CHAPTER 4

Effect of Lewis Acidic Metals on Aryl-Oxygen Bond Activation in Nickel(0) Diphosphine Model Systems

Abstract

The addition of Lewis acidic metal alkyls to a nickel terphenyl diphosphine aryl ether complex led to an acceleration of the observed aryl oxygen bond activation. It was found that Grignard reagents led to an order of magnitude increase while trialkyl aluminium species led to an up to three orders of magnitude rate increase over the unaccelerated rate. Treatment with trimethyl aluminum at -80 °C led to the observation of a nickel aluminum intermediate. Through low temperature ^{1}H NOESY NMR studies the intermediate was indentified as a complex where the aluminum center is coordinated to the ether moiety of the terphenyl ring on the face *trans* to the nickel center. The kinetics and activation parameters of aryl activation with trimethylaluminum are described and the proposed mechanism is discussed.

INTRODUCTION:

Aryl oxygen bonds are significantly stronger than their aryl halide counterparts making the direct activation of aryl-oxygen substrates challenging.[1] Typically aryl oxygen moieties must be converted to the more reactive phosphinates, sulfunates, or triflates. While catalytic systems are known for the cleavage and cross coupling of aryl-oxygen bonds these systems are typically limited by low turnover numbers or poor reactivity for anisoles.[1] Another strategy for the cleavage of aryl-X bonds is the assisted cleavage of aryl-X bonds in the presence of lewis acidic metals.

Currently there are several different nickel systems for the cross coupling of aryl oxygen bonds.[1] Most of these systems use high temperatures and long reaction times for homogeneous systems. The most common of these systems contain basic phosphines such as tricyclohexylphosphine or carbenes. The common catalytic systems for these activations are $Ni(COD)_2$ with 2 equivalents of PCy_3,[2] $NiCl_2(PCy_3)_2$,[2a 3] or $Ni(COD)_2$ with 2 equivalents of SIPr-HCl or a N-hetrocyclic carbene.[4] Others systems also use less basic phosphines.[5] While the phosphines vary, the presence of the Lewis acid does not. The transmetallation species in these reactions is typically either a Grignard reagent or an alkyl borane both of which are Lewis acidic species which can aid in aryl oxygen bond activation.

Lewis acids have been used in conjuction with nickel catalysts for the activation of nitrile groups. In 1984, Tolman et. al. observed that the catalytic hydrocyanation of olefins by Ni(0) phosphite complexes was changed in the presence of Lewis acids.[3g] This concept was later carried out in the carbocyanation of alkynes by nickel system by Nakao et al. in 2007. What the researchers observed was a large effect of the Lewis

acid on the activation of the arene nitrile bond where the increase in the rate of activation varied with the strength of the Lewis acidity of the additive.[3h] Using aluminum based Lewis acids they were able to determine the crystal structure of one of the intermediate species which among other things, revealed an aluminum center coordinated directly to the nitrogen of the nitrile group while the nickel center coordinated to the pi bond of the nitrile group, showing that the metal centers do indeed react in concert for the activation of the nitrile groups.[3i]

There is also precedence for the use of a secondary Lewis acidic metal center to assist the activation of aryl oxygen bonds in the literature. While the studies are not numerous, there are some reports, such as the catalytic system reported by Hartwig being able to cleave aryl oxygen bonds at lower temperatures with an equivalent of added trimethylaluminum.[4] More extensive studies in this area have been done by Shi et al. who found the presence of a Lewis acidic Grignard reagent allowed for cleavage of the aryl oxygen bond in napthanol and benzylic alcohols.[6] They proposed that the naptholate interacts with multiple Lewis acidic Grignards to form a regular framework. In these frameworks they hypothesized that the coordination would induce reorganization of the electronic structure of the phenolic aryl-oxygen bond (Figure 1).

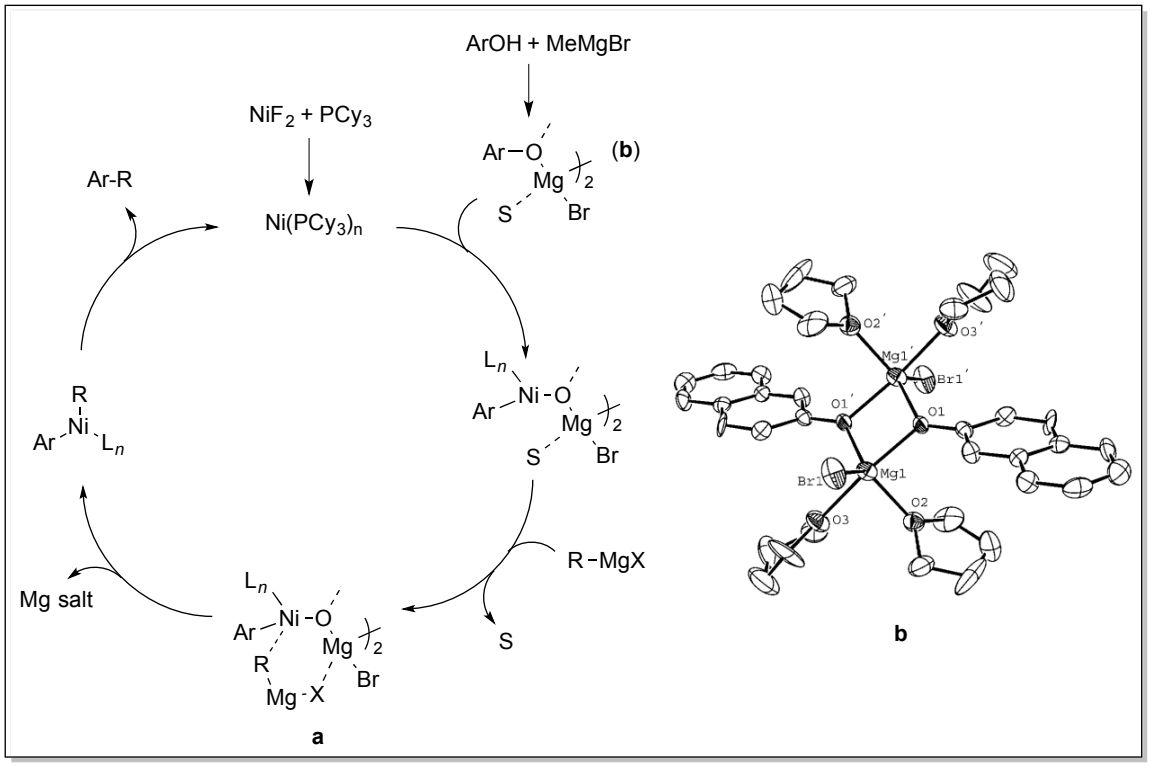


Figure 4.1: a: Catalytic cycle of Ni(0) catalyst with magnesium napthalate substrate. b: X-ray crystal structure of magnesium napthalate dimer.

This reorganization of electron density would activate the aryl oxygen bond for cleavage. Essentially, the metals would act both as electron withdrawing groups, simultaneously weakening the oxygen carbon bond and making the oxygen moiety a better leaving group. However, they noted that phenol derivatives did not successfully undergo this transformation.[6a]

More recently the Shi group extended this research to non-metallic Lewis acids.[6b] Using aryl boronic reagents the Shi group could observe a similar effect on the activation of phenolates. The addition of excess boronic reagents and triethyl borane leads to a similar effect as the Grignards on the phenolates. It is postulated that there is a double Lewis acid effect on the phenolate as they propose that both the boronic

acid and the triethyl borane contribute Lewis acidic effects on the phenolic aryl oxygen bond.

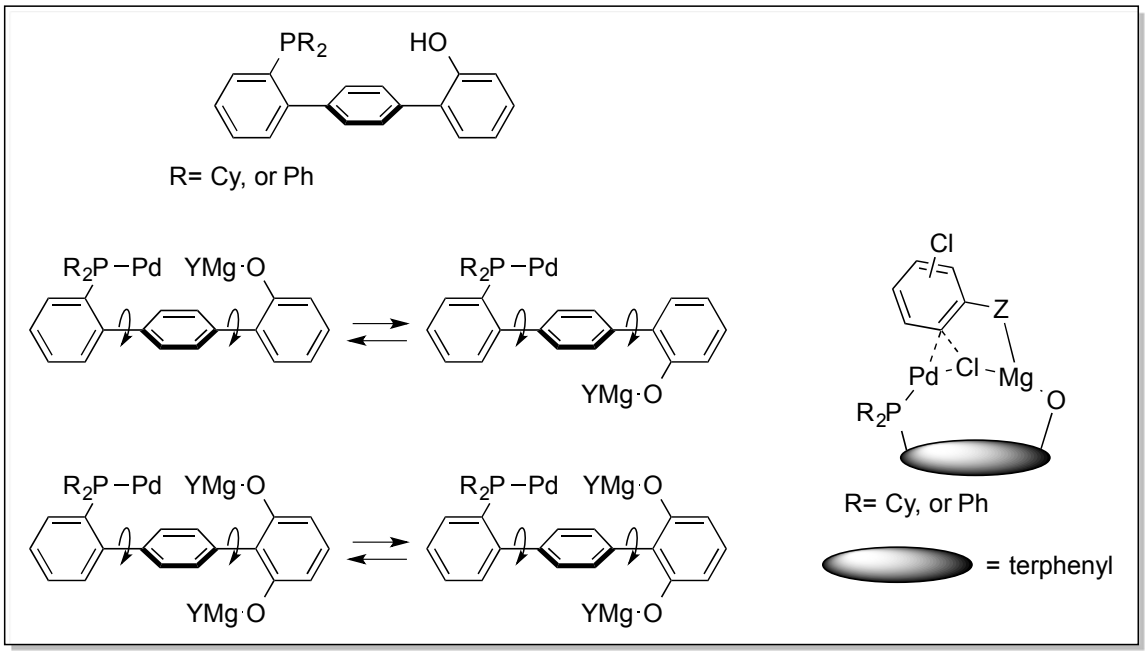


Figure 4.2: Palladium magnesium bimetallic system for the directed activation of aryl halide bonds

Some bimetallic systems have been developed where the Lewis acidic metal center has been used to impart selectivity on the activation of aryl heteroatom bonds. For example Manabe et. al. explored the use of a Lewis acid to guide the reactivity of a palladium center in oligoarene and terphenyl systems.[7] Their terphenyl system contains a phosphine arm and a phenolic arm. The phosphine arm is envisioned to bind a palladium(0) metal center for arene heteroatom bond activation while the phenolic arm is envisioned to bind a Lewis acidic Grignard reagent (Figure 5).

Using this system, Manabe et al. they were able to activate ortho arene heteroatom bonds on phenolate substrates preferentially to any other ortho arene

bonds. They proposed that substrate binds to the magnesium coordinated to the phenolic arm of the ligand allowing for the ortho positions of the substrate to be accessible to the palladium(0) center.[44] Substitution of both sides of the phenol arm led to an increase in the bond selectivity providing more support for their proposed mechanism and reactivity.[7d]

As these examples have shown the cleavage of aryl oxygen bonds can be activated through the use of a bimetallic system containing an electron-rich nickel center to coordinate the arene and a Lewis acidic metal to help activate the substrate. However systematic studies on the effect of the Lewis acid and the acceleration of the rate have not been undertaken. Such studies as described would allow for the development of better heterometallic catalysts for the cleavage of aryl oxygen bonds. As our group has recently developed a nickel(0) model system. In this model system the nickel readily undergoes oxidative addition giving us a unique platform from which to probe oxidative addition facilitated by nickel mechanistically and kinetically. With this in mind we extended our studies to aryl oxygen bond activation in the presence of Lewis acids. Herein is described the studies of Lewis acidic accelerated aryl oxygen bond activation in a nickel(0) model system.

RESULTS & DISCUSSION:

In our investigations of the rate of aryl-oxygen bond activation in nickel(0) diphosphine aryl ether complexes we have observed a rate acceleration in the presence of Grignard reagents. The treatment of **2** with ten equivalents of MeMgBr in toluene leads to an order of magnitude rate increase in the aryl-oxygen bond activation (Scheme 4.1, Table 4.1, and Figure 4.3). Interestingly, the addition of one to twenty three equivalents of Me_2MgTMEDA does not lead to a rate increase in aryl-oxygen bond activation *vide supra*. This is postulated to be due to the Lewis acidity of the metal as has been observed in other systems. The less Lewis acidic Me_2MgTMEDA does not lead to acceleration due to the bidentate ligand TMEDA, which effectively quenches the Lewis acidity of the metal center. Indeed the treatment of **2** with ten equivalents of MeMgBr in the presence of THF does not lead to an increase in the rate of oxidative addition. This is consistent with the coordinating solvent THF binding to the Grignard reagent, resulting in a less Lewis acidic metal center. It is possible that the MeMgBr is coordinating to the methoxy moiety of the terphenyl backbone weakening the oxygen arene oxygen bond and simultaneously making the methoxy a better leaving group leading to an accelerated oxidative addition forming a nickel(II) species. This nickel(II) can either be transmetallated by the coordinated Grignard reagent (a concerted process between the methoxy Grignard adduct) or transmetallated via another equivalent of the Grignard.

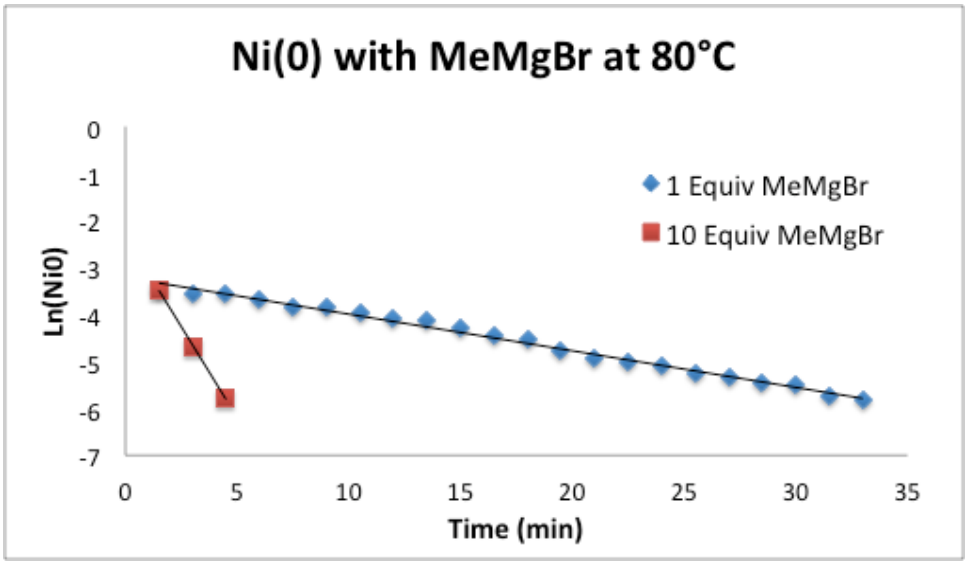
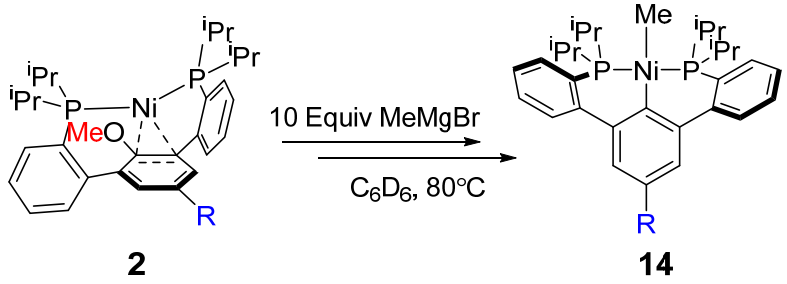


Figure 4.3: Rate acceleration of aryl-oxygen bond activation in 2 with 1 and 10 equivalents of MeMgBr.

	T(°C)	k_{obs} (min^{-1}) (x10^{-3})
Ni^0 w/1 Equiv MeMgBr	80	78
Ni^0 w/1.25 Equiv $Me_2MgTMEDA$	80	70
Ni^0 w/10 Equiv MeMgBr	80	774

Table 4.1: Rate acceleration of aryl-oxygen bond activation in 2

Scheme 4.1: Reactivity of 2 with excess Grignard reagent



Intrigued by the results with MeMgBr the effect of other Grignard reagents were investigated. It was found that other alkyl and aryl Grignard reagents also accelerate the rate of oxidative addition in **2**. Ethyl, phenyl, benzyl, and mesityl

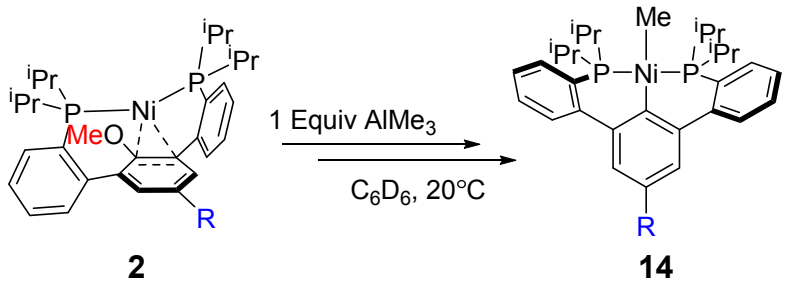
Grignards all resulted in rate increases. It was quite surprising that the bulkier Grignards (mesityl and phenyl) still resulted in an observed increase in rate.

Emboldened by the effect of Grignard reagents on aryl oxygen bond activation, other Lewis acids were tested for similar effects. The addition of MeLi lead to an increase in rate similar to what was observed with Grignard reagents. Surprisingly diethyl, dimethyl, and dipentafluorobenzyl zinc species did not result in an increase in aryl oxygen bond activation. Similarly metal tert-butoxides (Li, Na, and K) did not result in an increase in rate. It was proposed that the solubility of the metal tert-butoxides might inhibit their effect on the reactivity of the nickel complex, however, while changing the solvent to difluorobenzene did increase the amount of solubilized tert-butoxide the rate of aryl-oxygen bond activation was not found to increase. Even when a more soluble metal alkoxide was used (potassium 2-methylbutan-2-olate) no effect was observed. Several Lewis acidic metal salts were tried (MgX_2, FeX_3, FeX_2, $AlCl_3$, and CrX_3) however the salts were found to be insoluble under the reaction conditions and while difluorobenzene did seem to increase the amount of the metal salt solubilized the rate of aryl-oxygen bond cleavage was found to be the same as the rate without additive. Although no rate acceleration was observed, the addition of $AlCl_3$ did result in the formation and precipitation of a dark solid, which did not change upon heating. Hydrolysis of this solid with HCl and investigation of the oragnics by ESI mass spectrometry revealed the mass of the free diphosphine terphenyl anisole showing that the aryl-oxygen bond had not been cleaved.

Unexpectedly, the addition of alkyl boranes did not lead to increased reactivity in **2**. Alkyl boranes have been shown to increase oxidative addition in nickel catalytic systems for the activation of cyano groups and other catalytic systems.[8] Fortunately, the

addition of alkyl aluminum reagents led to increased rate of oxidative addition in **2**.[8c,8d,9] Addition of one equivalent of $AlMe_3$ lead to complete conversion of **2** into the previously characterized **14** (oxidative addition followed by a subsequent transmetallation) within minutes (Scheme 4.2). Without any additive the **2** undergoes complete conversion to the **3** within approximately seven days at 20 °C. This leads to an estimate of a three order of magnitude rate increase for the addition of $AlMe_3$.

Scheme 4.2: Addition of $AlMe_3$ to 2 leads to a room temperature aryl oxygen bond activation



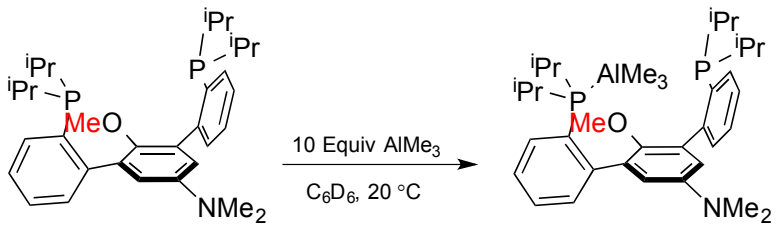
2 **14**

The addition of other alkyl aluminum reagents also leads to an observed rate increase. $AliBu_3$, $AlEt_3$, and $AlPh_3$ all lead to a rate acceleration for the formation of a nickel(II) species. The $AlPh_3$ lead to significantly slower rates than that observed for the aluminum alkyls ($AlMe_3$, $AliBu_3$, and $AlEt_3$), possibly due to the steric bulk of the triphenyl species.

In order to better understand the observed effect of Lewis acidic additives, studies were undertaken to better understand the binding of AlR_3 to the nickel(0) system and the method of aryl-oxygen bond activation. To test if nickel was required for the aryl-oxygen bond activation the diphosphine terphenyl anisole (**1**) was treated with ten equivalents of $AlMe_3$. Upon mixing a new species formed as observed by NMR spectroscopy. ^{1}H NMR shows shifts in the isopropyl methyls and methine

protons, where one methine shows a large shift upfield from 1.87 ppm to 1.18 ppm. Upfield shifts are also observed for the -NMe_2 and –OMe functional groups from 2.60 to 2.25 ppm and 3.10 to 2.63 ppm respectively. ^{31}P NMR shows two broad peaks at 18.25 and -4.82 ppm. The spectroscopic data is consistent with the aluminum coordinating to the diphosphine terphenyl anisole. There are multiple points where the $AlMe_3$ could coordinate, either through the methoxy group, the dimethyl amine, or through the phosphines. Coordination through the methoxy or dimethyl amine would not account for the large phosphorous shift in the ^{31}P NMR. It is likely that the $AlMe_3$ is coordinating through the phosphine, although coordination of multiple equivalents of $AlMe_3$ could be possible. Regardless, hydrolysis of this adduct results in the recovery of **1**. Trimethylaluminum does not cleave the aryl oxygen bond in the absence of nickel (Scheme 4.3).

Scheme 4.3: Reactivity of $AlMe_3$ with 1



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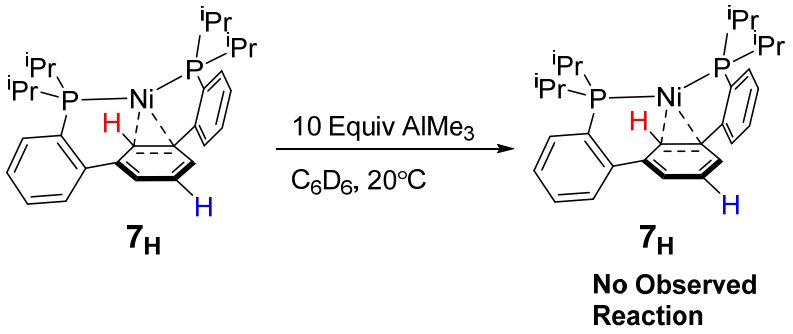
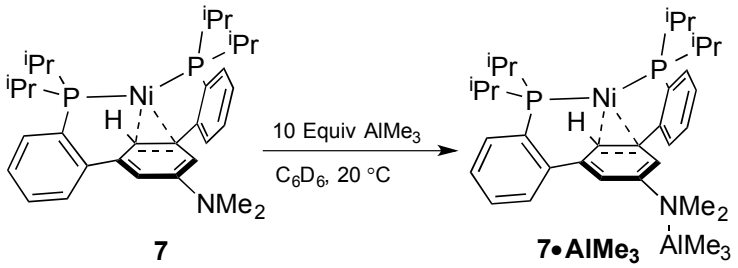
As nickel is required to cleave the aryl-oxygen bond it is possible that AlR_3 coordinates through nickel and the adduct cleaves the aryl-oxygen bond. To this end a nickel(0) diphosphine meta-terphenyl containing no *ipso*- or *para*- functionalities (**7$_H$**) was treated with $AlMe_3$. The addition of $AlMe_3$ leads to no change in the nickel complex as observed by NMR spectroscopy (Scheme 4.4). This suggests that the nickel does not interact with an added AlR_3 in the absence of the ligand functionalities.

Scheme 4.4: Reactivity of $AlMe_3$ with 7_H



Introduction of a $-NMe_2$ group in the *para*- position of the ligand backbone (**7**) leads to the observed coordination of $AlMe_3$ by spectroscopy. An upfield shift is observed for the $-NMe_2$ group resonance from 2.58 ppm to 2.36 ppm upon coordination. A similar shift is observed in the resonance of the *ipso*- proton from 5.37 to 4.85 ppm, while the while the central arene resonance shifts downfield from 5.83 to 6.04. There is a small shift of 2.8 ppm by ^{31}P NMR spectroscopy (38.55 to 41.33 ppm upon $AlMe_3$) indicating there is not much interaction of $AlMe_3$ with the phosphines in the nickel(0) model complexes. The shifts observed upon $AlMe_3$ coordination are mainly localized to the central arene ring of the terphenyl backbone in **7**, which leads to the proposal that the added aluminum is interacting with the free lone pair on the $-NMe_2$ group (Scheme 4.5).

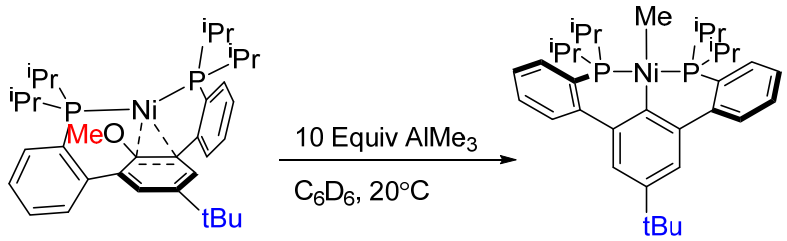
Scheme 4.5: Coordination of $AlMe_3$ to 7 through the NMe_2 moiety



7 **7•AlMe$_3$**

When the backbone contains a –NMe_2 group the AlR_3 coordinates to the –NMe_2 group, however it is not clear how that will accelerate the aryl-oxygen bond activation. Changing the *para*= group to a tBu should prevent *para*- coordination. As a tBu group should eliminate *para* coordination and binding is not observed in the absence of any groups, complex **2$_{tBu}$** should allow us to test for coordination of AlR_3 to the methoxy moiety of the terphenyl backbone. Treatment of **2$_{tBu}$** with ten equivalents of $AlMe_3$ leads to the formation of **13$_{tBu}$**. As the methoxy group is the only group capable of binding $AlMe_3$ (*vide supra*) this provides evidence that the $AlMe_3$ (and other AlR_3 or Lewis acidic reagents) is coordinating to the methoxy group when accelerating the rate of oxidative addition (Scheme 4.6).

Scheme 4.6: Addition of $AlMe_3$ to 2$_{tBu}$



2$_{tBu}$ **14$_{tBu}$**

Low temperature NMR spectroscopy studies were carried out in an attempt to observe intermediates in the Lewis acid accelerated aryl oxygen bond activation. At -80 °C, **2$_{tBu}$** gives a broad ^{1}H NMR spectrum with –OMe and central arene resonances at

3.19 and 6.44 ppm respectively. The addition of one equivalent of $AlMe_3$ leads to a downfield shift in the methoxy resonance to 3.39 ppm and an upfield shift in the central arene resonances to 6.15 ppm. A curious downfield shift is observed for the ortho protons of the outer terphenyl rings from 7.73 to 8.00 ppm upon $AlMe_3$ coordination (Figure 4.4). This intermediate is stable surprisingly stable at low temperatures, at -80 °C no decomposition was observed after eight hours. Warming leads to aryl-oxygen bond activation and formation of $\mathbf{14_{tBu}}$. No other intermediates are observed by 1H NMR for the conversion of the nickel aluminum intermediate to $\mathbf{14_{tBu}}$.

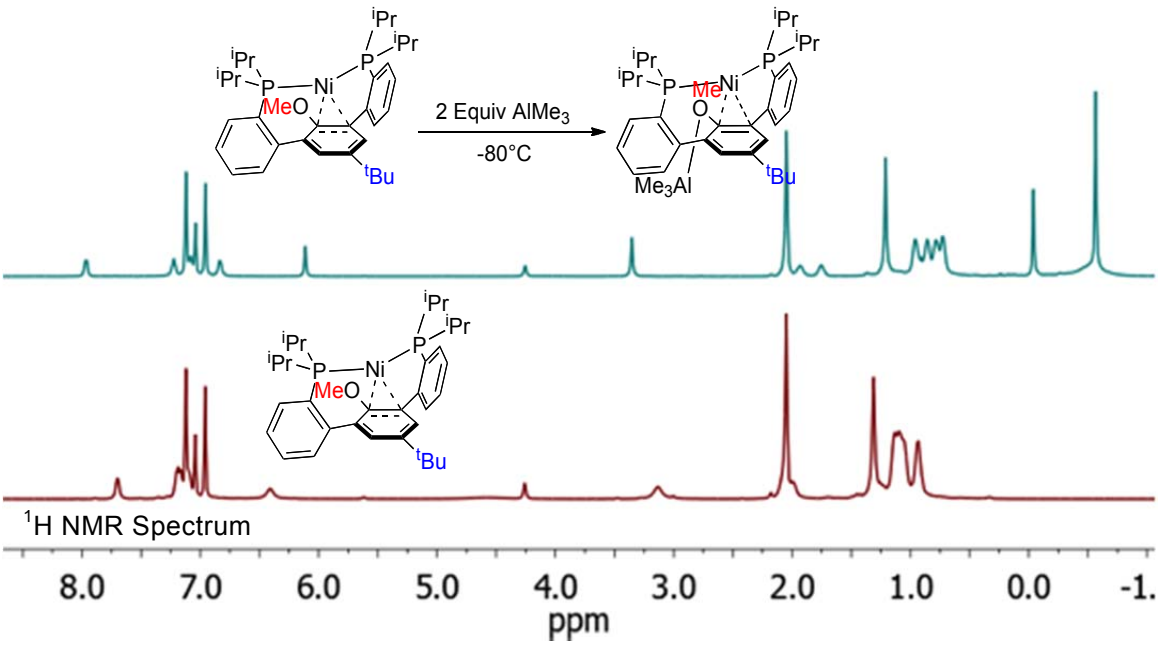


Figure 4.4: Addition of $AlMe_3$ to $\mathbf{2_{tBu}}$ at -80 °C

NOE experiments were used to provide further insight into structure of the intermediate. Homonuclear 2D NOESY spectra collected at -80 °C gratifyingly reveal interaction between the $AlMe_3$ methyl groups and the ipso methoxy group as observed as a cross peak at -0.5 and 3.5 ppm (Figure 4.5). Interestingly there is also an interaction between the aluminum alkyl and the ortho protons of the outer terphenyl

rings as shown by the cross peak at -0.5 and 8.0 ppm (Figure 4.5). The low temperature NOE data suggests that the $AlMe_3$ is coordinated to the methoxy on the face of the central arene ring opposite that of the nickel center. The methoxy group shows correlations to the isopropyl groups relating their close proximity in space (cross peak between 1 and 3.5 ppm, Figure 4.5). No methyl correlations were observed between the isopropyl groups of the phosphine and $AlMe_3$, which would be present if the aluminum center resided on the same side as the nickel center.

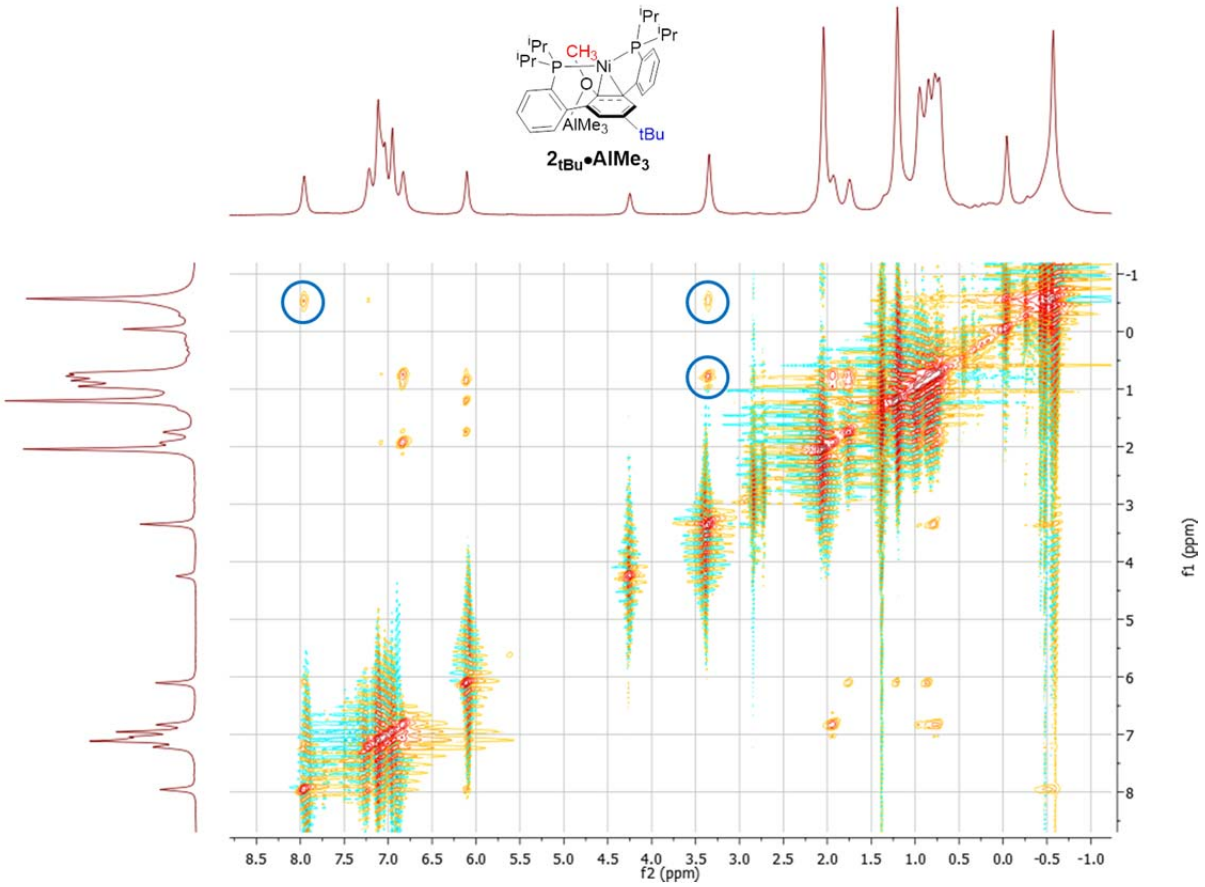


Figure 4.5: NOESY spectra of $\mathbf{2_{tBu}•AlMe_3}$ collected at -80 °C

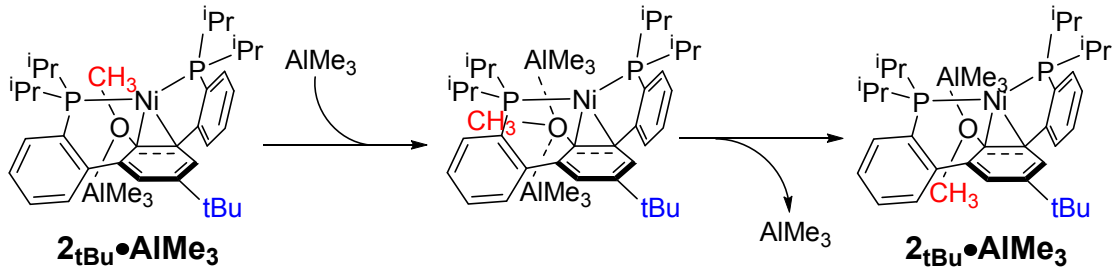
With a better understanding of where and how the aluminum alkyl is accelerating the rate of aryl oxygen bond activation in depth studies of the rate were under taken. The decay of the nickel(0) trimethyl aluminum intermediate ($\mathbf{2_{tBu}•AlMe_3}$)

was observed over time for three reaction half lives using 10 to 100 equivalents of $AlMe_3$ (Figure 4.6). As one can see from the rate data there is an increase in the rate of the aryl oxygen bond activation with increasing concentrations of $AlMe_3$. It should be noted that a similar rate increase is observed with increasing concentration with Grignard reagents. This rate increase is consistent with a bimolecular mechanism. However there is also a significant increase with just one equivalent of $AlMe_3$.

Determination of the activation parameters for the aryl oxygen bond assisted cleavage were undertaken with two and ten equivalents of $AlMe_3$. Suprisingly both two and ten equivalents gave similar values for $\Delta S^{\ddagger}$ (-4.83 and -2.23 cal K^{-1} respectively) and $\Delta H^{\ddagger}$ (14.78 and 14.92 kcal mol^{-1} respectively) of activation (Table 4.2). The small negative $\Delta S^{\ddagger}$ suggests that the mechanism is intramolecular, which is not consistent with the effect of $AlMe_3$ concentration on the rate that is observed. It is possible that there are two alternate mechanisms for the activation of the aryl oxygen bond. The first mechanism would only require a single equivalent of $AlMe_3$ coordinated to the oxygen bond. This single equivalent leads to a large rate increase (about three orders of magnitude) over what is observed in the absence of any additive. The second mechanism would involve several equivalents of $AlMe_3$, possibly to further activate the aryl-oxygen bond or form a lower energy transition state. Calculations performed by Sibo Lin suggest that the aryl oxygen bond activation in the presence of $AlMe_3$ proceeds through an intermediate where the $AlMe_3$ and Ni metal center are on the same side. While this is not observed by NOE studies, it does provide a possible explanation of how the presence of excess $AlMe_3$ could accelerate the rate of the assisted oxidative addition. Upon addition of one equivalent of $AlMe_3$, the aluminum

center coordinates to the face opposite of the metal center, possibly due to sterics (Scheme 4.7).

Scheme 4.7: Possible Mechanism for rate acceleration with excess $AlMe_3$



From here since the activation energy for oxidative addition in this intermediate is large the $AlMe_3$ must rearrange somehow from the local minimum to the active transition state. Another equivalent of $AlMe_3$ could coordinate to the methoxy from the top face of the ring causing dissociation of the first $AlMe_3$ equivalent leading to the calculated more favorable transition state for oxidative addition (Scheme 4.7). Increases in the concentration of $AlMe_3$ would lead to greater concentrations of this unstable intermediate leading to a faster rate, which coincides with what is observed. However, the rate increase by the additional equivalents of $AlMe_3$ is not as substantial as the first. Increasing the $AlMe_3$ from 2 to 10 equivalents only results in a 2.5x increase in rate. Similarly increasing the rate from 10 to 100 equivalents affords only a 5 fold increase.

	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1})
Ni(0) with No Additive	20 ± 2	-6 ± 1
Ni(0) with 2 Equivs of $AlMe_3$	15 ± 1	-5 ± 2
Ni(0) with 10 Equivs of $AlMe_3$	14.9 ± 0.7	-2 ± 1

Table 4.2: Observed activation parameters of aryl oxygen bond activation in $\mathbf{2_{tBu}}$ with 2 and 10 equivalents of $AlMe_3$

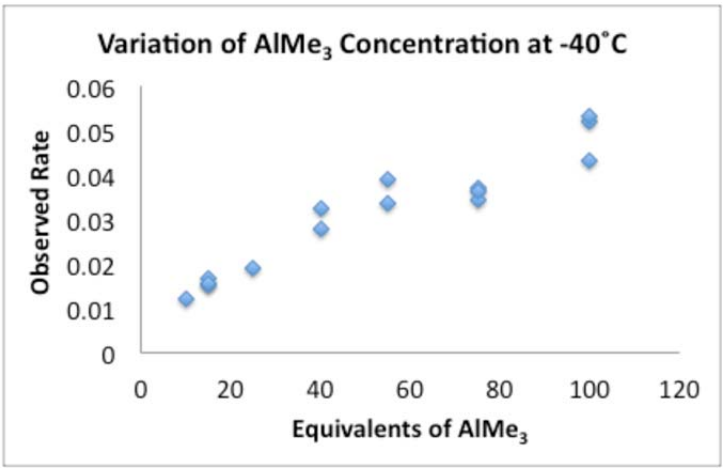


Figure 4.6: Rate of aryl oxygen bond activation in $\mathbf{2_{tBu}}$•$\mathbf{AlMe_3}$ with varying concentration of $AlMe_3$ at -40 °C

CONCLUSIONS:

The rate of oxidative addition observed in the nickel(0) diphosphine terphenyl ether model system was found to increase in the presence of Lewis acidic metals. Grignard reagents were found to increase the rate an order of magnitude while trimethylaluminum increases the rate about three orders of magnitude. At -80 °C an intermediate was identified by NOE coorelations where the $AlMe_3$ is coordinated to the ether moiety of the terphenyl ether trans to the nickel metal center. Warming this intermediate lead to the activation of the aryl ether bond. Increases in the concentration of $AlMe_3$ or MeMgBr leads to an increase in the observed rate. Although the rate increase is not as substantial as the increase from 0 to 1 equivalents of $AlMe_3$. This leads to the possibility two different mechanisms, one which requires only one equivalent and another, which requires multiple $AlMe_3$ centers.

EXPERIMENTAL SECTION:

General considerations: Unless otherwise specified, all compounds were manipulated using a glove box under a nitrogen atmosphere. Solvents for all reactions were dried by Grubbs' method. Benzene-d6 was purchased from Cambridge Isotope Laboratories and vacuum distilled from sodium benzophenone ketyl. All other materials were used as received. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Varian Mercury 300 spectrometer at ambient temperature, unless denoted otherwise. Chemical shifts are reported with respect to internal solvent: 7.16 ppm and 128.06 (t) ppm (C_6D_6) and for ^{1}H and ^{13}C NMR data, respectively. ^{31}P NMR chemical shifts are reported with respect to the instrument solvent lock when a deuterated solvent was used. IR spectra were recorded on a Thermo-Fisher Scientific Nicolet 6700 FT-IR spectrometer. Gas chromatography-mass spectrometry (GC-MS) analysis was performed upon filtering the sample through a plug of silica gel. Fast atom bombardment-mass spectrometry (FAB-MS) analysis was performed with a JEOL JMS-600H high-resolution mass spectrometer.

Kinetic Studies:

Special considerations: All kinetic data was collected on a Varian INOVA-500 MHz NMR spectrometer. In all experiments tri-*tert*-butylbenzene was used as a standard.

Example of a Kinetic Reaction:

In a glove box a J-Young tube was charged with 7.3 mg (0.012 mmol) of **2**$_{tBu}$ and 1.1 mg (0.004 mmol) of trimethoxybenzene in 200 µL d_8-toluene. This mixture in the J-Young tube was frozen in a liquid N_2 cooled cold well. After the solution was frozen a 100 µL d_8-toluene buffer layer was added to the tube and the frozen. On top of this layer was

added a solution of $AlMe_3$ in d_8-toluene. The J-Young tube was frozen and transferred to a dry ice acetone bath. The tube was transferred to the NMR at the desired temperature. NMR spectra were collected at regular intervals.

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