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## Aqueous Lanthanide Chemistry in Asymmetric Catalysis and Magnetic Resonance Imaging

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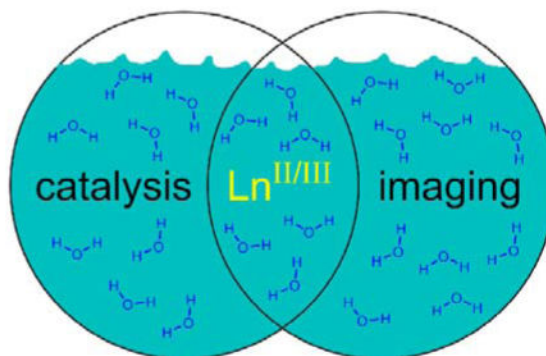
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### Abstract

This account describes lanthanide coordination chemistry with a focus on the similarities between lanthanide complexes used in catalysis and those used as contrast agents in magnetic resonance imaging.

### Graphical Abstract



### Keywords

catalysis; Mukaiyama aldol; lanthanides; contrast agents; magnetic resonance imaging

### 1 Introduction

The lanthanides compose an alluring region of the periodic table in part because of the wide range of magnetic and luminescence behaviors encompassed by these elements. The properties of these elements make them essential to many aspects of modern life including display screens, computers, automobiles, and medical diagnoses. Additionally, the entire series of elements has a propensity to favor the trivalent oxidation state, which leads to the ability to use one ligand to obtain a series of structurally similar complexes with diverse physicochemical properties. The ready access to structurally related complexes with diverse

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properties, the Lewis acidic nature of the lanthanide ions, and the ability of these ions to form water-tolerant complexes are some of the major factors that drive my interests and that have guided the research thus far in my career.

This account shares the findings of my research group that have arisen through exploring lanthanide chemistry along the boundary between catalysis and magnetic resonance imaging.

## 2 Lanthanide Coordination Chemistry

As a graduate student, my first experience with lanthanide chemistry was with Gd<sup>III</sup>-containing complexes relevant to magnetic resonance imaging.<sup>1</sup> At that time, my understanding was that these ions do not participate in covalent bonding, that multidentate ligands were necessary to form complexes with low lability because of purely electrostatic bonding, and that the ions rarely occurred outside of the +3 oxidation state. As I progressed in my research,<sup>2</sup> I began to see the beautiful intricacies of the coordination chemistry of these elements. While I refer readers elsewhere for detailed descriptions of the coordination chemistry of the lanthanides,<sup>3</sup> some aspects of lanthanide chemistry that specifically influence the research directions in my group include (1) the need for ligands with large denticities (usually >6) to form thermodynamically stable complexes; (2) the observation that even complexes with large conditional thermodynamic stabilities are fluxional; (3) that kinetic and thermodynamic stabilities are influenced by ligand design but differ in their importance depending on application; (4) that there is rich chemistry outside of the +3 oxidation state for lanthanides; and (5) that lanthanides in the +3 oxidation state tend to be hard acids (similar to Mn<sup>II</sup>) but in the +2 oxidation state they become relatively soft (similar to Ag<sup>I</sup>).<sup>4</sup>

There are several consequences to these five aspects of lanthanide chemistry that permeate the research in my group. The quest for stability in complexes often leads to ligands with large denticities. However, not only is denticity important for stability, but the arrangement of donors about the metal ion is critical for ligand design. For example, if a multidentate ligand blocks seven of nine coordination sites of a metal ion, then mono- or bidentate ligands (such as water or phosphate) can bind to the remaining sites. If the two remaining sites are adjacent to each other, then bidentate ligands tend to preferentially coordinate, blocking water from coordinating (which is of consequence to magnetic resonance imaging).<sup>5</sup> If the two binding sites are not adjacent to each other, then water can coordinate to each site with less interference from a bidentate ligand. Studies of water displacement have led to interesting findings with respect to anion sensing with lanthanides.<sup>6</sup> Additionally, while the lanthanide ions tend to be most stable in the +3 oxidation state, there is a wealth of chemistry of the +2 and +4 oxidation states for these elements.<sup>7</sup> In the other oxidation states, interesting characteristics of both f and d electrons can be observed, and often these characteristics are influenced by environmental factors such as light.<sup>8</sup> Furthermore, the trivalent ions tend to be oxophilic, but the divalent ions prefer softer bases.<sup>9</sup> These factors all influence ligand design.

Another interesting feature of lanthanides that arises from their large size is unique geometries. Although ligand donor atoms tend to not influence binding in some respects (minimal interactions with 4f orbitals), they can have an effect when linked together in a multidentate ligand or when d-character is involved, for example, with divalent lanthanide ions. Prior to beginning research in this area, I spent little time thinking about geometries larger than octahedrons, but now I am fascinated by larger geometries such as capped square antiprisms, bicapped trigonal antiprisms, muffins, and hula hoops.<sup>10</sup>

For relevancy to contrast agents for magnetic resonance imaging (molecules that influence contrast in images) or water-tolerant catalysis, lanthanide-containing complexes need to tolerate the presence of water, and coordination chemistry in water comes with a unique set of challenges. For example, when metalating a ligand that contains carboxylic acids with a lanthanide halide salt, a byproduct is HX (Scheme 1).<sup>11</sup> The acid lowers the pH of the reaction mixture and, consequently, can reverse the metalation to some extent. This drop in pH can be overcome by adjusting the pH with base or buffer, but the result of such adjustments is a solution of metal complex that contains salts from neutralization of the acid. Lanthanide hydroxides or oxides can be used for the metalation with the byproduct being replaced with water (Scheme 1), but the hydroxide and oxide salts have low aqueous solubility causing the need to heat metalation reactions to increase solubility. Long metalation times at high heat can be potentially damaging to ligands. These factors must be accounted for when planning reactions.

Studying paramagnetic ions in aqueous solutions that might contain other salts is often challenging. Crystallizations from these solutions are often onerous, and even if obtained, solid-state structures are often not representative of the highly fluxional complexes in solution. Depending on the ion, <sup>1</sup>H-NMR spectra are at best shifted and at worst (Gd<sup>III</sup> or Eu<sup>II</sup>) broadened to the point of not being useful. Consequently, other techniques are needed to study these complexes in solution including Job plots, <sup>17</sup>O-NMR spectroscopy, cyclic voltammetry, conductivity, luminescence and UV–visible spectroscopies, and electron paramagnetic resonance spectroscopy.<sup>12</sup> The challenges associated with studying lanthanide-containing complexes in solution is at times frustrating but is an enticing area of research, in my opinion, because of the great potential for new discoveries.

### 3 Study of Coordination Environment

The challenges associated with studying lanthanide-containing complexes in aqueous solution have been approached using a variety of innovative analytical methods.<sup>12</sup> Much of this innovation exploits luminescence and magnetic properties inherent to the ions and has been driven forward by research related to contrast agents for magnetic resonance imaging. At the start of my independent research career, my research focused on adapting some of these methods to study water-tolerant precatalysts for bond-forming reactions.

I was surprised that I was unable to find reports of the use of the technique to study catalysis; consequently, we began by studying luminescence-decay measurements that are often used to determine the water-coordination number of contrast agents for magnetic resonance imaging. Luminescence-decay measurements have been used to study lanthanide

ions in aqueous solution for decades.<sup>13</sup> This strategy seemed to be a great starting point because of the relative simplicity of the method and because the data it provided regarding coordination environment in solution was relevant to catalysis.

We used this technique to study the water-coordination number of  $\text{Eu}(\text{OTf})_3$ , a precatalyst for carbon–carbon bond-forming reactions in aqueous systems.<sup>14</sup> We were able to determine the water-coordination number of this lanthanide salt in the presence and absence of substrates and products of the water-tolerant Mukaiyama aldol reaction (Figure 1).<sup>15</sup> Our measurements were fast, water-tolerant, and worked under reaction-relevant conditions. Building on these results, we elucidated structural information about precatalysts that contained multidentate ligands (Scheme 2), and we used this information to propose a mechanism for chiral product formation.<sup>16</sup> We also reported the use of this technique, combined with high-performance liquid chromatography, to determine the influence of the water-coordination numbers of precatalysts on steady-state reaction rates.<sup>17</sup> From these measurements, correlations were observed between steady state reaction rate and water-coordination number as well as between yield and solvent composition. The methodology can be applied to other  $\text{Ln}^{\text{III}}$ -catalyzed bond-forming reactions in aqueous media to gain a better understanding of the influence of water on the structure–activity relationship between precatalysts and rates of catalysis.

Although we had success with the use of luminescence-decay measurements, our studies were limited to solvents that did not contain OH oscillators. Those oscillators contribute to luminescence quenching in a way that is indistinguishable from water. To include protic solvents, we empirically derived equations relating decay rate to coordination, as had previously been done in water,<sup>13</sup> in the presence of co-solvents that are commonly used in organic reactions.<sup>18</sup> These derivations resulted in the ability to determine water-coordination numbers in the presence of a wide range of co-solvents, including protic solvents. The results of this research enable the use of luminescence-decay measurements to study lanthanide-based catalytic systems in the presence of any of the seven co-solvents that we studied in any ratio with water.<sup>18</sup> The results of these efforts are in a web-based calculator to allow easy access to other researchers.<sup>19</sup> This research is important to understanding the dynamics of the inner- and outer-sphere environments of  $\text{Ln}^{\text{III}}$ -based precatalysts in aqueous solvent mixtures. The set of equations that we derived enables the facile acquisition of mechanistic and structural information regarding water-tolerant precatalysts and is a powerful tool for precatalyst design. We expect that our demonstration of the versatility and simplicity of this technique will enable its use by the synthetic community to study new bond-forming reactions.

#### 4 Catalysis with Trivalent Lanthanides

Similar to the application of an analytical technique from contrast agent research to catalysis, we used what we knew about aqueous lanthanide coordination chemistry from contrast agent research to design ligands for asymmetric catalysis.

Carbon–carbon bond-forming reactions are a foundation of synthetic chemistry, and many of these reactions can be catalyzed with water-tolerant lanthanide triflates.<sup>14</sup> Previous attempts

to use these water-tolerant precatalysts in stereoselective reactions were successful only in a few cases,<sup>20</sup> and we thought that viewing precatalysts from the vantage point of contrast agents would enable improvements in stereoselectivity in aqueous solution by enabling rational design of metal–ligand interactions.

We designed and synthesized a new series of ligands for lanthanides. These precatalysts originated from envisioning modifications to a common contrast agent, Gd<sup>III</sup> 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate, that is kinetically stable and water soluble: the modifications included space for substrate interactions as well as chiral centers to induce specific stereochemical outcomes (Figure 2).<sup>16</sup> We thought that if chiral centers were to induce specific stereochemical outcomes, then the chiral centers would need to be close to the reaction sites on the metal ions. With labile lanthanide ions, multidentate and macrocyclic ligands seemed to be the best way to achieve this goal. Consequently, we synthesized ligands that contained the modifications listed above with the prediction that they would enable efficient chiral induction during catalysis, while maintaining high solubility in water. After synthesizing a series of ligands, we demonstrated the utility of our precatalysts in the water-tolerant Mukaiyama aldol reaction with a wide range of substrates, including the often problematic alkyl aldehydes.<sup>16</sup> The new precatalysts yielded  $\beta$ -hydroxy carbonyls from aliphatic and aryl substrates with outstanding *syn:anti* ratios (up to 49:1) and *ee*'s (up to 97%). At the time of publication, these were the highest reported values for Lewis acid precatalysts in aqueous medium for the reactions that were studied.<sup>16,21</sup> Furthermore, the findings provide insight into the design and synthesis of potent chiral precatalysts for carbon–carbon bond-forming reactions in aqueous media.

After demonstrating the utility of our system, we used luminescence-decay measurements to infer a mechanism for catalysis and chiral induction (Figure 3). Further study of the ligand system was performed with respect to ligand synthesis, trends in stereoselectivity that result from changing lanthanide ions, and establishing the scope of compatible aldehydes and ketones.<sup>22</sup> We observed interesting trends in the relationship between both ionic radius and Lewis acidity to reactivity and selectivity. For example, ligand loading can be decreased when Nd<sup>III</sup> is used instead of Eu<sup>III</sup>. Additionally, a broad scope of substrates was compatible with the precatalysts, including aliphatic aldehydes and silyl enol ethers derived from aliphatic ketones. These studies resulted in a new class of Ln<sup>III</sup>-based chiral precatalysts for aqueous carbon–carbon bond-forming reactions that offers a broad substrate scope and generates products with high enantioselectivity. Furthermore, the stereochemical outcomes of reactions involving our precatalysts have been explored with computational analyses.<sup>23</sup>

We sought to understand the structural aspects of the new precatalysts that make them effective. To accomplish this objective, a series of complexes was synthesized that contained different metal-binding functional groups and that placed chiral centers in different positions on the ligand framework.<sup>24</sup> We studied these complexes as precatalysts with respect to the relationships among binding affinity, functional group identity, functional group position, reactivity, and selectivity. The complexes were studied using luminescence and NMR measurements to establish the coordination environments of the Eu<sup>III</sup>-based precatalysts in solution, and these data were compared with yields and selectivities of reactions. The data suggest that an excess of hexadentate ligand leads to complete encapsulation of Eu<sup>III</sup> and

diminished reactivity (Scheme 3). More specifically, the evidence suggests that two-to-one ligand-to-metal binding for hexadentate ligands occurs in the presence of excess ligand. This explanation is corroborated by the low yields of Mukaiyama aldol reactions performed in the presence of excess ligand. A comparison of ligand functional groups, the location of the chiral centers, steric bulk, and type of macrocyclic backbone has given insight into the factors that affect reactivity and selectivity of water-tolerant asymmetric precatalysts.<sup>24</sup> These results contribute to the further understanding of Ln<sup>III</sup>-based precatalysts to be used for asymmetric carbon-carbon bond-forming reactions in aqueous media.

In addition to the results detailed above, we optimized a synthetic route to trans-substituted rings for future synthesis of precatalysts.<sup>25</sup> We also studied exchange rates in ionic liquids and in the process observed an interesting reverse of the trend, relative to aqueous systems, between water-exchange rate and ionic radius.<sup>26</sup> This change is likely due to steric interactions caused by anion binding to the metal ions in the ionic liquids. These results have important implications to catalysis in ionic liquids in that they demonstrate that the reactivity of ions can be tuned over a wide range using solvent selection.

## 5 Contrast Agents from Divalent Europium

We have applied knowledge from contrast agents to catalysis, but we have also explored the chemistry of complexes relevant to contrast agents. Magnetic resonance imaging is a powerful, noninvasive technique that can be used to visualize the inside of opaque objects. It can produce images based on the behavior of nuclei, including relaxation times and chemical shifts, in a magnetic field. Consequently, molecules can alter the contrast of images by influencing the behavior of the nuclei of other molecules in a magnetic field. The molecules that alter contrast are referred to as contrast agents, and paramagnetic ions, commonly Gd<sup>III</sup>, are used to enhance contrast in images.<sup>27</sup> Therefore, understanding the coordination chemistry of Gd<sup>III</sup> and other trivalent lanthanide ions is critical to the design of new contrast agents because the coordination of these ions impacts their ability to alter contrast and also changes their properties with respect to biodistribution and toxicity. We have explored trivalent ions as contrast agents,<sup>28</sup> but recently have focused a great deal of effort into divalent europium as a contrast agent.

Eu<sup>II</sup> is isoelectronic with Gd<sup>III</sup>, making it accelerate the relaxation rate of nearby protons in a similar fashion.<sup>29</sup> However, the difference in charge density and redox activity between these ions influences their ability to alter contrast as function of field strength and to report redox environments. Despite the favorable properties of Eu<sup>II</sup>, this ion has not been used commonly for imaging because of its propensity to oxidize to Eu<sup>III</sup>.<sup>30</sup> Consequently, we have been extremely interested in stabilizing the electron-rich divalent state of europium to enable access to its electronic properties for imaging. Past research efforts aimed at increasing the stability of aqueous Eu<sup>II</sup> indicated that withdrawing electron density from ligands could increase the oxidative stability of Eu<sup>II</sup>.<sup>31,32</sup> Our strategy for favoring Eu<sup>II</sup> over Eu<sup>III</sup> in aqueous solution involved the synthesis and use of ligands that would preferentially coordinate to large, soft, electron-rich metals like Eu<sup>II</sup>. The template for our ligand design was (2.2.2)-cryptand because at the beginning of my independent career, this ligand produced the most oxidatively-stable, aqueous Eu<sup>II</sup> complex reported.<sup>32</sup> This stability is



partially due to the better size match between cryptand and the  $\text{Eu}^{\text{II}}$  ion relative to the  $\text{Eu}^{\text{III}}$  ion that favors binding of  $\text{Eu}^{\text{II}}$  over  $\text{Eu}^{\text{III}}$ .<sup>30</sup> We hypothesized that further oxidative stabilization could be achieved by modifying the structure of the cryptand to incorporate electron withdrawing groups and softer donors. To test this hypothesis, we synthesized and studied cryptands **1–6** (Figure 4).<sup>33</sup>

We observed dramatic oxidative stabilization of  $\text{Eu}^{\text{II}}$  using cryptands **1–6**.<sup>33</sup> In fact, our most stable complexes, **4**- $\text{Eu}^{\text{II}}$  and **6**- $\text{Eu}^{\text{II}}$ , were the most oxidatively stable aqueous  $\text{Eu}^{\text{II}}$  complexes reported at the time and were as or more oxidatively stable than  $\text{Fe}^{\text{II}}$  in hemoglobin. These results hinted at the possibility of using  $\text{Eu}^{\text{II}}$  as a contrast agent in vivo. After exploring the oxidative stability of  $\text{Eu}^{\text{II}}$ -containing cryptates, we studied their kinetic stability to transmetallation in vitro and found them to have stability to transmetallation with biologically relevant ions that depended on ligand structure.<sup>34</sup> We also explored the ability of our complexes to enhance contrast, and we found that these complexes were more effective contrast agents than conventional  $\text{Gd}^{\text{III}}$ -based agents at ultra-high field strengths ( $> 7 \text{ T}$ ),<sup>35</sup> and that they did not enhance contrast in  $T_1$ -weighted images after oxidation.<sup>36</sup> Furthermore, we observed interesting behaviors at ultra-high fields: our complexes increased in relaxivity with field strength with a maximum between 7 and 9 T.<sup>35,37</sup> This observation is particularly important because ultra-high field strengths offer advantages, in terms of resolution and scan time, over lower field strengths.<sup>38</sup> Consequently, ultra-high field strength scanners are of paramount importance in preclinical research.<sup>38c</sup> Based on the oxidative and kinetic stabilities of  $\text{Eu}^{\text{II}}$ -containing cryptates and their relaxivity at 7 T, we were excited to attempt in vivo imaging. To have the best chance of successful imaging in vivo, we chose one of our most oxidatively stable complexes and one of the least oxidizing environments in vivo.<sup>39</sup> This combination resulted in the first report of in vivo contrast-enhanced imaging using a divalent lanthanide (Figure 5).<sup>39</sup> The divalent species persisted for at least 3 h and selectively enhanced contrast in necrotic tissue. This result is exciting because it suggests the possibility for differentiation of redox environments with a complete lack of contrast enhancement in the oxidizing area.

The trends in stability that we observed with cryptates suggest that further stabilization of aqueous  $\text{Eu}^{\text{II}}$  and other lanthanide ions is possible.<sup>33</sup> In pursuing this further stabilization, we synthesized an aza-cryptate of  $\text{Eu}^{\text{II}}$  and serendipitously discovered that it displayed bright yellow luminescence in aqueous solution (Figure 6).<sup>40</sup> Solution-phase studies—including a Job plot,  $^{17}\text{O}$ -NMR spectroscopy, and conductivity measurements—indicated that a cause of the bright emission was the counter ion not being replaced by water, which quenches luminescence, in solution.<sup>40</sup> Interestingly, this divalent project relates back to our initial interest in the luminescence of lanthanides.<sup>15,18,24,41</sup>

## 6 Conclusions

Studying the aqueous chemistry of the lanthanides is an exciting and challenging area of research. My research group has been fortunate to have had the opportunity to make interesting discoveries that have blossomed from careful observations and a great deal of effort. Application of the wealth of knowledge reported from the pursuit of contrast agents to catalysis has been a particularly fruitful path for us. I anticipate that similar pursuits based in

careful reading of literature that spans a diverse range of topics will lead to the challenging of dogma, provide intellectual stimulation, and lead to important discoveries in the future.

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## Biography



**Matthew J. Allen** is an Associate Professor of chemistry at Wayne State University. After being inspired at Swartz Creek High School to study chemistry by the engaging teacher Phyllis Ziemer, Matt began his research career at Purdue University where he earned his B.S. in chemistry while researching the functionalization of porous silicon surfaces with Jillian Buriak. Throughout his undergraduate career he also had the great opportunity to be an intern at Eli Lilly and Company where he was trained by organic chemists including Tony Zhang and Richard Berglund. He earned his Ph.D. in chemistry from the California Institute of Technology under the mentorship of Thomas Meade in the area of cellular delivery of gadolinium complexes. Matt was an NIH postdoctoral fellow in the laboratories of Laura Kiessling and Ronald Raines at the University of Wisconsin–Madison before joining Wayne

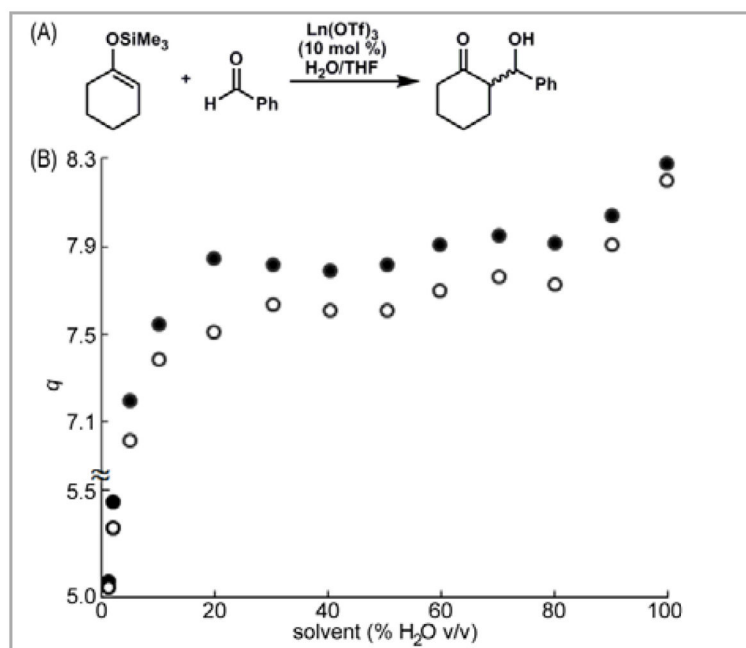
State as an Assistant Professor. His laboratory studies the aqueous chemistry of the lanthanides and related areas.

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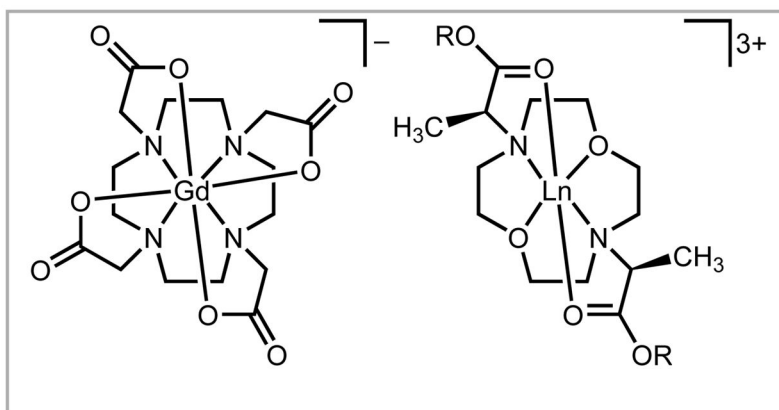
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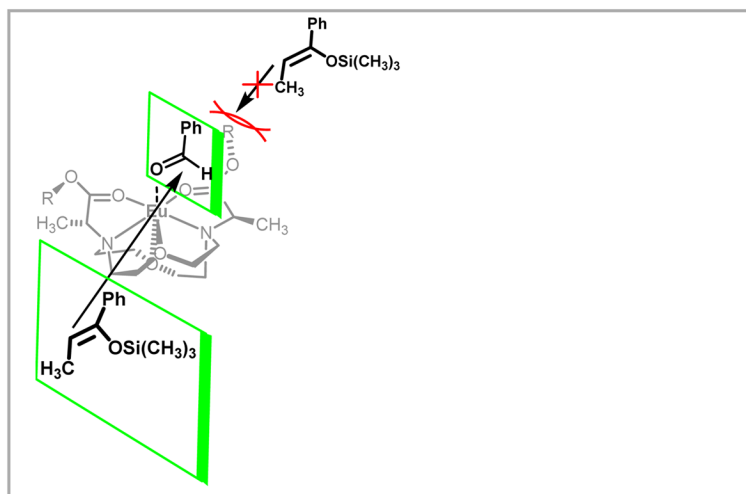
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**Figure 1.** (A) A Ln(OTf)<sub>3</sub>-catalyzed Mukaiyama aldol reaction; (B) Water-coordination number,  $q$ , of Eu<sup>III</sup> in THF containing different amounts of H<sub>2</sub>O before (●) and after (○) the addition of benzaldehyde. The difference in  $q$  values between the solid and hollow dots is a measure of the displacement of coordinated water by benzaldehyde. Adapted with permission from Dissanayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2009**, 6342. Copyright 2009 American Chemical Society

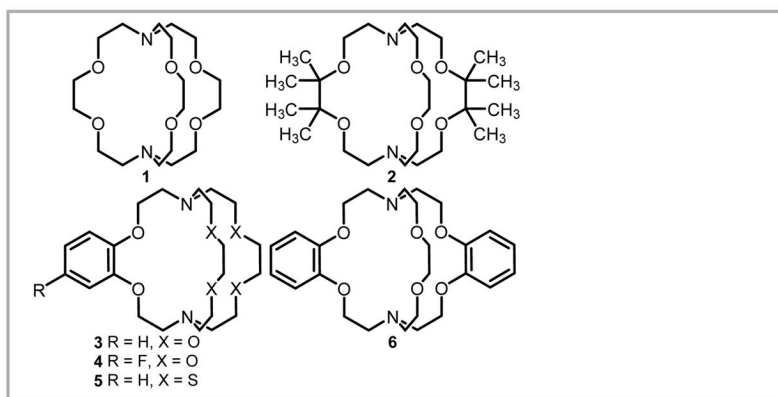


**Figure 2.** Structures of (left) a gadolinium-containing contrast agent and (right) our Ln<sup>III</sup>-containing precatalysts.<sup>16</sup> Counter ions are omitted for clarity.

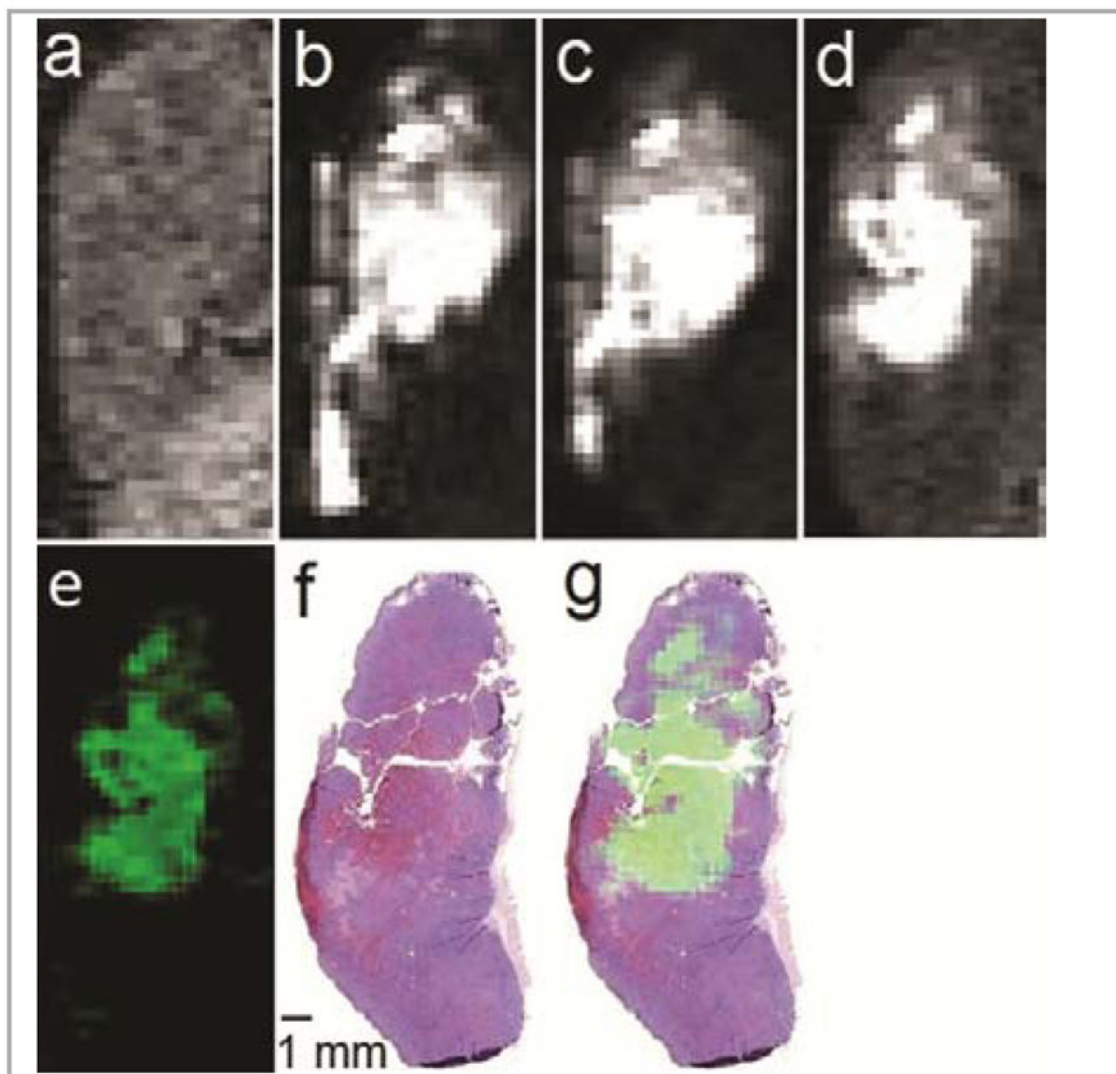


**Figure 3.** Proposed TS in the asymmetric Mukaiyama aldol reaction using our new ligands. Reprinted with permission from Mei, Y.; Dissanayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2010**, 12871. Copyright 2010 American Chemical Society

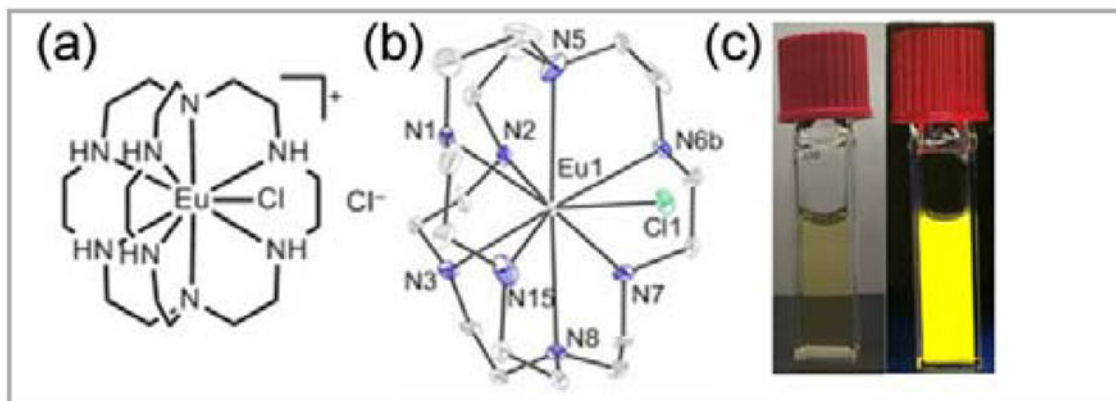




**Figure 4.** Ligands used to observe trends in oxidative stability of aqueous  $\text{Eu}^{\text{II.33}}$

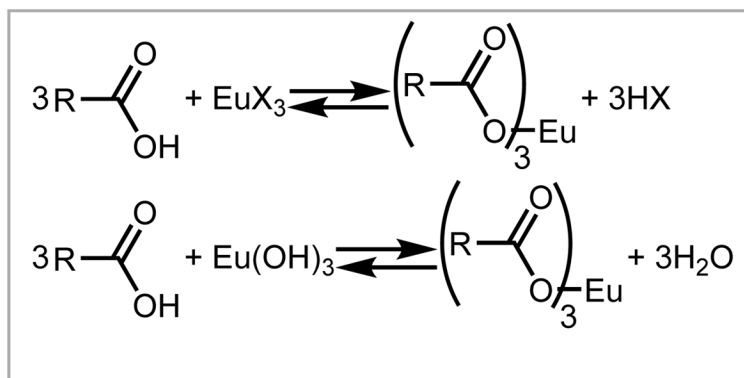


**Figure 5.** Images of a mouse tumor acquired using  ${}^4\text{-Eu}^{\text{II}}$ .  $T_1$ -weighted in vivo sagittal plane images of a tumor injected with  ${}^4\text{-Eu}^{\text{II}}$  (a) pre-injection; (b) 3 min, (c) 20 min, and (d) 120 min post-intratumoral injection; (e) difference between the 120 min and pre-injection images (image d minus image a) colored using the ImageJ green lookup table; (f) hematoxylin- and eosin-stained slice of tumor imaged in a–e; and (g) sum of images e and f. All images are on the same scale. Imaging parameters included an echo time of 1.5 ms, repetition time of 11 ms, flip angle of  $40^\circ$ , field of view of  $30\text{ mm} \times 90\text{ mm}$ , and an in-plane resolution of  $0.352 \times 0.352\text{ mm}$ . Adapted with permission from Ekanger, L. A.; Polin, L. A.; Shen, Y.; Haacke, E. M.; Allen, M. J. *Angew. Chem. Int. Ed.* **2015**, in press. Copyright 2015 John Wiley and Sons

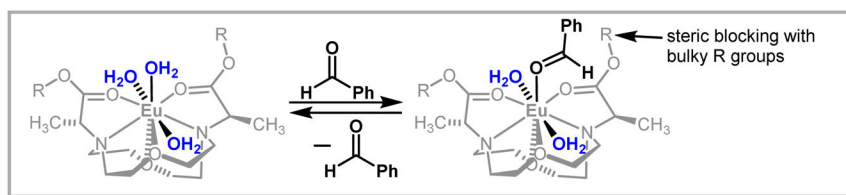


**Figure 6.**

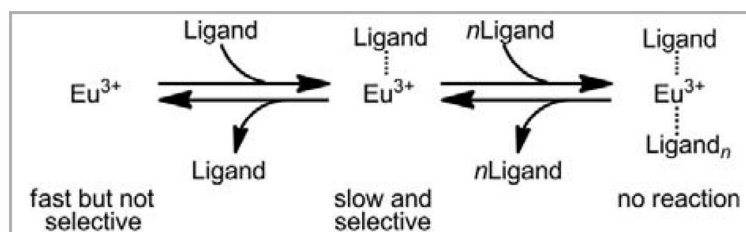
(a)  $\text{Eu}^{\text{II}}$ -containing aza-cryptate that has exciting bright yellow luminescence and (b) its crystal structure. Thermal ellipsoids are drawn at 50% probability. Hydrogen atoms, a non-coordinated  $\text{Cl}^-$  counter ion, and a molecule of methanol are not shown for clarity. R-factor = 0.0543. Resolution = 0.54 Å. (c) Pictures of the complex (5.0 mM) in 4 mL cuvettes in a pH 12.0 solution of KOH (left) in ambient light and (right) under a hand held UV lamp (254–400 nm). The 26% quantum yield in aqueous solution is the highest reported value for  $\text{Eu}^{\text{II}}$ , with previous values below 1%. Adapted with permission from Kuda-Wedagedara, A. N. W.; Wang, C.; Martin, P. D.; Allen, M. J. *J. Am. Chem. Soc.* **2015**, 4960. Copyright 2015 American Chemical Society

**Scheme 1.**

Simple balanced reactions between carboxylic acids and lanthanide salts. R and X represent the remainder of the ligand and halides, respectively.

**Scheme 2.**

Proposed equilibrium leading to activation of benzaldehyde for nucleophilic attack based on  $q$  measurements. Adapted with permission from Mei, Y.; Dissanayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2010**, 12871. Copyright 2010 American Chemical Society

**Scheme 3.**

Proposed equilibria involving multiple Eu<sup>III</sup> species with reactivity summarized under the species. The equilibria are based on luminescence-decay, steady-state luminescence measurements, and <sup>1</sup>H-NMR data with reactivity and selectivity from Mukaiyama aldol reaction results. Adapted with permission from Averill, D. J.; Allen, M. J. *Inorg. Chem.* **2014**, 6257. Copyright 2014 American Chemical Society