Lewis Acid Accelerated Aryl Ether Bond Cleavage with Ni: Orders of Magnitude Rate Enhancement by AlMe$_3$**

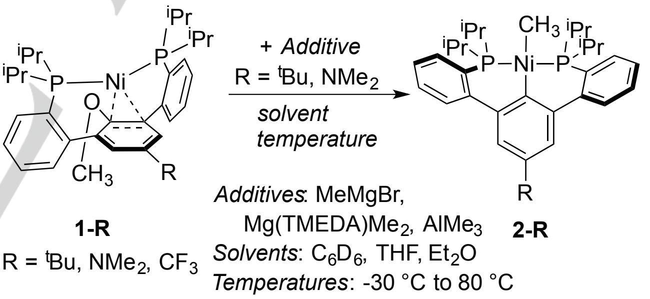
Paul Kelley, Guy A. Edouard, Sibo Lin, Theodor Agapie*

Abstract: *Study of the kinetics of intramolecular aryl ether C-O bond cleavage by Ni was facilitated by access to a family of metal complexes supported by diphosphines with pendant aryl-methyl ethers. The nature of the aryl substituents was found to have little effect on the rate of cleavage. In contrast, soluble Lewis acidic additives accelerate the aryl ether cleavage dramatically. The effect of AlMe$_3$ was studied in detail, and showed increase in rate by several orders of magnitude. Low temperature NMR spectroscopy studies demonstrate quantitative coordination of ether to Al. From the Lewis acid-bound precursor, the activation parameters for ether cleavage are significantly lower. These findings provide a mechanistic basis for milder catalyst design for the activation of strong bonds.*

The elaboration of aryl C–O bonds with Ni has emerged as a versatile synthetic tool in organic methodology as Ni is relatively inexpensive, phenol precursors are readily available, and synthetic modification of the aromatic ring is facile.[1] Typically, phenols are first converted to more reactive phosphinates, sulfonates, or triflates.[1a-d] The activation of less reactive aryl ether C–O bonds and even phenols has recently been reported as a feasible strategy to employ common precursors..[1b, 1e, 2] Notably, in these systems, Grignard reagents, alkyl boranes, alkyl aluminum, or silanes are used as electrophiles, all of which can act as Lewis acids to participate in aryl–heteroatom bond activation. The cleavage of aryl C–O bonds has been reported to proceed at lower temperatures (versus the reaction in the absence of additive) upon addition of an equivalent of AlMe$_3$.[3] The presence of Grignard reagent as well as boronic acid and triethyl borane allow for cleavage of the aryl C–O bond in naphthol.[2e, 2f]The naphtholate oxygen and multiple equivalents of Grignard reagent are proposed to associate in solution, weakening the C–O bond and making the oxygen moiety a better leaving group. In the case of boron-based reagents, both boronic acid and triethyl borane are proposed to interact with the phenolic aryl oxygen. Similarly, Al and Mg centers were shown by computation to coordinate to the ether oxygen and facilitate the oxidative addition step.[2m, 2n, 3b] Lewis acid effects have also been invoked for the cleavage of vinylic C–O and aryl–halide bonds.[4]

More broadly, Lewis acids have been used with Ni catalysts for the activation of nitrile groups.[5] Catalytic hydrocyanation of olefins by Ni^0 phosphite complexes is affected by the presence of Lewis acids.[5e] BPh$_3$ facilitates cleavage of the C–CN bond of allylnitrile with Ni.[5f] A solid state structure of an intermediate species reveals both Al coordination to the lone pair and Ni coordination to the π-system of the nitrile group, providing evidence for cooperative Ni-Lewis acid activation of nitrile.[5c]

Given the utility of Lewis acids in a variety of catalytic transformations of Ni, mechanistic insight into their role in the activation of aryl–heteroatom bonds for oxidative cleavage is of interest. We have employed metal complexes supported by a *m*-terphenyl diphosphine ligand containing an aryl ether functionality to gain insight specifically into the activation of aryl C–O bonds.[6] Ni^0 binds to the π-system in η^2-fashion proximal to the ether moiety, similar to the proposed intermediate for the activation of C–O bonds in the cross-coupling of phenolic derivatives.[7] It was demonstrated that the Ni^0 center performs oxidative addition of the aryl–ether stoichiometrically. Intermediates relevant to a reported catalytic system were observed, detailing the mechanism of aryl–ether hydrogenolysis.[3a] With this model system in hand, further insight into the activation of aryl ethers and the effect of added Lewis acids was sought. We report herein rate enhancement of up to several orders of magnitude promoted by Lewis acids.



Scheme 1. Model System for Studies of Aryl Ether C-O Bond Activation by Ni(0).

A series of complexes **1-R** (R=CF$_3$, ^{t}Bu, NMe$_2$, Scheme 1) with electronically distinct substituents was investigated to evaluate influence on the oxidative addition step. Depending on the reaction conditions, the resulting Ni-methoxide species undergo β-H elimination to release formaldehyde, which complicates analysis of the oxidative addition step by reacting with the starting materials **1-R** to produce Ni-CO complexes that do not undergo aryl–O bond activation. Thus to avoid the formation of formaldehyde, the Ni–OMe oxidative addition product was converted to Ni–Me species (**2-R**) by transmetallation *in situ* with MgMe$_2$(TMEDA) (See SI, Scheme SI.1). The decay of **1-R** was monitored by ^{1}H NMR spectroscopy. The kinetics of **1-NMe$_2$** conversion were found to be independent of the concentration of MgMe$_2$(TMEDA) at 60 °C with 1.2 (k = 10.5 x 10^{-3} min^{-1}), 10 (k = 10.2 x 10^{-3} min^{-1}), and 23 equiv (k = 10.7 x 10^{-3} min^{-1}), indicating that the rate of oxidative addition is not affected by this reagent. In agreement, at different

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Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) temperatures where subsequent steps are slower and do not complicate the kinetic measurements of the oxidative addition step, the rates in the absence (k = 2.09 ± 0.05 x 10^{-3} min^{-1} at 45 °C and k = 83 ± 2 x 10^{-3} min^{-1} at 80 °C for **1-NMe₂**) and presence of Mg(TMEDA)Me₂ (k = 2.19 ± 0.05 x 10^{-3} min^{-1} at 45 °C and k = 86 ± 3 x 10^{-3} min^{-1} at 80 °C) are similar.

Table 1. Activation Parameters for **1-NMe₂**, **1-^{t}Bu**, **1-CF₃**.

	1-NMe₂	**1-^{t}Bu**	**1-CF₃**
$\Delta H^\ddagger$(kcal mol^{-1})	21.7 ± 0.2	20 ± 2	21.2 ± 0.4
$\Delta S^\ddagger$(cal K^{-1} mol^{-1})	-2.66 ± 0.03	-6 ± 1	-6.6 ± 0.2

The activation parameters (Table 1) of the oxidative addition step in these model systems (using 1.2 equivalents of MgMe₂(TMEDA) for **1-NMe₂** and **1-tBu**) were calculated using the Eyring equation. Despite the differing electronic character of the arene substituents, the C–O bond activation parameters are generally similar. This is proposed to be a consequence of both ground and transition states being affected similarly (see Figure SI.5 and discussion in SI).

The effect of Lewis acidic additives was investigated. Treatment of **1-NMe₂** with 10 equiv. of MeMgBr in toluene leads to an order of magnitude rate increase of the aryl-oxygen bond cleavage reaction (Table SI.3). This is in contrast with the lack of effect by MgMe₂(TMEDA). We hypothesize that the bidentate ligand TMEDA inhibits the ability of the magnesium ion to interact with the Ni complex. Indeed, treatment of **1-NMe₂** with 10 equiv. of MeMgBr in THF does not lead to an increase in the rate of oxidative addition, consistent with THF coordination and lowering of Lewis acidity of the magnesium center. Notably, the catalytic cross-coupling of aryl ethers with Grignard reagents was reported to give higher yields in non-polar solvents.[2h, 2k] The use of non-polar solvents in the present systems limited the choice of Lewis acids tested due to solubility problems. Aluminum alkyl species were suitable for our kinetics investigations.

Qualitatively, AlMe₃, Al^{i}Bu₃, AlEt₃, and AlPh₃ all lead to rate acceleration for the formation of **2-R** or new species assigned as Ni^{II} based on spectroscopic similarity to **2-R**.[3a] The addition of alkyl boranes did not lead to increased reactivity in **1-NMe₂** although boranes have been shown to facilitate nickel catalysis for the activation of cyano groups and aryl C-O moieties.[2f, 5d]

AlMe₃ was investigated in detail. Addition of 2 equiv. of AlMe₃ leads to complete conversion of **1-NMe₂** to **2-NMe₂** within minutes (Scheme 1). Without any additive, **1-NMe₂** undergoes complete conversion to Ni^{II}-methoxide within ~7 d at 20 °C. Thus, AlMe₃ increases the rate of aryl–O oxidative addition by about three orders of magnitude. Although AlMe₃ coordinates to free phosphine, C–O bond cleavage is not observed indicating that Ni is required. The potential for a direct interaction of AlR₃ with the Ni center was evaluated with a previously reported Ni^0 compound displaying H at the OMe and R positions (**3-H**).[8] No reaction is observed upon treatment of **3-H** with AlMe₃ (NMR spectroscopy) indicating that a Ni-Al heterobimetallic complex is not formed in detectible amounts.

Low-temperature NMR spectroscopy studies were carried out with**1-^{t}Bu** and AlMe₃ in an attempt to observe intermediates. At -80 °C, **1-^{t}Bu** gives a broad ^{1}H NMR spectrum with –OMe and central arene resonances at 3.19 and 6.44 ppm respectively. The addition of 1 equiv. of AlMe₃ sharpens and shifts these peaks to 3.39 ppm and 6.15 ppm, respectively, which is assigned to Al binding of the ether moiety to generate complex **1-^{t}Bu·AlMe₃**. This intermediate is stable at low temperatures; at -80 °C no conversion is observed after 8 h. Warming leads to aryl–oxygen bond activation and formation of **2-^{t}Bu**. No intermediates are observed by ^{1}H NMR for the conversion of **1-^{t}Bu·AlMe₃** to **2-^{t}Bu**.

Table 2. Activation Parameters of Aryl Oxygen Bond Cleavage in **1-^{t}Bu**.

Additive	$\Delta H^\ddagger$ (kcal mol^{-1})	$\Delta S^\ddagger$ (cal K^{-1})
None	20 ± 2	-6 ± 1
2 equiv. AlMe₃	14 ± 2	-7 ± 1
10 equiv. AlMe₃	15 ± 1	-2.2 ± 0.2

Homonuclear 2D NOESY spectra collected at -80 °C reveal a cross-peak between the AlC*H*₃ and ether OC*H*₃ protons (Figure SI.4) consistent with ether coordination to Al. There is also a cross-peak between AlCH₃ and protons of the outer rings of the terphenyl unit, *ortho*- to the aryl–aryl linkage. The OC*H*₃ group shows correlations to the isopropyl groups. No correlations were observed between the isopropyl groups and AlC*H*₃. These data suggest that AlMe₃ is coordinated to the ether in a locked geometry placing the Lewis acid away from the Ni center relative to the plane of the central arene and the ether Me group toward the Ni center.

Kinetics studies of the conversion of **1-^{t}Bu·AlMe₃** to **2-^{t}Bu** were performed at -40 °C in the presence of several concentrations of AlMe₃ (Figure SI.11). Although the rate of the aryl oxygen bond activation rises with increasing concentrations of AlMe₃ (Figure 1), the effect is relatively small (~4 fold rate increase from 10 to 100 equiv. of AlMe₃ at -40 °C) compared to the acceleration provided by the addition of Lewis acid (~10^5 fold increase from no AlMe₃, as extrapolated with the Eyring equation, to 10 equiv. of AlMe₃ at -40 °C). The two distinct rate accelerations induced by AlMe₃ suggest two competing mechanisms. The activation parameters for the aryl oxygen bond cleavage were determined with 2 and 10 equiv. of AlMe₃. Similar values for $\Delta S^\ddagger$ (-7 ± 1 and -2.2 ± 0.2 cal K^{-1} respectively) and $\Delta H^\ddagger$ (14 ± 2 and 15 ± 1 kcal mol^{-1} respectively) were obtained (Table 2). The small negative $\Delta S^\ddagger$ is inconsistent with a bimolecular rate determining step for the major contributing pathway to the observed rate constant. The major mechanism involves a single equivalent of AlMe₃ bound to the ether moiety (**1-^{t}Bu·AlMe₃**) without additional AlMe₃ involved in a step affecting the rate expression. The minor mechanism involves additional AlMe₃, possibly to further activate the aryl–oxygen bond or to generate an isomer with a lower energy transition state for ether cleavage. Binding of two equivalents of Lewis acid to the ether moiety is expected to be sterically hindered. Therefore, the dependence on $AlMe_3$ concentration is proposed to be caused by the Lewis acid facilitating access to a more reactive species, in a slow associative step. This step could involve $AlMe_3$ association to one of the Me groups of ether bound $AlMe_3$, to generate a more Lewis acidic Al center. Since the observed rate constants begin to level off at high concentrations of $AlMe_3$, this pathway alone cannot explain the rate data (Figure 1; also see SI, kinetics analysis). Alternatively, *cis* coordination of $AlMe_3$ to the ether while displacing the *trans* $AlMe_3$ may occur (Figure 2).

To further study the $AlMe_3$-accelerated oxidative addition process, density functional theory (DFT) calculations were employed. The DFT models (Figure 2) use methyl substituents on the phosphines instead of isopropyl groups; this choice was made due to the greater computational resources required to analyze extra rotational conformations and vibrational degrees of freedom that would accompany computing isopropyl groups. Dispersion corrections, which are important for accurately calculating binding energies of $AlMe_3$ were included in single-point energy evaluations.[9]

The calculated energies of the model (**B**$_{\mathbf{trans}}$) of **1-^{t}Bu·AlMe$_3$** and its isomer, *cis*-facial relative to central arene and the Ni center (**B**$_{\mathbf{cis}}$) are very similar. However, it should be noted that **B**$_{\mathbf{cis}}$ would be sterically destabilized if full ^{i}Pr rather than Me phosphine substituents were present. Thus, **B**$_{\mathbf{trans}}$ represents the most likely structural model for **1-^{t}Bu•AlMe$_3$**, in agreement with the aforementioned NOE experiments. From **B**$_{\mathbf{trans}}$, oxidative addition can proceed through **C**$_{\mathbf{trans}}$. This barrier is calculated to be 17.0 kcal/mol. For comparison, direct oxidative addition without $AlMe_3$ coordination, proceeds through transition state **C**$_{\mathbf{AlFree}}$, which is 22.4 kcal/mol uphill. Thus, $AlMe_3$ lowers that activation barrier by *ca*. 5 kcal/mol, which is in notable agreement with the experimental values. Lowering of the activation barrier for oxidative addition to Ni by coordinated Lewis acids has been noted by previous computational studies.[2m, 2n, 3b] After oxidative addition and transmetallation, the Ni^{II}-Me species **D** (corresponding to **2-R**) is afforded. The computed transition state, **C**$_{\mathbf{cis}}$, for aryl–O cleavage from **B**$_{\mathbf{cis}}$ shows a methyl group of the $AlMe_3$ moiety bridging to the Ni center (r(C–Ni) = 2.33 Å). This interaction is precedented by a crystal structure[10] in which a Ni center and an $AlMe_2$ fragment are bridged by an alkoxide and a methyl group (r(C–Ni) = 2.29 Å).[10] **C**$_{\mathbf{cis}}$ is almost 4 kcal/mol lower in energy than **C**$_{\mathbf{trans}}$.

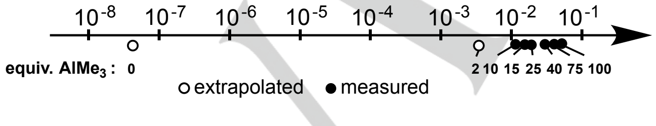

Figure 1. Rate constants (s^{-1}) for aryl ether C-O oxidative addition at 233 K (or extrapolated from higher temperature measurements) as a function of $AlMe_3$ addition.

The mechanism of the $AlMe_3$-assisted reaction of **1-R**, informed by the DFT models and accounting for the observed concentration dependence of $AlMe_3$ involves aryl-oxygen bond cleavage from a species with an Al-ether interaction. This process can proceed in a *trans*-facial manner (c.f. via **C**$_{\mathbf{trans}}$) with significantly lower activation barrier than the Al-free C-O cleavage. As a secondary mechanism, excess $AlMe_3$ is proposed to facilitate, in a slow step, the conversion of *trans*-facial $AlMe_3$ adduct to *cis*-facial $AlMe_3$ adduct (c.f. **B**$_{\mathbf{trans}}$ to **B**$_{\mathbf{cis}}$). A similar intermolecular process has been observed for scrambling between THF•$AlMe_3$ and Al_2Me_6.[11] *Cis*-facial aryl-oxygen cleavage (c.f. **C**$_{\mathbf{cis}}$) is then fast compared to *trans*-facial pathway. The combination of two mechanisms (Figure 2) for ether cleavage is consistent with the derived rate laws and kinetics data. Overall, these experimental and computational mechanistic studies show that Al binding to the aryl ether moiety significantly lowers the activation barrier for cleavage, likely by making the methoxide a better leaving group.

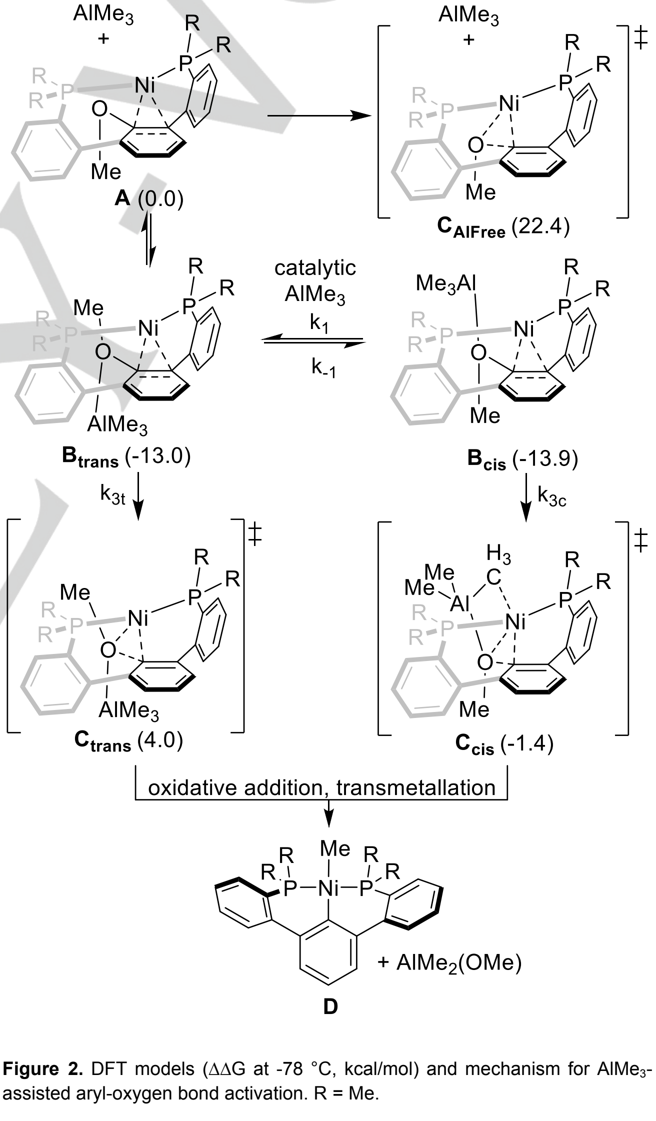

Figure 2. DFT models (ΔΔG at -78 °C, kcal/mol) and mechanism for $AlMe_3$-assisted aryl-oxygen bond activation. R = Me.

In summary, $AlMe_3$ was demonstrated to afford acceleration by several orders of magnitude of Ni-facilitated aryl ether C–O bond cleavage in a methylaryl ether substrate bearing pendant phosphines. This substrate allows for detailed mechanistic studies of the reaction by starting from a precursor that displays a Ni–arene interaction adjacent to the aryl C–O bond to be cleaved. From this precursor, observation of an intermediate consistent with coordination of Al to the ether is possible at low temperatures. Binding of Lewis acid to oxygen is proposed to make the alkoxide–Lewis acid adduct a better leaving group in the cleavage of the aryl C–O bond by Ni. Related ether activation pathways may occur for Lewis acid-facilitated aryl ether bond cleavage previously reported. Given the remarkably large effect on the rate of aryl C-O cleavage, addition of Lewis acids provides an appealing strategy for the design of catalytic systems for the activation aryl ethers and other strong bonds under mild conditions.

Keywords: aryl ether cleavage • nickel • Lewis acid • rate acceleration • cross coupling

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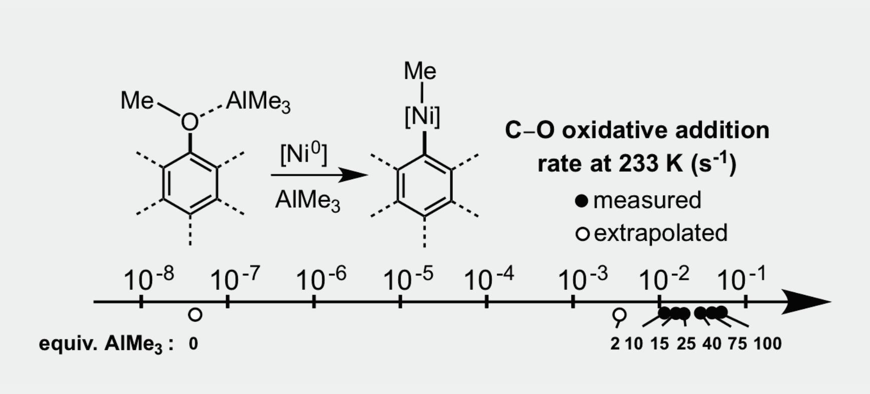

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