in  $89 \pm 1\%$  yield and **3-1** in  $90 \pm 3\%$  yield (eq. 20).



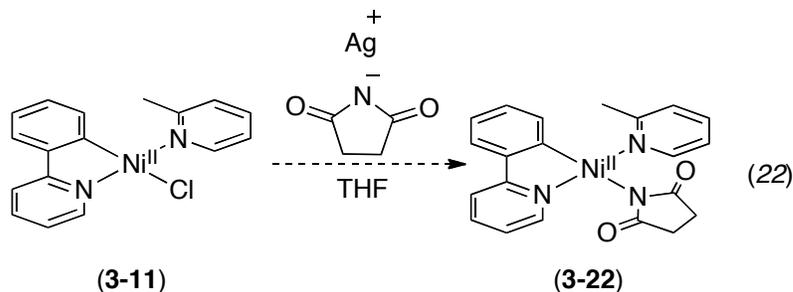
### 3.6 Investigation of C–N Product and the Succinimide-Bridged Dimer

The reactions of **3-9** with NBS also produced an unexpected third product (**3-12**, 7%), resulting from C–N bond-forming reductive elimination between the 2-phenylpyridine ligand and the succinimide. After screening different combinations of halogens on the metal, halogens on the oxidant, and solvent, the highest isolated yield (59%) of **3-12** was obtained by reacting **3-11** with four equivalents of NCS in pyridine (eq. 21).

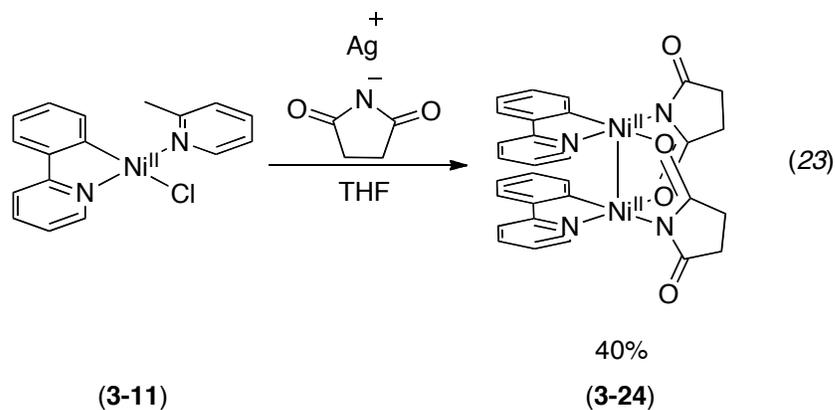


Given the unexpected nature of this product and potential utility of Ni-mediated C–N bond-forming reactions, we set out to design a system that would favor **3-12**. We

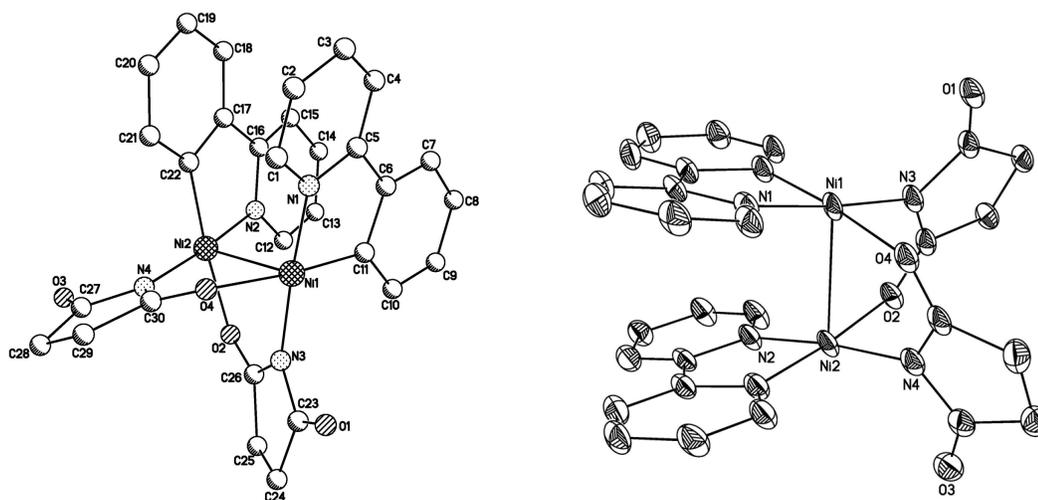
hypothesized that exchanging the halogen on the metal with a succinimide anion would generate a Ni complex containing both a 2-phenylpyridine and a succinimide ligand (**3-22**). Silver (I) succinimide (**3-23**) was synthesized by analogy to a literature preparation<sup>17</sup> and reacted with **3-11** in THF (eq. 22).



Interestingly, the desired complex **3-22** was not formed. The <sup>1</sup>H NMR spectrum of the product showed seven proton signals (8H) between 6.0 and 7.8 ppm along with an multiplet around 2.6 ppm (4H), suggesting that the new complex contained a phpy ligand and a succinimide ligand. The structure of this compound was established by X-ray crystallography (Figure 3.3). The product was determined to be a dimer containing two Ni<sup>II</sup> metal centers [Ni<sup>II</sup>(phpy)<sub>2</sub>(suc)<sub>2</sub>, **3-24**]. Each metal center of **3-24** has a cyclometallated 2-phenylpyridine ligand and one N-bound succinimide ligand. The remaining coordination site is occupied by a dative bond from an oxygen atom on the other succinimide. The bridging succinimide ligands hold the two metal centers in close proximity (2.7679 Å).



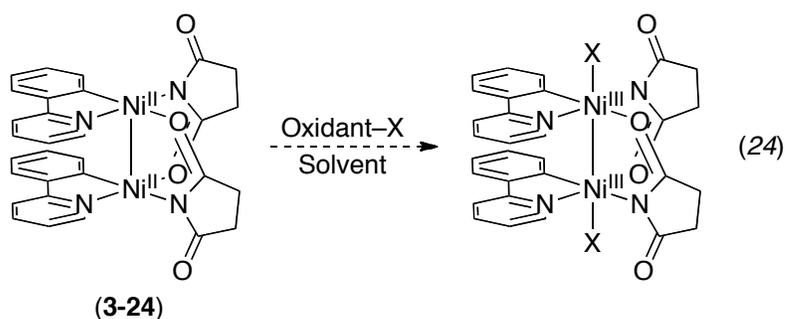
**Figure 3.3** – ORTEP View of  $[\text{Ni}^{\text{II}}(\text{phpy})_2(\text{suc})_2]$ , **3-24**



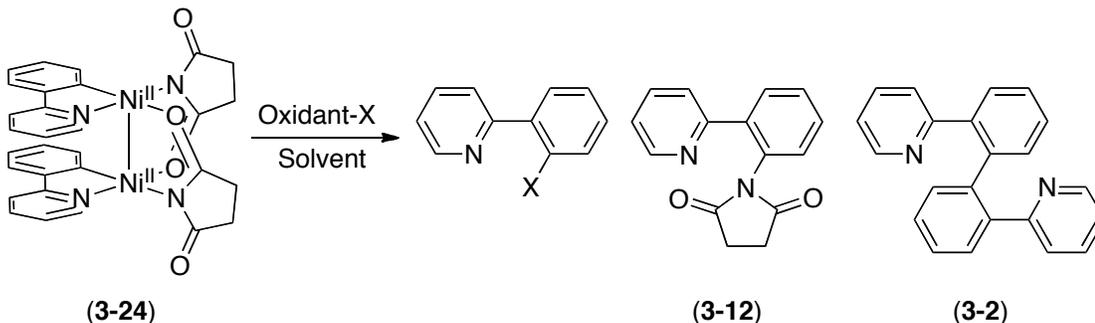
**Table 3.9** – Selected Bond Lengths (Å) and Angles (°) for **3-24**

Ni(1)–Ni(2)	2.7679(7)	N(1)–Ni(1)–C(11)	84.84(10)
Ni(1)–N(1)	1.890(2)	C(11)–Ni(1)–N(3)	94.74(10)
Ni(1)–C(11)	1.883(3)	N(3)–Ni(1)–O(4)	88.29(9)
Ni(1)–N(3)	1.893(2)	O(4)–Ni(1)–N(1)	92.46(9)
Ni(1)–O(4)	1.9693(19)	C(22)–Ni(2)–N(2)	84.68(11)
Ni(2)–N(2)	1.896(2)	N(2)–Ni(2)–O(2)	92.78(9)
Ni(2)–C(22)	1.882(3)	O(2)–Ni(2)–N(4)	88.98(9)
Ni(2)–N(4)	1.887(2)	N(4)–Ni(2)–C(22)	93.95(11)
Ni(2)–O(2)	1.9833(19)		

Other dimeric structures of group 10 metals have been found to stabilize unusual oxidation states like Pd<sup>III</sup>.<sup>18</sup> Thus, we envisioned that **3-24** might be converted into an analogous Ni<sup>III</sup> structure if exposed to an appropriate oxidant (eq. 24). **3-24** was reacted with both PhICl<sub>2</sub> and Br<sub>2</sub>; both of these oxidants could be a source of halogen radicals that could oxidize each metal center to Ni<sup>III</sup>.



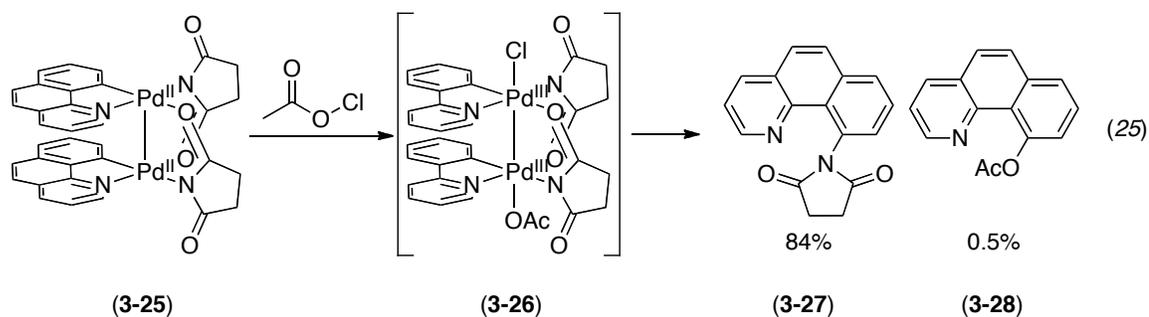
However, no stable Ni<sup>III</sup> complexes were observed by <sup>1</sup>H NMR or EPR spectroscopy. Instead, a variety of functionalized organic products were detected. The vast majority of the products were halogenated 2-phenylpyridine with only trace amounts (<15%) of the C–N product (**3-12**) observed (Table **3.10**).

**Table 3.10** – Oxidation of **3.24** with PhICl<sub>2</sub> and Br<sub>2</sub> (Workup B<sub>2</sub>)<sup>19</sup>

Entry	Oxidant	Solvent	C-X (Yield)	C-N (Yield)	C-C (Yield)
1	PhICl <sub>2</sub>	Benzene	72%	3%	<sup>a</sup> nd
2	PhICl <sub>2</sub>	Acetone	79%	<sup>a</sup> nd	<sup>a</sup> nd
3	PhICl <sub>2</sub>	Pyridine	82%	14%	<sup>a</sup> nd
4	Br <sub>2</sub>	Benzene	71%	2%	1%
5	Br <sub>2</sub>	Acetone	63%	<sup>a</sup> nd	5%
6	Br <sub>2</sub>	Pyridine	64%	9%	<sup>a</sup> nd

<sup>a</sup>nd = not detected

Ritter has isolated an analogous Pd complex using benzo[*h*]quinoline as the cyclometallating ligand (**3-25**). A Pd<sup>III</sup> species (**3-26**) was generated by oxidation with acetyl hypochlorite and this compound was detected by low temperature <sup>1</sup>H NMR spectroscopy. Warming **3-26**, however, resulted almost exclusively in C–Cl (**3-27**) bond-forming reductive elimination with only trace amounts of C–O product (**3-28**) and no observed C–N product (eq. 25). On the basis of this precedent and our own work with the monomeric Ni<sup>II</sup> complexes, we suspect that our transformation is also going through a high oxidation state intermediate. The dimeric structure, however, is not capable of stabilizing these Ni<sup>III</sup> species enough to be isolated or observed.



### 3.7 Conclusions

Our studies have demonstrated the first example of Ar–Br bond formation from the isolable Ni<sup>III</sup> complex (**3-6**). This complex undergoes conversion to the organic C–Br product (**3-7**) in low yields under forcing conditions. We also designed [Ni<sup>II</sup>(phpy)(Br)(pic), (**3-9**)] which underwent selective C–X bond formation in the presence of various oxidants. By rationally designing complex **3-9** that has only one cyclometallated 2-phenylpyridine ligand as opposed to complex **2-6** that has two 2-phenylpyridine ligands, we were able to minimize the C–C product. Upon oxidation of complex **3-9** with NBS or NCS, we observed a rare example of C–N bond formation. Interestingly, we were able to enhance or suppress this product depending on optimized conditions. Efforts to generate a monomeric Ni<sup>II</sup> complex containing the succinimide anion as an X-type ligand instead resulted in the formation of a succinimide-bridged bimetallic dimer (**3-24**). Oxidation of **3-24** did not result in the formation of an isolable Ni<sup>III</sup> complex. Instead a variety of functionalized organic products were formed. We propose that all of these reactions proceed through Ni<sup>III</sup> and/or Ni<sup>IV</sup> intermediates via an oxidatively-induced reductive elimination mechanism.

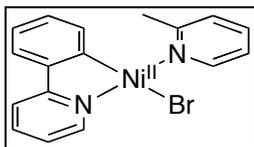
### 3.8 Experimental Procedures

**General Considerations.** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for  $^1\text{H}$ ; 125.70 MHz for  $^{13}\text{C}$ ), a Varian Inova 400 (399.96 MHz for  $^1\text{H}$ ; 100.57 MHz for  $^{13}\text{C}$ ; 376.34 MHz for  $^{19}\text{F}$ ), or a Varian Mercury 300 (300.07 MHz for  $^1\text{H}$  NMR, 75.45 MHz for  $^{13}\text{C}$ ) spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br).

**Materials and Methods.** 2-(2-Bromophenyl)pyridine and 2-(2-Chlorophenyl)pyridine were synthesized according to a literature procedure.<sup>20</sup>  $\text{Ni}^0(\text{COD})_2$  was purchased from Strem, stored in a glovebox at  $-35\text{ }^\circ\text{C}$ , and used without further purification. Tetrahydrofuran and pentanes were purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. Benzene, pyridine, and 2-picoline were distilled from  $\text{CaH}_2$ , and acetone was distilled from anhydrous calcium sulfate. Copper bromide,  $\text{Ce}^{\text{IV}}(\text{NH}_4)_2(\text{NO}_3)_6$ , and *N*-iodosuccinimide were purchased from General Chemical Company, Acros, and Aldrich, respectively, and dried under vacuum at  $100\text{ }^\circ\text{C}$  overnight. NBS and NCS (Acros) were recrystallized from boiling water and benzene respectively, dried under vacuum overnight, and stored in a glovebox.  $\text{PhICl}_2$  was prepared via a modification of a literature procedure<sup>21</sup> and was stored at  $-35\text{ }^\circ\text{C}$  in a glovebox.  $\text{Br}_2$  and  $\text{I}_2$  (sublimed) were purchased from Aldrich and Acros, respectively, and were used without further

purification. Ferrocenium tetrafluoroborate was prepared according to literature procedure.<sup>22</sup> Microwave heating was carried out with a CEM Discovery microwave reactor. The microwave reactions were run in closed reaction vessels with magnetic stirring and with the temperature controlled via IR detection.

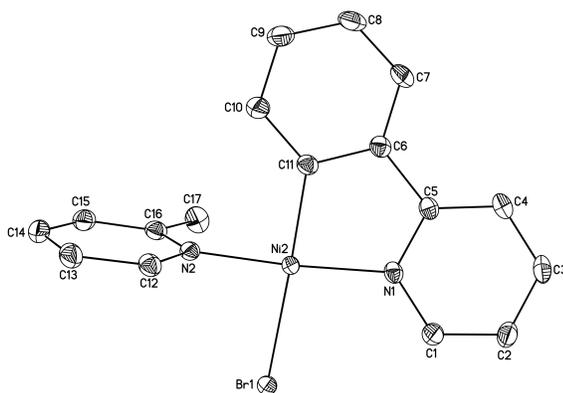
Gas chromatography was performed on a Shimadzu GC-17A equipped with a Restek Rtx®-5 column (15 m, 0.25 mm ID, 0.25 m df) and a flame ionization detector. The reported yields in all oxidation reactions represent the average of at least two independent trials. Authentic samples of each of the oxidation products **3.7**,<sup>23</sup> **3.1** (bromo-phpy),<sup>24</sup> **3.2** (C-C),<sup>25</sup> and **3.9** (Cl-phpy)<sup>26</sup> were prepared using literature methods. The iodinated product (2-(2-iodophenyl)pyridine) was prepared from **3-1** by lithium/halogen exchange followed by a quench with I<sub>2</sub>, using a modification of a literature procedure.<sup>27</sup>



**(2-picoline)(2-(2'-pyridyl)phenyl) Nickel (II) Bromide (3-9).**

Ni(COD)<sub>2</sub> (0.200 g, 0.73 mmol, 1.0 equiv) was dissolved in THF (10 mL) in a dry 20 mL scintillation vial. In a second 4 mL vial, 2-(2-bromophenyl)pyridine (0.201 g, 0.90 mmol, 1.2 equiv) and 2-picoline (0.083 g, 0.89 mmol, 1.2 equiv) were also dissolved in THF (2.0 mL). Both vials were placed in a freezer (-35 °C) for 12 h. Upon removal, the clear ligand solution was added to the yellow Ni(COD)<sub>2</sub> slurry, and the mixture was allowed warm to room temperature with stirring. The reaction gradually turned a deep orange color. After warming, the solvent was removed under vacuum, and the resulting yellow solid was dissolved in acetone (20 mL) and filtered through a plug of Celite. Pentanes (100 mL) was added to the clear

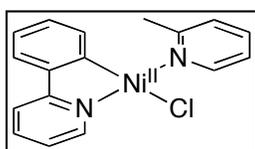
yellow filtrate, and this solution was cooled to  $-35$  oC overnight. The resulting yellow precipitate was collected on a fritted filter, washed with cold pentane (20 mL), and dried under vacuum to afford the product as a yellow microcrystalline solid (0.1828 g, 65% yield). Slow diffusion of pentanes into a benzene solution generated X-ray quality crystals and the structure was confirmed by X-ray crystal structure.  $^1\text{H}$  NMR (500 MHz, benzene- $d_6$ ):  $\delta$  10.01 (dd,  $J = 6$  Hz, 1 Hz, 1H), 9.00 (d,  $J = 5$  Hz, 1H), 7.05 (dd,  $J = 8$  Hz, 1 Hz, 1H), 6.94 (td,  $J = 8$  Hz, 1 Hz, 1H), 6.80-6.68 (multiple peaks, 3H), 6.59 (td,  $J = 8$  Hz, 2 Hz, 1H), 6.32 (d,  $J = 8$  Hz, 1H), 6.21 (t,  $J = 7$  Hz, 1H), 6.17 (ddd,  $J = 7$  Hz, 6 Hz, 2 Hz, 1H), 5.32 (dd,  $J = 8$  Hz, 1 Hz, 1H), 3.39 (s, 3H).  $^{13}\text{C}$  NMR (400 MHz, benzene- $d_6$ ):  $\delta$  164.07, 159.69, 155.43, 151.31, 150.62, 146.90, 137.58, 135.65, 133.70, 128.74, 124.82, 124.64, 121.78, 121.23, 120.81, 116.57, 26.84. Anal. Calc. for  $\text{C}_{17}\text{H}_{15}\text{BrN}_2\text{Ni}$ : C, 52.91, H, 3.92, N, 7.26; Found: C, 52.62, H, 4.01, N, 7.26.



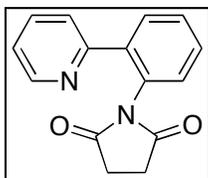
**Figure 3.4** – ORTEP View of  $[\text{Ni}^{\text{II}}(\text{phpy})(\text{Pic})(\text{Br})]$  (**3-9**)

**Table 3.11** – Selected Bond Lengths (Å) and Angles (°) for **3-9**

Ni(2)-C(11)	1.8944(15)	C(11)-Ni(2)-N(1)	84.36(6)
Ni(2)-N(1)	1.9168(13)	N(1)-Ni(2)-Br(1)	97.27(4)
Ni(2)-Br(1)	2.4035(3)	Br(1)-Ni(2)-N(2)	87.54(4)
Ni(2)-N(2)	1.8894(13)	N(2)-Ni(2)-C(11)	91.19(6)

**(2-picoline)(2-(2'-pyridyl)phenyl) Nickel (II) Chloride (3-11).**

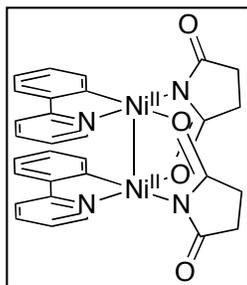
Ni(COD)<sub>2</sub> (0.200 g, 0.73 mmol, 1.0 equiv) was dissolved in THF (10 mL) in a dry 20 mL scintillation vial. In a second 4 mL vial, (2-chlorophenyl)pyridine (0.201 g, 0.90 mmol, 1.2 equiv) and 2-methylpyridine (0.083 g, 0.89 mmol, 1.2 equiv) were also dissolved in THF (2.0 mLs). Both vials were placed in the freezer (-35 °C) for several hours. Upon removal, the clear ligand solution was added to the yellow Ni<sup>0</sup>(COD)<sub>2</sub> slurry, and the mixture was allowed warm to room temperature with stirring. The reaction gradually turned a deep orange color. After warming, the solvent was removed under vacuum, and the resulting yellow material was dissolved in acetone (~20 mLs) and filtered through a plug of Celite. Pentanes (~100 mLs) was added to the clear yellow filtrate, and this solution was cooled to -35 °C overnight. The resulting yellow, microcrystalline solid was collected on a fritted filter, washed with cold pentanes (20 mLs), and dried under vacuum to afford the product as a yellow solid (0.1828 g, 65% yield). <sup>1</sup>H NMR (500 MHz, benzene-*d*<sub>6</sub>): δ 9.80 (ddd, *J* = 6.0, 2.0, 1.0 Hz, 1H), 9.00 (dd, *J* = 6.0, 1.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.95 (td, *J* = 8.0, 1.0 Hz, 1H), 6.77 (m, 3H), 6.59 (td, *J* = 8.0, 2.0, 1H), 6.31 (d, *J* = 8.0 Hz, 1H), 6.22 (m, 2H), 5.45 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.41 (s, 3H). <sup>13</sup>C NMR (400 MHz, benzene-*d*<sub>6</sub>): δ 164.40, 159.77, 153.17, 151.12, 150.38, 146.93, 137.63, 135.62, 134.33, 128.68, 124.65, 124.46, 121.71, 120.89, 120.77, 116.41, 26.67. Anal. Calc. For C<sub>17</sub>H<sub>15</sub>BrN<sub>2</sub>Ni: C, 59.80, H, 4.43, N, 8.20; Found: C, 59.85, H, 4.48, N, 8.00.



**1-(2-(pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (3-12).** Ni<sup>II</sup> complex

**3-11** (0.1038 g, 0.304 mmol, 1.00 equiv) and NCS (0.1575 g, 1.18 mmol, 3.88 equiv) were mixed with pyridine (15 mL) in a dry 20 mL

scintillation vial and stirred overnight with a magnetic stirbar. The next morning the pyridine was removed under vacuum. The resulting material was taken up in benzene and several scoops of PVP were added and stirred for several hours. The mixture was then filtered through a plug of basic alumina, which was then flushed with acetone (50 mLs). The solvent was removed from the filtrate via rotovap and the crude material was purified by column chromatography on silica gel with a solvent system of 30:70 hexanes:ethyl acetate (0.0767 g, 59% yield). <sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>): δ 8.78 (ddd, *J* = 5.0, 2.0, 1.0, 1H), 7.83 (td, *J* = 8.0, 2.0 Hz, 1H), 7.76 (dd, *J* = 7.0, 2.0), 7.58-7.52 (m, 3H), 7.31-7.28 (m, 2H), 2.80-2.62 (m, 4H).



**bis-(2-(2'pyridyl)phenyl) Nickel (II) Disuccinimide-Bridged**

**Dimer (3-24).** Ni<sup>II</sup> complex **3-11** (0.0253 g, 0.074 mmol, 1.0 equiv) and silver succinimide (0.0154 g, 0.075 mmol, 1.01 equiv) were dissolved in THF (15 mL) in a dry 20 mL scintillation vial. Upon

mixing, the solution immediately turned a dark orange-red color with a white-grey solid crashing out. After three hours of stirring, there was no visible change in appearance. The THF was removed under vacuum and the resulting reddish-white material was taken up in acetone before being filtered through a plug of Celite. The resulting clear red filtrate was mixed with a large excess of pentanes and placed in the freezer to crystallize. The next morning the red crystalline powder was filtered out on a medium frit and dried under

vacuum (0.0299g, 40% yield). The red solid was analyzed by  $^1\text{H}$  NMR. Slow diffusion of pentanes into a THF solution resulted in X-ray quality crystals and the structure was confirmed by X-ray crystal structure.  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ):  $\delta$  7.60 (ddd,  $J = 5.6, 1.6, 0.8$  Hz, 2H), 7.49 (8.0, 7.6, 1.6 Hz, 2H), 7.20 (d,  $J = 8.0$  Hz, 2H), 6.87 (dd,  $J = 7.6, 1.2$  Hz, 2H), 6.61 (m, 4H), 6.47 (td,  $J = 7.6, 1.2$  Hz, 2H), 6.12 (dd,  $J = 8.0, 0.8$  Hz, 2H), 2.68-2.49 (m, 8H).

**Thermally-Induced Reductive Elimination from 3-xx (van Koten complex) via Oil Bath Heating.** On the benchtop,  $\text{Ni}^{\text{III}}$  complex **3-6** (0.0050 g, 0.012 mmol) was weighed into a 4 mL vial and dissolved in pyridine (2.0 mL). The vial was equipped with a magnetic stir bar and sealed with a Teflon-lined cap, and the resulting mixture was submerged (>95%) in an oil bath at 150 °C for 12 h. No solvent loss was observed in the course of the reaction. The reaction mixture was cooled to room temperature, and poly-4-vinylpyridine (0.0300 g) was added to displace coordinated organic products and to sequester Ni by-products. The resulting heterogeneous mixture was stirred for 1 h and filtered through a plug of Celite. The plug was flushed with acetone (10 mL), a standard (nonadecane) was added and the reaction was analyzed by gas chromatography, which showed formation of brominated product **3-7** in  $16 \pm 3\%$  yield.

**Thermally-Induced Reductive Elimination from 3-6 (van Koten complex) via Microwave Heating.** On the benchtop,  $\text{Ni}^{\text{III}}$  complex **3-6** (0.0050 g, 0.012 mmol) was weighed into a microwave test tube and dissolved in pyridine (2.0 mL). The tube was equipped with a magnetic stir bar and sealed with a Teflon lined cap, and the reaction

mixture was heated in the microwave at 150 °C for 500 min (150 W, 150 °C, 500 min, 2 min ramp). The reaction mixture was cooled to room temperature, and poly-4-vinylpyridine (0.0300 g) was added to displace coordinated organic products and sequester the Ni by-products. The resulting heterogeneous mixture was stirred for 1 h and filtered through a plug of Celite. The plug was flushed with acetone (10 mL), a standard (nonadecane) was added and the reaction was analyzed by gas chromatography, which showed formation of brominated product **3-7** in  $32 \pm 3\%$  yield.

**Reaction of 3-9 with CuBr<sub>2</sub>, (NH<sub>4</sub>)<sub>2</sub>[Ce<sup>IV</sup>(NO<sub>3</sub>)<sub>6</sub>], Cp<sup>2</sup>Fe<sup>+</sup>, NIS, or I<sub>2</sub>.** In a glovebox, complex **3-9** (10.0 mg, 0.026 mmol, 1.0 equiv) and oxidant (0.104 mmol, 4.0 equiv) were suspended in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar, sealed with a Teflon lined cap, and the reaction mixture was stirred at room temperature for 12 h. The vial was removed from the drybox, and the solvent was then removed under vacuum. The resulting material was taken up in CH<sub>2</sub>Cl<sub>2</sub> (12 mL), and the CH<sub>2</sub>Cl<sub>2</sub> solution was extracted with a 1.0 M aqueous solution of sodium citrate (3 x 10 mL), a saturated aqueous solution of sodium thiosulfate (2 x 10 mL), and deionized water (2 x 10 mL). The organic layer was collected, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated under vacuum, a standard (1,3,5- trimethoxybenzene) was added, and the reaction was analyzed by <sup>1</sup>H NMR spectroscopy.

**Reaction of 3-9 with Br<sub>2</sub> (analysis of organic products).** In a glovebox, complex **3-9** (10.0 mg, 0.026 mmol, 1.0 equiv) was dissolved in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar, sealed with a rubber septum, and removed

from the glovebox. Br<sub>2</sub> (5 μL, 3.8 equiv) was added via microsyringe, and the reaction was stirred for 12 h at room temperature. The volatiles were then removed under vacuum. The resulting material was taken up in CH<sub>2</sub>Cl<sub>2</sub> (12 mL), and the CH<sub>2</sub>Cl<sub>2</sub> solution was extracted with 1.0 M aqueous solution of sodium citrate (3 x 10 mL), a saturated aqueous solution of sodium thiosulfate (2 x 10 mL), and deionized water (2 x 10 mL). The organic layer was collected, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated under vacuum, a standard (1,3,5-trimethoxybenzene) was added, and the reaction was analyzed by <sup>1</sup>H NMR spectroscopy.

**Reaction of 3-9 with Br<sub>2</sub> (analysis of organic and inorganic products).** In a glovebox, complex **3-9** (10.0 mg, 0.026 mmol, 1.0 equiv) was dissolved in the benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar, sealed with a Teflon septum, and removed from the glovebox. Br<sub>2</sub> (5 μL, 3.8 equiv) was added via microsyringe, and the reaction was stirred for 12 h at room temperature. The volatiles were removed under vacuum, and the resulting residue was dissolved in MeOH (1.0 mL). A solution of diphenylphosphinoethane (dppe) (0.0417 g, 0.105 mmol, 4.0 equiv) in toluene (1.0 mL) was added, and the resulting red solution was stirred for 1 h. The solvent was removed under reduced pressure, and mixture was characterized by <sup>1</sup>H and <sup>31</sup>P NMR spectroscopy. The yield of **3-21** was determined to be 89% based on integration of the <sup>31</sup>P NMR spectrum relative to a standard (triphenylphosphine oxide). The yield of **3-1** was determined to be 90 ± 3% based on integration of the <sup>1</sup>H NMR spectrum relative to a standard (1,3,5-trimethoxybenzene).

**Reaction of 3-9 with PhICl<sub>2</sub>.** In a glovebox, complex **3-9** (10.0 mg, 0.026 mmol, 1.0 equiv) and PhICl<sub>2</sub> (28.5 mg, 0.104 mmol, 4.0 equiv) were dissolved in benzene (2 mL) in a 4 mL vial. The vial was equipped with a magnetic stir bar, sealed with a Teflon-lined cap, and the reaction mixture was stirred for 12 h at room temperature. Poly-4-vinylpyridine (0.0300 g) was added to displace coordinated organic products and sequester Ni by-products. The resulting heterogeneous mixture was stirred for 1 h, and the reaction was filtered through a plug of Celite. The plug was flushed with acetone (10 mL), the filtrate was concentrated under vacuum, a standard (nonadecane) was added, and the reaction was analyzed by gas chromatography. The yield of this reaction was confirmed by <sup>1</sup>H NMR.

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<sup>1</sup> For examples, see: a) Fahey, D. R.; Mahan, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 2501. b) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319. c) Ceder, R. M.; Granell, J.; Muller, G.; Font-Bardía, M.; Solans, X. *Organometallics*, **1995**, 5544. d) Ceder, R. M.; Granell, J.; Muller, G.; Font-Bardía, M.; Solans, X. *Organometallics*, **1996**, 4618.

<sup>2</sup> Coronas, J. M.; Muller, G.; Rocamora, M. *J. Organomet. Chem.* **1986**, *301*, 227.

<sup>3</sup> Grove, D. M.; van Koten, G.; Mul, P.; Zoet, R.; van der Linden, J. G. M.; Legters, J.; Schmitz, J. E. J.; Murrall, N. W.; Welch, A. J. *Inorg. Chem.* **1988**, *27*, 2466.

<sup>4</sup> For examples, see: a) Fahey, D. R. *J. Organomet. Chem.* **1971**, *27*, 283. b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. c) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. d) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. e) Mei, T.-S.; Giri, R.; Mangel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215.

<sup>5</sup> Ceder, R. M.; Granell, J.; Muller, G.; Font-Bardía, M.; Solans, X. *Organometallics*, **1995**, 5544.

<sup>6</sup> The yield of Entry 1 was corrected using Workup C<sub>2</sub>. All other entries were obtained using Workup B<sub>2</sub>.

<sup>7</sup> This data was obtained using Workup C<sub>2</sub>.

<sup>8</sup> Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319.

<sup>9</sup> These reactions were worked up using Workup B<sub>2</sub> and analyzed by GC, using the calibration curve for **3-7**.

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<sup>11</sup> Lorkovic, I. M.; Noy, M. L.; Schenck, W. A.; Belon, C.; Weiss, M.; Sun, S.; Sherman, J. H.; McFarland, E. W.; Stucky, G. D.; Ford, P. C. *Catalysis Today* **2004**, *98*, 589.

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- <sup>12</sup> Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.
- <sup>13</sup> For recent examples of isolable Ni<sup>IV</sup> complexes, see: a) Klein, H. F.; Bickelhaupt, A.; Jung, T.; Cordier, G. *Organometallics* **1994**, *13*, 2557. b) Dimitrov, V.; Linden, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 26.
- <sup>14</sup> Koo, K.; Hillhouse, G. L. *Organometallics* **1998**, *17*, 2924.
- <sup>15</sup> (a) Koo, K.; Hillhouse, G. L. *Organometallics* **1998**, *17*, 2924. (b) Klein, H.-F.; Bickelhaupt, A.; Jung, T.; Cordier, G. *Organometallics* **1994**, *13*, 2557.
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- <sup>19</sup> These reactions were each performed a single time.
- <sup>20</sup> Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M.S. *Tetrahedron* **2006**, *62*, 11483.
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- <sup>25</sup> Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047.
- <sup>26</sup> Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M.S. *Tetrahedron* **2006**, *62*, 11483.
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## Chapter 4

# Further Attempts Toward High Oxidation State Nickel Complexes

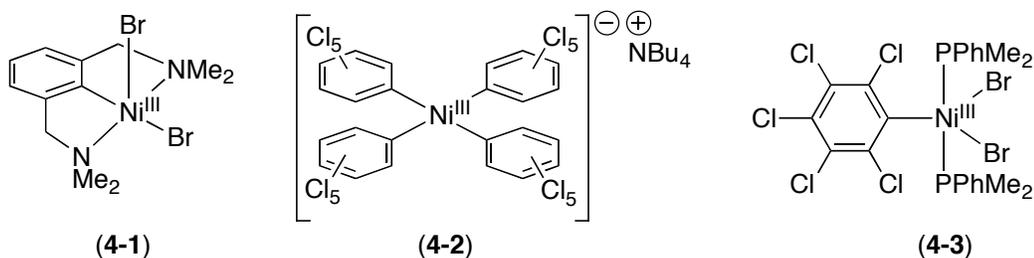
### 4.1 Introduction

The Sanford Group and others have demonstrated the viability of high oxidation state Pd complexes in mediating the formation of C–X bonds. While this research has been quite successful, we sought to extend this strategy to Ni, which is a substantially cheaper metal, hypothesizing that we might also discover new modes of reactivity. The desired strategy was to synthesize and isolate high oxidation state organometallic Ni complexes. Once the complexes were in hand, reductive elimination would be thermally induced, allowing us to study the viability of Ni to mediate C–X bond formation via high oxidation state species.

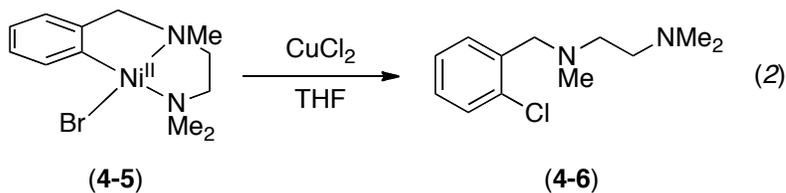
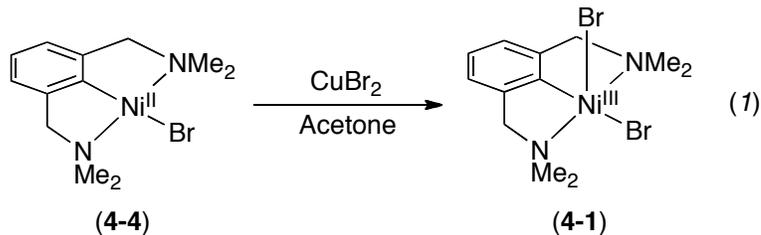
High oxidation state Ni complexes were not isolated using the strategies that are effective with Pd and Pt. By examining other strategies that had been previously employed at Ni, we sought to design a unique ligand set that would allow for the synthesis and isolation of a stable high oxidation state Ni<sup>III</sup> organometallic complex. The literature contains limited examples of isolated or directly observed Ni<sup>III</sup> organometallic

complexes, but none of these examples were suitable for studying C–X bond reductive elimination. Three examples, however, suggested two different strategies that could be used to stabilize Ni<sup>III</sup> complexes (Figure 1).<sup>1</sup> The first was to use a rigid, multi-dentate chelating ligand to occupy several coordination sites and the second was to use ligands that would not easily reductively eliminate.

**Figure 4.1.** Examples of Previously Isolated or Observed Ni<sup>III</sup> Complexes.

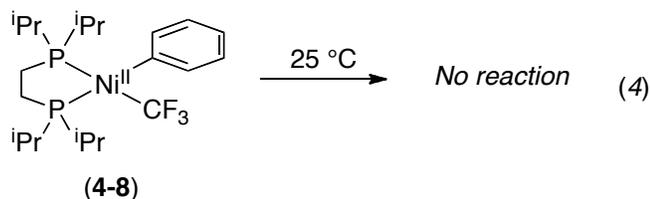
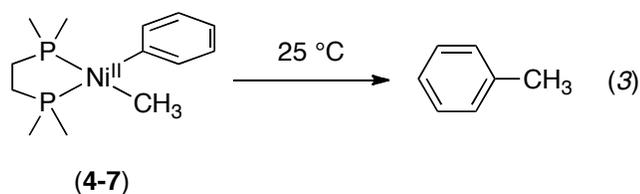


Van Koten and coworkers successfully used a multi-dentate pincer ligand to isolate Ni<sup>III</sup> complex **4-1** (eq. 1). A key feature of this ligand is that the X-type carbon is between two L-type nitrogen atoms, making reductive elimination pathways involving that carbon difficult to access. When the carbon is not protected by adjacent L-type ligands reductive elimination is much more facile. For example, Muller and coworkers synthesized Ni<sup>II</sup> complex **4-6**. This complex involves a C–N–N ligand, which is similar to van Koten's N–C–N ligand but with a different relative arrangement of the carbon and nitrogen ligands. Unlike oxidation of **4-4**, however, oxidation does not result in a stable Ni<sup>III</sup> complex, but rather oxidatively-induced reductive elimination of a C–Cl bond (eq. 2).<sup>2</sup> These results indicate that sterically protecting X-type ligands provides a large measure of stability.

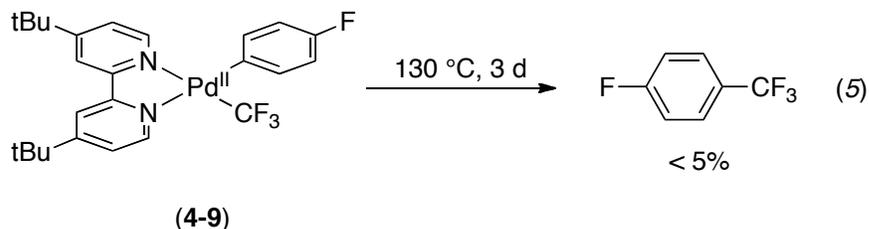


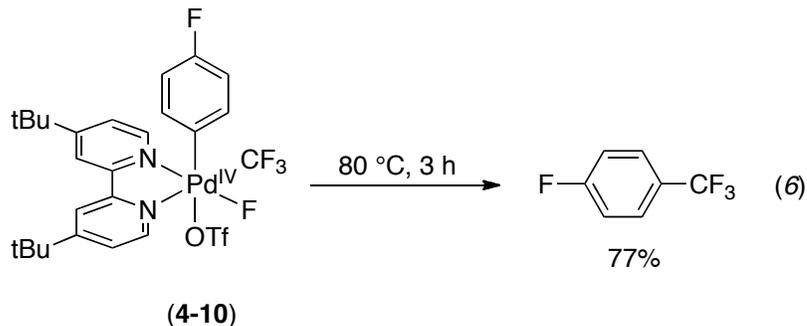
Our second strategy to isolate a stable Ni<sup>III</sup> complexes was to use monodentate and bidentate ligands that do not readily reductively eliminate. Rodríguez<sup>3</sup> and Wada<sup>4</sup> demonstrated that perhalogenated aryl groups are capable of stabilizing Ni<sup>III</sup> metal centers, allowing for the low-temperature observation and isolation of the first homoleptic Ni<sup>III</sup> complex (**4-2**) and for the isolation of a Ni<sup>III</sup> complex with no chelating ligands (**4-3**) (Figure 4.1).

Additionally, trifluoromethyl groups have been demonstrated to be resistant to reductive elimination. For example, Ar-CH<sub>3</sub> bonds are readily formed via reductive elimination from Ni<sup>II</sup>(Ph)(CH<sub>3</sub>)(dmpe) [dmpe = 1,2-*bis*-(dimethylphosphino)ethane] (**4-7**) at room temperature (eq. 3).<sup>5</sup> In contrast, an analogous complex Ni<sup>II</sup>(Ph)(CF<sub>3</sub>)(dipe) [dipe = 1,2-*bis*-(diisopropylphosphino)ethane] (**4-8**) is quite stable to reductive elimination under similar conditions and no Ar-CF<sub>3</sub> bond formation is reported (eq. 4).<sup>6</sup>



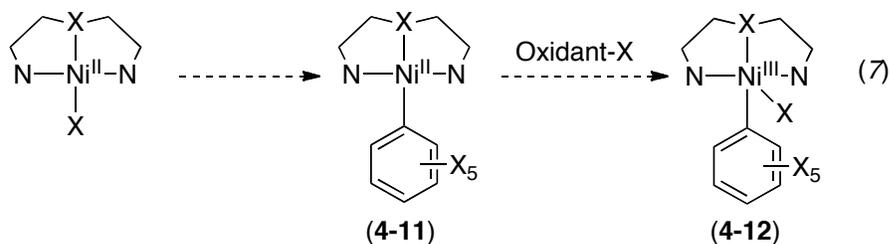
Trifluoromethyl groups exhibit similar behavior as ligands on other group 10 metals. Research in our group has shown that Pd<sup>II</sup> complexes like Pd<sup>II</sup>(*p*-FC<sub>6</sub>H<sub>4</sub>)(CF<sub>3</sub>)(*t*Bu-bpy) (*t*Bu-bpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine) (**4-9**) are resistant to Ar–CF<sub>3</sub> bond-forming reductive elimination even after sustained heating at high temperatures (130 °C, 3 days, eq. 5).<sup>7</sup> Reductive elimination could only be achieved in high yield when oxidatively induced. Oxidation of **4-9** with N-fluoropyridinium triflate affords Pd<sup>IV</sup> complex **4-10**, which is stable at room temperature. When heated to 80 °C, reductive elimination occurred to generate an Ar–CF<sub>3</sub> bond (eq. 6). The apparent reluctance of CF<sub>3</sub> to undergo reductive elimination from Pd suggests that trifluoromethyl groups may be suitable ligands for stabilizing high oxidation state Ni complexes.





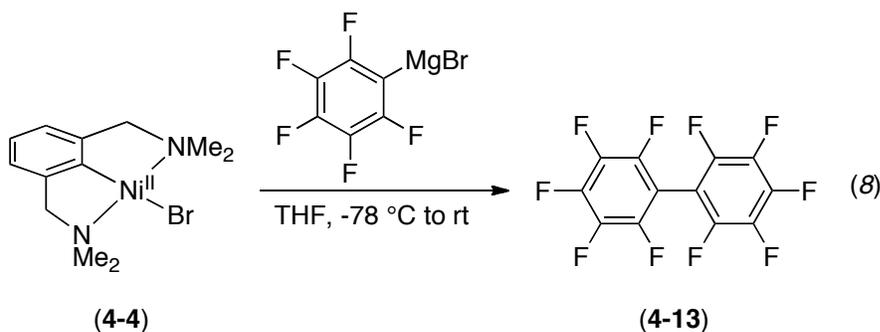
## 4.2 Tridentate and Perhalogenated Aryl Ligands

We hypothesized that employing these ligand-based strategies either singly or in combination could enable the isolation or observation of a high oxidation state Ni<sup>III</sup> or Ni<sup>IV</sup> complex. Our initial strategy combined the stabilizing effects of a rigid tridentate ligand with a perhalogenated aryl group to make Ni<sup>II</sup> complex **4-11** (eq. 7). Ideally, oxidation of **4-11** would result in an isolable Ni<sup>III</sup> complex **4-12**.

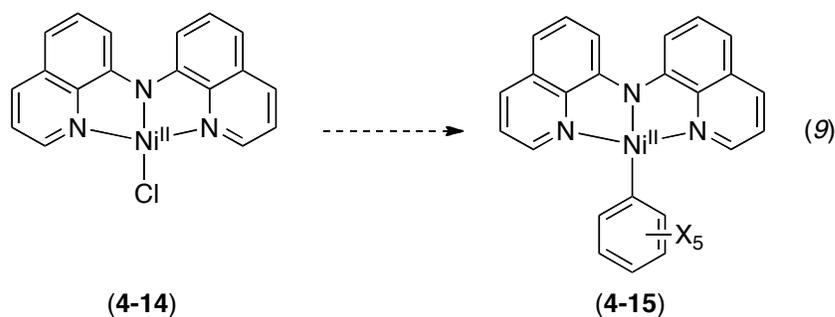


The synthesis of Ni complex **4-4** was accomplished according to literature procedure. Complex **4-4** was reacted with pentafluorophenyl Grignard reagent (eq. 8). The <sup>19</sup>F NMR spectrum of the resulting complex was suggestive of the desired complex with singlets at 140, 152, and -163, integrating in a 2:1:2 ratio.

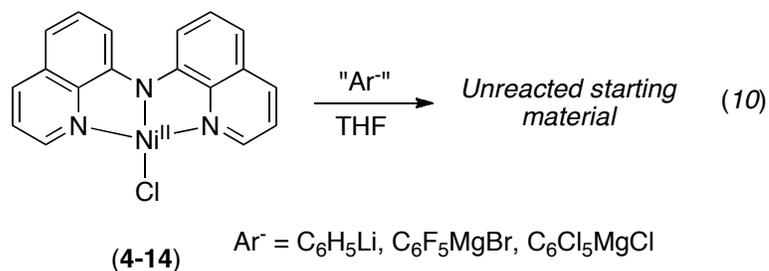
Several attempts were made to precipitate the product from acetone, chloroform, and benzene with hexanes. Slow diffusion of hexanes into an acetone solution generated crystals suitable for X-ray analysis, however, it was determined that the primary fluoride-containing species was perfluoro-1,1'-biphenyl (**4-13**). The observation of this major product suggests that transmetalation of the Grignard reagent onto complex **4-4** was not occurring. This indicates that the *trans* effect of the aryl ligands makes it unfavorable to install them *trans* to one another.



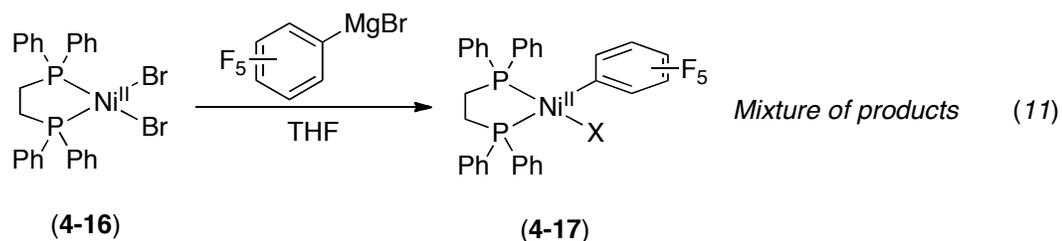
We next investigated complex **4-14** with an N–N–N ligand set analogous to the ligand in complex **4-4** with an X-type ligand flanked by L-type ligands.<sup>8</sup> By replacing the X-type carbon atom with an anionic nitrogen atom, we hypothesized that reductive elimination would be less likely because N–X bond reductive elimination is not a widely demonstrated reaction pathway.



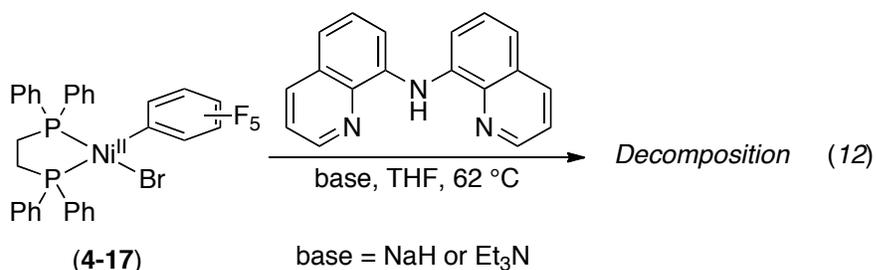
The synthesis of **4-14** was carried out according to the literature procedure affording a 26% overall yield over three steps. Our first goal was to substitute the chloride ligand for a perhalogenated aryl group to generate **4-15**. To this end we reacted **4-14** with a variety of Ar–Li reagents (eq. 10). Unfortunately, in all cases the only identifiable organometallic product appeared to be unreacted starting material.



As an alternative approach, we sought to install the aryl group onto the metal center prior to the addition of the N–N–N ligand. We targeted [NiBr<sub>2</sub>(dppe)] (**4-16**) (dppe = *bis*-diphenylphosphinoethane) for our initial efforts due to ease of synthesis and diamagnetic nature, which enables the use of NMR spectroscopy to follow the consumption of the starting material. C<sub>6</sub>F<sub>5</sub>MgBr was chosen as the Ar source because the fluorides provide a convenient handle for NMR analysis.

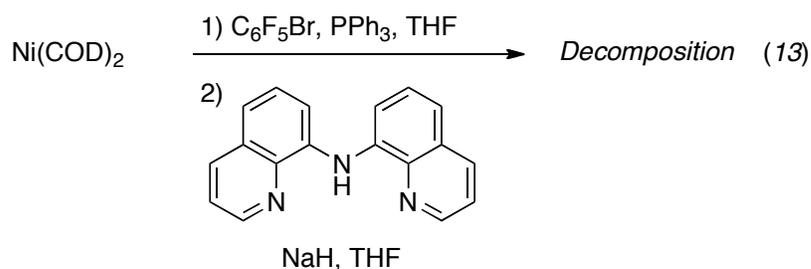


**4-16** was reacted with  $\text{C}_6\text{F}_5\text{MgBr}$  to afford a complex with a crude NMR spectrum consistent with our desired complex **4-17**. However, additional peaks in both the  $^{19}\text{F}$  and  $^{31}\text{P}$  NMR spectra could not be eliminated despite repeated crystallization. Thus, the impure material was carried forward. However, addition of the ligand to a solution of **4-17** along with a base (NaH or  $\text{Et}_3\text{N}$ ) in THF, did not result in the desired complex **4-xx**. The crude  $^{31}\text{P}$  and  $^{19}\text{F}$  NMR spectra were consistent with an intractable mixture of decomposition products (eq. 12).

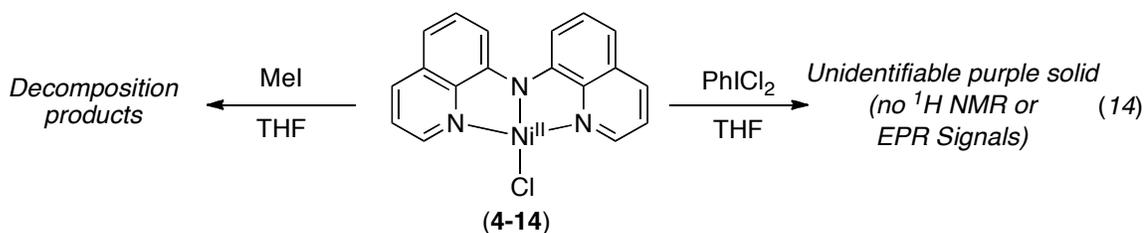


Since complex **4-17** could not be completely purified, we sought to generate an analogous complex *in situ* and then trap it by the addition of the N–N–N ligand. The results in eq. xx suggest that bidentate ligand dppf is difficult to displace, so monodentate triphenylphosphine ( $\text{PPh}_3$ ) was chosen as the temporary supporting ligand.  $\text{Ni}(\text{COD})_2$  was

stirred with  $C_6F_5Br$  and  $PPh_3$  for a few minutes before the N–N–N ligand and NaH were added (eq. 13). The reaction was analyzed by  $^{31}P$  and  $^{19}F$  NMR spectroscopy, but only inseparable unidentifiable decomposition products were observed. Analogous to the results in eq. 8 it appeared that the installation of an aryl ligand *trans* to the anionic nitrogen was unfavorable.



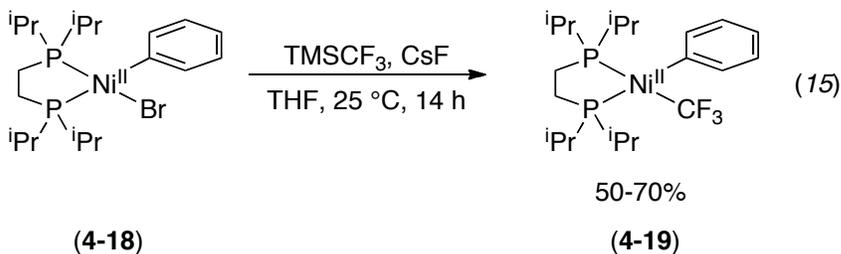
We next tested the ability of complex **4-14** to support a high oxidation state Ni complex, even without an Ar ligand. To this end, **4-14** was reacted with either  $PhICl_2$  or MeI in THF (eq. 14). The reaction with  $PhICl_2$  generated an unusual purple solid, but analysis by  $^1H$  NMR revealed no discernable signals. This might suggest the presence of paramagnetic species causing signal broadening. However, there was no observable signal in the EPR spectrum. This suggests that there may be paramagnetic  $Ni^{II}$  species with an even number of unpaired electrons. Such species would not be visible by either NMR spectroscopy or EPR spectroscopy using the instrument available. The reaction with MeI resulted in an intractable mixture of decomposition products and a Ni black precipitate. On the basis of these results, this ligand set was determined to be unsuitable for further investigations.



### 4.3 Attempts Toward Installing Trifluoromethyl Ligands

We envisioned two strategies for installing a trifluoromethyl group onto a metal center. The first was transmetalation from an appropriate transmetallating reagent, such as  $\text{TMS-CF}_3$ . Such an approach would generate a complex with the same oxidation state as the starting complex. Alternatively, the  $\text{CF}_3$  source could be an oxidant that would generate a  $\text{Ni}^{\text{III}}$  or  $\text{Ni}^{\text{IV}}$  complex with one or two trifluoromethyl groups installed.

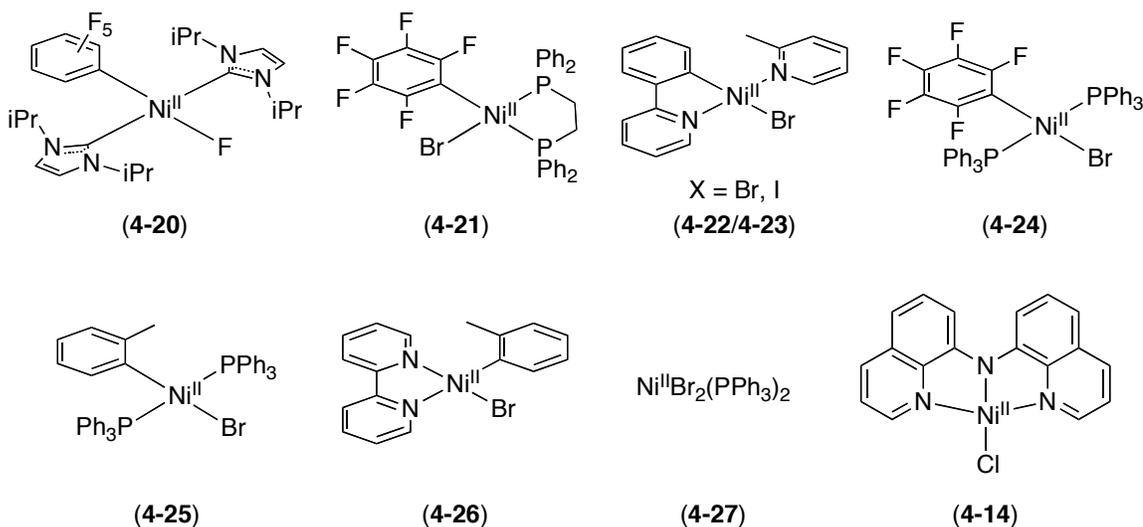
$\text{Ni-CF}_3$  complex **4-19** has been synthesized by the use of utilized Ruppert's reagent ( $\text{TMS-CF}_3$ ) as a transmetallating reagent to exchange the bromide ligand on **4-18** with the desired  $\text{CF}_3$  group (eq. 15). This complex exhibits a characteristic peak in the  $^{19}\text{F}$  NMR spectrum at approximately -20 ppm, providing a convenient NMR handle for analysis.



On the basis of this precedent, a variety of Ni complexes containing halogen ligands were synthesized and subjected to the  $\text{TMS-CF}_3$  conditions. The reaction

progress was monitored by  $^{19}\text{F}$  NMR in THF. Unfortunately, only trace amounts of the desired product were ever observed (Table 4.1). Extending the reaction time, increasing TMS- $\text{CF}_3$  equivalents, and increasing the reaction temperature to  $60\text{ }^\circ\text{C}$  did not have any impact on the total conversion.

**Table 4.1** – Screening Complexes for Trifluoromethylation



Entry	Complex	Diagnostic Peak Observed?
1	<b>4-20</b>	Yes <sup>a</sup>
2	<b>4-21</b>	No
3	<b>4-22</b>	No
4	<b>4-23</b>	No <sup>b</sup>
5	<b>4-24</b>	No
6	<b>4-25</b>	No
7	<b>4-26</b>	Yes <sup>c</sup>
8	<b>4-27</b>	No
9	<b>4-14</b>	No <sup>d</sup>

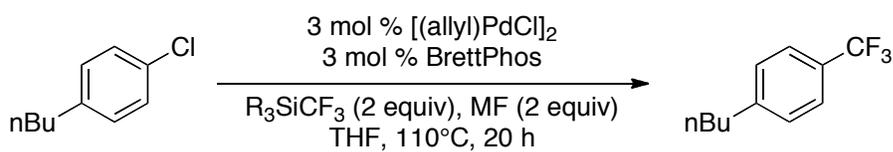
<sup>a</sup>A product would not be isolated. <sup>b</sup>Decomposition, with dozens of peaks in the  $^{19}\text{F}$  NMR spectrum. <sup>c</sup>Trace.

<sup>d</sup>A peak was observed at  $-30$  ppm in the  $^{19}\text{F}$  NMR spectrum, but no complex could be isolated.

While these conditions were not effective for our Ni complexes, examples with Pd suggested alternative reaction conditions. Buchwald demonstrated that the yield of Pd-

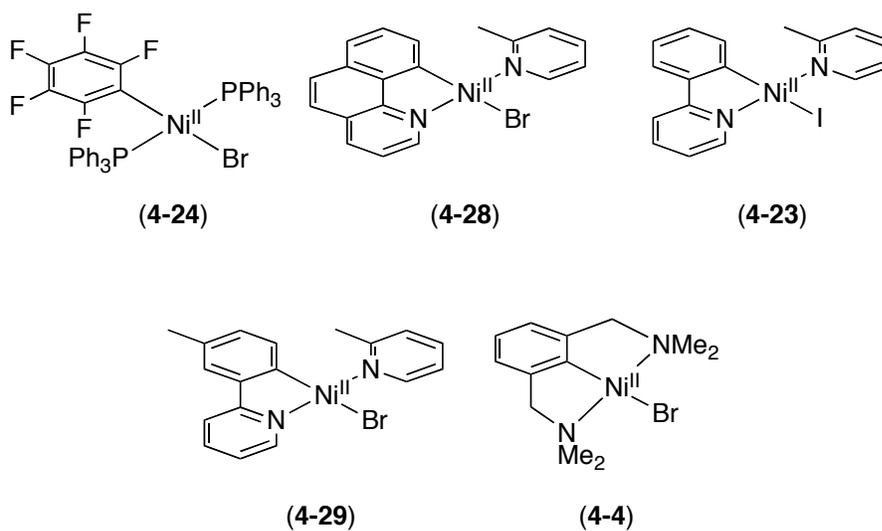
catalyzed trifluoromethylation could be increased dramatically by using TES-CF<sub>3</sub> instead of TMS-CF<sub>3</sub> and by using KF rather than CsF (Table 4.2).<sup>9</sup>

**Table 4.2** – Pd-Catalyzed Aryl Trifluoromethylation



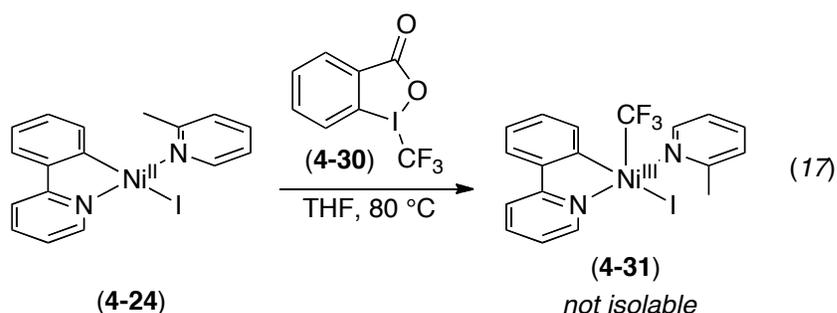
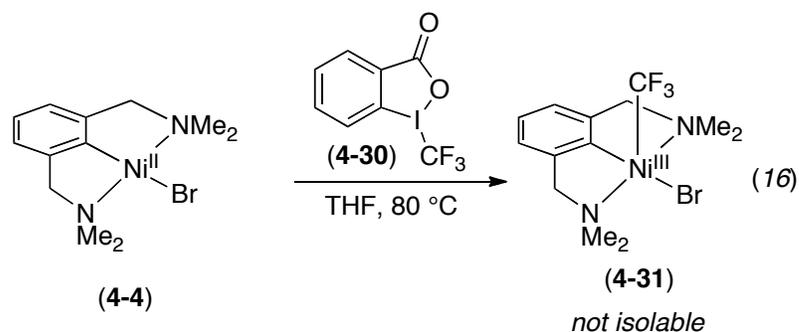
Entry	R <sub>3</sub> SiCF <sub>3</sub>	CsF	KF
1	TMSCF <sub>3</sub>	trace	7%
2	TESCF <sub>3</sub>	25%	67%

Five complexes were selected (Table 4.3), representing an assortment of mono-, bi-, and tridentate ligands. Each was combined with TES-CF<sub>3</sub> and a fluoride salt in THF and the reaction progress was followed by crude <sup>19</sup>F NMR spectroscopy. In all cases, however, the diagnostic trifluoromethyl peak at -20 ppm was not observed.

**Table 4.3** – Complexes Screened with TES–CF<sub>3</sub>

Entry	Complex	MF	Diagnostic Peak Observed?
1	<b>4-24</b>	CsF	No
2	<b>4-28</b>	CsF	No
3	<b>4-23</b>	CsF	No
4	<b>4-29</b>	CsF	No
5	<b>4-4</b>	CsF	No
6	<b>4-4</b>	KF	No

Transmetalation from Si-based reagents had proven to be ineffective at installing CF<sub>3</sub> groups on any of the complexes that we investigated. Therefore, we next sought to use trifluoromethyl-based oxidants. Research in our group and others has demonstrated that the trivalent iodide-based oxidant **4-30** can serve as a source of electrophilic CF<sub>3</sub> for Pd.<sup>10</sup> Complex **4-4** (eq. 16) and **4-24** (eq. 17) were reacted with at 80 °C overnight. Crude <sup>19</sup>F NMR spectroscopy revealed a diagnostic peak at -19 ppm indicative of the desired Ni–CF<sub>3</sub> product (**4-31**). Attempts to isolate the product removing the reaction solvent by rotary evaporation or vacuum resulted in the loss or decomposition of the product. Efforts to precipitate the product out of the crude mixture were also unsuccessful.



## 4.4 Conclusions

We wished to directly study the reductive elimination of C–X bonds from high oxidation state organometallic Ni species, so we pursued an isolable Ni<sup>III</sup> or Ni<sup>IV</sup> complex that could serve as a model compound for these transformations. Though only limited examples of Ni<sup>III</sup> complexes are known, we sought to apply two strategies to synthesize a high oxidation state Ni complex. One strategy was to use rigid, multi-dentate pincer ligands to occupy several coordination sites. Sequestration of the X-type ligand between two L-type ligands would prevent it from being involved in reductive elimination pathways. The second strategy was to use ligands like perhalogenated aryl groups and trifluoromethyl groups that do not readily undergo reductive elimination. Our attempts to combine these strategies by installing perhalogenated aryl groups on complexes

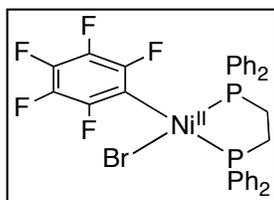
containing tridentate pincer ligands resulted in either no reaction or an intractable mixture of decomposition products. The installation of trifluoromethyl groups onto Ni either by transmetallation or electrophilic oxidation also proved to be fruitless. While this approach did not result in the isolation of a high oxidation state Ni complex, further screening of reaction conditions or the design of different ligand sets may yet prove successful for the isolation of a high oxidation state Ni complex that may serve as a model compound for the stoichiometric oxidatively induced reductive elimination of C–X bonds at Ni.

## 4.5 Experimental Procedures

**General Considerations.** NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for  $^1\text{H}$ ; 125.70 MHz for  $^{13}\text{C}$ ) and a Varian Inova 400 (399.96 MHz for  $^1\text{H}$ ; 100.57 MHz for  $^{13}\text{C}$ ; 376.34 MHz for  $^{19}\text{F}$ ).  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), quintet (quin), multiplet (m), and broad resonance (br).

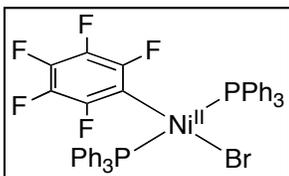
**Materials and Methods.** Tetrahydrofuran and pentanes were purified using an Innovative Technology (IT) solvent purification system composed of activated alumina, copper catalyst, and molecular sieves. Benzene was distilled from sodium, pyridine was distilled from  $\text{CaH}_2$ , and acetone was distilled from anhydrous calcium sulfate. 2-(2-Bromophenyl)pyridine (**4-32**) was synthesized according to a literature procedure,<sup>11</sup> while 2-(2-iodophenyl)pyridine was prepared by lithium halogen exchange on **4-32** followed by

a quench with I<sub>2</sub>, using a modification of a literature procedure.<sup>12</sup> Ni(COD)<sub>2</sub> (Strem) was stored in a glovebox at -35 °C. **4-23**, **4-29**, and **4-30** were synthesized by analogy to a literature procedure.<sup>13</sup> **4-24** was prepared via reaction of Ni(COD)<sub>2</sub> with Phpy-I and picoline via a modification of a literature procedure.<sup>14</sup> PhICl<sub>2</sub> was prepared via a modification of a literature procedure<sup>15</sup> and was stored at -35 °C in a glovebox. I<sub>2</sub> (sublimed, Acros) and *n*-BuLi (Acros) were used without further purification. NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (Strem) was stored in a glovebox without any further purification. MeI (Sigma Aldrich) was stored in a freezer (-35 °C) and used without further purification. **4-4** was synthesized according to a literature procedure.<sup>1a</sup> **4-14** was synthesized according to a literature procedure.<sup>1b</sup> **4-16** was synthesized according to a literature procedure.<sup>16</sup> **4-21** was synthesized according to a literature procedure.<sup>17</sup>



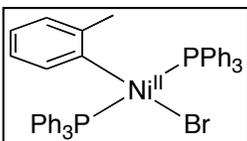
**Ni(dppe)(Br)(C<sub>6</sub>F<sub>5</sub>) – 4-22.** In the glovebox, Ni(COD)<sub>2</sub> (0.1000g, 0.36 mmol, 1 equiv) was mixed with THF (10.0 mLs) in a dry 20 mL scintillation vial. Pentafluorophenylbromide (45 μL, 0.36 mmol, 1 equiv) and 1,2-Bis(diphenylphosphino)ethane (0.1448 g, 0.36 mmol, 1 equiv) were dissolved in THF in a dry 4 mL scintillation vial. Both vials were cooled to -35 °C and then the vials were combined. The mixture was stirred with a Teflon stirbar and allowed to warm to room temperature, turning a dark yellow-black. Once the reaction reached room temperature, the solvent was removed under vacuum. The resulting solid material was taken up in benzene and filtered through a Celite plug. The resulting clear yellow filtrate was concentrated and mixed with a large quantity of pentanes before

being placed in the freezer overnight. The next morning the resulting bright yellow powder was filtered out on a frit and dried under vacuum.



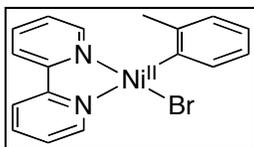
**Ni(C<sub>6</sub>F<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>(Br) – 4-25.** Ni(COD)<sub>2</sub> (0.5005 g, 1.82 mmol, 1 equiv) and PPh<sub>3</sub> (0.9531 g, 3.63 mmol, 2 equiv) were dissolved in toluene (10 mLs) in a dry 20 mL scintillation vial, turning a

dark purple red. The solution was cooled to -35 °C. Pentafluorophenylbromide (1.3464 g, 5.45 mmol, 3 equiv) was added to the cold solution and the reaction was warmed to room temperature while stirring. After 30 minutes, the reaction was transferred to a 250 mL flask and pentanes (~150 mLs) were added, crashing out a dark yellow solid. The solid was filtered out on a frit and dried under vacuum (0.4960 g, 33% yield).



**Ni(o-tol)(PPh<sub>3</sub>)<sub>2</sub>(Br) – 4-26.** Ni(COD)<sub>2</sub> (0.5000 g, 1.82 mmol, 1 equiv) and PPh<sub>3</sub> (0.9534 g, 3.63 mmol, 2 equiv) were dissolved in

toluene (10 mLs) in a dry 20 mL scintillation vial, turning a dark purple red. The solution was cooled to -35 °C. 2-bromotoluene (0.9326 g, 5.45 mmol, 3 equiv) was added to the cold solution and the reaction was warmed to room temperature while stirring. After 30 minutes, the reaction was transferred to a 250 mL flask and pentanes (~150 mLs) were added, crashing out a dark yellow solid. The solid was filtered out on a frit and dried under vacuum (1.1081 g, 81% yield). The material is nearly insoluble in acetone, but quite soluble in benzene.



**Ni(o-tol)(bpy)(Br) – 4-27.** Bipyridine (0.0208 g, 0.133 mmol, 4 equiv) and **4-26** (0.0250 g, 0.033 mmol, 1 equiv) were weighed into

a dry 4 mL scintillation vial and dissolved in toluene (~2 mLs), turning a blood red color almost immediately. The reaction was stirred for 20 minutes before being transferred to a 50 mL flask. Pentanes (~20 mLs) were added, crashing out a red powder. The solid material was filtered out on a frit and dried under vacuum.

**General Procedure for the Reaction of Ni Complexes with C<sub>6</sub>F<sub>5</sub>MgBr, C<sub>6</sub>H<sub>5</sub>Li, or C<sub>6</sub>Cl<sub>5</sub>MgCl.** The Ni complex was dissolved in dry THF and cooled to -78 °C in a dry ice-acetone bath under nitrogen. The transmetallating reagent was added dropwise via syringe and the reaction was allowed to warm to room temperature while stirring under nitrogen. The reaction was quenched by addition of a saturated NH<sub>4</sub>Cl solution. The organic layer was extracted, dried over MgSO<sub>4</sub>, and filtered through Celite. The filtrate was concentrated on the rotovap. The resulting material was analyzed by <sup>19</sup>F (where appropriate) and <sup>1</sup>H NMR spectroscopy.

**General Procedure for the Addition of Di(quinolin-8-yl)amine Ligand to Ni Complexes.** The Ni complex (1 equiv), di(quinolin-8-yl)amine (1.05 equiv), and base (NaH or Et<sub>3</sub>N, 2 equiv) were all weighed into a dry 20 mL scintillation vial in the glovebox before being mixed with THF (10 mLs). The reaction was heated to 62 °C overnight while stirring. The next morning the solvent was removed under vacuum and the resulting crude material was analyzed by <sup>19</sup>F and <sup>1</sup>H NMR spectroscopy.

**Reaction of 4-14 with PhICl<sub>2</sub>.** 4-14 (0.0200 g, 0.055 mmol, 1 equiv) and PhICl<sub>2</sub> (0.0376 g, 0.137 mmol, 2.5 equiv) were weighed into a dry 20 mL scintillation vial in the glovebox and mixed with THF (~15 mLs). The reaction was stirred in the glovebox for two hours, turning a light purple color. The solvent was removed under vacuum and the resulting purple powder was analyzed by <sup>1</sup>H NMR spectroscopy and EPR. It appeared to be insoluble in every solvent tried except for anhydrous methanol.

**Reaction of 4-14 with MeI.** 4-14 (0.0205 g, 0.056 mmol, 1 equiv) was weighed into a dry 4 mL scintillation vial in the glovebox and mixed with THF (2.0 mLs). MeI (4.0 μL, 0.064 mmol, 1.2 equiv) was added via syringe and the reaction was stirred at room temperature, wrapped in foil, overnight. The next morning the solvent was removed from the reaction and the resulting material was analyzed by <sup>1</sup>H NMR spectroscopy.

**General Procedure for Reaction of TMSCF<sub>3</sub> and TESCF<sub>3</sub> with Ni Complexes.** The Ni complex (1 equiv) was dissolved in THF (1.0 mL). The trifluoromethylating reagent (4 equiv) and fluoride salt (5 equiv) were added and the reaction was transferred to a screw-cap NMR tube. The reactions were followed by <sup>19</sup>F NMR spectroscopy.

**General Procedure for Reaction of 4-30 (CF<sub>3</sub> oxidant) with Ni Complexes.** The Ni complex (1 equiv) was dissolved in THF (2.0 mL). 4-xx (1.3 equiv) was added and the reaction was stirred overnight. The reactions were followed by <sup>19</sup>F NMR spectroscopy.

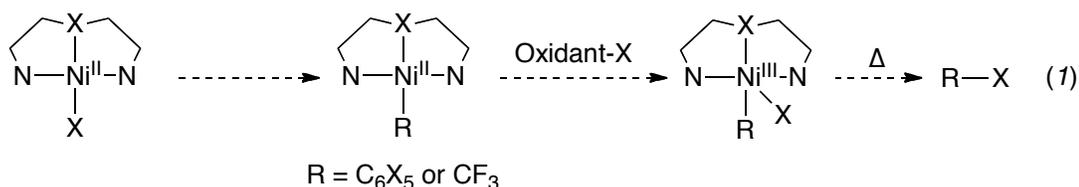
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## Chapter 5

### Future Work and Challenges

#### 5.1 Future Work

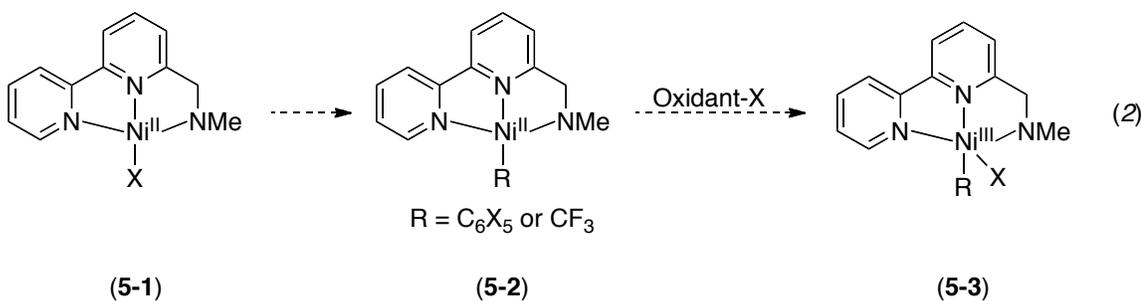
We hypothesized that using tridentate ligands, in conjunction with perhalogenated ligands that have been shown to be resistant to reductive elimination, would afford Ni<sup>II</sup> scaffolds. Upon oxidation, these could stabilize high oxidation state Ni<sup>III</sup> or Ni<sup>IV</sup> species, allowing for their isolation. We have demonstrated that reductive elimination pathways involving a tridentate ligand are not favorable when the reactive atom is sequestered between two chelating ligands. Thus, we would expect that thermally induced reductive elimination of the desired high oxidation state Ni complex would only result in R–X bond reductive elimination (eq. 1).

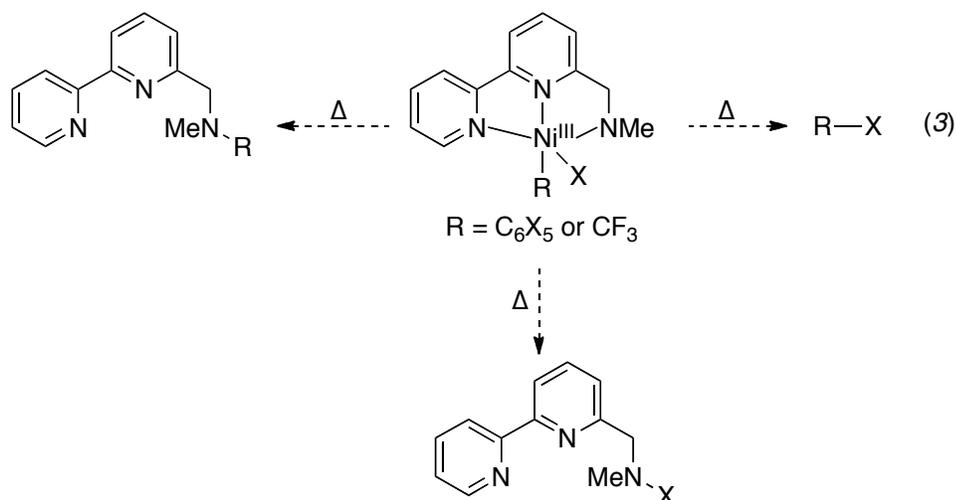


Unfortunately, installation of the desired perhalogenated ligands onto complexes of this general type was unsuccessful. This may indicate that installation of an anionic

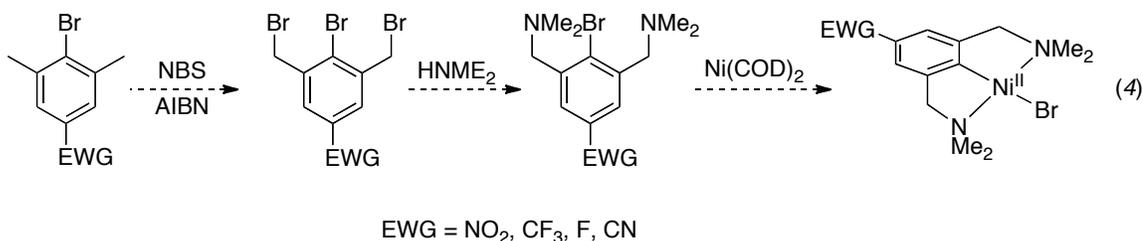
carbon ligand *trans* to an anionic carbon or nitrogen atom is either thermodynamically unfavorable or kinetically inaccessible. Two possible strategies may address this challenge.

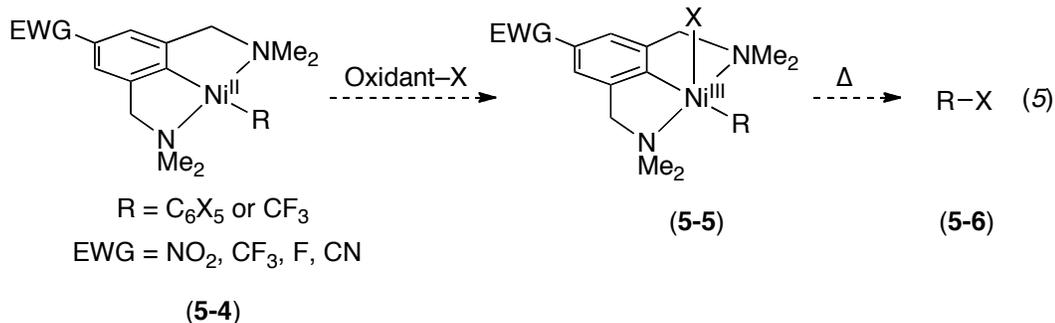
The first strategy involves designing a ligand set that places the perhalogenated ligand *cis* to the anionic atom of the tridentate ligand rather than *trans* (eq. 2). Such an approach would install the desired perhalogenated ligand *trans* to a neutral atom instead of an anionic atom. Coupling of the anionic atom of the tridentate ligand with the newly installed perhalogenated ligand may be problematic. However, an anionic nitrogen atom may be less susceptible to reductive coupling than an anionic carbon atom. Thus, starting with complex **5-1** may allow for the successful synthesis of complex **5-3**. Thermally induced reductive elimination of the desired C–X bond from **5-3** could be achieved preferentially over the undesired reductive elimination of a C–N or N–X bond. All three possibilities, however, may be observed (eq. 3).





A second strategy is to electronically alter the tridentate ligand to reduce the electron-donating ability of the anionic atom. This should reduce the impact of both the *trans* effect and *trans* influence. One example of this approach would be using van Koten's tridentate (NCN) ligand with electron-withdrawing groups substituted on the *para* position (eq. 4). Installation of a perhalogenated ligand would result in complex **5-4** and oxidation with an appropriate oxidant should then afford our desired high oxidation state Ni complex (**5-5**). Based on our research with van Koten's Ni<sup>III</sup> complex, reductive elimination involving the anionic carbon of the tridentate ligand is unfavorable, so the only observed product should be the desired R–X reductive elimination product (**5-6**) (eq. 5).



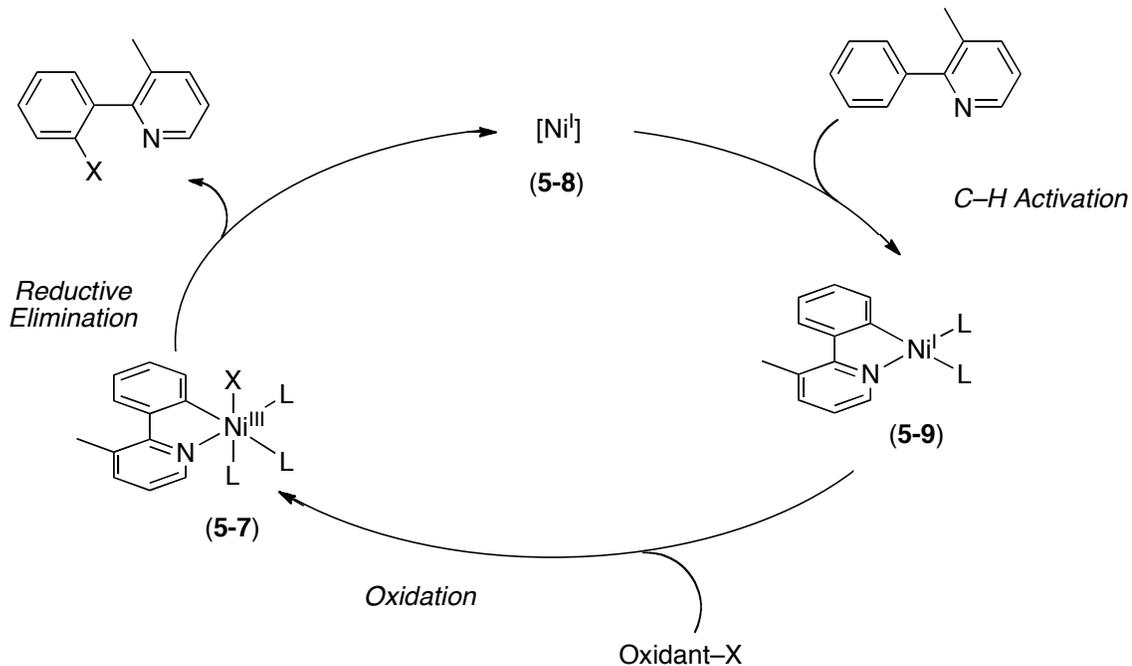


## 5.2 Long-Term Challenges

The ultimate goal for this research is the successful development of a catalytic system, using a substoichiometric Ni catalyst to mediate the formation of carbon-halogen bonds. The formation of such bonds is not thermodynamically viable at  $\text{Ni}^{\text{II}}$ . We have demonstrated, however, that oxidizing  $\text{Ni}^{\text{II}}$  to an unstable high oxidation state species results in decomposition via a C–X bond forming reductive elimination pathway, resulting in the desired bond.

We propose that this transformation proceeds via a transient  $\text{Ni}^{\text{III}}$  species. When thinking about incorporating this transformation into a catalytic cycle, however, a challenge arises. Two-electron reductive elimination from such a  $\text{Ni}^{\text{III}}$  species (**5-7**) would result in a  $\text{Ni}^{\text{I}}$  species (**5-8**) reentering the catalytic cycle (Fig. 1). At that point, the low valent  $\text{Ni}^{\text{I}}$  species would likely be oxidized by the stoichiometric oxidant. The challenge, therefore, is making sure that this new  $\text{Ni}^{\text{II}}$  species would be competent both for C–H activation and subsequent reoxidation to  $\text{Ni}^{\text{III}}$  to continue the catalytic cycle.

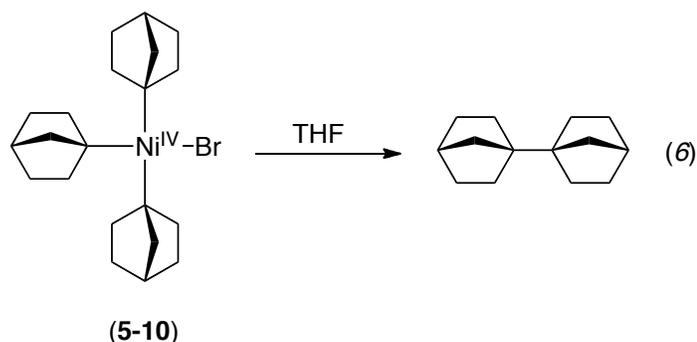
**Figure 5.1.** Potential Ni Catalytic Cycle for the Formation of C–X Bonds



There are no such issues with the commonly proposed  $Pd^{II}$ - $Pd^{IV}$  catalytic cycles because two-electron reductive elimination from  $Pd^{IV}$  regenerates a  $Pd^{II}$  species, which is inert to the functionalizing oxidant until it undergoes cyclometallation with the substrate via C–H activation. Subsequent oxidation results in the reactive  $Pd^{IV}$  species that then continues the catalytic cycle. This suggests that a  $Ni^{II}$ - $Ni^{IV}$  catalytic cycle would be ideal for avoiding the potentially problematic one-electron oxidation of the low valent byproducts of C–X bond forming reductive elimination.

However, little evidence exists that suggests that  $Ni^{IV}$  is an accessible oxidation state or that C–X bond formation is a viable transformation from  $Ni^{IV}$ . Furthermore, isolable  $Ni^{IV}$  species are very rare, so directly studying such a transformation will be challenging. Only one example of an organometallic  $Ni^{IV}$  species containing both carbon and halogen ligands appears in the literature (eq. 6, **5-10**). Unfortunately, **5-10** has not

been shown to undergo C–X bond forming reductive elimination and the only observed product is the result of C–C bond forming homocoupling.



The challenge to directly studying C–X bond forming reductive elimination from  $\text{Ni}^{\text{IV}}$  is designing an isolable  $\text{Ni}^{\text{IV}}$  containing carbon and halogen ligands that cleanly undergoes the desired process. Strategies that are similar to those discussed earlier (multidentate and perhalogenated ligands) may be utilized. The focus should be fixed on using known two-electron oxidants (*e.g.*,  $\text{XeF}_2$ ,  $\text{PhICl}_2$ ,  $\text{Br}_2$ ,  $\text{I}_2$ , NCS, NBS, and NIS) to oxidize the resulting complex while avoiding oxidants that are proposed to operate primarily via one-electron mechanisms (*e.g.*,  $\text{CuCl}_2$ ,  $\text{CuBr}_2$ ,  $\text{O}_2$ , ferrocenium salts, cerium IV salts). Fluoride-based oxidants would be especially attractive due to the relatively small size of the F<sup>-</sup> ligands. Given the small size of Ni relative to the other group 10 metals, steric crowding in a six-coordinate octahedral complex must be considered. Ultimately, the challenges in the effort towards the generation and isolation of a stable  $\text{Ni}^{\text{IV}}$  species will be preventing under-oxidation resulting in  $\text{Ni}^{\text{III}}$  and avoiding undesired oxidatively induced reductive elimination.