Regulating Access to Active Sites via Hydrogen Bonding and Cation-Dipole Interactions: A Dual Cofactor Approach to Switchable Catalysis

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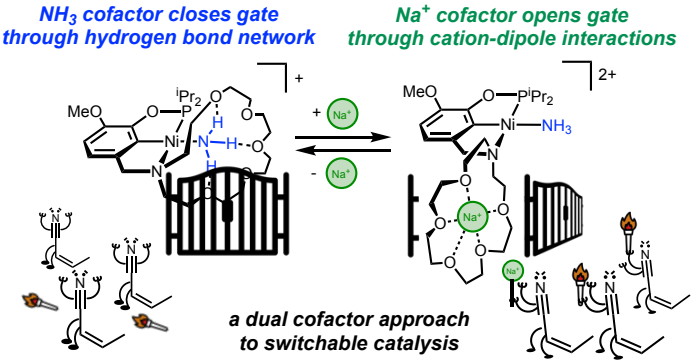


Abstract

Hydrogen bonding networks are ubiquitous in biological systems and play a key role in controlling the conformational dynamics and allosteric interactions of enzymes. Yet in small organometallic catalysts, hydrogen bonding rarely controls ligand binding to the metal center. In this work, a hydrogen bonding network within a well-defined organometallic catalyst works in concert with cation-dipole interactions to gate substrate access to the active site. An ammine ligand acts as one cofactor, templating a hydrogen bonding network within a pendent crown ether in the secondary coordination sphere, an interaction which prevents the binding of nitriles to the nickel center. Sodium ions are a second cofactor, disrupting hydrogen bonding to enable ligand substitution reactions and substrate binding. Thermodynamic analyses provide insight into the energetic

requirements of the different supramolecular interactions enabling substrate gating. Switchable ligand substitution and switchable hydroamination catalysis illustrate the dual cofactor approach.

Introduction

In biological systems, catalytic reactions are often modulated by "gating" mechanisms that regulate substrate access to active sites.[1] Enzymes rely on small molecule or ion cofactors to modulate substrate and solvent access to active sites and synchronize multistep reactions through the opening and closing of molecular gates.[2–5] Synthetic chemists have long sought to replicate the function of allosteric control over substrate gating to achieve controlled or switchable catalysis.[6–9] The most common gating mechanisms involve physical blocking groups, such as supramolecular constructs with switchable steric bulk or supramolecular cages with switchable access, catalyst solubility, and configurational changes like cis/trans isomerization or metal-ligand bond breaking reactions.[6,10–14]

One important gating mechanism employed by enzymes is tunable hydrogen bonding (H-bonding) networks.[15] For example, ß-carbonic anhydrase controls the hydration of CO_2 using a complex network of hydrogen bonds (**Figure 1A**).[16] In one state, carbonate H-bonds in one part of the enzyme while aspartate binds to a Zn^{2+} ion, inhibiting the catalytic reaction. When the bicarbonate cofactor is released (usually due to a pH change), the H-bonding network near the active site rearranges. This reorganization enables a water molecule critical for catalysis to bind to the Zn^{2+} ion and initiates catalysis.

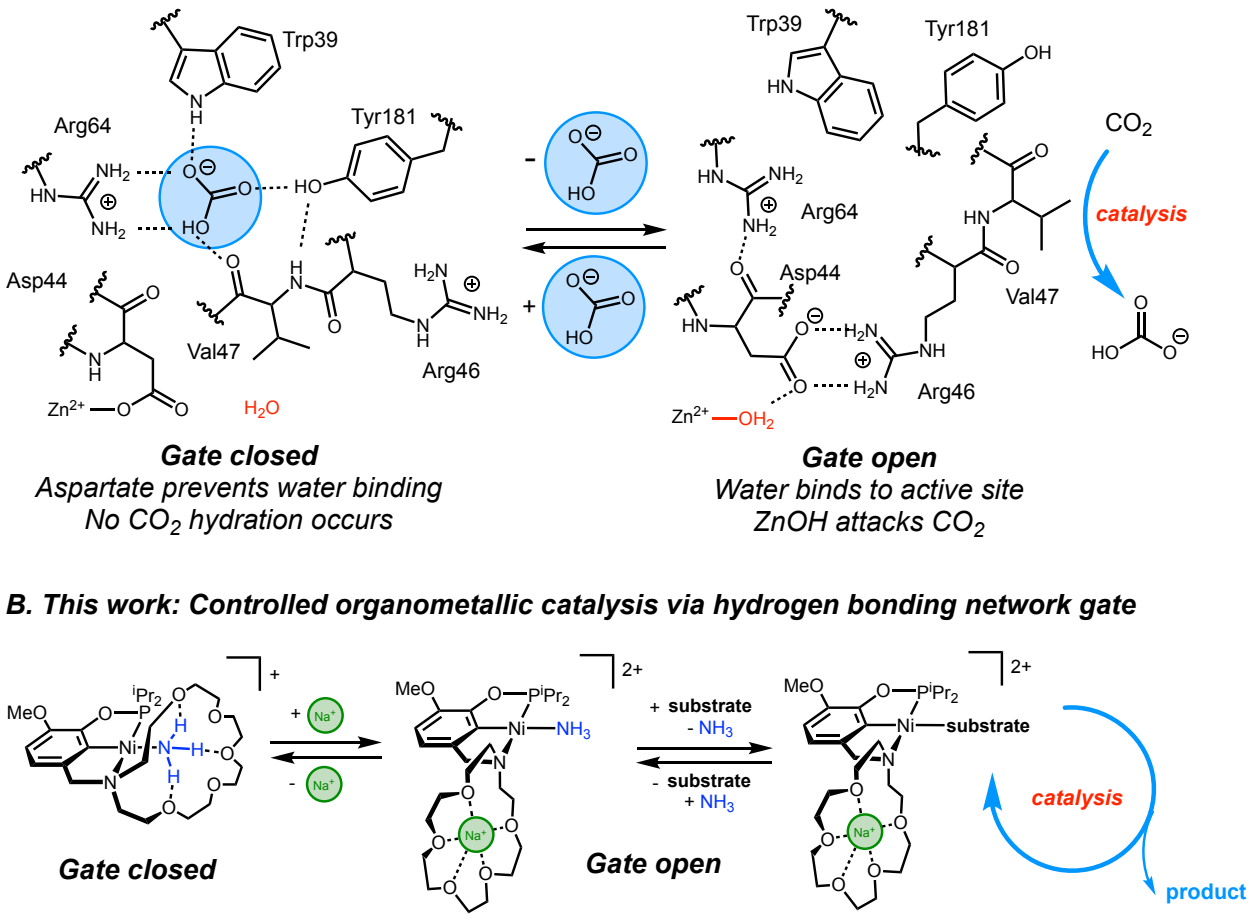


Figure 1. (A) Hydrogen bonding gate in ß-carbonic anhydrase for controlled bicarbonate formation. (B) New approach to switchable catalysis using hydrogen bonding gate in pincer-crown ether complexes.

Although H-bonding networks in the secondary coordination sphere have been explored in bio-inspired synthetic chemistry for stabilizing and fine-tuning reactive species,[17–19] examples where H-bonding networks are used to control substrate access in the context of allosteric model systems or switchable catalysis remain surprisingly rare.[6,20–23] Previously reported systems exclusively involve organocatalysts with H-bond donor active sites; we are not aware of examples where transition metal active sites are regulated by pendent H-bonding interactions. Considering the key role of H-bonding networks in regulating the conformational dynamics and allosteric

interactions of enzymes, we saw an opportunity to similarly utilize H-bonding networks in switchable catalysis of first-row organometallic complexes.

Our group has developed cation-responsive pincer-crown ether complexes that use ion-tunable hemilability as a gating mechanism for switchable reactivity.[24,25] These complexes feature an aza-crown-ether macrocycle incorporated into a pincer ligand, allowing for ether oxygen interactions with either the metal center or specific cations added to solution. In the closed state, the ether binds to the metal center and prevents substrate coordination. Cation cofactors open the gate, because the combined free energies of cation-dipole interactions and substrate binding to the metal center are thermodynamically favorable. In our recent report on a series of iridium aquo pincer-crown ether complexes capable of switchable regioselective olefin isomerization reactions, we noticed an intriguing H-bonding network between the aquo ligand and the aza-crown-ether macrocycle.[26] We hypothesized that small molecules such as water or ammonia could act as a secondary cofactor and enable new reactivity. It is rare for synthetic catalysts to employ multiple cofactors for switchable catalysis,[22,27] providing an opportunity for understanding how cation-dipole and H-bonding interactions with crown ethers can influence and control substrate access to active sites (**Figure 1B**).

In this work, we show how pendent crown ethers can establish H-bonding networks within organometallic complexes as part of a dual cofactor approach to controlled catalysis. When both ammonia and sodium ions are used as cofactors, balancing H-bonding and cation-dipole interactions enables a robust gating mechanism for switchable substrate binding and catalysis. The thermodynamics of these interactions are investigated and reveal insights into the switchable gating process. The importance of both H-bonding and cation-dipole interactions for switchable reactivity is examined through a series of comparison complexes. The dual cofactor approach is

leveraged to demonstrate switchable ligand substitution reactivity and catalytic alkene hydroamination reactions.

Synthesis of nickel complexes and characterization of H-bonding networks

Figure 2 describes the synthesis of the target nickel complexes. Pincer ligands with and without macrocycles were chosen to better understand the role of crown ethers in enabling switchable reactivity. Halide abstraction of (κ^3-^{18c6}NCOP)Ni(Br) (**^{18c6}NiBr**) with $AgPF_6$, followed by salt metathesis with $NaBAr^F{}_4$, provided [(κ^4-^{18c6}NCOP)Ni][$BAr^F{}_4$] (**^{18c6}Ni**). Complexes **^{18c6}NiBr** and **^{18c6}Ni** are similar to previously published variants,[28] with the exception that they contain a methoxy group in the backbone of the pincer ligand to prevent unwanted metalation byproducts.[24]

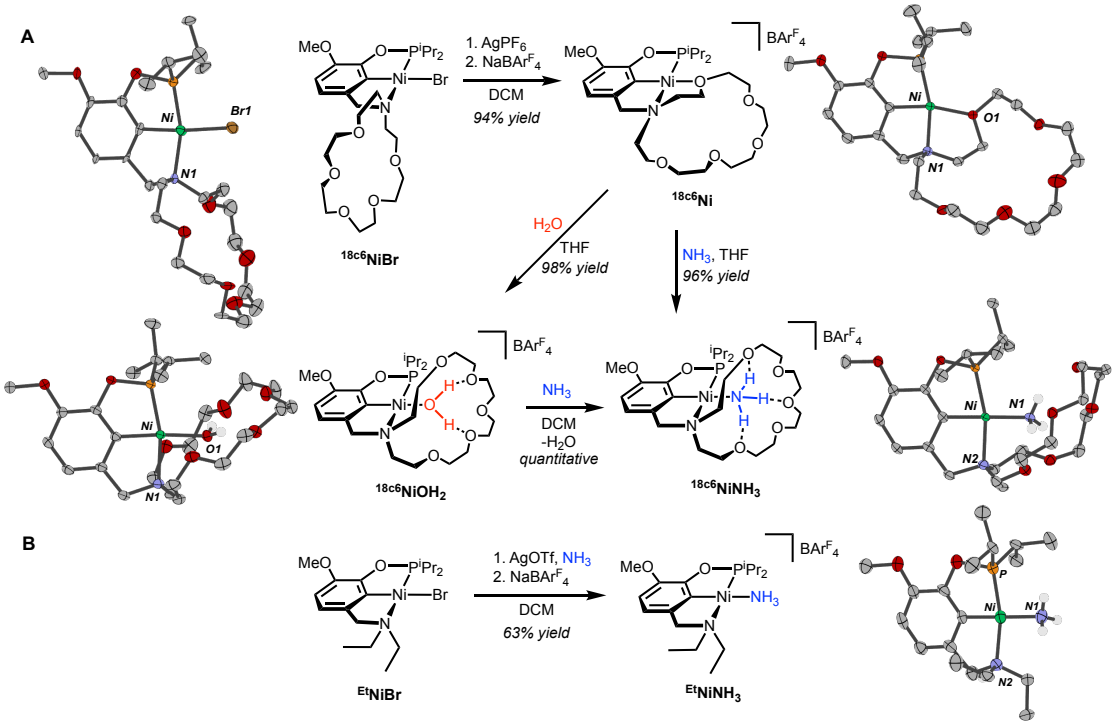


Figure 2. (A) Synthetic route to pincer-crown ether nickel ammine and aquo complexes. (B) Synthetic route to diethylamino pincer nickel ammine complex. Structural representations from single crystal X-ray diffraction, with ellipsoids at 50% and hydrogen atoms (except on aquo or ammine ligands) and anions omitted, are shown adjacent to the line drawing.

Treatment of **^{18c6}Ni** with 10 equiv of ammonia in THF led to the formation of the desired complex [(κ^3-^{18c6}NCOP)Ni(NH_3)][BAr^F_4] (**^{18c6}NiNH$_3$**), which was obtained as a yellow powder in 96% yield (**Figure 2A**). The ^{15}N-labeled isotopologue, [(κ^3-^{18c6}NCOP)Ni($^{15}NH_3$)][BAr^F_4] (**^{18c6}Ni^{15}NH$_3$**), was generated analogously. The diethyl-amine-containing complex [(κ^3-^{Et}NCOP)Ni(NH_3)][BAr^F_4] (**^{Et}NiNH$_3$**) lacks a crown ether and thus serves as an important control (**Figure 2B**).

The X-ray structure of **^{18c6}NiNH$_3$** reveals a remarkable H-bonding network. The crown ether curls up to encapsulate the Ni-NH_3 and bridge the primary and secondary coordination sphere (**Figure 2A**). This conformation is different than other reported four-coordinate nickel pincer-crown ether structures, which are oriented with the crown ether away from the metal center.[29] **Figure 3A** shows a detailed view of the H-bonding network of **^{18c6}NiNH$_3$**. All five oxygen donors on the macrocycle are within H-bonding distance, with five O-N distances ranging from 2.886(2) to 3.085(3) Å.[30] These distances are similar to reported X-ray structures of ammonium cations interacting with 15-crown-5 ether and transition metal ammine complexes interacting with external crown ethers.[31,32]

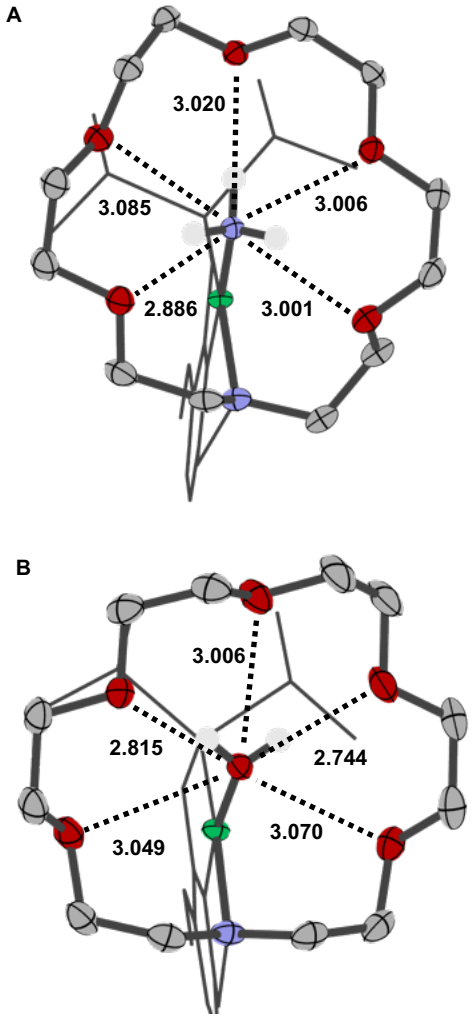
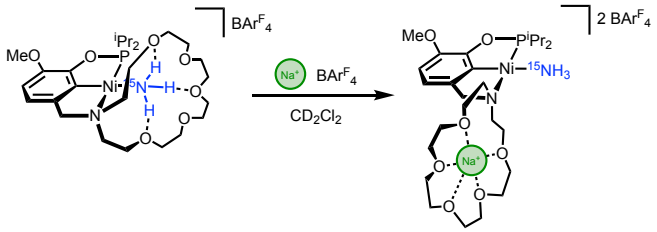


Figure 3. Perspective highlighting the H-bonding network in (a) ^{18c6}**NiNH$_3$** and (b) ^{18c6}**NiOH$_2$**. Structural representations from single crystal X-ray diffraction, with ellipsoids at 50% and hydrogen atoms (except on aquo or ammine ligands) and anions omitted, are shown adjacent to the line drawing. Inter-atomic distances given in angstroms (Å).

To compare H-bonding interactions with other ligands, the nickel aquo complex [(κ^3-^{18c6}NCOP)NiOH$_2$][BAr$^F{}_4$] (**^{18c6}NiOH$_2$**) was also synthesized (**Figure 2A**). The crystal structure of **^{18c6}NiOH$_2$** also features a H-bonding network, with donor-acceptor distances shown in **Figure 3B**. The conformational flexibility of the macrocycle is presumably essential for the formation of these complexes; in addition to these H-bonding interactions, we have observed a wide range of conformations including those with no H-bonding (empty crown), bound alkali metal cations, or with additional ether donor(s) binding to the transition metal center.[28,29,33]

Scheme 1. Addition of $NaBAr^F_4$ to $^{18c6}Ni^{15}NH_3$.



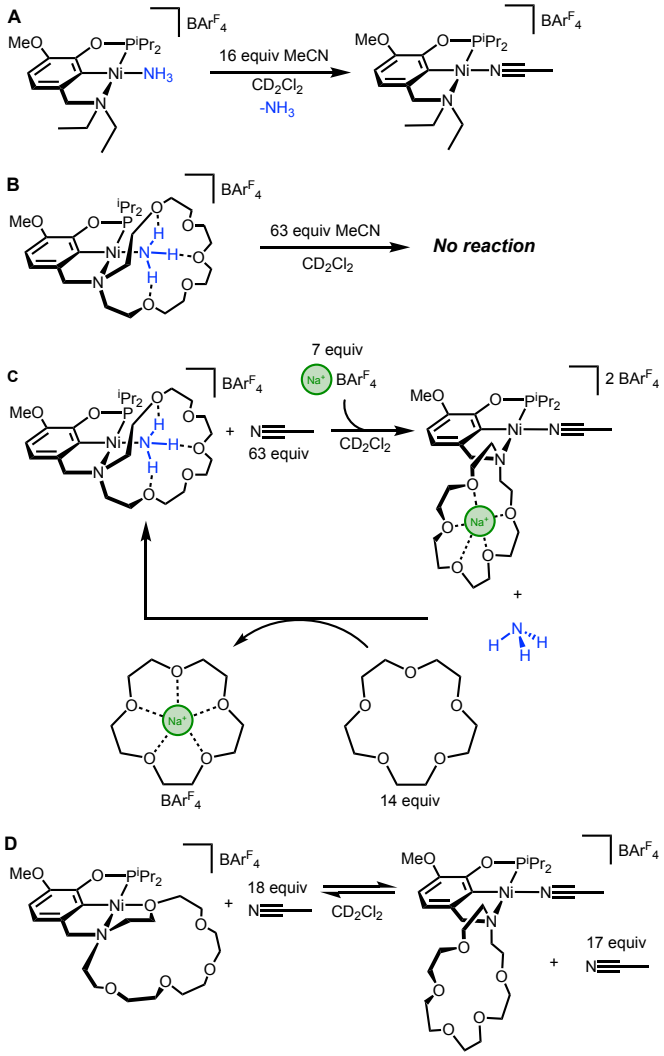
Multinuclear NMR spectroscopy can provide insight into the conformation of the crown ether. The ^{15}N NMR spectrum of $^{18c6}Ni^{15}NH_3$ exhibits a quartet at -400.2 ppm vs CH_3NO_2 ($^1J_{NH}$ = 67 Hz), typical of ammine complexes (**SI Figure 16**).[34,35] To disrupt the H-bonding, 1 equiv $NaBAr^F_4$ was added to $^{18c6}Ni^{15}NH_3$ in dichloromethane solvent (**Scheme 1**), resulting in the immediate formation of a new nickel species assigned as the Na^+ adduct $Na^+@^{18c6}NiNH_3$. The ^{15}N resonance shifts downfield by 0.5 ppm and additional coupling to phosphorus is observed (-399.7 ppm, qd, $^1J_{NH}$ = 67 Hz, $^2J_{NP}$ = 2.5 Hz). Significant shifts and changes in multiplicity are also observed for the crown ether proton resonances in the ^1H NMR spectrum, consistent with Na^+ localization in the macrocycle (**SI Figure 60**). Additionally, the NH_3 proton resonances shift from 2.26 to 1.30 ppm for $Na^+@^{18c6}NiNH_3$. Spectroscopic parameters of the complex without a crown ether, $^{Et}Ni^{15}NH_3$, which is not capable of H-bonding, are very similar to those of $Na^+@^{18c6}NiNH_3$, providing further evidence that Na^+ disrupts the H-bonding network.

Switchable ligand substitution of nickel ammine complexes

With a better understanding of the H-bonding present in the crown-containing complexes, we set out to examine how dual cofactors with distinct noncovalent interactions influence ligand substitution reactions. In the absence of any interactions with a crown ether, ligand substitution is facile with typical stronger donor ligands such as acetonitrile. Addition of just 16 equiv acetonitrile

to ^{Et}**NiNH$_3$** results in formation of a cationic nickel acetonitrile complex, [(κ^3-^{Et}NCOP)Ni(NCCH$_3$)]$^+$ (**^{Et}**NiMeCN**) (**Scheme 2A**).

Scheme 2.



Conversely, the H-bonding network in **^{18c6}NiNH$_3$** inhibits ligand substitution. No reaction was observed upon treating the H-bonded ammine complex **^{18c6}NiNH$_3$** with 63 equiv of acetonitrile (**Scheme 2B**). Yet, when 7 equiv of NaBAr$^F_4$ was added to the reaction solution, rapid substitution of ammonia with nitrile was observed to generate [Na@(κ^3-^{18c6}NCOP)Ni(NCCH$_3$)]$^{2+}$ **(Na$^+$@^{18c6}NiMeCN)** with the Na$^+$ cation in the crown ether (**Scheme 2C**). This formulation of the

Ni complex was confirmed by comparison to an authentic sample from an alternative synthesis, which was fully characterized by multinuclear NMR spectroscopy and elemental analysis.

The nitrile binding event can be reversed with a chemical stimulus. Previous studies have shown that 15-crown-5 ether (15c5) binds Na^+ stronger than analogous aza-18-crown-6-based pincer-crown ether complexes.[29] Accordingly, the addition of 14 equiv 15c5 to **Na^+@^{18c6}NiMeCN** ejected the nitrile ligand and ammonia was recaptured to reform starting complex **^{18c6}NiNH$_3$** (**Scheme 2C**).

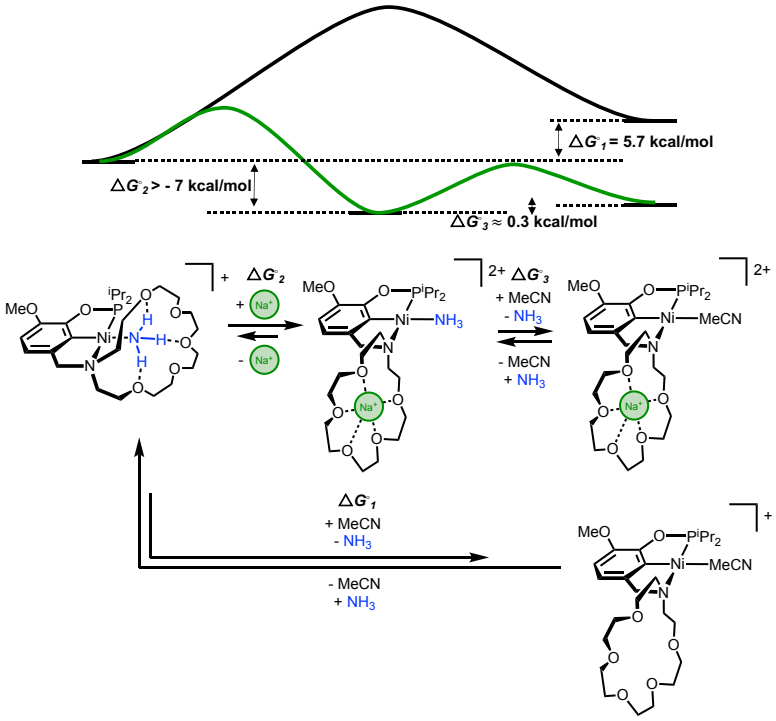
The ability of **^{18c6}NiNH$_3$** to capture ammonia in solution through the use of a chemical stimulus is noteworthy; here, the crown ether enhances ammonia's binding affinity to the nickel complex by H-bonding. These results demonstrate *cation-switchable ligand substitution* controlled by H-bonding networks with the pendent crown ether, providing an analogy to how some enzymes use H-bonding networks and ion cofactors to gate substrate access **(Figure 1A** above).

The ammonia cofactor is an essential component. Without NH_3 present, the κ^4-bound complex **^{18c6}Ni** is present in solution, which lacks a H-bonding network and instead has a weak Ni–O bond with one of the crown ether oxygen atoms. Upon addition of 19 equiv acetonitrile to **^{18c6}Ni**, broad, poorly resolved resonances are observed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy (**SI Figure 54-55**). This fluxional behavior is attributed to competitive binding between the acetonitrile and the crown-ether oxygen ligands (**Scheme 2D**).[36] This occurs without any Na^+ added, showing that the crown ether alone is not sufficient to regulate nitrile coordination to the metal center; the ammine ligand and the resulting H-bonding interactions enable the controlled nitrile binding reactivity.

Scheme 3 illustrates a free energy landscape that depicts the switchable acetonitrile/ammonia ligand substitution. Without cations present, ligand substitution to bind acetonitrile is unfavorable ($\Delta G^o_1 = 5.7$ kcal). Given that the NH_3 in **^{Et}NiNH$_3$**, which lacks any H-

bonding network, is readily displaced by MeCN, the unfavorable substitution of NH_3 in ^{18c6}**NiNH$_3$** can be largely ascribed to an energetically stabilizing effect of the H-bonding network. The H-bonding strength (i.e. the free energy required to break all of the H-bonds) is estimated to be ca. .4 kcal/mol (see the SI for a detailed thermodynamic analysis).

Scheme 3. Free energy landscape describing switchable ligand substitution.



When Na^+ is added, the substitution of NH_3 by MeCN becomes thermodynamically favorable. The switch in reactivity is attributed to an alteration in crown ether bonding, from H-bonding to cation-dipole interactions. The cation-crown interactions (ΔG^o_2) were directly probed by NMR spectroscopy. Changes in chemical shift were observed up to 1 equiv of $NaBAr^F_4$ added, and the addition of more than 1 equiv of $NaBAr^F_4$ to ^{18c6}**NiNH$_3$** did not result in any further changes detected by NMR. Thus, the cation binding energy is beyond the upper limit of quantification by NMR spectroscopy, K_a >10^5 M^{-1} ($\Delta G^o_2 < -7$ kcal/mol) in dichloromethane.[37,38] This behavior is strikingly distinct from the reactivity of nickel complexes lacking ammine ligands that feature

direct binding of an ether oxygen to nickel, which show no measurable interaction with alkali metal cations in dichloromethane ($K_a < 0.1$ M^{-1}).[28] In order to achieve switchable reactivity according to the reaction profile of **Scheme 3**, the cation-crown interaction must be stronger than the H-bonding energy, as was observed.

Switchable hydroamination catalysis by nickel ammine complexes

The ability to regulate ligand binding in **^{18c6}NiNH$_3$** provides an opportunity for switchable catalysis. The hydroamination of conjugated alkenyl nitriles was selected as a proof-of-principle test reaction, based on precedent for non-switchable catalysis by cationic pincer nickel complexes.[39–41] The key step in the mechanism is proposed to be nitrile coordination to an electrophilic metal center that activates the alkene for nucleophilic attack.[42]

The hydroamination of crotononitrile by morpholine in C_6H_5Cl, catalyzed by **^{18c6}NiNH$_3$**, was monitored by ^{1}H NMR spectroscopy (**Figure 4**). In the absence of $NaBAr^F_4$, the yield of 3-morpholinobutanenitrile was 2.7% after 48 h. Under the same conditions but with 1 equiv of $NaBAr^F_4$ present, the reaction proceeded cleanly to generate 53% yield of morpholinobutanenitrile after 48 h. A control reaction with $NaBAr^F_4$ present but no nickel catalyst showed no reaction even after 48 hours (**SI Figure 65**). The reaction is noteworthy for being almost completely "off" in the H-bonding-protected state and having a difference of more than 50-fold in activity between the two states (**Table 1**), an ideal situation for switchable catalysis.[6]

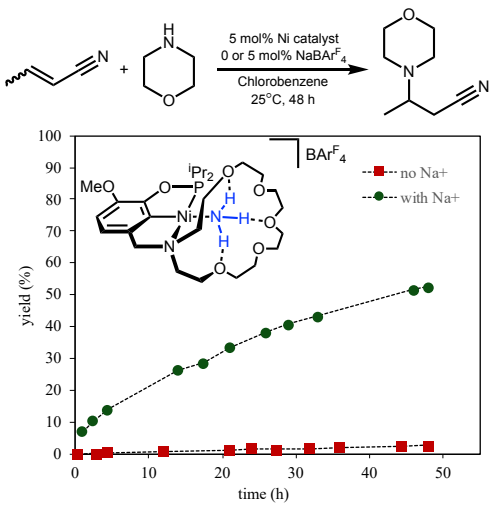


Figure 4. Hydroamination of crotononitrile with morpholine catalyzed by ^{18c6}**NiNH$_3$**, with no salt additive (red squares) and with NaBAr$^F_4$ (green circles). Conditions: 6 mM Ni (5 mol%), 0 or 6 mM NaBAr$^F_4$, 120 mM morpholine, and 240 mM crotononitrile, with 10 mM hexamethyldisolaxane (HMDSO) as an internal standard, in chlorobenzene solvent at 25°C.

Switchable catalytic activity was demonstrated with ^{18c6}**NiNH$_3$** by toggling between on and off states *in situ* using chemical additives (**Figure 5**). In its native state with strong H-bonding, the Ni catalyst is off (1% yield after 18 hours). Addition of Na^+ to the same flask initiated the reaction by disrupting the H-bonding, switching on reactivity to generate 13% yield of product after several hours. Addition of 15-crown-5 ether halted the reaction, reverting the catalyst back to the off state. The on state can be reinstated by adding 2 more equivalents of Na^+, and the reaction turns back on with similar activity as initially observed. These results highlight the reversible nature of this organometallic catalyst through the dual cofactors.

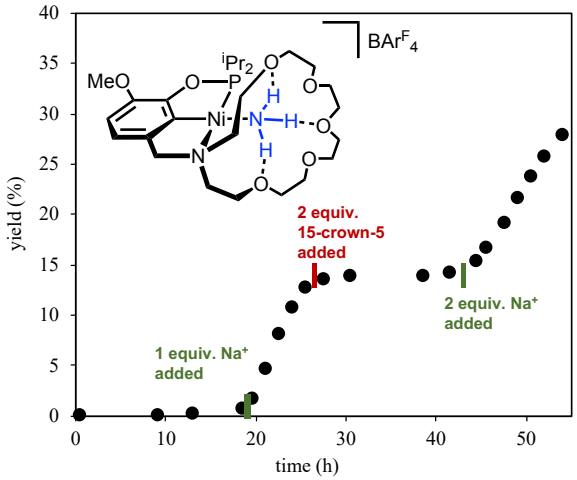


Figure 5. Cation-controlled hydroamination of crotononitrile with morpholine catalyzed by ^{18c6}**NiNH$_3$**. Conditions: 6 mM Ni (5 mol%), 120 mM morpholine, and 240 mM crotononitrile, with mesitylene as an internal standard, in chlorobenzene-*d5* at 25°C. The vertical lines mark the time at which amounts (relative to catalyst concentration) of NaBAr$^F_4$ or 15-crown-5 were added to start or stop the reaction.

The crown ether moiety and the dual cofactors NH_3 and Na^+ are all needed to achieve switchable catalysis of crotononitrile hydroamination. To systematically study the roles of each component, the reactivity of three other catalysts were compared: the ammine complex supported by a macrocycle-free diethylamine-based ligand, ^{Et}**NiNH$_3$**; the crown-containing aquo complex, ^{18c6}**NiOH$_2$**, an analogue of ^{18c6}**NiNH$_3$** that replaces ammonia with water as the H-bonding donor; and the complex without a monodentate ligand and only intramolecular crown ether binding to nickel, ^{18c6}**Ni**.

When diethylamino-substituted complex ^{Et}**NiNH$_3$** was subjected to the standard catalytic conditions, 3-morpholinobutanenitrile formed in 70% yield after 48 hours, even without Na^+. Under the same conditions but with 1 equiv NaBAr$^F_4$, the yield slightly decreased. Thus, there is no off state for this catalyst and it is not suitable for applications requiring switchable reactivity. The comparison also provides mechanistic insight. Because the ^{Et}**NiNH$_3$** complex exhibits similar hydroamination activity to ^{18c6}**NiNH$_3$** activated with Na^+, the primary role of the Na^+ is likely to

disrupt the H–bonding between the crown and the ammine ligand, enabling substrate binding. This comparison also indicates that the proximal Na^+ ion does not induce significant inductive or electrostatic effects, or else the rate of ^{Et}**NiNH$_3$** with and without Na^+ would differ (**SI Figure 69-70**).

Table 1. Yields of hydroamination of crotononitrile with morpholine catalyzed by nickel complexes, with and without $NaBAr^F{}_4$ after 48 hours. Conditions: 6 mM Ni (5 mol%), 6 mM $NaBAr^F{}_4$, 120 mM morpholine, and 240 mM crotononitrile, with HMDSO internal standard, in chlorobenzene at 25°C. Uncertainty is estimated to be 2% based on duplicate runs.

	^{18c6}**NiNH$_3$**	^{Et}**NiNH$_3$**	^{18c6}**Ni**	^{18c6}**NiOH$_2$**
final yield, no Na^+	2.7%	70%	67%	62%
final yield, with Na^+	53%	66%	89%	86%
initial reactivity ratio[a]	59	1.0	1.7	3.9

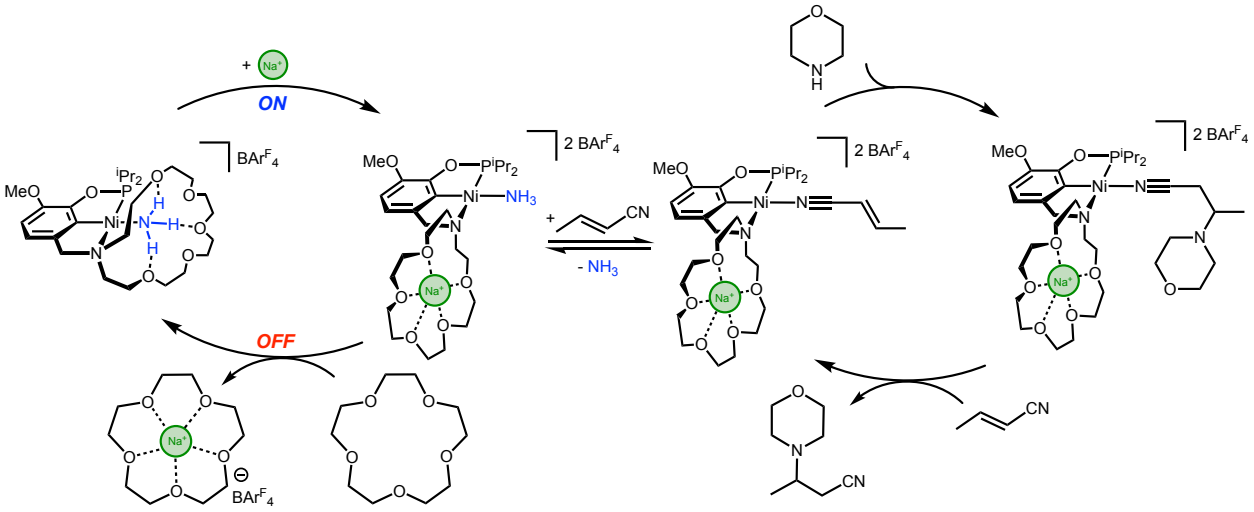
[a] the reactivity ratio is the ratio of the initial rate without salt and with $NaBAr^F{}_4$.

Comparisons were also carried out with ^{18c6}**NiOH$_2$**, which also features a H-bonding network. The H-bonding network was found to be weaker in the aquo complex, based on the reaction of ^{18c6}**NiOH$_2$** with 1 equiv NH_3 resulting in full conversion to nickel ammine ^{18c6}**NiNH$_3$** (**Figure 2A**). When ^{18c6}**NiOH$_2$** is subjected to standard conditions in the absence of $NaBAr^F{}_4$, a yield of 62% for 3-morpholinobutanenitrile is obtained. The aquo is therefore not a suitable secondary cofactor because it does not adequately gate access of the substrate to the active site. Catalysis proceeds even without the Na^+ cofactor present, preventing switchable reactivity. When $NaBAr^F{}_4$ is present, the yield increased to 86%. We attribute this to weakening of the H-bonding network making aquo ligand displacement even easier.

Similar behavior was observed for complex ^{18c6}**Ni**, in which a crown ether oxygen atom is bound directly to nickel. This catalyst lacking a H-bonding network produces 3-morpholinobutanenitrile in 67% yield, increasing to 89% in the presence of $NaBAr^F{}_4$. This is

consistent with the model studies above that show nitriles can readily displace the crown ether oxygen, again showing that the ammonia ligand is a crucial cofactor enabling switchable catalysis. Only ^{18c6}**NiNH$_3$** demonstrates on/off switchable behavior. These results emphasize the importance of the ammonia cofactor and the macrocycle working together to produce a gate that prevents nitrile and amine binding to the active site — yet this gate can still be opened using Na^+ cofactors to give good catalytic activity.

Scheme 4. Proposed mechanism of hydroamination reactions catalyzed by ^{18c6}**NiNH$_3$**.



The results observed in the catalytic reactions by ^{18c6}**NiNH$_3$** align nicely with the switchable ligand substitution reactions described earlier. When there is no Na^+ present, the nickel system is in the off state and minimal catalysis takes place (**Scheme 4**). Addition of Na^+ turns the system on, opening the gate and allowing for the nitrile substrate to displace the ammonia ligand to enable catalysis. Switchable hydroamination is possible with this system since the key step in the mechanism is proposed to be substrate binding to the metal center.[30] The on/off states can be differentiated by $^{31}P\{^1H\}$ NMR during catalysis. During the off state only one resonance signal for ^{18c6}**NiNH$_3$** is observed. In contrast, both ^{18c6}**NiNH$_3$** and a nickel crotononitrile species are observed throughout the on state (**SI Figure 77**). Additionally, increasing the concentration of

$NaBAr^F_4$ changes the ratio between the crotononitrile nickel species and ^{18c6}**NiNH$_3$**, resulting in higher yields in catalysis (**SI Figure 76**).

One significant challenge in switchable catalysis is the development of systems that can perform reactions with a wider range of substrates.[6] The difficulty arises from substrates that are often incompatible with reaction conditions and/or catalyst. For instance, with previous pincer-crown ether systems, switchable catalysis was not possible with neutral strongly donating ligands like nitriles.[24] These substrates were able to displace the hemilabile crown-ether donors without cofactors present, leading to the breakdown of the gating mechanism, so no controlled catalysis was possible. The control of H-bonding networks using dual cofactors provides a solution to this challenge, enabling switchable activity with a greater substrate scope.

Another notable challenge is that many (though certainly not all) systems exhibit only modest differences in on and off states of catalysis.[6] In comparison to previous pincer-crown ether systems, the dual cofactor enables a high degree of differences between two states of catalytic activity (**Table 1**). Ultimately, the ability to control H-bonding networks to regulate substrate access to a transition metal active site is a promising strategy that can improve reactivity ratios and may engender new forms of reactivity.

Conclusion

Pincer-crown ether nickel complexes have the ability to be regulated with two different cofactors: an ammonia molecule that enables a H-bonding network between the primary and secondary coordination sphere and Na^+ ion that is able to break the network to form cation-dipole interactions in the secondary coordination sphere. These interactions have been leveraged for a new approach to switchable catalysis through control of the H-bond network. Thermodynamic studies of pincer-crown ether complexes and non-macrocyclic variants confirm the essential role

of both cofactors in achieving on and off switching. The dual cofactor approach is a unique strategy to achieve an on/off system capable of withstanding relatively strong donor substrates that often disrupt gates in other systems. This molecular model draws analogies from enzymatic systems that regulate catalytic activity through H-bonding networks, while also enabling advances in switchable catalysis.

Supporting Information

Experimental details and characterization data (PDF)

Accession codes: CCDC 2295750-2295755 contains the supplementary crystallographic data for this paper. This datum can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

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References

(1) Gora, A.; Brezovsky, J.; Damborsky, J. Gates of Enzymes. *Chem. Rev.* **2013**, *113* (8), 5871–5923. https://doi.org/10.1021/cr300384w.
(2) Page, M.; Di Cera, E. Is Na+ a Coagulation Factor? *Thromb Haemost* **2006**, *95* (06), 920–921. https://doi.org/10.1160/TH06-05-0239.
(3) Hritz, J.; Žoldák, G.; Sedlák, E. Cofactor Assisted Gating Mechanism in the Active Site of NADH Oxidase from Thermus Thermophilus. *Proteins* **2006**, *64* (2), 465–476. https://doi.org/10.1002/prot.20990.
(4) Nechushtai, R.; Lammert, H.; Michaeli, D.; Eisenberg-Domovich, Y.; Zuris, J. A.; Luca, M. A.; Capraro, D. T.; Fish, A.; Shimshon, O.; Roy, M.; Schug, A.; Whitford, P. C.; Livnah, O.; Onuchic, J. N.; Jennings, P. A. Allostery in the Ferredoxin Protein Motif Does Not Involve a Conformational Switch. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108* (6), 2240–2245. https://doi.org/10.1073/pnas.1019502108.
(5) Li, Q.-A.; Mavrodi, D. V.; Thomashow, L. S.; Roessle, M.; Blankenfeldt, W. Ligand Binding Induces an Ammonia Channel in 2-Amino-2-Desoxyisochorismate (ADIC) Synthase PhzE. *Journal of Biological Chemistry* **2011**, *286* (20), 18213–18221. https://doi.org/10.1074/jbc.M110.183418.
(6) Blanco, V.; Leigh, D. A.; Marcos, V. Artificial Switchable Catalysts. *Chem. Soc. Rev.* **2015**, *44* (15), 5341–5370. https://doi.org/10.1039/C5CS00096C.
(7) Ginovska, B.; Gutiérrez, O. Y.; Karkamkar, A.; Lee, M.-S.; Lercher, J. A.; Liu, Y.; Raugei, S.; Rousseau, R.; Shaw, W. J. Bioinspired Catalyst Design Principles: Progress in Emulating Properties of Enzymes in Synthetic Catalysts. *ACS Catal.* **2023**, 11883–11901. https://doi.org/10.1021/acscatal.3c00320.
(8) Thaggard, G. C.; Haimerl, J.; Fischer, R. A.; Park, K. C.; Shustova, N. B. Traffic Lights for Catalysis: Stimuli-Responsive Molecular and Extended Catalytic Systems. *Angew Chem Int Ed* **2023**, *62* (29), e202302859. https://doi.org/10.1002/anie.202302859.
(9) Winkler, C. K.; Schrittwieser, J. H.; Kroutil, W. Power of Biocatalysis for Organic Synthesis. *ACS Cent. Sci.* **2021**, *7* (1), 55–71. https://doi.org/10.1021/acscentsci.0c01496.
(10) Deng, S.; Jolly, B. J.; Wilkes, J. R.; Mu, Y.; Byers, J. A.; Do, L. H.; Miller, A. J. M.; Wang, D.; Liu, C.; Diaconescu, P. L. Spatiotemporal Control for Integrated Catalysis. *Nat Rev Methods Primers* **2023**, *3* (1), 28. https://doi.org/10.1038/s43586-023-00207-0.

(11) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. Enzyme Mimics Based upon Supramolecular Coordination Chemistry. *Angew. Chem. - Int. Ed.* **2011**, *50*, 114.
(12) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 1: Non-Covalent Interactions as a Tool for Building and Modifying Homogeneous Catalysts. *Chem. Soc. Rev.* **2014**, *43*, 1660.
(13) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. Supramolecular Catalysis. Part 2: Artificial Enzyme Mimics. *Chem. Soc. Rev.* **2014**, *43*, 1734.
(14) Vlatković, M.; Collins, B. S. L.; Feringa, B. L. Dynamic Responsive Systems for Catalytic Function. *Chem. Eur. J.* **2016**, *22* (48), 17080–17111. https://doi.org/10.1002/chem.201602453.
(15) Ali, M. H.; Imperiali, B. Protein Oligomerization: How and Why. *Bioorganic & Medicinal Chemistry* **2005**, *13* (17), 5013–5020. https://doi.org/10.1016/j.bmc.2005.05.037.
(16) Rowlett, R. S. Structure and Catalytic Mechanism of the β-Carbonic Anhydrases. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **2010**, *1804* (2), 362–373. https://doi.org/10.1016/j.bbapap.2009.08.002.
(17) Barman, S. K.; Jones, J. R.; Sun, C.; Hill, E. A.; Ziller, J. W.; Borovik, A. S. Regulating the Basicity of Metal–Oxido Complexes with a Single Hydrogen Bond and Its Effect on C–H Bond Cleavage. *J. Am. Chem. Soc.* **2019**, *141* (28), 11142–11150. https://doi.org/10.1021/jacs.9b03688.
(18) Lee, J. L.; Ross, D. L.; Barman, S. K.; Ziller, J. W.; Borovik, A. S. C–H Bond Cleavage by Bioinspired Nonheme Metal Complexes. *Inorg. Chem.* **2021**, *60* (18), 13759–13783. https://doi.org/10.1021/acs.inorgchem.1c01754.
(19) Reek, J. N. H.; De Bruin, B.; Pullen, S.; Mooibroek, T. J.; Kluwer, A. M.; Caumes, X. Transition Metal Catalysis Controlled by Hydrogen Bonding in the Second Coordination Sphere. *Chem. Rev.* **2022**, *122* (14), 12308–12369. https://doi.org/10.1021/acs.chemrev.1c00862.
(20) McGuirk, C. M.; Mendez-Arroyo, J.; Lifschitz, A. M.; Mirkin, C. A. Allosteric Regulation of Supramolecular Oligomerization and Catalytic Activity via Coordination-Based Control of Competitive Hydrogen-Bonding Events. *J. Am. Chem. Soc.* **2014**, *136* (47), 16594–16601. https://doi.org/10.1021/ja508804n.
(21) McGuirk, C. M.; Stern, C. L.; Mirkin, C. A. Small Molecule Regulation of Self-Association and Catalytic Activity in a Supramolecular Coordination Complex. *J. Am. Chem. Soc.* **2014**, *136* (12), 4689–4696. https://doi.org/10.1021/ja500214r.
(22) McGuirk, C. M.; Mendez-Arroyo, J.; d'Aquino, A. I.; Stern, C. L.; Liu, Y.; Mirkin, C. A. A Concerted Two-Prong Approach to the *in Situ* Allosteric Regulation of Bifunctional Catalysis. *Chem. Sci.* **2016**, *7* (11), 6674–6683. https://doi.org/10.1039/C6SC01454B.
(23) Beswick, J.; Blanco, V.; De Bo, G.; Leigh, D. A.; Lewandowska, U.; Lewandowski, B.; Mishiro, K. Selecting Reactions and Reactants Using a Switchable Rotaxane Organocatalyst with Two Different Active Sites. *Chem. Sci.* **2015**, *6* (1), 140–143. https://doi.org/10.1039/C4SC03279A.
(24) Acosta-Calle, S.; Miller, A. J. M. Tunable and Switchable Catalysis Enabled by Cation-Controlled Gating with Crown Ether Ligands. *Acc. Chem. Res.* **2023**, *56* (8), 971–981. https://doi.org/10.1021/acs.accounts.3c00056.
(25) Yoo, C.; Dodge, H. M.; Miller, A. J. M. Cation-Controlled Catalysis with Crown Ether-Containing Transition Metal Complexes. *Chem. Commun.* **2019**, *55* (35), 5047–5059. https://doi.org/10.1039/C9CC00803A.

(26) Camp, A. M.; Kita, M. R.; Blackburn, P. T.; Dodge, H. M.; Chen, C.-H.; Miller, A. J. M. Selecting Double Bond Positions with a Single Cation-Responsive Iridium Olefin Isomerization Catalyst. *J. Am. Chem. Soc.* **2021**, *143* (7), 2792–2800. https://doi.org/10.1021/jacs.0c11601.
(27) Lifschitz, A. M.; Rosen, M. S.; McGuirk, C. M.; Mirkin, C. A. Allosteric Supramolecular Coordination Constructs. *J. Am. Chem. Soc.* **2015**, *137* (23), 7252–7261. https://doi.org/10.1021/jacs.5b01054.
(28) Smith, J. B.; Kerr, S. H.; White, P. S.; Miller, A. J. M. Thermodynamic Studies of Cation–Macrocycle Interactions in Nickel Pincer–Crown Ether Complexes Enable Switchable Ligation. *Organometallics* **2017**, *36* (16), 3094–3103. https://doi.org/10.1021/acs.organomet.7b00431.
(29) Smith, J. B.; Camp, A. M.; Farquhar, A. H.; Kerr, S. H.; Chen, C.-H.; Miller, A. J. M. Organometallic Elaboration as a Strategy for Tuning the Supramolecular Characteristics of Aza-Crown Ethers. *Organometallics* **2019**, *38* (22), 4392–4398. https://doi.org/10.1021/acs.organomet.9b00462.
(30) Arunan, E.; Desiraju, G. R.; Klein, R. A.; Sadlej, J.; Scheiner, S.; Alkorta, I.; Clary, D. C.; Crabtree, R. H.; Dannenberg, J. J.; Hobza, P.; Kjaergaard, H. G.; Legon, A. C.; Mennucci, B.; Nesbitt, D. J. Definition of the Hydrogen Bond (IUPAC Recommendations 2011). *Pure and Applied Chemistry* **2011**, *83* (8), 1637–1641. https://doi.org/10.1351/PAC-REC-10-01-02.
(31) Colquhoun, H. M.; Lewis, D. F.; Williams, D. J. Crown Ethers as Second-Sphere Ligands. The Interactions of Transition-Metal Ammines with 18-Crown-6 and Dibenzo-I8-Crown-6 t. *J. CHEM. SOC. DALTON TRANS.* **1983**.
(32) Akutagawa, T.; Takamatsu, N.; Hasegawa, T.; Nakamura, T.; Inabe, T. Crystal Structure and Magnestism of [Ni(Dmit) 2] − Salts With Supramolecular Cations of M + (15-Crown-5). *Molecular Crystals and Liquid Crystals* **2002**, *376* (1), 39–46. https://doi.org/10.1080/10587250210736.
(33) Kita, M. R.; Miller, A. J. M. Cation-Modulated Reactivity of Iridium Hydride Pincer-Crown Ether Complexes. *J. Am. Chem. Soc.* **2014**, *136* (41), 14519–14529. https://doi.org/10.1021/ja507324s.
(34) Gu, N. X.; Oyala, P. H.; Peters, J. C. Hydrazine Formation via Coupling of a Nickel(III)–NH_2 Radical. *Angew. Chem. Int. Ed.* **2021**, *60* (8), 4009–4013. https://doi.org/10.1002/anie.202013119.
(35) Dunn, P. L.; Cook, B. J.; Johnson, S. I.; Appel, A. M.; Bullock, R. M. Oxidation of Ammonia with Molecular Complexes. *J. Am. Chem. Soc.* **2020**, *142* (42), 17845–17858. https://doi.org/10.1021/jacs.0c08269.
(36) Smith, J. B.; Miller, A. J. M. Connecting Neutral and Cationic Pathways in Nickel-Catalyzed Insertion of Benzaldehyde into a C–H Bond of Acetonitrile. *Organometallics* **2015**, *34* (19), 4669–4677. https://doi.org/10.1021/acs.organomet.5b00405.
(37) Fielding, L. Determination of Association Constants (Ka) from Solution NMR Data. *Tetrahedron* **2000**, *56* (34), 6151–6170. https://doi.org/10.1016/S0040-4020(00)00492-0.
(38) Thordarson, P. Determining Association Constants from Titration Experiments in Supramolecular Chemistry. *Chem. Soc. Rev.* **2011**, *40* (3), 1305–1323. https://doi.org/10.1039/C0CS00062K.

(39) Fadini, L.; Togni, A. Asymmetric Hydroamination of Acrylonitrile Derivatives Catalyzed by Ni(II)-Complexes. *Tetrahedron: Asymmetry* **2008**, *19* (22), 2555–2562. https://doi.org/10.1016/j.tetasy.2008.11.010.
(40) Mitsudo, K.; Imura, T.; Yamaguchi, T.; Tanaka, H. Preparation of a Cationic Bisoxazolinic Nickel Pincer Catalyst and Its Applications to Michael Addition and Mizoroki–Heck Reaction. *Tetrahedron Letters* **2008**, *49* (51), 7287–7289. https://doi.org/10.1016/j.tetlet.2008.10.029.
(41) Castonguay, A.; Spasyuk, D. M.; Madern, N.; Beauchamp, A. L.; Zargarian, D. Regioselective Hydroamination of Acrylonitrile Catalyzed by Cationic Pincer Complexes of Nickel(II). *Organometallics* **2009**, *28* (7), 2134–2141. https://doi.org/10.1021/om800840u.
(42) Lapointe, S.; Zargarian, D. On the Mechanism of Ni(II)-Promoted Michael-Type Hydroamination of Acrylonitrile and Its Substituted Derivatives. *Dalton Trans.* **2016**, *45* (40), 15800–15810. https://doi.org/10.1039/C6DT02105K.