

Expanding the Rare-Earth Metal BINOLate Catalytic Multitool beyond Enantioselective Organic Synthesis

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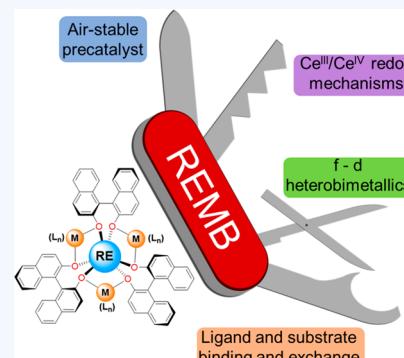
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CONSPECTUS: Shibasaki's rare earth alkali metal BINOLate (REMB) framework has provided chemists with a general catalyst platform to access a range of enantioenriched small molecules from the single, commercially available pro-ligand (*R*)- or (*S*)-BINOL. A defining feature of these heterobimetallic frameworks is the high level of catalyst tunability, achieved through the simple modulation of the central rare-earth cation and peripheral alkali metal cations. While this family of multifunctional catalysts displays impressive generality and catalytic capability, detailed mechanistic understanding of these complex, multimetallic systems was lacking prior to our investigations. This backdrop served as initial inspiration for our investigations of this privileged class of complexes over the past decade, which have led to new and exciting advances in catalysis and beyond.

In this Account, we describe our investigations using Shibasaki's framework focusing on the central metal-ion, the BINOLate ligands, and the secondary sphere cations. Our studies began with an investigation into the Lewis acidity of the complexes, where we demonstrated that Lewis bases readily coordinate to REMB frameworks when lithium occupies the secondary coordination sphere. This observation was contrasted by the complexes containing sodium or potassium in the secondary coordination sphere, as the rare earth cation is evidently less accessible for substrate binding. Our efforts in understanding the ligand exchange of the complexes enabled the discovery that associative processes dominate the mechanism of ligand exchange and LA/LA (Lewis acid/Lewis acid) and LA/BB (Lewis acid/Brønsted base) catalysis by the REMB frameworks. Replacing metal cations in the secondary coordination sphere with the *N,N,N',N'*-tetramethylguanidinium cation delivered an effective precatalyst that is air and water stable over the course of 6 months.

To expand the reactivity of the REMB, we investigated the ability of U^{IV} cations to occupy the primary coordination sphere and ZnEt^+ and $\text{Cu}(\text{DBU})^+$ cations to occupy the secondary coordination sphere. Synthesizing the REMB complexes using the thiol congener monothioBINOL provided an unusual anionic REMB framework, driven by the oxophilicity of the lithium cations. Using the REMB as a platform for investigating the $\text{Ce}^{\text{III}}/\text{Ce}^{\text{IV}}$ redox couple, we demonstrated that, while oxidative cerium functionalization is observed in the case of lithium containing REMBs, salt elimination is observed in the sodium, potassium, and cesium containing REMBs. Furthermore, we found that while the rate of heterogeneous electron transfer for Ce^{III} was $k_s(\text{Cs}^{\text{I}}) > k_s(\text{K}^{\text{I}}) > k_s(\text{Na}^{\text{I}}) > k_s(\text{Li}^{\text{I}})$, the rates of reaction with the oxidant trityl chloride trended in the opposite order with $k_{\text{obs}}(\text{Li}^{\text{I}}) \gg k_{\text{obs}}(\text{Na}^{\text{I}}) > k_{\text{obs}}(\text{K}^{\text{I}}) > k_{\text{obs}}(\text{Cs}^{\text{I}})$. We attribute this to the ability to form inner-sphere complexes with the oxidant, rather than differences in redox potential or reorganization energies.

Applying our knowledge in ligand exchange and redox behavior of Ce containing REMB complexes, we detailed the mechanism for oxidation of the heterochiral cerium REMB frameworks, reiterating the importance of the formation of inner-sphere complexes in the oxidation chemistry of cerium. There are many different avenues for both organic and inorganic investigation of Shibasaki's REMB framework, and our works have demonstrated the richness of the structural chemistry and properties of this framework that inform mechanism and properties of these privileged catalysts.

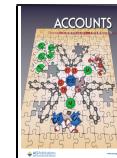


KEY REFERENCES

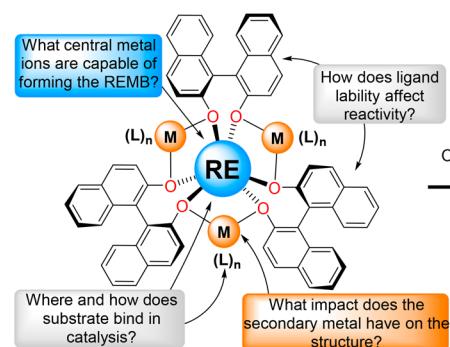
- Wooten, A. J.; Carroll, P. J.; Walsh, P. J. Insight into Substrate Binding in Shibasaki's $\text{Li}_3(\text{THF})_n(\text{BINOLate})_3\text{Ln}$ Complexes and Implications in Catalysis. *J. Am. Chem. Soc.* 2008, 130, 7407–7419.¹ Solid- and solution-state structural studies of the Shibasaki frameworks, which unambiguously determined binding of substrates at the rare earth cations.

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Our questions regarding the REMB:



Over 10 years of investigations

In this Account:

Modification and investigation of the REMB framework

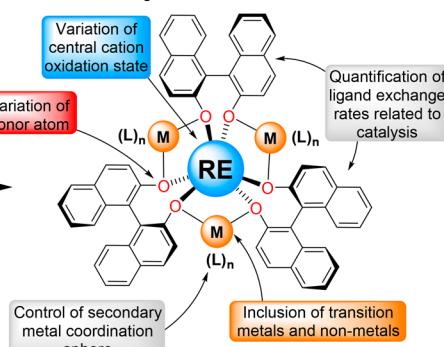
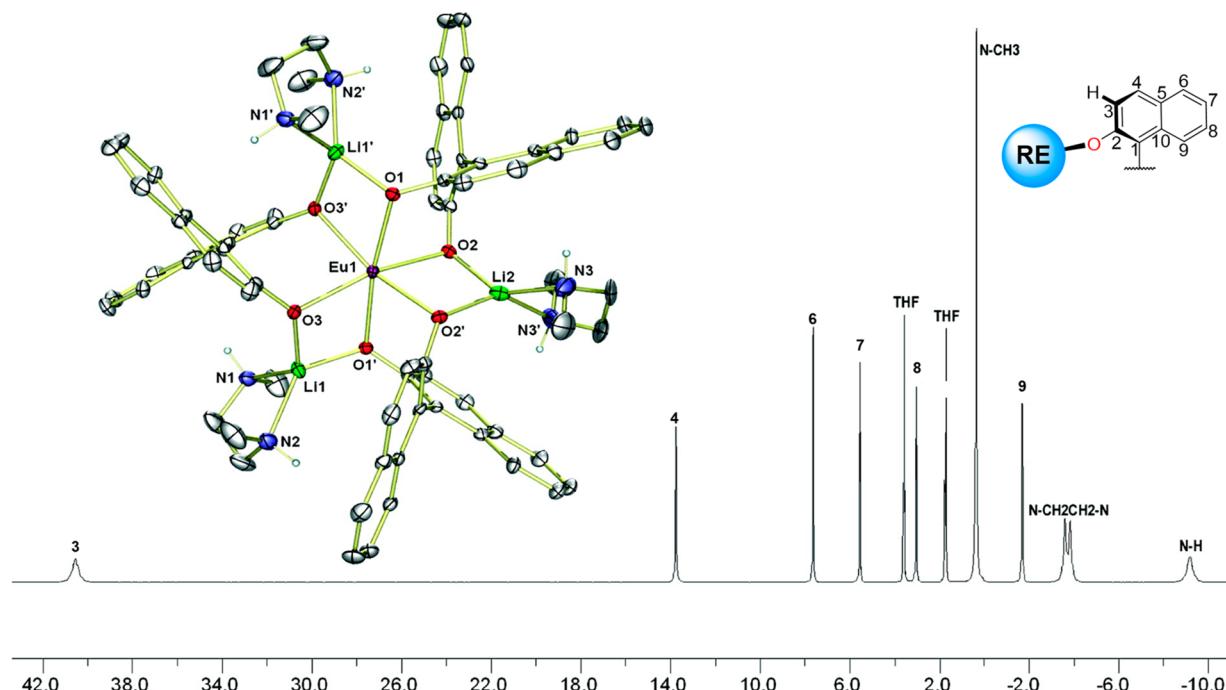


Figure 1. (left) Our questions about the REMB framework. (right) Variations and investigations addressed in this Account.

Figure 2. ^1H NMR spectrum of EuLiB-DMEDA in $\text{THF}-d_8$ and ORTEP representation with 30% probability thermal ellipsoids. Numbering scheme for (S)-BINOLate C–H resonances included. Adapted with permission from ref 1. Copyright 2008 American Chemical Society.

- Robinson, J. R.; Gordon, Z.; Booth, C. H.; Carroll, P. J.; Walsh, P. J.; Schelter, E. J. Tuning Reactivity and Electronic Properties through Ligand Reorganization within a Cerium Heterobimetallic Framework. *J. Am. Chem. Soc.* **2013**, *135*, 19016–19024.² A comprehensive study into the $\text{Ce}^{\text{III}}/\text{Ce}^{\text{IV}}$ redox couple of the REMB framework. An extensive kinetic investigation of outer-sphere and inner-sphere electron transfer is detailed.
- Robinson, J. R.; Fan, X.; Yadav, J.; Carroll, P. J.; Wooten, A. J.; Pericàs, M. A.; Schelter, E. J.; Walsh, P. J. Air- and Water-Tolerant Rare Earth Guanidinium BINOLate Complexes as Practical Precatalysts in Multifunctional Asymmetric Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 8034–8041.³ Investigation and synthesis of tetramethyl-guanidinium containing REMBs as air-stable precatalysts.

1. INTRODUCTION

The ability of chemists to access enantioenriched small molecules and materials is paramount to the advancement of

fields such as chemical biology, pharmaceuticals, and materials science.^{4–6} While the diversity of such molecules was limited to those accessible from bioderived stereocenters, the advent of asymmetric catalysis has dramatically broadened the library of chiral structural motifs accessible to chemists, including on industrially relevant scales.^{7–10} Across the many classes of asymmetric catalysts, the rare-earth–alkali-metal heterobimetallic complexes (REMB, $[\text{M}(\text{L})_n]_3[\text{RE}(\text{BINOLate})_3]$, RE = Sc, Y, La–Lu, M = Li, Na, K, Figure 1) reported by Shibasaki and co-workers are among the most broadly applicable and highly enantioselective catalysts to date.^{11–13} These privileged catalysts promote the enantioselective formation of C–C, C–N, C–P, and C–O bonds by activating nucleophilic and electrophilic substrates through cooperative Lewis acid/Lewis acid (LA/LA) or Lewis acid/Brønsted base (LA/BB) reaction mechanisms.^{14–16}

The broad generality of these catalysts derives from the highly modular nature of the heterobimetallic framework. Typical transition-metal based systems require the generation

and screening of large chiral ligand libraries to imbue the desired steric and electronic catalyst properties, while REMB frequently uses a single, commercially available pro-ligand, (*R*)- or (*S*)-BINOL. The properties of the framework are instead precisely tuned through the size, Lewis acidity, and bonding preferences of the central RE cations ($\text{La}^{\text{III}}-\text{Lu}^{\text{III}}$: $\Delta\text{radius} \approx 0.17 \text{ \AA}$) and peripheral alkali metal cations ($\text{Li}^{\text{I}}-\text{K}^{\text{I}}$: $\Delta\text{radius} \approx 0.62 \text{ \AA}$).^{17,18} The various heterobimetallic combinations promote dramatically different reactivity and selectivity, all through a single, unifying scaffold.

The remarkable empirical performance of these “simple” catalysts raised several important questions. What impact do the central and secondary metals have in catalyst structure and function? How and where do substrates bind? What active species are responsible for productive catalysis? Could other reactivity modes, including redox, be accessed through modification of these frameworks? In this Account, we describe our advances in the mechanistic understanding of the REMB frameworks, which have led to fundamental connections of structure and function and expanded applications of these dynamic heterobimetallic systems in catalysis and beyond (Figure 1). This includes use of these systems to address fundamental questions in the f-element community relevant to ligand exchange, Ce^{III} oxidation, and air stability. These studies begin to reveal the true nature of heterobimetallic cooperativity in these systems, and we expect these to enable the use and further functionalization of REMB and other heterobimetallic frameworks in academic and industrial settings.

2. UNDERSTANDING AND EXPANSION OF THE CATALYSIS OF SHIBASAKI’S REMB

2.1. Binding of Substrates to the RE Cation

With few exceptions,^{18,19} substrate binding in REMB catalysts is proposed to occur at the RE center rather than the peripheral alkali metal cations. This hypothesis was driven by the solid-state structures of several RENaB, which feature a single water molecule bound at the RE^{III},¹⁴ yet unambiguous evidence for solution-binding was lacking at the time of our initial studies. For example, substrate binding at a paramagnetic RE^{III} center (e.g., Pr^{III} , Eu^{III}) would induce significant changes in substrate chemical shifts (lanthanide-induced shifts, LISs); however, minimal shifts were observed for the formyl C–H of pivaldehyde in the presence of PrNaB and EuNaB . Therefore, we undertook a series of binding studies to understand the activation mode of REMB.^{1,20}

We compared chemical shift differences of substrate analogues using ^1H NMR in the presence of diamagnetic LaLiB and paramagnetic EuLiB. To exclude the possibility of substrate binding to Li^{I} , THF was replaced with a strong Li^{I} chelator, *N,N'*-dimethylethylenediamine (DMEDA; LaLiB-DMEDA and EuLiB-DMEDA, Figure 2). From comparison of the ^1H NMR shifts observed between LaLiB-DMEDA and EuLiB-DMEDA, the impact of the RE paramagnetism was clear. The LIS of 1-cyclohex-2-enone vinyl resonances observed with EuLiB-DMEDA were 0.66 ppm for H_{α} and 0.18 ppm for H_{β} , an order of magnitude greater than those observed using diamagnetic LaLiB-DMEDA (Figure 3). Differences in chemical shifts between EuLiB-DMEDA and EuLiB were minimal, indicating binding to the lithium cation was not likely causing the observed LIS. When the same experiment was performed using a RE with an anisotropic g-tensor of opposite sign (Pr^{III}),²¹ the LISs observed were -0.46

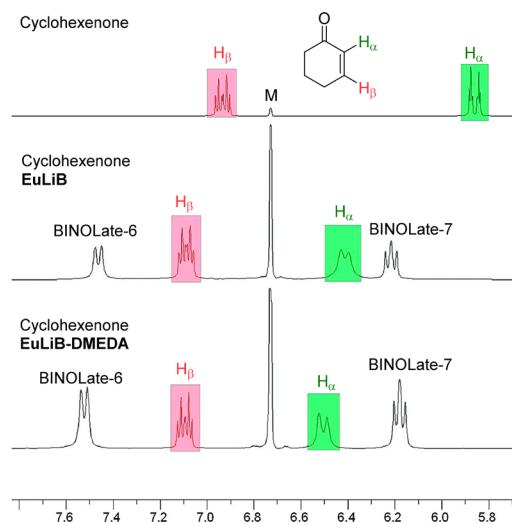
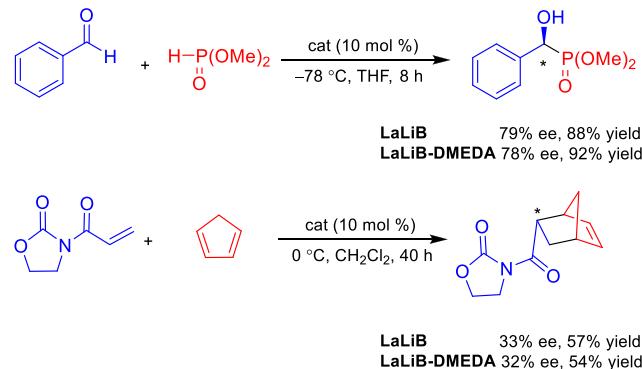


Figure 3. Stacked plots of the ^1H NMR spectra of the sp^2 region of 1-cyclohex-2-enone (top) and 1-cyclohex-2-enone in the presence of EuLiB (middle) and EuLiB-DMEDA (bottom). The α - and β -hydrogens are highlighted in green and red, respectively. M = mesitylene internal standard. Adapted with permission from ref 1. Copyright 2008 American Chemical Society.

ppm and -0.28 ppm for H_{α} and H_{β} , respectively, strongly supporting binding at the RE center.^{21,22} Further evidence for substrate binding at the RE was obtained from single-crystal X-ray diffraction (SC-XRD) studies, which revealed the 7-coordinate $[\text{Li}_3(\text{THF})_4][\text{RE}((\text{S})\text{-BINOLate})_3(\text{THF})]$, (RE = La^{III} , Pr^{III} , Eu^{III}).¹

To assess the importance of RE–substrate versus alkali metal–substrate binding interactions, catalytic activity of LaLiB (La^{III} and Li^I sites are accessible) and LaLiB-DMEDA (only La^{III} sites are accessible) in the asymmetric hydrophosphonylation of aldehydes and Diels–Alder reactions were chosen as they proceed through LA/BB and LA/LA mechanisms, respectively. LaLiB and LaLiB-DMEDA produced comparable yield and enantioselectivities and indicate that substrate binding at peripheral metal sites was not critical for activity or selectivity in RELiB catalysts (Scheme 1).

Scheme 1. Comparing the Catalytic Reactivity of LaLiB and LaLiB-DMEDA



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2.2. Impact of Alkali Metal Cations

If substrate binding at alkali metal sites is not essential for catalysis, what role do these cations play and why do they lead to such significant changes in reactivity and selectivity? Salvadori²³ reported that YbNaB does not bind water, and related observations were made by Shibasaki¹⁵ and Aspinall.²⁴ We found that the DMF formyl C–H shifted over 4 ppm in the presence of YbLiB in THF,²⁰ but no LIS was observed in the presence of RENaB ($\text{RE} = \text{Yb}$ and Eu) or YbKB under identical conditions.²⁵ Further insight came from the SC-XRD studies of anhydrous RENaB ($\text{RE} = \text{La}^{\text{III}}$ and Eu^{III}). Unlike RELiB , RENaB structures are dominated by extensive cation– π interactions (Na–binaphthyl) in the secondary coordination sphere (Figure 4) and feature six-coordinate

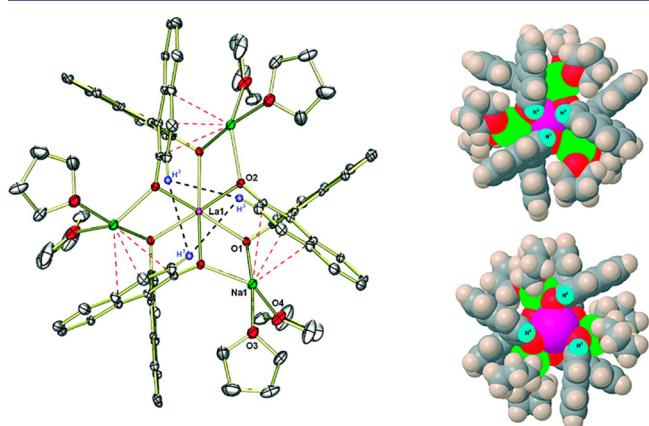


Figure 4. (left) Structure of LaNaB indicating the $\text{Na}-\text{C}$ π -interactions via red-dashed lines. (right) Two space-filling models viewed down the C_3 -axes with the 3-H protons in blue. Reproduced with permission from ref 25. Copyright 2007 American Chemical Society.

RE^{III} . Therefore, the alkali metal identity is the primary determinant for substrate binding to RE^{III} ($\text{Li} \gg \text{Na} > \text{K}$), while substrate access to the peripheral cations minimally impacts catalysis. We subsequently exploited this to non-covalently immobilize RENaB on functionalized Merrifield resins and apply them as recyclable catalysts for the asymmetric Michael addition.²⁶

2.3. Ligand Exchange: Impact on Catalysis

While LA/BB catalysis accounts for the overwhelming majority of REMB catalyzed reaction pathways, little is known about the structure of the active species in these processes and pertinent elementary steps. For example, the only investigations of ligand exchange had centered on heterochiral REMB frameworks.^{23,24,27,28} Equipped with a better structural understanding of these systems, we set out to identify the relevant active species and elementary steps involved in catalysis.

We turned to 2D ^1H and ^7Li exchange spectroscopy (EXSY) NMR to probe relevant exchange processes in solution.²⁹ First, we investigated the background intermolecular self-exchange of both ligand and Li^{I} in RELiB . Pr^{III} and Eu^{III} were chosen to probe these as the corresponding RELiB are isostructural, have similar ionic radii, and display LIS of opposite sign. The exquisite spectral resolution enabled facile quantification of exchange (Figure 5). Eyring analysis of VT-EXSY studies revealed large, positive enthalpies of activation (ΔH^{\ddagger}) and large, negative entropies of activation (ΔS^{\ddagger}) for both Li^{I} and

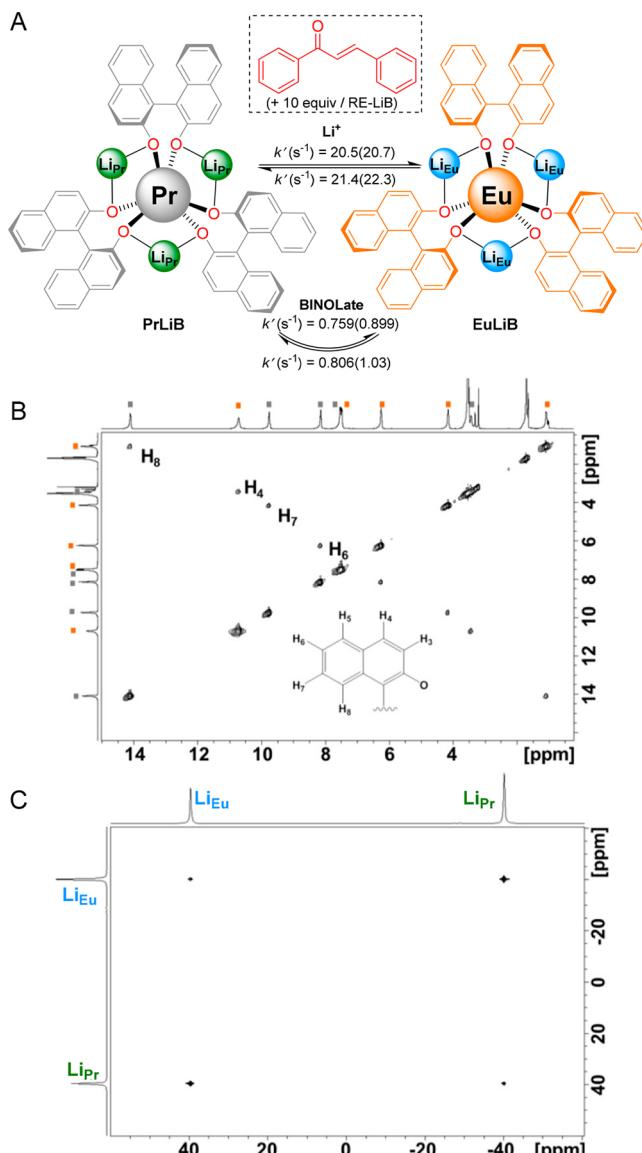


Figure 5. (A) Intermolecular exchange observed by ^1H and ^7Li 2D EXSY NMR experiments with forward and backward reaction rates. Values in parentheses are exchange rates in the presence of 10 equiv of chalcone. Representative 2D EXSY NMR spectra recorded for the mixture of $\text{PrLiB}/\text{EuLiB}$ (13.1/14.6 mM) in $\text{THF}-d_8$ at 300 K observing: (B) ^1H NMR (400 MHz, $t_{\text{mix}} = 140$ ms; gray ■ = PrLiB , orange ■ = EuLiB) and (C) ^7Li NMR (126 MHz, $t_{\text{mix}} = 10$ ms $\text{Li}_{\text{Pr}} = \text{PrLiB}$, $\text{Li}_{\text{Eu}} = \text{EuLiB}$). Adapted with permission from ref 29. Copyright 2015 American Chemical Society.

BINOLate exchange, consistent with associative mechanisms. Addition of 10 equiv of chalcone, a substrate in aza-Michael reactions, to EXSY experiments did not significantly impact either exchange rate. Notably, the rate of Li^{I} exchange was ~ 20 times faster than BINOLate exchange, and both extrapolated exchange rates, at relevant reaction temperatures, exceeded the rate of the aza-Michael reaction by 100–1000-fold.^{16,28,30}

We focused on the enantioselective Michael reaction to investigate LA/BB catalyzed processes. LIS from the Pr^{III} cation allowed interrogation of the species present in the PrLiB catalyzed Michael addition by ^7Li NMR ($\text{PrLiB}/\text{dibenzyl malonates}$ 1:10, Figure 6). We identified that the three major species present in THF are PrLiB (Li_A , 25%),

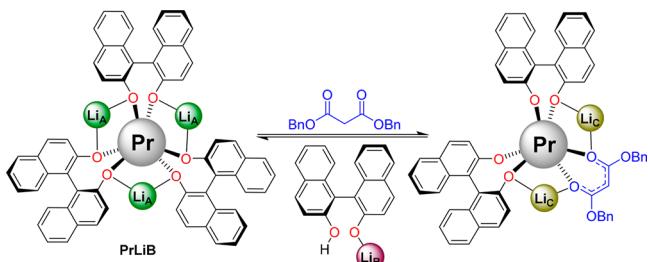


Figure 6. Major exchange processes and proposed species observed by 2D ^7Li NMR EXSY experiment of PrLiB/DBM (45.5 mM/455 mM; $t_{\text{mix}} = 15$ ms, 300 K). Bound solvents not shown. Adapted with permission from ref 29. Copyright 2015 American Chemical Society.

LiHBINOLate (Li_B), and a new paramagnetically shifted species (Li_C). Both PrLiB and the new species exhibited ^7Li exchange with LiHBINOLate on the order of the exchange seen between PrLiB and EuLiB. This indicated that the observed species may arise from deprotonation of dibenzyl malonate, liberating LiHBINOLate. Importantly, these studies implicate the involvement of species with less than three bound BINOLate ligands are likely active in some reactions catalyzed by REMB in THF (Figure 6).

2.4. Precatalyst Studies

Despite the great utility of the Shibasaki catalysts, their use by other researchers has been sparse. Major limitations of the REMB frameworks are their difficult synthesis, instability toward hydrolysis, incompatibility with high-throughput

screening techniques, and cost and sensitivity of the RE starting materials. To overcome these challenges, we set out to develop precatalysts for the Shibasaki family of REMB catalysts. The idea was to replace the alkali metal cations with nitrogen-centered cations capable of H-bonding interactions.³ We found that the commercially available, inexpensive $\text{RE}(\text{NO}_3)_3 \cdot (\text{H}_2\text{O})_x$ salts could be used in the synthesis of RETMGHB up to a 25 g scale in combination with 3 equiv of (*S*)-BINOL and 6 equiv of tetramethyl guanidine (TMG, Figure 7).³¹ Remarkably, tetramethyl guanidinium cation-containing (TMG^+) complexes $[(\text{TMG}^+)_3][\text{RE}^{\text{III}}((\text{S})\text{-BINOLate})_3]$ (RETMGHB) withstand hydrolysis, which we attribute to the strong directionality of H-bonding between TMG^+ and BINOLate oxygens. This limits structural reorganization needed for water coordination, a key requirement for hydrolysis.

With reliable, cheap syntheses of RETMGHB, we proceeded to investigate their potential as precatalysts. We hypothesized that the significant enthalpic energy release from generating M–O bonds to the BINOLate ligands would drive the ion exchange to form REMB complexes and TMGH salts. Treatment of EuTMGHB with 3 equiv of LiI led cleanly to EuLiB, as judged by ^1H and ^7Li NMR (Figure 7). The TMG^+ precatalysts were benchmarked for their performance in the asymmetric Michael addition, aza-Michael addition, and aldol reactions, as these covered a range of REMB combinations and both LA/LA and LA/BB catalysis (Scheme 2). In each of these reactions, the products were generated with comparable or higher yields and ee's to the literature

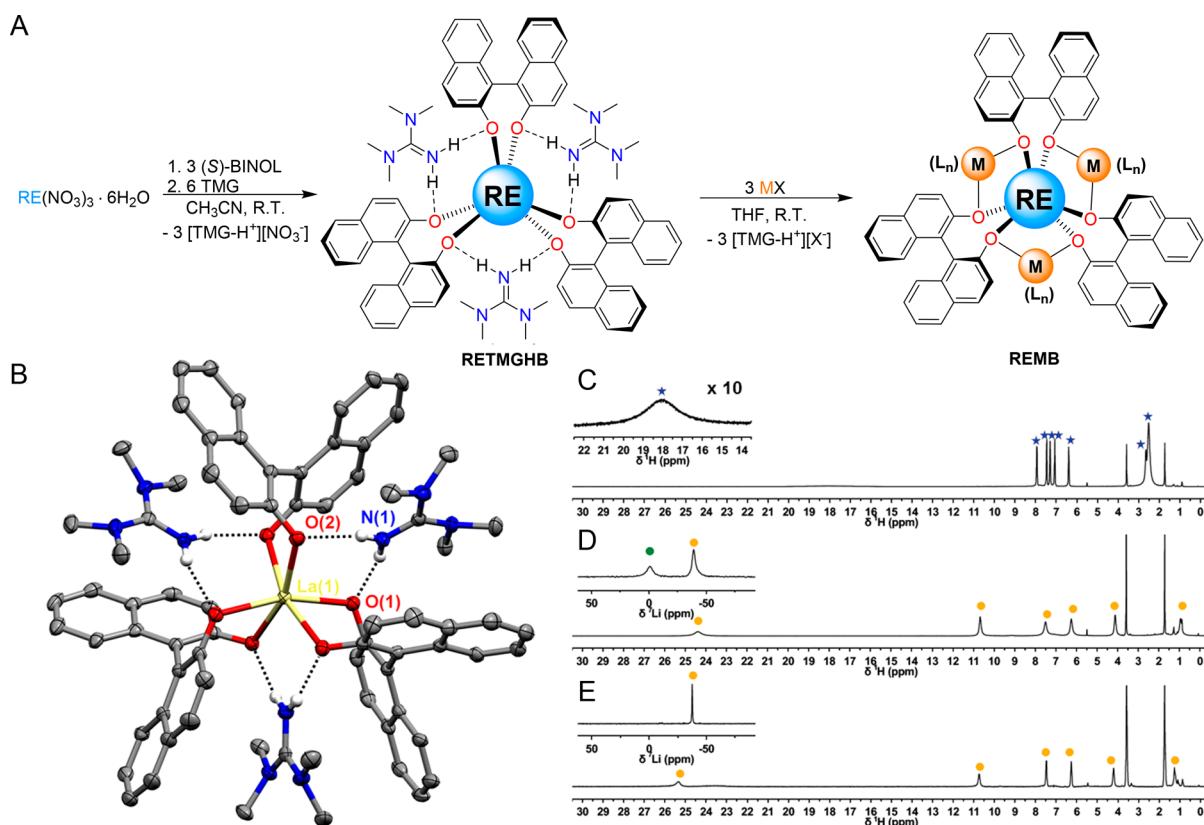
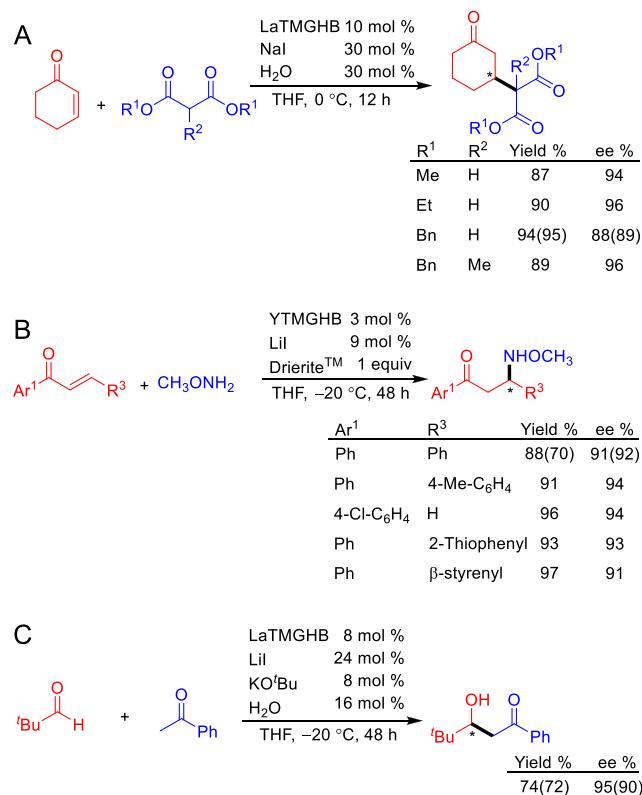


Figure 7. (A) Generation of RETMGHB from $\text{RE}(\text{NO}_3)_3 \cdot (\text{H}_2\text{O})_x$ and conversion to REMB through cation-exchange. (B) Thermal ellipsoid plot (30% probability) of LaTMGB. (C) ^1H NMR spectra of EuTMGHB (blue \star) in $\text{THF}-d_8$. (D) ^1H and ^7Li NMR (inset) spectra of EuTMGHB treated with excess LiI in $\text{THF}-d_8$. EuLiB (orange \bullet) and LiI (green \bullet). (E) ^1H and ^7Li NMR (inset) spectra in $\text{THF}-d_8$ of independently synthesized EuLiB (orange \bullet). Adapted with permission from ref 3. Copyright 2014 American Chemical Society.

Scheme 2. Catalytic Activity of RETMGHB Precatalysts in (A) Asymmetric Michael Addition, (B) Aza-Michael Addition, and (C) Direct Aldol Reaction^a



Adapted with permission from ref 3. Copyright 2014 American Chemical Society. ^aYields and ee% in parentheses are using RETMGHB that was exposed to ambient atmosphere for 6 months.

reports, and comparable activity and selectivity were observed with RETMGHB which had been exposed to air for 6 months (Scheme 2). These results demonstrate the ability for hydrogen-bonding to stabilize complexes toward hydrolysis, a very important, and underutilized tool in the synthesis of f-element complexes.

3. EXPANDING THE REMB FAMILY

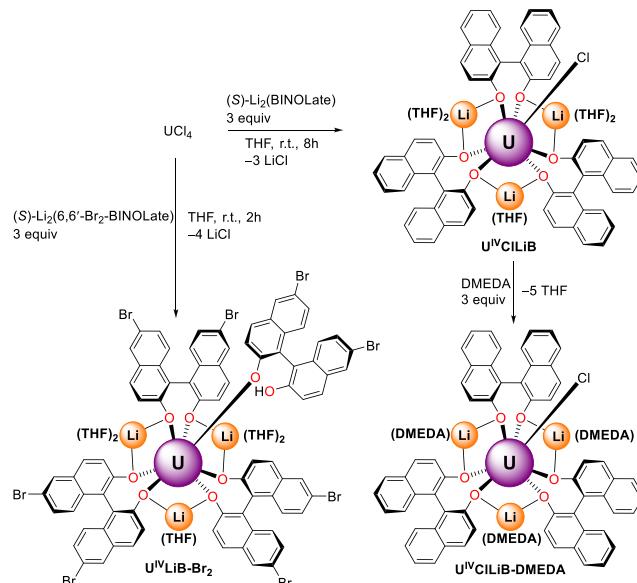
Given the success of the Shibasaki catalysts, we were attracted to the idea of expanding this family of complexes. Could the central RE^{III} and peripheral alkali-metal cations be replaced with different metal ions, including those with different oxidation states? Can BINOLate derivatives be tolerated, and how might they impact structure and function? Such compounds could access new reactivity beyond LA/LA and LA/BB and motivated our further studies.

3.1. U^{IV} Complexes

A range of trivalent metal ions across the periodic table can generate tris-BINOLate frameworks,^{32–36} but the introduction of metal ions in alternative redox states had yet to be realized. Higher oxidation-state REMB analogues are attractive targets that should display enhanced Lewis acidity and access novel structures with distinct catalytic activities. Although molecular cerium complexes have readily accessible tetravalent states, early actinides such as uranium can access +3 to +6 oxidation states. Furthermore, depleted uranium (primarily ²³⁸U) is a weak alpha emitter, making safe experimental working

conditions possible with simple monitoring procedures. With this in mind, we investigated uranium derivatives, UMB, to understand the impact of using a central metal with several readily available redox states (U^{III}–U^{VI}).³⁷ Although U^{III} starting materials resulted in complex mixtures, reacting UCl₄ with 3 equiv of Li₂-(S)-BINOLate resulted in the desired 1:3:3 framework U^{IV}ClLiB (Scheme 3). In solution, U^{IV}ClLiB

**Scheme 3. Synthesis of [Li₃(sol)_n][((S)-BINOLate)₃U–Cl]
(sol = THF (U^{IV}ClLiB), DMEDA (U^{IV}ClLiB-DMEDA)) and [Li₃(THF)₅][6,6'-Br₂-(S)-BINOLate₃U–(6,6'-Br₂–H₁BINOL)] (U^{IV}LiB-Br₂)**



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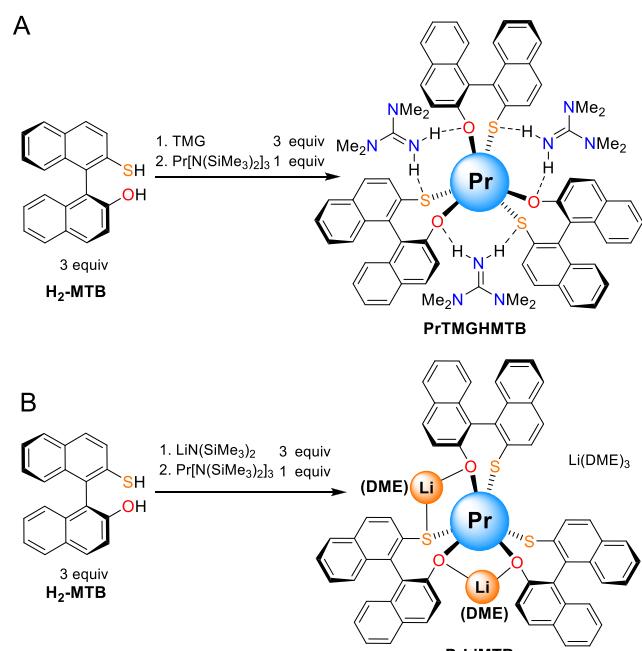
displayed lower symmetry compared to the trivalent RE^{III} counterparts (C₃ versus D₃), which was also seen in the solid-state structure obtained from SC-XRD. U^{IV}ClLiB also underwent facile ligand exchange upon addition of 3 equiv of DMEDA to generate U^{IV}ClLiB-DMEDA. Attempts to use the functionalized Li₂[6,6'-Br₂-(S)-BINOLate] in place of Li₂-(S)-BINOLate resulted in a UMB complex with a singly deprotonated H-6,6'-Br₂-(S)-BINOLate⁻ ligand in the apical position instead of Cl⁻. The isolated [Li₃(THF)₅][6,6'-Br₂-(S)-BINOLate₃U–(6,6'-Br₂-(S)-H₁BINOL)] (U^{IV}LiB-Br₂) was produced as the major product whether 3 or 4 equiv of Li₂[6,6'-Br₂-(S)-BINOLate] was used. We then moved to investigate the three complexes' ability to perform asymmetric catalysis.

Given the seven-coordinate U^{IV}Cl center, the ability of uranium to bind substrates was viewed as unlikely. Therefore, we were attracted to the asymmetric Diels–Alder reaction, as it was proposed to be promoted by the peripheral metals of the heterobimetallic catalyst. The use of U^{IV}LiB-Br₂ under Shibasaki and co-workers' optimized conditions using YbLiB-Br₂¹⁸ afforded the product in moderate ee (63%), the most enantioselective transformation catalyzed by uranium at the time. One of the concerns with the use of uranium catalysts is contamination; however, we found that running the crude reaction mixture through a silica plug followed by an aqueous workup brought measurements of the already weak radioactivity back to background levels.

3.2. Use of MonothioBINOLate (MTB)

To investigate the potential of using “soft” Lewis bases in the REMB framework, we turned to the previously synthesized ligand monothioBINOLate (MTB) that contains one sulfur donor and one oxygen donor.^{38–41} After slight reoptimization of the synthesis, we obtained (S)-H₂MTB over three steps. We chose Lewis acids that are considered to make the most stable complexes for the secondary coordination sphere, TMGH⁺ and Li^I, to initiate our exploration of the impact of the sulfur atoms. Reaction of Pr[N(SiMe₃)₂]₃, TMG, and (S)-H₂MTB in a 1:3:3 ratio produced the desired product [TMGH]₃[Pr((S)-MTB)]₃ (PrTMGHMTB) in 66% yield (Scheme 4). The complex

Scheme 4. (A) Synthesis of PrTMGHMTB and (B) Synthesis of PrLiMTB



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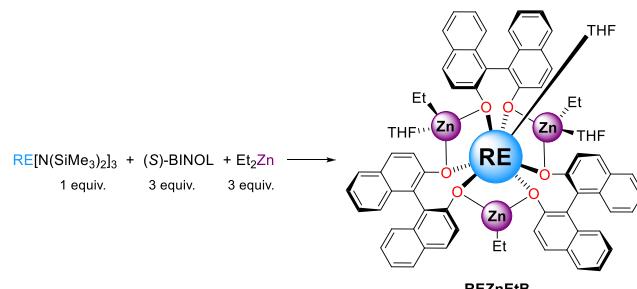
exhibited a C₃ symmetric structure, with the thiolates in a pseudo-*fac* orientation. Reacting Pr[N(SiMe₃)₂]₃, LiN(SiMe₃)₂, and (S)-H₂MTB in a 1:3:3 ratio in DME resulted in an unusual, anionic REMB complex {Li(DME)₃}{{Li(DME)}₂[Pr((S)-MTB)]₃} (PrLiMTB). PrLiMTB exhibited a pseudo-*mer* orientation of the sulfur atoms. We attribute this unusual geometry to the relative oxophilicity of the Li^I ion,⁴² as this structure reduces the amount of Li–S interactions. Given the observed coordination preferences upon changing the hard–soft acid–base matching of the supporting ligand, further exploration is warranted to stabilize a diverse range of heterobimetallic frameworks.

3.3. Alkyl Zinc Cations

Replacement of the peripheral group I cations (Li, Na, or K) with 3d cations would generate novel 3d–4f REMB scaffolds, which would likely promote new modes of catalytic reactivity. Divalent Zn^{II} was targeted,⁴³ as it shares similar ionic radius to Li^I, and is employed extensively in asymmetric catalysis. Pure [(EtZn(THF)_n)₃[RE^{III}((S)-BINOLate)₃(THF)]] (REZnEtB) was synthesized by protonolysis with RE[N(SiMe₃)₂]₃, (S)-

BINOL, and Et₂Zn precursors. Consistent with the similar ionic radius of Zn^{II} and Li^I, the novel REMB frameworks shared several structural similarities with RELiB (Scheme 5).

Scheme 5^a



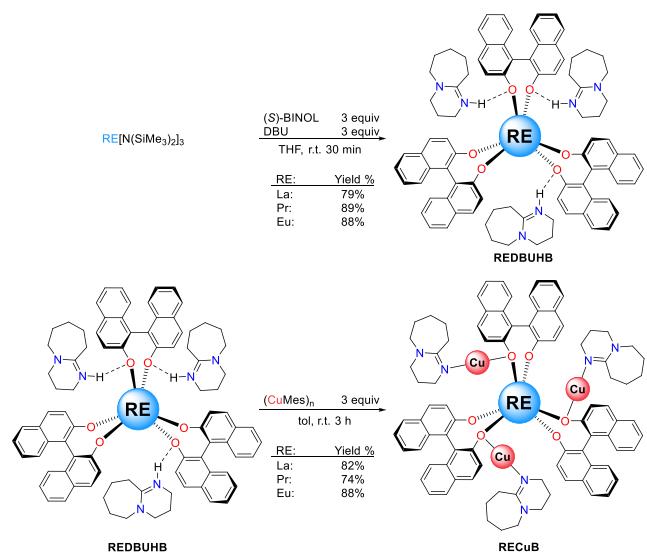
Adapted with permission from ref 43. Copyright 2013 American Chemical Society. ^aReaction conditions: THF, RT, 1 d, RE = La, Pr, Eu.

With these new complexes in hand, we set out to establish their catalytic competence using the enantioselective ethylation of benzaldehyde with ZnEt₂ as a benchmark to more broadly connect structure and function. Both REZnEtB and RELiB catalyze this transformation in high yields, albeit with modest ee’s (~50%), and control experiments with (S)-BINOL support that catalyst activity is the result of discrete heterobimetallic species rather than decomposition to Zn–(BINOLate) species. Similar to reports by Shibasaki and co-workers,¹⁹ catalyst selectivity could be increased with the addition of phosphine oxide, where one equivalent of triphenylphosphine oxide (TPPO) with respect EuZnEtB increased the ee of the addition to ~70%.

3.4. DBU and Copper Cations

A long-standing goal of our team was to facilitate enantioselective redox catalysis with REMB frameworks, which motivated our pursuit of RE/Cu^I heterobimetallics. Cu has been extensively employed as a redox mediator and Lewis acid, while Cu^I/Cu^{II} are again similar in size to Li^I and Zn^{II}.^{44–46} To access these frameworks, we employed 1,8-diazobicyclo[5.4.0]undec-7-eneium (DBUH) containing REMB ([DBUH]₃[RE((S)-BINOLate)₃], REDBUHB, Scheme 6), as it contained only a single hydrogen bond per cation to the [RE((S)-BINOLate)₃]³⁻ moiety (two are in RETMGHB). Reacting REDBUHB with 3 equiv of mesityl-copper resulted in the formation of a new D₃ symmetric product by ¹H NMR, where SC-XRD verified that the product was [Cu(DBU)]₃[RE((S)-BINOLate)₃] (RECuB, Scheme 6). The Cu^I cation replaced the proton in the structure of REDBUHB, with retention of the DBU as a ligand for copper. While 2-coordinate geometries are not uncommon for Cu^I, the low coordination numbers are unprecedented for peripheral metal ions found in REMB. Such structures may be expected to display significant lability; therefore, we explored the kinetics of ligand exchange processes by studying EuCuB and PrCuB with 2D EXSY NMR. Similar to RELiB, RECuB activation parameters were consistent with associative mechanisms of ligand exchange; however, RECuB displayed higher rates of BINOLate exchange (3-fold). We attribute this difference to the combination of the lower oxophilicity and coordination numbers of the Cu^I ion in RECuB. Although RECuB was employed in catalytic asymmetric transformations,

Scheme 6. Synthesis of (A) Complexes REDBUHB from the Corresponding RE Amide Bases and (B) Complexes RECuB from REDBUHB



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it exhibited greater sensitivity than previous REMB complexes and readily decomposed under the reaction conditions.

4. APPLICATIONS IN PHYSICAL INORGANIC CHEMISTRY

4.1. Ce^{III} Oxidation Chemistry

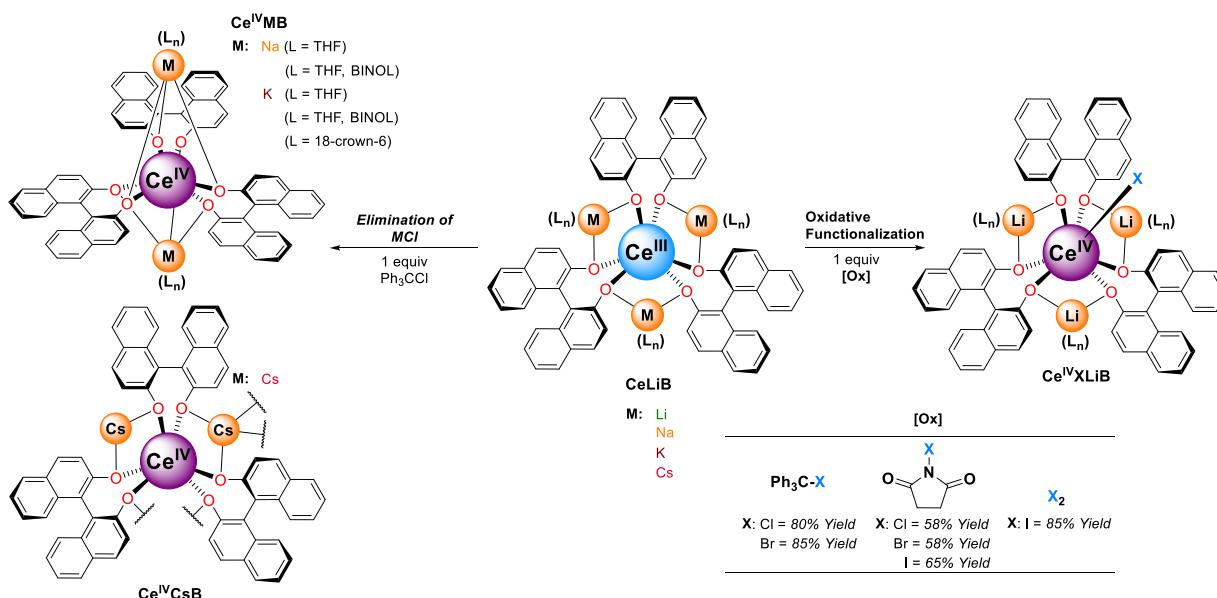
Our mechanistic studies of the REMB frameworks revealed how noncovalent interactions in the secondary coordination sphere can regulate thermodynamic and kinetic properties of the central RE^{III}. Though common in nature, such behavior in small-molecule systems is rare (especially in rare earths), and

precise control over complex reorganization and electronics made this system an excellent platform to interrogate fundamental questions related to the redox chemistry of rare earths.^{2,47} While the Ce^{III/IV} couple has enabled numerous applications in organic, inorganic, and materials chemistries, the inorganic Ce products were often unpredictable and the result of ligand redistribution. Ligand reorganization is a central tenet of electron transfer theory; however, the impact of ligand reorganization on reaction outcomes in the redox chemistry of REs was effectively an unanswered question.

Chemical oxidation of CeMB frameworks revealed key structural and kinetic considerations for controlled redox activity. Treatment of CeLiB or CeLiB-DMEDA with different halogen atom transfer agents formed [Li(L)]₃[Ce(X)((S)-BINOLate)]₃ (CeXLiB or CeXLiB-DMEDA) in 58–93% yield (Scheme 7). In contrast to oxidation of CeLiB, the addition of trityl chloride to CeNaB, CeKB, and CeCsB resulted in the elimination of one equivalent of alkali metal chloride and structures that underwent significant structural reorganization. For Ce^{IV}NaB and Ce^{IV}KB, the alkali metal cations migrated to a κ^3 binding mode in the axial position of the [Ce^{IV}((S)-BINOLate)]₃²⁻ moiety (Scheme 7, left). While solid-state structures obtained of Ce^{IV}CsB contained intermolecular Cs– π interactions, DOSY NMR in THF suggests a monomeric species in solution.

When evaluating the oxidation of CeMB through chemical oxidation and electrochemistry, we observed opposing trends (Figure 8). The heterogeneous electron transfer rates were $k_s(\text{Cs}^{\text{I}}) > k_s(\text{K}^{\text{I}}) > k_s(\text{Na}^{\text{I}}) > k_s(\text{Li}^{\text{I}})$ in both neat THF and 6:1 CH₃CN/THF. In contrast, reaction rates of the complexes with Ph₃CCl revealed the trend $k_{\text{obs}}(\text{Li}^{\text{I}}) \gg k_{\text{obs}}(\text{Na}^{\text{I}}) > k_{\text{obs}}(\text{K}^{\text{I}}) > k_{\text{obs}}(\text{Cs}^{\text{I}})$. We reconciled these differences with the ability of the CeMB complexes to bind substrate at the Ce^{III} center. CeLiB readily adopts a 7-coordinate geometry and can engage in inner-sphere oxidation through coordination of the Cl atom of Ph₃CCl. Comparable substrate access is inaccessible in 6-coordinate CeNaB, CeKB, and CeCsB, and

Scheme 7. Divergent Oxidative Reactivity of Ce Containing REMB Complexes



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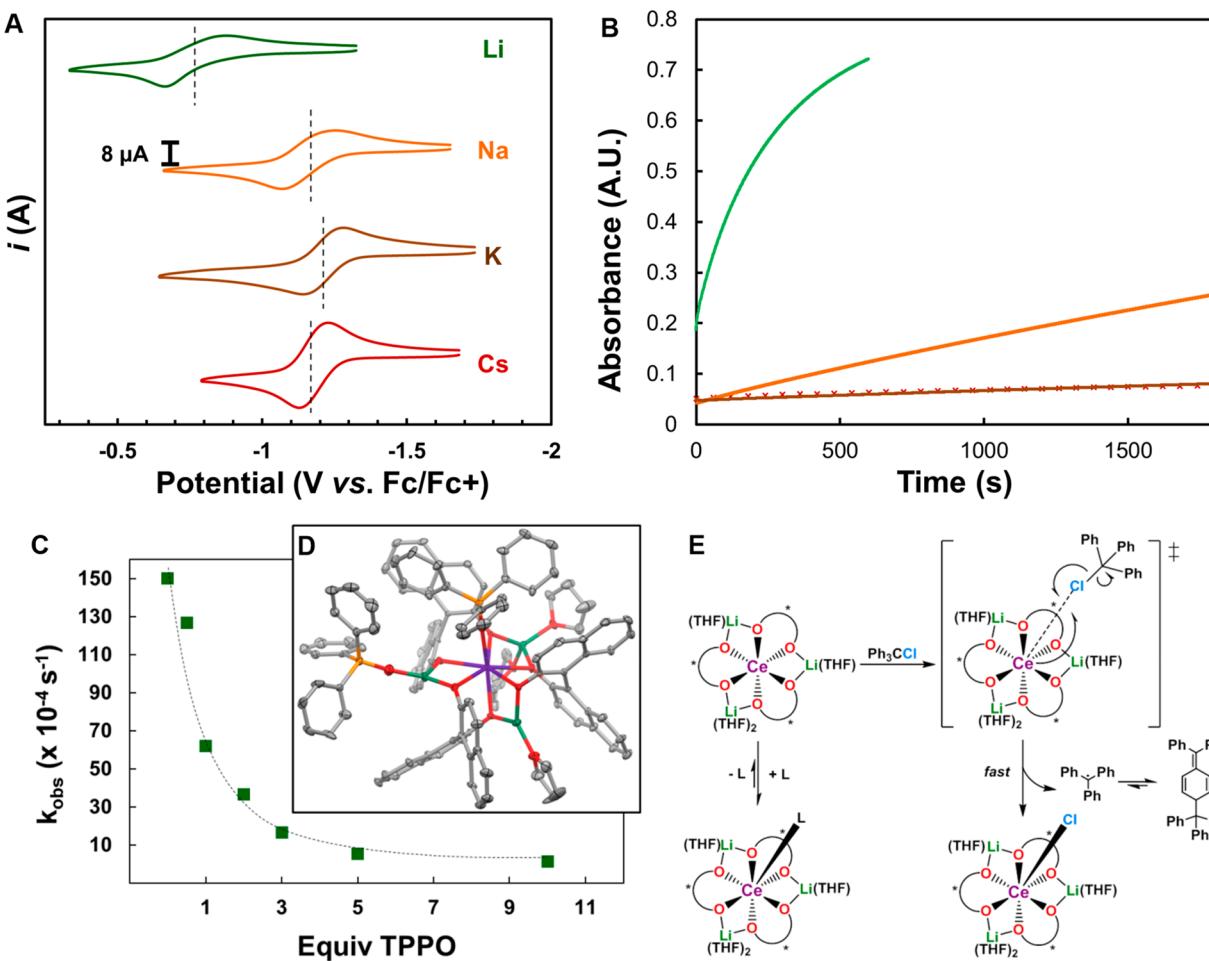


Figure 8. (A) Cyclic voltammograms measured for Ce^{IV}MB. Dashed lines included to illustrate positions of $E_{1/2}$. (B) Pseudo-first-order rate data for CeLiB (green), CeNaB (orange), CeKB (brown), and CeCsB (red). (C) k_{obs} under pseudo-first-order kinetics in the oxidation with Cl—CPh₃ in the presence of varying equivalents of TPPO (dotted line drawn as a guide for the eye). (D) Thermal ellipsoid plot of CeLiB-(OPPh₃)₂, with ellipsoids shown at 30% probability. (E) Proposed inner-sphere mechanism for the formation of Ce^{IV}ClLiB from trityl chloride and CeLiB. Adapted with permission from ref 2. Copyright 2013 American Chemical Society.

oxidation proceeds via outer-sphere electron transfer. To verify this hypothesis, we followed the rates of oxidation in the presence of a ligand that would competitively bind the Ce site. Phosphine oxides such as TPPO are excellent neutral donors for hard RE^{III} cations, and addition of TPPO led to dramatically decreased rates of oxidation for CeLiB. Limited accessibility to the Ce^{III} center was further supported in the solid-state by the X-ray structure of CeLiB(OPPh₃)₂, where TPPO is bound to both Ce and one Li (Figure 8D), as well as detailed multinuclear NMR solution studies. Ultimately the choice of redox-inactive M not only controls important redox properties of Ce but also the accessibility of Ce^{III} to substrates. Taken together, our studies clearly demonstrated the importance of ligand reorganization in the oxidation chemistry of Ce^{III} and provided a new platform to access predictive redox chemistry.

4.2. Impact of Ligand Exchange on Redox Chemistry

While our studies clearly supported a prominent role for ligand reorganization in controlling the redox processes at Ce, the prevalence and mechanism of other dynamic processes such as ligand redistribution had yet to be determined. REMB frameworks are known to form both homochiral and heterochiral diastereomers,^{19,23,24,28} and we envisioned that

the corresponding Ce^{III} complexes, CeLiB(homo) and CeLiB-(het), could provide controlled and systematic frameworks to elucidate these effects.⁴⁸ Synthesis of the racemic CeLiB(het) was achieved via protonolysis in THF using a 1:3:3 mixture of Ce[N(SiMe₃)₂]₃/(*rac*)-BINOL/LiN(SiMe₃)₂. While X-ray crystallography revealed exclusive formation of CeLiB(het) in the solid-state, both CeLiB(het) and CeLiB(homo) were observed in solution (NMR; \sim 6:1 ratio).

Cyclic voltammetry studies revealed increased rates of heterogeneous electron transfer and a more negative Ce^{III} oxidation event (\sim 270 mV) for CeLiB(het) compared to CeLiB(homo). Unlike CeLiB(homo), reaction of CeLiB(het) with trityl chloride led to the formation of a salt elimination product. Chemical kinetic studies employing CeLiB of varying enantiopurities established that the rate of chemical oxidation of Ce^{III} was dictated by the availability of the Ce^{III} center (e.g., inner-sphere oxidation) rather than the driving force for ET (i.e., outer-sphere process; $E_{1/2}(\text{Ce}^{\text{III/IV}})$). While our kinetic data supported a rate-determining inner-sphere oxidation by trityl chloride, salt-elimination from Ce^{IV}ClLiB was without synthetic precedent. Insight into the unique product selectivity was provided by mixing a 1:1 ratio of independently synthesized enantiomers of Ce^{IV}ClLiB(homo), which resulted in quantitative formation of Ce^{IV}LiB(het) and LiCl (i.e.,

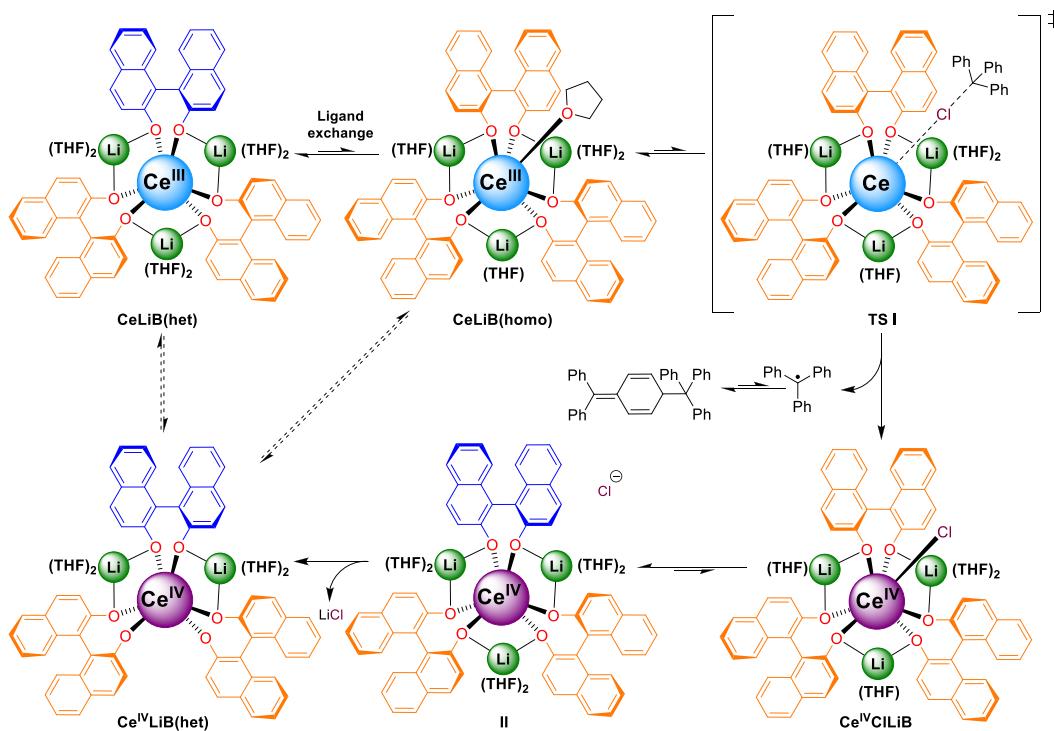


Figure 9. Proposed mechanism and ligand exchange processes for the oxidation reaction of CeLiB(het). Dashed equilibria are exchange pathways that have not been directly measured but likely can occur under reaction conditions. Adapted with permission from ref 48. Copyright 2016 The Royal Society of Chemistry.

immediate ligand redistribution and salt elimination). Taken together, we proposed an oxidation mechanism that involved facile ligand exchange and redistribution both preceding and following the rate-determining inner-sphere oxidation of Ce^{III} by trityl chloride (Figure 9). While accessibility of Ce^{III} controls the rate-determining step (inner-sphere oxidation), the selectivity-determining steps (ligand redistribution and salt elimination) occur after this point and are kinetically invisible. Although kinetic control over processes at molecular f-element systems can be challenging due to their high lability, our studies underscore the importance of managing dynamic ligand exchange and redistribution to control the outcome of redox reactions.

5. SUMMARY AND PROSPECTS

Herein we have summarized our efforts in connecting structure and function of Shibasaki's REMB framework, which are impacted significantly by the identity of the central metal ion, the primary ligands, and the secondary coordination sphere. Our studies not only delivered novel, valuable mechanistic insight into privileged asymmetric catalysts, but developed new fundamental advances and applications in coordination chemistry, redox chemistry, and catalysis. Qualitative and quantitative experiments detailing cation and ligand exchange processes were central to addressing fundamental questions surrounding the mechanism of LA/LA and LA/BB catalysis as well as the impact of ligand reorganization and exchange in electron transfer of f-elements. Furthermore, investigating available species in the secondary coordination sphere enabled practical applications like solid-supported, recyclable catalysts and air-stable precatalysts, which can be readily deployed in high-throughput screening methodologies and used without the need for gloveboxes. Additionally, the successful

introduction of zinc and copper into the peripheral metal sites demonstrates that the secondary coordination sphere could be expanded to include divalent and redox-active cations, respectively.

We plan to continue our investigation of the impact of ligand modification and secondary metal cation identity. With the introduction of even the poorly oxophilic Cu^I cation into the secondary coordination sphere, one can imagine the incorporation of many more of the elements into these frameworks. Likewise, the impact of some of the chiral and achiral additives used by Shibasaki and co-workers on the structure (and activity) of the catalyst remains poorly understood. With the adoption of high-throughput experimentation (HTE), the screening of these additives has become relatively simple. With these goals in mind, the future looks bright for new reactivity of Shibasaki's REMB framework, highlighting how cross disciplinary chemistry can impact adjacent fields.

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Notes

The authors declare no competing financial interest.

Biographies

Grace B. Panetti received her B.S. degree in chemistry from Clemson University in 2015. In her undergraduate studies, she conducted research under the direction of Prof. Modi Wetzler into peptoid (*N*-functionalized glycine) synthesis for the encapsulation of lanthanide and actinide cations. Grace began Ph.D. research in 2015 at the University of Pennsylvania under the direction of professors Eric J. Schelter and Patrick J. Walsh. Her research interests include synthetic and computational f-block metal coordination, organometallic chemistry, and catalysis.

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Patrick J. Walsh received his B.A. from UCSD and his Ph.D. at UC Berkeley with Prof. Robert G. Bergman (1991) and did postdoctoral research with Prof. K. B. Sharpless at Scripps. He was an assistant professor at San Diego State University (1994–1999) and a professor

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