Cation-Controlled Catalysis with Crown Ether-Containing Transition Metal Complexes

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FEATURE ARTICLE

Cation-Controlled Catalysis with Crown Ether-Containing Transition Metal Complexes

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Transition metal complexes that incorporate crown ethers into the supporting ligands have emerged as a powerful class of catalysts capable of cation-tunable reactivity. Cations held in the secondary coordination sphere of a transition metal catalyst can pre-organize or activate substrates, induce local electric fields, adjust structural conformations, or even modify bonding in the primary coordination sphere of the transition metal. This Feature Article begins with a non-comprehensive review of the structural motifs and catalytic applications of crown ether-containing transition metal catalysts, then proceeds to detail the development of catalysts based on "pincer-crown ether" ligands that bridge the primary and secondary coordination spheres.

Introduction

The discovery of crown ethers in 1960 is often considered to mark the birth of supramolecular chemistry.[1–3] Thousands of crown ethers have now been synthesized,[4–7] tailored to host an array of ionic and neutral guests. Fundamental studies of cation–crown interactions helped reveal the potential utility of crown ethers in applications ranging from phase transfer catalysis to separations science and ion sensing. Increased structural and dynamic complexity, in particular the ability to reversibly engage and disengage cation–crown interactions, underpinned the development of molecular machines.[8–10]

By the 1980s, crown ethers were being incorporated into transition metal complexes. Most designs featured distinct binding pockets, one for a transition metal and one for another metal cation, leading to applications including ion pair recognition, dual activation of small molecules, fluorescent sensing, and redox tuning. The synthesis and applications of these structures have been comprehensively reviewed.[11,12]

This Feature Article considers the roles that crown ethers can play in catalysis, where there has been less activity compared to the aforementioned applications. While supramolecular systems beyond crown ethers are outside the scope of this Feature Article, there are several excellent reviews that highlight the full structural diversity of supramolecular catalysis.[13–21] Here, a non-comprehensive review of the structural designs of crown ether-containing transition metal complexes will be provided at the outset. The various roles that crown ethers can play in cation-controlled catalysis will then be discussed, highlighting examples in substrate preorganization, substrate activation, and ligand conformational gating. The uncommon ability to tune the primary coordination sphere through cation–crown interactions will be explored in detail using the "pincer-crown ether" ligand framework, which incorporates an aza-crown ether moiety into a meridional tridentate organometallic ligand.

Classifying transition metal complexes that incorporate features of crown ethers

In this review, the term "metalla-crown ether" is used to describe the broad array of transition metal complexes that incorporate structural features of crown ether macrocycles.[12] The similarly named "metallacrowns" are a distinct class of cyclic polymetallic structures.[22] Another related class of complexes are metallomacrocycles, which can be defined in a way that would include metalla-crown ethers,[11] or in a way that focuses on polymetallic clusters.[23] Because the nomenclature describing transition metal complexes with crown ether features is not deeply codified, this Perspective strives to clearly define terms and maintain consistency wherever possible.

Among the large array of metalla-crown ethers, some structural trends emerge based on the position of the macrocycle relative to the transition metal center. Three categories of transition metal complexes bearing crown ethers can be defined: enchained, pendent, and bridging. Figure 1 illustrates the three classes in conceptual form. This section compares the salient features of these different classes of metalla-crown ethers.

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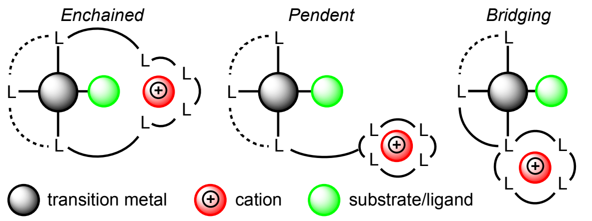


Figure 1. Schematic representation of different metalla-crown ether designs, where L denotes Lewis basic sites.

Enchained metalla-crown ethers are comprised of a single large macrocycle that contains distinct transition metal and cation binding sites. Enchained structures can be produced from a single organic macrocycle (or macrobicycle, also called "lateral macrobicyclic" molecules)[24] or through chelation of a bidentate poly(ether) to produce a metal-containing macrocycle. Figure 2 collects representative examples of enchained metalla-crown ethers.

Many of the earliest examples of metalla-crown ethers can be classified as enchained.[24–27] Several examples with pyridine-containing[24,28] macrocycles and Schiff-base-containing[27,29–33] macrocycles marked this early period of development. Other noteworthy systems are based on tetra-aza-macrocycles that bind the transition metal center.[34,35] Many of these studies aimed to establish the fundamental host–guest properties of metalla-crown ethers and explore the bonding motifs in heterobimetallic systems, including metal–metal interactions.[36,37]

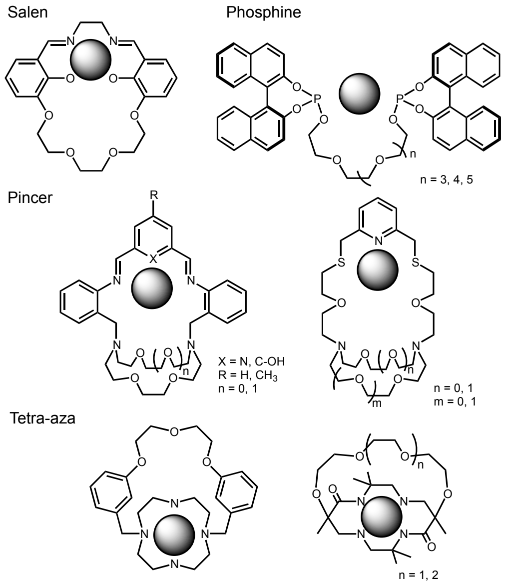


Figure 2. Representative enchained metalla-crown ethers, where the grey sphere represents a transition metal center and any additional ancillary ligands.

Another noteworthy class of enchained metalla-crown ethers feature bidentate phosphine ligands (to bind transition metals) linked by a poly(ether) chain (to bind cations, Figure 2).[12,38–49] In many of the phosphine-based systems the free ligand is not macrocyclic. It is not until the two phosphine-decorated ends of the poly(ether) bind to a transition metal that a binding pocket is presented. Molybdenum carbonyl complexes were the focus of initial studies,[25,26] and were used as a platform for the development of NMR titration methods for metalla-crown ethers.[40] Related amine-containing macrocycles have also been explored.[50,51]

In *pendent metalla-crown ethers*, the transition metal center is tethered to a macrocycle as shown in Figure 3. These systems provide good control over spatial separation and orientation, with different designs holding the guest either in close proximity or far from the transition metal center. Starting with the pioneering monodentate ligand of McLain,[52,53] phosphine-based systems have been widely explored. Another early crown ether-containing phosphine ligand was reported as part of a phase transfer catalysis study.[54,55] Such systems remain under active study,[56] with examples of cation-promoted migratory insertion[57] and the development of tridentate phosphine-based metalla-crown ethers.[58]

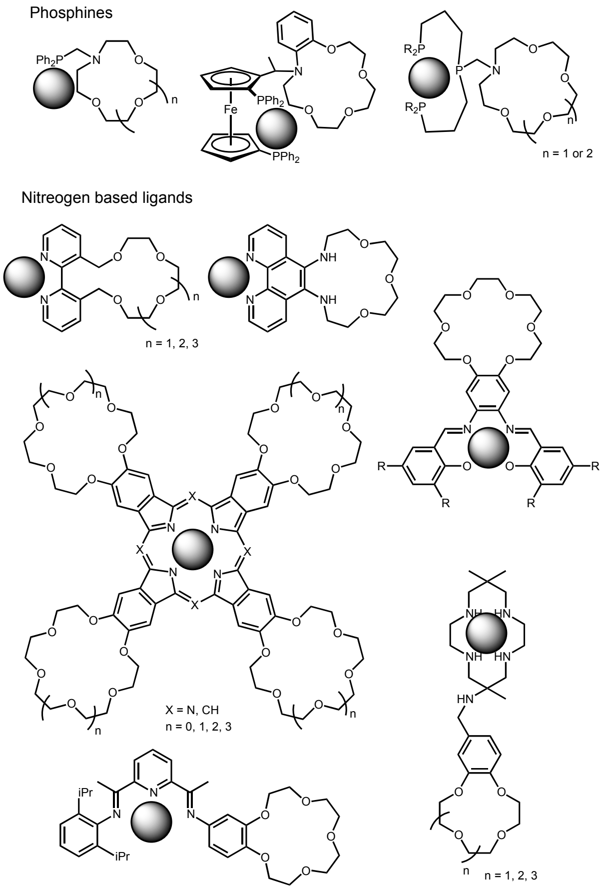


Figure 3. Representative pendent metalla-crown ethers, where the grey sphere represents a transition metal center and any additional ancillary ligands.

Several nitrogen donor ligands have been fitted with pendent crown ethers (Figure 3). Porphyrin-based systems[59] were developed early on.[60–64] Porphyrazine-based systems[65–67] and phthalocyanine-based systems[68–77] have also been studied extensively. These systems have shown promising behavior related to sensing, functional materials, and catalysis.[59] Other chelates such as bipyridine[78–84] ligands and Schiff-base[85–88] (salen-type) ligands have received special attention in the development of pendent crown ether systems.[89] Gilbertson has led the development of crown ether-appended pyridinediimine ligands for applications in redox tuning and small molecule activation.[90–92]

In *bridging metalla-crown ethers*, one of the cation receptor site donors (permanently or temporarily) binds to the transition metal center (Figure 4). Some bridging systems can also be classified as enchained, wherein one or more ether donor binds the transition metal as observed for a few heavy metal complexes.[93,94]

The Miller group recently introduced "pincer-crown ether" ligands in which the amine of an aza-crown ether acts as one of the three donors of a pincer ligand for transition metal ions, leaving four or five oxygen donors available to bind a cationic guest.[95] With the crown ether in close proximity to the metal center, the oxygen atoms can also donate to the transition metal in the absence of a suitable cationic guest.

The Fan group has incorporated aza-crown ether moieties into phosphine ligands and demonstrated that the macrocycle ethers bind the rhodium center.[96] Whereas the ether donors typically only interact with a cationic guest in the aforementioned phosphine ligands with pendent crown ethers, here the oxygen and nitrogen donors also interact with the rhodium center directly. A related series of complexes features non-macrocyclic poly(ether) groups bridged to the transition metal center.[97–99]

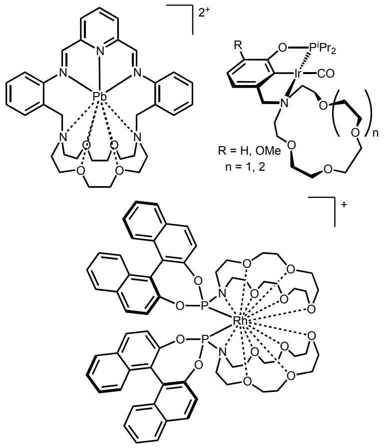


Figure 4. Representative bridging metalla-crown ethers.

Across all the three classifications, a few structural themes emerge. A key distinction is the position of the guest binding pocket relative to the transition metal center. Enchained systems almost always hold the guest in a position proximal to the transition metal center. Similarly, the guest binding pocket is necessarily located close to the transition metal binding pocket in bridging systems. Pendent metalla-crown ethers, on the other hand, can be designed to position the guest binding pocket far from the transition metal center (although there are examples with proximal positions as well). This arrangement has found wide utility in sensing and redox tuning applications.[100]

Another consideration is the relative rigidity or flexibility of the metalla-crown ether. Many enchained systems feature a relatively rigid region for binding a transition metal ion and a more flexible poly(ether) region for binding alkali or alkaline earth metal cations. The diphosphine-based enchained systems are typically quite flexible. Pendent metalla-crown ethers can have very rigid structures (as in the porphyrin-based systems) or quite flexible structures (typified by the phosphine-based systems). The choice of flexibility in the design is often related to the desired application, with more rigid systems better suited for redox tuning or sensing and more flexible systems better suited for transition-metal-bound substrate interactions.

Metalla-crown Ethers in Catalysis

While metalla-crown ethers have found widespread utility in a range of areas, from sensing to molecular machines,[100–105] their use in catalysis remains less explored. Figure 5 illustrates how cation–crown interactions can enable phase transfer catalysis; support substrate activation by acid-base interactions or electrostatic effects; control complex conformational changes; and influence the primary coordination sphere by changing the ligand binding mode at the transition metal center. Some leading examples of crown ether-containing catalysts are highlighted in this section.

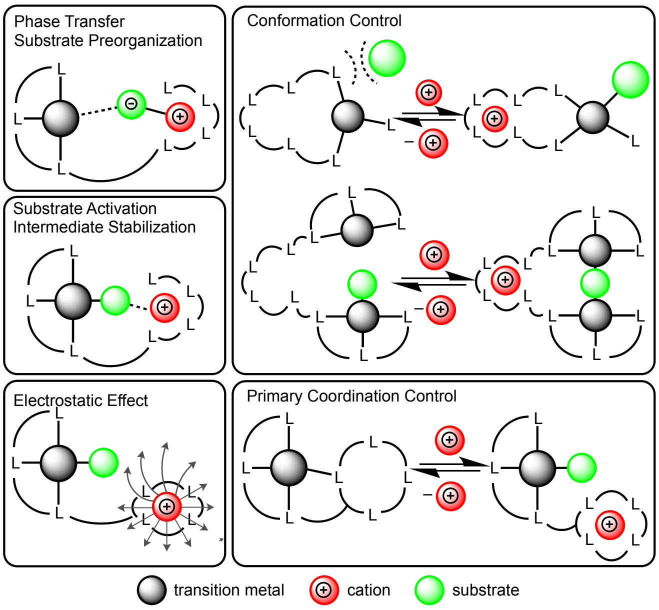
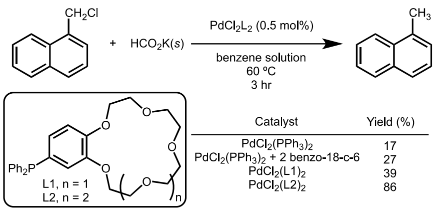


Figure 5. Modes of catalyst promotion in metalla-crown ethers.

Early applications of metalla-crown ethers in catalysis focused on *phase transfer*. The Okano group reported pendent-type phosphino-crown Pd catalysts for 1-chloromethylnaphthalene reduction with potassium formate (Scheme 1).[54,55] The reaction was faster with the crown-containing phosphine ligands than with the combination of PPh_3 and free benzo-18-crown-6, implicating a role of the crown ether improving solubility of the formate salts in organic solvent. Pendent metalla-crown ethers are convenient for this type of application because the macrocycle can be far from the transition metal center and still provide solubility.

Scheme 1. Example of *phase transfer* catalysis.



Ion pairing or ion-dipole interactions between a substrate and either the crown ether itself or a cation in the crown ether can result in *substrate preorganization*. By helping position the substrate in a precise location, higher rates and more selective reactions are possible. The Gilbertson group, for example, reported that pyridinediimine complexes with a pendent crown ether can facilitate NO_2^- reduction to NO. The reaction proceeds 6-fold faster in the presence of Na^+, which is attributed to the ability of the crown-bearing cation to bring the NO_2^- anion close to the Fe center (Figure 6).[91] Substrate preorganization can also influence selectivity. The crown-tethered ferrocenylphosphine ligand of Figure 6 improves both yield and enantioselectivity in Pd-catalyzed β-diketone allylation.[106,107] The ternary interaction involving the crown ether, alkali metal cation, and enolate anion results in effective enantiofacial selection. In a particularly impressive recent example, a manganese complex bearing two pendent crown ethers catalyzed site-selective aliphatic C–H oxidation.[108] The ammonium group of a protonated primary amine binds to one of the crown ethers, positioning one methylene unit near the manganese center and resulting in highly regioselective oxidation (Figure 6).

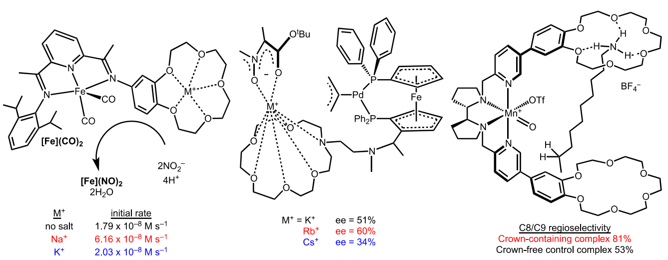


Figure 6. Examples of catalysts proposed to operate by *substrate preorganization*.

In some cases, the Lewis acidic cation is more directly involved in *activation and stabilization of substrates*. In influential stoichiometric studies, the groups of Powell and McLain independently demonstrated activation of carbonyl ligand by the Li^+ and Na^+ ions toward nucleophilic attack in metalla-crown ether with phosphine donors.[25,26,52] In a key catalytic application, the Gray group found that the selectivity of styrene hydroformylation by Rh enchained crown ether catalysts changes in the presence of Li^+ or Na^+ ions (Figure 7).[39] A specific interaction between the cation and a carbonyl or acyl ligand was hypothesized.

Clear demonstrations of direct substrate-cation interactions in catalysis remain rare, and the nature of these interactions (Lewis acid/base, electrostatic effects, electric field effects, steric adjustments, etc.) is often hard to characterize. In a related example, the Do group found that non-macrocyclic poly(ether)-based Ni and Pd catalysts support cation-modulated ethylene polymerization.[97–99] Electrostatic effects, conformation changes, and inductive electronic effects are all possible pathways of tuning.

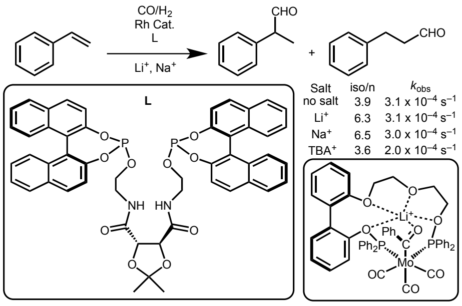


Figure 7. Cation-modulated rhodium-catalyzed hydroformylation and a molybdenum complex that models *substrate activation*.

Cationic charge embedded in the crown ether can be utilized to control redox potential by *electrostatic effects*. The Reinhoudt group reported a salen-based Ni complex having an enchained macrocycle moiety.[109] The incorporation of Ba^{2+} led to a shift in redox potential and enhanced the rate of electrocatalytic benzyl chloride reduction. The Yang group reported the same type of salen-based complex with Fe, catalyzing aerobic C-H oxidation of cyclohexene (Figure 8).[110] The cation binding not only accelerates the rate-determining oxidation of an organic hydroperoxide, but also inhibits the μ-oxo-forming deactivation pathway from the Fe(II) reaction with O_2. The Yang group also reported that a Mn nitride complex supported by the same ligand shows an enhanced rate of N_2 formation in the presence of cations.[18,111]

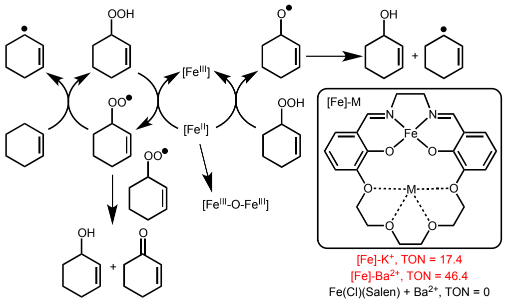


Figure 8. Example catalyst system with cation-enhanced oxidation attributed to *electrostatic effects*.

Cation binding can lead to dramatic changes in *catalyst conformation*, which can in turn change the reaction rate or selectivity. This strategy has received ample attention based on the concept of changing the catalyst structure to open or close substrate access to the active site, thus switching catalysis on or off.[13,18] An analogy to the “allosteric regulation” of biological systems provides further motivation, as noted in recent reviews.[13,112]

Smaller conformational changes can fine-tune the selectivity of a catalyst. Diphosphine ligand bite angle has a pronounced influence on activity and selectivity.[113–115] Catalysts bearing poly(ether)-based diphosphine ligands have been found to undergo cation-triggered conformational changes that influence bite angle and thus catalytic performance. Such systems have been studied extensively for asymmetric hydroformylation and hydrogenation.[41,116–122] Figure 9 summarizes some noteworthy systems for hydrogenation, hydroformylation and allylic substitution. Both enchained and pendent structures are present in Figure 9, and with appropriate design either motif can achieve the desired effect. Some ligands include two crown ether groups in close proximity, which enables cooperative cation binding that can effectively alter the diphosphine bite angle.[41]

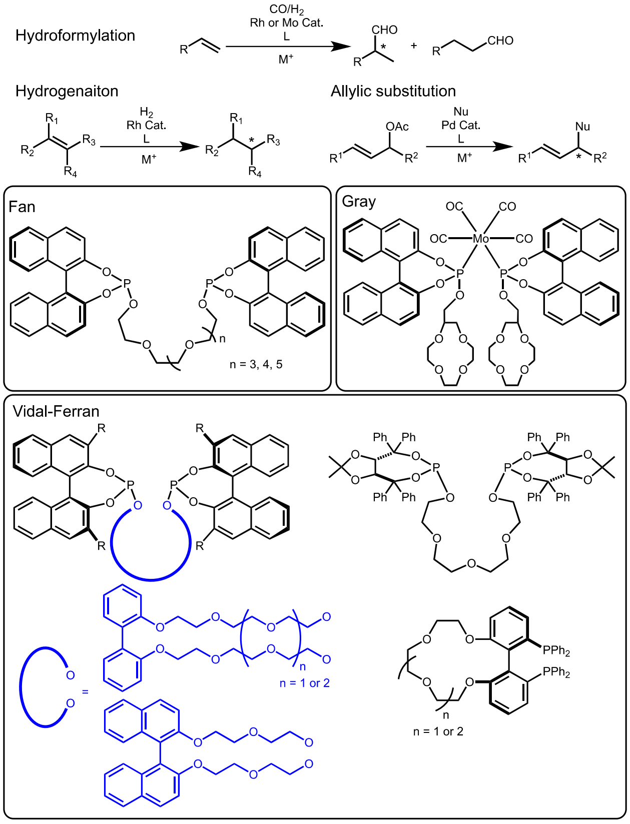
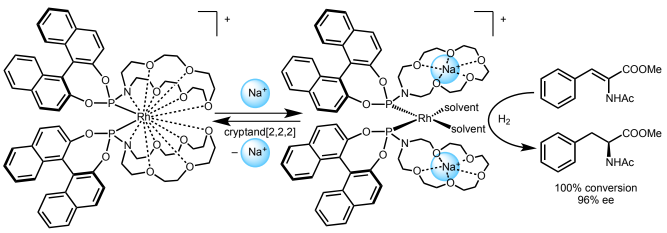


Figure 9. Three catalytic transformations of alkenes that have been controlled by cation addition when using appropriate diphosphine ligands designed for *conformation control*.

Controlled catalysis has also been achieved using bridging metalla-crown ethers that can influence the *primary coordination sphere of the transition metal*. The Fan group reported a rhodium complex supported by two crown ether-appended phosphoramidite ligands that provide additional donation from the oxygen donors of the macrocycles (Scheme 2). Addition of Na$^+$ is proposed to promote dissociation of the crown ether from the Rh center, opening binding sites for substrate access. Catalytic hydrogenation of dehydroamino acids can be reversibly switched on/off by addition/removal of Na$^+$ ion.

Scheme 2. A rhodium catalyst proposed to operate via *primary coordination control*.



Bridging metalla-crown ethers are uniquely suited for controlling substrate binding because the ionophore occupies a site in the primary coordination sphere. The close proximity of the macrocycle also raises the possibility of secondary coordination sphere interactions, wherein the crown ether holds a cation in position to interact with substrates or provide a local electric field. This class of metalla-crown ether has received little attention, however. The prototypical bridging “pincer-crown ether” system is the subject of the following sections.

Controlling the Primary Coordination Sphere in Pincer-Crown Ether Complexes: Tunable Hemilability and Controlled Catalysis

Introduction

Pincer-crown ether ligands incorporate an aza-crown ether into the design of a phosphinite pincer ligand. As shown in Figure 10, a modular synthesis enables facile elaboration to adjust the donor ability or nature of the macrocycle. So far, research has focused on aza-15-crown-5 and aza-18-crown-6 ethers.

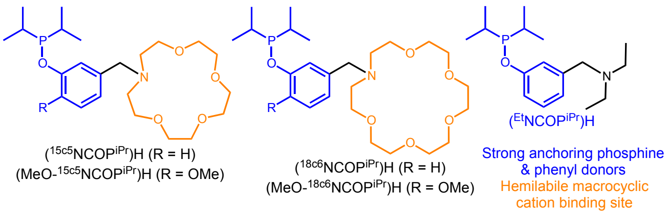


Figure 10. Pincer-crown ether ligands.

This section examines the ability of pincer-crown ether complexes to take on a variety of transition metal coordination modes, including interactions with the crown ether group that can be manipulated to achieve switchable reactivity and controlled catalysis.[95]

Pincer-crown ether transition metal binding modes

Pincer-crown ether ligands can adopt several distinct transition metal binding modes, “flexidentate” behavior that is enabled by the presence of several nitrogen and oxygen atoms of intermediate donor ability in the macrocycle. The amine and ether donors of the macrocycle can either donate to the primary coordination sphere of a transition metal center or dissociate to support cation–crown interactions in the secondary coordination sphere. The solid-state coordination modes of pincer-crown ether ligands have been established for a number of complexes, as summarized in Figure 11.

The tridentate (κ^3) transition metal binding mode most commonly associated with pincer ligands is observed when pincer-crown ether ligands are allowed to react with Ir(Cl)(CO)$_2$(*p*-toluidine).[123] In the resulting iridium(III) product, κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)(Cl), the pincer-crown ether ligand binds the transition metal through P,C,N coordination. With only the nitrogen donor binding to iridium, all oxygen donors of the macrocycle are held in the secondary coordination sphere of the complex.

Tridentate transition metal binding is also observed for square planar complexes with d^8 configurations.[124–126] Iridium carbonyl complexes of the type (NCOP)Ir(CO), with varying macrocycle size and backbone substitution patterns, have been prepared. Nickel halide complexes of the type (NCOP)Ni(X) (X = Cl, Br) have also been synthesized. The tridentate configuration makes available all possible ether donors, an ideal scenario for promoting cation–crown interactions. Structural details of the cation adducts of nickel complexes have been elucidated, confirming that the amine remains bound to the transition metal center while the four oxygen donors bind the cation (Figure 11).

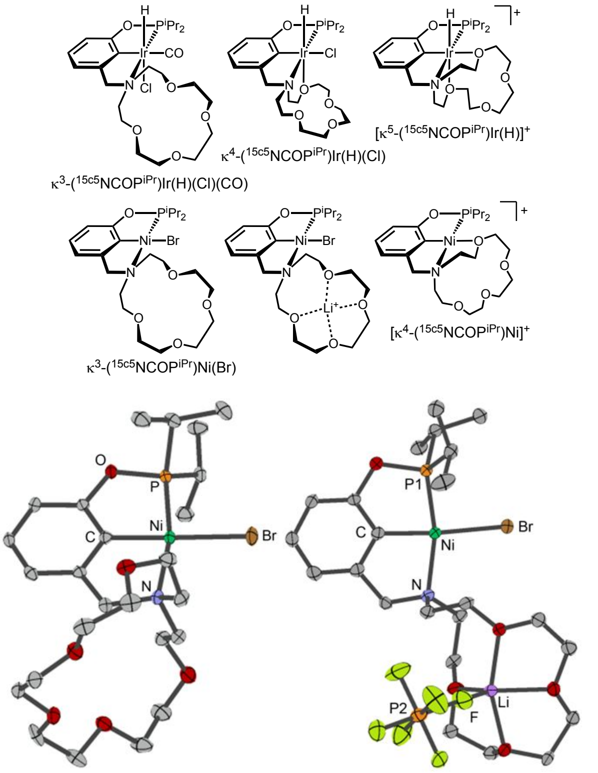


Figure 11. Different pincer-crown ether binding in iridium and nickel complexes. Adapted with permission from ref [124], copyright 2017 American Chemical Society.

Several tetradentate (κ^4) complexes have been structurally characterized, including the iridium(III) complex κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) shown in Figure 11.[127] In the tetradentate binding mode, in addition to the nitrogen donor, one crown ether oxygen donates to iridium to complete a pseudo-octahedral coordination sphere. Analogous coordination chemistry is observed upon halide abstraction from square planar κ^3-(NCOP)Ni(Br) to provide cationic tetradentate nickel complexes of the type [κ^4-(NCOP)Ni]$^+$.[124]

Pentadentate (κ^5) binding modes are also accessible via halide abstraction. Treatment of κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) with NaBAr$^F_4$ yields the cationic iridium(III) hydride complex [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$, in which two crown-ether oxygens bind iridium in the solid-state structure derived from X-ray diffraction studies.[127]

Insight into the transition metal binding mode of pincer-crown ether complexes in solution is important for understanding catalytic mechanisms, so efforts were made to compare the solid-state and solution coordination chemistry. To start, the solution structure of several aza-15-crown-5-based pincer-crown ether complexes was rigorously determined using a suite of multidimensional, multinuclear NMR experiments.[123] NOE experiments provided key evidence for κ^4 and κ^5 structures in solution. The chemical shifts of crown ether protons proved to be extremely sensitive to diamagnetic anisotropic effects arising from other ligands in the primary coordination sphere. This is reflected in a large difference in chemical shift (Δδ) for the two geminal protons on a crown ether methylene unit (Figure 12). Halide ligands have the most profound effect ($I^- > Br^- > Cl^-$), but a significant effect is observed for all complexes containing a bound crown ether oxygen.

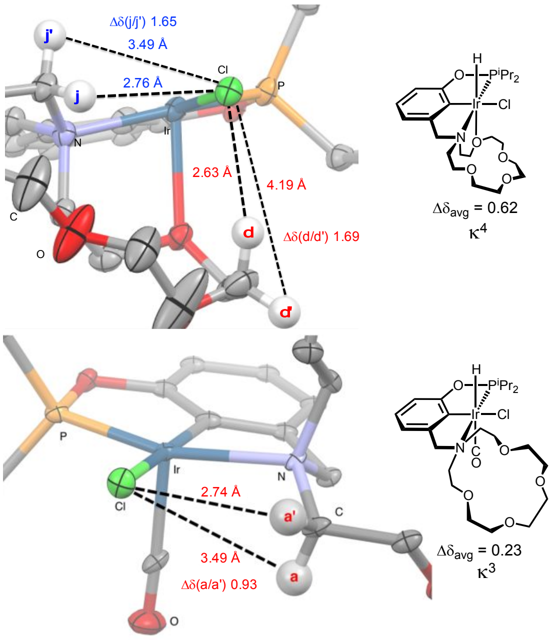


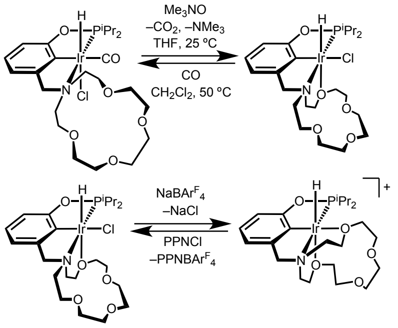
Figure 12. Structural representations of κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) and κ^3-(^{15c5}NCOP^{iPr})Ir(H)(Cl)(CO) showing origin of differences in chemical shift between geminal protons (Δδ) in the macrocycle. Adapted with permission from ref [123], copyright 2017 American Chemical Society.

The average change in chemical shift (Δδ$_{avg}$) for all crown ether protons, acquired rapidly via ^{1}H, ^{1}H–^{1}H COSY, and ^{1}H–^{13}C HSQC NMR experiments, accurately reflects the pincer-crown ether binding mode. The value Δδ$_{avg}$ for geminal crown ether protons is approximately two times larger when an oxygen is bound directly the metal center (κ^4 or κ^5) than when no oxygens are bound (κ^3). The method of $\Delta\delta$ analysis thus constitutes a reliable way to determine the binding mode of pincer crown ether complexes in solution (Figure 12). Such information is important for predicting the stability and reactivity of the complexes.

Changing pincer-crown ether transition metal binding modes

Addition or removal of external ligands has proven to be a useful strategy for moving between transition metal binding modes, as exemplified in Scheme 3. The carbonyl ligand in κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)(Cl) is lost (as CO_2) upon treatment with trimethylamine-N-oxide, resulting in the tetradentate complex κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl).[123] The transition metal coordination mode can be switched back by addition of CO.

Scheme 3. Synthetic methods for reversible switching of pincer-crown ether coordination mode.



Chloride abstraction from κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) leads to a second crown ether oxygen binding to iridium in the cationic complex [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$.[124,127] The reaction can be reversed by addition of a free halide ion (Scheme 3). Other donors, including coordinating solvents like acetonitrile, can also displace the weak ether donors.[127] The crown ether group helps avoid coordinative unsaturation: when removal of a ligand could leave a low-coordinate transition metal center, an ether donor can bind to complete the transition metal primary coordination sphere.

Switchable catalysis

The ability to switch between transition metal binding modes has been harnessed for applications in switchable catalysis, based on the observation that pincer crown-ether complexes with different binding modes exhibit distinct reactivity. Consider the example of olefin isomerization.[128] Tetradentate hydridochloride κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl), in which a single crown ether donor occupies the position trans to the hydride, is inactive for allylbenzene isomerization. The cationic, pentadentate complex [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$, however, in which two crown ether donors are bound directly to the metal center, is an active catalyst for allylbenzene isomerization. This is attributed to the stronger chloride donor preventing the cis substitution required for olefin binding and 1,2-insertion at the iridium center; exchanging a chloride ligand for a weak ether ligand cis to the hydride thus facilitates olefin binding.

These two activity states can be interconverted via chloride association/dissociation at iridium, suggesting a method for *in situ* switchable catalysis by toggling between the two complexes: the cationic, pentadentate complex is the “on” state and the neutral tetradentate complex is the “off” state of the catalyst. In a start/stop isomerization experiment monitored by ^{1}H NMR spectroscopy, tetradentate complex κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) was repeatedly activated to [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ then deactivated back to κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl). Switchable olefin isomerization is rare and primarily limited to redox switchable hemilabile ligands.[129,130]

A more careful investigation of the catalytic rate upon “switching on” the catalyst revealed a surprising trend. The rate of isomerization during the active portion of switchable catalysis ($t_{1/2}$ = 82 min^{-1}) was substantially faster than the rate of isomerization when isolated [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ was used as the catalyst. Monitoring the addition of 2 equivalents of NaBAr$^F_4$ to κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) by ^{1}H HMR spectroscopy revealed a new hydride intermediate. As shown in Figure 13, the rate of allylbenzene isomerization triggered by *in situ* Na$^+$ activation mirrors the rate of disappearance of the intermediate formed during halide abstraction. The highly active intermediate is proposed to be a bridging Na$^+$ adduct (Figure 13) along the pathway of chloride abstraction, with the increased activity attributed to the cation-macrocycle interaction preventing ether donation to iridium. A similar structure with a bridging halide was observed in the nickel complex [(Na$^+$@κ^3-^{15c5}NCOP^{iPr})Ni(Br)][BAr$^F_4$].[124]

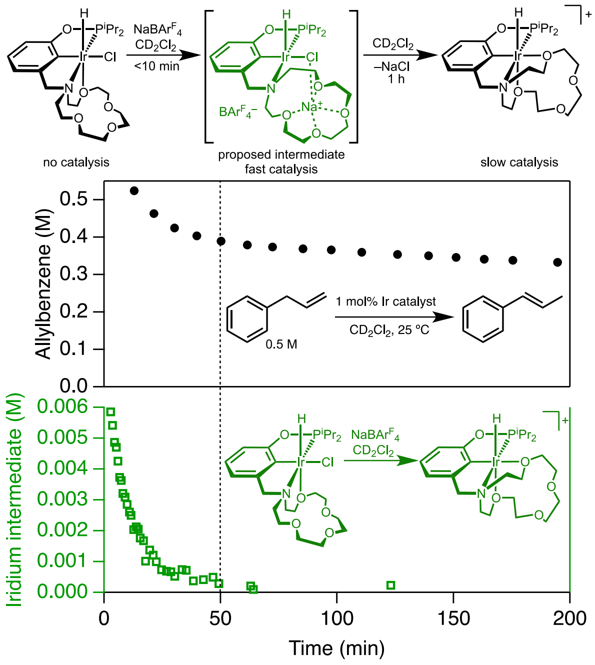


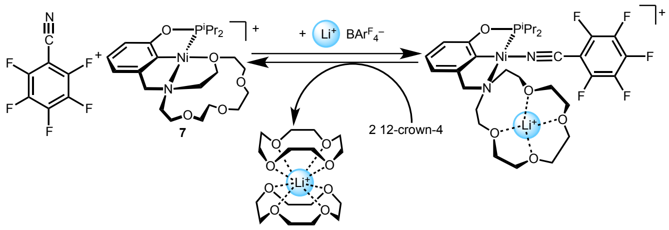
Figure 13. Scheme showing proposed intermediate and plots of separate experiments monitoring allylbenzene consumption (filled black circles) after *in situ* activation of κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) with NaBAr$^F_4$ and monitoring the concentration of iridium-containing intermediate formed during halide abstraction (in the absence of olefin) from κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl) (empty green squares).

Tunable catalysis

As might be surmised from the increase in activity of the Na^+ adduct intermediate, further catalytic enhancement can be achieved by intentionally engaging cation–macrocycle interactions. In iridium-catalyzed olefin isomerization, the pentadentate iridium complex [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ slowly catalyzes allylbenzene isomerization to β-methyl styrene (TOF = 1.8 h^{-1}). In the presence of NaBAr$^F_4$, catalysis occurs roughly three times faster (TOF = 5.4 h^{-1}). A much more dramatic rate enhancement occurs when LiBAr$^F_4$ is present in solution. In this regime, allylbenzene isomerization is complete in minutes (maximum TOF = 2750 h^{-1}).[128] The dramatic rate enhancement is consistent with cation–crown interactions facilitating olefin substrate binding to the transition metal center by stabilizing a pincer-crown ether binding mode in which all ethers are dissociated.

A related nickel complex serves as a model for cation-modulated substrate binding (Scheme 4).[124] Precise control over substrate binding has been realized with the tetradentate-bound complex [κ^4-(^{15c5}NCOP^{iPr})Ni]$^+$. In CD_2Cl_2 solution, pentafluorobenzonitrile does not bind to the nickel complex, indicating that displacement of the crown ether ligand by the Lewis base is unfavorable. Addition of 1 equivalent of Li^+ triggers quantitative nitrile binding in conjunction with lithium intercalation into the crown. This cation-induced substrate binding is dependent on the binding affinity of the crown ether complex for different cations: addition of Na^+ engages only partial nitrile binding, and addition of K^+ does not lead to any observable reaction. Furthermore, this is a reversible process: addition of 2 equivalents of 12-crown-4 to the nitrile adduct sequesters the Li^+ and leads to nitrile ligand ejection and coordination of a crown-ether oxygen to nickel.

Scheme 4. Lithium-mediated switchable ligand binding and release.



The hemilability and cation binding ability of the crown ether group allows for direct modulation of the primary coordination sphere of the transition metal. When substrates and cations interact with pincer-crown ether complexes, the nature of the bridging interaction changes, thereby providing control over catalysis.

Controlling the Secondary Coordination Sphere in Pincer-Crown Ether Complexes: Promoting Reactions via Cation-Substrate Interactions

Introduction

Chemists have long recognized the potential of tuning reactivity via secondary coordination sphere interactions. Often inspired by the functionality-rich, three-dimensional structures of enzyme active sites, an array of synthetic molecular systems featuring functional groups in the secondary coordination sphere have been developed.[131–133]

Lewis acid promotion via the secondary coordination sphere has received attention since at least the 1980s, when Shriver demonstrated Lewis acid-promoted stoichiometric carbonylation reactions and McLain developed pendent metalla-crown ether complexes to support cation stabilization of acyl ligands.[52,53,134] As noted above, very few catalytic reactions have been promoted using this strategy.

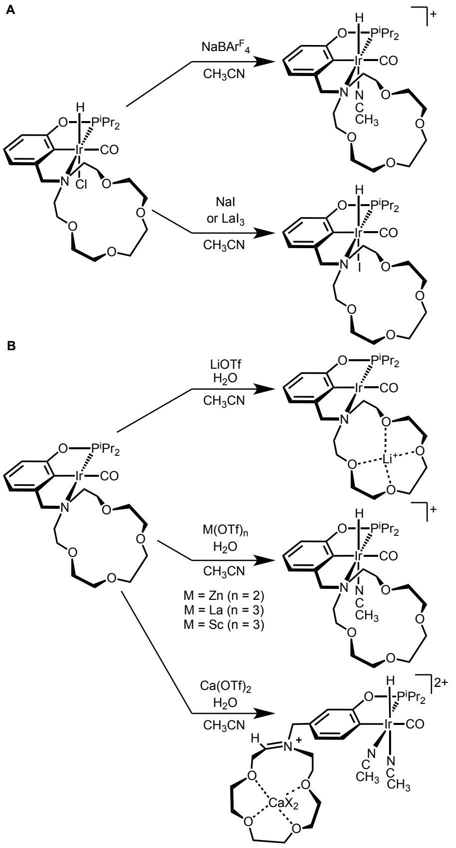
Pincer-crown ether ligands bring a crown ether in close proximity to a transition metal center, presenting an opportunity to foster interactions between cations and substrates in the secondary coordination sphere. Whereas ether donation to the transition metal center proved critical for controlling substrate binding in catalysis, secondary coordination sphere interactions are most likely to be seen when all of the oxygen donors are available to bind a cationic guest. Coordinating solvents can be used to enforce a situation where all of the crown ether oxygen atoms are available for binding a cationic guest. Acetonitrile has been a particular focus as a polar, coordinating medium that can dissolve a range of salts to enable screening of Lewis acid promotion. This section will summarize current progress towards cation promotion via secondary coordination sphere interactions with substrates, starting with stoichiometric examples and moving to catalytic reactions.

Stoichiometric reactions

In an initial foray into understanding interactions in the secondary coordination sphere of pincer-crown ether complexes, iridium complexes were allowed to react with a variety of metal salts in acetonitrile solution.[125] A surprisingly diverse range of reactivity was observed, even in the absence of a specific substrate that might further interact with a cation, as summarized in Scheme 5.

Iridium(III) halide complex κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)(Cl) undergoes halide abstraction to afford cationic [κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)($NCCH_3$)][BAr$^F_4$]. Halide exchange can also occur: when the chloride complex is treated with NaI, the iodide complex κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)(I) is formed.

Scheme 5. Diverse reactivity of iridium pincer-crown ether complexes with various salts.

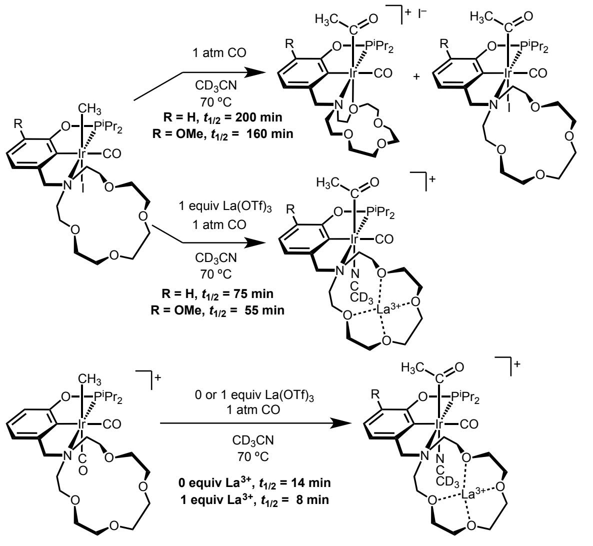


The iridium(I) carbonyl complex κ^3-(^{15c5}NCOP^{iPr})Ir(CO) engages in the expected cation-macrocycle interactions with LiOTf in acetonitrile solution. But when the stronger Lewis acids Zn(OTf)$_2$, Sc(OTf)$_3$, and La(OTf)$_3$ are added, oxidative protonation of the iridium center produces [κ^3-(^{15c5}NCOP^{iPr})Ir(H)(CO)(NCCH$_3$)][OTf]. This reactivity is attributed to acidification of trace water after binding to the dicationic and tricationic metal ions. The same reactivity proceeds on a similar timescale for the non-macrocyclic complex κ^3-(^{Et}NCOP^{iPr})Ir(CO), suggesting that the crown ether does not play any special promotive role in this case.

The macrocycle is essential, however, in promoting unique reactivity of Ca(OTf)$_2$. Non-macrocyclic κ^3-(^{Et}NCOP^{iPr})Ir(CO) reacts with Ca(OTf)$_2$ to give the expected protonation product [κ^3-(^{Et}NCOP^{iPr})Ir(H)(CO)(NCCH$_3$)][OTf]. On the other hand, the 15-crown-5-containing complex κ^3-(^{15c5}NCOP^{iPr})Ir(CO) reacts with Ca(OTf)$_2$ to give a new cationic species that has undergone macrocycle oxidation to an iminium, with concomitant cyclometallation at a different position of the pincer arene backbone (Scheme 5). These reactions show that pincer-crown ether iridium carbonyl complexes can support cation–macrocycle interactions, but that iridium(I) complexes can undergo protonation. Reactivity at iridium(III) centers would avoid some complications.

Iridium(III) methyl complexes were selected for subsequent explorations of cation-promoted reactivity with the thought that a methyl migratory insertion could be a key step in carbonylation catalysis. The methyl complex κ^3-(^{15c5}NCOP^{iPr})Ir(CH$_3$)(CO)(I) undergoes migratory insertion under 1 atmosphere of CO in acetonitrile at 70 ºC (Scheme 6).[126] In the absence of salt, the half-life ($t_{1/2}$) for the reaction is 200 min. In the presence of La(OTf)$_3$, the reaction proceeds about 3 times faster ($t_{1/2}$ = 75 min).

Scheme 6. Cation-promoted migratory insertion reactivity of pincer-crown ether complexes.



The lanthanum salt plays two roles. First, La(OTf)$_3$ abstracts iodide and generates a cationic iridium center, as indicated by the rapid rate of migratory insertion in isolated samples of the cationic methyl complex [κ^3-(^{15c5}NCOP^{iPr})Ir(CH$_3$)(CO)$_2$]$^+$ ($t_{1/2}$ = 14 min). Second, La(OTf)$_3$ promotes the reaction via the secondary coordination sphere, based on the observation that migratory insertion in [κ^3-(^{15c5}NCOP^{iPr})Ir(CH$_3$)(CO)$_2$]$^+$ is accelerated by salt addition ($t_{1/2}$ = 8 min; no La(OTf)$_3$ promotion for the non-macrocyclic complex [(^{Et}NCOP^{iPr})Ir(CH$_3$)(CO)$_2$]$^+$). Mechanistic studies are consistent with either a direct interaction of La^{3+} with the carbonyl oxygen or a weakening of the electron donation of the aza-crown ether nitrogen.

The reactivity was also explored with a methoxy-substituted pincer-crown ether complex. Substitution ortho to the phosphinite is generally useful for preventing unwanted metallation at this position (e.g., Scheme 5). In this case, the methoxy group also provides a comparison between synthetic tuning of electron density at the metal center and non-covalent tuning through cation-macrocycle interactions. The methoxy-substituted complexes undergo migratory insertion at essentially the same rate as the unsubstituted complexes, so in this case it is more convenient and effective to add a simple salt. The pincer-crown ether system enables cation-promoted migratory insertion without the formation of strong bonds between the metal cation and the acyl oxygen.

Catalytic reactions

Secondary coordination sphere promotion of pincer-crown ether catalysts was targeted based on the hypothesis that interactions between Lewis acidic cations and Lewis basic substrates could result in controlled activity or selectivity.

The formal insertion of an aldehyde into a C–H bond of acetonitrile — a hydrocyanomethylation reaction — was chosen initially based on the possibility of cation-aldehyde interactions accelerating key step(s) in the cycle.[135] Nickel pincer complexes can facilitate hydrocyanomethylation of aldehydes,[136,137] and the proposed mechanisms for these reactions involve either nucleophilic attack of aldehyde by a stabilized carbanion or migratory insertion of a cyanomethyl group with an aldehyde. Either mechanism might be promoted by aldehyde Lewis acid activation. In a related ruthenium system, the reaction is promoted by $NaPF_6$.[138]

The nickel pincer-crown ether complex κ^3-(^{15c5}NCOP^{iPr})Ni(O^{t}Bu) proved capable of catalyzing the insertion of benzaldehyde into a C–H bond of acetonitrile.[135] Under the typical conditions of Figure 14, a turnover number (TON) of approximately 100 was obtained without any added base in acetonitrile solution. No rate enhancements were observed with $NaPF_6$ or KPF_6, however. And $LiPF_6$ is actually an *inhibitor*: catalysis stops almost entirely when the lithium salt is added.

Mechanistic studies showed that Li^+ rapidly abstracts alkoxide ligands (OR^-) from nickel with precipitation of LiOR. The reduced activity is consistent with the fact that the cationic complex [κ^3-(^{15c5}NCOP^{iPr})Ni($NCCH_3$)]$^+$ is completely inactive in the absence of added base. In this case, $LiPF_6$ was inadvertently found to be an "off switch", enabling a version of switchable catalysis in which an active nickel alkoxide complex can be switched off by $LiPF_6$ addition. Adding base re-starts catalysis (Figure 14). Interestingly, the non-macrocyclic diethylamine-containing nickel catalyst does not shut down to nearly the same extent as the crown-ether-containing catalyst. The crown ether likely helps bring the Li^+ ion into proximity of the alkoxide, facilitating precipitation the lithium alkoxide salt.

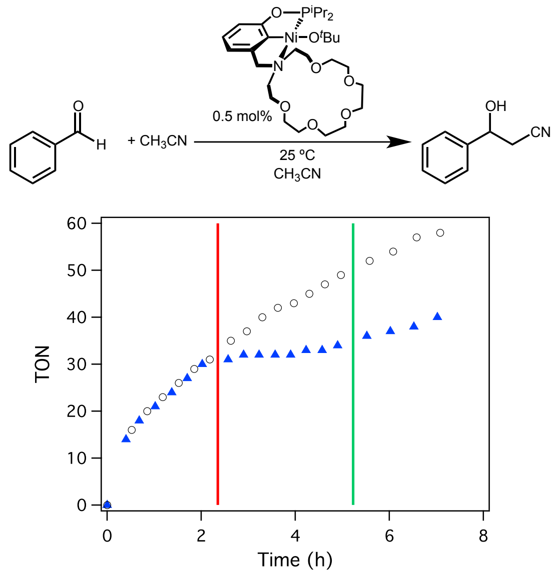


Figure 14. Scheme of typical catalytic conditions and turnover number (TON) vs. time for two parallel reactions containing 0.5 mol% κ^3-(^{15c5}NCOP^{iPr})Ni(O^{t}Bu) and 1 M benzaldehyde in CH_3CN. The first experiment (empty black circles) was allowed to continue unabated for 17 h, while the second experiment (filled blue triangles) was treated with 0.5 mol% $LiPF_6$ (red line), resulting in catalyst deactivation; the activity was reinitiated by the addition of 1 mol% DBU (green line). Adapted with permission from ref [135], copyright 2015 American Chemical Society.

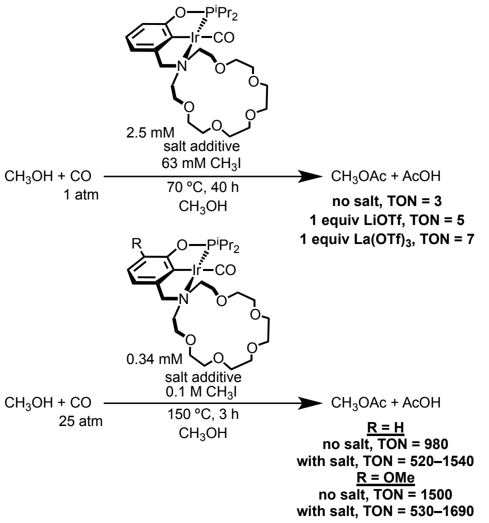
In the hydrocyanomethylation reaction, any possible influence of Li^+ salts on the aldehyde is obscured by the irreversible precipitation of lithium alkoxide. Later studies showed that Na^+ and K^+ binding by nickel pincer-crown ether complexes is much weaker than Li^+ binding in acetonitrile, consistent with the lack of cation promotion by the heavier alkali metal salts.[124] Nonetheless, the system provided new mechanistic insight into hydrocyanomethylation catalysis and illuminated potential pitfalls in promoting catalysis via the secondary coordination sphere.

The pincer-crown ether iridium complexes also appeared promising for cation-promoted catalysis, based on the prior observation of La($OTf)_3$-promoted stoichiometric migratory insertion.[125] Building on this result, the carbonylation of methanol to acetic acid was targeted for cation promotion.

Methanol carbonylation is among the largest scale homogeneously catalyzed industrial reactions.[139,140] Rhodium- and iridium-catalyzed processes have been developed, with the latter operating best with a ruthenium promoter that abstracts iodide from the iridium center to accelerate migratory insertion. Surprisingly, there are very few molecular iridium catalysts capable of methanol carbonylation beyond the simple anionic species $[Ir(I)_2(CO)_2]^-$ that is used industrially.[141]

The methyl complex κ^3-(^{15c5}NCOP^{iPr})Ir(CH_3)(CO)(I) undergoes migratory insertion to produce a stable acyl complex in acetonitrile.[126] Simply changing the solvent to methanol results in C–C bond formation and release of free methyl acetate under the same conditions of 1 atmosphere CO and 70 ºC, along with a well-defined iridium hydride complex (Scheme 7).[142] When the same reaction is conducted in the presence of methyl iodide, methyl acetate was produced (TON = 3). The activity increased in the presence of LiOTf (TON = 5) and La($OTf)_3$ (TON = 7). While this would be consistent with some degree of cation promotion, ^{31}P NMR monitoring revealed the formation of decomposition products.

Scheme 7. Salt-promoted methanol carbonylation using iridium pincer-crown ether precatalysts.



High temperature, high pressure multireactor studies were conducted to screen conditions and salt additives.[142] Catalyst decomposition under the harsh conditions of industrial methanol carbonylation hindered these efforts, although again some cation promotion — and a notable electrolyte effect — were observed (Scheme 7). Spectroscopic monitoring is consistent with partial pincer ligand decomposition generating a complex bound by a monodentate hydrolyzed phosphinite ligand.

These initial attempts to influence catalysis via the secondary coordination sphere highlight some of the challenges faced in designing complex ligand architectures for Lewis acid promoted catalysis. Indeed, decades after the first metalla-crown ethers were reported, there is scant evidence for well-defined cases of cationic Lewis acid promotion via direct substrate activation in the secondary coordination sphere.

Outlook

An impressive range of metalla-crown ether structures have been synthesized. While applications in catalysis have lagged behind those in sensing and redox tuning, cationic guests can improve activity and selectivity via several different pathways. A few themes relating to the design of catalysts for controlled catalysis emerge. First, consider the size of the catalyst. The crown ether-containing catalysts described here are often somewhat smaller than other supramolecular systems for controlled catalysis, such as molecular cages or multimetallic constructs.[15–19,21] Some metalla-crown ether systems can achieve impressive control with relatively concise synthesis, such as with poly(ether) linkers that do not require macrocyclization reactions.

Another theme is the balance between flexibility and rigidity. A more flexible ligand can adopt many conformations to maximize productive interactions, but this can incur significant entropic costs. More rigid ligands can place the Lewis acidic site in a specific position of desired proximity, but this can be a significant synthetic challenge and slight deviations from ideal positioning can render the system ineffective.

A final theme to highlight is the interplay between salts and solvents. Most simple and readily available salts feature trifluoromethanesulfonate, tetrafluoroborate, or hexafluorophosphate anions and are only soluble in relatively polar solvents. Increasing solvent polarity broadly correlates with increasing solvent Lewis basicity, however, and Lewis basic solvents can cause problems by quenching the Lewis acidity of the metal cations and/or binding to the transition metal center. Many studies circumvent these problems by using lipophilic counter anions such as tetra(aryl)borate salts, which often require custom synthesis. Solvents that are sufficiently polar to dissolve simple metal salts, but non-coordinating enough to maintain the Lewis acidity of the salts, could have a significant impact in this area.

Bridging systems have emerged as a new and interesting class of metalla-crown ethers, capable of interacting with the transition metal center via the primary coordination sphere and influencing reactivity via the secondary coordination sphere. Pincer-crown ether ligands have been the subject of detailed studies examining the nature of interactions with cations and how these interactions can modulate reactivity.

Pincer-crown ether ligands provide outstanding control over the primary coordination sphere through tunable hemilability. Detailed mechanistic studies provide a blueprint for designing cation-triggered ligand substitution reactions.[95] Examples of controlled and reversible ligation,[124] cation-modulated H_2 splitting,[127] and cation-tunable and -switchable olefin isomerization catalysis[128] demonstrate the power of this approach. Looking forward, tunable hemilability appears to be a general way to balance activity and stability and to provide temporal control over catalytic reactions. Furthermore, it is easy to envision coupling pincer-crown ether catalysts into tandem catalytic systems.

Pincer-crown ether catalysts need further development when it comes to tuning via substrate/cation interactions in the secondary coordination sphere. While cation binding has been shown to accelerate C–C bond formation in pincer-crown ether complexes,[126] this significant observation has not yet been successfully translated to cation-accelerated catalysis.[135,142] Because pincer-crown ether complexes can bring a positive charge into proximity of a substrate, altering the local electric field around the catalyst may prove to be fruitful.[143] There is reason for optimism that certain catalytic reactions, under the right conditions, will benefit from cation-substrate interactions.

Conflicts of interest

There are no conflicts to declare.

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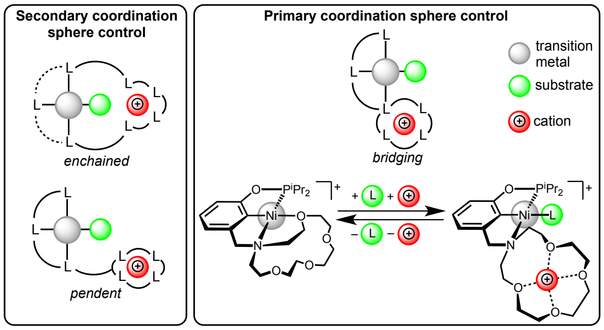
Graphical Abstract



This Feature Article reviews the structural motifs and catalytic applications of crown ether-containing catalysts and details the development of “pincer-crown ether” ligands for applications in controlled catalysis.