Tunable and Switchable Catalysis Enabled by Cation-Controlled Gating with Crown Ether Ligands

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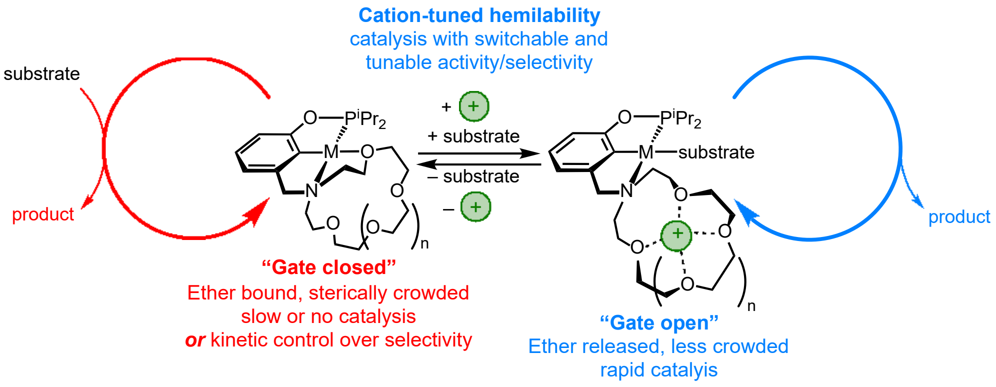
Catalysis has become an essential tool in science and technology, impacting the discovery of pharmaceuticals, the manufacture of commodity chemicals and plastics, the production of fuels, and much more. In most cases, a particular catalyst is optimized to mediate a particular reaction, continually producing a desired product at a given rate. There is enormous opportunity in developing catalysts that are *dynamic*, capable of responding to a change in the environment to alter structure and function. Controlled catalysis, in which the activity or selectivity of a catalytic reaction can be adjusted through an external stimulus, offers opportunities for innovation in catalysis. Catalyst discovery could be simplified if a single thoughtfully designed complex could work synergistically with additives to optimize performance, rather than trying a multitude of different metal/ligand combinations. Temporal control could be gained to facilitate the execution of multiple reactions in the same flask, for example by activating one catalyst and deactivating another to avoid incompatibilities. Selectivity switching could enable copolymer synthesis with well-defined chemical and material properties. These applications might sound futuristic for synthetic catalysts, but in Nature, such a degree of controlled catalysis is commonplace. For example, allosteric interactions and/or feedback loops modulate enzymatic activity to enable complex small molecule synthesis and sequence-defined polymerization reactions in complex mixtures containing many catalytic sites. In many cases, regulation is achieved by "gating" substrate access to the active site. Fundamental advances in catalyst design are needed to better understand the factors that enable controlled catalysis in the arena of synthetic chemistry,

particularly in achieving substrate gating outside of macromolecular environments. In this Account, the development of design principles for achieving cation-controlled catalysis are described. The guiding hypothesis was that gating substrate access to a catalyst site could be achieved by controlling the dynamics of a hemilabile ligand through secondary Lewis acid/base and/or cation-dipole interactions. To enforce such interactions, catalysts sitting at the interface of organometallic catalysis and supramolecular chemistry were designed. A macrocyclic crown ether was incorporated into a robust organometallic pincer ligand, and these "pincer-crown ether" ligands have been explored in catalysis. Complementary studies of controlled catalysis and detailed mechanistic analysis guided the development of iridium, nickel, and palladium pincer-crown ether catalysts capable of substrate gating. Toggling the gate between open and closed states leads to switchable catalysis, where cation addition/removal changes the turnover frequency or the product selectivity. Varying the degree of gating leads to tunable catalysis, where the activity can be tuned based on the identity and amount of salt added. Research has focused on reactions of alkenes, particularly isomerization reactions, which has in turn led to design principles for cation-controlled catalysts.



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- Camp, A.; Kita, M.; Blackburn, P. T.; Dodge, H.; 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*, 2792-2800.[3] *A larger aza-18-crown-6 ether macrocycle enables sodium-ion-controlled selectivity of positional isomerization of butenes, with* Na^+*-free isomerization from 1- to 2-position and* Na^+*-promoted isomerization to 3-alkenes.*

- Farquhar, A.; Gardner, K.; Acosta-Calle, S.; Camp, A.; Chen, C.-H.; Miller, A.J.M. “Cation-Controlled Olefin Isomerization Catalysis with Palladium Pincer Complexes.” *Organometallics* **2022**, *41*, 3366-3372.[4] *Palladium pincer-crown ether complexes also exhibit cation-controlled catalytic reactivity, not only for isomerization but also for cyclodimerization and polymerization reactions.*

1. Introduction

Since the advent of homogeneous catalysis, chemists have been continually asking more of catalysts designed in the laboratory. If finding the right metal/ligand combination could streamline organic reactions, could it not also be applied to enantioselective transformations, site-selective functionalizations, or couplings of exceptionally strong bonds? Examples of these extraordinary reactions, and many more, have been realized, usually by optimizing a particular catalyst for the target reaction. Discovering a catalyst with the desired activity and selectivity often requires exhaustive screening of metal-ligand combinations, onerous synthesis, or both.

It seems reasonable for the chemist to again ask more of a catalyst: can a *single* catalyst produce more than one product, or operate in multiple rate regimes, changing its function in a controlled manner? Stimuli-responsive or “controlled” catalysts can build complexity into catalytic reactions. Multiple catalysts could work in the same flask, one switched on while the other is dormant, or vice versa, to enable one-pot multi-step reactions that might otherwise be incompatible. Or a single catalyst could be optimized for several reactions without a fundamental redesign, allowing additives to tune structure and function. Such controlled catalysis is reminiscent of biological catalysis in living cells, where many catalysts operate in the same place at the same time, but with spatial and temporal control over function that enables exquisitely controlled chemical synthesis.[5]

Controlled catalysis can be categorized based on the type of stimulus employed, with redox reagents, photons (light), and acids/bases being the most common. Comprehensive reviews have appeared that elegantly describe progress in this field.[6–13] For each of these mechanisms, controlling substrate access to the catalyst active site — *substrate gating* — has attracted significant interest, in part because of the analogy to catalysis in Nature. Such gating most commonly relies on macromolecular control, with bulky organic groups or porous cages physically blocking substrates from accessing the active site.

Our research began with the question of whether similar degrees of control could be attained in small and readily synthesized organometallic catalysts. We sought catalysis modulated by ions that can alter the *primary coordination sphere* to gate substrate access to the active site. The guiding hypothesis was that a hemilabile ligand could serve as the basis for cation-controlled catalysis through competing interactions with the metal catalyst and a cationic additive. Hemilabile ligands can reversibly bind or dissociate from a metal center to reveal a catalytically active site in the complex.[14–17] If, upon dissociation, the hemilabile ligand is stabilized by a Lewis acid/base or ion-dipole interaction with a cation, the hemilability equilibrium and thus the extent of substrate binding to active site could be modulated (Figure 1).

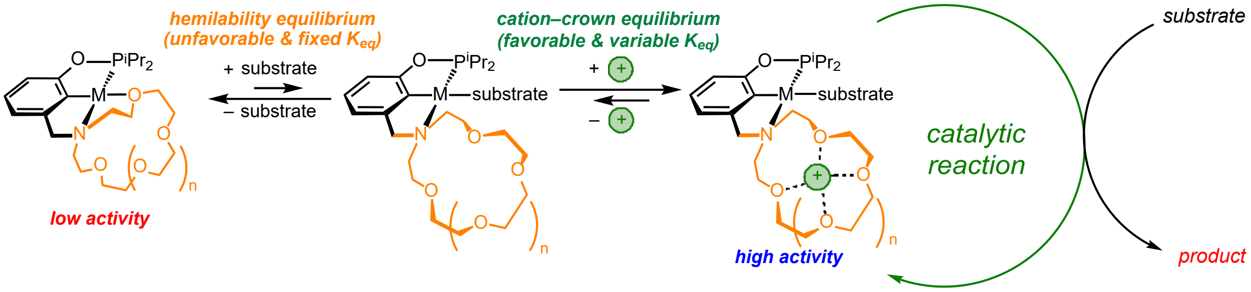


Figure 1. Overview of cation-tunable hemilability in pincer-crown ether catalysts.

Pincer-crown ether catalysts were designed in response to this hypothesis. To utilize “tunable hemilability” as a gating mechanism, a complex would require a few key features. First, a macrocyclic hemilabile ligand was envisioned, with ether or amine groups that could reversibly associate/dissociate from the transition metal center. Ligand hemilability has been identified as an enabling attribute in catalysis,[14–17] but it is often difficult to synthetically tune. By utilizing a crown ether as the hemilabile ligand, upon dissociation the free macrocycle could engage in noncovalent ion-dipole or “cation–crown” interactions that would be tunable based on the identity and concentration of cations in solution. As shown in Figure 1, the overall free energy of substrate binding could therefore be controlled through a dual hemilability/cation-crown equilibrium. This tunable substrate gating would enable both switchable catalysis, with reversible on/off control over activity or selectivity (gate fully open or closed), and tunable catalysis, with activity smoothly modulated over a wide range (gate open to varying degrees). These studies would add new levels of control to metalla-crown ether catalysts.[13,18]

A prior perspective article focused on the individual steps of hemilability and cation-crown interactions, building towards small molecule activation and initial catalysis studies.[19] In this Account, we focus on catalysis mediated by pincer-crown ether complexes, highlighting recent advances in olefin isomerization with rate and selectivity that can be controlled by salt additives.

2. Proof-of-principle reactions: H_2 activation and ligand catch-and-release.

Key examples of cation-controlled reactivity came in initial studies of small molecule binding and activation by iridium and nickel complexes. The cationic iridium hydride complex **[κ^5-(^{15c5}NCOP)IrH]$^+$** was the focus of initial studies. Bold text is used for abbreviated complex formulae, with the binding mode denoted by the κ symbol (a pentadentate, κ^5 binding mode in this case, involving two crown ether oxygen donors bound to Ir) and the macrocycle size given in the superscript. Complex **[κ^5-(^{15c5}NCOP)IrH]$^+$** undergoes slow H/D exchange when placed under 1 atm D_2. In the presence of $LiBAr^F_4$ (Ar^F = 3,5-bis(trifluoromethyl)phenyl), however, the rate of H/D exchange is dramatically enhanced (Figure 2).[1] The rate can be tuned based on the identity and quantity of salt, with Li^+ salts promoting the reaction more than Na^+ salts. The cation is proposed to perturb a ligand substitution equilibrium to favor D_2 displacement of the crown ether oxygen cis to the hydride, which would accelerate hydrogen activation and scrambling.

Given that many reactions, such as hydrogenations, involve formation of dihydrogen complexes,[20,21] this was a promising indicator for catalysis.

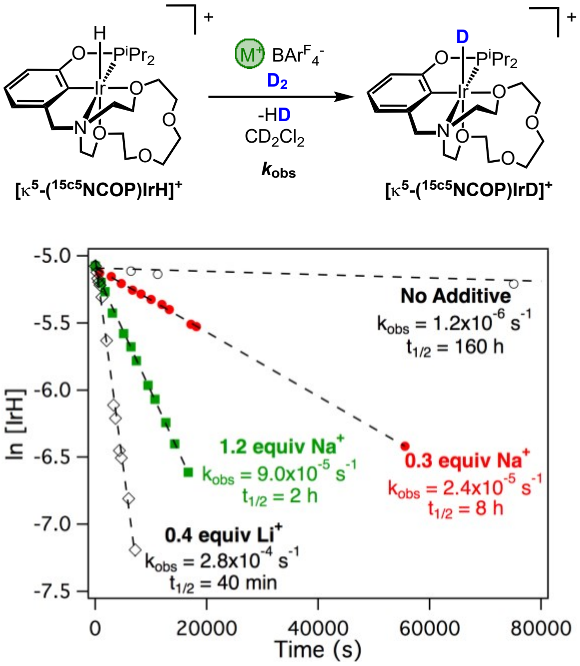


Figure 2. Cation-controlled H_2 splitting by iridium pincer-crown ether complex. Adapted with permission from *J. Am. Chem. Soc.* **2014**, *136*, 14519. Copyright 2014 American Chemical Society.

Another promising example came from a nickel(II) pincer-crown ether complex in a square planar geometry with tetradentate ligation involving one ether donor.[22,23] When cationic **$[\kappa^4\text{-}(^{15c5}NCOP)Ni]^+$** was treated with C_6F_5CN, no reaction was apparent. Similarly, no Li^+ binding was observed when $LiBAr^F{}_4$ and **$[\kappa^4\text{-}(^{15c5}NCOP)Ni]^+$** were mixed. Yet, when both $LiBAr^F{}_4$ and the nitrile were added to **$[\kappa^4\text{-}(^{15c5}NCOP)Ni]^+$**, complete conversion to a tridentate-ligated nickel nitrile complex **$[\kappa^3\text{-}(^{15c5}NCOP)Ni(NCC_6F_5)]^+$** was achieved (Figure 3). The reactivity was sensitive to the nature of the cation: $NaBAr^F{}_4$ led to partial nitrile binding, while $KB(C_6F_5)_4$ did not produce any detectable nitrile complex. Mechanistic studies showed similar trends in binding affinity, with Li^+ salts binding much more tightly to model complexes than Na^+ and K^+ salts.[23,24]

Studies of model complexes revealed that free 12-crown-4 ether binds Li^+ much more strongly than the aza-15-crown-5-based complexes.[23,24] Thus, 12-crown-4 can be added to the Li^+-intercalated nitrile complex to excise the cation from the crown and eject the nitrile ligand, reverting to the original starting materials. These initial studies corroborated the hypothesis that cation–crown interactions could shift equilibria to favor ligand substitution reactions in these late transition metal complexes, reversibly and with predictable control.[23–25]

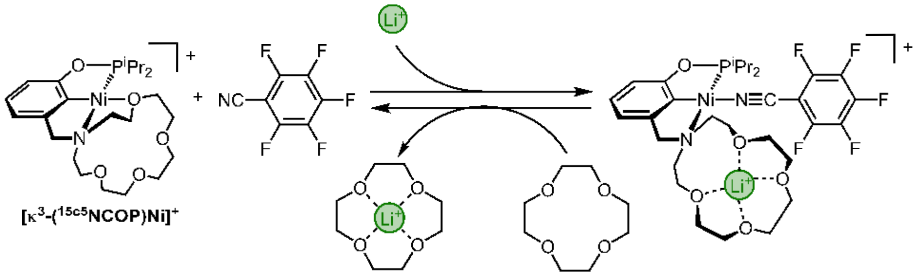


Figure 3. Ligand “catch and release” by a nickel pincer-crown ether complex.

3. Switchable and tunable catalysis of allylbenzene isomerization: a three-state ion-controlled catalyst system.

Olefin isomerization catalysis was the focus of initial studies with iridium pincer-crown ether complexes. Stereochemical (*E/Z*) and positional isomerizations (i.e. alkene transposition along a chain) are deceptively simple transformations.[26–30] Most catalysts operate under thermodynamic control, and relatively similar energies of various alkene isomers can lead to complex distributions of products. Yet, separating various alkene isomers can be challenging, and in applications such as the fragrance industry, extremely high purity materials are required (sometimes because of a minor isomer with an odious aroma!).[31] Catalyst development has recently focused on accessing high stereoselectivity, particular regioisomers (specific alkene position), or even “contrathermodynamic” conversion to high-energy isomers (using light).[29,30,32]

We saw in olefin isomerization an opportunity for cation-controlled catalysis. The reaction involves alkene binding to a transition metal center, a process that could be controlled through a gating mechanism. Furthermore, the reaction involves only a single substrate, minimizing opportunities for unwanted side reactions. Examples of controlled catalysis of alkene isomerization are rare,[33,34] despite opportunities to address selectivity issues or gain control over tandem catalysis reactions in which isomerization reactions are the initial step in a multi-catalyst sequence.[35]

The cationic iridium hydride pincer-crown ether complex **[κ^5-(^{15c5}NCOP)IrH]$^+$** was chosen for olefin isomerization because the hemilabile ether ligand cis to the hydride could facilitate insertion/elimination reactivity needed for double bond transposition. Based on stoichiometric studies of model reactions,[1,23] we studied non-coordinating solvents to avoid competitive binding of cations, and utilized lipophilic BAr^F_4 salts to ensure good solubility (although this limits access to divalent or trivalent salts).[36,37] Indeed, the cationic hydride complex isomerizes allylbenzene to β-methylstyrene with modest activity (turnover frequency, TOF ca. 2 h^{-1}).[2] Consistent with the need for a hemilabile ligand cis to the hydride, the neutral hydrido chloride complex **κ^4-(^{15c5}NCOP)IrH(Cl)** does not react to any observable extent with allylbenzene. The chloride ligand can be abstracted with $NaBAr^F_4$, however, to regenerate the catalytically active cationic complex. The neutral and cationic forms of the catalyst thus constitute a two-state system for on/off switchable isomerization (Figure 4, left).

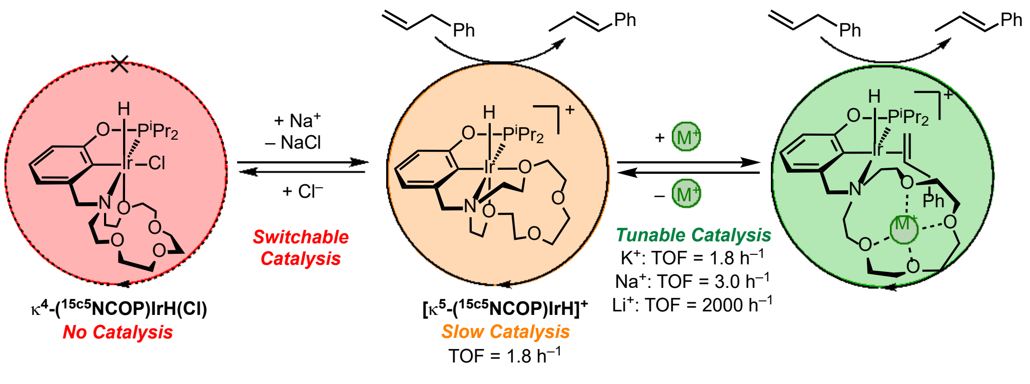


Figure 4. Three-state iridium catalyst for olefin isomerization.

Tunable rates of isomerization are also possible using the strategy of cation-modulated hemilability (Figure 2, right).[2] The activity of cationic **[κ^5-(^{15c5}NCOP)IrH]$^+$** varies based on the identity and quantity of alkali metal salt additives. Potassium salts gave no rate enhancement, while sodium salts led to ca. 2-fold increases in rate. Dramatic rate enhancement was observed when $LiBAr^F_4$ was included, however, with the activity increasing more than 1000-fold (TOF = 2000 h^{-1}). With excess Li^+ eventually the reaction rate saturated at a maximum, taken to be the state where the gate is "fully open" and substrate can bind without any inhibition. A reaction that took several days without any Li^+ present was complete within 10 minutes when Li^+ salts were present!

Several important findings emerged from this study. First, the pincer-crown ether framework enabled a rare example of multi-state catalysis, with off/slow/fast states accessible via ionic stimuli. Reversibly accessing the various states enabled excellent control over the activity. Second, a remarkable cation specificity was observed, with Li^+ giving orders of magnitude higher activity than Na^+. This is particularly surprising because the organic macrocycle 12-crown-4 ether, which also has four oxygen donors, has similar binding affinity for Na^+/Li^+.[38] Binding affinity studies of model pincer-crown ether complexes reveal that, relative to closely related organic crown ethers, the metalla-crown ether complexes have lower cation affinity overall but also much higher specificity — just as observed in catalysis.[23,24] Third, in the presence of Li^+, allylbenzene could be isomerized to β-methylstyrene with activities that compare favorably with leading systems from the literature.[27] Furthermore, the product is generated with exceptionally high >99% *E* selectivity, primarily due to the low reaction temperature. Although *E* isomers are often produced in 80-90% purity at ca. 80-100 ºC, the fragrance industry requires extremely high purity *E* isomers for certain products,[31] highlighting the need for catalysts that generate exclusively *E* alkenes.

4. Mechanism of olefin isomerization and avoiding decomposition pathways.

A detailed mechanistic study involving kinetic modeling and in situ spectroscopic monitoring provided a comprehensive picture of cation-controlled olefin isomerization catalysis by iridium pincer-crown ether complexes, summarized in Figure 5.[2,39] In the absence of alkali metal salts, slow isomerization proceeds in a reaction that is first order in catalyst and alkene, consistent with unfavorable equilibrium alkene binding followed by insertion/elimination isomerization. The reaction exhibits saturation kinetics with increasing concentrations of $LiBAr^F_4$, eventually becoming zero-order in alkene: this indicates that the resting state has shifted, and the limiting step becomes the organometallic insertion process.

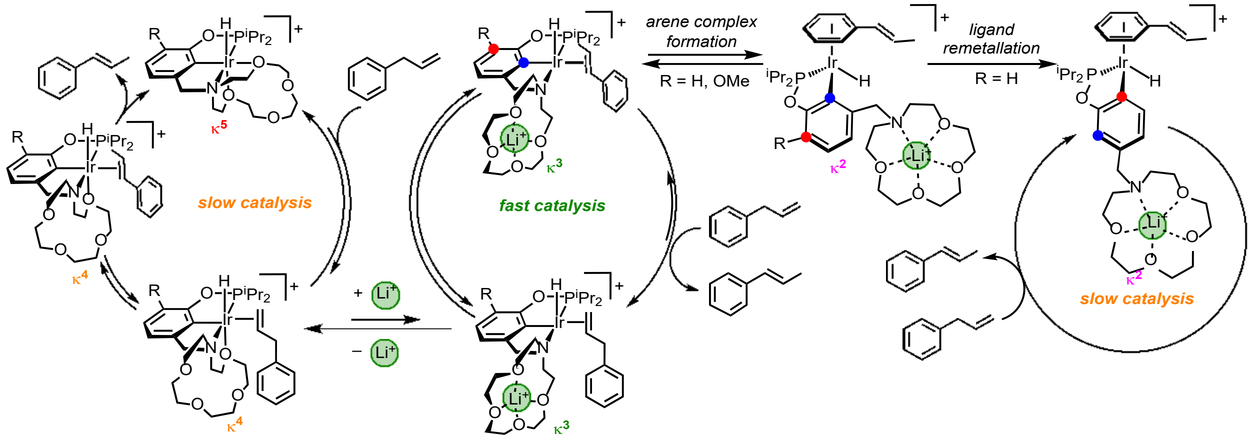
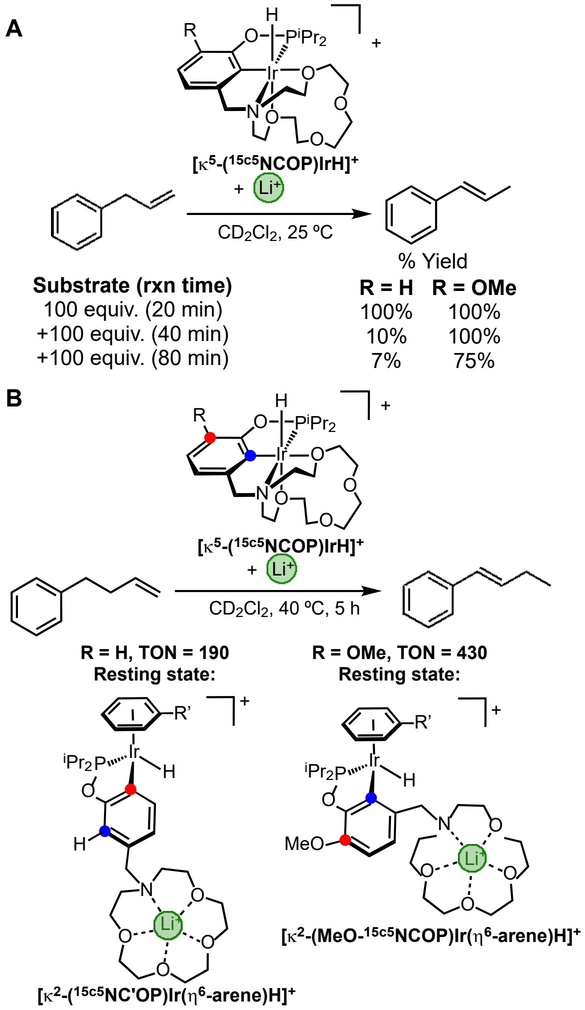


Figure 5. Complete proposed mechanistic scheme for cation-controlled olefin isomerization with pincer-crown ether complexes.

When isomerization of allylbenzene was conducted at elevated temperatures or with large excess of Li^+ salt, a new iridium species was observed. Isolation of this species enabled its assignment as an η^6-arene (“piano stool”) complex, **[κ^2-(^{15c5}NC'OP)Ir(η^6-β-methylstyrene)H]$^+$**, wherein the pincer ligand had undergone a “remetallation” reaction to form a M–C bond in a new position on the aryl backbone and provide a bidentate binding mode.[39] Similar complexes could be accessed directly by addition of arenes to cationic complex **[κ^5-(^{15c5}NCOP)IrH]$^+$** in the presence of Li^+ salts. These arene complexes proved to be poor catalysts for olefin isomerization (TOF ca. 3 h^{-1}). A labeling study using deuterated styrene established that remetallation is an irreversible catalyst deactivation process.

A new ligand was designed to prevent metallation at unwanted sites on the ligand backbone. This ligand was first introduced in the context of iridium (de)carbonylation chemistry.[40–42] The catalyst with the methoxy "blocking" group in the backbone, **[κ^5-(MeO-^{15c5}NCOP)IrH]$^+$,** showed similar activity to the original catalyst in allylbenzene isomerization reactions. Under conditions where the original catalyst deactivated, however, the new catalyst remained active.[39] In the recycling experiment of Figure 6A, the first-generation catalyst with no backbone substitution, **[κ^5-(^{15c5}NCOP)IrH]$^+$,** lost almost all activity after the first isomerization, giving only low yields of product when another 100 equiv allylbenzene was added to the reaction mixture. Conversely, the second-generation catalyst with the methoxy group in the backbone, **[κ^5-(MeO-^{15c5}NCOP)IrH]$^+$,** retained high activity with each addition of substrate. Figure 6B presents the multi-positional isomerization of 4-phenyl-1-butene. The original catalyst **[κ^5-(^{15c5}NCOP)IrH]$^+$** gave a low turnover number (TON = 190), with deactivation occurring as the complex underwent remetallation to form the low-activity species **[κ^2-(^{15c5}NC'OP)Ir(η^6-arene)H]$^+$**. The methoxy-blocked catalyst **[κ^5-(MeO-^{15c5}NCOP)IrH]$^+$** retained much higher activity (TON = 430). Even with the methoxy group in the backbone, the arene complex **[κ^2-(MeO-^{15c5}NCOP)Ir(η^6-arene)H]$^+$** forms; this species can reversibly lose arene to re-form the active catalyst and thus maintains high activity.



Substrate (rxn time)	% Yield R = H	% Yield R = OMe
100 equiv. (20 min)	100%	100%
+100 equiv. (40 min)	10%	100%
+100 equiv. (80 min)	7%	75%

Figure 6. A: Allylbenzene positional isomerization recycling experiment. B: 4-phenyl-1-butene positional isomerization experiment.

Several key findings emerged from the development of a new catalyst featuring a methoxy group in the backbone. The presence of arene complexes featuring a κ^2 ligand binding mode was identified during isomerization of arene-containing olefins, which is not detrimental unless the ligand backbone undergoes a remetallation process to reach a less active form of the catalyst. When the blocking methoxy group is installed on the backbone, the rate of isomerization is maintained for longer periods and the catalyst can be recycled repeatedly. The methoxy group also enabled access to iridium complexes with diethylamine groups,[42,43] which can serve as useful comparisons in future studies. The methoxy blocking group design feature has been retained for most studies since its introduction.

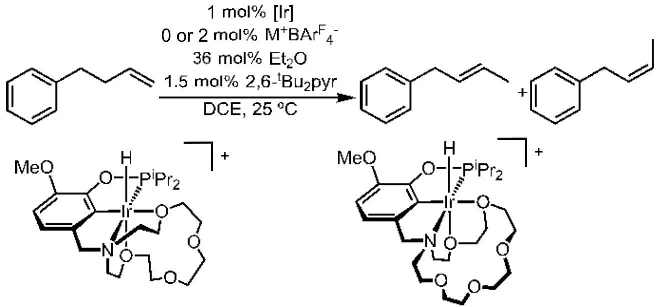
5. Larger crowns enable multi-site isomerization and switchable selectivity.

In the context of olefin isomerization, designing a single catalyst capable of accessing sterically similar internal olefins remains a challenge. Usually, two different catalysts with distinct metal/ligand combinations that fine-tune the steric bulk are required to achieve different regioisomers. We envisioned a complementary alternative approach that uses a single catalyst system that responds to external stimuli to control selectivity, with the identity of the observed product controlled by the choice of alkali metal salt. The initial goal was to have a single catalyst toggle between transposition of 1-alkenes to either 2-alkenes or 3-alkenes using cation-crown interactions.

To control regioselectivity in this way, however, requires alkene transposition over multiple positions, whereas earlier work had focused on a single positional isomerization from 1-alkenes to 2-alkenes. The fastest possible catalyst was therefore sought. In prior studies,[23,24] we had noticed that complexes featuring larger 18-crown-6 macrocycles exhibited higher binding affinity for cations than the original 15-crown-5-containing complexes. We therefore hypothesized that the iridium complex containing aza-18-crown-6 ether, **[κ^5-(MeO-^{18c6}NCOP)IrH]$^+$,** would, when activated with Na^+ salts, isomerize alkenes with high activity and enable double bond chain walking under practical reaction conditions.

Benchmarking isomerization of allylbenzene at room temperature, the larger macrocycle-containing complex **[κ^5-(MeO-^{18c6}NCOP)IrH]$^+$** catalyzed the isomerization of 4-phenyl-1-butene to 4-phenyl-2-butene with 23:1 *E*:*Z* stereoselectivity and a TOF of 0.44 h^{-1}. The addition of $NaBAr^F_4$ triggered a 4,500-fold rate enhancement in 2-olefin generation, with TOF = 1800 h^{-1} (and reduced stereoselectivity of 4:1 *E*:*Z*). Under identical conditions, the maximum TOF of the

15-crown-5-containing catalyst **[κ^5-(MeO-^{15c5}NCOP)IrH]$^+$** was only 160 h^{-1} in the presence of Li$^+$; with Na$^+$, the TOF was only 6 h^{-1} (Figure 7). The binding affinity studies again accurately informed catalyst design, leading to a new 18-crown-6-based catalyst that is superior to the previously reported 15-crown-5-based catalyst, boasting more than 10 times faster rates, the utilization of commercially available NaBAr$^F{}_4$, and improved water tolerance.



[κ^5-(MeO-^{15c5}NCOP)IrH]$^+$

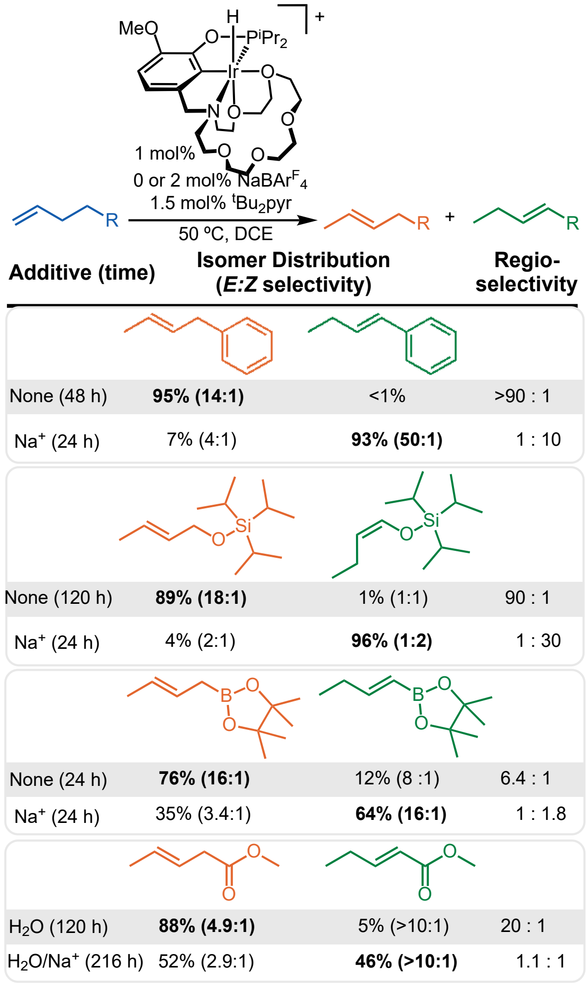
Additive	**TOF (*E*:*Z*)**
No salt	2 h^{-1} **(20:1)**
Li$^+$	160 h^{-1} **(6:1)**
Na$^+$	6 h^{-1} **(4:1)**

[κ^5-(MeO-^{18c6}NCOP)IrH]$^+$

Additive	**TOF (*E*:*Z*)**
No salt	0.4 h^{-1} **(23:1)**
Li$^+$	190 h^{-1} **(4:1)**
Na$^+$	1,800 h^{-1} **(4:1)**

Figure 7. Comparing activity of positional isomerization as a function of macrocycle size. DCE is 1,2-dichloroethane and pyr is pyridine.

The 18-crown-6-based catalyst **[κ^5-(MeO-^{18c6}NCOP)IrH]**$^+$ was the focus of studies aimed at multi-positional isomerizations with regioselectivity and stereoselectivity controlled by cations.[3] Butenes containing a range of functional groups were selected to study whether cations could modulate the selectivity between 2-alkene and 3-alkene products, with mild heating found to provide synthetically reasonable reaction times. At 1 mol% catalyst loading and 50 ºC in the absence of salts, the isomerization of various 4-aryl-1-butenes was highly selective for the 2-alkene regioisomer, with yields ranging from 84 to 95% and *E*:*Z* ratios in the range of 7:1 to 15:1. Under the same conditions, but including NaBAr$^F{}_4$, the regioselectivity changed more than 900-fold in some cases, with the formation of the 3-ene regioisomer in 79 to 96% yields (36:1 to >90:1 E:Z). Figure 8 shows selected 1-butene derivatives that were also successfully isomerized, such as terminal silyl ethers and boronic esters. Alkenes containing Lewis bases are also viable, sometimes requiring longer reaction times, higher catalyst loading, and the use of water as a promoter.



Additive (time)	Isomer Distribution (*E:Z* selectivity)		Regio-selectivity
None (48 h)	**95% (14:1)**	<1%	>90 : 1
Na^+ (24 h)	7% (4:1)	**93% (50:1)**	1 : 10
None (120 h)	**89% (18:1)**	1% (1:1)	90 : 1
Na^+ (24 h)	4% (2:1)	**96% (1:2)**	1 : 30
None (24 h)	**76% (16:1)**	12% (8 :1)	6.4 : 1
Na^+ (24 h)	35% (3.4:1)	**64% (16:1)**	1 : 1.8
H_2O (120 h)	**88% (4.9:1)**	5% (>10:1)	20 : 1
H_2O/Na^+ (216 h)	52% (2.9:1)	**46% (>10:1)**	1.1 : 1

Figure 8. Substrates that were amenable to cation-controlled isomerization to different regio- and stereoisomers. DCE is 1,2-dichloroethane and pyr is pyridine. Adapted with permission from *J. Am. Chem. Soc.* **2021**, *143*, 2792. Copyright 2021 American Chemical Society.

The pincer-crown ether approach enables a single catalyst to switch product selectivity between either of two internal isomers. The mechanism of switchable reactivity is proposed to hinge on noncovalent interactions, which can switch the catalyst to operate in either the kinetic or thermodynamic control regime. In the absence of salt, the kinetic barrier to convert the terminal alkene to the internal 2-ene isomer is surmountable, but further isomerization to the 3-ene isomer is not observed. This regime of kinetic control leads to high regioselectivity for the 2-

ene. When reactions were performed with NaBAr$^F{}_4$, the barriers for all isomerization are reduced dramatically and the reactions proceed under thermodynamic control to the most stable regioisomer. This regime of thermodynamic control will provide high 3-ene regioselectivity when the 3-ene is at least 1 kcal/mol more stable than the other isomers. This is the case for the substrates in Figure 8, supported by computational studies of isomer stability. But for other alkenes, such as methyl pentenoate, DFT predicts that the 2-ene isomer is more stable than the 3-ene isomer, so there are no differences in product distribution with or without salts (Figure 9A).

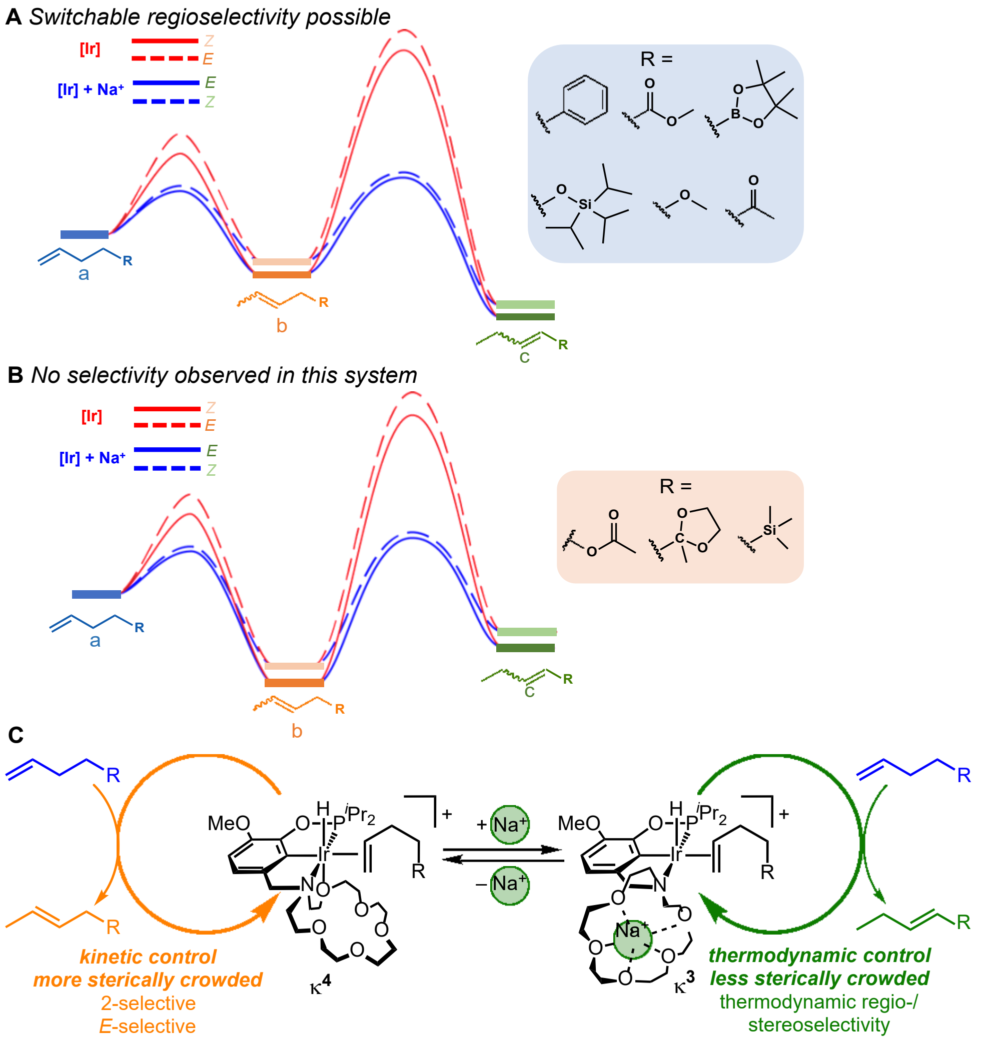


Figure 9. A: Proposed free energy landscape showing kinetic and thermodynamic requirements for successful cation-controlled selectivity. B: Proposed free energy landscape showing situation where no control would be observed. C: Proposed structural origin of kinetic vs thermodynamic

control. Adapted with permission from *J. Am. Chem. Soc.* **2021**, *143*, 2792. Copyright 2021 American Chemical Society.

The system is a rare catalyst capable of facilitating a single positional isomerization with exceptional stereoselectivity.[44–48] Mechanistic studies support that 2-selective isomerization stems from a catalyst state featuring a *tetradentate* binding mode of the ligand, with one crown ether oxygen bound during turnover (Figure 9C). Although one could imagine slightly different degrees of electron density at the metal center based on the number of oxygen donors coordinated, we hypothesize that the high stereoselectivity in this case results primarily from the steric pressure imparted by the partially bound crown ether. The 3-selective isomerization, conversely, takes place from a catalyst state with a *tridentate* binding mode due to strong Na^+—O interactions leading to dissociation of the ethers from the iridium ion and release of steric pressure near the active site.

This mechanistic model explains why the stereoselectivity for the 2-ene product is much lower when Na^+ is present. This shows that one could not just use a Na^+-promoted system and have two different reaction times to generate the two desired products: the selectivity would be compromised if a switchable system was not employed, because each catalytic state has a distinct structure and thus a distinct stereoselectivity.

6. Expanding to other metals: Palladium-catalyzed isomerization.

The key to switchable reactivity with the iridium system stemmed from control over gating substrate binding to the metal center, a seemingly general concept. Yet, it was easy to imagine possible challenges when extending to other metals: some complexes might favor alkene binding over the hemilabile ether donors, which would prevent controlled catalysis; or perhaps lower-coordinate complexes (e.g. square planar complexes) might undergo associative alkene binding that would circumvent any gating effect of the bound crown ether.

Palladium complexes provided a test of the challenges noted above. Furthermore, previous studies of cation binding affinity to pincer-crown ether complexes revealed that Pd complexes bind Li^+ ions stronger than analogous Ni, Pt, and Ir complexes.[24] We therefore explored switchable olefin isomerization with palladium and wondered whether we could achieve a higher degree of control based on these stronger cation-crown interactions. We also wondered if such reactivity could still be controlled through these interactions despite expected differences in the mechanism of isomerization between iridium and a hydride-free palladium system.

In the absence of alkali metal salts, no reactivity of 1-hexene is observed with palladium pincer crown-ether complex **$[\kappa^4$-(MeO-^{15c5}NCOP)Pd$]^+$**. However, isomerization of the alkene to internal olefins proceeds in the presence of Li^+ salts (Figure 10). Control experiments with a diethylamine pincer complex **$[\kappa^4$-(MeO-^{Et}NCOP)Pd$]^+$**, with no ethers near the Pd center, did not exhibit controlled catalysis. The rate of isomerization with or without Li^+ salts present was roughly the same as observed for the fully activated crown-ether-containing catalyst. These results show that (a) the crown ether acts primarily as a gate, with the Li^+ promoting activity to a maximum that matches ungated control complexes, and (b) that on/off switchable behavior is only possible when the crown ether gate is present. We demonstrated controlled catalysis, reversibly toggling between “on/off” states by sequential addition of Li^+ salt and free 12-crown-4 ether (Figure 10C). Other alkenes react with the palladium catalyst in a manner indicative of carbocation intermediates, producing oligomers, polymers, or cyclodimerization products.[4]

Comparisons between the palladium and iridium systems are instructive. The hydridoiridium catalyst proceeds via an insertion-elimination mechanism for positional isomerization. In contrast, the palladium catalyst is proposed to proceed via an electrophilic π-allyl mechanism. Substrate binding is a key step in both mechanistic pathways, however, and both catalysts exhibit cation-controlled activity. Despite being square planar, with the possibility for associative substitution to “open the gate”, the Pd system still exhibits switchable behavior. In fact, the palladium catalyst shows no activity at all in the absence of salts. In contrast, the iridium catalyst slowly isomerizes alkenes even without alkali metal salts. This highlights how the nature of the metal can influence the dynamics of cation-controlled gating: the lower activity in the absence of promoters is attributed to stronger binding of the crown ether oxygens to the more electrophilic palladium center.

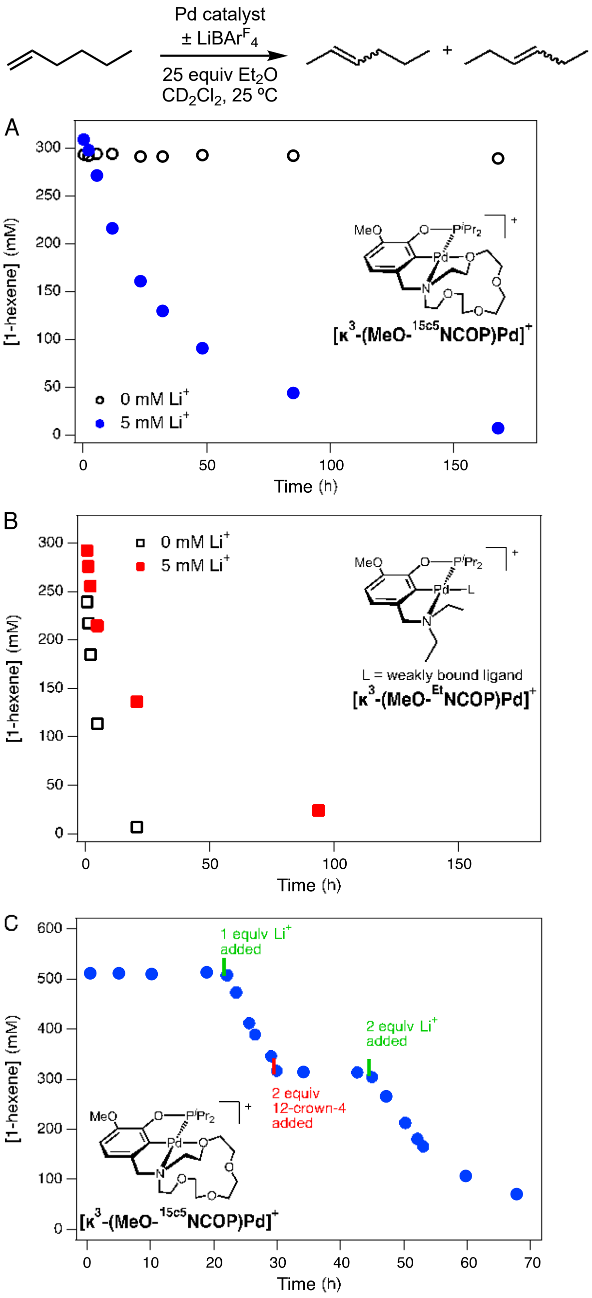
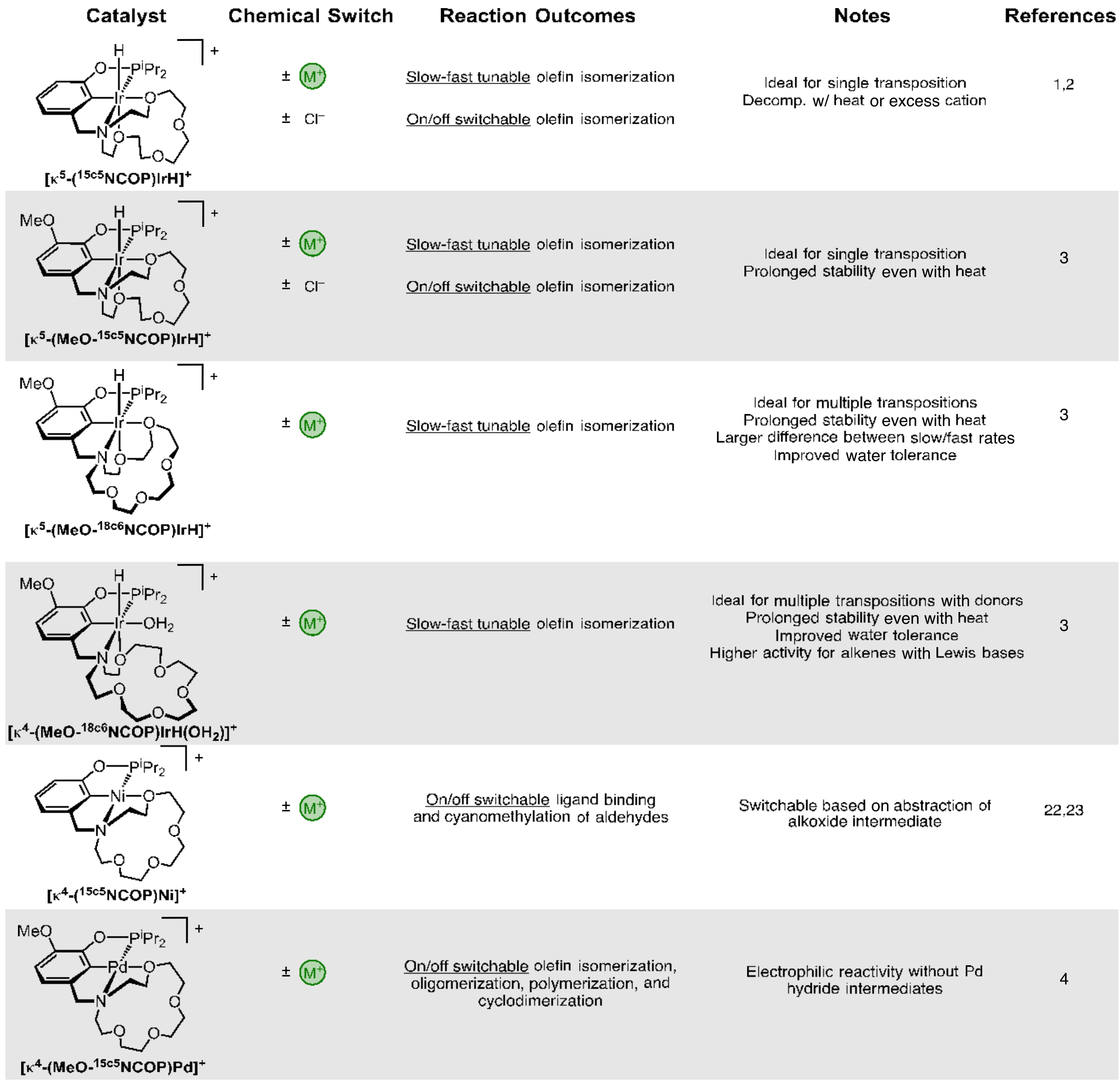


Figure 10. (A) Isomerization of 1-hexene catalyzed by **[κ^4-(MeO-^{15c5}NCOP)Pd]$^+$** with no salt (empty symbols) and with LiBAr$^F{}_4$ (filled symbols). (B) Isomerization of 1-hexene catalyzed by **[(MeO-^{Et}NCOP)Pd]$^+$** , with no salt (empty symbols) and with LiBAr$^F{}_4$ (filled symbols). (C) *In situ* "on" and "off" switching of 1-hexene isomerization by **[κ^4-(MeO-^{15c5}NCOP)Pd]$^+$**. Adapted with permission from *Organometallics* **2022**, *41*, 3366. Copyright 2022 American Chemical Society.

7. General principles of controlled organometallic catalysis with crown ethers: gating substrate binding.

Several pincer-crown ether metal catalysts have now been developed and applied to a range of switchable and tunable catalytic reactions. Figure 11 summarizes the catalyst structures, mode of controlled catalysis, reaction class, and pertinent notes. The evolution of ligand design and differences in the transition metal centers are apparent in this summary.



Catalyst	Chemical Switch	Reaction Outcomes	Notes	References
$[\kappa^5\text{-}(^{15c5}\text{NCOP})\text{IrH}]^+$	± M^+ ± Cl^-	Slow-fast tunable olefin isomerization On/off switchable olefin isomerization	Ideal for single transposition Decomp. w/ heat or excess cation	1,2
$[\kappa^5\text{-}(\text{MeO-}^{15c5}\text{NCOP})\text{IrH}]^+$	± M^+ ± Cl^-	Slow-fast tunable olefin isomerization On/off switchable olefin isomerization	Ideal for single transposition Prolonged stability even with heat	3
$[\kappa^5\text{-}(\text{MeO-}^{18c6}\text{NCOP})\text{IrH}]^+$	± M^+	Slow-fast tunable olefin isomerization	Ideal for multiple transpositions Prolonged stability even with heat Larger difference between slow/fast rates Improved water tolerance	3
$[\kappa^4\text{-}(\text{MeO-}^{18c6}\text{NCOP})\text{IrH}(\text{OH}_2)]^+$	± M^+	Slow-fast tunable olefin isomerization	Ideal for multiple transpositions with donors Prolonged stability even with heat Improved water tolerance Higher activity for alkenes with Lewis bases	3
$[\kappa^4\text{-}(^{15c5}\text{NCOP})\text{Ni}]^+$	± M^+	On/off switchable ligand binding and cyanomethylation of aldehydes	Switchable based on abstraction of alkoxide intermediate	22,23
$[\kappa^4\text{-}(\text{MeO-}^{15c5}\text{NCOP})\text{Pd}]^+$	± M^+	On/off switchable olefin isomerization, oligomerization, polymerization, and cyclodimerization	Electrophilic reactivity without Pd hydride intermediates	4

Figure 11. Summary of catalyst structures and the controlled catalysis applications.

Guiding principles in controlled catalysis have emerged from our work, particularly pertaining to the “gating” of substrate access to a catalyst active site through controlled hemilability. Mechanistic studies have established that the primary role of the cation is to assist in a ligand substitution reaction that results in (a) substrate binding to the transition metal center, (b) crown ether oxygen dissociation from the transition metal center, and (c) the crown ether engaging in cation-macrocycle interactions with the cationic additive. Several key factors influence the ability of a catalyst to achieve cation-controlled substrate gating (Figure 12).

First, a **hemilabile ligand** is required (Figure 12A). The catalyst must have one accessible state that is coordinatively saturated, preventing or slowing substrate access. (This is true even for the four-coordinate Pd complexes, either because the binding is unfavorable or because it is kinetically prohibited.) When the "gate is closed" the hemilabile donor(s) of the macrocycle in the pincer-crown ether ligand limit substrate binding to the transition metal ion. If substrate binding is negligible, the catalyst will be completely inactive in the absence of salt promoters (as seen for Pd catalysts), whereas if some degree of substrate binding is possible slow catalysis in the absence of salts will be observed. The choice of solvent can be critical, as strongly coordinating solvents (e.g. acetonitrile) can "break the gate" by displacing the hemilabile crown ether donors and prevent substrate binding, inhibiting catalysis.[1,23]

Second, **thermodynamically differentiated interactions** are required (Figure 12B). In pincer-crown ether complexes, strong cation binding is observed when no oxygen atoms are bound to the transition metal ion. But when one or more crown ether oxygens are donating to the transition metal, the binding affinity for cations becomes negligible.[23] The large difference in binding affinity between these two states provides the driving force for "opening the gate" and binding substrate. The transition metal identity, macrocycle size, and cation identity all influence substrate gating. Our studies have shown that different combinations of host-guest pairings can lead to different rates in olefin isomerization. For example, the 18-crown-6-based iridium catalyst with Na^+ isomerizes butene substrates ten times faster than the 15-crown-5-based iridium catalyst with Li^+.[3] These results can be rationalized through binding affinity studies that showed that pincer crown-ether complexes containing 18-crown-6-ether bind Na^+ two orders of magnitude stronger than 15-crown-5 ether complexes with Li^+ cations.[24] Solvent is again key in the secondary coordination sphere, since polar coordinating solvents can competitively bind to cationic species, shifting the cation-crown ether equilibrium that controls the substrate gating. For example, adding 25 equivalents of Et_2O during catalytic isomerization of allylbenzene by **[κ^{5}-(^{15c5}NCOP)IrH]$^{+}$**/LiBAr$^{F}_{4}$ decreased the TOF by ca. 2 orders of magnitude.[2]

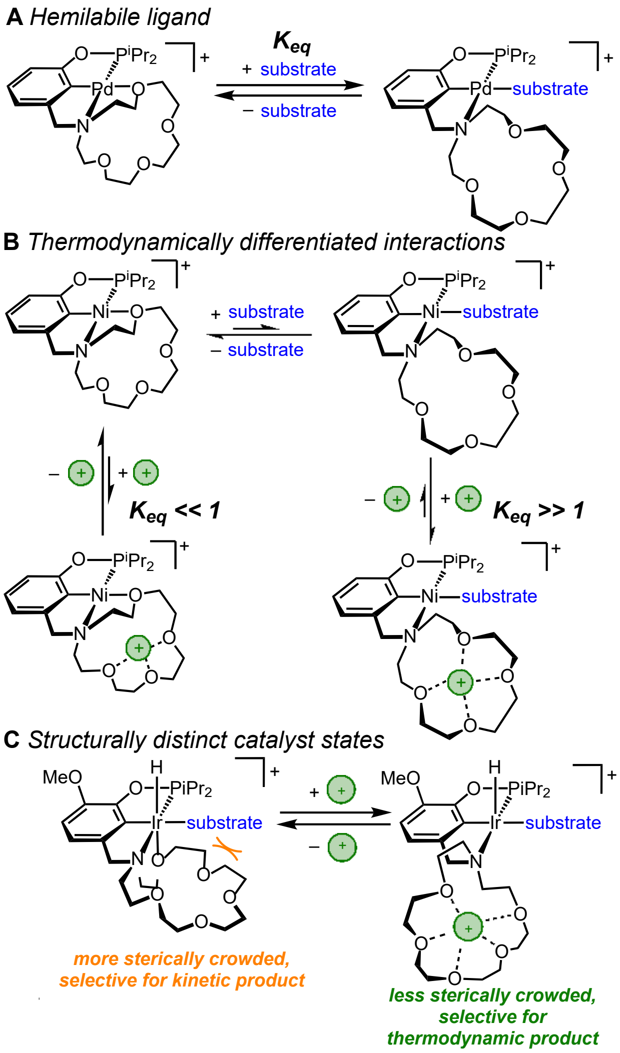


Figure 12. Selected design principles for cation-controlled catalysis.

Successfully balancing these factors can lead to excellent controlled catalysis. An example where catalyst redesign was needed to achieve the ideal balance is in aza-crown ether amine dissociation. Especially with 15-crown-5 ether derivatives, we have observed that at high temperatures in the presence of cations, not only the crown ether oxygen donors but also the amine can dissociate.[39–42] This can trigger reductive elimination reactions involving the phenyl backbone, deactivating the catalyst. A new catalyst with a methoxy group preventing unwanted metalation after reductive elimination led to better performance. Another example demonstrating the importance of these parameters is the differences in activity with palladium and iridium catalysts. While gated substrate binding was the key step in both systems, the palladium catalyst was the only system to show no activity in isomerization due to the stronger binding of crown-ether oxygen to the more electrophilic metal center. Yet the maximum rate of the iridium system was far higher.

In cases where distinct selectivity is targeted, **structurally distinct catalyst states** are likely necessary (Figure 12C). The iridium complexes here show distinct stereoselectivity during isomerization with and without Li^+ salts. Without Li^+ salts, one Ir–O bond is proposed to be maintained throughout catalysis, enforcing steric pressure near the active site and giving excellent regio- and stereoselectivity for 2-*E*-alkenes. In the presence of Li^+ salts, conversely, the crown is proposed to fully dissociate, and this distinct structure relieves steric congestion leading to purely thermodynamic control with reduced stereoselectivity.

These principles should apply broadly to various reaction classes, because so many reactions rely on substrate access to the active site. Some factors to consider in designing new reactions include balancing the donor ability of the substrates to avoid “breakthrough” of the gate in the absence of cations. It is also worth noting that many of the concepts introduced here are likely to apply to systems beyond pincer-crown ether complexes. For example, there are many complexes featuring polyether groups, some of which have been used in controlled catalysis.[13,49] And other classes of hemilabile ligands could be designed to engage in secondary interactions after dissociation using similar principles.

Looking forward with a firm grasp of design principles in hand, it should be easier to design cation-controlled catalysts for advanced applications. Multi-catalyst reactions carried out in one pot will be possible if the gating mechanism is robust to all of the components. Rate-matching in tandem reactions or cascades should be possible through fine-tuning the gate to reach a desired activity. Beyond gating, applications that take advantage of the electric field or Lewis acid properties of the cation held near the active site could lead to synergistic effects. Instead of reaching a maximum dictated by the equilibrium of binding, additional changes in rate or selectivity could lead to behavior different from control complexes that do not hold cations near the active site. New modes of control in catalysis offer new possibilities for reaction design and innovation.

Biographical Information

Sebastian Acosta-Calle received his B.S. in chemistry at the University of Florida, performing research with David Wei. He is currently a Ph.D candidate at the University of North Carolina at Chapel Hill working with Alexander Miller.

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