Multi-stage Catalysis

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An Ion-Responsive Pincer-Crown Ether Catalyst System for Rapid and Switchable Olefin Isomerization

*Matthew R. Kita and Alexander J. M. Miller**

Abstract: *Rapid, selective, and highly controllable iridium-catalyzed allylbenzene isomerization is described, enabled by tunable hemilability based on alkali metal cation binding with a macrocyclic "pincer-crown ether" ligand. An inactive chloride-ligated complex can be activated by halide abstraction with sodium salts, with the resulting catalyst [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ exhibiting modest activity. Addition of Li$^+$ provides a further boost in activity, with up to 1000-fold rate enhancement. Ethers and chloride salts dampen or turn off reactivity, leading to three distinct catalyst states with activity spanning several orders of magnitude. Mechanistic studies suggest that the large rate enhancement and high degree of tunability stem from control over substrate binding.*

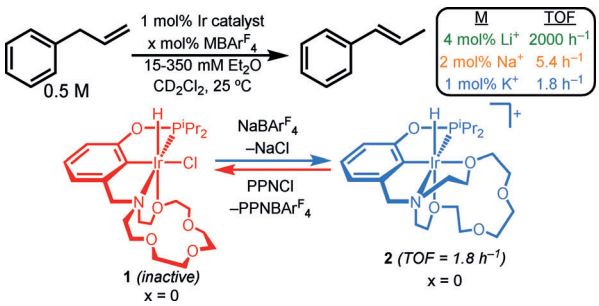
Catalytic reactions are often limited by the rate of substrate binding to a transition metal center. Control over ligand substitution would provide a method for optimizing catalysis and tuning reactivity, but general methods to tune substrate binding are lacking. In small organometallic catalysts, ligand hemilability provides some control over substrate access. Hemilabile chelates feature a mix of strong and weak donors, completing the metal coordination sphere with a weak donor that can be displaced by substrate to initiate catalysis. In many cases, hemilability provides an ideal balance of activity and stability,[1–3] particularly with alkene substrates in olefin isomerization,[4,5] oligomerization,[6,7] and metathesis.[8] The hemilabile donor acts as a "gate" that mediates substrate binding based on the metal–ligand bond strengths of the particular donor and the chelate size. But it has proven difficult to tune the degree of gating in hemilabile ligands.[9–11]

Substrate access has been most effectively controlled with supramolecular catalyst constructs that use large groups or encapsulation to physically block a substrate from reaching the catalyst.[12–14] Like allosteric regulators in enzymes, chemical effectors can bind the supramolecular construct and trigger a conformational change that enables substrate access and switches on catalysis. The main drawback in these elegant systems is the synthetic complexity, stemming from the need to use large blocking groups or capsules to prevent substrate binding. Methods that directly control the primary coordination sphere of the catalyst would be compatible with smaller, synthetically accessible catalysts.

Considering the lack of methods for controlling substrate binding in small organometallic catalysts, we have initiated a program to develop ligands with ion-tunable hemilability.[15–18] With a macrocycle as hemilabile ligand, dissociation of the chelate reveals a receptor for cation binding. With iridium pincer-crown ether complexes, cations in solution can adjust the extent of acetonitrile binding and the rate of H_2 activation.[15] Only degenerate H/D exchange was observed, rather than productive catalysis, with mechanistic studies suggesting a tunable continuum between two different activity states.

Ion-responsive olefin isomerization by a small organometallic catalyst is reported herein. Mechanistic studies indicate that Na$^+$ and Li$^+$ can generate distinct catalyst states with negligible, moderate and high activity. This is, to our knowledge, the first organometallic catalyst that can be readily switched in situ between three states of activity.

The catalytic isomerization of allylbenzene to β-methylstyrene was targeted as an ideal benchmark reaction applicable to a wide range of biomass- and petroleum-derived substrates.[19] The tetradentate hydrido chloride complex [κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl)] (**1**; the structure of ^{15c5}NCOP^{iPr} is shown in Scheme 1)[15] was tested for isomerization activity under standard conditions (5 mM **1** (1 mol%) and 0.5 M allylbenzene in CD_2Cl_2; Scheme 1). After 140 h at 25 °C, β-methylstyrene was observed in <0.1% yield. Hypothesizing that the chloride ligand was blocking olefin binding adjacent to the hydride ligand, we turned to the cationic hydride [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ (**2**) with [BAr$^F_4$]$^-$ as the anion, which features a pentadentate binding mode and a hemilabile ether donor (Scheme 1).[15] Catalyst **2** converted allylbenzene to β-methylstyrene in >96% yield over 141 h, with an initial turnover frequency (TOF) of 1.82 h^{-1}. Greater than 99% selectivity for the *E* isomer, *trans*-β-methylstyrene, was observed. Other catalysts typically provide only up to 92%



Scheme 1. Isomerization conditions and structures of the two catalyst states [κ^4-(^{15c5}NCOP^{iPr})Ir(H)(Cl)] (**1**) and [κ^5-(^{15c5}NCOP^{iPr})Ir(H)]$^+$ (**2**). PPN = bis(triphenylphosphino)iminium; Ar^F = 3,5-bis(trifluoromethyl)-phenyl.

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selectivity after isomerization at 60 °C or above for multiple hours.[19–22] The activity of catalyst **2** is attributed to the hemilability of the ether ligand *cis* to the hydride ligand. The high selectivity is attributed to the mild reaction conditions, with the *E* isomer being thermodynamically favored at lower temperatures.[23]

We next sought to tune the activity of **2** using cation–crown interactions to adjust substrate-binding tendencies (Scheme 1). Carrying out allylbenzene isomerization in the presence of 1 mol% $KBAr^F_4$ and 350 mM Et_2O did not provide any rate enhancement. Including 2.2 mol% $NaBAr^F_4$ and 78 mM Et_2O on the other hand, led to a 3-fold rate enhancement (TOF = 5.4 h^{-1}) relative to salt-free conditions, reaching completion after about 100 h.[24] Lithium salts foster remarkable increases in catalytic activity: Upon injection of allylbenzene into an NMR tube containing 1 mol% **2** and 0.8 mol% $LiBAr^F_4$ in CD_2Cl_2, complete isomerization occurred within 10 min. The selective response of catalyst **2** to Li^+ is striking, given that Na^+ and Li^+ have similar binding affinity with 12-crown-4.[25]

The dramatic increase in activity caused by lithium salts enabled a reduction in the required amount of precious metal catalyst. At 0.1 mol% (0.5 mM) **2** in the presence of 10 equiv of $LiBAr^F_4{\cdot}3\,Et_2O$, full conversion of allylbenzene to β-methylstyrene (>99% *trans*) was observed in 24 min (11.6 min half-life, TOF = 2750 h^{-1}). Isomerization by **2** alone, even at 5 mol% loading, proceeded with a 530 min half-life. The cation-tuning approach thus enabled a 50-fold reduction in Ir loading while still producing *trans*-β-methylstyrene 46 times faster than 5 mol% **2**!

Rapid olefin isomerization is not confined to allybenzene. The phenylpropenoid 4-methoxyallylbenzene is isomerized by the **2**/Li^+ system in less than 10 min, forming the fragrance additive anethole[26] in 98% yield and with 97.3% selectivity for the *trans* isomer. Isomerization of 0.5 M 1-hexene by 1 mol% **2** (without added salt) reached 97% conversion after 40 h ($t_{1/2}$ = 487 min) with a distribution of isomers favoring *trans*-2-hexene (81% yield). In the presence of 1.3 mol% $LiBAr^F_4{\cdot}3\,Et_2O$, it took only 2 min to reach a similar distribution ($^0t_{1/2}$ = 0.59 min), indicating an 825-fold rate enhancement. Allowing the Li^+-containing mixture to react further led to about 17% yield of 3-hexenes after 190 min, compared to roughly 3% 3-hexenes in the absence of Li^+ after 40 h, suggesting that cations can also influence regioselectivity patterns. The **2**/Li^+ system is among the fastest isomerization catalysts at room temperature.[4,5,19,26,27]

Detailed kinetic studies were carried out to provide insight into the mechanism of this cation-tuned catalysis. Allylbenzene isomerization was monitored by ^1H NMR spectroscopy. With catalyst **2** (without alkali metal salts), the concentration of allylbenzene decreased exponentially (Figure S2 in the Supporting Information), indicating that the reaction is first-order in olefin ($k_{obs} = 3.83 \times 10^{-4}$ min^{-1}, $t_{1/2}$ = 1810 min). The reaction is also first-order in **2**, on the basis of k_{obs} increasing linearly with increasing catalyst concentration (Figure S6).

The broad mechanistic features did not change in the presence of Na^+. The rate of isomerization increased linearly as the Na^+/**2** ratio increased from 1.1 to 7.5 (constant 0.5 M Et_2O), with each plot exhibiting exponential decay of allylbenzene (Figure 1 A). A plot of k_{obs} vs. [Na^+] is linear (Figure S13) with a non-zero intercept (3.06×10^{-4} min^{-1}) close to the experimentally observed value for cation-free isomerization under comparable conditions (Figure S3). The presence of an additional Na^+-dependent term in the rate law [Eq. (S1)] is consistent with a cation–crown binding equilibrium. NMR spectroscopy confirms that **2** is the resting state in each case.

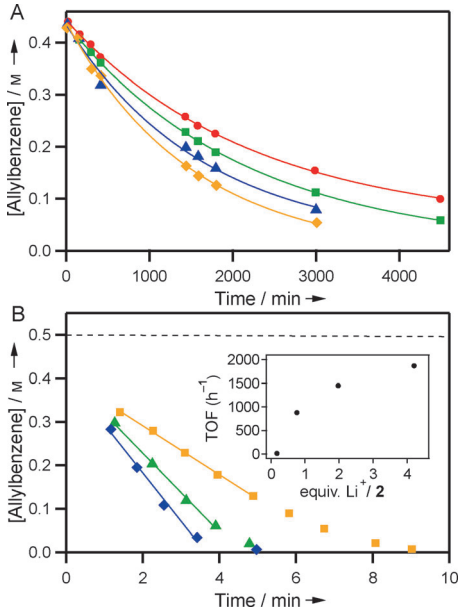
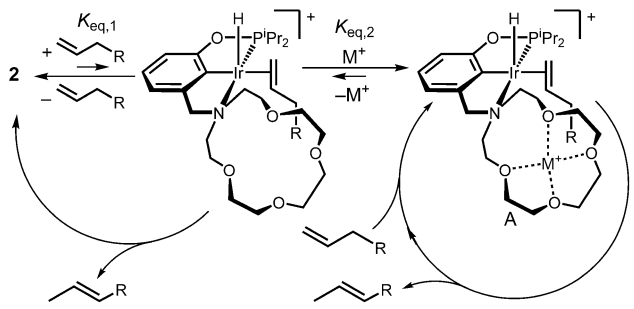


Figure 1. Allylbenzene isomerization by 5 mM **2** (A) with 1.1 (red circles), 2.5 (green squares), 5.0 (blue triangles), and 7.4 (yellow diamonds) equiv of $NaBAr^F_4$, and (B) with 0.8 (orange squares), 2.0 (green triangles), 4.2 (blue diamonds) equiv of $LiBAr^F_4{\cdot}3\,Et_2O$, and without salt (dashed line). Inset: Li^+ influence on TOF.

The dramatic Li^+-promoted rate enhancement is accompanied by a striking change in the kinetic profile (Figure 1 B). In the presence of Li^+, the concentration of allylbenzene decreases *linearly* over time, indicating a shift to a regime that is zero-order in olefin. As the Li^+/**2** ratio increases, the rate of isomerization increases dramatically before eventually leveling off (Figure 1 B, inset). The fastest Li^+-accelerated trial (TOF = 1870 h^{-1} and zero-order half-life, $^0t_{1/2}$ = 1.6 min) features a 1100-fold enhancement compared to the standard conditions (TOF = 1.8 h^{-1} and $t_{1/2}$ = 1810 min).

A mechanism consistent with the data is shown in Scheme 2. In the absence of cations, the reaction is first-order in catalyst and allylbenzene, consistent with a pre-equilibrium displacement of crown ether by allylbenzene ($K_{eq,1}$) influencing the observed rate. The rate accelerates as the alkali metal salt concentration increases, indicating a parallel catalytic cycle in which cation–crown interactions stabilize the proposed olefin adduct **A** ($K_{eq,2}$). Li^+ salts shift $K_{eq,2}$ further towards **A**, reaching a regime that is zero-order in allylbenzene and eventually zero-order in Li^+, with turnover-limiting insertion or elimination at Ir. Accordingly, the hydride resonance of **2** diminishes (Figure S16) and other



Scheme 2. Proposed mechanism of ion-controlled catalysis.

spectral features broaden as the concentration of Li^+ increases. We hypothesize that **A** is the predominant resting state when the reaction becomes Li^+-independent, at which point the maximum rate is achieved. A simple kinetic model based on Scheme 2 provides excellent fits to the experimental data (Figure S17), suggesting that Li^+ binding generates a new catalyst state that is highly active because it is not limited by substrate binding.

We next sought to reverse the effects of cation modulation to provide full control over the catalytic activity. The impact of Li^+ salts is readily dampened by donor ligands. The effect of Et_2O on the Li^+-enhanced allylbenzene isomerization with **2** was quantified by monitoring the **2**-catalyzed isomerization of allylbenzene with 1 mol% $LiBAr^F_4{\cdot}3\,Et_2O$ and 0–23 equiv of Et_2O. By varying the ratio of Et_2O/Li^+, the isomerization rate could be tuned across two orders of magnitude (Figure S28). In the presence of extra ether, allylbenzene decays exponentially, indicating pre-equilibrium steps involving hemilability. The Et_2O likely ligates Li^+, reducing its Lewis acidity and disrupting the cation–crown interactions ($K_{eq,2}$) that enable rate enhancement.

Ether dampening helps explain why the readily available salt $LiBPh_4{\cdot}3\,(MeOCH_2CH_2OMe)$, with six ether donors per Li^+, does not produce dramatic enhancements. On the other end of the spectrum are soluble, donor-free salts, such as $LiAl(OC(CF_3)_3)_4$.[28] Catalysis under standard conditions with 1.6 mol% $LiAl(OC(CF_3)_3)_4$ proceeded rapidly (TOF = 2010 h^{-1}) and with a zero-order half-life ($^0t_{1/2} = 1.62$ min), achieving the same maximum rate reached with $LiBAr^F_4{\cdot}3\,Et_2O$.

Chloride salts can stop the catalytic activity entirely. If there are Na^+ or Li^+ ions in solution, addition of Cl^- promotes NaCl or LiCl precipitation and restores the activity to the level of **2** alone. Additional Cl^- binds the Ir center, converting **2** into the catalytically inactive hydrido chloride complex **1**, as shown in Scheme 1.

Recognizing that $NaBAr^F_4$ is capable of converting an inactive catalyst state (chloride **1**) into an active catalyst state (cation **2**), we targeted in situ switchable catalysis using Na^+ salts and chloride salts as external stimuli. Figure 2 A shows that according to in situ NMR spectroscopic monitoring the initial mixture of **1** and allylbenzene in CD_2Cl_2 did not isomerize over 1 h. Addition of 2 equiv of $NaBAr^F_4$ initiated catalysis. After 1 h, addition of 2 equiv of PPNCl prompted precipitation of NaCl and formation of **1**, halting catalysis. The catalyst was switched on and off in this fashion three

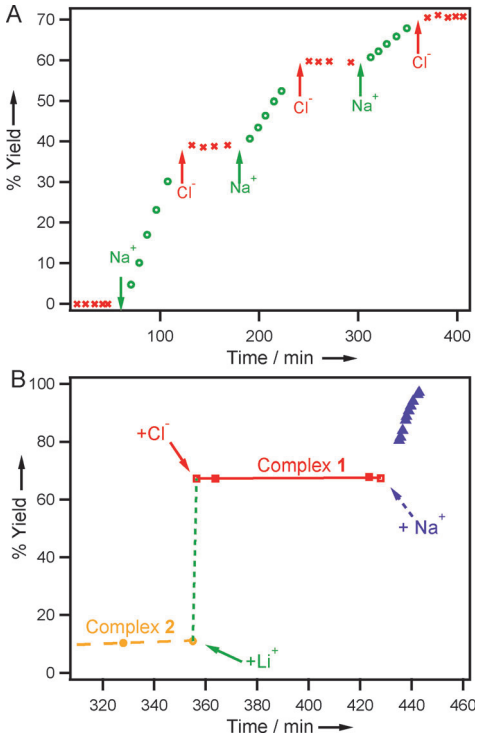
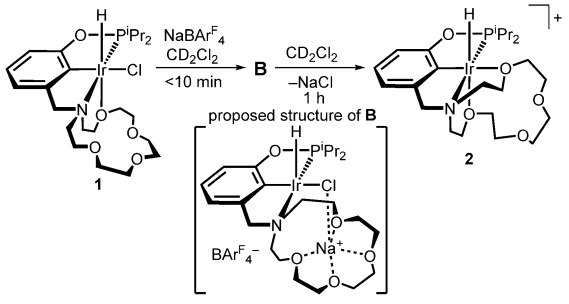


Figure 2. Switchable allylbenzene isomerization catalysis monitored by ^1H NMR spectroscopy in CD_2Cl_2 (5 mM catalyst, 0.5 M allylbenzene). A) Starting from chloride complex **1**; green arrows marked "Na^+" indicate points at which 2 equiv of $NaBAr^F_4$ were added, and red arrows marked "Cl^-" indicate points at which 2 equiv of PPNCl were added. B) Multi-state in situ switching starting from cationic complex **2**; the arrows indicate addition of 1.0 equiv of $LiBAr^F_4$ (green), 2.5 equiv of PPNCl (red), and 6.3 equiv of $NaBAr^F_4$ (purple).

times successfully. This is a rare example of switchable olefin isomerization,[29,30] with excellent rate differentiation between the on and off states attributed to direct control over substrate binding.[13,31]

Although $NaBAr^F_4$ successfully switched on the two-state system of Scheme 1, the isomerization rate of the "switched-on" catalyst was surprisingly fast ($k_{obs} = 8.46 \times 10^{-3}$ min^{-1}, $t_{1/2} = 82$ min^{-1}) compared to that of isolated samples of **2** containing excess Na^+ ($t_{1/2} = 992$ min). Evidence for an unexpected intermediate along the path of halide abstraction was obtained in the absence of olefin. Upon injection of about 2 equiv of $NaBAr^F_4$ into a solution of **1** (Scheme 3), the color



Scheme 3. Dehalogenation of chloride complex **1**.

changed from yellow to burnt orange and ^{1}H NMR spectroscopy revealed one hydride resonance for **2** ($\delta = -29.8$ ppm), and a second, previously unobserved resonance for **B** ($\delta = -32.5$ ppm). Only **2** was present after 50 min. Similar behavior is apparent during catalysis (Figure S35), with the reaction progressing rapidly at early times when substantial amounts of an intermediate **B** are present. After 50 min, complete dehalogenation leaves only **2** in solution and catalysis slows considerably. We propose that an intermediate with Na^+ bridging the crown ether and the Ir–Cl unit, [κ^3-(^{15c5}NCOP^{iPr})Ir(H)(NaCl)]$^+$ (**B**), facilitates chloride substitution.

The different activity regimes can be toggled in situ, illustrating comprehensive control over activity using simple ions as switches and tuning agents (Figure 2B). Allylbenzene isomerization is initiated by addition of complex **2**, a slow "on" state. After 355 min (11% yield of β-methylstyrene), $LiBAr^F_4 \cdot 3Et_2O$ was added and the mixture was allowed to react for 1 min before 2.5 equiv of PPNCl was added to precipitate LiCl and bind Ir; in just 1 min of ion-enhanced catalysis, the yield increased to 70%. Chloride complex **1** is the "off" state, and the reaction progress was halted entirely for 73 min when Ir was present in the form of **1**. Addition of excess $NaBAr^F_4$ restarted isomerization at the intermediate rate of metastable species **B**. This catalysis with a small organometallic complex is complementary to catalysis using supramolecular complexes that have made great strides in two-state switchable catalysts.[32–34] In 2011, a unique three-state supramolecular system, capable of generating racemic mixtures or the desired enantiomer by switchable encapsulation of chiral organocatalysts, was reported.[35] Catalyst systems with three or more well-defined states with different activity levels are rare, and facile in situ modulation of such a catalyst system may be unprecedented.

More broadly, the ability to precisely control substrate binding by accessing and tuning ligand hemilability has sparked the development of an extremely active, highly selective catalyst. Simple alkali metal cations and chloride anions act as in situ switches to tune activity in isomerization, with a massive span in turnover frequency ranging from inactive to more than 2000 h^{-1}. The approach introduced herein could be applicable to many catalytic reactions that are limited by substrate binding or involve ligand hemilability.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: hemilability · homogeneous catalysis · iridium · olefin isomerization · switchable catalysis

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Communications

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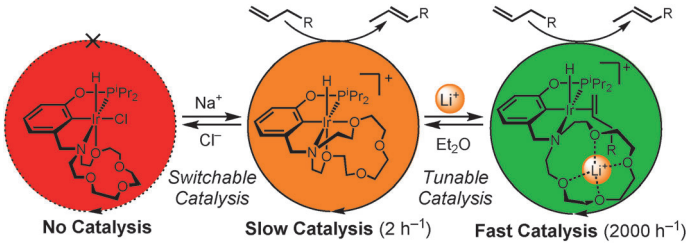
An Ion-Responsive Pincer-Crown Ether Catalyst System for Rapid and Switchable Olefin Isomerization



Multi-stage cati-ON booster: Complete control over activity is achieved for olefin isomerization with the system shown. Mechanistic studies suggest that cations help control substrate binding through interaction with the hemilabile macrocycle of "pincer-crown ether" ligands. Acceleration using an appropriate cation and deceleration using ether or chloride sources provide exquisite control over the catalytic activity.

