

AN ABSTRACT OF THE CAPSTONE REPORT OF

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Title: The Influence of Alkali and Alkaline Earth Metals on Transition-metal Catalyzed Reactions

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Alkali and alkaline earth metals are useful co-catalysts in many inorganic and organometallic reactions. The interactions of these metals to transition-metal complexes modulate the overall structures. The alkali and alkaline earth metal ions withdraw electron density from transition metal center and tune the reduction potentials. The stabilization of anion intermediates by alkali and alkaline earth metal ions reduces transition-state energy and enhance the reactivity kinetically. In homogeneous catalysis, alkali and alkaline earth metals have been shown to bind to electron-rich anionic ligands that then stabilize the formation of heterobimetallic complexes. This is especially important when key transition states are stabilized by such coordination as this can lead to greatly enhanced catalytic efficiency. These metal ions can also collaboratively bind to crown-ether installed ligands and control metal-ligand cooperativity. In addition, reaction selectivity could also be enhanced by using different sizes of alkali or alkaline earth metal ions. Thus, incorporation of alkali and alkaline earth metals to transition-metal catalysts can modulate or completely change the reactivity.

The Influence of Alkali and Alkaline Earth Metals on Transition-metal Catalyzed Reactions

By
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Neil C. Tomson, Academic Advisor, representing Area of Concentration

I understand that my Capstone Report will become part of the permanent collection of the University of Pennsylvania Master of Chemical Sciences Program. My signature below authorizes release of my final report to any reader upon request.

Jia Qi, Author

Dedication and acknowledgements

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Introduction

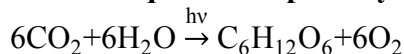
Catalysts have now been widely used in industrial production of fuels, fertilizers, fibers, plastics, and pharmaceuticals.¹ The applicability of catalysts in many areas arises from its ability of lowering activation energy and enabling reactivity. Although the reactivity of these transition-metal catalysts is diverse, many of them consist of expensive transition metals such as platinum, iridium, and palladium and require high temperatures and pressures.² Recently, research focus has been shifted to generate green catalysts that consist of inexpensive and harmless reagents and react under mild conditions.³ Cooperativity of inexpensive transition-metal catalysts and alkali and alkaline earth metals could enable or surpass the reactivity those expensive catalysts contain. In addition, the integration of these metals to transition-metal catalysts could lower the anionic transition state intermediate and enable unique methods of small molecule activation.⁴⁻⁶ For instance, the natural-occurring oxygen evolving complex (OEC) of photosystem II is comprised of a core Mn_4Ca structure.⁷ Although the role of calcium in promoting the oxidation of water to dioxygen remains an open topic of research, calcium has shown to enhance the water oxidation cooperatively with manganese in OEC. The cooperativity of transition metals and alkali and alkaline earth metals has also been demonstrated in molecular systems, where alkali metals have shown to improve catalytic performance in terms of both yield and reaction rate. For example, halide activation and subtraction were triggered by alkali metal ions in iridium(III) carbonyl complexes supported by aminophosphinite pincer ligands containing crown ether.⁸ These coordination modes enable and accelerate many reactions and their rates. Combination of crown-ether type ligand and alkali metal ions brings new perspective to switch between ligand binding modes. Alkali and alkaline earth metal ions have been found to bind to nucleophilic ligands and molecules to stabilize the reactive intermediate. During methanol dehydrogenation reaction, the release of carbon dioxide from formate anion is an essential step in the catalytic cycle, the transition-state energy was lowered dramatically in the presence of sodium cation.⁹ The cation stabilizes the anionic charge and enables the successful release of carbon dioxide. Regioselectivity in coupling reactions could also be controlled by the size of alkali metal ions. For instance, the cation- π interaction between potassium and aryl groups selectively generates one product over the other using small-sized cation lithium in the absence of such interaction.¹⁰ In the report, the stabilization of alkali and alkaline earth metal ions on anionic transition-state intermediates lowers the activation energy, which enhances reactivity kinetically by accelerating reaction rates. In this review, reactions that make use of the cooperative action of transition metals and alkali and alkaline earth metals are described, with a focus on OEC and the modified complexes, structural, and reactivity modulation. The use of alkali and alkaline earth metals in anionic transition state intermediates which lower activation energies will also be demonstrated.

Studies towards OEC structure determination.

Oxygenic organisms such as plants and cyanobacteria convert water and carbon dioxide to carbohydrates and oxygen in the presence of sunlight.^{11,12} (Scheme 1). Photosynthesis occurs at two main enzymes: photosystem II and photosystem I. Photosystem II oxidizes water and transfers electrons to photosystem I, which then produces NADPH (nicotinamide adenine dinucleotide phosphate bonded to a hydrogen

ion).¹² Both the structure of active site of photosystem II and its mechanism of action are still under active investigation, despite decades of research that have gone into attempting to understand these features of the OEC.

Scheme 1. The equation of photosynthesis.



The first great leap towards investigating the OEC was realized when OEC-containing proteins were isolated from *Thermosynechococcus elongatus* and the active center of OEC was visualized. A cubane structure of Mn_3CaO_5 was found; however, the low resolution of the structure and the presence of over 99 cofactors around photosystem II limited the visualization of OEC.^{13–17} In 2011, the Umena group reported a structure photosystem II with a resolution to 1.9 Å, which allowed for greater resolution of Mn_4CaO_5 active site. The complex is comprised of four manganese, one calcium, and five oxygens (**Figure 1**).¹⁷ Notably, the cubane core exhibits an oxygen-metal alternating pattern and a calcium is linked to a fourth Mn by an oxo bridge (**Figure 1**).

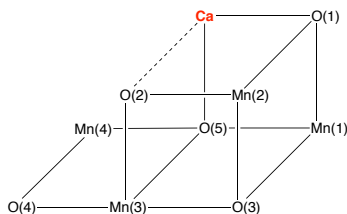


Figure 1. Core structure of the OEC in photosystem II consisting of Mn_4CaO_5 in an alternating metal-oxo pattern. Dashed line shows the interaction between calcium and oxygen.¹⁷

To gain insight into the oxidation states of the Mn ions, the Dau group used X-ray absorption fine-structure (EXAFS) to determine the Mn oxidation states within OEC. This study allowed for the analysis of four different stable intermediate stages (S_0 , S_1 , S_2 , S_3).¹⁵ From S_0 to S_1 , $\text{Mn}(3)^{\text{III}}$ is oxidized to $\text{Mn}(3)^{\text{IV}}$, but $\text{Mn}(1)^{\text{III}}$, $\text{Mn}(2)^{\text{III}}$, and $\text{Mn}(4)^{\text{IV}}$ remain the same oxidation states (**Figure 2**). From S_1 to S_2 , $\text{Mn}(2)^{\text{III}}$ is oxidized to $\text{Mn}(2)^{\text{IV}}$, with the remaining Mn ions unchanged, then from S_2 to S_3 , the last Mn^{III} is oxidized to $\text{Mn}(1)^{\text{IV}}$ (**Figure 2**). It should be noted, however, the X-ray photoreduction may hamper identification of Mn oxidation states along the S cycle. With the core structure of the OEC from X-ray crystallographic data and the oxidation states of manganese ions from XAS determined, further studies into the mechanism and role of each Mn and Ca are done.

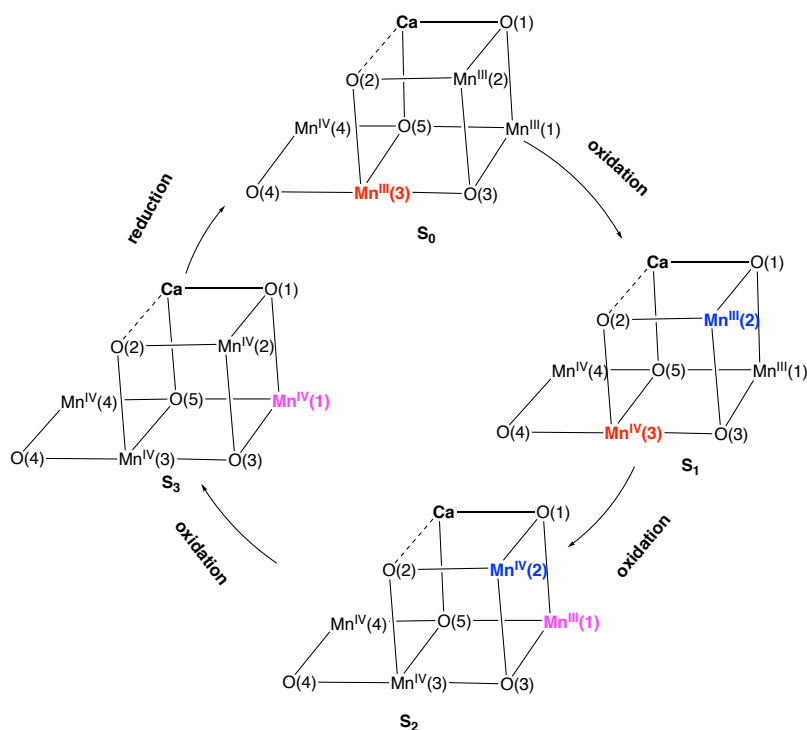


Figure 2. Proposed S cycle with assigned Mn oxidation states.¹⁵

There are two competing theories at this time for the mechanism of the OEC. The Dau group proposed that Mn(4) is the most likely site to bind water molecules and promote dioxygen formation, due to the unsaturated coordination sphere Mn(4).¹⁵ In contrast, the Barber and Iwata groups proposed a more detailed water oxidation mechanism detected by electron density map.¹³ Their ideas of Mn ion binding water molecule were advocated by the Siegbahn, Brudvig, and Pecoraro groups.^{18–21} These groups suggested that the binding of the dangling Mn(4) ion to a water molecule during one of the S-states promotes the formation of a highly reactive electrophilic intermediate: either a Mn(IV) oxyl radical or a Mn(V) oxo.¹³ Subsequently, the water molecule ligated to Ca^{2+} is used to generate an O–O bond via nucleophilic attack. The radical mechanism could be tested using radical quench approach. The Mn(IV) oxyl radical could be captured by TEMPO and result in reduction in yield. LCMS or GCMS confirms whether the Mn(IV) oxyl TEMPO is produced. Although a comprehensive mechanism has not been grasped, developing OEC-based biomimetic studies gives evidence to understand it. The mechanism of water splitting could possibly be probed by the combination of surface-enhanced Raman scattering (SERS), Density Functional Theory (DFT), and isotope labeling.²² SERS monitors continuous water oxidation process and isotope labeling traces the position of water molecule. The DFT calculation optimizes the intermediate geometry.

Biomimetic synthesis (OEC)

As a better understanding of photosystem II and OEC has been obtained, an increasing number of researchers have synthesized biomimetic molecules in an attempt to understand the mechanisms of water oxidation and imitate OEC reactivity. In this area, the Christou group reported the synthesis of a high oxidation state Mn^{IV} –Ca cluster

Mn₁₃Ca₂ cluster (**Figure 3**).⁶ The core structure of the multinuclear complex is centrosymmetric with mix-valent manganese (Mn^{II}, Mn^{III}, and Mn^{IV}) and calcium binding outside the metal-oxygen alternating Mn₄O₄ cube.⁶ Two Mn₄O₄ cubes reside on each side of the compound linked by two calcium and five manganese and six oxygens (**Figure 3**). The complex was synthesized successfully. However, water splitting reactivity using their manganese complexes is limited. By comparing the core structure of OEC **1** (**Figure 1**) with **2** (**Figure 3**), the calcium is embedded in the cube in OEC, while calcium is linked by an oxygen outside the cube in Christou's example. One of the explanations could be the long distances of Mn–Ca restrict the electron-withdrawing property of calcium, thus hindering reactivity. This is plausible because calcium withdraws electron from the manganese to form highly oxidized manganese. In this way, the complex could go through three continuous oxidation to complete the catalytic cycle of water splitting. However, the electron withdrawing ability decreases with decrease; therefore, having the calcium outside the cube structure could possibly restrict reactivity.

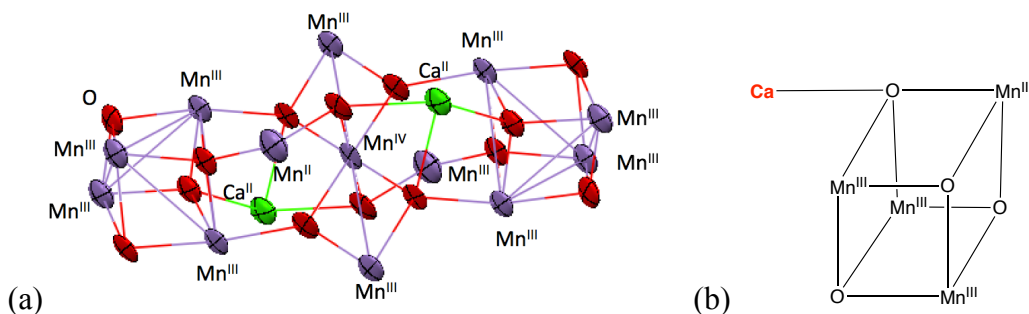


Figure 3. (a) Molecular core structure of Mn₁₃Ca₂ cluster with phenyl groups on carbonate, and hydrogen atoms omitted for clarity. Thermal ellipsoids are shown (red: oxygen; green: calcium; violet: manganese). (b) Core cubane structure in Mn₁₃Ca₂ cluster. The crystal structure was obtained in 3.5 Å resolution.⁶

As stated earlier, determination of the different manganese oxidation states during the S-state cycle are complicated by the possibility of X-ray-induced photoreduction during spectroscopic interrogation.²³ Powell and his coworkers attempted to resolve the complication and developed new models by synthesizing three MMn₄ (M = Na, Ca) clusters ([CaMn^{III}₃Mn^{II}(μ₄-O)L₃Cl₂(O₂CMe)_{1.2}(H₂O)_{1.5}(MeOH)_{0.3}]Cl_{0.8}•5MeOH, [NaMn^{III}₃Mn^{II}(μ₃-O)L₃(N₃)_{2.7}(O₂CMe)_{1.3}(MeOH)]•2MeOH•0.5H₂O, and [{NaMn^{III}₄(μ₃-O)L'₄(N₃)₃(MeOH)}₂]Cl•3MeOH) supported by Schiff-base ligands (L or L') to understand the OEC in photosystem II (**Figure 4**). The ligand binds to the metals through deprotonated hydroxyl groups and nitrogen. The molecule coordinates to three ligands. They compared 2.7 Å Mn–Mn distance in OEC based off of the 1.9 Å resolution structure with those in their systems; however, Mn–Mn bond distances in the synthesized complexes are longer than 3.0 Å with the shortest one at 3.015 Å. Therefore, they suggested that manganese in OEC are at high oxidation states (Mn^{IV}) compared to the manganese in three Mn/Ca or Mn/Na complexes. The Powell group hypothesized that the low-oxidation Mn^{II} and Mn^{III} complexes could possibly enter S state catalytic cycle at stage S₀ and S₁ in OEC because of almost identical oxidation states. The authors successfully presented the mix-valent manganese sodium/calcium complexes and also compared them with OEC to provide insight about synthesizing high-valent manganese

clusters. Their hypothesis is plausible because of low oxidation states of manganese (+2) at S_0 state in the catalytic cycle. Therefore, in the biomimetic studies, the manganese should be able to be oxidized to Mn^{IV} easily to oxidize water molecules.

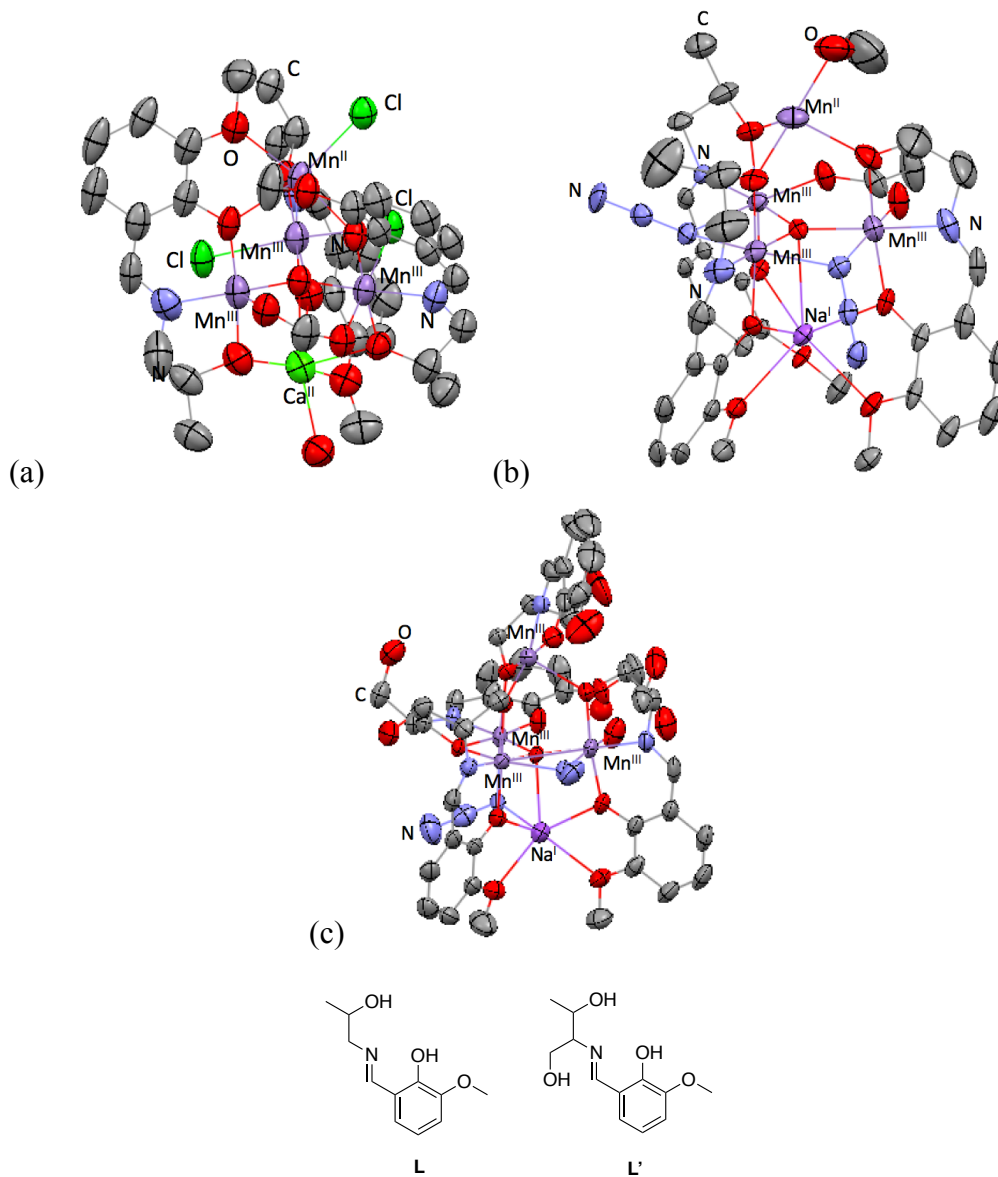


Figure 4. Molecular structures of three synthesized molecules a, b, and c ($[CaMn^{III}_3 Mn^{II}(\mu_4-O)L_3Cl_2(O_2CMe)_{1.2}(H_2O)_{1.5}-(MeOH)_{0.3}]Cl_{0.8} \cdot 5MeOH$, $[NaMn^{III}_3Mn^{II}(\mu_3-O)L_3(N_3)_{2.7}(O_2CMe)_{1.3}(MeOH)] \cdot 2MeOH \cdot 0.5H_2O$, and $[NaMn^{III}_4(\mu_3-O)L'_4(N_3)_3(MeOH)_2]Cl \cdot 3MeOH$) supported by Schiff-base ligands (L or L'). Thermal ellipsoids are shown above with colors representing different atoms (grey: carbon; red: oxygen; blue: nitrogen; green: chloride or calcium; violet: manganese; purple: sodium). The crystal structure was obtained in 3.2-3.8 Å resolution.²³

In related research, the Milios group reported the synthesis of a Mn_6Ca_2 cluster with exclusively Mn(III) ions.²⁴ Five of the manganese ions exhibit pseudo-octahedral

coordination geometry, while a fifth manganese resides in square pyramidal geometry.²⁴ The core structure of manganese and calcium forms a tetrahedron with bridging oxygens and nitrogens (**Figure 5**). The Mn–Mn distance (3.2 Å) in the synthesized complex fits well with the Mn–Mn distance range of 2.7–3.3 Å in OEC, suggesting that the Mn ions in both Milios cluster and OEC are in high oxidation states. X-ray crystallographic data from a single-crystal shows that each calcium in the complex binds to a water molecule, which might facilitate water oxidation due to direct coordination. The authors proposed that the calcium acts as a Lewis acid, binding a water molecule and tuning the electron density of the adduct. Compound **3** in the presence of Mn^{III} ions may be a good model of OEC at the S₄ ground state in the S state catalytic cycle. This is reasonable because at the terminal water oxidation catalytic cycle, all the manganese would be reduced into low oxidation states.

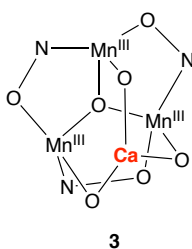


Figure 5. The core structure of Mn₆Ca₂ cluster.²⁴

To further probe the role of calcium in the OEC, the Kurz group synthesized manganese oxides (Mn₂O₃) and calcium-manganese oxides (CaMn₂O₄•4H₂O, CaMn₂O₄•H₂O, CaMn₂O₄) materials.²⁵ A Clark-type polarographic oxygen electrode was used to identify formation of oxygen when the oxides materials were added to solutions of hydrogen peroxide.^{25,26} It was found that the oxides have the catalytic activity for hydrogen peroxide disproportionation with the CaMn₂O₄•H₂O converting hydrogen peroxide at 72% yield. The rate was determined in mmol_{O₂}•mol_{Mn}⁻¹•s⁻¹ from Clark electrode detector.²⁵ The manganese oxides produce oxygen at a rate of 0.03 mmol_{O₂}•mol_{Mn}⁻¹•s⁻¹, while the calcium-manganese moieties generates dioxygen at a rate of 0.90 mmol_{O₂}•mol_{Mn}⁻¹•s⁻¹) using [Ce^{IV}] as the oxidant. Notably, during the study of light-induced disproportionation, it was found that the calcium-manganese oxide materials also have a better oxygen generation performance than manganese oxides from the same detector. From these studies, it was concluded that the amount of available surface area (measured in a combination of a Quantachrome Autosorb-1 MP instrument and BET theory analysis) did not change much of the catalytic performance; however, the addition of Ca²⁺ improves the catalytic rate significantly. In addition, water oxidation has been shown to exhibit limited activity when calcium is removed from the OEC.

To explore the role of calcium ion in its proposed water binding and redox tuning properties, there have been studies replacing calcium with different redox-inactive metals in OEC and investigating their reactivity.²⁷ The Shen group substitutes Sr to Ca in OEC extracted from spinach and compared the water oxidation performance.²⁸ The results displayed that strontium is the only metal among other alkaline earth metals that could retain the catalytic reactivity of water oxidation, albeit at 46 % of the activity of the calcium-containing enzyme.^{27,29–31} When overlapping the crystal structure of Ca-

containing and Sr-containing OEC, the structures are very similar. A crystal structure of Sr-containing protein shows short distances between Mn–Ca(Sr) at 3.4–3.5 Å.²⁷ The similarity in Mn–Ca and Mn–Sr bond length might support the plausible catalytic activity, while the mechanisms of using strontium or calcium to promote water oxidation are still not clear.

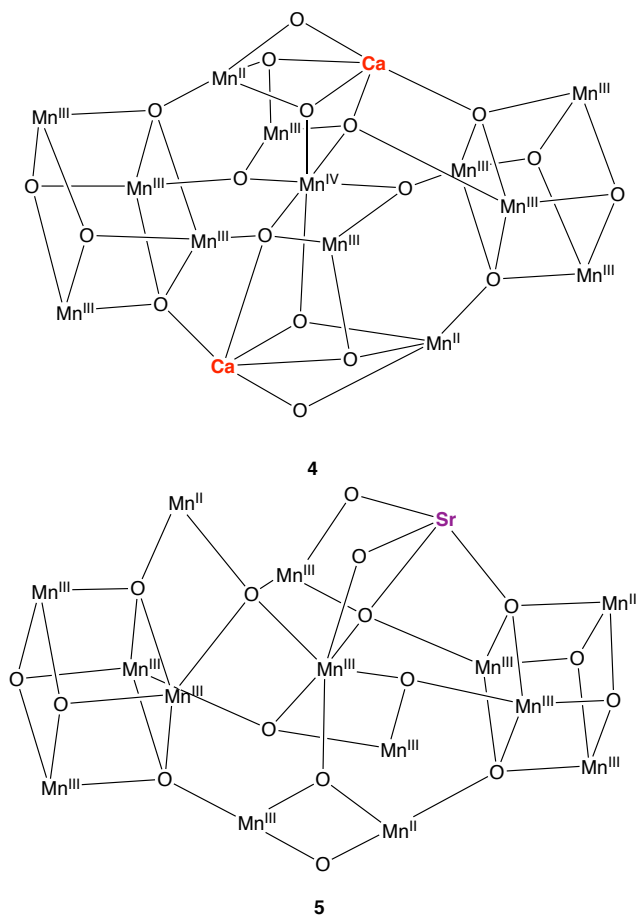


Figure 6. The core structures of $[\text{Ca}_2\text{Mn}^{\text{IV}}\text{Mn}^{\text{III}}_{10}\text{Mn}^{\text{II}}_2\text{O}_{10}(\text{OH})_2(\text{OMe})_2(\text{O}_2\text{CPh})_{18}(\text{H}_2\text{O})_4] \cdot 10\text{MeCN}$ **4** and $[\text{SrMn}^{\text{III}}_{13}\text{Mn}^{\text{II}}\text{O}_{11}(\text{OMe})_3(\text{O}_2\text{CPh})_{18}(\text{MeCN})_2] \cdot 12\text{MeCN}$ **5** complexes. The methoxyl, hydroxyl, water, acetonitrile and carboxylate groups were removed for clarity.²⁷

To investigate the effect of exchanging Ca for Sr, the Christou group synthesized Mn–Ca $[\text{Ca}_2\text{Mn}^{\text{IV}}\text{Mn}^{\text{III}}_{10}\text{Mn}^{\text{II}}_2\text{O}_{10}(\text{OH})_2(\text{OMe})_2(\text{O}_2\text{CPh})_{18}(\text{H}_2\text{O})_4] \cdot 10\text{MeCN}$ and Mn–Sr $[\text{SrMn}^{\text{III}}_{13}\text{Mn}^{\text{II}}\text{O}_{11}(\text{OMe})_3(\text{O}_2\text{CPh})_{18}(\text{MeCN})_2] \cdot 12\text{MeCN}$ complexes using the Mn–Ca core of OEC as a model (**Figure 6**).²⁷ It was found that the Mn–Ca and Mn–Sr complexes were similar with both calcium and strontium being eight coordinates. The major difference is that the Mn–Ca complex contains two calcium ions while Mn–Sr complex has only one strontium ion. Notably, the shortest Mn–Ca and Mn–Sr distances are 3.51 Å and 3.29 Å respectively, in line with the high end of the proposed OEC Mn–Ca bond length. The single oxygen-atom bridges in synthesized complexes **4** and **5** allowing the similarity of the Mn–Ca and Mn–Sr distances suggest that strontium is an alternative alkaline earth metal that could substitute calcium. Studies substituting calcium with

strontium retain 40% catalytic performance in photosystem II indicate that other factors, such as interactions with other atoms, hydrogen bonding, and tuning of the reduction potential results in some structural changes and electronic changes of the complex. Those factors could contribute to the low catalytic activity, but the exact reasons for the low yield are still not clear. The comparison of $\text{Ca}_2\text{Mn}_{13}$ and SrMn_{14} clusters gives insight into the factors needed for retaining catalytic activity in photosystem II.

The Dau and Kurz groups reported that the addition of calcium to manganese oxides or hydroxides improves the catalytic efficiency of water oxidation by 10 to 20 fold.⁷ The authors synthesized manganese-calcium oxides ($\text{CaMn}^{\text{IV}}_{1.6}\text{Mn}^{\text{III}}_{0.4}\text{O}_{4.5}(\text{OH})_{0.5}$ and $\text{CaMn}^{\text{IV}}_{1.6}\text{Mn}^{\text{III}}_{0.4}\text{O}_{4.5}(\text{OH})_{0.5}\cdot 3\text{H}_2\text{O}$) to mimic the function and structure of OEC in photosystem II. This result is especially promising upon further analysis of the geometric structure and oxidation states of the synthesized cluster. Based on Mn–O bond distances from EXAFS data, there are two $\text{Mn}^{\text{IV}}\text{O}_6$ in an octahedral geometry (Mn–O = 1.90 Å) and one Mn^{III} (Mn–O = 2.34 Å). The oxidation states match observed in the OEC, suggesting that this material and OEC may exhibit similar redox activity in water oxidation from Mn^{III} to Mn^{IV} .

The bridging $\mu_2\text{-O}$ between manganese ions may facilitate dioxygen ligand binding during water oxidation in photosystem II.⁷ Furthermore, deprotonation of bridging hydroxyl group has been proposed as an essential step, as it alleviates the buildup of positive charge and promotes for proton-coupled electron transfers (PCET) and redox potential change.⁷ In contrast, experimental results show that the calcium/manganese oxides promote the water oxidation without PCET. The Dau and Kurz groups compared their complexes with the OEC and concluded with similar mean oxidation states of Mn, unsaturated oxido bridging to Mn, and connection of redox-inactive Ca with Mn.⁷ The authors also observed that the synthesized complexes exhibit catalytic activity of water oxidation but not as good as OEC.

Great strides have been made in generating biomimetic models of the OEC especially in regards to understanding the role of water binding to calcium and determining the oxidation states of manganese at various stages of the catalytic cycle.³² One of the major concerns left though was the fact that these models did not share a Mn_4Ca monomer core. The Reedijk group took a step forward in this regard when they reported the syntheses of two trigonal propeller-shaped clusters $[\text{Mn}_3\text{CaNa}]$ and $[\text{Mn}_4\text{Na}]$ incorporating alkali and alkaline earth metals supported by Schiff base ligands (**Figure 7**). The ligands coordinate to metals through nitrogen and deprotonated hydroxyl groups. One molecule consists of three ligands and five metal ions. The group proposed that Mn–Ca interaction in $[\text{Mn}_3\text{CaNa}]$ cluster resembles that in OEC. Thus, water oxidation catalysis was performed in water-methanol solution in the presence of $[\text{Mn}_3\text{CaNa}]$ cluster and oxidants such as sodium hypochloride, potassium peroxysulfate, or tertiary butyl hydrogen peroxide. Immediate formation of dioxygen supports the catalytic ability of $[\text{Mn}_3\text{CaNa}]$ cluster and the important role of calcium in binding water oxidation because $[\text{Mn}_4\text{Na}]$ cluster was unable to perform similar catalysis.

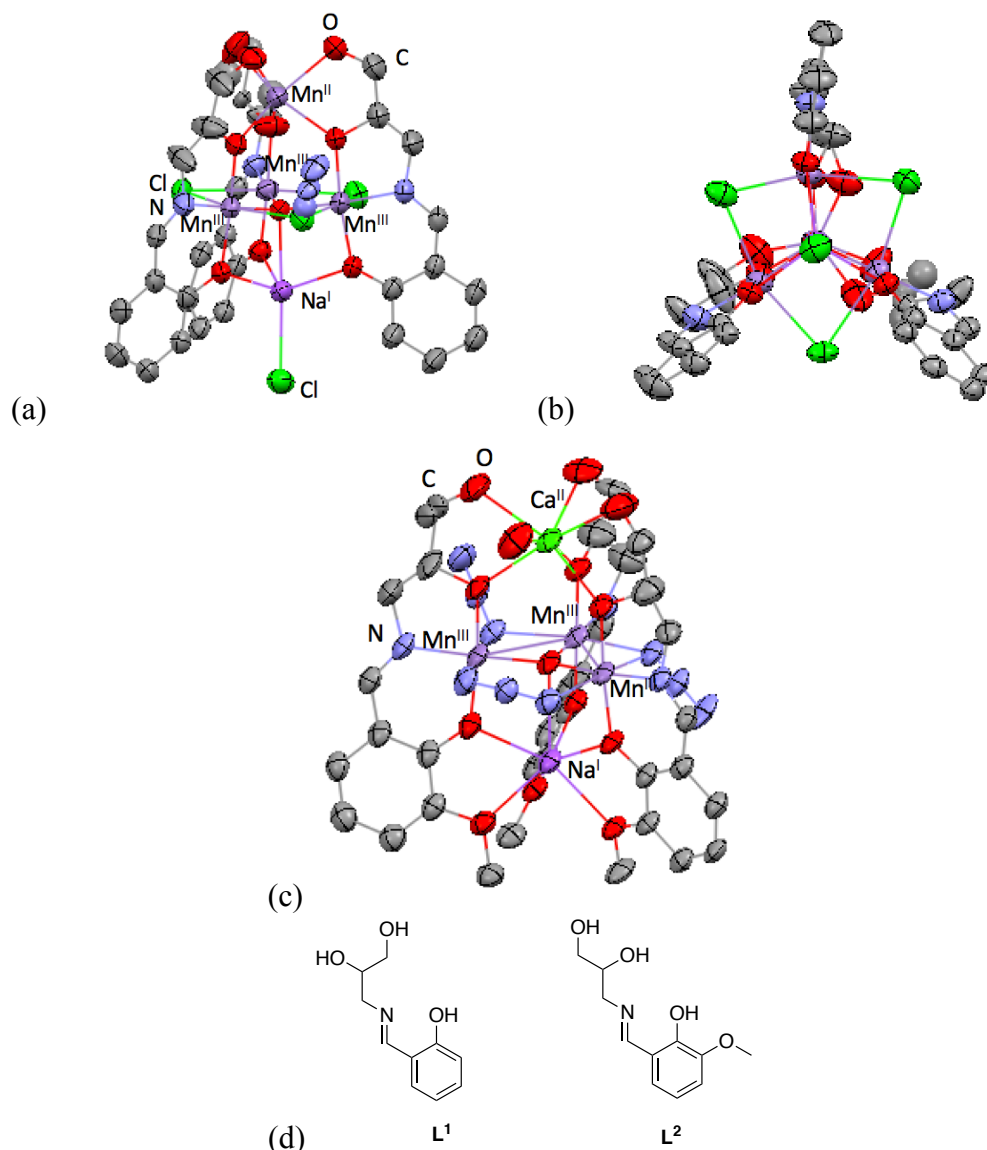


Figure 7. (a) Molecular structure of $[\text{Mn}^{\text{II}}\text{Mn}^{\text{III}}_3\text{Na}(\text{L}^1\text{H})_3(\mu_4\text{-O})(\text{N}_3)\text{Cl}_3]\cdot\text{MeOH}$ (b) Propeller-shaped view of (a). (c) Molecular structure of $[\text{CaMn}^{\text{III}}_3\text{Na}(\text{L}^2\text{H})_3(\mu_4\text{-O})(\text{N}_3)_3(\text{MeOH})]\text{Cl}$. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown above with colors representing different atoms (grey: carbon; red: oxygen; green: chloride in (a) and (b), calcium in (c); violet: manganese; purple: sodium). (d) Schiff-base ligands. The crystal structure was obtained in 2.9 Å resolution.³²

In the same year as the Reedijk group, the Agapie group synthesized complexes very similar in structure to the OEC (**Figure 8**).¹¹ With these Mn_3CaO_4 and Mn_4O_4 compounds, they were able to study the electronic effects of the alkaline earth metal, something that had not been studied up to this point. The experimental data supports the concept that the presence of calcium facilitates the formation of manganese at high oxidation states because electron-poor calcium withdraws electron density from manganese. The studies suggest that the calcium could modulate the reduction potential

of the complex, which allows formation of high-valent manganese, thus promoting water oxidation and generation of dioxygen in OEC.

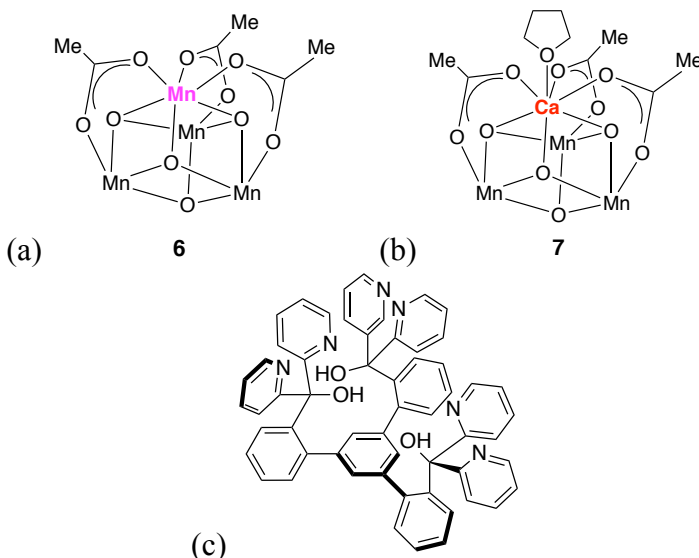


Figure 8. Molecular core structures of Mn_4O_4 (a) and Mn_3CaO_4 (b) complexes. Complete structures of **6** and **7** include a 1,3,5-triarylbenzene spacer containing six pyridines and three alcohol groups (c) on the bottom of cubes of **6** and **7**.¹¹

To further probe the redox tuning effects of the redox-inactive metals in the OEC the Agapie group expanded their research to synthesize complexes with both other redox inactive metals and Fe in place of Mn **10** (**Figure 9**).³³ They found that the pKa of the redox-inactive metal hydrates exhibits a positive correlation with the reduction potential of the clusters (**Figure 10**) by plotting the pKa from references and experimental reduction potentials. One theory to explain this correlation is that pKa is a direct measure of Lewis acidity. The correlation between pKa of aqueous metal ions and reduction potentials could be influenced by a few factors such as number of oxido ligands, protonation states, metal identity, and oxidation states of the transition metals. The dominant factor is still not clear at this point. However, Borovik also pointed out that the electron-withdrawing ability is also implied by the charge of the redox-inactive metals, which is encapsulated in Lewis acidity but is not necessarily directly correlated. By Borovik's analysis, highly charged metals such as Y^{3+} and Sc^{3+} opposed to Na^+ and Ca^{2+} withdraw more electron density from manganese ions and make them more likely to be reduced.³⁴ One befuddling set of data points is that the Sr- and Ca-containing complexes have almost identical redox potentials, but the Zn analog has an almost +0.2 V difference (**Figure 10**). All three species share a characteristic +2 charge at the redox inactive metal ion, but Zn has a more acidic center with a lower pKa (**Figure 10**).^{33,35,36}

Another structural feature the Agapie group probed was how the number of oxido groups effects the redox activity. They found that as the number of the oxido bridges to the redox-inactive metal is reduced to two, the slope of correlation of reduction potential and pKa shifts positively. This is thought to occur because having fewer oxido groups

causes the clusters to become more electron-deficient and destabilizes highly oxidized manganese.^{33,35}

From these data, it can be surmised that redox-inactive metals facilitate electron transfer during water oxidation.³⁷ Calcium facilitates oxygen release, whereas almost all other redox inactive metals cannot. Further, the strontium is the only metal that can substitute for calcium and retain the function of OEC. The reasons behind the feasibility of strontium ion in the catalytic reactivity is still under debate.

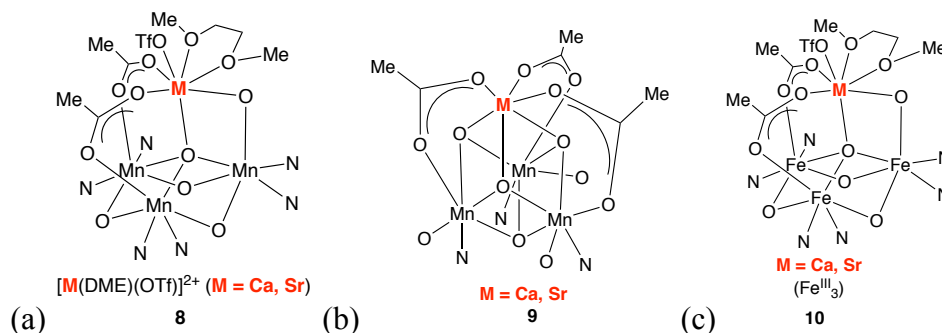


Figure 9. Molecular structure of (a) Mn_3MO_2 , (b) Mn_3MO_4 , and (c) Fe_3MO_4 complexes ($M = \text{Ca, Sr}$).^{33,35,36}

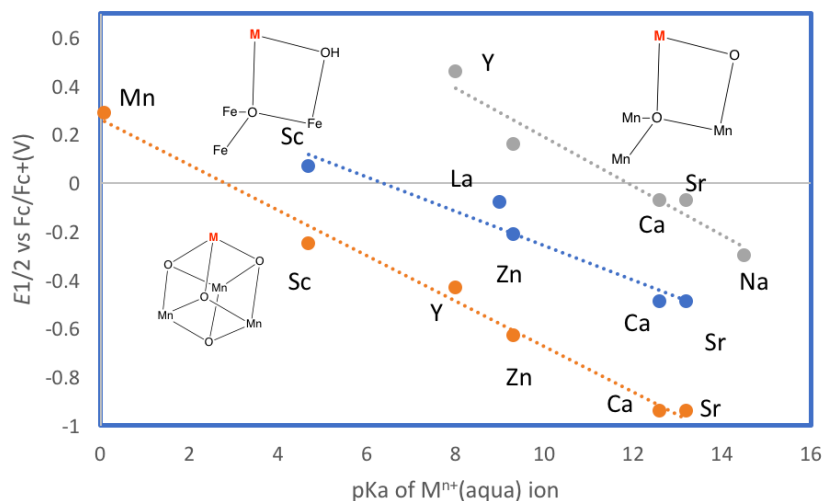


Figure 10. Plot of reduction potentials versus pK_a of redox-inactive metal containing OEC model complexes.³⁶

In order to investigate the influence of metal ion on the secondary coordination sphere alkali and alkaline earth metal ions on transition metal-based reactivity, the Borovik group used the interaction of Mn-O-Ca in OEC as a model and developed a new ligand-metal system with Co-OH-Ca interactions.³⁸ They reported the synthesis of four heterobimetallic Co/Ca complexes **11**, **12**, **13**, and **14** supported by tripodal ligands (**Figure 11**). The crystallographic data show that the bridging pattern (Co-OH-Ca) in complexes **11** and **12** resembles the Mn-O-Ca component of OEC. A comparison of the Co-O bond distances in $[\text{Co}^{\text{II}}(\mu\text{-OH}_2)\text{Ca}^{\text{II}}\text{OH}_2]^+$, $[\text{Co}^{\text{III}}(\mu\text{-OH})\text{Ca}^{\text{II}}\text{OH}_2]^+$,

$[\text{Co}^{\text{II}}\text{MST}(\text{OH}_2)]^-$, and $[\text{Co}^{\text{III}}\text{MST}(\text{OH}_2)]$ revealed divergence (**Figure 11**). The axial Co–O distance in $[\text{Co}^{\text{III}}(\mu\text{-OH})\text{Ca}^{\text{II}}\text{OH}_2]^+$ is 0.080 Å shorter than that in $[\text{Co}^{\text{III}}\text{MST}(\text{OH}_2)]$ and 0.367 Å shorter than $[\text{Co}^{\text{II}}(\mu\text{-OH}_2)\text{Ca}^{\text{II}}\text{OH}_2]^+$. Complexes **11** and **12** have similar N–Co–O(H) angles, but upon one electron oxidation at cobalt, the Ca–O distance in complex **12** is 0.265 Å shorter than in complex **11** and the Ca–Co distance in complex **12** is 0.5 Å shorter than in complex **11**. The oxidation state of cobalt is thought to change the interaction mode of Co–OH–Ca and their further catalytic behavior. The Borovik group suggest that the oxygen attached to sulfur has hydrogen bonding with axial hydroxyl group, thus preparing a spatial area for calcium coordination. In addition, upon coordination of calcium ion, the redox potential of cobalt complexes changes by up to 200 mV positively.

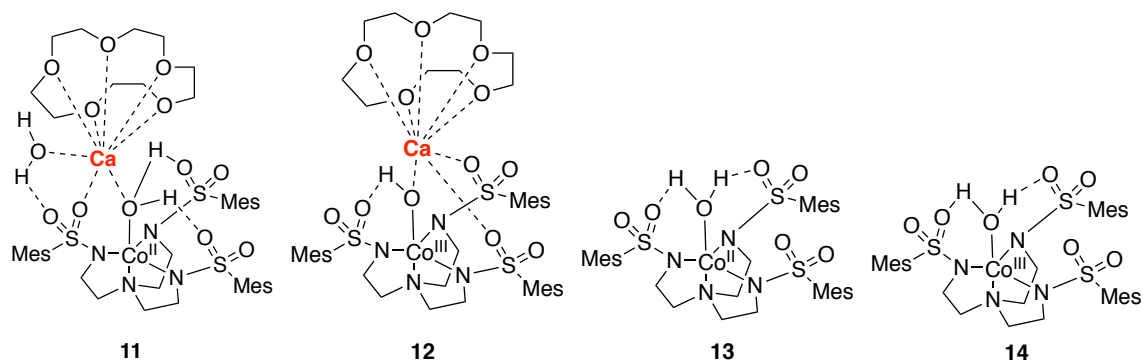


Figure 11. Structures of complexes **11** $[\text{Co}^{\text{II}}(\mu\text{-OH}_2)\text{Ca}^{\text{II}}\text{OH}_2]^+$, **12** $[\text{Co}^{\text{III}}(\mu\text{-OH})\text{Ca}^{\text{II}}\text{OH}_2]^+$, **13** $[\text{Co}^{\text{II}}\text{MST}(\text{OH}_2)]^-$, and **14** $[\text{Co}^{\text{III}}\text{MST}(\text{OH}_2)]$. Dashed line shows the interaction between atoms.³⁸

In the presence of 10 equivalents of diphenylhydrazine, complex **14** is converted to **11** and produces azobenzene at 70% yield. They proposed that the role of calcium ion in their system promotes electron transfer and enables bond cleavage reactivity.

Reactivity and structural changes tuned by alkali and alkaline earth metals

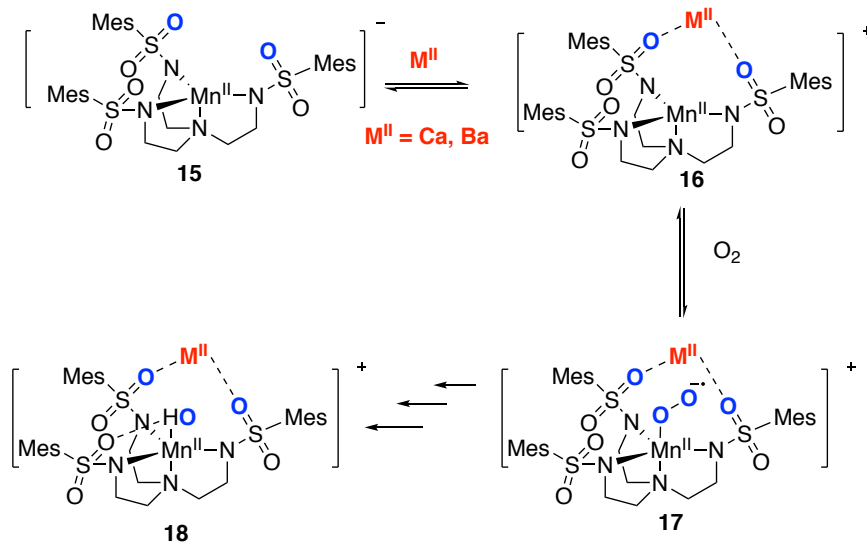
Alkali and alkaline earth metals have been used to alter coordination modes or promote reactivity of transition-metal catalysts. When these metal ions bind on the secondary coordination sphere, they induce structural changes and alter reactivity. Alkali and alkaline earth metal ions also changes the electronic density of transition metal complexes and allow small molecule activation. In addition, reactivity of transition-metal catalysts could be improved by addition of the metal ions due to alleviation of rich electron density and stabilization of transition states.

Alkali and alkaline earth metals induced compound structural changes

Inspired by the idea that redox-active metal ions promote electron transfer and activate water molecules, the Borovik group reported dioxygen reduction accelerated by a monomeric Mn complex **11** supported by the sulfonamido-based tripodal ligand (MST³⁻) in the presence of alkaline earth metal ions (**Scheme 2**).³⁹ The addition of $[\text{NMe}_4][\text{Mn}^{\text{II}}\text{MST}]$ to dioxygen displayed limited reactivity with initial rate at $6.2 \times 10^{-6} \text{ s}^{-1}$; however, the initial reaction rates increased to $5.8 \times 10^{-4} \text{ s}^{-1}$ and $1.8 \times 10^{-5} \text{ s}^{-1}$ when treated with $\text{Ca}(\text{OTf})_2$ or $\text{Ba}(\text{OTf})_2$ respectively and yield improved up to 60%. The Ca or Ba

ions coordinate to oxygens on the sulfonamido ligands and form Mn–Ca/Ba complexes **12** (Scheme 2). The heterobimetallic clusters promote dioxygen to bind Mn through electron transfer to form superoxido adducts. The alkaline earth metal ions stabilize the complexes by withdrawing electron density from the nucleophilic oxido group.

Scheme 2. Calcium and barium ions facilitating dioxygen reduction.³⁹



Sparked by redox-inactive metal ions tuning the oxo-transfer of high-valent manganese in OEC, the Fukuzumi and Nam groups reported Ca^{2+} or Sc^{3+} binding to a non-haem oxoiron(IV) complex supported by TMC ligand (TMC = TMC 5 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) (Figure 12). The binding of redox-inactive metal ions to the oxoiron complex results in two-electron reduction by ferrocene whereas one-electron reduction takes place in the absence of these ions. Also, the interaction of these metal ions with oxo shortens Sc–O(oxo) distance (1.933(3) Å) compared to other Sc–OH distance (2.188(3) Å). At the same time, the Fe–O(oxo) bond (1.754(3) Å) is much longer than Fe–O(oxo) in the absence of Ca^{2+} or Sc^{3+} ions (1.643(3) Å). This binding behavior promotes electron transfer. The electron-deficient $\text{Ca}(\text{OTf})_2$ or $\text{Sc}(\text{OTf})_3$ withdraws electrons from nucleophilic oxoiron and facilitate further reduction. The elongation of iron-oxo bond and shortening of Sc/Ca-oxo distance are also consistent with that $\text{Sc}^{3+}/\text{Ca}^{2+}$ pulls electrons out of the non-haem complex. In this case, ten times more Ca^{2+} ions are required to perform similar reduction as Sc^{3+} due to the Lewis acidity.^{40,41}

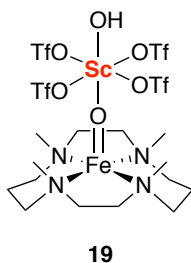
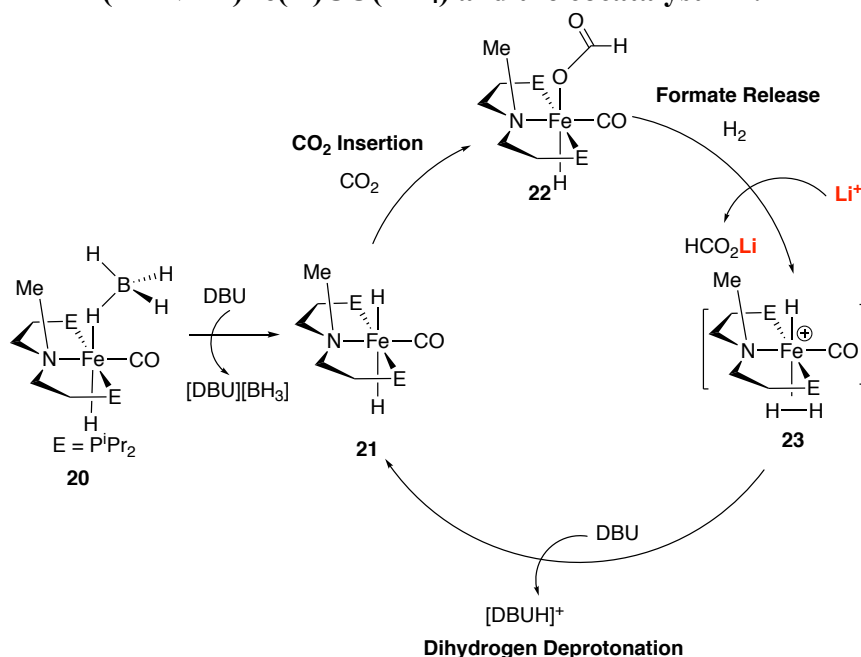


Figure 12. Molecular structure of $[(\text{TMC})\text{Fe}^{\text{IV}}(\text{O})\text{--}\text{Sc}(\text{OTf})_4(\text{OH})]$.⁴¹

Small molecule activation

Carbon dioxide is a useful carbon resource in the atmosphere as a building block for chemicals. One such prominent chemical that has been synthesized using CO₂ is formic acid, which can be used as a fuel source.² Most of the catalysts to form formic acid requires strong bases and expensive and rare metals such as ruthenium, rhodium, or iridium as catalysts under high pressure up to 59 atm and temperature up to 220 °C. Although the turnover numbers and turnover frequency reach up to 3.5×10⁶ and 150,000 h⁻¹, the reaction conditions are still harsh with high cost. Great strides have recently been taken in using alkali metals to aid the transition-metal catalyzed transformation of carbon dioxide to formic acid. Low cost of catalysts and co-catalysts with equivalent turnover numbers and frequency are good alternatives to previous methods.

Scheme 3. Proposed mechanism of CO₂ hydrogenation using the catalyst (iPrPN^{Me}P)Fe(H)CO(BH₄) and the cocatalyst Li⁺.²

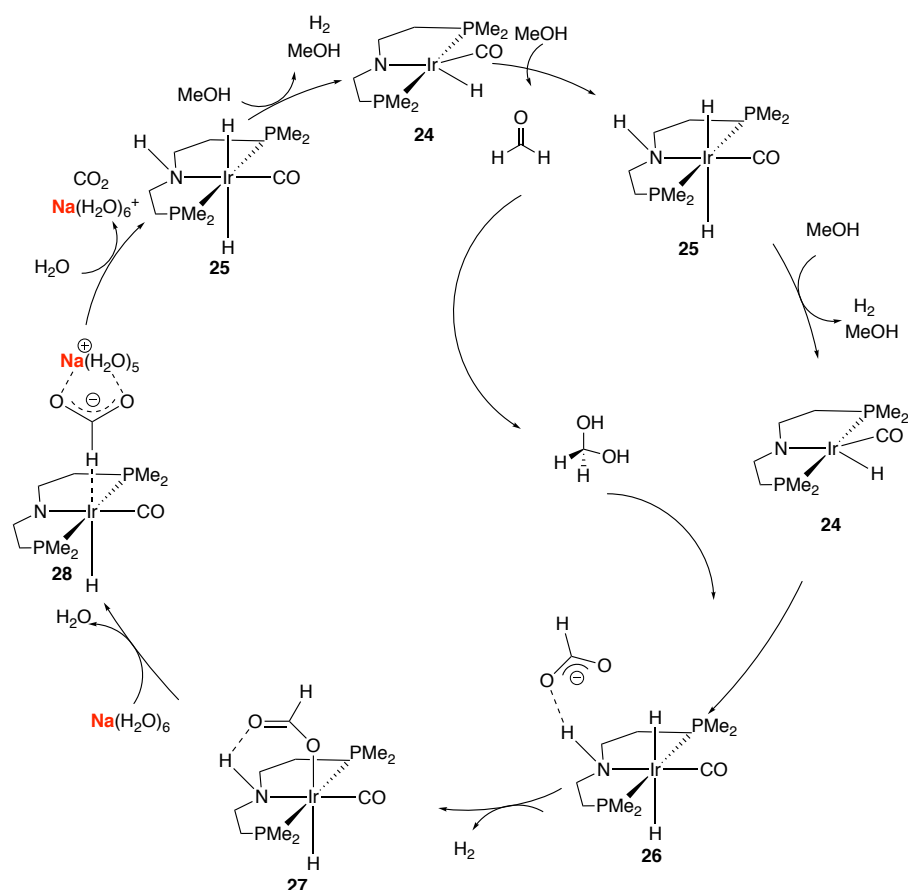


The Bernskoetter group reported that addition of Lewis acids such as LiBF₄, LiOTf, NaOTf, and KOTf to CO₂ hydrogenation reactions catalyzed by iron carbonyl hydride supported by a PNP pincer ligand **21** enhance the reaction rate (Scheme 3).² The turnover number and turnover frequency of the reactions increased dramatically on addition of Lewis acids. The iron complex coordinated to borohydride **20** as a precatalyst initiates the catalytic cycle in the presence of DBU. CO₂ insertion to an axial hydride gives a formate adduct **22**. The lithium ion is proposed to stabilize the formate anion and assist the release of it. When lithium is excluded from the reaction conditions then no free formate is observed, but addition of Li⁺ to this mixture resulted in the immediate formation of formate as determined by ³¹P NMR. The experimental evidence indicates that CO₂ hydrogenation was not able to be completed without the cation stabilization effects of lithium, sodium, or potassium. The authors highlight the ability of using generally cheap iron catalysts and alkali metal co-catalyst that can reduce the cost

of CO₂ hydrogenation reactions dramatically and removes extremely basic reaction conditions under high pressure and temperatures.

Methanol dehydrogenation has been considered as an important process because it produces hydrogen gas and carbon dioxide.⁹ However, the catalysts to facilitate this conversion are commonly expensive transition metals such as Ru and the reaction conditions require high temperatures and pressures. In many cases, the dehydrogenation produces not only the desired products but also carbon monoxide gas, which causes further problems such as its ability to damage fuel cells during energy conversion. The Bernskoetter group demonstrated that an iron complex supported by a pincer ligand and a Lewis acid co-catalyst facilitates methanol dehydrogenation. The Lewis acids accelerated the reaction significantly and enhanced turnover numbers to *ca.* 20,000. This is twice as efficient as the previous state-of-the-art system by the Beller group that needed strong base (8M KOH) to reach 10,000 TON. A maximum of turnover number of 51,000 was reached when the Lewis acid LiBF₄ was added to the mixture.⁹

Scheme 4. Proposed methanol dehydrogenation mechanisms.⁹



The Bernskoetter group ran a series of DFT calculations to investigate the mechanisms of the dehydrogenation reactions (**Scheme 4**).⁹ The alkali metal ion stabilizing the formate anion is kinetically driven. In the calculations, the

isopropyl/cyclohexyl groups attached to the phosphines were substituted by methyl groups for simplicity. The iron complex **24** is the resting state in the catalytic cycle (**Scheme 4**). The subsequent immediate **25** is generated by hydrogen atom transfer from methanol, followed by hydrogen elimination to reform the resting state species **24**. A methanediol is formed by 1,2-addition of water to the formadehyde. The complex **26** forms as dehydrogenation occurs with methanediol, where the formate is stabilized through hydrogen bonding. At this key step, the sodium cation is proposed to stabilize the formate anion better than hydrogen bonding interaction. The Na cation in complex **28** lowers the energy by 19.1 kcal/mol more than solely hydrogen bonding computationally. This DFT calculation overestimates the energy difference because this huge difference in energy was not observed in NMR spectroscopy when adding sodium cation in. The cycle completes with carbon dioxide release and hydrogen elimination. Although the reaction could proceed in the absence of Lewis acids, the stabilization of anionic transition state intermediate improves reaction rates and turnover numbers. Overall, Lewis acids contributes to the enhanced reaction rates and turnover numbers, the extension of catalyst life time, and the mild reaction conditions.

Bernskoetter's Fe pincer catalyst is also competent for formic acid dehydrogenation, and the catalyst exhibits dramatic increases to both turnover number and turnover frequencies on addition of Lewis acids.³ X-ray crystallographic data supports that formic acid can add across a five coordinate amido iron-pincer complex **31** to produce complex a six-coordinate iron complex **32** supported by the pincer ligand, carbon monoxide, and formate (**Scheme 5**). Lewis acids stabilize the formate anion by change the coordination geometry from complex **30** to complex **33** and enable the release of carbon dioxide. The addition of a second equivalent of formic acid to the reaction mixture liberates dihydrogen and regenerates a six-coordinate iron-pincer supported by formate (**Scheme 5**).²⁵ When 10 equivalents of LiBF₄ were used with the catalyst containing ligands (E=PCy₂), the highest reaction rates were observed.³ The negative charge from the formate anion is stabilized by the Lewis acids, thus the activation energy of decarboxylation is lowered. Evidently, the Lewis acid is essential to stabilize the transition state and achieve high reaction rate and turnover numbers.

Scheme 5. Proposed mechanisms of formic acid decarboxylation.³

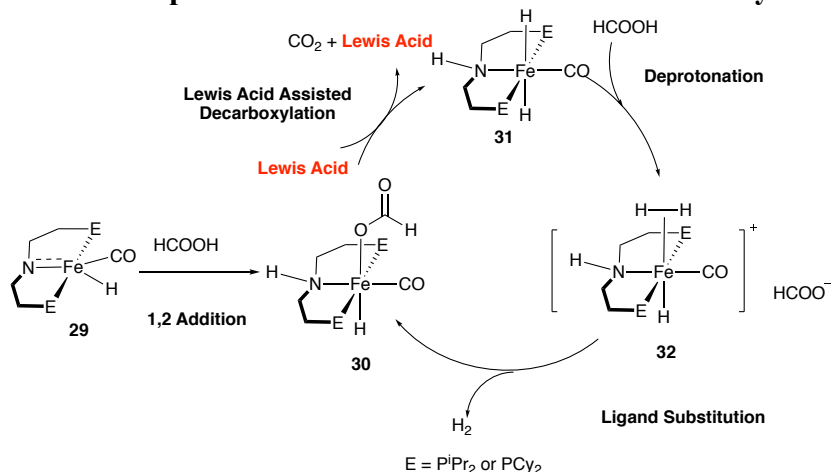
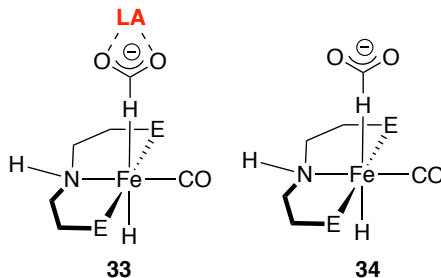
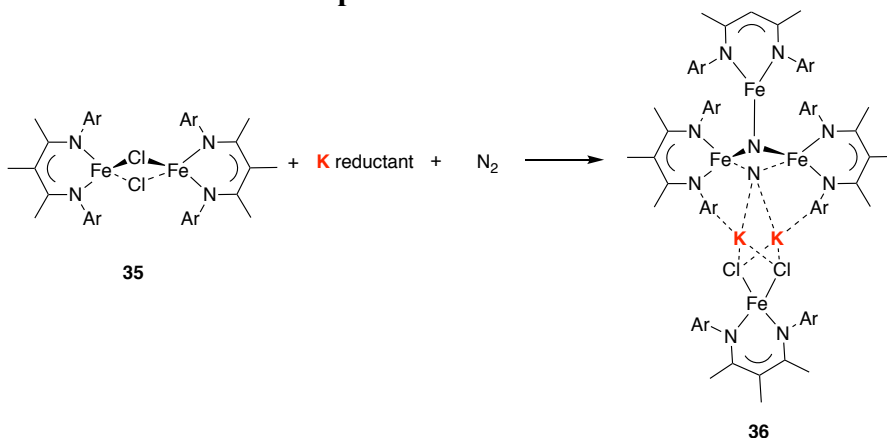


Figure 13. Proposed comparative pincer-iron complexes with formate anion stabilization in the presence of **33** or in the absence of **34** Lewis acid.³



In early 1900s, Mittasch developed a new low-cost Haber Bosch dinitrogen reduction catalyst using iron- β -diketiminate complexes **35** with potassium as promoters (Scheme 6).⁴² The Holland group reported a DFT computational study towards understanding the mechanism of potassium/iron cooperativity upon nitrogen reduction.⁴³ The complex **36** containing a K–N–Fe interaction occurs when two equivalents of iron- β -diketiminate compounds react with potassium metal and nitrogen gas (Scheme 6).⁴³ The reaction is not catalytic, but complete cleavage of the nitrogen-nitrogen triple bond cleavage yields insight into understanding dinitrogen reduction in the solution phase. The iron complexes donate electrons to π^* orbitals of N_2 , therefore elongating the N–N bond lengths and shortening Fe–N bond distances. The authors proposed that potassium could change the steric profile of complex, stabilize the nitride, and/or enhance the diiron back-donating ability. According to computational study (DFT, B3LYP/6-31+G(d)) into this system, the N–N bond distance lengthens from 1.234 Å to 1.268 Å upon addition of potassium cation. The strong interaction between potassium and nitride species stabilizes the complex and enables N–N bond cleavage.

Scheme 6. Nitrogen fixation reactions promoted by iron- β -diketiminate complex and potassium ions.⁴²



Catalytic reactivity modulation

In addition to the activation of small molecules, alkali and alkaline earth metals are also known to work cooperatively with transition metals to change reactivity. For example, the Collins group has done extensive studies on the development of oxygen atom transfer (OAT) reagents.⁴⁴ The group had previously synthesized Mn porphyrin and

salen complexes that failed to perform the desired OAT reactivity. They hypothesized that the redox-inactive cations would weaken the donating ability of the amides and increase the electrophilicity of the oxygen bound Mn. They tested oxygen-atom transfer in electron-rich olefins by synthesizing a tetraamide macrocyclic ligand with a manganese oxo **41** in the presence of redox-inactive metals (**Figure 14**). Experimental results show that oxygen atom transfer is more likely to occur between the electron-poor oxo ligand and electron-rich olefins. The metal ions including Na^+ , Ba^{2+} , Mg^{2+} , Li^+ , Zn^{2+} , and Sc^{3+} increase the reaction rates; however, Sc accelerates the reaction (three folds) much more than the rest ions.

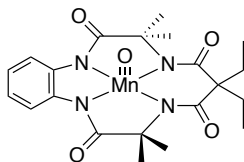
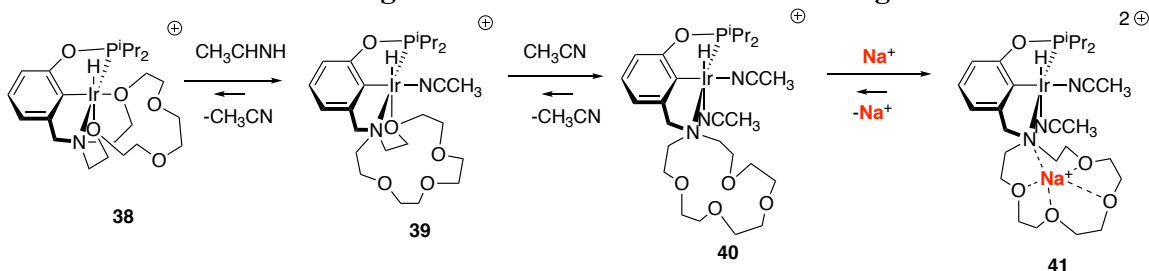


Figure 14. Molecular structure of the Mn-oxo porphyrins complex.⁴⁴

One area of chemistry that has received considerable attention in recent years is the use of hemilabile catalysts.⁵ The Miller group has contributed this area great by attaching a crown ether moiety onto a pincer ligand. This crown ether can then bind alkali metals and change the coordination of the complex. Initial studies found an iridium hydride pincer-crown ether complex that had improved dihydrogen splitting reactivity on addition of alkali metals, such as lithium and sodium. The complexes display unique metal-ligand cooperativity such that the addition of acetonitrile to **38** can displace an oxygen from the crown ether bound to iridium-NCOP pincer complex to form complex **39**. Subsequently, a second acetonitrile can displace the other oxygen bound to Ir to form a free crown ether (**Scheme 7**). Complex **40** can be further tuned by bonding alkali metals such as Na in crown ether to form complex **41** (**Scheme 7**).

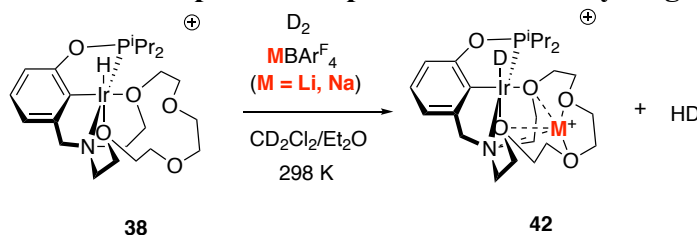
Scheme 7. The tuning of crown-ether/ acetonitrile binding of iridium.⁵



The hemilability of the pincer-crown ether ligand or solvent acetonitrile indicate the possibility of catalytic reactivity that makes use of the weak coordination of the ether ligands.⁵ Preliminary studies on H_2 activation revealed that a mixture of complex **38**, diethyl ether, and one atmosphere of D_2 gas in CD_2Cl_2 results in the formation of slow deuterium exchange with hydrogen in the axial of complex **38**. However, the rate of H/D exchange increased significantly (20-fold increase) in the presence of lithium and sodium ions (**Scheme 8**). More specifically, the addition of lithium ions exhibits an even higher rate than sodium ions. They proposed that the size of the crown ether favors the binding of smaller sized cations. An enhancement in cation concentration showed a nonlinear

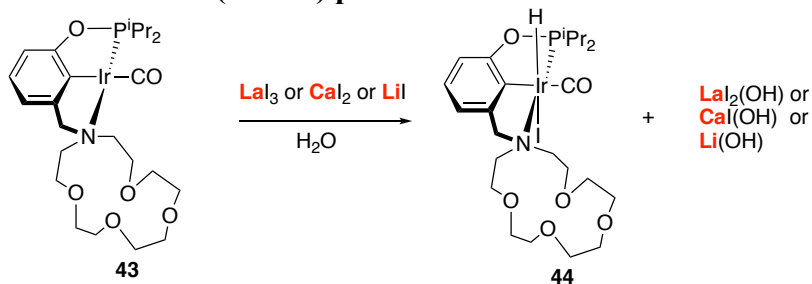
exponential increase in reaction rate. This is caused by the cation coordination to diethyl ether in the reaction mixture. The experimental data suggest that lithium preferably binds to diethyl ether and therefore the reaction rate is slow when the concentration of cation is low. After raising the concentration of the cation, the interference of diethyl ether reduced, thus resulting in higher overall reaction rate.

Scheme 8. Iridium-NCOP pincer complex facilitated dihydrogen activation.⁵



In an attempt to understand the transition metal-Lewis acidic metal cooperativity, the Miller group reported that facilitates reactions such as protonation, cation-crown ether interactions, halide abstraction, and halide exchange occurs at an iridium carbonyl pincer-crown ether complex in the presence of Lewis acidic metal ions.⁸ In the absence of Lewis acidic cations, the protonation of complex **43** does not occur (**Scheme 9**). The yield of protonation products improves with the increase of Lewis acidity of the metal cation. The authors proposed that the water coordinates to redox-inactive metal ions and subsequently the water-bound complexes act as Brønsted acids to promote proton coordination.⁸

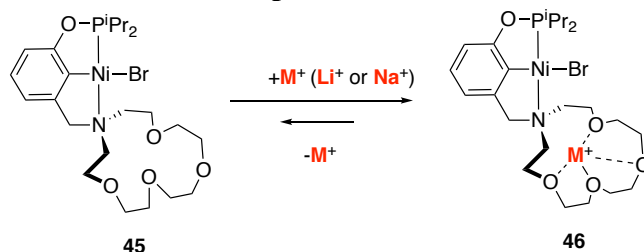
Scheme 9. Lewis acidic metal induced protonation on iridium-aminophosphinite (NCOP) pincer from water.⁸



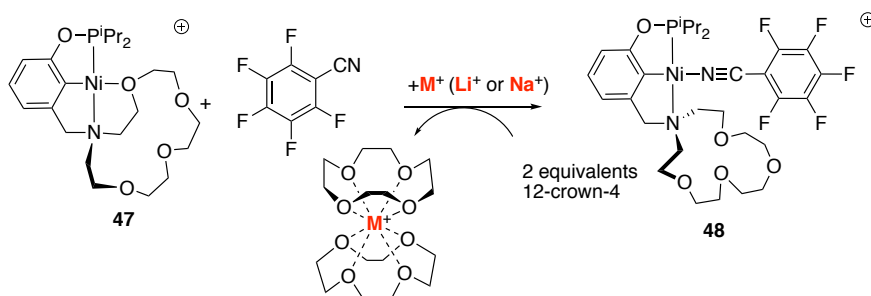
The Miller group also reported that the alkali metals such as lithium, sodium, and potassium are able to switch the coordination modes of nickel pincer-crown ether complexes.⁴⁵ A large crown ether (18c6) induces cation binding. In contrast, a smaller crown ether (15c5) results in a mixture of halide abstraction and cation binding. When nickel complex **47** was supported by tetradentate pincer ligand, little cation interaction occurred. Tridentate coordination **45** promotes a binding interaction between the alkali metal ions and crown ether. The binding affinity of the crown ether and alkali metal cation exhibits a positive relationship between the number of oxygen in crown ether and the size of alkali metal ions. Polar solvents such as acetonitrile undermines the cation-crown ether interaction. They proposed that cation switches the ligand binding modes (**Scheme 11**).⁴⁵ The experimental results show that cation triggers tridentate coordination

and nitrile ligand binding. Without the presence of cation, the tetradentate complex was stable and no nitrile coordination was observed.

Scheme 10. Lewis acidic metal cation interaction with crown ether in nickel- NCOP pincer.⁴⁵



Scheme 11. Cation triggered reversible ligand interaction.⁴⁵



In studies of cross coupling catalysis, the Nakamura group reported an aryl halide bond activation promoted by a nickel phosphine/magnesium alkoxide complex.⁴⁶ They reported the coupling of aryl halides and aryl groups. Their previous studies of C–Br bond cleavage were reached by using the cooperativity of Cu¹⁰ and Li⁺. This time, they designed a similar new catalyst using Ni¹⁰ and Mg²⁺ with a hydroxylphosphine ligand (PO), which could bind both metals. The coupling reaction between unactivated aryl halides and Grignard reagent occurs because electron-rich nickel and electrophilic magnesium activate aryl halide synergistically (**Scheme 12**). A parallel experiment using PP ligand in the absence of magnesium generating low-yield coupling products has been compared with PO ligand. DFT studies shows **51** decomposed without activation barrier to give the complex **52**. Geometry optimization were performed for the C–X bond cleavage. The energy drops as the length of C–X bond lengthens as the formation of **52** is exothermic. This suggests a bimetallic synergy for nickel catalyst and magnesium. The catalytic mechanism proposed upon density functional theory (DFT) in the presence of magnesium is quite different from the one without. The complex incorporating magnesium is proposed to form a five-membered ring transition state **51** with low activation energy, while the complex in absence of magnesium established a three-membered ring system **53** at high energy levels (**Figure 15**). The presence of magnesium stabilizes negative charge from oxygen and halide X **51** and also promotes aryl coupling reactions for synthesizing complex molecule.

Scheme 12. The halide activation reaction promoted by Ni(acac)₂/PO and ArMgX in diethyl ether.⁴⁶

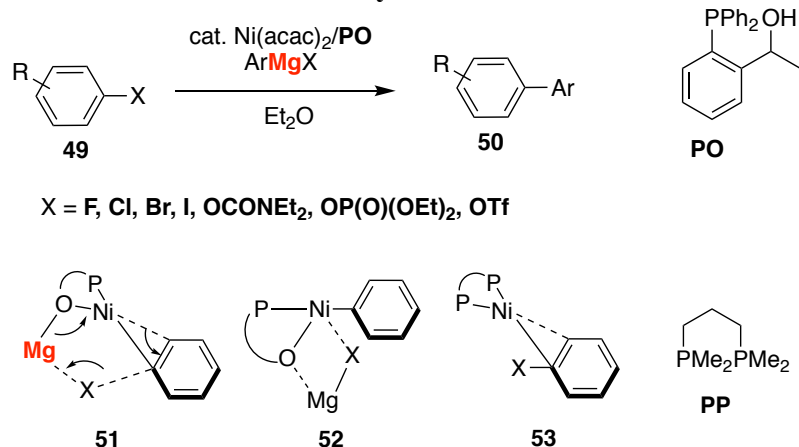
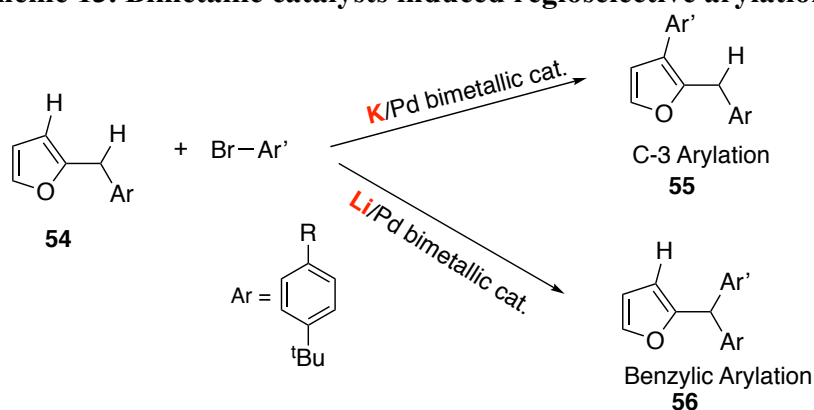


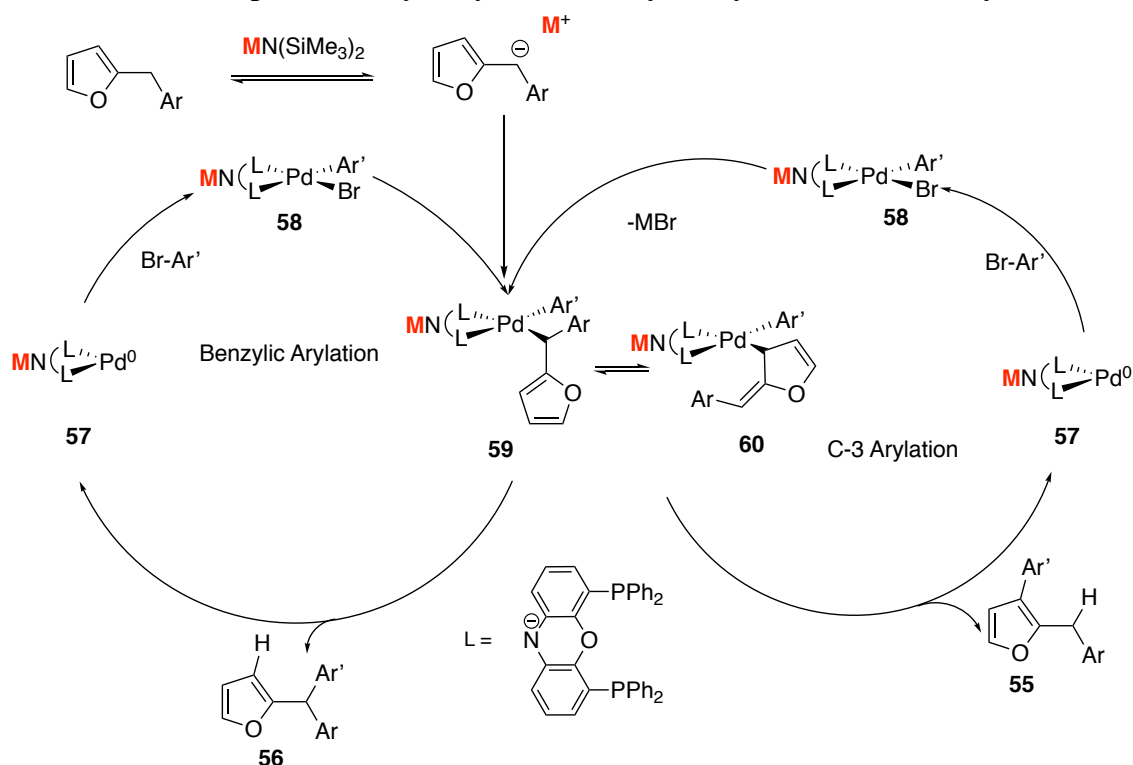
Figure 15. Transition state intermediates with magnesium and without.⁴⁶

The Walsh and Tomson groups have also studied the effects of alkali metals as components of bimetallic catalysts for C–H functionalization.¹⁰ The authors discovered that using different alkali metal ions induces cation- π interactions and selectively produce different 2-benzylfurans (**Scheme 13**). Arylation reactions have been performed using catalysts Pd(OAc)₂ and cocatalysts Li, Na, or K ions based on the 4,6-Bis(diphenylphosphino)phenoxazine (NIXANTPHOS) scaffolding. Regioselective arylation was only observed by producing compounds **55** and **56** in the presence of alkali metal ions. In order to understand the difference in regioselectivity, the group proposed the mechanisms of the benzylic arylation and C-3 arylation. MN(SiMe₃)₂ (M = Li, Na, K) deprotonates benzylic furan to form a carbanion (**Scheme 14**). The carbanion associates to the palladium to form **59** (**Scheme 14**). A subsequent reductive elimination generates the benzylic arylation products (**Scheme 14**). When the oxidative added intermediate **III** tautomerizes to a C3 adduct **60**, the subsequent reductive elimination produces a different C3 arylated compounds (**Scheme 14**). According to DFT studies, the authors proposed that the selectivity C-3 arylation and benzylic arylation mechanisms that the potassium bound benzylic area group promotes the palladium to bind at C-3, whereas palladium could also bind furan **60** as potassium is captured by crown ether to produce benzylic aryl product. This example highlights the ability of alkali metals to not only affect the rates of reactions but also the selectivity of products that are formed.

Scheme 13. Bimetallic catalysts induced regioselective arylation.¹⁰



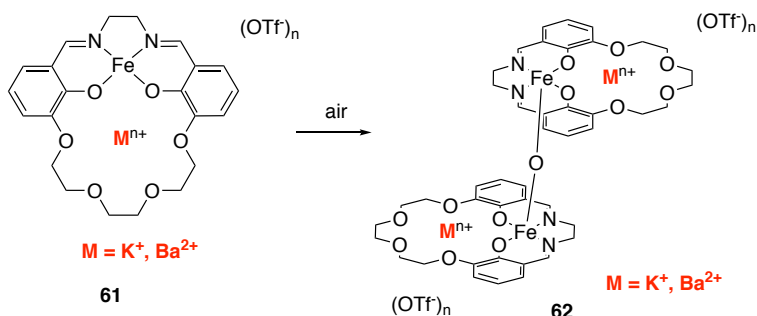
Scheme 14. Proposed catalytic cycles of benzylic arylation and C-3 arylation.¹⁰



Modulating reactivity using redox-inactive metals, the Yang group developed a Schiff base iron (II) and iron (III) complexes containing crown ether (18-crown-6) (**Scheme 15**).⁴⁷ In this case, introducing redox-inactive metals to these iron system shifted the redox potentials positively compared to $\text{Fe}(\text{salen})$ and $\text{Fe}(\text{salen})\text{Cl}$. The Yang group studied the influence of the cation on redox potentials and C-H oxidation chemistry. The cations (potassium and barium) shift the redox potential of iron salen dimer complexes positively by up to 640 mV. Experimental results show that the addition of redox-inactive metals salts to the iron catalyst in hexene in the presence of oxygen-saturated acetonitrile generates oxidation products: alcohols, and ketones. Hydroperoxide as an intermediate indicating a stop of oxidation process was mainly produced when

using Fe(salen) as the catalyst. However, iron Schiff-base complexes **61** oxidize hydroperoxide and complete oxidation (**Scheme 15**). The authors suggested enhanced reactivity was caused by either ligand-cation binding or the interaction between cations and lone electron pairs on hydroperoxide, which allows intramolecular electron transfer. Overall, the redox-inactive metals, potassium and barium activate the catalysts for successful oxidation.

Scheme 15. Schiff base supported Fe^{II} and Fe^{III} complexes.⁴⁷



Conclusions

The integration of alkali and alkaline earth metals extend the reactivity of transition metal complexes and enables the reactions that could not be achieved by solely transition metal catalysts. The reactivity could be improved kinetically by reducing the transition-state energy and accelerating reaction rates. Studies have shown that alkali and alkaline earth metals stabilize complexes by lowering transition-state energy or withdrawing electrons from nucleophilic metal centers and ligands. Such binding interactions between metal ions and heteroatoms could be applied to many other peroxide-related or other anionic molecules or atoms to delocalize charge. In this way, the metal ions stabilization may reduce activation energy barrier and enables new or improves reaction activity. The cooperativity of these metal ions and ligand or reaction intermediates also enhance reaction selectivity and rate by switching coordination modes. The selective association between ligand-based crown ether or free crown ether and alkali metal ions enables such binding modes. In addition, replacing noble metal catalysts and harsh reaction condition by synergistic cheap transition metal and alkali and alkaline earth metals reduces cost and keeps equivalent or better yield and reaction rate. In aryl coupling reactions, using different-sized alkali metal ions in addition to transition metal catalysts manage the regioselectivity of products. Such selectivity could also be applied to reactions that potentially have cation- π interaction. Although a number of research projects highlight the influence of alkali and alkaline earth metals on transition metal catalysts, many reaction mechanisms have not been well understood. In the future, more studies should be taken on understanding calcium in OEC. Incorporation of alkali and alkaline earth metal ions to the secondary coordination sphere to alleviate electron density from electron-rich ligands and metal centers. Designing new cooperativity between ligand and alkali and alkaline earth metal ions would bring in new reactivity and selectivity.

References

- (1) Muetterties, E. L. Molecular Metal Clusters. *Science* **1977**, *196* (4292), 839–848.
- (2) Zhang, Y.; MacIntosh, A. D.; Wong, J. L.; Bielinski, E. A.; Williard, P. G.; Mercado, B. Q.; Hazari, N.; Bernskoetter, W. H. Iron Catalyzed CO₂ Hydrogenation to Formate Enhanced by Lewis Acid Co-Catalysts. *Chem. Sci.* **2015**, *6* (7), 4291–4299.
- (3) Bielinski, E. A.; Lagaditis, P. O.; Zhang, Y.; Mercado, B. Q.; Würtele, C.; Bernskoetter, W. H.; Hazari, N.; Schneider, S. Lewis Acid-Assisted Formic Acid Dehydrogenation Using a Pincer-Supported Iron Catalyst. *J. Am. Chem. Soc.* **2014**, *136* (29), 10234–10237.
- (4) Lee, H. B.; Tsui, E. Y.; Agapie, T. A CaMn₄O₂ Model of the Biological Oxygen Evolving Complex: Synthesis via Cluster Expansion on a Low Symmetry Ligand. *Chem. Commun.* **2017**, *53* (51), 6832–6835.
- (5) Kita, M. R.; Miller, A. J. M. Cation-Modulated Reactivity of Iridium Hydride Pincer-Crown Ether Complexes. *J. Am. Chem. Soc.* **2014**, *136* (41), 14519–14529.
- (6) Mishra, A.; Wernsdorfer, W.; Abboud, K. A.; Christou, G. The First High Oxidation State Manganese–calcium Cluster: Relevance to the Water Oxidizing Complex of Photosynthesis. *Chem. Commun.* **2005**, 54–56.
- (7) Zaharieva, I.; Najafpour, M. M.; Wiechen, M.; Haumann, M.; Kurz, P.; Dau, H. Synthetic Manganese–calcium Oxides Mimic the Water-Oxidizing Complex of Photosynthesis Functionally and Structurally. *Energy Environ. Sci.* **2011**, *4* (7), 2400.
- (8) Grajeda, J.; Kita, M. R.; Gregor, L. C.; White, P. S.; Miller, A. J. M. Diverse Cation-Promoted Reactivity of Iridium Carbonyl Pincer-Crown Ether Complexes. *Organometallics* **2016**, *35* (3), 306–316.
- (9) Bielinski, E. A.; Förster, M.; Zhang, Y.; Bernskoetter, W. H.; Hazari, N.; Holthausen, M. C. Base-Free Methanol Dehydrogenation Using a Pincer-Supported Iron Compound and Lewis Acid Co-Catalyst. *ACS Catal.* **2015**, *5* (4), 2404–2415.
- (10) Zhang, J.; Sha, S.-C.; Bellomo, A.; Trongsirawat, N.; Gao, F.; Tomson, N. C.; Walsh, P. J. Positional Selectivity in C–H Functionalizations of 2-Benzylfurans with Bimetallic Catalysts. *J. Am. Chem. Soc.* **2016**, *138* (12), 4260–4266.
- (11) Kanady, J. S.; Tsui, E. Y.; Day, M. W.; Agapie, T. A Synthetic Model of the Mn₃Ca Subsite of the Oxygen-Evolving Complex in Photosystem II. *Science* **2011**, *333* (6043), 733–736.
- (12) James P. McEvoy, G. W. B. Water-Splitting Chemistry of Photosystem II. *Chem. Rev.* **2006**, *106* (11), 4455–4483.
- (13) Ferreira, K. N.; Iverson, T. M.; Maghlaoui, K.; Barber, J.; Iwata, S. Architecture of the Photosynthetic Oxygen-Evolving Center. *Science* **2004**, *303* (5665), 1831–1838.
- (14) Loll, B.; Kern, J.; Saenger, W.; Zouni, A.; Biesiadka, J. Towards Complete Cofactor Arrangement in the 3.0 Å Resolution Structure of Photosystem II. *Nature* **2005**, *438* (7070), 1040–1044.
- (15) Dau, H.; Grundmeier, A.; Loja, P.; Haumann, M. On the Structure of the Manganese Complex of Photosystem II: Extended-Range EXAFS Data and Specific Atomic-Resolution Models for Four S-States. *Philos. Trans. R. Soc. Lond.*

- B. Biol. Sci.* **2008**, *363* (1494), 1237–1244.
- (16) Yano, J.; Kern, J.; Sauer, K.; Latimer, M. J.; Pushkar, Y.; Biesiadka, J.; Loll, B.; Saenger, W.; Messinger, J.; Zouni, A.; et al. Where Water Is Oxidized to Dioxygen: Structure of the Photosynthetic Mn₄Ca Cluster. *Science* **2006**, *314* (5800), 821–825.
 - (17) Umena, Y.; Kawakami, K.; Shen, J.-R.; Kamiya, N. Crystal Structure of Oxygen-Evolving Photosystem II at a Resolution of 1.9 Å. *Nature* **2011**, *473* (7345), 55–60.
 - (18) Siegbahn, P. E. . Quantum Chemical Studies of Manganese Centers in Biology. *Curr. Opin. Chem. Biol.* **2002**, *6* (2), 227–235.
 - (19) Siegbahn, P. E. M.; Crabtree, R. H. Manganese Oxyl Radical Intermediates and O–O Bond Formation in Photosynthetic Oxygen Evolution and a Proposed Role for the Calcium Cofactor in Photosystem II. *J. Am. Chem. Soc.* **1999**, *121* (1), 117–127.
 - (20) Vrettos, J. S.; Limburg, J.; Brudvig, G. W. Mechanism of Photosynthetic Water Oxidation: Combining Biophysical Studies of Photosystem II with Inorganic Model Chemistry. *Biochim. Biophys. Acta - Bioenerg.* **2001**, *1503* (1–2), 229–245.
 - (21) Pecoraro, V. L.; Baldwin, M. J.; Caudle, M. T.; Hsieh, W.-Y.; Law, N. A. A Proposal for Water Oxidation in Photosystem II. *Pure Appl. Chem.* **1998**, *70* (4), 925–929.
 - (22) Wilson, A. J.; Jain, P. K. Structural Dynamics of the Oxygen-Evolving Complex of Photosystem II in Water-Splitting Action. *J. Am. Chem. Soc.* **2018**, *140* (17), 5853–5859.
 - (23) Hewitt, I. J.; Tang, J.-K.; Madhu, N. T.; Clérac, R.; Buth, G.; Anson, C. E.; Powell, A. K. A Series of New Structural Models for the OEC in Photosystem II. *Chem. Commun.* **2006**, 2650–2652.
 - (24) Kotzabasaki, V.; Siczek, M.; Lis, T.; Milios, C. J. The First Heterometallic Mn–Ca Cluster Containing Exclusively Mn(III) Centers. *Inorg. Chem. Commun.* **2011**, *14* (1), 213–216.
 - (25) Najafpour, M. M.; Ehrenberg, T.; Wiechen, M.; Kurz, P. Calcium Manganese(III) Oxides (CaMn₂O₄·xH₂O) as Biomimetic Oxygen-Evolving Catalysts. *Angew. Chemie Int. Ed.* **2010**, *49* (12), 2233–2237.
 - (26) Rorth, M.; Jensen, P. K. Determination of Catalase Activity by Means of the Clark Oxygen Electrode. *Biochim. Biophys. Acta* **1967**, *139* (1), 171–173.
 - (27) Mishra, A.; Yano, J.; Pushkar, Y.; Yachandra, V. K.; Abboud, K. A.; Christou, G. Heteronuclear Mn–Ca/Sr Complexes, and Ca/Sr EXAFS Spectral Comparisons with the Oxygen-Evolving Complex of Photosystem II. *Chem. Commun.* **2007**, 1538–1540.
 - (28) Hammad, F.; Koua, M.; Umena, Y.; Kawakami, K.; Shen, J.-R. Structure of Sr-Substituted Photosystem II at 2.1 Å Resolution and Its Implications in the Mechanism of Water Oxidation.
 - (29) Ghanotakis, D. F.; Topper, J. N.; Youcum, C. F. Structural Organization of the Oxidizing Side of Photosystem II. Exogenous Reductants Reduce and Destroy the Mn-Complex in Photosystems II Membranes Depleted of the 17 and 23 kDa Polypeptides. *Biochim. Biophys. Acta - Bioenerg.* **1984**, *767* (3), 524–531.
 - (30) Boussac, A.; Rutherford, A. W. Nature of the Inhibition of the Oxygen-Evolving Enzyme of Photosystem II Induced by Sodium Chloride Washing and Reversed by

- the Addition of calcium(2+) or strontium(2+). *Biochemistry* **1988**, 27 (9), 3476–3483.
- (31) Boussac, A.; Rappaport, F.; Carrier, P.; Verbavatz, J.-M.; Gobin, R.; Kirilovsky, D.; Rutherford, A. W.; Sugiura, M. Biosynthetic $\text{Ca}^{2+}/\text{Sr}^{2+}$ Exchange in the Photosystem II Oxygen-Evolving Enzyme of *Thermosynechococcus Elongatus*. *J. Biol. Chem.* **2004**, 279 (22), 22809–22819.
 - (32) Nayak, S.; Nayek, H. P.; Dehnen, S.; Powell, A. K.; Reedijk, J. Trigonal Propeller-Shaped $[\text{Mn}^{\text{III}}_3\text{MII}^{\text{II}}\text{Na}]$ Complexes (M = Mn, Ca): Structural and Functional Models for the Dioxygen Evolving Centre of PSII. *Dalt. Trans.* **2011**, 40 (12), 2699.
 - (33) Tsui, E. Y.; Tran, R.; Yano, J.; Agapie, T. Redox-Inactive Metals Modulate the Reduction Potential in Heterometallic Manganese–oxido Clusters. *Nat. Chem.* **2013**, 5 (4), 293–299.
 - (34) Cook, S. A.; Borovik, A. S. Deconstructing Water Oxidation. *Nat. Chem.* **2013**, 5 (4), 259–260.
 - (35) Tsui, E. Y.; Agapie, T. Reduction Potentials of Heterometallic Manganese-Oxido Cubane Complexes Modulated by Redox-Inactive Metals. *Proc. Natl. Acad. Sci.* **2013**, 110 (25), 10084–10088.
 - (36) Herbert, D. E.; Lionetti, D.; Rittle, J.; Agapie, T. Heterometallic Triiron-Oxo/Hydroxo Clusters: Effect of Redox-Inactive Metals. *J. Am. Chem. Soc.* **2013**, 135 (51), 19075–19078.
 - (37) Lionetti, D.; Agapie, T. How Calcium Affects Oxygen Formation. *Nature* **2014**, 513 (7519), 495–496.
 - (38) Lacy, D. C.; Park, Y. J.; Ziller, J. W.; Yano, J.; Borovik, A. S. Assembly and Properties of Heterobimetallic $\text{Co}^{\text{II/III}}/\text{Ca}^{\text{II}}$ Complexes with Aquo and Hydroxo Ligands. *J. Am. Chem. Soc.* **2012**, 134 (42), 17526–17535.
 - (39) Park, Y. J.; Ziller, J. W.; Borovik, A. S. The Effects of Redox-Inactive Metal Ions on the Activation of Dioxygen: Isolation and Characterization of a Heterobimetallic Complex Containing a $\text{Mn}^{\text{III}}-(\mu\text{-OH})\text{-Ca}^{\text{II}}$ Core. *J. Am. Chem. Soc.* **2011**, 133 (24), 9258–9261.
 - (40) Karlin, K. D. Redox Control of oxoiron(IV). *Nat. Chem.* **2010**, 2 (9), 711–712.
 - (41) Fukuzumi, S.; Morimoto, Y.; Kotani, H.; Naumov, P.; Lee, Y.-M.; Nam, W. Crystal Structure of a Metal Ion-Bound oxoiron(IV) Complex and Implications for Biological Electron Transfer. *Nat. Chem.* **2010**, 2 (9), 756–759.
 - (42) Rodriguez, M. M.; Bill, E.; Brennessel, W. W.; Holland, P. L. N_2 reduction and Hydrogenation to Ammonia by a Molecular Iron-Potassium Complex. *Science* **2011**, 334 (6057), 780–783.
 - (43) Figg, T. M.; Holland, P. L.; Cundari, T. R. Cooperativity Between Low-Valent Iron and Potassium Promoters in Dinitrogen Fixation. *Inorg. Chem.* **2012**, 51 (14), 7546–7550.
 - (44) Miller, C. G.; Gordon-Wylie, S. W.; Horwitz, C. P.; Strazisar, S. A.; Davi K. Peraino; Clark, G. R.; Weintraub, S. T.; Terrence J. Collins. A Method for Driving O-Atom Transfer: Secondary Ion Binding to a Tetraamide Macrocyclic Ligand. *J. Am. Chem. Soc.* **1998**, 120, 11540–11541.
 - (45) Smith, J. B.; Kerr, S. H.; White, P. S.; Miller, A. J. M. Thermodynamic Studies of Cation–Macrocyclic Interactions in Nickel Pincer–Crown Ether Complexes Enable

- Switchable Ligation. *Organometallics* **2017**, 36 (16), 3094–3103.
- (46) Yoshikai, N.; Matsuda, H.; Nakamura, E. Hydroxyphosphine Ligand for Nickel-Catalyzed Cross-Coupling through Nickel/Magnesium Bimetallic Cooperation. *J. Am. Chem. Soc.* **2009**, 131 (27), 9590–9599.
- (47) Chantarojsiri, T.; Ziller, J. W.; Yang, J. Y. Incorporation of Redox-Inactive Cations Promotes Iron Catalyzed Aerobic C–H Oxidation at Mild Potentials. *Chem. Sci.* **2018**, 9 (9), 2567–2574.

