ROLES OF CATION-MACROCYCLE INTERACTIONS IN MODULATING THE
REACTIVITY OF TRANSITION METAL PINCER-CROWN ETHER COMPLEXES

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ABSTRACT

Jacob B. Smith: Roles of Cation-Macrocycle Interactions in Modulating the Reactivity of Transition Metal Pincer-Crown Ether Complexes (Under the direction of Alexander J. M. Miller)

Pincer-crown ether ligands were designed to exhibit hemilability and also support cation-macrocycle interactions. These ligands feature strong phosphine and phenyl donors, and a pendent aza-crown ether group that provides hemilabile donors that can bind to the transition metal center and serve as a docking site for cations. Cation-macrocycle interactions can be exploited to directly control the primary coordination sphere of these complexes leading to control over ligand substitution reactions and catalysis. When the macrocycle acts simply as a docking site for cations, bound cation-substrate interactions can be harnessed to modulate reactivity.

In chapter 2, nickel catalysts supported by diethylamine- or aza-crown ether-containing aminophosphinite (NCOP) pincer ligands catalyze the insertion of benzaldehyde into a C–H bond of acetonitrile. Neutral tert-butoxide precatalysts are active without any added base and give good yields of product after 24 h, while the cationic precatalysts require a base cocatalyst and operate much more slowly. In situ spectroscopic studies identified several intermediates and a common deactivated species. The deactivated cationic species is inactive under standard base-free conditions, but catalysis can be reinitiated by the addition of base.

In Chapter 3, the thermochemistry of cation–macrocycle interactions in nickel pincer complexes bearing a hemilabile aza-15-crown-5 or aza-18-crown-6 macrocycle is investigated
and applied to cation-controlled reversible ligand binding. Cation–crown interactions were examined in the solid-state and in solution (dichloromethane, and acetonitrile). Tridentate-bound pincer complexes bind cations more than 100,000 times more strongly than the tetradentate counterparts with a crown ether oxygen donating to nickel. The newfound thermodynamic insight guided the development of in situ switchable ligand binding and release at nickel using cations.

In Chapter 4, the impact of post-macrocyclization modification of 1-aza-15-crown 5 through synthetic organic and organometallic tuning is discussed. Binding affinities for Li\(^+\) and Na\(^+\) salts are reduced substantially moving from the simple organic macrocycle to an organometallic pincer-crown ether. The selectivity for Li\(^+\) over Na\(^+\) increases dramatically, by as much as 30-fold. The impact of transition metal and ligand substitution at the metal center significantly impacts Li\(^+\) binding strength. Preliminary heteroditopic binding of LiCl by an iridium pincer-crown ether is also demonstrated.
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<td>Greek gamma: crystallographic angle</td>
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<tr>
<td>$\delta$</td>
<td>Greek delta: denotes chemical shift reference scale</td>
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<td>$\theta$</td>
<td>Greek theta: general angle</td>
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<td>$\Delta$</td>
<td>Greek capital delta: denotes separation between values or applied heat</td>
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g  Gram
h  hour(s)
Hz  Hertz
PF$_6^-$  Hexafluorophosphate
'^Pr  Isopropyl, -CH(CH$_3$)$_2$
IR  infrared
$^x$J$_{YZ}$  magnetic coupling between atoms X and Y through a distance of x bonds
K  Kelvin
kcal  kilocalorie
L  general ligand, usually 2 e$^-$ donor
M  Molar
M  general metal atom
µL  Microliter
mg  Milligram
mL  Milliliter
mM  Millimolar
mmol  Millimole
m  multiplet
m  meta
Me  methyl, -CH$_3$
min  minute
mol  mole
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CHAPTER 1: INTRODUCTION

1.1 Controllable Catalysts

Catalysts play a vital role in biology and in the chemical and pharmaceutical industries by providing efficient, low-energy pathways for selectively breaking and making chemical bonds. In biology, enzymes catalyze a wide variety of complex biochemical reactions that are vital to our lives.\textsuperscript{1,2} In the chemical and pharmaceutical industries, synthetic catalysts have been employed successfully for over 100 years. They have enabled breakthrough discoveries in chemical synthesis and have lowered the energy needed to operate critical processes on large scales, providing molecular building blocks and chemical compounds that save lives and help continue to increase the standard of living worldwide.\textsuperscript{3} Over 75\% of chemicals from industry are produced with the aid of catalysts.\textsuperscript{4} Catalyst development and improvement paves the way for the discovery of new chemicals, improves the energy efficiency of industrial processes, and aids in the avoidance of the generation of toxic by-products, maximizing social and economic benefits while minimizing negative environmental impacts.\textsuperscript{3,4}

One class of catalysts that is particularly promising both practically and fundamentally is in situ controllable catalysts. A controllable catalyst is one that exhibits a change in activity or selectivity upon in situ exposure to an external stimulus or a change in experimental conditions.\textsuperscript{5,6} Regulating the behavior of catalysts in situ can give these molecules unique properties such as the capability for on/off switchability, stimuli-induced rate tuning, and stimuli-induced changes in reaction specificity or selectivity, all without the need for synthetic modifications to the catalyst itself. Additionally, the ability to trigger or modify the rate of a reaction with an external
stimulus allows for temporal control over chemical reactions, a property generally only associated with complex biocatalysts.\textsuperscript{5-6}

Controllable catalysts could find use in a wide array of applications, especially the growing field of tandem catalysis.\textsuperscript{7-11} For example, tunable catalysts could be optimized to be kinetically compatible with other processes occurring in a chemical reaction. Switchable catalysts could be switched on to complete a portion of the tandem catalysis and then switched off to a protected state until needed again or until recovery occurs. Controllable catalysts that alter selectivity could be used to generate specific regioisomers or stereoisomers of products based on the stimulus added. Eventually controllable catalysts could be designed to synthesize a variety of different products from a pool of building blocks simply by varying the order and type of stimuli applied. Two promising ways to control catalyst reactivity using this approach rely on controlling substrate binding to the catalyst active site and controlling substrate activation through secondary interactions with an added stimulus.

1.2 Controlling Catalysis by Gating Substrate Binding

Enzymes catalyze a plethora of biochemical reactions in nature through complex metabolic pathways. These pathways generally consist of several different enzymes that work in concert to form a single product.\textsuperscript{12} In order to control the amount of product produced by these pathways, many enzymes use allosteric regulation. Allosteric regulation uses the binding of specific cofactors at an allosteric site (a site other than the catalytically active site) to trigger a change in conformation that directly affects the enzyme’s ability to catalyze a given reaction.\textsuperscript{12} Upon exposure to the allosteric regulator, these enzymes shift between structures that have unique properties such as increased substrate affinity or properly positioned catalytic side chains that directly impact catalytic rates.\textsuperscript{12}
There are several modes of action by which allosteric regulation modulates enzyme affinity for a substrate. In some enzymes, access to the active site is physically blocked in the inactive state. A cofactor interacts with the allosteric site of the enzyme and triggers a change in confirmation that unblocks the active site and allows substrate access and catalysis to occur.\textsuperscript{12} Such a pathway is proposed in human isocitrate dehydrogenase, which oxidatively decarboxylates isocitrate to $\alpha$-ketoglutarate.\textsuperscript{13} Allosteric regulation is achieved through binding of magnesium adenosine diphosphate (ADP) and citrate to an allosteric portion of the enzyme. This triggers a significant structural rearrangement facilitating isocitrate access to the enzyme active site and catalytic turnover (Figure 1.1).\textsuperscript{13}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Native structure of human isocitrate dehydrogenase before and after citrate and MgADP binding; the major changes are surrounding Tyr126 (green) and Asp230 (blue) residues.}
\end{figure}

Beyond enzymes, artificial allosteric regulation has been achieved using large supramolecular assemblies that undergo structural changes upon addition of an external stimulus.\textsuperscript{14} These synthetic constructs operate in a manner analogous to many enzymes, with large groups physically block the catalyst active site preventing substrate access and catalytic
turnover. Addition of an allosteric regulator, for example ions, small molecules, or other ligands, triggers a structural rearrangement that unblocks the active site and allows substrate access and catalytic turnover.

Mirkin and co-workers have developed sophisticated supramolecular systems based on the “Weak Link Approach” that can be allosterically regulated by chloride and carbon monoxide.\textsuperscript{15-17} In these systems, the allosteric regulators trigger structural reorganization through coordination to a transition metal center in part of the supramolecular scaffold.\textsuperscript{15} In Scheme 1.1, a triple-layer catalyst for the switchable polymerization of $\varepsilon$-caprolactone is depicted.\textsuperscript{18} Two square planar rhodium(I) subunits containing phosphinoamine ligands with large biaryl blocking groups flank an aluminum catalyst and prevent substrate access. Addition of chloride results in displacement of the amine ligands from the rhodium centers unblocking the aluminum active site and triggering catalysis.
Scheme 1.1 Supramolecular allosteric regulation via the Weak Link Approach. Blocking groups disrupt substrate access to the Al active site. Chloride displaces the amine donors tethered to the large blocking groups to enable catalysis.

Supramolecular machines have also been shown to control catalysis harnessing a similar conformational gating or blocking approach. A molecular rotor with catalyst subunits installed remotely as end groups was reported as a switchable catalyst for Michael addition reactions. The photo- and thermo-isomerizable assembly could be rotated upon light or heat exposure to control both activity and selectivity of the reactions. Rotaxanes have also shown promise as controllable catalysts, with macrocycles as reversible blocking groups, shuttling back and forth depending on protonation states to reveal and conceal active sites. Supramolecular cages and polymer networks offer control of the environment around the catalyst and can regulate substrate access into and out of the supramolecular assembly to modulate catalysis.
In situ control over substrate binding and catalysis in small organometallic systems is less developed, particularly in terms of using post-synthetic modifications and non-covalent interactions to control substrate binding and catalysis.\textsuperscript{29-31} Select systems capable of some degree of control over catalysis or ligand substitution are shown in Figure 1.2. In situ modification of a ligand by changing pH to reach different protonation states with varying reactivity has been achieved.\textsuperscript{32-35} Ligands have also been designed to incorporate receptors for additives such as Lewis acids where binding of the Lewis acid to the ligand directly affects the electron donating ability of the ligand.\textsuperscript{36-38} Light- and redox-triggered substitution have also been extensively studied.\textsuperscript{30, 39-44}
A major goal of the work described in this thesis was to develop a new way to control substrate binding to small organometallic systems. Hemilabile ligands were identified as promising candidates for development of controllable catalyst systems. A hemilabile ligand is a chelate that contains a strong donor along with a weaker donor capable of reversible association/dissociation (Figure 1.3). These ligands have unique properties dependent on the...
identity of the donors and the identity of the linker between the donors and have been shown to support optimization using the traditional synthetic approach to catalyst optimization.46-48

![Diagram](https://via.placeholder.com/150)

**Figure 1.3** Cartoon depiction of ligand hemilability.

A number of remarkable catalysts are constructed using ligands with hemilabile oxygen donors (Figure 1.4). Highly active Hoveyda-Grubbs-type catalysts feature styrenyl ether ligands that impart an extraordinary amount of stability allowing select catalysts to be recovered by column chromatography and recycled after olefin metathesis reactions.49-50 Phosphinoamide chromium catalysts with hemilabile aryl ether moieties also display increased catalytic productivity attributed to an increase in stability imparted by the pendent hemilabile donors.51-53 Hemilabile, P,O-donor phosphino-ether ligands have been found to be particularly suitable for various palladium catalyzed cross-coupling reactions.54-55 These ligands stabilize the highly active catalysts while preventing the coordinative saturation problems that generally plague phosphine-based catalyst systems. Additionally, N,O-chelate amide ligands are among the most successful catalysts for titanium catalyzed polymerization reactions and hydroamination of terminal alkynes.56
Figure 1.4 Select catalysts featuring ligands with hemilabile ether oxygen donors.

These ligands impart a unique combination of activity and stability to catalysts that help them outperform and outlast catalysts lacking hemilabile motifs. Unlike the preceding examples of complexes and catalysts that can be tuned in situ, however, synthetic modifications are generally required to alter the properties of this ligand class. These synthetic modifications often shift the activity/stability balance of the catalysts unpredictably, highlighting the need for an easily modifiable and tunable subclass of these highly useful ligands.\textsuperscript{57-60}

In targeting a subclass of tunable hemilabile ligands, inspiration was taken from the rich fields of metallomacrocycle chemistry\textsuperscript{61} and metallacrown ether chemistry.\textsuperscript{62} These complexes incorporate moieties capable of secondary interactions with metal cations or organic guests and have been studied for modulating redox behavior,\textsuperscript{63} triggering allosteric effects,\textsuperscript{64-71} forming
supramolecular aggregates, and bimetallic activation and catalysis. Often these moieties consist of polyethylene glycol-based bridges or crown ethers synthetically incorporated into a ligand scaffold that positions guests in the secondary coordination sphere of transition metal complexes (Figure 1.5).

**Figure 1.5** Metallomacrocycles capable of complexing an additional cation in the secondary coordination sphere of the complex.

We envisioned a system capable of exploiting this type of secondary interaction to exhibit in situ control over ligand substitution and catalysis through tunable hemilability. The pincer-crown ether system incorporates an aza-crown ether donor as part of an aminophosphinite pincer scaffold featuring strong, anchoring phosphine and phenyl donors (Scheme 1.2). The oxygen atoms of the aza-crown ether macrocycle can act as weak, hemilabile donors to the metal center. When phosphine, phenyl, amine, and ether donors are bound to a metal center in a
tetradentate ($\kappa^4$) configuration, dissociation or displacement of the ether oxygen presents an opportunity for ligand substitution. Additionally, upon dissociation or displacement, the pendent macrocycle becomes available for secondary, non-covalent interactions with cationic guests. These interactions can be harnessed to offset unfavorable ligand substitution using the dual equilibrium approach to tunable hemilability and control substrate access to the metal center.\textsuperscript{86}

\textbf{Scheme 1.2} Dual equilibrium for tunable hemilability with pincer-crown ether complexes.

Using this approach, a wide variety of simple cationic additives can be used to tune ligand substitution and catalysis in situ with pincer-crown ether complexes, all without any synthetic modifications to the complexes. The pentadentate-bound Ir hydride complex [\(\kappa^5-(^{15}\text{c}5\text{NCOP}^\text{Pr})\text{Ir}(H)][\text{BAR}^\text{F}_4]\) (\(\text{Ar}^\text{F} = 3,5\text{-bis-(trifluoromethyl)phenyl}\)) was shown to undergo alkali metal-dependent H\(_2\) activation.\textsuperscript{87} The rate of the reaction could be tuned over two orders of magnitude based on the identity and amount of cation present. The same Ir hydride cation also catalyzes the isomerization of allylbenzene to $\beta$-methylstyrene (Scheme 1.3).\textsuperscript{88} Catalysis was again shown to be modulated by alkali metal cations with lithium giving up to 1000-fold rate enhancements for the reaction.
Scheme 1.3 Proposed mechanism for the cation-modulated isomerization of allylbenzene with an Ir hydride pincer-crown ether complex.

As detailed previously as well as in chapter 3, two equilibria govern cation-modulated ligand substitution and catalytic activity with pincer-crown ether complexes: 1) association/dissociation of the weak ether donor(s) of the ligand and 2) host-guest interactions between cationic additives and the pendent macrocycle. It should also be noted that for this approach to be successfully applied to reversible, controllable ligand substitution and tunable catalysis, kinetic access to the associated and dissociated forms of the ligand must be facile, and host-guest interactions should be kinetically rapid and reversible.

Controlling ligand binding and catalysis using the dual equilibrium approach requires that the system meet several thermodynamic criteria as follows and as depicted in the idealized potential energy surface shown in Figure 1.6. Firstly, solvent displacement of the hemilabile donor must be unfavorable for maximum control. For instance, the binding of a coordinating solvent can interfere with hemilability and compete with substrate binding thereby limiting the extent of control over ligand substitution and slowing catalysis. Secondly, ligand or substrate displacement of the weak donor should be slightly unfavorable. If the ligand/substrate bound species is thermodynamically favored, the secondary equilibrium will offer little to no control over ligand substitution and catalysis. Lastly, interactions between the cationic stimulus and the
fully associated form of the catalyst must be weaker than those with the dissociated form. If secondary interactions were strong for both associated and dissociated forms of the catalyst, thermodynamic stabilization of all species would simply shift the entire energy surface lower.

**Figure 1.6** Idealized free energy landscape of cation-modulated substrate binding and catalysis.

The first equilibrium in the dual equilibrium approach, the dissociation/association of the weak donor(s) of the pincer-crown ether ligand, will vary from catalyst to catalyst based on the metal–oxygen bond strength. The second equilibrium, host-guest interactions between cationic additives and the pendent macrocycle, will vary based on the identity of the macrocycle and the identity and concentration of the additives. A variety of macrocycles can be installed during ligand synthesis.

The true power in this strategy lies in the availability of a wide variety of cationic guests that can be used to tune this second equilibrium. Similarly to organic crowns, pincer-crown ether complexes of a given ligand are expected to show trends in affinity and selectivity for additives. Knowledge of cation-crown association constants will allow for predictions of reactivity and a
high level of control over ligand substitution and catalysis. Additionally, a deeper understanding of these interactions will aid in the development of strategies employing pincer-crown ether catalysts and cationic co-catalysts for alteration of product selectivity and bimetallic catalysis via substrate activation.

1.3 Controlling Catalysis Through Substrate Activation

Further applications of pincer-crown ether complexes can be envisioned based on the ability of the pendent aza-crown ether moiety to dock cations in close proximity to the metal center of the catalyst. Commonly employed alkali metal, alkaline earth, transition metal, and lanthanide cations exhibit varying degrees of Lewis acidity. Lewis acids have a rich history of promoting a wide array of organic transformations through substrate activation and organization.\textsuperscript{89} These electron pair acceptors form a donor-acceptor complex upon coordination to a Lewis basic site on a substrate (Figure 1.8). This complexation results in a partial charge transfer to the Lewis acid and a resulting polarization of the donor molecule making it more reactive. Lewis acids increase the electrophilicity of carbonyl groups, increase the acidity of hydroxy groups, and make coordinated hydroxy, ether, and thioether functionalities better leaving groups.\textsuperscript{89}
Convenient metrics of Lewis acidity include the \( pK_a \) of \([\text{M–OH}_2]^{n+}\) complexes and fluorescence maxima shifts of 10-methylacridone–metal ion salt complexes (Table 1.1). The Lewis acidity of these ions varies widely allowing for a wide range of control over substrate activation.

**Figure 1.7** General Lewis acid activation of a variety of organic molecules.
Table 1.1 Lewis acid induced shifts of 10-methylacridone fluorescence $\lambda_{\text{max}}$ as a measure of relative Lewis acidity.\textsuperscript{91}

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>$\lambda_{\text{max}}$</th>
<th>Florescence Energy (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe(ClO$_4$)$_3$</td>
<td>478</td>
<td>2.59</td>
</tr>
<tr>
<td>Sc(OTf)$_3$</td>
<td>474</td>
<td>2.62</td>
</tr>
<tr>
<td>Fe(ClO$_4$)$_2$</td>
<td>471</td>
<td>2.63</td>
</tr>
<tr>
<td>Cu(ClO$_4$)$_2$</td>
<td>471</td>
<td>2.63</td>
</tr>
<tr>
<td>Co(ClO$_4$)$_2$</td>
<td>470</td>
<td>2.64</td>
</tr>
<tr>
<td>(C$_6$F$_5$)$_2$SnBr$_2$</td>
<td>470</td>
<td>2.64</td>
</tr>
<tr>
<td>Lu(OTf)$_3$</td>
<td>461</td>
<td>2.69</td>
</tr>
<tr>
<td>Y(OTf)$_3$</td>
<td>460</td>
<td>2.7</td>
</tr>
<tr>
<td>La(OTf)$_3$</td>
<td>458</td>
<td>2.71</td>
</tr>
<tr>
<td>Zn(OTf)$_2$</td>
<td>456</td>
<td>2.72</td>
</tr>
<tr>
<td>Ph$_3$SnCl</td>
<td>455</td>
<td>2.72</td>
</tr>
<tr>
<td>Bu$_2$SnCl$_2$</td>
<td>453</td>
<td>2.74</td>
</tr>
<tr>
<td>(C$_6$F$_5$)$_3$SnBr</td>
<td>452</td>
<td>2.74</td>
</tr>
<tr>
<td>Mg(ClO$_4$)$_2$</td>
<td>451</td>
<td>2.75</td>
</tr>
<tr>
<td>Ca(ClO$_4$)$_2$</td>
<td>449</td>
<td>2.76</td>
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<tr>
<td>Sr(ClO$_4$)$_2$</td>
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<tr>
<td>Ba(ClO$_4$)$_2$</td>
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<td>2.79</td>
</tr>
<tr>
<td>LiClO$_4$</td>
<td>442</td>
<td>2.81</td>
</tr>
<tr>
<td>NaClO$_4$</td>
<td>437</td>
<td>2.84</td>
</tr>
<tr>
<td>Mn(ClO$_4$)$_2$</td>
<td>435</td>
<td>2.85</td>
</tr>
<tr>
<td>10-methylacridone</td>
<td>432</td>
<td>2.87</td>
</tr>
</tbody>
</table>

Cooperation between transition metal catalysts and Lewis acids as substrate or intermediate activators has been realized as a powerful strategy for controlling chemical reactivity and catalysis in organic synthesis.\textsuperscript{92-93} In these reactions, generally either the transition metal complex or substrate is too inert to allow the reaction to proceed in the absence of the Lewis acid. Lewis acid cooperation via activation of the substrate lowers barriers and promotes the reaction. For example, the reaction of zirconacyclopentadienes with isocyanates requires a Lewis acid cocatalyst (Figure 1.9).\textsuperscript{94} The Lewis acid is proposed to activate the isocyanate and promote insertion into the zirconacyclopentadiene. Upon insertion, the Lewis acid was also proposed to interact with reaction intermediates to promote metathesis and product formation. In
another example, the palladium catalyzed dimerization of vinyl arenes is promoted by an In(OTf)₃ Lewis acid cocatalyst. The indium trication activates vinyl arenes to nucleophilic attack by Pd(0) complexes. The resulting proposed zwitterionic Pd⁺–alkyl–In⁻ intermediate then inserts an additional vinyl arene and eliminates the product to regenerate the Pd(0) and In³⁺ cocatalysts.

**Figure 1.8** Lewis acid promoted reaction of zirconacyclopentadienes with isocyanates to form iminocyclopentadienes.

Lewis acids can accelerate numerous transition metal-catalyzed reactions. The positive influence of the Lewis acid has, in many cases, been attributed to interactions between the Lewis acid and the metal-bound substrate. For reactions involving carbon monoxide as a substrate, for example, the carbonyl ligand can interact with a Lewis acid during or after C–C bond formation. In cases where pendent macrocycles were present as part of a ligand scaffold and positioned the Lewis acid near the metal center, carbonyl activation or acyl stabilization has been proposed (Figure 1.7). Pincer-crown ether Ir complexes have previously been shown to promote lithium- and lanthanum-accelerated migratory insertion and salt-responsive methanol
carbonylation catalysis.\textsuperscript{104-105} Although the role of the Lewis acid in the mechanisms of these reactions is not fully understood, postulated transition states include those wherein a cation complexed in the pendent crown ether of the molecule interacts with a carbonyl ligand, activating it towards nucleophilic attack by a methyl ligand (Figure 1.7).

\textbf{Figure 1.9} Select examples of macrocycle containing complexes in which a Lewis acid is proposed to interact with carbonyl or acyl ligands bound to the metal center.

Positioning activated substrates near the active site of a pincer-crown ether complex provides an opportunity for controlling catalysis based on the extent of substrate activation via the Lewis acidity of the cationic additive. If the substrate is involved in the rate-determining steps of the reaction, activation with Lewis acids could lower barriers to make the reactions proceed faster. Additionally, if a given reaction does not proceed with an unactivated substrate, but proceeds in the presence of a Lewis acid additive, switchable bimetallic catalysis or substrate selective reactivity becomes possible.
REFERENCES


CHAPTER 2: CONNECTING NEUTRAL AND CATIONIC PATHWAYS IN NICKEL-CATALYZED INSERTION OF BENZALDEHYDE INTO A C−H BOND OF ACETONITRILE


2.1 Introduction

Organonickel complexes orchestrate an array of molecular elaborations,1-8 but nickel catalysts have lagged behind precious metals in the functionalization of C−H bonds.6-8 The choice of substrate can be a deciding factor in nickel-mediated C−H functionalization: substrates containing a directing group can hold a C−H bond in close proximity to the metal center,9-13 or substrates containing relatively acidic C−H bonds can facilitate pathways that rely on deprotonation.14-15

Acetonitrile is an attractive substrate for nickel-catalyzed C−C bond-forming reactions because the sp3 C−H bond is relatively acidic (pKₐ = 25 in H₂O)16 and the products would contain a valuable nitrile functionality. Direct deprotonation of acetonitrile is often impractical or not tolerated by nearby functional groups, motivating the development of catalytic methods that avoid stoichiometric amounts of strong base.

This article describes the insertion of benzaldehyde into a C−H bond of acetonitrile (Scheme 2.1) catalyzed by asymmetric Ni aminophosphinite (NCOP) pincer complexes with little or no base added. Only two nickel catalysts are found among the handful17-22 of late-transition-metal catalysts known to carry out this cyanomethylation reaction,23-24 which produces
synthetically useful β-hydroxy nitriles.\textsuperscript{25-27} In 2005, Ozerov and co-workers reported a cationic Ni catalyst that required stoichiometric base to couple nitriles and aldehydes.\textsuperscript{21} In 2013, Guan and co-workers isolated a C-bound cyanomethyl species (Ni−CH$_2$CN) that proved to be a highly active catalyst for C−H insertion without added base, with a turnover number (TON) of up to 82,000.\textsuperscript{24}

![Scheme 2.1](image)

**Scheme 2.1** Insertion of benzaldehyde into a C−H bond of acetonitrile.

The two Ni catalysts were proposed to operate through quite different mechanisms, despite the fact that both are supported by pincer ligands. The cationic, base-promoted catalyst was proposed to react through the Lewis acid mechanism shown in Scheme 2.2A: nitrile binding to the Ni catalyst would render the acetonitrile more acidic, facilitating deprotonation by the added base; the resulting N-bound cyanomethyl species would then undergo nucleophilic attack on the aldehyde to form the C−C bond.\textsuperscript{23} The neutral, base-free catalyst was proposed to react through the organometallic mechanism shown in Scheme 2.2B: a highly nucleophilic Ni alkoxide would facilitate C−H bond activation by a “concerted metalation–deprotonation”-type pathway,\textsuperscript{28} followed by 1,2-insertion of the aldehyde into the resulting C-bound cyanomethyl species.\textsuperscript{24}
Considering the proposed mechanisms in Scheme 2, we hypothesized that a Ni catalyst supported by our pincer-crown ether ligand framework could utilize the aza-crown ether donor to hold a Lewis acidic cation near the Ni center and accelerate the catalytic reaction. In addition to numerous examples of Lewis acid-promoted insertion reactions, we were also aware that a related Ru catalyst showed improved aldehyde cyanomethylation yields in the presence of 10% NaPF₆. With this hypothesis in mind, we set out to synthesize new pincer-crown ether complexes of nickel and assess their catalytic activity for the insertion of benzaldehyde into a C–H bond of acetonitrile. While the asymmetric NCOP pincer framework can indeed support catalytic insertion of benzaldehyde into acetonitrile, we were surprised to find that lithium salts inhibit the reaction (Na⁺ and K⁺ had no effect on the rate). Mechanistic studies to probe the origin of the cation-triggered deactivation revealed that catalysis could be reinitiated by the addition of base, suggesting a connection between the neutral and cationic precatalysts.

2.2 Synthesis and Characterization

Metalation of the previously reported pincer-crown ether ligand containing an aza-15-crown-5 macrocycle, \(^{(15c5NCOP^Ph)}_H\), was accomplished by heating a toluene solution of the
ligand and NiBr$_2$(DME) (DME = dimethoxyethane) at 65 °C for 3 h in the presence of 3 equiv of NEt$_3$ (Scheme 2.3). The bromide complex ($\kappa^3$-$^{15}$c$_5$NCOP$_{\text{Pr}}$)Ni(Br) (1-$^{15}$c$_5$) was isolated in high yield using this procedure adapted from Zargarian, who reported the first nickel NCOP complexes using related ligands featuring simple secondary or tertiary amine donors.\textsuperscript{33-34} Full synthetic details are provided in the Experimental Section.

![Scheme 2.3 Synthesis of ($\kappa^3$-$^{15}$c$_5$NCOP$_{\text{Pr}}$)Ni(Br) (1-$^{15}$c$_5$).](image)

The $^1$H NMR spectrum of 1-$^{15}$c$_5$ is consistent with a $C_5$-symmetric solution structure, as a single benzylic methylene linker resonance and two isopropyl doublets of doublets were observed. A singlet ($\delta$ 200) was observed in the $^{31}$P{$^1$H} NMR spectrum. Slow evaporation of an ether solution of 1-$^{15}$c$_5$ under fostered the growth of yellow crystals suitable for X-ray diffraction analysis. The solid-state structure of 1-$^{15}$c$_5$ (Figure 2.1) confirmed the expected tridentate meridional coordination mode of the ligand in a distorted square-planar geometry, with bond distances and angles similar to those in previously reported NCOP analogues.\textsuperscript{33}
Figure 2.1 Structural representation of 1-15c5 with ellipsoids drawn at the 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Ni–P 2.103(2), Ni–N 2.032(4), Ni–Br 2.343(1), Ni–C1 1.844(5), P–Ni–Br 94.40(5), P–Ni–C1 81.98(17), N–Ni–Br 99.38(12), N–Ni–C1 83.9(2).

Addition of 1-15c5 to 1.1 equiv of KOtBu suspended in toluene resulted in an immediate color change from yellow to red-orange accompanied by precipitation of KBr and the clean formation of (κ3-15c5NCOPiPr)Ni(OtBu) (2-15c5) (Scheme 2.4). The 1H NMR spectrum of 2-15c5 was similar to that of 1-15c5, with an additional characteristic tert-butoxide methyl singlet (δ 1.42). The 31P{1H} spectrum of 2-15c5 showed a significant upfield shift relative to the corresponding bromide complex 1-15c5 (δ 190). An analogous diethylamino-substituted nickel precatalyst, (κ3-EtNCOPiPr)Ni(OtBu) (2-Et), was prepared by treating the previously reported bromide complex (κ3-EtNCOPiPr)Ni(Br) (1-Et)33 with KOtBu (Scheme 2.4). In contrast to the reaction with the macrocycle-containing 1-15c5, the color did not change immediately, and complete conversion required excess KOtBu and extended reaction times (5 h for 2-Et vs 1 h for 2-15c5). We hypothesize the pendent crown aids in solubilizing the base, facilitating the reaction. The 1H and 31P{1H} NMR spectra of 2-Et were similar to those of 2-15c5. Complexes 2-15c5
and 2-Et are hygroscopic and decompose on contact with moisture (apparently to form a Ni hydroxide and free 'BuOH); samples were stored under N₂ at −30 °C.

Scheme 2.4 Synthesis of (κ³-15c5NCOPiPr)Ni(OtBu) (2-15c5) and (κ³-EtNCOPiPr)Ni(O'Bu) (2-Et).

Cationic nickel complexes were also accessible from the corresponding bromide.

Addition of AgPF₆ to bromide 1-15c5 in CH₂Cl₂ containing acetonitrile resulted in precipitation of AgBr and the formation of [(κ³-15c5NCOPiPr)Ni(NCCH₃)][PF₆] (3-15c5) (Scheme 2.5). Two new signals were noted in the ³¹P{¹H} NMR spectrum, a singlet corresponding to the bound ligand (δ 203) and a septet corresponding to the PF₆⁻ counterion (δ −143). The diethyl analogue [(κ³-EtNCOPiPr)Ni(NCCH₃)][PF₆] (3-Et) was obtained using a similar procedure (Scheme 2.5).

Scheme 2.5 Synthesis of [(κ³-15c5NCOPiPr)Ni(NCCH₃)][PF₆] (3-15c5) and [(κ³-EtNCOPiPr)Ni(NCCH₃)][PF₆] (3-Et).

The acetonitrile complexes 3-15c5 and 3-Et exhibit distinct NMR spectra when dissolved in CD₂Cl₂, in contrast to the similar spectra observed in CD₃CN. In the case of 3-Et, the NMR resonances in CD₂Cl₂ were sharp and clearly showed a singlet corresponding to the methyl group of a bound acetonitrile ligand. The crown ether-containing complex 3-15c5 exhibited broad,
poorly resolved resonances at room temperature, however. The fluxional behavior is attributed to competitive Ni binding by the ether groups in the macrocycle, in analogy to related Ir systems.\textsuperscript{29} When the NMR probe was cooled to $-50 \, ^\circ\text{C}$, the resonances for free acetonitrile and Ni-bound acetonitrile sharpened, and the major product was the bound acetonitrile complex (Figure 2.2). Consistent with a labile acetonitrile ligand, elemental analysis of solid 3-15c5 exposed to high vacuum was consistent with loss of acetonitrile.

![Figure 2.2](image_url)\textsuperscript{1H NMR spectra of a CD$_2$Cl$_2$ solution containing CH$_3$CN and [(15c5NCOPr)Ni(NCCH$_3$)][PF$_6$] (3-15c5) between 213 K and 298 K]

### 2.3 Catalytic Hydrocyanomethylation of Benzaldehyde

The nickel complexes were assessed as C–H insertion catalysts, as shown in Scheme 2.6 and summarized in Table 2.1. The tert-butoxide complexes 2-15c5 and 2-Et are active catalysts under typical reaction conditions of 0.5 mol % catalyst in 3 mL of a 1 M solution of
benzaldehyde in acetonitrile (~10% v/v) at ambient temperature. Reactions with the diethylamino- and aza-15-crown-5-containing complexes each proceeded with a turnover number (TON) of ~100 (Table 2.1, entries 1 and 2). The uncertainty in the TON is estimated at ±5 turnovers on the basis of triplicate catalytic runs under identical conditions. Given that some strong bases can catalyze similar reactions,\textsuperscript{35} 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), LiO'Bu, and KO'Bu were tested as catalysts in the absence of Ni (Table 2.1, entries 7–9). DBU and LiO'Bu did not catalyze the reaction, while KO'Bu showed sluggish catalytic activity compared with the Ni catalyst.

![Scheme 2.6](image)

**Scheme 2.6** Hydrocyanomethylation catalysis conditions.

**Table 2.1** Comparing catalysts and conditions for benzaldehyde insertion into acetonitrile.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Time</th>
<th>TON</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-15c5</td>
<td>None</td>
<td>24 h</td>
<td>104</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>2-Et</td>
<td>None</td>
<td>24 h</td>
<td>105</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>3-15c5</td>
<td>None</td>
<td>120 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3-15c5</td>
<td>1 mol % DBU</td>
<td>120 h</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>3-Et</td>
<td>None</td>
<td>120 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3-Et</td>
<td>1 mol % DBU</td>
<td>120 h</td>
<td>91</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>1 mol % DBU</td>
<td>120 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>None</td>
<td>0.5 mol % KO'Bu</td>
<td>24 h</td>
<td>24</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>None</td>
<td>0.5 mol % LiO'Bu</td>
<td>24 h</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Conditions: 0.5 mol % catalyst, 3 mL 1 M benzaldehyde in CH\textsubscript{3}CN, 298 K.

The cationic complexes 3-15c5 and 3-Et were completely inactive under the typical conditions described above (Table 2.1, entries 3 and 5), consistent with Ozerov’s observation that added base is required for activity with [(PNP)Ni(NCCH\textsubscript{3})][OTf].\textsuperscript{23} Accordingly, catalysis commenced when 1 mol % DBU (2 equiv relative to the catalyst) was added to the reaction mixture under typical conditions of 1 M benzaldehyde in acetonitrile and 0.5 mol % cationic
catalyst (3-15c5 or 3-Et). Reaction monitoring by $^1$H NMR spectroscopy revealed >50% conversion after 120 h at room temperature. The cationic species are significantly less active than the tert-butoxide precatalysts even in the presence of a base. As with the neutral precatalysts, the diethylamino- and aza-15-crown-5-containing complexes showed essentially identical results (Table 2.1, entries 4 and 6).

![Figure 2.3](image)

**Figure 2.3** Turnover number (TON) for the insertion of benzaldehyde into acetonitrile catalyzed by 0.5 mol % [$(\kappa^{3-15c5}NCOPiPr)Ni(NCCH_3)][PF_6]$ (3-15c5) as a function of added DBU. Conditions: 0.5 mol % 3-15c5, 3 mL 1 M benzaldehyde in CH$_3$CN, 25° C, 24 h.

The cationic catalyst system is noteworthy for operating with only catalytic amounts of base. The other cationic Ni catalyst required elevated temperatures and stoichiometric base for best results.$^{23}$ In fact, additional base had almost no impact on the efficiency of 3-15c5. Variation of the concentration of base revealed saturation behavior at low levels of DBU (Figure 2.3), with base beyond 1 mol % giving no significant rate enhancement.

Having assessed the baseline catalytic performance for neutral and cationic catalysts, we turned to an examination of the effect of cationic Lewis acids on the catalytic performance. We expected the crown ether to hold the cations near the active site, providing ample opportunity for
interactions between the substrates and the Lewis acid. However, no rate enhancement was observed when the catalysis was carried out in the presence of added NaPF₆ or KPF₆ (Table 2.2), regardless of the overall charge of the precatalyst or whether a crown ether group was present. This result stands in contrast to Ru-catalyzed cyanomethylation of aldehydes, which exhibit significant rate enhancements in the presence of NaPF₆.²¹

**Table 2.2** Hydrocyanomethylation in the presence of Lewis acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>Cation (equiv. to catalyst)</th>
<th>Time</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-15c5</td>
<td>None</td>
<td>1 LiPF₆</td>
<td>24 h</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td></td>
<td>1 NaPF₆</td>
<td>24 h</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td></td>
<td>1 KPF₆</td>
<td>24 h</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>2-Et</td>
<td>None</td>
<td>1 LiPF₆</td>
<td>24 h</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td></td>
<td>1 NaPF₆</td>
<td>24 h</td>
<td>106</td>
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<tr>
<td>6</td>
<td>None</td>
<td></td>
<td>1 KPF₆</td>
<td>24 h</td>
<td>109</td>
</tr>
<tr>
<td>7</td>
<td>3-15c5</td>
<td>1 mol% DBU</td>
<td>1 LiPF₆</td>
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<td>117</td>
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<td>1 NaPF₆</td>
<td></td>
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<td>9</td>
<td>1 mol% DBU</td>
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<td>1 LiPF₆</td>
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<td>1 mol% DBU</td>
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<td>96</td>
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</tbody>
</table>

*Conditions: 0.5 mol% catalyst, 3 mL 1M benzaldehyde in CH₃CN, 298 K.*

Even more surprisingly, addition of LiPF₆ had a dramatic inhibitory effect on the catalysis. As illustrated in Figure 2.4, under conditions in which 2-15c5 proceeded to 105 turnovers in the absence of Li⁺, the reaction halted after less than 15 turnovers in the presence of small amounts of LiPF₆. Some deactivation was also observed in reactions catalyzed by 2-Et, but the effect was much less dramatic than with 2-15c5, suggesting that the macrocycle aids the deactivation process. Catalyst deactivation was unique to the tert-butoxide complexes 2-15c5 and 2-Et, as the lithium salts did not inhibit catalysis by the cationic complexes 3-15c5 and 3-Et.
Figure 2.4 (A) Turnover number (TON) for the insertion of benzaldehyde into acetonitrile catalyzed by 2-15c5 alone (filled dark blue circles), 2-15c5 with 0.5 mol % Li+ (empty light blue circles), 2-Et alone (filled dark red squares), and 2-Et with 0.5 mol % Li+ (empty light red squares). (B) TON after 24 h as a function of the equivalents of LiPF6 added relative to catalyst. Conditions: 0.5 mol % catalyst, 3 mL 1 M benzaldehyde, 25°C.

2.4 Mechanistic Studies

In order to better understand the origin of the Li+ inhibition, NMR studies were carried out to probe the individual steps of the reaction. Dissolution of tert-butoxide complex 2-15c5 in
CD$_3$CN at room temperature led to complete conversion to a new species as observed by $^1$H and $^{31}$P{$^1$H} NMR spectroscopy after 40 min, along with a resonance characteristic of free t-BuOH.\textsuperscript{36} The product is assigned as the C-bound cyanomethyl complex ($\kappa^3$-15c$^5$NCOP$^{iPr}$)Ni(CD$_2$CN) (4-15c$^5$-$d_2$), as shown in Scheme 2.\textsuperscript{7,15,24} This formulation was confirmed by the preparation of an authentic sample via the reaction of LiCH$_2$CN with bromide 1-15c$^5$. The spectroscopic signatures of authentic ($\kappa^3$-15c$^5$NCOP$^{iPr}$)Ni(CH$_2$CN) (4-15c$^5$) confirmed that the tert-butoxide complex 2-15c$^5$ reacts with acetonitrile to give 4-15c$^5$ (or 4-15c$^5$-$d_2$ in CD$_3$CN). The Ni alkyl hydrogen atoms appear as a doublet ($\delta$ 0.11, $J_{PH}$ = 5 Hz) in the $^1$H NMR spectrum of 4-15c$^5$ and the methylene carbon atom as a doublet ($\delta$ −15.16, $J_{PC}$ = 12 Hz) in the $^{13}$C{$^1$H} NMR spectrum, confirming the presence of a Ni−C bond.\textsuperscript{24,37-39} No broadening or other signs of fluxionality that might suggest interconversion between C-bound and N-bound forms of the cyanomethyl ligand were observed.\textsuperscript{15}

Cyanomethyl species have been proposed as intermediates in related systems,\textsuperscript{24} so a catalytic run was carried out with 0.5 mol \% isolated 4-15c$^5$ in a 1 M benzaldehyde solution in CH$_3$CN. The observed TON of 100 is similar to the TON for 2-15c$^5$ (104±5); 4-15c$^5$ is therefore a viable catalytic intermediate.
Figure 2.5 $^1$H NMR spectra showing formation of cyanomethyl complex 4-15c5-$d_2$ and alkoxide complex 5-15c5-$d_2$.

Figure 2.6 $^{31}$P{$_1^1$H} NMR spectra showing formation of cyanomethyl complex 4-15c5-$d_2$ and alkoxide complex 5-15c5-$d_2$. 
After formation of the Ni–CD₂CN fragment, addition of 1 equiv of benzaldehyde led to complete conversion to another new species (Scheme 2.7 and Figures 2.5 and 2.6). ¹H NMR spectroscopy showed four sets of isopropyl methyl doublets of doublets, consistent with a lowering of the symmetry due to the presence of a chiral center. A broad new resonance was observed in a region consistent with a benzylic position (δ 4.59) formed upon aldehyde insertion. The resonance at δ 4.59 correlated with a nitrile carbon (δ 121.1) and several aromatic carbons in a ¹H–¹³C HMBC experiment, further suggesting C–C bond formation. To aid characterization, the protio analogue was generated in CH₃CN and characterized by NMR spectroscopy with the aid of a C₆D₆ capillary to lock and shim. In CH₃CN solvent, a diastereotopic pair of methylene protons (absent in samples prepared using CD₃CN) appeared around 3.5 ppm, and the benzylic resonance at δ 4.59 became a sharp triplet (Figure 2.7). These two resonances exhibited strong correlation in a ¹H–¹H COSY experiment (Figures 2.8). On the basis of this spectroscopic evidence, the product is assigned as the cyanoalkoxide complex (κ³⁻¹⁵c₅NCOPᵢPr)Ni(OC(H)(Ph)(CH₂CN)) (5-15c₅).
Figure 2.7 $^1$H NMR spectrum of ($^{15}$c$^5$NCOP($^{i}$Pr)Ni(OC($^3$H)(Ph)(CH$_2$CN)) (5-15c5) in CH$_3$CN. Made from 2-15c5 in situ. Capillary containing C$_6$D$_6$ and HMDSO used to lock and shim.

Figure 2.8 $^1$H-$^1$H COSY NMR spectrum of ($^{15}$c$^5$NCOP($^{i}$Pr)Ni(OC($^3$H)(Ph)(CH$_2$CN)) (5-15c5) in CH$_3$CN. Made from 2-15c5 in situ. Capillary containing C$_6$D$_6$ and HMDSO used to lock and shim.
Cyanoalkoxide species have been proposed as intermediates in Ni-catalyzed cyanomethylation but have not been isolated or fully characterized because of their high reactivity in the presence of acetonitrile. For example, treatment of $(\text{POCOP})\text{Ni}(\text{CH}_2\text{CN})$ with benzaldehyde in $\text{CD}_3\text{CN}$ formed the deuterated product $(\text{POCOP})\text{Ni}(\text{CD}_2\text{CN})$ and the free cyanoalcohol, and the cyanoalkoxide was not observed. The surprising stability of cyanoalkoxide 5-15c5 has allowed for a much more detailed characterization of this species, presumably because the $(\text{NCOP})\text{Ni}$ system is less reactive with acetonitrile.

Catalytic reactions under typical conditions (0.5 mol % catalyst, 1 M benzaldehyde, 25 °C) were also monitored in situ by NMR spectroscopy in $\text{CH}_3\text{CN}$. The precatalyst 2-15c5 formed both $(\kappa^3\text{-}15\text{c}5\text{NCOP}^\text{ipr})\text{Ni}(\text{CH}_2\text{CN})$ (4-15c5) and $(\kappa^3\text{-}15\text{c}5\text{NCOP}^\text{ipr})\text{Ni}(\text{OC(H)Ph}(\text{CH}_2\text{CN}))$ (5-15c5) at early times (4-15c5:5-15c5 ratio ≈ 50:50), but the ratio of the intermediates changed over the course of the reaction, with cyanoalkoxide complex 5-15c5 slowly diminishing over 48 h. The two intermediates constituted >70% of the Ni species during the reaction. When precatalyst 2-Et was monitored analogously, $^{31}\text{P}$ NMR resonances were observed at chemical shifts very similar to those for 4-15c5 and 5-15c5, suggesting that once again both the cyanomethyl complex 4-Et and the cyanoalkoxide complex 5-Et were present at the onset of catalysis (4-Et:5-Et ratio ≈ 60:40) before the speciation shifted almost entirely to the cyanoalkoxide complex 5-Et. The differences in speciation over time for 2-Et and 2-15c5 were surprising and suggest that relatively minor changes in the catalyst structure might lead to changes in the turnover-limiting step. Interestingly, the cationic species 3-15c5 and 3-Et were observed among several unidentified Ni species that grew in slowly over time during the reaction. Under these base-free conditions, the cationic species are likely deactivated forms of the catalyst (Table 2.1, entries 3 and 5).
The presence of both cyanomethyl and cyanoalkoxide species during catalysis led us to investigate the reversibility of the insertion step. To probe for reversibility, 5-15c5 was synthesized in CH$_3$CN as described above, isolated as a crude solid by removal of volatiles under vacuum, and redissolved in CD$_3$CN. Over the course of 2 h, the diastereotopic methylene protons of 5-15c5 disappeared and the benzylic triplet resonance was replaced by a broad singlet. The data are consistent with reversible C–C bond formation (Scheme 2.8): deinsertion of benzaldehyde would be followed by activation of CD$_3$CN to form a Ni–CD$_2$CN fragment and reinsertion of benzaldehyde to generate the isotopologue 5-15c5-d$_2$. Rapid H/D exchange of cyanomethylnickel species has been previously observed, and aldehyde insertion has been proposed to be reversible in related systems.

![Scheme 2.8](image)

**Scheme 2.8** Reversibility of benzaldehyde insertion into the C–H or C–D bonds of CH$_3$CN or CD$_3$CN with catalyst 5-15c5.

When tert-butoxide catalyst 2-15c5 was treated with LiPF$_6$ and monitored during turnover, alkoxide abstraction occurred immediately to form the cationic acetonitrile complex 3-15c5 in >90% yield. Essentially no turnover was observed under these conditions; 3-15c5 is
inactive in the absence of a base additive (Table 2.1). The identity of the deactivated Ni catalyst strongly suggests that the inhibitory role of Li$^+$ involves alkoxide abstraction to form \([(\text{NCOP})\text{Ni(NCCH}_3)]^+\) and either LiO'Bu or LiOC(H)(Ph)(CH$_2$CN). Accordingly, a white precipitate was observed upon addition of LiPF$_6$ to 2-15c5. The lack of inhibition by Na$^+$ and K$^+$ salts is attributed to the greater solubility of the alkoxide salts that would be formed.$^{40-41}$

The catalytic activity could be stopped and started by addition of LiPF$_6$ followed by addition of DBU. A catalytic reaction was initiated under standard conditions of 0.5 mol % 2-15c5 and 1 M benzaldehyde in CH$_3$CN (C$_6$D$_6$ capillary for lock signal) and followed by $^1$H NMR spectroscopy (Figure 2.9). Addition of 0.5 mol % LiPF$_6$ (red line in Figure 2.9) effectively shut down the reaction. After $\sim$3 h, catalysis was reinitiated by injection of 1 mol % DBU (green line in Figure 2.9), albeit at a lower rate consistent with the longer reaction times required by cationic catalysts paired with DBU (Table 2.1). Alkoxide abstraction by lithium additives connects the neutral catalysts 2-15c5 and 2-Et with the cationic acetonitrile complexes 3-15c5 and 3-Et.

![Figure 2.9](image_url) 

**Figure 2.9** TON over time for two parallel reactions containing 0.5 mol % 2-15c5 and 1 M benzaldehyde in CH$_3$CN (C$_6$D$_6$ capillary) assessed by $^1$H NMR. The first experiment (filled blue circles) was allowed to continue unabated for 17 h, while the second experiment (empty light-blue circles) was treated with 0.5 mol % LiPF$_6$ after 2.4 h (red line), resulting in catalyst deactivation; activity was re-initiated by addition of 1 mol % DBU (5.2 h, green line).
Independently synthesized samples of the cationic precatalyst 3-15c5 exhibited no reaction upon dissolution in CD$_3$CN, with no evidence for the formation of a Ni cyanomethyl species. Addition of 1 equiv of DBU ($pK_a = 24.3$ in CH$_3$CN),$^{42}$ however, led to a mixture of species, including a broad resonance indicating a fluxional process attributed to competitive binding of DBU and CD$_3$CN (Scheme 2.9 and Figures 2.10 and 2.11).$^{23}$ Addition of 10 equiv of benzaldehyde to this solution initiated catalysis (Figures 2.10 and 2.11). Benzaldehyde was consumed, and the cyanoalcohol product grew in. The major Ni species during catalysis were the DBU adduct and 3-15c5, but about 10% of the Ni was present in the form of the insertion product, cyanoalkoxide 5-15c5-$d_2$. Significantly less of this cyanoalkoxide complex 5-15c5-$d_2$ was present in the case of the cationic catalyst paired with base, compared with catalytic reactions involving tert-butoxide complex 2-15c5. These studies establish the viability of nickel cyanomethyl and cyanoalkoxide species as cyanomethylation intermediates. Furthermore, the neutral and cationic precatalysts both generate the same cyanoalkoxide intermediate, albeit in different steady-state concentrations.
**Figure 2.10** $^1$H NMR spectra showing equilibrium DBU binding by 3-15c5 and speciation during turnover.

$[^{15}N\text{COPP}^3\text{N}]\text{[N}([\text{NCCH}_3])\text{][PF}_6]$ (3-15c5)

$[^{15}N\text{COPP}^3\text{N}](\text{DBU})\text{[PF}_6]$ $\rightarrow$ $[^{15}N\text{COPP}^3\text{N}](\text{OC}(\phi)(\text{Ph})(\text{CD}_3\text{CN}))$ (s-15c5-δ$_6$)

**Figure 2.11** $^{31}$P $\{^1$H$\}$ NMR spectra showing equilibrium DBU binding by 3-15c5 and speciation during turnover.
In an attempt to avoid the formation of a base adduct of nickel, the strong, bulky phosphazene base \( t\text{BuNP-(pyrrolidinyl)}_3 \) (\( pK_a = 28.4 \) in \( \text{CH}_3\text{CN} \))\(^{42} \) was also examined. The addition of a slight excess of \( t\text{BuP}_1 \) to the acetonitrile complex 3-15c5 in \( \text{CD}_3\text{CN} \) resulted in rapid deprotonation to form the cyanomethyl complex 4-15c5-\( d_2 \) (Scheme 9). In contrast to the analogous reaction with DBU, no evidence of \( t\text{BuP}_1 \) coordination to Ni was observed. A sharp singlet in the \( ^{31}\text{P}\{^1\text{H}\} \) NMR spectrum (\( \delta = 197 \)) indicated that 4-15c5-\( d_2 \) was formed in high yield, and broad resonances for \( t\text{BuP}_1 \) and its conjugate acid were also observed (Figure 2.12). As expected of a solution containing the cyanomethylnickel complex, the addition of 25 equiv of benzaldehyde initiated catalysis. During turnover, a sharp singlet characteristic of the conjugate acid of \( t\text{BuP}_1 \) suggested that the base was fully protonated. The cyanoalkoxide complex 5-15c5-\( d_2 \) was the major species during catalysis, again contrasting with the situation with DBU, which generated only a small amount of 5-15c5-\( d_2 \).

**Scheme 2.9** Reaction of 3-15c5 and 3-Et with DBU and \( t\text{BuP}_1 \).
Subsequent addition of $tB$uP$_1$ and benzaldehyde to 3-15c5.

In a separate experiment, 0.5 mol % cationic precatalyst 3-15c5 and 1.0 mol % $tB$uP$_1$ were combined in a 1 M benzaldehyde solution in CH$_3$CN. Benzaldehyde insertion proceeded smoothly, with the TON reaching 109 after 24 h. Whereas the 3-15c5/DBU combination was much slower than the neutral tert-butoxide precatalyst 2-15c5, the 3-15c5/$tB$uP$_1$ combination provided similar levels of activity as 2-15c5. (In the absence of any Ni species, $tB$uP$_1$ exhibited a TON of only 12).

Scheme 2.10 depicts a proposed mechanism that is consistent with the experimental data. The neutral pathway, shown in green, involves interconversion of nickel cyanomethyl (4-15c5 and 4-Et) and cyanoalkoxide (5-15c5 and 5-Et) species. Both of these species were independently synthesized and observed during turnover, and the isolated cyanomethyl complex 4-15c5 exhibited catalytic activity essentially identical to that of the tert-butoxide complex 2-15c5. The deuterium-labeling study (Scheme 2.8) provides strong evidence that both the
aldehyde insertion and C–H bond activation steps are reversible. In further support of the key role of equilibria, catalytic reactions containing 0.5 mol % 2-15c5 and 50 mol % tBuOH showed markedly decreased activity (TON = 62 vs TON = 104 in the absence of added alcohol). Product inhibition might therefore explain why reactions tended to slow down before reaching completion (50–60% yield).

Scheme 2.10 Proposed catalytic mechanism.

Deactivation of the neutral cycle occurs when Li⁺ abstracts the tert-butoxide or cyanoalkoxide, leading to insoluble precipitates and generating cationic species 3-15c5 or 3-Et, as shown in dashed red. The cationic pathway, shown in blue, requires a base for activity. DBU can deprotonate Ni-bound acetonitrile, but DBU also displaces the acetonitrile ligand, engaging an unproductive binding equilibrium. This is consistent with the pseudo-zeroth-order dependence of the catalysis rate on DBU (Figure 2.3). The conjugate acid H–DBU⁺ (pKₐ = 24.3 in CH₃CN)⁴² is also more acidic than tBuOH (pKₐ ~ 40 in CH₃CN)⁴³ which may facilitate removal of the cyanoalkoxide species from the cycle by protonolysis. It is difficult to rule out the alternative pathway shown in Scheme 2.2, in which deprotonation of acetonitrile by DBU forms a reactive
N-bound cyanomethyl complex that undergoes outer-sphere nucleophilic attack on benzaldehyde. We observed the same cyanoalkoxide intermediate when monitoring catalytic reactions carried out with neutral and cationic precatalysts, however, suggesting a relationship between the neutral and cationic cycles. When the stronger, bulkier phosphazene base $^{t\text{Bu}}\text{P}_1$ is employed, the unproductive binding equilibrium is avoided (Scheme 2.10), and the base can be considered an initiator that quickly generates the more active cyanomethyl catalyst 4-15c5. The fully protonated state of the phosphazene during catalysis suggests a mechanism in which $^{t\text{Bu}}\text{P}_1$ deprotonates the Ni-bound acetonitrile to enter the neutral cycle in Scheme 2.10.

2.5 Conclusions

Neutral and cationic NCOP Ni complexes are viable catalysts for the insertion of benzaldehyde into a C−H bond of acetonitrile. Subtle differences between the catalyst resting states were observed for macrocycle-containing pincer-crown ether complexes and pincer complexes with a diethylamine donor. A surprising deactivation occurred when neutral Ni tert-butoxide catalysts were treated with LiPF$_6$, which revealed a pathway connecting the neutral catalysts to cationic Ni species that are catalytically inactive in the absence of base. Catalytic activity switched off by the addition of Li$^+$ could be switched back on by addition of DBU. These in situ mechanistic studies revealed a link between the two precatalysts and provided more detailed characterization of a proposed cyanoalkoxide intermediate.

2.6 Experimental Section

General Considerations

Standard vacuum line and glovebox techniques were utilized to maintain a N$_2$ atmosphere during manipulation of all compounds, unless otherwise noted. NMR-scale reactions were prepared in a glovebox and monitored in Teflon-sealed tubes. Organic solvents were dried and
degassed with argon using a Pure Process Technology solvent system and stored over 3 Å molecular sieves. Under standard glovebox operating conditions, pentane, diethyl ether, benzene, toluene, and tetrahydrofuran were used without purging, so traces of those solvents were present in the atmosphere and in the solvent bottles. $^1$H, $^{31}$P, and $^{13}$C NMR spectra were recorded on 400, 500, or 600 MHz spectrometers. NMR characterization data are reported at 25 °C, unless specified otherwise. All of the NMR solvents were purchased from Cambridge Isotopes Laboratories. Acetonitrile-$d_3$ (CD$_3$CN), benzene-$d_6$ (C$_6$D$_6$), chloroform-$d$ (CDCl$_3$), and methylene chloride-$d_2$ (CD$_2$Cl$_2$) were freeze–pump–thaw-degassed three times, dried by passage through a small column of activated alumina, and stored over 3 Å molecular sieves. $^1$H and $^{13}$C chemical shifts are reported in parts per million relative to residual protio solvent resonances.$^{44}$ All of the $^{31}$P resonances are reported relative to 85% H$_3$PO$_4$ external standard (0 ppm). ($^{15}$c$_5$NCOP$_2$Bu)$_2$, ($^{29}$EtNCOP$_2$Bu)$_2$, ($^{33}$k$_3$-EtNCOP$_2$Bu)$_2$Ni(Br)$_2$, and LiCH$_2$CN$^{24,45}$ were synthesized according to literature procedures. KO'Bu was sublimed under reduced pressure (0.01 Torr) at 175 °C prior to use. All of the other reagents were commercially available and used without further purification. Elemental analyses were performed by Robertson Microlit Laboratories (Ledgewood, NJ).

Single-crystal X-ray diffraction data were collected on a Bruker Smart Apex-II diffractometer at 100 ± 2 K with Cu Kα radiation ($\lambda = 1.54175$ Å). Diffraction profiles were integrated using the SAINT software program. Absorption corrections were applied using SADABS. The structure was solved using direct methods and refined using the XL refinement package via the least-squares method. Hydrogen atoms were generated theoretically and refined isotropically with fixed thermal factors.
**Synthetic Procedures**

*Synthesis of (\(^{15}\text{c}_5\text{NCOP}i\text{Pr})\text{Ni(Br)}\ (1-15c5)*

In a glovebox, a glass Teflon-sealed pressure tube was charged with 168.7 mg (0.547 mmol) of NiBr\(_2\)(DME) and 10 mL of toluene. In a separate flask, 241.4 mg (0.547 mmol) of (\(^{15}\text{c}_5\text{NCOP}i\text{Pr})\text{H} was stirred with 0.229 mL (1.643 mmol) of triethylamine in 15 mL of toluene for 10 min, and then the resulting mixture added dropwise to the stirring suspension of NiBr\(_2\)(DME). The flask was sealed and heated at 65 °C for 3 h. After heating, the solution was filtered under N\(_2\), and the filtrate was evaporated to dryness. The resulting yellow oil was extracted with Et\(_2\)O and filtered. Slow evaporation yielded yellow crystals that were washed with 3 × 5 mL of pentane and dried under vacuum (288 mg, 91% yield). Single crystals suitable for an X-ray diffraction study were grown by slow evaporation of an Et\(_2\)O solution of 1-15c5. \(^1\text{H}\) NMR (600 MHz, C\(_6\)D\(_6\)): \(\delta\) 1.18 (dd, \(^3J_{HP} = 14\) Hz, \(^3J_{HH} = 7\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.50 (dd, \(^3J_{HP} = 17\) Hz, \(^3J_{HH} = 7\) Hz, 6H, CH(CH\(_3\))\(_2\)), 2.23 (m, 2H, CH(CH\(_3\))\(_2\)), 3.16 (m, 2H, crown-CH\(_2\)), 3.24 (m, 4H, crown-CH\(_2\)), 3.31 (m, 4H, crown-CH\(_2\)), 3.40 (m, 2H, crown-CH\(_2\)), 3.63 (m, 2H, crown-CH\(_2\)), 3.80 (m, 2H, crown-CH\(_2\)), 4.07 (m, 2H, 22 crown-CH\(_2\)), 4.14 (m, 2H, crown-CH\(_2\)), 4.47 (s, 2H, ArCH\(_2\)N), 6.52 (d, \(^3J_{HH} = 7\) Hz, \(^1\text{H}, \text{ArH}\)), 6.63 (d, \(^3J_{HH} = 8\) Hz, \(^1\text{H}, \text{ArH}\)), 6.90 (t, \(^3J_{HH} = 8\) Hz, \(^1\text{H}, \text{ArH}\)). \(^{13}\text{C}\ \{^1\text{H}\}\) NMR (150 MHz, C\(_6\)D\(_6\)): \(\delta\) 16.58 (d, \(^2J_{CP} = 2\) Hz, CH\(_3\)), 17.99 (d, \(^2J_{CP} = 4\) Hz, CH\(_3\)), 28.16 (d, \(^1J_{CP} = 24\) Hz, CH), 56.89 (s, crown-CH\(_2\)), 65.28 (s, ArCH\(_2\)N), 69.49 (s, crown-CH\(_2\)), 70.27 (s, crown-CH\(_2\)), 70.56 (s, crown-CH\(_2\)), 70.58 (s, crown-CH\(_2\)), 107.58 (d, \(^3J_{CP} = 13\) Hz, C\(_{Ar}\)), 115.38 (d, \(^4J_{CP} = 2\) Hz, C\(_{Ar}\)), 126.68 (s, C\(_{Ar}\)), 142.08 (d, \(^2J_{CP} = 33\) Hz, C\(_{Ar}\)), 153.35 (s, C\(_{Ar}\)), 165.58 (d, \(^2J_{CP} = 11\), C\(_{Ar}\)). \(^{31}\text{P}\ \{^1\text{H}\}\) NMR (161 MHz, C\(_6\)D\(_6\)): \(\delta\) 200.4. Anal. Calcd for C\(_{23}\)H\(_{39}\)O\(_5\)PNiBr: C, 47.70; H, 6.79; N, 2.42. Found: C, 47.60; H, 6.50; N, 2.38.
Figure 2.13 $^1$H NMR spectrum of ($^{15}$C$_5$NCOP$_{iPr}$)NiBr (1-15c5) in C$_6$D$_6$.

Figure 2.14 $^{31}$P{H} NMR spectrum of ($^{15}$C$_5$NCOP$_{iPr}$)NiBr (1-15c5) in C$_6$D$_6$. 
Figure 2.15 $^{13}$C{H} NMR spectrum of $(^{15}$c$_5$NCOP$_{iPr}$)NiBr (1-15c5) in C$_6$D$_6$.

Table 2.3 Crystal data and structure refinement for $(^{15}$c$_5$NCOP$_{iPr}$)NiBr (1-15c5).

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</table>
Synthesis of \(\text{C}_{15}\text{C}_{5}\text{NCOP}^{\text{Pr}}\text{Ni(O'Bu)}\) (2-15c5)

In a glovebox, a 20 mL vial was charged with 10.9 mg (0.097 mmol) of KO\text{t}Bu and 2 mL of toluene. A solution of 51.2 mg (0.088 mmol) of \(\text{C}_{15}\text{C}_{5}\text{NCOP}^{\text{Pr}}\text{Ni(Br)}\) in toluene was added dropwise, and the resulting solution was allowed to stir for 1 h. The solvent was removed in vacuo, and the reaction mixture was extracted with cold pentane (−30 °C) and filtered. The solution was evaporated to yield a hygroscopic red-orange oil (47 mg, 93% yield). 1H NMR (400 MHz, C\text{6}D\text{6}): \(\delta\) 1.19 (dd, \(^3J_{\text{HP}} = 13\) Hz, \(^3J_{\text{HH}} = 7\) Hz, 6H, CH(CH\text{3})\text{2}), 1.45 (s, 9H, Ni−OC(CH\text{3})\text{3}), 1.56 (dd, \(^3J_{\text{HP}} = 18\) Hz, \(^3J_{\text{HH}} = 7\) Hz, 6H, CH(CH\text{3})\text{2}), 2.20 (m, 2H, CH(CH\text{3})\text{2}), 3.36 (m, 14H, crown-CH\text{2}), 3.80 (m, 2H, crown-CH\text{2}), 4.06 (m, 2H, crown-CH\text{2}), 4.35 (s, 2H, ArCH\text{2}N), 4.44 (m, 2H, crown-CH\text{2}), 6.51 (d, \(^3J_{\text{HH}} = 7\) Hz, 1H, ArH), 6.58 (d, \(^3J_{\text{HH}} = 8\) Hz, 1H, ArH), 6.90 (t, \(^3J_{\text{HH}} = 8\) Hz, 1H, ArH). 13C \{1H\} NMR (150 MHz, C\text{6}D\text{6}): \(\delta\) 17.34 (d, \(^2J_{\text{CP}} = 4\) Hz, CH(CH\text{3})\text{2}), 19.32 (d, \(^2J_{\text{CP}} = 6\), CH(CH\text{3})\text{2}), 29.92 (d, \(^1J_{\text{CP}} = 20\) Hz, CH(CH\text{3})\text{2}), 36.49 (s, Ni−OC(CH\text{3})\text{3}), 56.38 (s, crown-CH\text{2}), 66.46 (s, 1C, ArCH\text{2}N), 68.64 (s, Ni−OC(CH\text{3})\text{3}), 69.64 (s, crown-CH\text{2}), 70.84 (s, crown-CH\text{2}), 71.00 (s, crown-CH\text{2}), 71.47 (s, crown-CH\text{2}), 107.11 (d, \(^3J_{\text{CP}} = 12\) Hz, C\text{Ar}), 115.32 (d, \(^4J_{\text{CP}} = 2\) Hz, C\text{Ar}), 126.05 (s, C\text{Ar}), 138.24 (d, \(^2J_{\text{CP}} = 35\) Hz, C\text{Ar}), 154.25 (s, C\text{Ar}), 165.98 (d, \(^2J_{\text{CP}} = 10\) Hz, C\text{Ar}). 31P \{1H\} NMR (161 MHz, C\text{6}D\text{6}): \(\delta\) 189.57. Anal. Calcd for C\text{27}H\text{48}NNiO\text{6}P: C, 56.66; H, 8.45; N, 2.45. Found: C, 55.83; H, 7.98; N, 2.29. Complex 2- 15c5
is an extremely hygroscopic oil; the high reactivity led to some deviation from the expected elemental analysis values.

Figure 2.16 $^1$H NMR spectrum of $(^{15}$c5NCO$iPr$)$NiO'Bu (2-15c5) in C$_6$D$_6$.

Figure 2.17 $^{31}$P{H} NMR spectrum of $(^{15}$c5NCO$iPr$)$NiO'Bu (2-15c5) in C$_6$D$_6$. 

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Figure 2.18 $^{13}$C{H} NMR spectrum of (15c5NCOP$iPr$)NiO$tBu$ (2-15c5) in C$_6$D$_6$.

**Synthesis of (EtNCOP$iPr$)Ni(O$tBu$) (2-Et)**

In a glovebox, a 20 mL vial was charged with 17.0 mg (0.152 mmol) of KO$tBu$ and 2 mL of toluene. A solution of 26.2 mg (0.061 mmol) of (EtNCOP$iPr$)Ni(Br) in 2 mL of toluene was added dropwise, and the resulting solution was allowed to stir for 6 h. The solvent was removed in vacuo, and the oily residue was extracted with cold pentane (−30 °C) and filtered. The filtrate was evaporated to yield a red-orange powder (24 mg, 93% yield). $^1$H NMR (400 MHz, C$_6$D$_6$): δ 1.17 (dd, $^3$J$_{HP}$ = 12 Hz, $^3$J$_{HH}$ = 7 Hz, 6H, CH(CH$_3$)$_2$), 1.36 (s, 9H, Ni–OC(CH$_3$)$_3$), 1.58 (dd, $^3$J$_{HP}$ = 18 Hz, $^3$J$_{HH}$ = 7 Hz, 6H, CH(CH$_3$)$_2$), 1.62 (t, $^3$J$_{HH}$ = 7 Hz, 6H, CH$_2$CH$_3$), 1.94 (m, 2H, CH$_2$CH$_3$), 2.22 (m, 2H, CH(CH$_3$)$_2$), 3.37 (m, 2H, CH$_2$CH$_3$), 3.54 (s, 2H, ArCH$_2$N), 6.42 (d, $^3$J$_{HH}$ = 7 Hz, $^1$H, ArH), 6.55 (d, $^3$J$_{HH}$ = 8 Hz, $^1$H, ArH), 6.89 (t, $^3$J$_{HH}$ = 8 Hz, $^1$H, ArH). $^{13}$C {H} NMR (150 MHz, C$_6$D$_6$): δ 13.57 (s, CH$_2$CH$_3$), 17.31 (d, $^3$J$_{CP}$ = 4 Hz, CH(CH$_3$)$_2$), 19.50 (d, $^3$J$_{CP}$ = 6 Hz,
CH(CH₃)₂, 30.33 (d, J₇CP = 20 Hz, CH(CH₃)₂), 36.30 (s, Ni–OC(CH₃)₃), 54.67 (d, J₇CP = 2 Hz, CHCH), 63.84 (d, J = 2 Hz, ArCHN), 68.38 (s, Ni–OC(CH₃)₃), 107.00 (d, J₇CP = 12 Hz, CAr), 114.15 (d, J₇CP = 2 Hz), 125.80 (s, CAr), 138.29 (d, J = 34 Hz, CAr), 154.54 (s, CAr), 165.90 (d, J₇CP = 10 Hz, CAr). ³¹P{¹H} NMR (161 MHz, C₆D₆): δ 188.6. Complex 2-Et is extremely hygroscopic; the high reactivity confounded characterization by elemental analysis or high-resolution mass spectrometry.

Figure 2.19¹H NMR spectrum of (EtNCOPr)NiO'Bu (2-Et) in C₆D₆.
Figure 2.20 $^{31}$P{H} NMR spectrum of (EtNCOP$i^\text{Pr}$)NiO'Bu (2-Et) in C$_6$D$_6$.

Figure 2.21 $^{13}$C{H} NMR spectrum of (EtNCOP$i^\text{Pr}$)NiO'Bu (2-Et) in C$_6$D$_6$. 
Synthesis of [(15c\textsuperscript{5}NCOP\textsuperscript{ipr})Ni(NCCH\textsubscript{3})][PF\textsubscript{6}] (3-15c\textsuperscript{5})

In a glovebox, a 20 mL vial covered with foil was charged with 150 µL (2.872 mmol) of CH\textsubscript{3}CN, 49.0 mg (0.193 mmol) of AgPF\textsubscript{6}, and 3 mL of CH\textsubscript{2}Cl\textsubscript{2}. A solution of 102.0 mg (0.176 mmol) of (15c\textsuperscript{5}NCOP\textsuperscript{ipr})-Ni(Br) in 1 mL of CH\textsubscript{2}Cl\textsubscript{2} was slowly added to the stirring silver solution. After 1 h, 4 mL of pentane was added to the mixture, and the resulting solution was filtered. The solvent was removed in vacuo to yield a yellow oil. The oil was washed with 3 × 5 mL of Et\textsubscript{2}O to yield a yellow powder (97 mg, 85% yield). 1H NMR (500 MHz, CD\textsubscript{2}Cl\textsubscript{2}, −50 °C): δ 1.29 (dd, \textit{J}\textsubscript{HP} = 17 Hz, \textit{J}\textsubscript{HH} = 7 Hz, 6H, CH(CH\textsubscript{3})\textsubscript{2}), 1.33 (dd, \textit{J}\textsubscript{HP} = 17 Hz, \textit{J}\textsubscript{HH} = 7 Hz, 6H, CH(CH\textsubscript{3})\textsubscript{2}), 2.31 (m, 2H, CH(CH\textsubscript{3})\textsubscript{2}), 2.45 (s, 3H, Ni−NC\textsubscript{3}CH), 3.16 (m, 2H, crown-CH\textsubscript{2}), 3.35 (m, 2H, crown-CH\textsubscript{2}), 3.53 (m, 12H, crown-CH\textsubscript{2}), 3.96 (s, 2H, ArCH\textsubscript{2}N), 3.98 (m, 2H, crown-CH\textsubscript{2}), 4.61 (m, 2H, crown-CH\textsubscript{2}), 6.49 (d, \textit{J}\textsubscript{HH} = 8 Hz, 1H, ArH), 6.64 (d, \textit{J}\textsubscript{HH} = 7 Hz, 1H, ArH), 6.99 (t, \textit{J}\textsubscript{HH} = 8 Hz, 1H, ArH). 13C \{1H\} NMR (150 MHz, CD\textsubscript{2}Cl\textsubscript{2}): δ 3.11 (s, Ni−NC\textsubscript{3}CH), 16.90 (d, \textit{J}\textsubscript{CP} = 3 Hz, CH(CH\textsubscript{3})\textsubscript{2}), 17.77 (d, \textit{J}\textsubscript{CP} = 5 Hz, CH(CH\textsubscript{3})\textsubscript{2}), 28.87 (d, \textit{J}\textsubscript{CP} = 24 Hz, CH(CH\textsubscript{3})\textsubscript{2}), 57.93 (s, crown-CH\textsubscript{2}), 66.36 (s, ArCH\textsubscript{2}N), 69.99 (s, crown-CH\textsubscript{2}), 70.11 (s, crown-CH\textsubscript{2}), 70.20 (s, crown-CH\textsubscript{2}), 72.45 (s, crown-CH\textsubscript{2}), 72.49 (s, crown-CH\textsubscript{2}), 109.42 (d, \textit{J}\textsubscript{CP} = 13 Hz, C\textsubscript{Ar}), 117.13 (d, \textit{J}\textsubscript{CP} = 2 Hz, C\textsubscript{Ar}), 123.74 (s, Ni−NC\textsubscript{3}CH), 129.17 (s, C\textsubscript{Ar}), 152.80 (s, C\textsubscript{Ar}), 166.19 (d, \textit{J}\textsubscript{CP} = 9 Hz, C\textsubscript{Ar}). Note: the ipso carbon bound to Ni was not observed, perhaps because of broadening of this signal due to fluxional acetonitrile binding. 31P \{1H\} NMR (161 MHz, CD\textsubscript{3}CN): δ −143.4 (sept, PF\textsubscript{6}), 202.7 (s). 31P \{1H\} NMR (161 MHz, CD\textsubscript{2}Cl\textsubscript{2}): δ −144.5 (sept, PF\textsubscript{6}), δ 199.12 (s). Note: The CH\textsubscript{3}CN ligand was lost under high vacuum; elemental analysis was calculated for [(κ\textsuperscript{4}-15c\textsuperscript{5}NCOP\textsuperscript{ipr})Ni][PF\textsubscript{6}]. Anal. Calcd for C\textsubscript{23}H\textsubscript{39}F\textsubscript{6}NNiO\textsubscript{5}P\textsubscript{2}: C, 42.88; H, 6.10; N, 2.17. Found: C, 42.78; H, 5.92; N, 2.17.
Figure 2.22 $^1$H NMR spectrum of $\left[\left(\text{^{15}c5NCOP}^{\text{Pr}}\right)\text{Ni(NCCH}_3\right)\left[\text{PF}_6\right]\left(3-\text{^{15}c5}\right)$ in CD$_2$Cl$_2$.

Figure 2.23 $^{31}$P{$^1$H} NMR spectrum of $\left[\left(\text{^{15}c5NCOP}^{\text{Pr}}\right)\text{Ni(NCCH}_3\right)\left[\text{PF}_6\right]\left(3-\text{^{15}c5}\right)$ in CD$_2$Cl$_2$. 
Figure 2.24 $^{13}$C{H} NMR spectrum of [(15c$^5$NCOP$iPr$)Ni(NCCH$_3$)][PF$_6$] (3-15c5) in CD$_2$Cl$_2$.

Figure 2.25 $^1$H NMR spectrum of [(15c$^5$NCOP$iPr$)Ni(NCCH$_3$)][PF$_6$] (3-15c5) in CD$_3$CN.
Figure 2.26 $^{31}$P{H} NMR spectrum of $([15c5NCOP^iPr]Ni(NCCH_3))[PF_6]$ (3-15c5) in CD$_3$CN.

Synthesis of $[EtNCOP^iPr]Ni(NCCH_3)][PF_6]$ (3-Et)

In a glovebox, a 20 mL vial covered with foil was charged with 34.6 mg (0.137 mmol) of AgPF$_6$, 3 mL of CH$_2$Cl$_2$, and 150 µL (2.872 mmol) of CH$_3$CN. A solution of 53.7 mg (0.125 mmol) of $^{(3)}$EtNCOP$^iPr$Ni(Br) in 2 mL of CH$_2$Cl$_2$ was slowly added to the stirring silver solution. After 1 h, 5 mL of pentane was added to the mixture, and the resulting solution was filtered. The solvent was removed in vacuo to yield a yellow oil, which was washed with $3 \times 5$ mL of Et$_2$O to yield a yellow powder (65 mg, 97% yield). $^1$H NMR (600 MHz, CD$_2$Cl$_2$): $\delta$ 1.36 (dd, $^3J_{HP} = 15$ Hz, $^3J_{HH} = 7$ Hz, 6H, CH(CH$_3$)$_2$), 1.42 (dd, $^3J_{HP} = 19$ Hz, $^3J_{HH} = 7$ Hz, 6H, CH(CH$_3$)$_2$), 1.66 (t, $^3J_{HH} = 7$ Hz, 6H, CH$_2$CH$_3$), 2.36 (m, 2H, CH$_2$CH$_3$), 2.45 (s, 3H, NCCH$_3$), 2.81 (m, 2H, CH(CH$_3$)$_2$), 3.06 (m, 2H, CH$_2$CH$_3$), 4.06 (s, 2H, ArCH$_2$N), 6.52 (d, $^3J_{HH} = 8$ Hz, $^1$H, ArH), 6.63 (d, $^3J_{HH} = 8$ Hz, $^1$H, ArH), 7.03 (t, $^3J_{HH} = 8$ Hz, $^1$H, ArH). $^{13}$C $^{(1)}$H NMR (150 MHz, C$_6$D$_6$): $\delta$
3.74 (s, Ni–NCCH₃), 13.42 (s, CH₂CH₃), 16.85 (d, Jₐp = 3 Hz, CH(CH₃)₂), 17.64 (d, Jₐp = 5 Hz, CH(CH₃)₂), 28.80 (d, Jₐp = 24 Hz, CH(CH₃)₂), 56.47 (d, Jₐp = 2 Hz, CH₂CH₃), 65.12 (d, Jₐp = 2 Hz, ArCH₂N), 109.06 (d, Jₐp = 13 Hz, CAr), 115.80 (d, Jₐp = 2 Hz, CAr), 127.12 (s, 1C, Ni–NCCH₃), 129.16 (s, CAr), 136.18 (d, Jₐp = 32 Hz, CAr), 154.54 (s, CAr), 166.01 (d, Jₐp = 9 Hz, CAr). ³¹P{¹H} NMR (242 MHz, CD₂Cl₂): δ −144.49 (sept, PF₆), 199.0 (s). Anal. Calcd for C₁₉H₃₂F₆NiOP₂: C, 42.33; H, 5.98; N, 5.20. Found: C, 42.06; H, 5.88; N, 4.97.

Figure 2.27 ¹H NMR spectrum of [(EtNCOPiPr)Ni(NCCH₃)][PF₆] (3-Et) in CD₂Cl₂.
Figure 2.28 $^{31}$P{H} NMR spectrum of [($^{1}$NCOP$i$Pr)Ni(NCCH$_3$)]$^{[6]}$[PF$_6$] (3-Et) in CD$_2$Cl$_2$.

Figure 2.29 $^{13}$C{H} NMR spectrum of [($^{1}$NCOP$i$Pr)Ni(NCCH$_3$)]$^{[6]}$[PF$_6$] (3-Et) in CD$_2$Cl$_2$. 
**Synthesis of \((^{15}c_5 NCOP^{iPr})Ni(CH_2CN)\) (4-15c5)**

In a glovebox, a 20 mL vial was charged with 1.5 mL of THF, 3.3 µL (0.063 mmol) of CH₃CN, and a stirbar. The mixture was frozen at −196 °C, and 36.8 µL (0.059 mmol) of n-BuLi (1.6 M in hexanes) was slowly added. The resulting solution was allowed to warm to room temperature and was stirred for 20 min. It was then cooled to −30 °C in the glovebox freezer. A solution of 28.4 mg (0.049 mmol) of \((^{15}c_5 NCOP^{iPr})Ni(Br)\) in THF at −30 °C was then added, and the mixture was allowed to warm to room temperature again and stirred for 2 h. The volatiles were removed, and the residue was extracted with toluene and filtered. The toluene was removed to yield an amber oil (19 mg, 72% yield).

1H NMR (400 MHz, CD₂Cl₂): δ 0.11 (d, \(^3J_{HP} = 5\) Hz, 2H, Ni−CH₂CN), 1.30 (dd, \(^J_{HP} = 14\) Hz, \(^J_{HH} = 7\) Hz, 6H, CH(CH₃)₂), 1.38 (dd, \(^J_{HP} = 17\) Hz, \(^J_{HH} = 7\) Hz, 6H, CH(CH₃)₂), 2.37 (m, 2H, CH(CH₃)₂), 3.38 (m, 4H, crown-CH₂), 3.61 (m, 12H, crown-CH₂), 4.04 (m, 4H, crown-CH₂), 4.35 (s, 2H, ArCH₂N), 6.46 (d, \(^3J_{HH} = 8\) Hz, \(^1H\), ArH), 6.60 (d, \(^J_{HH} = 7\) Hz, \(^1H\), ArH), 6.90 (t, \(^J_{HH} = 8\) Hz, \(^1H\), ArH).

13C \{^1H\} NMR (150 MHz, CH₃CN): δ −15.16 (d, \(^3J_{CP} = 12\) Hz, Ni−CH₂CN), 17.37 (d, \(^3J_{CP} = 2\) Hz, CH(CH₃)₂), 18.33 (d, \(^3J_{CP} = 5\) Hz, CH(CH₃)₂), 28.77 (d, \(^1J_{CP} = 24\) Hz, CH(CH₃)₂), 58.09 (s, crown-CH ), 68.62 (s, ArCH N), 69.86 (s, crown-CH ), 71.15 (s, 222 crown-CH₂), 71.28 (s, crown-CH₂), 71.57 (s, crown-CH₂), 107.88 (d, \(^3J_{CP} = 13\) Hz, C₆), 116.08 (s, C₆), 126.41 (s, Ni−CH₂CN), 130.87 (s, C₆), 148.94 (d, \(^2J_{CP} = 31\) Hz, C₆), 153.27 (s, C₆), 165.28 (d, \(^2J_{CP} = 10\) Hz, C₆).

31P \{^1H\} NMR (161 MHz, CD₂Cl₂): δ 196.7. The highly reactive cyanomethyl complex was not suitably stable to pass elemental analysis.
Figure 2.30 $^1$H NMR spectrum of ($^{15}$C$^5$NCOP$i$Pr)$\text{NiCH}_2\text{CN}$ (4-$^{15}$C$^5$5) in CD$_2$Cl$_2$.

Figure 2.31 $^{31}$P{H} NMR spectrum of ($^{15}$C$^5$NCOP$i$Pr)$\text{NiCH}_2\text{CN}$ (4-$^{15}$C$^5$5) in CD$_2$Cl$_2$. 
Figure 2.32 $^{13}$C{H} NMR spectrum of $(^{15}$c5)NCOP(iPr)$\text{NiCH}_2$CN (4-15c5) in CH$_3$CN. Capillary containing C$_6$D$_6$ and HMDSO used to lock and shim. Satellite artifacts near CH$_3$CN/HMDSO peak due to field inhomogeneity and receiver overflow.

**General Procedure for Nickel-Catalyzed Insertion of Benzaldehyde into a C-H Bond of Acetonitrile**

In a glovebox, a 20 mL vial was charged with 306 µL (3.0 mmol) of benzaldehyde, 2.5 mL of acetonitrile, and optional base (e.g., 4.5 µL, 0.03 mmol of DBU). After addition of a 500 µL aliquot of a solution of 2-15c5 or 3-15c5 in acetonitrile (0.03 M, 0.015 mmol), the solution was capped and allowed to stir at room temperature for 24–120 h. After the desired reaction time, a 300 µL aliquot was evaporated to dryness under reduced pressure and dissolved in CDCl$_3$, and 6.4 µL (30 µmol) of hexamethyldisiloxane internal standard was added before NMR spectroscopic analysis.
**General Procedure for NMR-Scale Reactions**

In a glovebox, a standard catalytic solution was prepared as described in the general procedure. A 600 µL aliquot of the reaction mixture was added to a Teflon-capped NMR tube. Most of the reactions were run in protio solvent (CH₃CN), so a sealed capillary of C₆D₆ was added to the tube to provide a signal on which to lock and shim. Chemical shifts are reported relative to the residual C₆D₅H signal of the capillary tube. The tube was capped and monitored for 24–120 h by ¹H and ³¹P{¹H} NMR spectroscopy. Stoichiometric reactions were prepared and monitored analogously.
REFERENCES


CHAPTER 3: THERMODYNAMIC STUDIES OF CATION–MACROCYCLE INTERACTIONS IN NICKEL PINCER–CROWN ETHER COMPLEXES ENABLE SWITCHABLE LIGATION


3.1 Introduction

Control over ligand substitution processes poses a fundamental challenge in coordination chemistry and catalysis. Nature achieves impressive temporal control over chemical reactions through allosteric regulation.\(^1\)\(^-\)\(^2\) An active site might be physically inaccessible to substrate until a cofactor triggers a structural reorganization that permits substrate binding and initiates catalysis. These concepts have been successfully translated to large synthetic supramolecular constructs, enabling elegant advances in artificial switchable catalysis.\(^3\)\(^-\)\(^7\)

A similar degree of in situ control over ligand binding has not yet been widely realized in small organometallic complexes. Modification of a supporting ligand, such as through (de)-protonation\(^8\)\(^-\)\(^9\) or binding with a Lewis acid,\(^10\)\(^-\)\(^12\) can change the electronic structure of the metal center and alter substitution rates. Similarly, ligand substitution can be promoted by photochemical methods\(^13\)\(^-\)\(^14\) or redox reagents.\(^15\)

We are targeting in situ control over ligand substitution through tunable hemilability.\(^16\) Hemilabile ligands are chelates with a strong donor to anchor the ligand to the metal center and a weak donor that is readily displaced by an incoming ligand.\(^17\)\(^-\)\(^21\) Ethers are widely used as the weak donor in hemilabile complexes, but tuning is usually limited to synthesis of different
ligands of varying linker length or substituents. Our strategy combines design elements of hemilabile ligands with the knowledge of metallacrown ether chemistry. “Pincer–crown ether” ligands utilize aza-crown ether macrocycles as hemilabile ether donors, such that ether dissociation reveals a macrocycle capable of interacting with cations.

**Figure 3.1** Tunable hemilability approach to controlled ligand substitution. The pincer-crown ether ligand has a strong donor backbone (blue) and a hemilabile aza-crown ether (orange). If ether dissociation by ligand (green) binding ($\Delta G^\circ_1$) is uphill, cation-crown interactions can stabilize the overall process ($\Delta G^\circ_2$).

The dual equilibrium approach to tunable hemilability is summarized in Figure 3.1. In pincer–crown ether complexes containing a hemilabile ether donor with the pincer ligand bound in a tetradentate ($\kappa^4$) fashion, ligand substitution is often unfavorable ($\Delta G^\circ_1$). Upon ether dissociation, the pincer coordination mode switches and the aza-crown ether can better support cation–macrocycle interactions, with each cation providing different stability and thus tuning the overall binding energy ($\Delta G^\circ_2$). By introducing a tunable secondary equilibrium, the free energy landscape for the vital elementary step of ligand substitution can be tuned using simple additives.
The promise of tunable hemilability with the pincer–crown ether framework has been demonstrated in small molecule activation and catalysis.\textsuperscript{16} The pentadentate-bound Ir hydride complex \([\kappa^5-(15c^5\text{NCOP}^{iPr})\text{Ir}(\text{H})][\text{BAR}^F_4]\) (\text{Ar}^F = 3,5-(trifluoromethyl)phenyl) cleaves \(\text{H}_2\) at a rate widely tunable based on the identity of the alkali metal cation and the amount of cation present.\textsuperscript{30} The same Ir hydride cation also catalyzes isomerization of allylbenzene to \(\beta\)-methylstyrene; in the presence of lithium salts, the rate of catalysis increases 1000-fold.\textsuperscript{31} This approach has recently been utilized by other groups, including in sodium-triggered enantioselective hydrogenation by rhodium catalysts bearing aza-crown ether-substituted phosphine ligands.\textsuperscript{32}

Not all pincer–crown ether complexes show dramatic rate enhancements in the presence of cations, however. For example, the cationic methylcarbonyl complex \([\kappa^3-(15c^5\text{NCOP}^{iPr})\text{Ir}(\text{CH}_3)(\text{CO})(\text{NCCH}_3)][\text{BAR}^F_4]\) undergoes cation-accelerated migratory insertion reactivity in acetonitrile, but the effects are relatively modest.\textsuperscript{33} The nickel complex \((15c^5\text{NCOP}^{iPr})\text{Ni}(\text{O}^\text{Bu})\) catalyzes hydrocyanomethylation of benzaldehyde in \(\text{CH}_3\text{CN}\), and in this case, \(\text{Li}^+\) salts actually inhibit the reaction.\textsuperscript{34}

We set out to quantify cation–macrocycle interactions in nickel pincer–crown ether complexes and to define the salient design features that enable cation-modulated ligand substitution. The role of macrocycle size was probed using a new ligand featuring the larger aza-18-crown-6 macrocycle, and the role of solvent was clarified through comparative studies in dichloromethane and acetonitrile. The thermodynamic studies provide a blueprint for the development of systems capable of switchable ligation based on the introduction of a tunable secondary equilibrium with appropriate kinetic and thermodynamic parameters. Following this
blueprint, a nickel-based system capable of in situ lithium-switchable pentafluorophenylnitrile binding was developed.

3.2 Synthesis and Characterization of Nickel Complexes

The bromide complex $\kappa^3-(15c5\text{NCOP}^{iPr})\text{NiBr}$ (1-15c5) was previously reported.\textsuperscript{34} Complexes bearing a larger aza-crown ether macrocycle would be expected to have distinct binding affinity trends, which could enable a tailored response to specific cations based on the thermochemistry of cation–crown interactions in different organometallic complexes.

A new ligand was synthesized to access complexes with a larger macrocycle (Scheme 3.1). Reductive amination of 3-hydroxybenzaldehyde with aza-18-crown-6 was accomplished using sodium triacetoxyborohydride (STAB) in THF.\textsuperscript{33, 35} The aminomethylphenol was treated with $^{iPr}_2\text{PCl}$ and triethylamine (NEt$_3$) to yield $(18c6\text{NCOP}^{iPr})\text{H}$ as a colorless oil.

![Scheme 3.1 Synthesis of $(18c6\text{NCOP}^{iPr})\text{H}$.](image)

A Ni complex containing the larger aza-18-crown-6 macrocycle, $\kappa^3-(18c6\text{NCOP}^{iPr})\text{NiBr}$ (1-18c6), was accessed by metalation of $(18c6\text{NCOP}^{iPr})\text{H}$ with (DME)Ni(Br)$_2$ (DME is 1,2-dimethoxyethane) in toluene at 65 °C in the presence of 3 equiv NEt$_3$ (Scheme 3.2).
Scheme 3.2 Synthesis of 1-15c5 and 1-18c6

Single crystals of 1-18c6 were grown by slow evaporation of a dilute solution of 1-18c6 in diethyl ether. The solid-state structure of 1-18c6 (Figure 3.2) showcases tridentate pincer binding without any Ni–O interactions, as expected for a $d^8$ metal complex with 16 valence electrons.

Figure 3.2 Structural representation of $\kappa^3$-(18c6NCOP$i^*$P)$_2$Ni(Br) (1-18c6) with ellipsoids drawn at 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Ni–P 2.1096(6), Ni–N 2.028(2), Ni–Br 2.3573(6), Ni–C 1.859(2), P–Ni–Br 94.44(2), P–Ni–C 81.47(6), N–Ni–Br 97.87(5), N–Ni–C 85.19(8).
Addition of lithium trifluoromethanesulfonate (LiOTf) or lithium hexafluorophosphate (LiPF$_6$) to the Ni complex 1-15c5 in Et$_2$O resulted in a precipitate. Vapor diffusion of Et$_2$O into CH$_2$Cl$_2$ solutions of the compounds provided crystals suitable for X-ray diffraction (XRD) analysis.

Figure 3.3 shows the LiPF$_6$ adduct of 1-15c5, [(Li$^+$@$\alpha^3$-15c5NCOP$i$Pr)Ni(Br)][PF$_6$] (Li$^+$·1-15c5). Along with the analogous LiOTf adduct shown in Figure 3.4, these are the first structurally characterized cation adducts with this ligand framework. The primary coordination sphere of Ni in Li$^+$·1-15c5 is not greatly perturbed relative to 1-15c5. The amine of the aza-crown ether remains coordinated only to Ni and does not interact with the Li$^+$ ion. The Li$^+$ ion is coordinated by four crown ether oxygen atoms (2.005(8)–2.077(9) Å) and a fluorine atom (1.922(5) Å) from the PF$_6$ anion. The Li–O bond lengths are comparable to those in the LiOTf adduct of 12-crown-4 (Li–O: 2.053(3)–2.109(4) Å).$^{36}$ Molybdenum complexes featuring cis-coordinated R$_2$P(OCH$_2$CH$_2$)$_3$OPR$_2$ ligands with four oxygen donors also have similar Li–O bond lengths (2.003–2.195 Å),$^{37-38}$ whereas a pyridinediimine (PDI) iron complex with a pendent 15-crown-5 ether has significantly longer Li–O bonds (avg. Li–O 2.20 Å vs 2.05 Å).$^{39}$ The structural similarities suggest that macrocycles with four crown oxygen atoms are good models for the binding in Li$^+$·1-15c5.
Figure 3.3 Structural representation of \([\text{Li}^+\kappa^{3.15c5}\text{NCOP}^\text{ipr})\text{Ni(Br)}][\text{PF}_6] (\text{Li}^\cdot\text{1-15c5})\) with ellipsoids drawn at 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Ni–P1 2.1099(8), Ni–N 2.046(2), Ni–Br 2.3584(8), Ni–C 1.860(3), avg. Li–O 2.05, Li–F 1.922(5), P1–Ni–Br 94.76(3), P1–Ni–C 81.61(8), N–Ni–Br 100.87(6), N–Ni–C 83.4(1).

Figure 3.4 Structural representation of \([\text{Li}^+\kappa^{3.15c5}\text{NCOP}^\text{ipr})\text{Ni(Br)}][\text{OTf}] (\text{LiOTf}^\cdot\text{1-15c5})\) with ellipsoids drawn at the 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Ni–P 2.108(1), Ni–N 2.046(2), Ni–Br 2.360(1), Ni–C 1.857(4), avg. Li–O 2.05, Li–OTf 1.940(7), P–Ni–Br 94.24(4), P–Ni–C 81.5(2), N–Ni–Br 100.97(8), N–Ni–C 83.7(1).
The solid-state structure of the sodium adduct [(Na⁺@κ³,15c5NCOPPr)Ni(Br)][BArF₄] (Na⁺·1-15c5) was also determined. Crystals suitable for XRD analysis were grown by vapor diffusion of pentane into a Et₂O solution containing 1-15c5 and 2 equiv NaBArF₄ at −30 °C (Figure 3.5). The Na⁺ ion in Na⁺·1-15c5 has a distorted octahedral geometry and is facially coordinated by only three of the four oxygen atoms of the crown ether. The Na−O bond lengths are similar to the 2:1 12-crown-4 complex with Na⁺ and the 1:1 15-crown-5 complex of Na⁺. Organometallic complexes with 15-crown-5 or polyether ligands also have similar Na−O distances. However, the Na⁺ ion in Na⁺·1-15c5 sits well outside of the center of the crown ether cavity and the conformation of the crown allows Na⁺ to interact with an Et₂O molecule, a fluorine of the BArF₄ counterion, and even the bromide ligand attached to the Ni center. Crown ethers can adopt a wide range of geometries in order for alkali metal guests to participate in stabilizing secondary interactions with solvent molecules or halogen atoms. The structural differences between the Li⁺ and Na⁺ adducts of 1-15c5 suggest that the binding affinity for each cation will be different.
Figure 3.5 Structural representation of [(Na⁺@κ²-15c5NCOPiPr)Ni(Br)][BArF₄] (Na⁺•1-15c5) with ellipsoids drawn at 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Ni–P 2.1065(8), Ni–N 2.047(2), Ni–Br 2.3572(5), Ni–C 1.862(3), avg. Na–O₁ crown 2.41, Na–O₂ 2.319(2), Na–F BArF₄ 2.612(2), Na-Br 2.814(1), P–Ni–Br 92.78(2), P–Ni–C 81.18(8), N–Ni–Br 102.53(6), N–Ni–C 84.6(1).

Pincer–crown ether Ni complexes were previously studied in acetonitrile, where solvent displacement of the macrocyclic ether donors prevents hemilability. In CH₂Cl₂, halide abstraction from 1-15c5 or 1-18c6 by addition of AgPF₆ results in AgBr precipitation and formation of the tetradeinate-bound complexes [κ⁴-(15c5NCOPiPr)Ni][PF₆] (2-15c5) and [κ⁴-(18c6NCOPiPr)Ni][PF₆] (2-18c6), each containing one crown ether oxygen atom donating to Ni (Scheme 3.3).
Scheme 3.3 Synthesis of 2-15c5 and 2-18c6.

Vapor diffusion of Et₂O into a CDCl₃ solution of 2-15c5 provided crystals suitable for XRD analysis. The solid-state structure of 2-15c5 (Figure 3.6) confirms the tetradeinate coordination mode of the ligand, in which one crown ether oxygen is bound to the Ni center. The Ni system can readily support either tridentate (1-15c5) or tetradeinate (2-15c5) transition metal binding, as needed for crown ether hemilability. The distorted square planar geometry, with C₁ symmetry and all donors in the same plane, contrasts with Ir complexes that adopt a mer,fac configuration when a crown ether oxygen binds to give tetradeinate ligand coordination in an octahedral geometry.³⁰,³³
Figure 3.6 Structural representation of $[\kappa^4-(15c5\text{NCOP}^\text{ipr})\text{Ni}][\text{PF}_6]$ (2-15c5) with ellipsoids drawn at the 50% probability level. Hydrogen atoms and PF$_6$ anion omitted for clarity. Selected distances (Å) and angles (deg): Ni–P 2.1427(6), Ni–N 1.966(2), Ni–O 1.965(2), Ni–C 1.848(2), P–Ni–O 110.34(4), P–Ni–C 81.32(6), N–Ni–O1 83.94(6), N–Ni–C1 84.60(8), C1–Ni–O1 167.36(7).

The $^1$H NMR spectra of 2-15c5 and 2-18c6 are consistent with $C_s$ symmetry in solution at room temperature. The resonances of 2-15c5 and 2-18c6 are sharp at room temperature, but they broaden upon cooling to $-80$ °C without completely decoalescing, suggesting a low barrier for ligand exchange (Figures 3.7 and 3.8). The spectral data are consistent with dynamic hemilability involving rapid and reversible exchange of ether ligands on the time scale of the experiment (Scheme 3.4).
Figure 3.7 Variable temperature $^1$H NMR spectra of $[\kappa^4-(^{15}\text{c}^5\text{NCOD}^{\text{iPr}})\text{Ni}][\text{PF}_6]$ (2-15c5) in CD$_2$Cl$_2$.

Figure 3.8 Variable temperature $^1$H NMR spectra of $[\kappa^4-(^{18}\text{c}^6\text{NCOD}^{\text{iPr}})\text{Ni}][\text{PF}_6]$ (2-18c6) in CD$_2$Cl$_2$. 
In order to avoid LiPF$_6$ precipitation during subsequent studies, an anion exchange was performed on 2-15c5. The PF$_6$ salt 2-15c5 is treated with NaBAR$_4$ in CH$_2$Cl$_2$ to form [$\kappa^4$-(15c5NCOIPr)$_2$Ni][BAR$_4$] (3-15c5). The spectroscopic signatures of 3-15c5 were completely analogous to 2-15c5, indicating a similar structure.

Isolation of complexes 1 and 2 confirms that the pincer–crown ether ligand can act as a hemilabile ligand on nickel complexes, with facile access to two different pincer ligand coordination modes in noncoordinating solvents. The structural studies provide direct evidence of cation–crown interactions in the solid state.

3.3 Cation–Crown Interactions in Dichloromethane

To learn more about the thermochemistry of cation–macrocycle interactions in nickel pincer–crown ether complexes, cation binding affinity data in solution were targeted. Titration of the small macrocycle-containing bromide complex 1-15c5 with LiBAR$_4$ in CD$_2$Cl$_2$ (15 equiv Et$_2$O to salt) led to the broadening and shifting of $^1$H NMR resonances expected for a rapid equilibrium process (Figure 3.9). Signals corresponding to the isopropyl methyl protons did not shift significantly during these experiments, and only small shifts were observed in the isopropyl methine ($\Delta\delta_{\text{max}} = 0.05$) and aryl backbone resonances ($\Delta\delta_{\text{max}} = 0.09$). The resonances...
corresponding to the crown ether exhibited the largest shifts ($\Delta\delta_{\text{max}} = 0.62$), indicating a host–guest interaction localized in the macrocycle of the complex.

Figure 3.9 A) $^1$H NMR spectra from titration of 5 mM $\kappa^2$-($^{15}$c5NCOP$^{i}$Pr)$^\wedge$Ni(Br) (1-15c5) with LiBAR$_4^\wedge$ in CD$_2$Cl$_2$ (15 equiv Et$_2$O to Li$^+$). B) Cation binding isotherm data for the titration of 5 mM 1-15c5 with LiBAR$_4^\wedge$ (green circles) at 20 ± 1 ºC in CD$_2$Cl$_2$ (15 equiv Et$_2$O to cation).

Plotting the change in chemical shift ($\Delta\delta$) of the benzylic linker or crown ether resonances as a function of added cation gives binding isotherms that plateau sharply at 1 equiv
of salt with respect to Ni. The data indicate strong cation binding by 1-15c5, which lacks any Ni–O interactions. Under these conditions, Li⁺ binding occurs with \( K_a > 10^5 \text{ M}^{-1} (\Delta G^\circ > 7 \text{ kcal} \cdot \text{mol}^{-1}) \), beyond the upper limit of quantification for NMR titration studies.\(^{44-45}\)

**Figure 3.10** Cation binding isotherm data for the titration of 5 mM \( \kappa^3-(15c5\text{NCOP}^{\text{ipr}})\text{NiBr} (1-15c5) \) with LiBAR\(^{\text{F}}\)\(_4\) (filled green circles) and NaBAR\(^{\text{F}}\)\(_4\) (filled blue triangles) and 5 mM \( \kappa^3-(18c6\text{NCOP}^{\text{ipr}})\text{NiBr} (1-18c6) \) with LiBAR\(^{\text{F}}\)\(_4\) (hollow green circles) and NaBAR\(^{\text{F}}\)\(_4\) (hollow blue triangles) at 20 ± 1 °C in CD\(_2\)Cl\(_2\) (15 equiv Et\(_2\)O to cation).

Similar binding isotherms were obtained with NaBAR\(^{\text{F}}\)\(_4\) (Figure 3.10, 15 equiv Et\(_2\)O to salt), in accord with strong cation binding (\( K_a > 10^5 \text{ M}^{-1} \)). Partial halide abstraction complicated NaBAR\(^{\text{F}}\)\(_4\) titrations of 1-15c5, however. In tubes with higher salt concentrations, up to 40% conversion to the BAR\(^{\text{F}}\)\(_4\) salt 3-15c5 was present in the \(^1\text{H} \)NMR spectra (Figure 3.11).
Figure 3.11 $^1$H NMR spectra from the titration of 5 mM $\kappa^3$-($^{15}$c$^5$NCOP$i$Pr)$\text{NiBr}$ (1-15c5) with NaBAr$^F_4$ with $^1$H NMR spectrum of $[\kappa^4$-($^{15}$c$^5$NCOP$i$Pr)$\text{Ni}[\text{BAr}^F_4]$ (3-15c5) at top of stack for reference.

The larger aza-18-crown-6-containing bromide complex 1-18c6 also exhibits strong binding ($K_a > 10^5 \text{ M}^{-1}$) of both LiBAr$^F_4$ and NaBAr$^F_4$ based on titration studies in CD$_2$Cl$_2$ (Figure 3.10, Scheme 3.5). Interestingly, no halide abstraction from 1-18c6 was observed during titrations with Na$^+$, indicating a thermodynamic preference for cation–crown interactions over formation of the NaBr lattice. Indeed, when 2-18c6 is added to a suspension of NaBr in CD$_2$Cl$_2$ with 100 mM Et$_2$O, signals for Na$^+\cdot$1-18c6 are observed.$^{46}$ The analogue containing a smaller macrocycle, 3-15c5, did not react with NaBr to form a Ni bromide complex.$^{46}$
Scheme 3.5 Equilibrium Li⁺ and Na⁺ Binding by 1-15c5 and 1-18c6 in CD₂Cl₂.

The tetradentate-bound BAr₄⁻ salt 3-15c5 does not bind Li⁺ to any significant extent. Upon addition of up to 3 equiv LiBAr₄ • 3Et₂O to CD₂Cl₂ solutions of 3-15c5, the ¹H NMR resonances of the crown ether protons did not shift (Figure 3.12). The Li⁺ binding affinity of 3-15c5 is less than 1 M⁻¹ in CD₂Cl₂.

Figure 3.12 Addition of 1-3 equivalents of LiBAr₄ • 3Et₂O to [κ¹-(15c5NCOPiPr)Ni][BAr₄⁻] (3-15c5) in CD₂Cl₂.
When one of the crown ether oxygen atoms is bound to the nickel center, as in tetradentate-bound complex 3-15c5, interactions with alkali metal cations are negligible. In the case of complex 1-15c5, all four ether donors are available for cation binding, leading to a striking coordination-mode-dependent binding affinity. When the hemilabile ligand switches from tetradentate to tridentate coordination allowing all four ether donors to participate in host–guest interactions, cation binding becomes more than 100,000 times more favorable. This difference suggests a large energetic stabilization will be possible upon ligand binding in the presence of cations. Organic macrocycles with different numbers of available oxygen donors sometimes show large changes in binding affinity. For example, calorimetric titrations in acetonitrile show that barium cations bind to 12-crown-4 about 13,000 times more strongly than they bind to 9-crown-3.47

The titration data for Ni complexes ligated in a tridentate fashion also provide insight into the dynamics of cation–crown interactions in catalysis. The plateau at a cation:complex ratio of 1 indicates a 1:1 binding stoichiometry. The titrations indicate that cation–macrocycle binding is rapid and reversible on the time scale of the NMR acquisition. Maintaining low barriers of cation exchange could be important in supporting rapid catalysis. Additionally, these experiments suggest that cation–crown interactions can offset uphill substrate binding ($\Delta G^\circ$, Figure 3.1) by at least 7 kcal·mol$^{-1}$ (based on the limiting value of $K_a > 10^5$ M$^{-1}$ in CD$_2$Cl$_2$).

3.4 Cation–Crown Interactions in Acetonitrile

Titrations in dichloromethane indicate that both Li$^+$ and Na$^+$ are bound tightly by 1-15c5 and 1-18c6, but quantitation of cation selectivity was elusive. The more polar, donor solvent acetonitrile was expected to temper binding affinities enough to allow quantitative measurement of cation binding by $^1$H NMR spectroscopy. Moving to acetonitrile also allows direct
comparisons with many organic macrocycles\textsuperscript{48-50} and provides better alkali metal salt solubility to improve precision in titrations.

Preliminary \textsuperscript{1}H NMR studies showed that addition of either \textit{Li}\textsuperscript{+} or \textit{Na}\textsuperscript{+} salts to 1-15c5 in CD\textsubscript{3}CN caused significant broadening and systematic shifts in resonances corresponding to the crown ether and benzylic linker protons without evidence of formation of two distinct species on the \textsuperscript{1}H NMR time scale. This behavior is consistent with rapid and reversible equilibrium cation–crown interactions on the \textsuperscript{1}H NMR time scale at room temperature. In contrast to the CD\textsubscript{2}Cl\textsubscript{2} titrations, these resonances continued to shift even as the cation:Ni ratio increased above 1, suggesting weaker—and quantifiable—binding in CD\textsubscript{3}CN. Interactions were also evident in electrospray ionization mass spectrometry (ESI–MS), where Li\textsuperscript{+}·1-15c5 (m/z calcd 586.12; found 586.22) and Na\textsuperscript{+}·1-15c5 (m/z calcd: 602.10; found 602.15) were observed.

In order to obtain quantitative binding affinity data, a model that takes into account the binding stoichiometry is needed. Using the method of continuous variations (MCV),\textsuperscript{51} the change in chemical shift of the benzylic linker of 1-15c5 in solutions containing varying amounts of LiOTf (maintaining a total concentration of 12 mM) was used to construct a Job plot (Figure 3.13). The maximum at 0.5 mole fraction Li\textsuperscript{+} indicates a 1:1 binding stoichiometry. A similar experiment with 1-15c5 and NaBAR\textsubscript{4} was also consistent with 1:1 binding stoichiometry. Attempts to obtain the binding stoichiometry for 1-15c5 and K\textsuperscript{+} were unsuccessful because the changes in chemical shift were unreliably small (indicating quite weak interactions). As shown in Figure 3.13, 1-18c6 also exhibits 1:1 binding stoichiometry with all three alkali metal salts.
Figure 3.13 Job plots for $\kappa^3$-(15c5NCOP$i$Pr)Ni(Br) (1-15c5) with LiOTf (hollow green circles) and NaBAR$_F^4$ (hollow blue triangles), and Job plots for $\kappa^3$-(18c6NCOP$i$Pr)Ni(Br) (1-18c6) with LiOTf (filled green circles), NaBAR$_F^4$ (filled blue triangles), and KPF$_6$ (filled orange squares) at 24 ± 1°C in CD$_3$CN. Concentrations of 1-15c5 or 1-18c6 and cations were varied within a total concentration of 12 mM.

Binding affinities were next determined by titration of CD$_3$CN solutions of Ni complexes with increasing amounts of LiOTf. Resonances corresponding to the crown ether and benzylic linker protons broadened and smoothly shifted as the concentration of Li$^+$ increased. The nonlinear changes in chemical shift and the leveling off of the binding isotherm at a Li$^+$:Ni ratio of 8 are appropriate for quantitative modeling (Figure 3.14).$^{45,52}$ Fitting the binding isotherm with a 1:1 model gave $K_a = 91$ M$^{-1}$ for LiOTf. A similar experiment was performed with LiPF$_6$ and gave $K_a = 76$ M$^{-1}$, indicating that anions can slightly impact binding affinity in this system (Figure 3.15).
Figure 3.14 A) Cation binding equilibrium in CD$_3$CN. B) $^1$H NMR spectra from titration of 10 mM $\kappa^3$-$^{15c5}$NCOP$iPr$Ni(Br) (1-15c5) with LiOTf in CD$_3$CN. C) Binding isotherm data for titration of 10 mM $\kappa^3$-$^{15c5}$NCOP$iPr$Ni(Br) (1-15c5) with LiPF$_6$ (green circles), NaBAR$_4$ (blue triangles), and KPF$_6$ (orange squares) at 24 ± 1°C in CD$_3$CN.
Figure 3.15 Binding isotherm data for titration of 10 mM $\kappa^2$-($^{15}$c5NCOP$i$Pr)Ni(Br) (1-15c5) with LiPF$_6$ at 24 ± 1°C in CD$_3$CN.

Titration of 1-15c5 with NaBAR$_4$ or KPF$_6$ gave small chemical shifts and nearly linear binding isotherms that do not appear to approach a maximum $\Delta \delta$ value within the limits of salt solubility. Consistent with the MCV analysis, the data suggest that 1-15c5 does not interact strongly with Na$^+$ or K$^+$ under these conditions, $K_a < 10$ M$^{-1}$.

Simply changing the solvent from dichloromethane to acetonitrile results in a decrease in binding affinity of at least 3 orders of magnitude! The solvent-dependent binding affinity provides some insight into previously observed solvent effects in cation-tuned organometallic transformations of pincer–crown ether complexes. Whereas 1,000-fold rate enhancements have been observed in CH$_2$Cl$_2$ solution,$^{30}$ only moderate cation effects have been observed for reactions facilitated by pincer–crown ether complexes in acetonitrile solvent.$^{33-34}$ The decrease in binding affinity moving from CH$_2$Cl$_2$ to CH$_3$CN may be partially responsible for the smaller cation-induced rate enhancements observed in CH$_3$CN.$^{33}$
The macrocyclic pincer ligand is essential for fostering the observed interactions with cations. An identical titration experiment performed with $\kappa^2-(\text{EtNCOP}i\text{Pr})\text{Ni}(\text{Br})$, which contains ethyl substituents in place of the aza-crown ether, showed negligible broadening or shifting (Figure 3.16). Treatment of 1-15c5 with 10 equiv $[\text{Bu}_4\text{N}][\text{PF}_6]$ did not result in any perceptible change to the NMR spectrum,\textsuperscript{46} ruling out the possibility of changes in ionic strength affecting chemical shift.

Figure 3.16 Titration of 10 mM $\kappa^3-(\text{EtNCOP}i\text{Pr})\text{Ni}(\text{Br})$ with $\text{LiPF}_6$ at $24 \pm 1^\circ\text{C}$ in CD$_3$CN.
binding isotherm data for titration of 10 mM $\kappa^2$-$(^{18c6}$NCOP$iPr$)Ni(Br) (1-18c6) with LiPF$_6$ (green circles), NaBAR$_6^+$ (blue triangles), and KPF$_6$ (orange squares) at 24 ± 1°C in CD$_3$CN.

It is well-known that the size of the crown ether macrocycle (i.e., number of ether donors) has a dramatic effect on cation binding affinity.$^{49-50, 53-55}$ To probe whether similar trends would hold in our organometallic complexes, the alkali metal cation binding affinity of 1-18c6 (containing the larger aza-18-crown-6 macrocycle) was determined in CD$_3$CN using the titration methods described above (Figure 3.17 and Table 3.1). The equilibrium constant for Li$^+$ binding by 1-18c6 ($K_a = 34$ M$^{-1}$) is somewhat smaller than that of 1-15c5. The affinity of 1-18c6 for the Na$^+$ salt, on the other hand, was quite high: $K_a = 1490$ M$^{-1}$ is the highest cation binding affinity we measured in CD$_3$CN. Due to the high binding affinity of 1-18c6 with Na$^+$, the titration was performed at three different concentrations of 1-18c6 to confirm $K_a$ within 6% uncertainty.$^{46, 56}$ The binding affinity of 1-18c6 with K$^+$, $K_a = 60$ M$^{-1}$, indicates significant cation–crown interactions (in contrast to the very weak K$^+$ binding in 1-15c5).
Table 3.1 Association Constants in CD$_3$CN.

<table>
<thead>
<tr>
<th>Complex</th>
<th>Salt</th>
<th>$K_a$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-15c5</td>
<td>LiPF$_6$</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>LiOTf</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>NaBAr$_4^+$</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>KPF$_6$</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>1-18c6</td>
<td>LiPF$_6$</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>NaBAr$_4^+$</td>
<td>1260</td>
</tr>
<tr>
<td></td>
<td>KPF$_6$</td>
<td>60</td>
</tr>
</tbody>
</table>

**Conditions:** CD$_3$CN, 10 mM 1, 0-120 mM salt. Analyzed by $^1$H NMR spectroscopy at 24 ± 1°C. Estimated uncertainty ≤ 10%.

3.5 Comparisons with Organic Crown Ethers and Variable Temperature Studies

Extensive binding affinity data is available for organic crown ethers in acetonitrile, facilitating comparisons between organometallic and organic systems in this solvent. Because all structural and spectroscopic evidence suggests that the amine nitrogen remains bound to the transition metal center under the present experimental conditions, we considered the four-oxygen-donor 12-crown-4 a good starting point for comparisons with aza-15-crown-5-derived organometallic complexes.

The organic macrocycle 12-crown-4 binds Li$^+$ with modest selectivity. In CH$_3$CN solution, Li$^+$ ions bind to 12-crown-4 1.2 times more tightly than Na$^+$ ions.$^{48}$ The same trend in cation specificity is observed for the aza-15-crown-5-containing pincer–crown ether complex, with 1-15c5 preferentially binding Li$^+$ over Na$^+$ and K$^+$. Surprisingly, the organometallic macrocycle exhibits more selective Li$^+$ binding than 12-crown-4: 1-15c5 binds Li$^+$ greater than 7 times more tightly than Na$^+$ in CH$_3$CN.

Moving from 12-crown-4 to 15-crown-5 leads to a change in cation selectivity, with the larger macrocycle 15-crown-5 selectively binding Na$^+$ ions. The same general trend is observed in Ni complexes with the larger aza-18-crown-6 macrocycle, as 1-18c6 selectively binds Na$^+$
ions over Li$^+$ or K$^+$ ions. Complex 1-18c6 binds Na$^+$ 44-times more strongly than Li$^+$ and 25-times more strongly than K$^+$. Again, the Ni complex is more selective for Na$^+$ than the analogous organic macrocycle; 15-crown-5 has an equilibrium constant for Na$^+$ binding that is only 6–8 times larger than for Li$^+$ and K$^+$.48

The Ni complexes bind cations orders of magnitude less strongly than similar organic crown ethers. Both 12-crown-4 and 1-15c5 present the same array of four oxygen donors, but 12-crown-4 binds Li$^+$ with $K_a = 2512\ \text{M}^{-1}$, nearly 40 times higher than that of 1-15c5.48 Similarly, five-oxygen donor 15-crown-5 binds Na$^+$ ($K_a = 126\ 000\ \text{M}^{-1}$) 85 times more tightly than five-oxygen donor 1-18c6 ($K_a = 1490\ \text{M}^{-1}$).48

![Figure 3.18](image-url) Binding isotherm data for titration of 0.01 M $\kappa^3-(15c5\text{NCOPiPr})\text{Ni(Br)}$ (1-15c5) with LiOTf in CD$_3$CN at various temperatures (left) and binding isotherm data for titration of 0.01 M $\kappa^3-(18c6\text{NCOPiPr})\text{Ni(Br)}$ (1-18c6) with NaBAR$_4$ in CD$_3$CN at various temperatures (right).

To probe the origin of the large differences in binding affinity between organic and organometallic macrocycles, the enthalpy and entropy of binding were determined. Thermodynamic parameters for Li$^+$ binding by 1-15c5 and Na$^+$ binding by 1-18c6 were extracted
on the basis of variable-temperature NMR experiments using a van ‘t Hoff analysis (Figure 10).

Six tubes containing 10 mM Ni and increasing equivalents of Li⁺ or Na⁺ salts were prepared, and $K_a$ was determined every 10 degrees from 253 to 293 K.

![Graph showing van ‘t Hoff analysis of LiOTf binding by $\kappa^3-(15c5\text{NCOP}^{\text{iPr}})\text{Ni(Br)}$ (green circles) and NaBAR$_4^+$ binding by $\kappa^3-(18c6\text{NCOP}^{\text{iPr}})\text{Ni(Br)}$ (1-18c6) (blue triangles).]

Figure 3.19 Van ‘t Hoff analysis of LiOTf binding by $\kappa^3-(15c5\text{NCOP}^{\text{iPr}})\text{Ni(Br)}$ (1-15c5) (green circles) and NaBAR$_4^+$ binding by $\kappa^3-(18c6\text{NCOP}^{\text{iPr}})\text{Ni(Br)}$ (1-18c6) (blue triangles).

Thermodynamic analysis of Li⁺ ion binding by 1-15c5 reveals an enthalpy-driven process ($\Delta H = -2.50 \pm 0.46 \text{ kcal}\cdot\text{mol}^{-1}$) with a negligible entropic term ($\Delta S = 0.0 \pm 1.7 \text{ cal}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$).

A comparison with 12-crown-4 under similar conditions is shown in Table 3.2. Both macrocycles have small entropy terms, so the difference in binding affinity can be ascribed to reduced enthalpy of Li⁺ binding to the Ni complex. This could be due to conformational restrictions reducing bonding interactions or inductive effects from the electropositive Ni center pulling electron density out of the crown ether. Inductive effects have been invoked in benzylaza-15-crown-5 ethers. The parent benzylaza-15-crown-5 ether binds NaClO$_4$ ($K_a = 478\ 600$...
M−1) nearly 2 full orders of magnitude stronger than the p-nitro- substituted compound (Ka =
9300 M−1).57 Similarly, electronic effects seemed to dominate in a study of crown ethers that link
the oxygen atoms with linkers of variable length and electronic structure (alkyl vs acetyl).58

Na+ binding by 1-18c6 is also enthalpy-driven (ΔH = −5.10 ± 0.46 kcal·mol−1), with a
relatively small entropic contribution (ΔS = −2.6 ± 1.7 cal·mol−1·K−1). The binding enthalpy is
significantly more favorable than 1-15c5 and Li+, consistent with the pair 1-18c6 and Na+
exhibiting the highest binding affinity of all the pincer–crown ether complexes and alkali metal
cations in CH3CN at 24 ± 1 °C. The organic crown ether 15-crown-5 binds Na+ with enthalpy
and entropy terms that are both slightly more favorable than 1-18c6 (Table 3.2).

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<th>ΔS (cal·mol−1·K−1)</th>
<th>TΔS (kcal·mol−1) at 298 K</th>
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<td>−1.1</td>
<td>−0.33</td>
<td>Danil et al.58</td>
</tr>
<tr>
<td>1-18c65</td>
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<td>−2.6 ± 1.7</td>
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<td>Okorafor et al.59</td>
</tr>
</tbody>
</table>

a Parameters determined in CD3CN by van ‘t Hoff analysis of variable temperature NMR
titrations at 253, 263, 273, 283, and 293 K.

3.6 Cation Switchable Ligand Binding

With a deep understanding of cation–macrocycle interactions in nickel pincer–crown
ether complexes, we set out to demonstrate control over ligand substitution. Tetradentate-bound
Ni complex 3-15c5 could block ligand access to the site trans to the phenyl backbone through
interaction with a crown ether oxygen atom, whereas a tridentate analogue formed after ligand
binding and ether dissociation could support cation–crown interactions. The effect of alkali
metal salts on pentafluorobenzonitrile (C6F5CN) binding at 3-15c5 was examined.
The tetradeative-bound complex 3-15c5 does not bind C₆F₅CN in CD₂Cl₂. Displacement of the weakly bound ether in 3-15c5 by either solvent CD₂Cl₂ or Lewis base C₆F₅CN is unfavorable. The ether donor thus acts as an effective “gate” for ligand binding.

Scheme 3.6 Reversible C₆F₅CN binding by 3-15c5.

Addition of K⁺ to a solution containing 3-15c5 and C₆F₅CN in CD₂Cl₂ had no discernible effect within the limits of KB(C₆F₅)₄ solubility. No K⁺-triggered ligation is observable. On the other hand, addition of Na⁺ to a solution containing 3-15c5 and C₆F₅CN results in equilibrium nitrile binding as indicated by broadening and shifting of the resonances of the ¹H NMR spectrum (Figures 3.20, 3.21, and 3.22). Two sets of broad resonances are observed in ³¹P{¹H} and ¹⁹F{¹H} NMR spectra, reflecting roughly 70% 3-15c5 and 30% of a species assigned as the Na⁺ and nitrile adduct of Ni (Scheme 3.6 and Figures 3.23, 3.24, 3.25).
Figure 3.20 $^1$H NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN and [K][B(C$_6$F$_5$)$_4$] to [$\kappa^4$(15c5NCOP$_{iPr}$)Ni][BAr$_4^-$] (3-15c5) in CD$_2$Cl$_2$ (top to bottom).

Figure 3.21 $^{31}$P NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN and [K][B(C$_6$F$_5$)$_4$] to [$\kappa^4$(15c5NCOP$_{iPr}$)Ni][BAr$_4^-$] (3-15c5) in CD$_2$Cl$_2$ (top to bottom).
Figure 3.22 $^{19}$F NMR spectra from sequential addition of one equivalent $\text{C}_6\text{F}_5\text{CN}$ and $[\text{K}][\text{B}($$\text{C}_6\text{F}_5$)$_4\text{]}$ to $[\pi^d$-$^{15}\text{c}5\text{NCOP}$]$\text{iPr}]$$\text{Ni}$$[\text{BAr}$$_4$$\text{]}$ (3-$^{15}\text{c}5\text{)}$ in CD$_2$Cl$_2$ (top to bottom).

Figure 3.23 $^1$H NMR spectra from sequential addition of 1 equivalent $\text{C}_6\text{F}_5\text{CN}$, 1 equivalent NaBAR$_4$, and 2 equivalents 12-crown-4 to $[\pi^d$-$^{15}\text{c}5\text{NCOP}$]$\text{iPr}]$$\text{Ni}$$[\text{BAr}$$_4$$\text{]}$ (3-$^{15}\text{c}5\text{)}$ in CD$_2$Cl$_2$ (15 equivalents Et$_2$O to Na$^+$ added for solubility) (top to bottom).
**Figure 3.24** $^{31}$P{${}^1$H} NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN, 1 equivalent NaBAR$_4^-$, and 2 equivalents 12-crown-4 to [κ$^4$-(15c5NCOPiPr)Ni][BAR$_4^-$] (3-15c5) in CD$_2$Cl$_2$ (15 equivalents Et$_2$O to Na$^+$ added for solubility) (top to bottom).

**Figure 3.25** $^{19}$F NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN, 1 equivalent NaBAR$_4^-$, and 2 equivalents 12-crown-4 to [κ$^4$-(15c5NCOPiPr)Ni][BAR$_4^-$] (3-15c5) in CD$_2$Cl$_2$ (15 equivalents Et$_2$O to Na$^+$ added for solubility) (top to bottom).
Upon addition of 1 equiv Li⁺ to a CD₂Cl₂ solution containing 3-15c5 and C₆F₅CN, complete conversion to a new species is observed (Scheme 3.6). ⁷Li NMR spectra confirm that Li⁺ is tightly bound to the nickel pincer–crown ether complex,⁴⁶ and ¹⁹F {¹H} NMR spectra indicate stoichiometric nitrile binding based on a dramatic downfield shift in the para-F resonance of C₆F₅CN (Figures 3.26, 3.27, and 3.28).⁵⁹-⁶⁰ The spectrum is not fluxional in this case; the equilibrium for ligand binding lies far toward nitrile ligation. The macrocyclic “gate” can thus be fully opened with the aid of Li⁺ binding.

**Figure 3.26** ¹H NMR spectra from sequential addition of 1 equivalent C₆F₅CN, 1 equivalent LiBARF₄•3Et₂O, and 2 equivalents 12-crown-4 to [η⁴-(¹⁵c₅NCOPiPr)Ni][BARF₄] (3-15c5) in CD₂Cl₂ (top to bottom).
**Figure 3.27** $^{31}$P NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN, 1 equivalent LiBAr$_F^4$•3Et$_2$O, and 2 equivalents 12-crown-4 to [A$^d$-{(15c$_5$NCO$^{iPr}$)Ni}]BAr$_F^4$ (3-15c5) in CD$_2$Cl$_2$ (top to bottom).

**Figure 3.28** $^{19}$F NMR spectra from sequential addition of 1 equivalent C$_6$F$_5$CN, 1 equivalent LiBAr$_F^4$•3Et$_2$O, and 2 equivalents 12-crown-4 to [A$^d$-{(15c$_5$NCO$^{iPr}$)Ni}]BAr$_F^4$ (3-15c5) in CD$_2$Cl$_2$ (top to bottom).
The titration data above suggest that Li\(^+\) forms a stronger adduct with 12-crown-4 than with 3-15c5 in acetonitrile, so we hypothesized that the organic crown could be used to reverse nitrile binding in dichloromethane. After Li\(^+\)-triggered nitrile binding to Ni, addition of 2 equiv 12-crown-4 leads to rapid sequestration of Li\(^+\), with release of free C\(_6\)F\(_5\)CN and reformation of 3-15c5 apparent by NMR spectroscopy (Scheme 3.6 and Figures 3.26, 3.27, and 3.28). Similar behavior is observed in equilibrium mixtures formed upon addition of Na\(^+\) and C\(_6\)F\(_5\)CN to 3-15c5: addition of 12-crown-4 leads to sharp signals for 3-15c5 and the \(^1\)H resonances of 12-crown-4 shift downfield indicating Na\(^+\) complexation. Cation-controlled in situ switchable ligand binding and release is enabled through cation interactions with the hemilabile pincer–crown ether framework.

### 3.7 Conclusions

A quantitative understanding of the interactions of alkali metal cations with pincer–crown ether complexes has enabled the development of a nickel complex wherein cation–crown interactions in the secondary coordination sphere regulate ligand binding in the primary coordination sphere.

The information gleaned from mechanistic studies provides a blueprint for designing systems capable of controllable ligand substitution. The tunable energy landscape is provided by equilibrium dissociation of a hemilabile chelate to form a partially dissociated ligand state that engages in a tunable second equilibrium. Any number of secondary interactions, such as hydrogen bonding or \(\pi-\pi\) stacking interactions, could theoretically be used. In the present case, the aza-crown ether macrocycle provides hemilabile ether ligands that support strong cation–crown interactions in their dissociated state, as illustrated in Figure 3.1.
Several thermodynamic factors control ligand binding. Thermodynamically, displacement of the weak donor of the hemilabile chelate by a substrate must be unfavorable in the absence of an external stimulus; the chelating “gate” must remain closed until the appropriate additive is present. Conversely, the secondary equilibrium should be thermodynamically favorable. When the energetics of the two equilibria are matched, ligand binding is rendered favorable by strong cation–crown interactions. Titrations indicate that Li⁺ or Na⁺ binding to tridentate-bound pincer–crown ether species can provide more than 7 kcal·mol⁻¹ of stabilization in dichloromethane. Finally, tunable ligand binding is possible only when the dissociated state of the ligand interacts with cations more strongly than the fully bound state. Alkali metal cations have negligible interactions with the tetradebate-bound complexes in which a crown oxygen atom is donating to the metal center, leading to preferential stabilization of the tridentate-bound species present when a substrate binds.

Solvent choice is also key to the effectiveness of this strategy. Dichloromethane is an ideal choice for cation-promoted reactivity. It is sufficiently polar to dissolve salts (albeit with lipophilic, weakly coordinating anions) and it is sufficiently noncoordinating that cation–crown interactions are strong ($K_a > 10^5$ M⁻¹) relative to cation–solvent interactions. Dichloromethane also facilitates hemilability by avoiding solvent displacement of the weak crown ether donors. On the other hand, previous work demonstrated that the polar, coordinating solvent acetonitrile displaces ethers bound to the transition metal in complex 2-15c5 to form the acetonitrile adduct, disrupting ligand hemilability and preventing control over substrate binding. Cation–crown interactions are also weaker in acetonitrile, limiting the stabilization of tridentate-bound Ni species to less than 4.3 kcal·mol⁻¹.
The foregoing findings help identify ideal conditions for future systems. Weakly coordinating solvents will be preferred because they enforce strong, highly stabilizing cation–crown interactions. Li$^+$ is a promising regulator of catalysts containing the aza-15-crown-5 macrocycle, but Na$^+$ is predicted to be more effective for catalysts containing the aza-18-crown-6 macrocycle.

3.8 Experimental Section

General Considerations

Standard vacuum line and glovebox techniques were utilized to maintain a N$_2$ atmosphere during manipulation of all compounds, unless otherwise noted. Organic solvents were dried and degassed with argon using a Pure Process Technology solvent system and stored over 3 Å molecular sieves. Under standard glovebox operating conditions, pentane, diethyl ether, benzene, toluene, and tetrahydrofuran were used without purging, so traces of those solvents might be present in the atmosphere and in the solvent bottles. $^1$H, $^{31}$P, $^{19}$F, and $^{13}$C NMR spectra were recorded on 400, 500, or 600 MHz spectrometers. NMR spectroscopic characterization data are reported at 25 °C, unless specified otherwise. All NMR solvents were purchased from Cambridge Isotope Laboratories. Acetonitrile-$d_3$ (CD$_3$CN), benzene-$d_6$ (C$_6$D$_6$), chloroform-$d$ (CDCl$_3$), and methylene chloride-$d_2$ (CD$_2$Cl$_2$) were freeze–pump–thaw–degassed three times, dried by passage through a small column of activated alumina, and stored over 3 Å molecular sieves. $^1$H and $^{13}$C chemical shifts ($\delta$) are reported in parts per million relative to residual protio solvent resonances. All $^{31}$P resonances are reported relative to 85% H$_3$PO$_4$ external standard ($\delta$ 0). The following compounds were synthesized according to literature procedures: $(^{15}$c$_5$NCOP$_{iPr})$H$_3$,$^{30}$ NaBAR$_4$,$^6$ LiBAR$_4$$^3$Et$_2$O,$^{30}$ $\kappa^3$-$(^{15}$c$_5$NCOP$_{iPr})$Ni(Br)$_3$,$^{34}$ and $\kappa^3$-$(^{1}$Et$^{1}$NCOP$_{iPr})$Ni(Br)$_3$.$^{62}$ LiOTf was dried under reduced pressure at 100 °C for 24 h prior to storage
in a N₂ glovebox. All other reagents were commercially available and used without further purification.

Elemental analyses were performed by Robertson Microlit Laboratories (Ledgewood, NJ). Mass spectrometry was carried out with an LTQ FT (ICR 7T) (ThermoFisher, Bremen, Germany) mass spectrometer. Samples (in acetonitrile solution) were introduced via a micro-electrospray source at a flow rate of 3 µL/min. Xcalibur (Thermo-Fisher, Breman, Germany) was used to analyze the data.

Single-crystal X-ray diffraction data were collected on a Bruker Smart Apex-II diffractometer at 100 ± 2 K with Cu Kα radiation (λ = 1.54175 Å). Diffraction profiles were integrated using the SAINT software program. Absorption corrections were applied using SADABS. Using Olex 2, the structure was solved using SHELXS direct methods and refined using the XL refinement package via the least-squares method. Hydrogen atoms were generated theoretically and refined isotropically with fixed thermal factors.

**Synthetic Procedures**

**Synthesis of m-(Aza-15-crown-5)methylphenol**

A 200 mL Schlenk flask was charged with 0.849 g (6.952 mmol) 3-hydroxybenzaldehyde, 1.016 g (4.635 mmol) 1-aza-15-crown-5, and 35 mL THF. The mixture was allowed to stir for one hour and then 1.96 g (9.248 mmol) sodium triacetoxyborohydride was added in 0.5 g increments every ~6 hours. The reaction was stirred for an additional 24 hours and then quenched with aqueous saturated NaHCO₃. The product was extracted into 4 x 25 mL of CH₂Cl₂ and the solvent of the combined extracts was removed. The crude product was purified using a short silica plug. Unreacted aldehyde and the byproduct 3-hydroxymethylphenol were eluted with a 60/40 (%) v/v CH₂Cl₂/EtOAc mobile phase until TLC showed no remaining
traces of alcohol. The product was then eluted with an 85/10/5 (% v/v/v) CH$_2$Cl$_2$/NEt$_3$/MeOH mobile phase. Fractions containing the product were combined and the solvent was removed to yield an off-white oil which was dried under vacuum over P$_2$O$_5$ overnight (1.490 g, 98.8% yield). Spectroscopic data matched that previously published.\textsuperscript{30}

**Synthesis of m-(Aza-18-crown-6)methylphenol**

A 200 mL Schlenk flask was charged with 348.6 mg (2.855 mmol) 3-hydroxybenzaldehyde, 501.2 mg (1.903 mmol) 1-aza-18-crown-6, and 25 mL THF. The mixture was stirred for one hour and then 806.8 mg (3.807 mmol) sodium triacetoxyborohydride was added in 200 mg increments every ~6 hours over 24 hours. The reaction was stirred for an additional 24 hours and then quenched with aqueous saturated NaHCO$_3$. The product was extracted into 4 x 20 mL of CH$_2$Cl$_2$ and the solvent of the combined extracts was removed. The crude product was purified using a short silica plug. Unreacted aldehyde and 3-hydroxymethylphenol were eluted with a 60/40 (% v/v) CH$_2$Cl$_2$/EtOAc mobile phase until TLC showed no remaining traces of alcohol. The product was then eluted with an 85/10/5 CH$_2$Cl$_2$/NEt$_3$/MeOH (% v/v/v) mobile phase. Fractions containing the product were combined and the solvent was removed to yield an off-white oil which was dried under vacuum over P$_2$O$_5$ overnight (689.1 mg, 98.0%). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.71 (s, 4H, crown-CH$_2$), 3.64 (m, 22H, crown-CH$_2$, ArCH$_2$N), 6.66 (d, $J = 7.6$ Hz, $^1$H, ArH), 6.69 (d, $J = 7.9$ Hz, $^1$H, ArH), 7.09 (t, $J = 7.8$ Hz, $^1$H, ArH), 7.42 (s, $^1$H, ArH), 7.55 (s, $^1$H, ArOH). $^{13}$C {$^1$H} NMR (151 MHz, CDCl$_3$): $\delta$ 55.75 (s, crown-CH$_2$), 59.53 (s, ArCH$_2$N), 70.05 (s, crown-CH$_2$), 70.13 (s, crown-CH$_2$), 70.56 (s, crown-CH$_2$), 70.75 (s, crown-CH$_2$), 71.26 (s, crown-CH$_2$), 113.55 (s, C$_{Ar}$), 115.73 (s, C$_{Ar}$), 118.73 (s, C$_{Ar}$), 128.90 (s, C$_{Ar}$), 142.90 (s, C$_{Ar}$), 156.99 (s, C$_{Ar}$). Anal. Calcd for C$_{19}$H$_{31}$NO$_6$: C,
61.77; H, 8.46; N, 3.79. Found: C, 61.51; H, 8.20; N, 3.80. HRMS (ESI⁺) m/z: [m-(Aza-18-crown-6)methylphenol+H]⁺ Calcd for C₁₉H₃₂NO₆ 370.22241; Found 370.22231.

Figure 3.29 ¹H NMR spectrum (600 MHz) of m-(aza-18-crown-6)methylphenol in CDCl₃.

Figure 3.30 ¹³C {¹H} NMR spectrum (151 MHz) of m-(aza-18-crown-6)methylphenol in CDCl₃.
Synthesis of \((^{18c}NCOP^{iPr})H\)

This compound was synthesized according to the literature procedure for the synthesis of \((^{15c}NCOP^{iPr})H\). In a 100 mL Schlenk flask, 278 µL (1.992 mmol) NEt₃ was added dropwise to a stirring solution of 669.1 mg (1.811 mmol) \(m\)-(Aza-18-crown-6)methylphenol in 15 mL THF. The solution was stirred for 15 minutes and then a solution of 0.299 mL (1.808 mmol, 96%) chlorodiisopropyl phosphine in 10 mL THF was added dropwise. The resulting reaction mixture was stirred at 25 °C for 12 hours. The solvent was then removed and the colorless oil was extracted with 4 x 10 mL Et₂O. The solvent of the combined extracts was removed to yield a colorless oil (802.1 mg, 91% yield).

\(^1\)H NMR (600 MHz, CDCl₃): \(\delta\) 1.08 (dd, \(J = 15.9, 7.2\) Hz, 6H, CH(CH₃)₂), 1.16 (dd, \(J = 10.9, 7.3\) Hz, 6H, CH(CH₃)₂), 1.90 (m, 2H, CH(CH₃)₂), 2.78 (t, \(J = 5.9\) Hz, 4H, crown-CH₂), 3.65 (m, 22H, crown-CH₂, ArCH₂N), 6.93 (d, \(J = 7.5\) Hz, \(^1\)H, ArH), 6.95 (d, \(J = 7.9\) Hz, \(^1\)H, ArH), 7.04 (s, \(^1\)H, ArH), 7.15 (t, \(J = 7.8\) Hz, \(^1\)H, ArH).

\(^13\)C \{\(^1\)H\} NMR (151 MHz, CDCl₃): \(\delta\) 17.17 (d, \(J = 8.6\) Hz, CH(CH₃)₂), 17.91 (d, \(J = 20.0\) Hz, CH(CH₃)₂), 28.40 (d, \(J = 17.3\) Hz, CH(CH₃)₂), 53.96 (s, crown-CH₂), 60.07 (s, ArCH₂N), 70.23 (s, crown-CH₂), 70.52 (s, crown-CH₂), 70.93 (s, crown-CH₂), 71.00 (s, crown-CH₂), 117.03 (d, \(J = 11.0\) Hz, C₆Ar), 119.00 (d, \(J = 9.4\) Hz, C₆Ar), 122.14 (s, C₆Ar), 129.07 (s, C₆Ar), 141.49 (s, C₆Ar), 159.40 (d, \(J = 8.3\) Hz, C₆Ar).

\(^31\)P \{\(^1\)H\} NMR (243 MHz, CDCl₃): \(\delta\) 149.12 (s). Anal. Calcd for C₂₅H₄₅NO₆P: C, 61.84; H, 9.13; N, 2.88. Found: C, 61.80; H, 9.40; N, 2.88. HRMS (ESI⁺) m/z:

\([(^{18c}NCOP^{iPr})H+H]^+\) Calcd for C₂₅H₄₅NO₆P 486.29790; Found 486.29782.
Figure 3.31 $^1$H NMR spectrum (600 MHz) of ($^{18}$c$_6$NCOP$_{iPr}$)$_2$H in CDCl$_3$.

Figure 3.32 $^{31}$P{$^1$H} NMR spectrum (243 MHz) of ($^{18}$c$_6$NCOP$_{iPr}$)$_2$H in CDCl$_3$. 
Synthesis of $\kappa_3$-(18c6NCOPiPr)NiBr (1-18c6)

A 100 mL Schlenk flask was charged with 281.0 mg (0.912 mmol) (DME)NiBr$_2$ and 15 mL toluene. In a separate flask, 442.9 mg (0.912 mmol) (18c6NCOPiPr)$_2$H was stirred with 381 $\mu$L (2.737 mmol) NEt$_3$ in 15 mL toluene for 10 minutes, and the resulting mixture was then added dropwise to the stirring suspension of (DME)NiBr$_2$. The flask was heated at 65 ºC for 12 h. After heating, the solution was filtered via cannula under N$_2$, and the filtrate was evaporated to dryness. The resulting yellow oil was extracted with toluene and filtered. Diffusion of pentane into a saturated toluene solution at -30 ºC yielded a first crop of yellow crystals that were washed with 3 × 5 mL of cold pentane (-30 ºC) and dried under vacuum. The mother liquor was then removed in vacuo to give a yellow oil which was again recrystallized to give a second crop of yellow crystals that were washed with cold pentane and dried under vacuum (total 0.491 g, 86.3% yield). $^1$H NMR (600 MHz, C$_6$D$_6$): $\delta$ 1.20 (dd, $J = 14.5$, 7.0 Hz, 6H, CH(CH$_3$)$_2$), 1.52 (dd,
$J = 17.3, 7.2 \text{ Hz}, 6\text{H}, \text{CH(CH}_3)_2$, 2.24 (m, 2H, \text{CH(CH}_3)_2), 3.25 (m, 8H, crown-CH$_2$), 3.43 (m, 4H, crown-CH$_2$), 3.56 (m, 6H, crown-CH$_2$), 3.67 (m, 2H, crown-CH$_2$), 4.03 (m, 2H, crown-CH$_2$), 4.10 (m, 2H, crown-CH$_2$), 4.61 (s, 2H, ArCH$_2$N), 6.63 (d, $J = 7.9$ Hz, $^1$H, ArH), 6.66 (d, $J = 7.4$ Hz, $^1$H, ArH), 6.93 (t, $J = 7.6$ Hz, $^1$H ArH). $^{13}$C $^1$H NMR (151 MHz, C$_6$D$_6$): $\delta$ 16.98 (s, CH(CH$_3)_2$), 18.38 (d, $J = 3.9$ Hz, CH(CH$_3)_2$), 28.55 (d, $J = 24.2$ Hz, CH(CH$_3)_2$), 57.48 (d, $J = 1.9$ Hz, crown-CH$_2$), 65.88 (d, $J = 1.7$ Hz, ArCH$_2$N), 69.58 (s, crown-CH$_2$), 70.42 (s, crown-CH$_2$), 70.64 (s, crown-CH$_2$), 70.97 (s, crown-CH$_2$), 71.39 (s, crown-CH$_2$), 107.83 (d, $J = 13.1$ Hz, C$_{Ar}$), 115.96 (d, $J = 2.0$ Hz, C$_{Ar}$), 127.02 (s, C$_{Ar}$), 142.30 (d, $J = 33.2$ Hz, C$_{Ar}$), 154.49 (s, C$_{Ar}$), 165.85 (d, $J = 10.8$ Hz, C$_{Ar}$). $^{31}$P $^1$H NMR (243 MHz, C$_6$D$_6$): $\delta$ 198.80 (s). Anal. Calcd for C$_{25}$H$_{43}$O$_6$NPNiBr: C, 48.18; H, 6.96; N, 2.25. Found: C, 48.44; H, 6.70; N, 2.32.

![Figure 3.34](image_url)  

**Figure 3.34** $^1$H NMR spectrum (600 MHz) of $\kappa^3$-(C$_{18}C$NCO$i$Pr)NiBr (1-18c6) in C$_6$D$_6$. 

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Figure 3.35 $^3$P{${}^1$H} NMR spectrum (243 MHz) of $\kappa^3$-(18c6 NCOP$i$Pr)NiBr (1-18c6) in C$_6$D$_6$.

Figure 3.36 $^{13}$C{${}^1$H} NMR spectrum (151 MHz) of $\kappa^3$-(18c6 NCOP$i$Pr)NiBr (1-18c6) in C$_6$D$_6$. 
Table 3.3 Crystal data and structure refinement for \( \kappa^3-(18c6\text{NCOP}^\text{ip})\text{NiBr} \) (1-18c6).

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</table>

*Synthesis of \([\kappa^4-(15c5\text{NCOP}^\text{ip})\text{Ni}]\text{PF}_6\) (2-15c5)*

In a glovebox, a solution of 41.2 mg (0.071 mmol) \( \kappa^3-(15c5\text{NCOP}^\text{ip})\text{NiBr} \) (1-15c5) in 2 mL CH\(_2\)Cl\(_2\) was slowly added to a stirring solution of 18.8 mg (0.075 mmol) AgPF\(_6\) in 3 mL CH\(_2\)Cl\(_2\) in a 20 mL vial covered with foil. After 1 hour, 4 mL of pentane was added to the mixture and the resulting solution was filtered. The solvent was removed *in vacuo* to yield a yellow oil. The oil was triturated with Et\(_2\)O overnight and then the solution was decanted to yield a yellow powder (44.0 mg, 96.0% yield). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 1.33 (dd, \(J = 14.4, 6.9\) \text{Hz})
Hz, 6H, CH(CH₃)₂), 1.51 (dd, J = 19.0, 7.3 Hz, 6H, CH(CH₃)₂), 2.25 (m, 2H, CH(CH₃)₂), 3.19 (m, 2H, crown-CH₂), 3.56 (m, 2H, crown-CH₂), 3.65 (m, 4H, crown-CH₂), 3.75 (m, 6H, crown-CH₂), 3.95 (m, 4H, crown-CH₂), 4.16 (s, 2H, ArCH₂N), 4.29 (m, 2H, crown-CH₂), 6.43 (d, J = 8.3 Hz, ¹H, ArH), 6.52 (d, J = 7.5 Hz, ¹H, ArH), 6.97 (t, J = 7.8 Hz, ¹H, ArH). ¹³C {¹H} NMR (151 MHz, CDCl₃): δ 16.66 (d, J = 2.9 Hz, CH(CH₃)₂), 17.54 (d, J = 5.8 Hz, CH(CH₃)₂), 28.58 (d, J = 24.1 Hz, CH(CH₃)₂), 54.61 (s, crown-CH₂), 64.83 (s, ArCH₂N), 68.64 (s, crown-CH₂), 69.31 (s, crown-CH₂), 69.46 (s, crown-CH₂), 75.02 (s, crown-CH₂), 109.27 (d, J = 12.1 Hz, CAr), 116.78 (s, CAr), 128.35 (s, CAr), 130.72 (d, J = 30.3 Hz, CAr), 152.61 (s, CAr), 165.82 (d, J = 8.2 Hz, CAr). ³¹P {¹H} NMR (162 MHz, CDCl₃): δ 197.42 (s), –143.06 (hept, J = 712.8 Hz, PF₆).

Anal. Calcd for C₂₃H₃₉F₆NNiO₅P₂: C, 42.88; H, 6.10; N, 2.17. Found: C, 42.78; H, 5.92; N, 2.17.

Figure 3.37 ¹H NMR spectrum (600 MHz) of [α₄-(15c₅NCOPiPr)Ni][PF₆] (2-15c₅) in CDCl₃.
Figure 3.38 $^{31}$P \{H\} NMR spectrum (162 MHz) of $[\kappa^4-(15c5\text{NCOP}^\text{iPr})\text{Ni}]\text{[PF}_6\text{]}$ (2-15c5) in CDCl$_3$.

Figure 3.39 $^{13}$C \{H\} NMR spectrum (151 MHz) of $[\kappa^4-(15c5\text{NCOP}^\text{iPr})\text{Ni}]\text{[PF}_6\text{]}$ (2-15c5) in CDCl$_3$. 
Table 3.4 Crystal data and structure refinement for [\(\kappa^d-(15c5\text{NCOP}^{iPr})\text{Ni}\)]\([\text{PF}_6]\) (2-15c5).

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<td>c/(\text{Å})</td>
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<td>(\gamma/°)</td>
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<td>(Z)</td>
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<td>Independent reflections</td>
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<td>Data/restraints/parameters</td>
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<td>Largest diff. peak/hole / (e \text{Å}^3)</td>
<td>0.34/-0.33</td>
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</tbody>
</table>

**Synthesis of [\(\kappa^d-(18c6\text{NCOP}^{iPr})\text{Ni}\)]\([\text{PF}_6]\) (2-18c6)**

The procedure described above for the preparation of [\(\kappa^d-(15c5\text{NCOP}^{iPr})\text{Ni}\)]\([\text{PF}_6]\) (5-15c5) was used to prepare [\(\kappa^d-(18c6\text{NCOP}^{iPr})\text{Ni}\)]\([\text{PF}_6]\) from \(\kappa^3-(18c6\text{NCOP}^{iPr})\text{Ni}(\text{Br})\) (1-18c6) and AgPF\(_6\) to yield a yellow powder. \(^1\text{H} \text{NMR (600 MHz, CD}_2\text{Cl}_2): \delta 1.35 \text{ (dd, } J = 14.4, 6.9 \text{ Hz, 6H, CH(CH}_3\text{)_2}, 1.44 \text{ (dd, } J = 19.0, 7.3 \text{ Hz, 6H, CH(CH}_3\text{)_2), 2.22 \text{ (m, 2H, CH(CH}_3\text{)_2), 3.24 \text{ (m, 2H, crown-CH}_2\text{), 3.64 \text{ (m, 18H, crown-CH}_2\text{), 4.02 \text{ (m, 2H, crown-CH}_2\text{), 4.18 \text{ (m, 4H, crown-CH}_2; ArCH}_2\text{N), 6.47 \text{ (d, } J = 8.0 \text{ Hz, } ^1\text{H, ArH), 6.58 \text{ (d, } J = 7.5 \text{ Hz, } ^1\text{H, ArH), 7.00 \text{ (t, } J = 7.8 \text{ Hz, } ^1\text{H, ArH), 7.09 \text{ (m, 4H, crown-CH}_2; ArCH}_2\text{N), 7.72 \text{ (m, 2H, crown-CH}_2; ArCH}_2\text{N))}\).
$^{13}$C $^1$H NMR (151 MHz, CD$_2$Cl$_2$): $\delta$ 16.80 (s, CH(CH$_3$)$_2$), 17.71 (d, $J = 5.9$ Hz, CH(CH$_3$)$_2$), 28.70 (d, $J = 24.1$ Hz, CH(CH$_3$)$_2$), 64.63 (s, ArCH$_2$N), 69.92 (s, crown-CH$_2$), 70.57 (s, crown-CH$_2$), 70.86 (s, crown-CH$_2$), 74.18 (s, crown-CH$_2$), 109.61 (d, $J = 12.1$ Hz, $C_{Ar}$), 117.49 (s, $C_{Ar}$), 128.75 (s, $C_{Ar}$), 131.35 (s, $C_{Ar}$), 152.98 (s, $C_{Ar}$), 166.15 (d, $J = 8.3$ Hz, $C_{Ar}$).

$^{31}$P $^1$H NMR (243 MHz, CD$_2$Cl$_2$): $\delta$ 196.28 (s), $\sim$144.30 (hept, $J = 7.11$ Hz, PF$_6$) HRMS (ESI$^+$) m/z: [A$^0$-$^{18}$c$_6$NCOP$_{iPr}$Ni]$^+$ Calcd for C$_{26}$H$_{43}$NNiO$_6$P 542.21815; Found 542.21678.

Figure 3.40 $^1$H NMR spectrum (600 MHz) of [A$^0$-$^{18}$c$_6$NCOP$_{iPr}$Ni][PF$_6$] (2-18c6) in CD$_2$Cl$_2$. 
Figure 3.41 $^{31}$P $^1$H NMR spectrum (243 MHz) of $[\kappa^4-(18c6)NCOP^{iPr}]NI][PF_6]$ (2-18c6) in CD$_2$Cl$_2$.

Figure 3.42 $^{13}$C $^1$H NMR spectrum (151 MHz) of $[\kappa^4-(18c6)NCOP^{iPr}]NI][PF_6]$ (2-18c6) in CD$_2$Cl$_2$. 
**Synthesis of \([\kappa^4-(15\ell C5NCOPiPr)]Ni][BArF_4\) (3-15c5)**

A solution of 32.6 mg (0.0506 mmol) \([\kappa^4-(15\ell C5NCOPiPr)]Ni][PF_6\) (2-15c5) in 1 mL CH_2Cl_2 was added to a stirring suspension of 47.0 mg (0.0530 mmol) NaBArF_4 in 2 mL CH_2Cl_2. The suspension was stirred for 1 hour after which 3 mL pentane was added, and the resulting solution was filtered. The solvent was removed to yield a yellow oil. The oil was triturated with Et_2O and then the solution was decanted to yield a tacky solid which when dried under vacuum gave a yellow powder (0.0662 g, 96.0% yield).

^1H NMR (500 MHz, CD_2Cl_2): δ 1.32 (dd, \(J = 14.5, 7.0\) Hz, 6H, CH(C_6H_3)_2), 1.47 (dd, \(J = 18.9, 7.3\) Hz, 6H, CH(CH_3)_2), 2.20 (m, 2H, CH(CH_3)_2), 3.22 (m, 2H, crown-C_6H_2), 3.64 (m, 14H, crown-C_6H_2), 3.91 (m, 2H, crown-C_6H_2), 4.15 (s, 2H, ArCH_2N), 4.42 (m, 2H, crown-C_6H_2), 6.48 (d, \(J = 8.0\) Hz, \(^1\)H, ArH), 6.56 (d, \(J = 7.6\) Hz, \(^1\)H, ArH), 7.01 (t, \(J = 7.8\) Hz, \(^1\)H, ArH), 7.56 (s, 4H, m-B-Ar-H), 7.72 (s, 8H, m-B-Ar-H).

^13C \{^1H\} NMR (151 MHz, CD_2Cl_2): δ 16.78 (d, \(J = 2.5\) Hz, CH(CH_3)_2), 17.76 (d, \(J = 5.8\) Hz, CH(CH_3)_2), 29.00 (d, \(J = 24.2\) Hz, CH(CH_3)_2), 54.63 (s, crown-C_6H_2), 64.66 (s, ArCH_2N), 68.88 (s, crown-C_6H_2), 69.60 (s, crown-C_6H_2), 69.89 (s, crown-C_6H_2), 75.39 (s, crown-C_6H_2), 109.94 (d, \(J = 12.2\) Hz, C_Ar), 117.51 (d, \(J = 2.1\) Hz, C_Ar), 117.85 (m, para-CH, BArF_4), 124.95 (q, \(J = 272.3\) Hz, CF_3, BArF_4), 129.03 (s, C_Ar), 129.21 (qdd, \(J = 32.1, 5.8, 2.8\) Hz, C–CF_3, BArF_4), 130.74 (d, \(J = 29.9\) Hz, C_Ar), 135.15 (s, ortho-CH, BArF_4), 152.59 (s, C_Ar), 162.10 (q, \(J = 50.0\) Hz, B–C, BArF_4), 166.16 (d, \(J = 8.2\) Hz, C_Ar).

^31P \{^1H\} NMR (202 MHz, CD_2Cl_2): δ 195.42 (s). HRMS (ESI^+) m/z: \([\kappa^4-(15\ell C5NCOPiPr)]Ni]^+\) Calcd for C_{23}H_{39}NNiO_5P 498.19193; Found 498.19075.
**Figure 3.43** $^1$H NMR spectrum (500 MHz) of $[\kappa^4-{(15c5)}^{\text{NCOP}^{\text{iPr}}}]\text{Ni}[^{15}\text{C}]\text{Cl}2$ (3-15c5) in CD$_2$Cl$_2$.

**Figure 3.44** $^{31}$P-$^1$H NMR spectrum (202 MHz) of $[\kappa^4-{(15c5)}^{\text{NCOP}^{\text{iPr}}}]\text{Ni}[^{15}\text{C}]\text{Cl}2$ (3-15c5) in CD$_2$Cl$_2$. 
**Figure 3.45** $^{13}$C $^{1}$H NMR spectrum (151 MHz) of $[\kappa^3-(15c^5\text{NCOP}^\text{iiPr})\text{Ni}][\text{BAR}_4]$ (3-15c5) in CD$_2$Cl$_2$.

**General Procedure for Titrations in CD$_2$Cl$_2$**

A 10 mM stock solution of the corresponding Ni complex was prepared in CH$_2$Cl$_2$, and 250 µL aliquots ($2.5 \times 10^{-3}$ mmol) of the solution were added to seven glass vials. The protio solvent was completely evaporated. A 10 mM stock solution of LiBAR$_4$·3Et$_2$O or NaBAR$_4$ was prepared in CD$_2$Cl$_2$. For LiBARF·3Et$_2$O solutions, 12 equiv of Et$_2$O were added for a total of 15 equiv, and for NaBAR$_4$ solutions, 15 equiv of Et$_2$O were added. Aliquots of the alkali metal stock solution corresponding to 0.25–2.0 equiv (between $6.3 \times 10^{-4}$ and $5.0 \times 10^{-3}$ mmol) of alkali metal to transition metal complex were then added to the vials containing the Ni complexes. The samples were diluted to a total volume of 500 µL with CD$_2$Cl$_2$, transferred to NMR tubes, and analyzed at 20 ± 1 °C by $^1$H NMR spectroscopy. The final concentration of the Ni complex in solution was 5 mM. The final concentration of alkali metal in the samples ranged from 0 to 10 mM.
General Procedure for CD$_3$CN Titrations

A 12 mM stock solution of the corresponding Ni complex and a 48 mM stock solution of the corresponding alkali metal salt were prepared in CH$_3$CN. 500 µL aliquots (6.0 × 10$^{-3}$ mM) of the Ni stock solution were added to eight glass vials. Aliquots of the alkali metal stock solution corresponding to 0.5–10 equiv (between 3.0 × 10$^{-3}$ and 60 × 10$^{-3}$ mM) of alkali metal salt to Ni complex were then added to the vials containing the Ni complex. The protio solvent was completely evaporated. The samples were then dissolved in 600 µL of CD$_3$CN, transferred to NMR tubes, and analyzed by $^1$H NMR spectroscopy at 24 ± 1 °C. The final concentration of Ni in solution was 10 mM. The final concentration of alkali metal in the samples ranged from 0 to 120 mM. On the basis of triplicate titrations of 1-15c5 with LiOTf and 1-18c6 with NaBAR$_4$F, the estimated uncertainty of each equilibrium constant is 10% or less.

Table 3.5 Crystal data and structure refinement for [(Li$^+@\kappa^3-15c5\mathrm{NCOP}^{iPr})\mathrm{Ni(Br)}][\mathrm{PF}_6]$ (Li$^+\cdot$1-15c5).

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Table 3.6. Crystal data and structure refinement for [(Li+[@κ3-15c5NCOPiPr]Ni(Br))[OTf] (LiOTf•1-15c5).

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Table 3.7. Crystal data and structure refinement for \([\text{Na}^+]@\kappa^{3,15c5}\text{NCOP}^{6}\text{iPr}\text{Ni(Br)}][\text{BArF}_4]\) (Na⁺·1-15c5).

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<td>Goodness-of-fit on (F^2)</td>
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<tr>
<td>Final R indexes [I&gt;=2σ(I)]</td>
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</tr>
<tr>
<td>Final R indexes [all data]</td>
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</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
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CHAPTER 4: ORGANOMETALLIC ELABORATION OF AZA-CROWN ETHERS: POST-MACROCYCLIZATION CONTROL OF BINDING AFFINITY AND SELECTIVITY FOR CATIONS AND ION PAIRS

4.1 Introduction

Crown ethers are the quintessential example of supramolecular hosts capable of strong ion binding and selective ion recognition. The early chemistry of crown ethers helped spark development\(^1\) of host-guest complexes with synthetically tunable molecular recognition and has led to acclaimed impact on applications\(^2\) in a variety of fields including sensing,\(^3\) separations,\(^4\)-\(^5\) and molecular machines.\(^6\)

Hundreds of macrocyclic structures have been prepared using synthetic organic methods in the search for crown ethers with desirable ion recognition properties.\(^7\)-\(^8\) New crown ethers are typically prepared via macrocyclization reactions that can be tedious, unselective, and low-yielding.\(^9\)-\(^10\) Post-macrocyclization synthetic modification, such as in the installation of side chains in “lariat” ethers, offers another attractive strategy.\(^11\)-\(^12\) A less studied, but no less intriguing, strategy involves allosteric modulation of host-guest properties in analogy to enzymatic cofactor-triggered structural and chemical changes.\(^13\) Transition metal coordination chemistry has enabled allosteric regulation of the host-guest properties of supramolecular constructs.\(^14\)-\(^16\) A bipyridine unit incorporated into the macrocycle often serves to bind a transition metal, thereby altering the binding properties of crown ethers,\(^17\)-\(^19\) calix[4]arenes\(^20\) and polycationic cyclophanes.\(^21\)

Organometallic moieties have rarely been employed to tune the cation-binding properties of macrocycles,\(^22\) despite promising several advantages over inorganic coordination complexes.
Firstly, the strong metal–ligand interactions of organometallic complexes would prevent competing binding by the guest molecules. In addition, mature organometallic synthetic transformations could allow elaboration of the organometallic unit for further tuning. The inclusion of a tightly bound metal center proximal to a cation-selective macrocycle could also serve to enable ion pair recognition. Examples of the latter phenomenon were recently reported, with the installation of alkyltin groups converting simple crown ethers from cation receptors to ion pair receptors.\textsuperscript{23-25} New strategies for rapid organometallic elaboration of crown ethers could provide robust, flexible platforms for allosteric modulation of host-guest properties.

Our group recently developed pincer-crown ether ligands that incorporate an aza-crown ether macrocycle into a phenylphosphinite “pincer-crown ether” framework.\textsuperscript{26} For applications in organometallic catalysis, the \textit{macrocycle} acts as an allosteric receptor whereby cation binding tunes the hemilability of the metal-oxygen bonds and modulates substrate access to the transition metal center.\textsuperscript{27-31} In the course of a detailed thermodynamic study of cation-crown binding affinity relevant of nickel pincer-crown ether complexes (Chapter 3),\textsuperscript{32} it became clear that organometallic macrocycles have quite different properties from simple organic crown ethers. Thus, the \textit{phenylphosphinite site} might act as an allosteric receptor whereby the properties of the transition metal center can tune the cation binding properties of the crown ether. The pincer-crown ether framework, accessible from 1-aza-15-crown-5 in just two synthetic steps, provides a convenient platform to understand how organometallic elaborations of a simple crown ether can modulate host-guest properties (Figure 4.1).
Figure 4.1 Depiction of an iridium pincer-crown ether complex highlighting the macrocyclic cation receptor and the coordination site that offers tunability through organometallic elaboration.

This report demonstrates that facile synthetic elaboration of 1-aza-15-crown-5 to form organometallic pincer-crown ether complexes results in dramatic changes in binding affinity and cation selectivity, including strikingly high selectivity for Li⁺ over Na⁺. The binding affinity can be fine-tuned based on the choice of transition metal ion in the organometallic site, or by adjusting the supporting ligands or oxidation state of the transition metal after installation. A change in topicity is also observed, with the cation-binding 1-aza-15-crown-5 converted into a heteroditopic ion pair receptor.

4.2 Impact of Ir Metalation on Binding Affinity and Selectivity

To illustrate the ability of organometallic chemistry to alter the cation binding properties of a simple aza-crown ether, the Li⁺ and Na⁺ binding affinities were measured in CD₃CN for each species along the synthetic pathway of Scheme 4.1 (see Experimental Section for titration/isotherm data). Starting from the well-characterized macrocycle 1-aza-15-crown-5 ether,³³ reductive amination provides m-(Aza-15-crown-5)methylphenol (1).³¹-³² The pincer-crown ether ligand precursor 1 binds Li⁺ and Na⁺ cations tightly and in a 1:1 fashion in CD₃CN at 25 ± 1 °C, as evidenced by the nearly linear response of crown and benzylic linker protons in
H NMR spectroscopic titrations until 1 added equiv of cation relative to the macrocycle. A competitive binding technique provided association constants \((K_a)\) with both LiOTf \((K_a = 126,000 \text{ M}^{-1})\) and NaBAR\(_4\) \((K_a = 79,400 \text{ M}^{-1})\). These values are similar to affinities of substituted N-benzylaza-15-crown-5 ethers under similar conditions. Both systems show only modest selectivity between Li\(^+\) and Na\(^+\); the prior work had \(K_{Li}/K_{Na} \sim 0.09\), while 1 has \(K_{Li}/K_{Na} \sim 2\). Phosphination of 1 provides the known pincer-crown ether ligand \(\text{NCOP}^{\text{Pr}}\)H (2), which maintains strong interactions with Li\(^+\) and Na\(^+\) in CD\(_3\)CN at 25 ± 1 °C. Binding affinities for 2, determined using the competition method, were identical to 1 within experimental error.

Scheme 4.1: Synthetic pathway and association constants for lithium and sodium binding to (pre)ligands and iridium pincer-crown ether complexes. (i) 3-hydroxybenzaldehyde, sodium triacetoxyborohydride, THF. (ii) \text{^{3}Pr_2PCl, NEt}_3, THF. (iii) Ir(\text{p-toluidine})(CO)\(_2\)(Cl), toluene. (iv) KO'Bu, toluene. See Experimental Section for full synthetic details.

The phenylphosphinite motif of 2 provides a binding pocket for transition metal ions. Metallation with Ir(\text{p-toluidine})(CO)\(_2\)(Cl) provides the d\(^6\) Ir(III) complex \((\kappa^3\text{NCOP}^{\text{Pr}})\text{IrH(CO)(Cl)} (3)\). Titration of 3 with LiOTf and NaBAR\(_4\) revealed association constants of \(K_a = 560 \text{ M}^{-1}\) and \(K_a = 19 \text{ M}^{-1}\) respectively. Metallation of the ligand with Ir leads to a 3-4 order of magnitude decrease in Li\(^+\) and Na\(^+\) binding strength. Dehydrohalogenation of complex 3 with KO'Bu provides another neutral iridium species, \((\kappa^3\text{NCOP}^{\text{Pr}})\text{Ir(CO)} (4)\). The formal oxidation state of iridium changes from +3 to +1 during this synthetic step, and the coordination geometry changes from octahedral to square planar. These changes at the transition
metal center lead to a three-fold change in Li\(^+\) binding affinity, based on NMR titrations of 4 with LiOTf and NaBARF\(_4\) that provide \(K_a(\text{Li}^+) = 184\ \text{M}^{-1}\) and \(K_a(\text{Na}^+) = 26\ \text{M}^{-1}\).

A straightforward series of synthetic steps increases Li\(^+\) selectivity almost 30-fold while significantly reducing the binding affinity for each cation. It is striking that alkylation and phosphination of 1-aza-15-crown-5 ether hardly perturb the host-guest properties at all, while metalation and a subsequent organometallic step significantly modulate the binding affinity and cation selectivity. We attribute the reduction in binding affinity to the amine donation to the transition metal center, which reduces the crown ether donor number and opens a pathway for inductive electron withdrawing effects (a resonance structure with a positive charge on N can be drawn). In CH\(_3\)CN, the larger 1-aza-15-crown-5 ether binds Li\(^+\) and Na\(^+\) with \(K_{\text{Li}} = 158,500\ \text{M}^{-1}\) and \(K_{\text{Na}} = 39,800\ \text{M}^{-1}\) while the smaller, N-donor lacking 12-crown-4 ether binds Li\(^+\) and Na\(^+\) with \(K_{\text{Li}} = 2,500\ \text{M}^{-1}\) and \(K_{\text{Na}} = 2000\ \text{M}^{-1}\). The origin of the change in cation selectivity is less clear, although it is noteworthy that some of the crown ethers with the highest Li\(^+\) selectivity over Na\(^+\) feature long linker lengths between some of the oxygen atoms. These observations led us to undertake a more systematic study of the ability of organometallic synthetic alterations to tune the host-guest properties of the crown ether.

4.3 Central Transition Metal Influence on Affinity and Selectivity

Noting the large differences in binding affinity and cation selectivity upon metalation to form an organometallic macrocycle, we set out to explore the influence of the transition metal on host-guest properties. An isoelectronic series with \(d^8\) square planar organometallic fragments was targeted starting from \((\kappa^3\text{NCOPiPr})\text{Ni(Cl)}\) (5-Cl). The nickel chloride complex 5-Cl was accessed by heating a toluene solution of ligand 2 with NiCl\(_2\)(DME) (DME is 1,2-dimethoxyethane), in analogy to the procedure for the bromide complex. The Pd complex
(κ³-15c⁵NCOPiPr)Pd(Cl) (6) was prepared by refluxing ligand 2 with PdCl₂(COD) (COD is 1,4-cyclooctadiene) in toluene for 2 h. The Pt complex (κ³-15c⁵NCOPiPr)Pt(Cl) (7) was synthesized by refluxing ligand 2 and PtCl₂(SMe₂)₂ in toluene for 5 h. Multinuclear NMR spectroscopy and single-crystal X-ray diffraction (XRD) analysis confirm a tridentate binding mode for 5-Cl, 6, and 7 that leaves all four ether oxygen atoms free for binding cations (see Experimental Section for full characterization details and solid state structures of 6 and 7).

![Metalation of (15c⁵NCOPiPr)H (2) with Ni, Pd, or Pt and the corresponding Kₐ(Li⁺) for the metalated complexes.](image)

**Figure 4.2** Metalation of (15c⁵NCOPiPr)H (2) with Ni, Pd, or Pt and the corresponding Kₐ(Li⁺) for the metalated complexes.

<table>
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<th>Kₐ(Li⁺) (M⁻¹)</th>
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<tr>
<td>Ni</td>
<td>92</td>
</tr>
<tr>
<td>Pd</td>
<td>277</td>
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<tr>
<td>Pt</td>
<td>184</td>
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Kₐ(Li⁺) = \(126,000 \text{ M}^{-1}\), 5-Cl; Kₐ(Li⁺) = \(277 \text{ M}^{-1}\), 6; Kₐ(Li⁺) = \(184 \text{ M}^{-1}\), 7.
Figure 4.3 Structural representation of 6 with ellipsoids drawn at the 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Pd–P 2.1871(5), Pd–N 2.185(2), Pd–Cl 2.3788(5), Pd–C1 1.959(2), P–Pd–Cl 99.80(2), P–Pd–C1 80.83(6), N–Pd–Cl 97.96(4), N–Pd–C1 81.16(7).

Figure 4.4 Structural representation of 7 with ellipsoids drawn at the 50% probability level. Hydrogen atoms omitted for clarity. Selected distances (Å) and angles (deg): Pt–P 2.1717(9), Pt–N 2.183(2), Pt–Cl 2.3825(9), Pt–C1 1.954(3), P–Pt–Cl 101.05(3), P–Pt–C1 81.92(9), N–Pt–Cl 95.94(7), N–Pt–C1 80.9(1).
The binding affinity of each group 10 organometallic complex with LiOTf was established by $^1$H NMR titration. The nickel complex 5-Cl ($K_a = 92 \text{ M}^{-1}$) binds Li$^+$ weakest, while Pd complex 6 ($K_a = 277 \text{ M}^{-1}$) and Pt complex 7 ($K_a = 184 \text{ M}^{-1}$) bind the Li$^+$ salt approximately 3-fold and 2-fold tighter, respectively. Plotting the natural log of the binding affinity of the group 10 complexes and the isoelectronic Ir(I) complex 4 versus Allred-Rochow electronegativity (A-R EN) reveals a good linear correlation (Figure 4.3).

![Figure 4.3](image-url)

**Figure 4.5** Correlation of the natural log of $K_a$(Li$^+$) of 5-Cl, 6, and 7 with Allred-Rochow Electronegativity.

The correlation with electronegativity suggests that the electronic structure of the metal can significantly influence the binding affinity inductively through the bound amine of the aza-crown ether. The metals with higher electronegativity parameters will withdraw more electron density from the amine and in turn withdraw more electron density from the ether oxygen atoms, leading to weaker binding.$^{32,35}$
4.4 Further Organometallic Elaboration

The various organometallic crown ethers could be further elaborated using routine inorganic synthetic techniques that modify the transition metal ion primary coordination sphere. Halide ligand substitution was selected as an example of a synthetically facile interconversion with minimal structural change. The binding affinity of a series of three pincer-crown ether nickel halide complexes with LiOTf was examined. The chloride complex 5-Cl ($K_a = 92 \text{ M}^{-1}$) was introduced above, while the bromide analogue, 5-Br ($K_a = 91 \text{ M}^{-1}$), was previously characterized as a model system for cation-tunable catalysis. These two macrocyclic complexes have similar $\text{Li}^+$ binding affinities. The iodide complex ($\kappa^3$-$^{15c5}$NCOP$_{iPr}$)Ni(I) (5-I) was prepared by addition of excess NaI to a stirring acetone solution of 5-Br.$^{41}$ The iodide complex binds LiOTf slightly stronger than the other halide complexes, $K_a = 117 \text{ M}^{-1}$. The halide lone pairs may act as additional donors to the cationic guests, as evidenced by a solid state structure of ($\kappa^3$-$^{15c5}$NCOP$_{iPr}$)Ni(Br){NaBAr$_4^+$} in which the bromide bridges the nickel and sodium ions.$^{32}$ A strong bridging interaction of this type might explain the increased affinity of 5-I for LiOTf.

To further investigate the influence of the nickel coordination sphere on cation-crown interactions, the halide was replaced by a neutral acetonitrile donor ligand to form the cationic complex [(($\kappa^3$-$^{15c5}$NCOP$_{iPr}$)Ni(NCCD$_3$))[BAr$_4^+$]] (8).$^{28,32}$ Titration of 8 with LiBAr$_4^+$•3 Et$_2$O gave $K_a \leq 10 \text{ M}^{-1}$, an order-of-magnitude decrease in binding affinity achieved by a simple halide abstraction. This decrease in binding affinity is attributed to unfavorable electrostatic interactions between the cationic alkali metal and the cationic nickel center.
Figure 4.6 Effects of ligand substitution and charge on the $K_a(L^+)$ of nickel and iridium pincer-crown ether complexes.

The iridium hydridocarbonyl chloride complex 3 also undergoes facile halide abstraction to produce the cationic nitrile complex $[[k^{3,15c5}NCOP^{nPr})Ir(H)(CO)(NCCH_3)][BArF_4]$ (9).

Titration of 9 with LiBArF_4 • 3 Et_2O gave $K_a = 45$ M⁻¹. This result suggests that the strategy of changing the charge on the transition metal center is a general method for tuning binding affinity, with a roughly 10-fold change in affinity for both Ni and Ir cases. Simple post-macrocyclization ligand substitution reactions can significantly alter the cation binding affinity of the pincer-crown ethers.

### 4.5 Ditopic Binding

Incorporating a transition metal center into a crown ether provides a proximal site for anion binding. The proclivity of the late transition metal ions for halides is clear from the abundance of halide complexes described above. Thus, beyond providing a handle for tuning cation affinity and selectivity, the elaboration with pincer complexes provides an opportunity to turn a simple cation-binding aza-crown ether into a ditopic receptor that binds both cations and anions. Heteroditopic receptors have emerged as promising structures for binding specific pairs of ions. Ion-pair receptors can provide energetic advantages through cooperative effects, and have shown promise in the development of a number of applications including membrane
transport, salt extraction, salt solubilization, and sensors.\textsuperscript{42-45} Few organotransition metal ditopic receptors exist.\textsuperscript{42}

The complex $(\kappa^4_{\text{15c5NCOPipPr}})\text{Ir(H)(Cl)}$ (10) has been shown to engage in equilibrium binding of additional halide equivalents (Bu$_4$N$^+$ X$^-$) to form anionic complexes of the type $[(\kappa^3_{\text{15c5NCOPipPr}})\text{Ir(H)(X)}_2][\text{A}]$.\textsuperscript{29, 46} In CD$_2$Cl$_2$, complex 10 does not bind cations in the absence of a donor ligand to displace the crown ether. Addition of solid LiCl to 10 in CD$_2$Cl$_2$ resulted in $\sim$ 35\% conversion to $[(\kappa^3_{\text{15c5NCOPipPr}})\text{Ir(H)(Cl)}_2][\text{Li}]$ (11) after 12 h at room temperature. This is evidenced by appearance of new resonances in the crown region and a new hydride resonance downfield of that of 10 ($\delta$ –23.8 vs. –31.4) in $^1$H NMR spectra as well as a new $^{31}$P resonance downfield of that corresponding to 10 ($\delta$ 142.8 vs 142.1). The large hydride shift is indicative of crown displacement to position a halide ligand trans to the hydride. Additionally, $^7$Li NMR spectra show a well resolved resonance indicating that LiCl has been pulled into solution. Under the same conditions, LiCl alone is undetectable by $^7$Li NMR spectroscopy and addition of an excess of the partially soluble chloride salt tetramethylammonium chloride ([Me$_4$N][Cl]) to 10 results in only 12\% conversion to $[(\kappa^3_{\text{15c5NCOPipPr}})\text{Ir(H)(Cl)}_2][\text{Me}_4\text{N}]$. These preliminary results indicate that binding of the LiCl ion pair to 10 is more favorable than the binding of either ion alone.

\textbf{Scheme 4.2} Proposed heteroditopic LiCl binding by $(\kappa^4_{\text{15c5NCOPipPr}})\text{Ir(H)(Cl)}$ (10).
4.6 Conclusions

Fitting an aza-crown ether with a phenylphosphinite ligand provides an entry for organometallic tuning of the host-guest properties. Three dramatic changes are observed upon moving from the simple organic macrocycle to an organometallic pincer-crown ether. (1) The binding affinity for Li$^+$ and Na$^+$ salts is reduced substantially; the amine donates to the transition metal center, reducing the crown ether donor number and providing a pathway for inductive electronic withdrawing effects. (2) The selectivity for Li$^+$ over Na$^+$ increases dramatically, by as much as 30-fold; the long linking unit between ethers that contains the transition metal center may provide better conformations for the smaller cation. (3) The ion binding properties shift fundamentally to enable heteroditopic binding of ion pairs; the transition metal center provides an anion binding site in close proximity to the cation-binding crown ether, with direct cation–anion bridges possible.

Each of these properties can be further tuned through organometallic synthesis. The choice of transition metal ion has a significant impact on the binding affinity, for example. Ligand substitution on a particular transition metal complex leads to substantial shifts in the crown ether Li$^+$ binding affinity. The electronic structure of the transition metal can favor or disfavor ditopic binding, as well, with neutral square planar transition metal complexes expected to have low halide affinity relative to cationic transition metal complexes with $d^6$ configurations. No competition for the binding sites is observed in this system, thanks to the strong phenylphosphinite donor set.

This new strategy for post-macrocyclization modification takes advantage of the synthetic versatility and structural diversity of organometallic complexes to give both transformational changes and fine-tuned adjustments in the host-guest properties of crown ethers.
4.7 Experimental Section

General Considerations

Standard vacuum line and glovebox techniques were utilized to maintain a N\textsubscript{2} atmosphere during manipulation of all compounds, unless otherwise noted. Organic solvents were dried and degassed with argon using a Pure Process Technology solvent system and stored over 3 Å molecular sieves. Under standard glovebox operating conditions, pentane, diethyl ether, benzene, toluene, and tetrahydrofuran were used without purging, so traces of those solvents were present in the atmosphere and in the solvent bottles. \textsuperscript{1}H, \textsuperscript{31}P, and \textsuperscript{13}C NMR spectra were recorded on 400, 500, 600, or 850 MHz spectrometers. NMR characterization data are reported at 25 °C, unless specified otherwise. All NMR solvents were purchased from Cambridge Isotopes Laboratories. Acetonitrile-\textit{d}_3 (CD\textsubscript{3}CN), benzene-\textit{d}_6 (C\textsubscript{6}D\textsubscript{6}), and methylene chloride-\textit{d}_2 (CD\textsubscript{2}Cl\textsubscript{2}) were freeze–pump–thaw-degassed three times, dried by passage through a small column of activated alumina, and stored over 3 Å molecular sieves. \textsuperscript{1}H and \textsuperscript{13}C chemical shifts are reported in parts per million relative to residual protio solvent resonances. All \textsuperscript{31}P resonances are reported relative to 85% H\textsubscript{3}PO\textsubscript{4} external standard (δ 0). The following compounds were synthesized according to literature procedures: \((\kappa^{3-15c5\text{NCOP}}^{\text{Pr}})\text{H},\text{NaBAr}_4\text{F}_4,\text{LiBAr}_4\text{F}_4,\text{Pd(COD)}\text{Cl}_2,\text{Pt(SMe}_2\text{)}_2\text{Cl}_2,\text{(κ}_3\text{-15c5\text{NCOP}}^{\text{Pr}})\text{Ni(Br)},\text{[(κ}_4\text{-15c5\text{NCOP}}^{\text{Pr}})\text{Ni)][BAr}_4\text{F}_4],\text{(κ}_3\text{-15c5\text{NCOP}}^{\text{Pr}})\text{Ir(CO)},\text{and (κ}_3\text{-15c5\text{NCOP}}^{\text{Pr}})\text{Ir(H)(CO)(Cl)}\text{, [(κ}_3\text{-15c5\text{NCOP}}^{\text{Pr}})\text{Ir(H)(CO)(NCCH}_3\text{)][BAr}_4\text{F}_4].\text{LiOTf was dried under reduced pressure at 100 °C for 24 h prior to storage in a N}_2\text{ glovebox. All other reagents were commercially available and used without further purification. Elemental analyses were performed by Robertson Microlit Laboratories (Ledgewood, NJ).}

Single-crystal X-ray diffraction data were collected on a Bruker Smart Apex-II diffractometer at 100 ± 2 K with Cu K\textsubscript{α} radiation (λ = 1.54175 Å). Diffraction profiles were
integrated using the SAINT software program. Absorption corrections were applied using SADABS. The structure was solved using direct methods and refined using the XL refinement package via the least-squares method. Hydrogen atoms were generated theoretically and refined isotropically with fixed thermal factors.

**Synthetic Procedures**

*Synthesis of (15c5NCOPiPr)Ni(Cl)*

The procedure described for the preparation of (15c5NCOPiPr)Ni(Br) was used to prepare (15c5NCOPiPr)Ni(Cl) from 145.4 mg (0.662 mmol) NiCl₂(DME), 291.8 mg (0.661 mmol) (15c5NCOPiPr)H, and 0.230 mL (1.65 mmol) NEt₃. The crude product was isolated as a red-yellow oil and was recrystallized from a saturated toluene solution layered with pentane at -30 °C to yield yellow crystals that were washed with pentane and dried in-vacuo (170.3 mg, 44.5% yield).

**1H NMR** (600 MHz, C₆D₆): δ 1.17 (dd, J = 14.4, 7.0 Hz, 6H, CH(CH₃)₂), 1.47 (dd, J = 17.4, 7.2 Hz, 6H, CH(CH₃)₂), 2.13 (m, 2H, CH(CH₃)₂), 3.29 (m, 12H, crown-CH₂), 3.55 (m, 2H, crown-CH₂), 3.69 (m, 2H, crown-CH₂), 4.06 (m, 2H, crown-CH₂), 4.17 (m, 2H, crown-CH₂), 4.42 (s, 2H, ArCH₂N), 6.50 (d, J = 7.4 Hz, 1H, ArH), 6.59 (d, J = 7.9 Hz, 1H, ArH), 6.88 (t, J = 7.7 Hz, 1H, ArH).

**13C{¹H} NMR** (151 MHz, C₆D₆): δ 16.89 (s, CH(CH₃)₂), 17.95 (d, J = 4.6 Hz, CH(CH₃)₂), 28.07 (d, J = 23.5 CH(CH₃)₂), 57.00 (s, crown-CH₂), 66.04 (s, ArCH₂N), 69.75 (s, crown-CH₂), 70.66 (s, crown-CH₂), 70.95 (s, crown-CH₂), 70.98 (s, crown-CH₂), 107.95 (d, J = 13.0 Hz, Ar), 115.72 (s, Ar), 126.94 (s, Ar), 140.80 (d, J = 34.2 Hz, Ar), 153.68 (s, Ar), 166.26 (d, J = 10.9 Hz, Ar).

**31P{¹H} NMR** (162 MHz, C₆D₆): δ 197.65 (s).

Figure 4.7 $^1$H NMR spectrum (600 MHz) of ($\kappa^3$-15c5 NCOP$iPr$)Ni(Cl) (5-Cl) in C$_6$D$_6$.

Figure 4.8 $^{31}$P($^1$H) NMR spectrum (162 MHz) of ($\kappa^3$-15c5 NCOP$iPr$)Ni(Cl) (5-Cl) in C$_6$D$_6$. 
Figure 4.9 $^{13}$C{$^1$H} NMR spectrum (151 MHz) of ($\kappa^3$-$^{15}$C5NCOP$^{i}$Pr)Ni(Cl) (5-Cl) in C$_6$D$_6$.

Synthesis of ($^{15}$C5NCOP$^{i}$Pr)Ni(I)

In a glovebox, a vial was charged with 117.0 mg (0.202 mmol) of ($^{15}$C5NCOP$^{i}$Pr)Ni(Br), 148.7 mg (0.896 mmol) of KI, and 8 mL of acetone. The solution was allowed to stir for 5 days and then evaporated to dryness yielding a yellow oil. The resulting oil was extracted with benzene, filtered, and pumped to dryness. The crude product was recrystallized by layering a saturated toluene solution with pentane and placing in a -30 °C freezer. The mother liquor was decanted after 48 hours and the isolated yellow crystals were washed with pentane (88.5 mg, 70.0% yield). $^1$H NMR (600 MHz, C$_6$D$_6$): 1.16 (dd, $J = 14.5$, 7.0 Hz, 6H, CH(CH$_3$)$_2$), 1.50 (dd, $J = 17.3$, 7.2 Hz, 6H, CH(CH$_3$)$_2$), 2.32 (m, 2H, CH(CH$_3$)$_2$), 3.26 (m, 12H, crown-C$_2$H$_2$), 3.74 (m, 2H, crown-C$_2$H$_2$), 3.95 (m, 2H, crown-C$_2$H$_2$), 4.06 (m, 4H, crown-C$_2$H$_2$), 4.52 (s, 2H, ArCH$_2$N), 6.53 (d, $J = 7.4$ Hz, 1H, ArH), 6.67 (d, $J = 7.8$ Hz, 1H, ArH), 6.92 (t, $J = 7.7$ Hz, 1H, ArH).

$^{13}$C{$^1$H} NMR (151 MHz, C$_6$D$_6$): $\delta$ 16.94 (s, CH(CH$_3$)$_2$), 18.89 (d, $J = 3.0$ Hz, CH(CH$_3$)$_2$), 29.26
(d, $J = 25.7$ Hz, CH(CH$_3$)$_2$), 57.69 (s, crown-CH$_2$), 64.76 (s, ArCH$_2$N), 69.95 (s, crown-CH$_2$), 70.44 (s, crown-CH$_2$), 70.74 (s, crown-CH$_2$), 107.75 (d, $J = 13.1$ Hz, C$_{Ar}$), 115.70 (s, C$_{Ar}$), 127.05 (s, C$_{Ar}$), 145.41 (d, $J = 31.6$ Hz, C$_{Ar}$), 153.73 (s, C$_{Ar}$), 165.21 (d, $J = 10.8$ Hz, C$_{Ar}$).

$^{31}$P{$^1$H} NMR (243 MHz, C$_6$D$_6$): $\delta$ 203.81 (s). **Anal. Calcd** for C$_{23}$H$_{39}$O$_5$NPNiI: C, 44.12; H, 6.28; N, 2.24. Found: C, 44.32; H, 6.09; N, 2.18.

**Figure 4.10** $^1$H NMR spectrum (600 MHz) of ($\kappa^3$-15c$^5$NCOP$_{iPr}$)Ni(I) (5-I) in C$_6$D$_6$.  

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Figure 4.11 $^{31}$P{${}^1$H} NMR spectrum (243 MHz) of ($\kappa^3$-$^{15}$COP$i$Pr)Ni(I) (5-I) in C$_6$D$_6$.

Figure 4.12 $^{13}$C{${}^1$H} NMR spectrum (151 MHz) of ($\kappa^3$-$^{15}$COP$i$Pr)Ni(I) (5-I) in C$_6$D$_6$. 
**Synthesis of (\(^{15c5}\text{NCOP}^\text{iPr})\text{Pd(Cl)}\)**

A 5 mL solution of (\(^{15c5}\text{NCOP}^\text{iPr})\text{H}\) in toluene was slowly added dropwise to a stirring suspension of Pd(COD)Cl\(_2\) in 5 mL toluene in a 50 mL Schlenk flask. The resulting solution was refluxed for 2 hours and then the solvent was removed *in vacuo* yielding an off-white oil. The oil was extracted into as little toluene as possible, filtered, layered with pentane, and placed in a \(-30^\circ\text{C}\) freezer. The mother liquor was decanted after 48 hours and the isolated white crystals were washed with pentane yielding analytically pure product. ¹H NMR (600 MHz, C\(_6\)D\(_6\)): δ 1.08 (dd, \(J = 15.8, 7.0\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.33 (dd, \(J = 18.9, 7.2\) Hz, 6H, CH(CH\(_3\))\(_2\)), 2.10 (m, 2H, CH(CH\(_3\))\(_2\)), 3.33 (m, 8H, crown-CH\(_2\)), 3.43 (m, 4H, crown-CH\(_2\)), 3.54 (m, 2H, crown-CH\(_2\)), 3.66 (m, 2H, crown-CH\(_2\)), 3.93 (m, 2H, crown-CH\(_2\)), 4.22 (m, 2H, crown-CH\(_2\)), 4.29 (s, 2H, ArCH\(_2\)N), 6.58 (d, \(J = 7.5\) Hz, 1H, ArH), 6.72 (d, \(J = 7.9\) Hz, 1H, ArH), 6.87 (td, \(J = 7.8, 1.0\) Hz, 1H, ArH). ¹³C\{¹H\} NMR (151 MHz, C\(_6\)D\(_6\)): δ 16.84 (s, CH(CH\(_3\))\(_2\)), 17.54 (d, \(J = 5.8\) Hz, CH(CH\(_3\))\(_2\)), 29.26 (d, \(J = 25.3\) Hz, CH(CH\(_3\))\(_2\)), 58.32 (s, crown-CH\(_2\)), 67.89 (s, ArCH\(_2\)N), 69.44 (s, crown-CH\(_2\)), 70.70 (s, crown-CH\(_2\)), 70.89 (s, crown-CH\(_2\)), 108.76 (d, \(J = 15.8\) Hz, C\(_{Ar}\)), 117.11 (s, C\(_{Ar}\)), 126.61 (s, C\(_{Ar}\)), 145.60 (s, C\(_{Ar}\)), 151.36 (s, C\(_{Ar}\)), 163.89 (d, \(J = 6.6\) Hz, C\(_{Ar}\)).

³¹P\{¹H\} NMR (243 MHz, C\(_6\)D\(_6\)): δ 201.05 (s).
Figure 4.13 $^1$H NMR spectrum (600 MHz) of ($\kappa^3$-$^{15}$C$_5$NCOP$_{\text{Pr}}$)Pd(Cl) (6) in C$_6$D$_6$.

Figure 4.14 $^{31}$P$^1$H NMR spectrum (243 MHz) of ($\kappa^3$-$^{15}$C$_5$NCOP$_{\text{Pr}}$)Pd(Cl) (6) in C$_6$D$_6$. 
Figure 4.15 $^{13}$C-$^1$H NMR spectrum (151 MHz) of $(\kappa^3$-$^{15c5}$NCOP$iPr)$Pd(Cl) (6) in C$_6$D$_6$.

Table 4.1 Crystal data and structure refinement for $(^{15c5}$NCOP$iPr)$Pd(Cl) (6).

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Synthesis of \((^{15c_5}\text{NCOP}^{\text{ipr}})\text{Pt(Cl)}\)

A 3 mL solution of \((^{15c_5}\text{NCOP}^{\text{ipr}})\text{H}\) in toluene was slowly added dropwise to a stirring suspension of Pt(SMe\(_2\))\(_2\)Cl\(_2\) in 3 mL toluene in a 25 mL Schlenk flask. The resulting solution was refluxed for 5 hours and then the solvent was removed \textit{in vacuo} yielding an off-white oil. The oil was extracted into as little toluene as possible, filtered, layered with pentane, and placed in a -30 °C freezer. The mother liquor was decanted after 48 hours and the isolated white crystals were washed with pentane yielding analytically pure X. \(^1\text{H NMR}\) (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 1.07 (dd, \(J = 15.9, 7.0\) Hz, 6H, CH(CH\(_3\))\(_2\)), 1.28 (dd, \(J = 18.7, 7.2\) Hz, 6H, CH(CH\(_3\))\(_2\)), 2.15 (m, 2H, CH(CH\(_3\))\(_2\)), 3.32 (m, 12H, crown-CH\(_2\)), 3.61 (m, 2H, crown-CH\(_2\)), 3.86 (m, 4H, crown-CH\(_2\)), 4.17 (m, 2H, crown-CH\(_2\)), 4.44 (s, 2H, ArCH\(_2\)N), 6.61 (d, \(J = 7.5\) Hz, 1H, ArH), 6.78 (d, \(J = 7.9\) Hz, 1H, ArH), 6.92 (t, \(J = 7.7\) Hz, 1H, ArH). \(^{13}\text{C}\{^1\text{H}\}\text{NMR}\) (151 MHz, C\(_6\)D\(_6\)): \(\delta\) 16.78 (s, CH(CH\(_3\))\(_2\)), 17.15 (d, \(J = 4.3\) Hz, CH(CH\(_3\))\(_2\)), 29.25 (d, \(J = 37.3\) Hz, CH(CH\(_3\))\(_2\)), 58.98 (d, \(J = 3.0\) Hz, crown-CH\(_2\)), 68.87 (s, crown-CH\(_2\)), 69.63 (d, \(J = 2.7\) Hz, ArCH\(_2\)N), 70.69 (s, crown-CH\(_2\)), 70.86 (s, crown-CH\(_2\)), 70.93 (s, crown-CH\(_2\)), 108.47 (d, \(J = 12.6\) Hz, C\(_\text{Ar}\)), 116.50 (s, C\(_\text{Ar}\)), 125.42 (s, C\(_\text{Ar}\)), 136.30 (d, \(J = 5.3\) Hz, C\(_\text{Ar}\)), 148.63 (s, C\(_\text{Ar}\)), 162.81 (d, \(J = 3.5\) Hz, C\(_\text{Ar}\)). \(^{31}\text{P}\{^1\text{H}\}\text{NMR}\) (202 MHz, C\(_6\)D\(_6\)): \(\delta\) 159.41 (s).
Figure 4.16 $^1\text{H}$ NMR spectrum (500 MHz) of (κ$^{3}$-15c5NCOP$^{i}$Pr)Pt(Cl) (7) in C$_6$D$_6$.

Figure 4.17 $^{31}\text{P}^{'\text{H}}$ NMR spectrum (202 MHz) of (κ$^{3}$-15c5NCOP$^{i}$Pr)Pt(Cl) (7) in C$_6$D$_6$. 
Figure 4.18 $^{13}$C{$^1$H} NMR spectrum (151 MHz) of ($\kappa^3$-15c5NCOP$i$Pr)Pt(Cl) (7) in C$_6$D$_6$.

Table 4.2 Crystal data and structure refinement for ($^{15}$c5NCOP$i$Pr)Pt(Cl) (6).

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<td>CuKα ($\lambda = 1.54178$)</td>
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<tr>
<td>Index ranges</td>
<td>-30 ≤ h ≤ 29, -30 ≤ k ≤ 29, -9 ≤ l ≤ 9</td>
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</table>
Reflections collected 51263
Independent reflections 4830 \[R_{int} = 0.0283, R_{sigma} = 0.0125\]
Data/restraints/parameters 4830/0/293
Goodness-of-fit on F^2 1.223
Final R indexes [I>=2\(\sigma\) (I)] \(R_1 = 0.0219, wR_2 = 0.0477\)
Final R indexes [all data] \(R_1 = 0.0222, wR_2 = 0.0479\)
Largest diff. peak/hole / e Å^{-3} 0.55/-0.78

**Determining binding affinity by competition with organic macrocycles**

The calibrated competitive method for determining binding constants by NMR spectroscopy reported by Heath et al. was used to determine binding affinities of 1 and 2 via competition with 15-crown-5 and 18-crown-6 (1 only). Calibration curves were constructed for 15-crown-5 and LiOTf and NaBArF\(_4\) in CD\(_3\)CN. A Calibration curve was constructed with 18-crown-6 and NaBArF\(_4\) in CD\(_3\)CN (18-crown-6 does not exhibit a linear response to [Li\(^+\)] due to a lower binding affinity). The reference value \((K_{ref})\) used for Li\(^+\) complexation by 15-crown-5 was \(\log K_{ref} = 4.96\). The \(K_{ref}\) used for Na\(^+\) complexation by 15-crown-5 was \(\log K_{ref} = 5.1\). The \(K_{ref}\) used for Na\(^+\) complexation by 18-crown-6 was \(\log K_{ref} = 4.6\).

Triplicate samples of each reference/(pre)ligand/salt combination were prepared and analyzed as follows. A 60 mM stock solution of a reference molecule (15-crown-5 or 18-crown-6), A 60 mM stock solution of a (pre)ligand (1 or 2), and a 24 mM stock solution of salt (LiOTf or NaBArF\(_4\)) was prepared in CD\(_3\)CN. 100 µL aliquots of the reference and (pre)ligand stock solutions and 250 µL aliquots of the salt solution were combined in a 4 mL glass vial. The samples were diluted to 600 µL with CD\(_3\)CN, transferred to NMR tubes, and analyzed by \(^1\)H NMR spectroscopy at 25 ± 1 °C. The resulting concentrations of all three species in each sample were 10 mM.
Figure 4.19 Calibration curves for binding of LiOTf and NaBAr$_4^F$ by 15-crown-5.

Figure 4.20 Calibration curves for binding of NaBAr$_4^F$ by 18-crown-6.
**General Procedure for Titrations**

The following general procedure is for titrations with a final analyte concentration of 10 mM. A 12 mM stock solution of the corresponding analyte [(pre)ligand or pincer-crown ether complex] and a 48 mM stock solution of the corresponding alkali metal salt (24 mM for NaBArF₄) were prepared in CH₃CN. 500 µL aliquots (6.0 × 10⁻³ mmol) of the analyte solution were added to ten glass vials. Aliquots of the alkali metal stock solution corresponding to 0.5–12 equiv (between 3.0 × 10⁻³ and 72 × 10⁻³ mmol) of alkali metal salt to analyte were then added to the vials containing the analyte. The protio solvent was completely evaporated. The samples were then dissolved in 600 µL of CD₃CN, transferred to NMR tubes, and analyzed by ¹H NMR spectroscopy at 25 ± 1 °C. The final concentration of analyte in solution was 10 mM. The final concentration of alkali metal in the samples ranged from 0 to 120 mM.

An effort was made to perform titrations at varying concentrations of analyte, 2.5 mM, 5 mM, and 10 mM using the same general procedure above. In these cases, the uncertainty is based on the standard deviation of $K_a$ values obtained from fitting the binding isotherm data at the three different concentrations. In cases where triplicate measurements at the different concentrations have not been completed, the estimated uncertainty of each equilibrium constant is 10% or less.

**Titration data**

Conditions: Isotherms were collected at 25 ± 1 °C in CD₃CN
Figure 4.21 Binding isotherms for the titration of $m$-(Aza-15-crown-5)methylphenol (1) with LiOTf.

Figure 4.22 Binding isotherms for the titration of $m$-(Aza-15-crown-5)methylphenol (1) with NaBArF₄.
Figure 4.23 Binding isotherms for the titration of \((^{15}c^5\text{NCOP}^\text{iPr})\text{H} \ (2)\) with LiOTf.

Figure 4.24 Binding isotherms for the titration of \(\kappa^3-(^{15}c^5\text{NCOP}^\text{iPr})\text{Ir(H)(CO)(Cl)} \ (3)\) with LiOTf.
Figure 4.25 Binding isotherms for the titration of $\kappa^3$-($^{15}$C$_5$NCOP$^{iPr}$)$_2$Ir(H)(CO)(Cl) (3) with NaBAR$_4$.

Figure 4.26 Binding isotherms for the titration of ($\kappa^3$-($^{15}$C$_5$NCOP$^{iPr}$))Ir(CO) (4) with LiOTf.
Figure 4.27 Binding isotherms for the titration of \((^{15}\text{COPiPr})\text{Pd(Cl)}\) (6) with LiOTf.

Figure 4.28 Binding isotherms for the titration of \((^{15}\text{COPiPr})\text{Pt(Cl)}\) (6) with LiOTf.
Figure 4.29 Binding isotherms for the titration of \([({k_{15C5NCOPiPr}})Ni(NCCD_3)][BaF_4]\) (8) with LiBArF_4.

Figure 4.30 Binding isotherms for the titration of \([({k_{3.5NCOPiPr}})Ir(H)(CO)(NCCH_3)][BaF_4]\) (9) with LiBArF_4.
REFERENCES


