

# Air- and Water-Tolerant Rare Earth Guanidinium BINOLate Complexes as Practical Precatalysts in Multifunctional Asymmetric Catalysis

Jerome R. Robinson,<sup>†</sup> Xinyuan Fan,<sup>‡</sup> Jagjit Yadav,<sup>‡</sup> Patrick J. Carroll,<sup>†</sup> Alfred J. Wooten,<sup>†,||</sup> Miquel A. Pericàs,<sup>\*,‡,§</sup> Eric J. Schelter,<sup>\*,†</sup> and Patrick J. Walsh<sup>\*,†</sup>

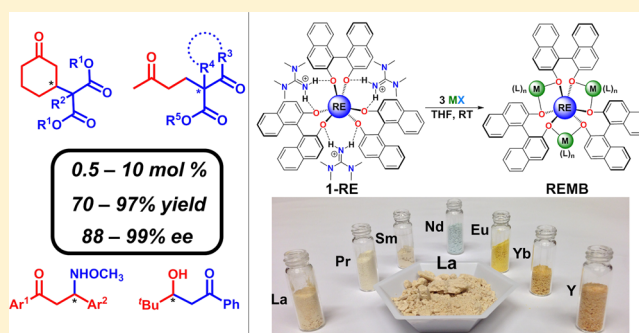
<sup>†</sup>P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

<sup>‡</sup>Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

<sup>§</sup>Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain

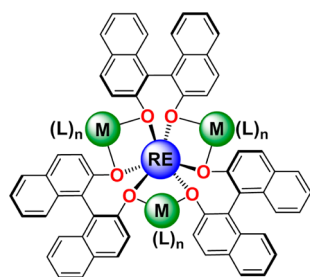
## Supporting Information

**ABSTRACT:** Shibasaki's **REMB** catalysts (**REMB**; RE = Sc, Y, La–Lu; M = Li, Na, K; B = 1,1'-bi-2-naphtholate; RE/M/B = 1/3/3) are among the most enantioselective asymmetric catalysts across a broad range of mechanistically diverse reactions. However, their widespread use has been hampered by the challenges associated with their synthesis and manipulation. We report here the self-assembly of novel hydrogen-bonded rare earth metal BINOLate complexes that serve as bench-stable precatalysts for Shibasaki's **REMB** catalysts. Incorporation of hydrogen-bonded guanidinium cations in the secondary coordination sphere leads to unique properties, most notably, improved stability toward moisture in solution and in the solid state. We have exploited these properties to develop straightforward, high-yielding, and scalable open-air syntheses that provide rapid access to crystalline, nonhygroscopic complexes from inexpensive hydrated RE starting materials. These compounds can be used as precatalysts for Shibasaki's **REMB** frameworks, where we have demonstrated that our system performs with comparable or improved levels of stereoselectivity in several mechanistically diverse reactions including Michael additions, aza-Michael additions, and direct Aldol reactions.



## 1. INTRODUCTION

Multifunctional asymmetric catalysts show marked improvements in reactivity and selectivity over traditional catalysts, due to cooperative activation of reaction partners within a single catalyst framework.<sup>1</sup> Shibasaki's heterobimetallic complexes [ $M_3(THF)_n[(BINOLate)_3RE]$  (**REMB**; RE = Sc, Y, La–Lu; M = Li, Na, K; B = 1,1'-bi-2-naphtholate; RE/M/B = 1/3/3; Figure 1) are the most successful heterobimetallic catalysts,



**Figure 1.** Shibasaki's **REMB** framework. RE = Sc, Y, La–Lu; M = Li, Na, K; B = (S)-BINOLate; RE/M/B = 1/3/3.

where simple modulation of RE, M, and BINOLate substitution patterns produces a diverse library of catalysts. These privileged frameworks catalyze the formation of C–C and C–E (E = N, O, P, S) bonds<sup>2</sup> with high levels of stereoselection and atom economy. The products generated by these catalysts have been used as key intermediates toward the synthesis of natural products and biologically active compounds.<sup>2b,e,h–k,3</sup> Despite their exceptional performance, there are several challenges that have prevented the widespread practical application of **REMB** catalysts.

One such challenge arises because both the structure and the catalytic performance of the **REMB** frameworks are sensitive to trace amounts of moisture.<sup>2c–e,i,k,l,4</sup> As such, **REMB** syntheses typically require the rigorous exclusion of water.<sup>2k–m,4a,5</sup> This restriction represents a significant synthetic impediment and also increases the cost of the catalyst, because expensive anhydrous functionalized RE starting materials must be employed rather than inexpensive RE hydrates.<sup>1d,6</sup> A key

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attribute of the **REMB** catalysts is the tunability in reactivity and selectivity by simply changing RE and M.

Current synthetic strategies to prepare these catalysts require each RE/M combination to be prepared independently. Such an approach is not attractive to high-throughput experimentation (HTE) strategies,<sup>7</sup> where ideally a single precatalyst could be used to generate multiple catalysts to screen against a large parameter space of reactions and conditions. To overcome these challenges, we envisioned air- and water-tolerant **REMB** precatalysts that could provide a rapid, simple, and user-friendly entry into multiple heterobimetallic frameworks.

Herein, we report the self-assembly of novel hydrogen-bonded rare earth metal BINOLate complexes that serve as bench-stable precatalysts for Shibasaki's **REMB** catalysts. Incorporation of hydrogen-bonded guanidinium cations in the secondary coordination sphere leads to unique properties, most notably, markedly improved stability toward moisture in solution and in the solid state. We have exploited these properties to develop straightforward, high-yielding, and scalable open-air syntheses that provide rapid access to crystalline, nonhygroscopic complexes from inexpensive hydrated RE starting materials. Using the precatalysts, Shibasaki's **REMB** M = Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup> frameworks can be quantitatively generated through either acid–base or cation-exchange methods. Our approach provides a general strategy to various RE/M combinations without the use of pyrophoric or moisture-sensitive reagents. It also provides a general precatalyst system for the **REMB** catalysts that can be applied to mechanistically diverse reactions with comparable or improved levels of stereoselectivity.

## 2. RESULTS AND DISCUSSION

### 2.1. Synthesis and Characterization of Rare Earth BINOLate Ammonium Complexes.

Recent work from our laboratories<sup>5c,8</sup> has demonstrated the importance of non-covalent interactions in the secondary coordination sphere with respect to tuning the reactivity and properties of **REMB** frameworks. In these examples, the alkali metal cations modulate the electronics at the RE cation and BINOLate oxygen atoms, and are the primary determinant for the ability of the RE cation to act as a Lewis acid. Given these observations, we hypothesized that the isoelectronic replacement of alkali metal cations with the appropriate ammonium cations would result in the formation of complexes with intramolecular ionic hydrogen-bonding networks.<sup>9</sup> Hydrogen bonds (H-bonds) are essential noncovalent interactions that can direct self-assembly processes and stabilize reactive fragments in nature and synthetic systems.<sup>9b,10</sup> The strength of H-bonding varies greatly with the directionality and charge of the donor/acceptor pair, where bond strengths of up to ~35 kcal mol<sup>-1</sup> can be found for ionic/charged systems.<sup>9</sup> We expected that these relatively weak interactions should allow for facile exchange of H-bonded ammonium cations for alkali metal cations, which would provide a rapid and unified entry to various **REMB** frameworks. With this approach in mind, we embarked on the synthesis of **REMB** precatalysts supported by hydrogen bonds.

Commercially available 1,1,3,3-tetramethylguanidine (TMG) appeared as an ideal candidate for our synthetic investigation, because, when protonated, it is a dual H-bond donor that could replace the interactions of the main group metal with two BINOLate ligands (see Figure 1) in **REMB** complexes. TMG is sufficiently basic, pK<sub>a</sub>(TMG–H<sup>+</sup>) = 13.6 in H<sub>2</sub>O,<sup>11</sup> to

deprotonate the phenolic BINOLate hydrogens, pK<sub>a</sub>(ArOH) = 10.0 in H<sub>2</sub>O.<sup>12</sup> Guanidines are known H-bond donors for a variety of anionic hosts.<sup>10c,13</sup> Under anhydrous conditions, addition of 3 equiv of TMG to a mixture of 1 equiv of RE[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub> and 3 equiv of (S)-BINOL in THF resulted in instantaneous and quantitative formation of a new 1:3:3 complex, [TMG–H<sup>+</sup>]<sub>3</sub>[RE(BINOLate)<sub>3</sub>] (**1–RE**), RE = La, Eu, Yb, Y. Removal of the volatiles followed by dissolution of the residue in CH<sub>2</sub>Cl<sub>2</sub> and layering with pentane furnished **1–RE** in excellent crystalline yields; **1–RE**, RE = La, 91%; Eu, 92%; Yb, 93%; Y, 91% (Figure 2).

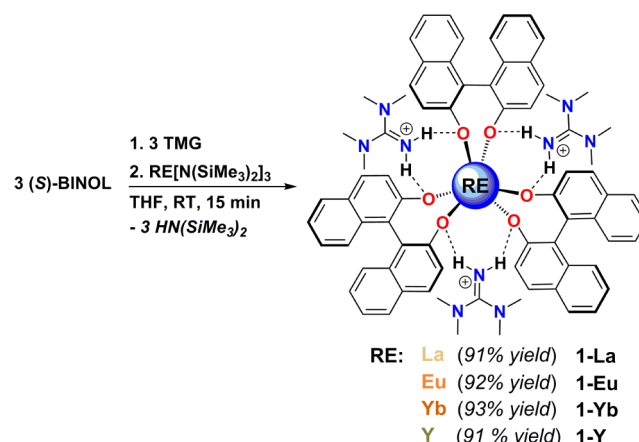
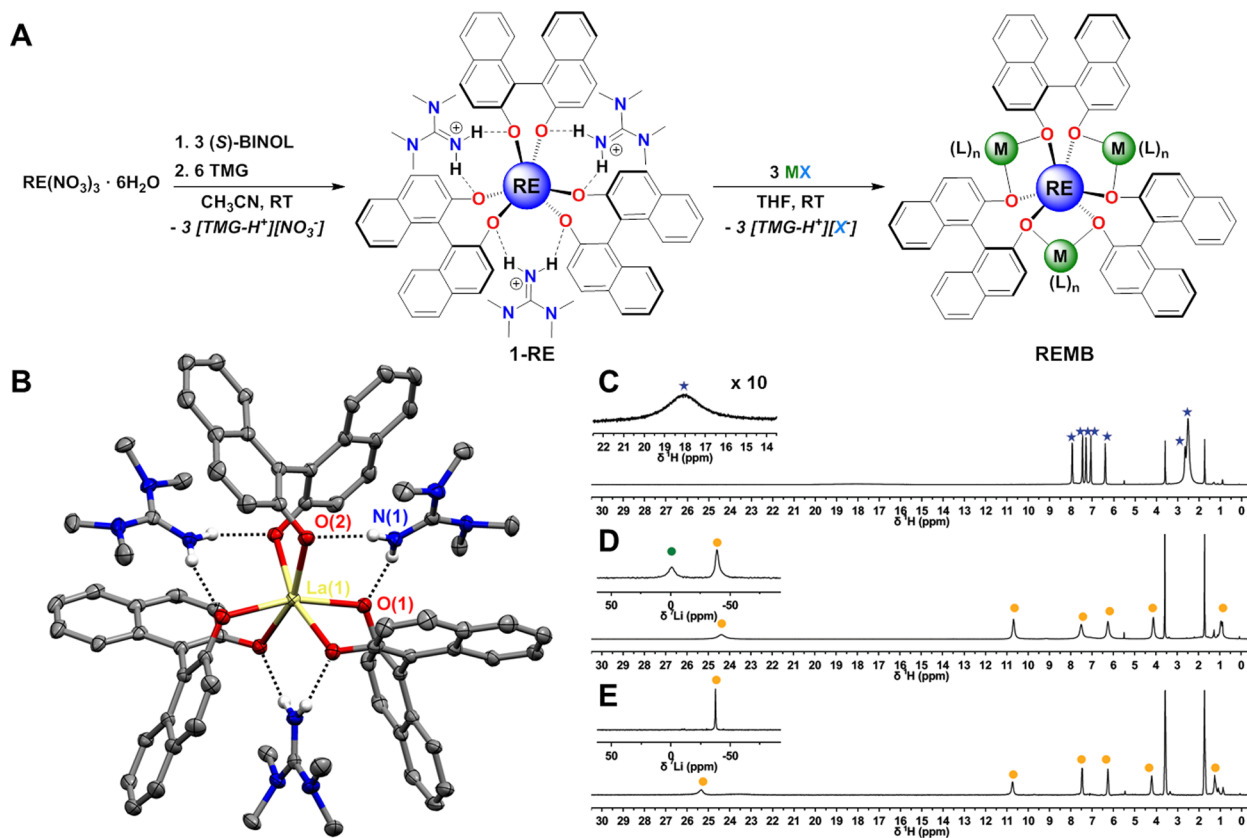


Figure 2. Synthesis of **1–RE** from rigorously anhydrous conditions.

Single-crystal X-ray diffraction data for **1–La** supported the formation of a 1:3:3 complex (Figure 3B). The primary coordination sphere at the La(III) cation formed a distorted octahedron consisting of the six-BINOLate oxygen atoms. RE–O<sub>BINOLate</sub> distances ranged from 2.3996(15)–2.4154(14) Å, similar to the reported six-coordinate **REMB** frameworks<sup>4a,5,8a,14</sup> after accounting for differences in ionic radii of the RE cations.<sup>15</sup> As expected, the tetramethylguanidinium cations were engaged in bifurcated H-bonding interactions, where each guanidinium cation participated in two H-bonds with neighboring anionic BINOLate oxygen atoms. The N<sub>TMG</sub>–H<sup>+</sup>⋯O<sub>BINOLate</sub> distances ranged from 2.782(2) to 2.811(2), and were consistent with reported charged guanidinium N<sup>+</sup>–H<sup>+</sup>⋯O<sup>-</sup> hydrogen bonds.<sup>13a,16</sup>

<sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were consistent with D<sub>3</sub> symmetric **1–RE** complexes in solution. The <sup>1</sup>H NMR spectra revealed six sharp BINOLate resonances and two resonances belonging to the methyl and ammonium protons of TMG–H<sup>+</sup> (Figure 3C). Given the importance of Lewis base coordination at the central RE cation, binding studies were pursued with the paramagnetic analogues, **1–Eu** and **1–Yb**. Contrary to RE/Li frameworks, addition of cyclohexenone to **1–Eu** and **1–Yb** resulted in negligible shifts (≤0.012 ppm) of the alkenyl protons (Supporting Information, Figure S15 and Table S3), which suggested that no binding of the cyclohexenone occurred at the RE cation.

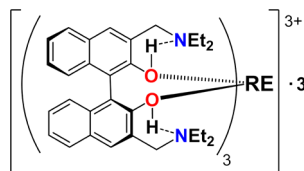
Intrigued by the inability of **1–RE** to bind cyclohexenone, we extended our investigations to a smaller Lewis base, H<sub>2</sub>O. While H<sub>2</sub>O can coordinate to **REMB** systems,<sup>2c,4a</sup> partial ligand hydrolysis occurs where the formation of polynuclear hydroxide clusters has been observed and characterized in the solid state.<sup>4b</sup> Addition of H<sub>2</sub>O (1–200 equiv) to **1–RE** does not result in the appearance of free protonated BINOL in the <sup>1</sup>H



**Figure 3.** (A) Generation of **1-RE** using hydrated starting materials and conversion to **REMB** through cation-exchange. (B) Thermal ellipsoid plot (30% probability) of **1-La**. (C)  $^1H$  NMR spectra of **1-Eu** (blue ★) in  $THF-d_8$ . (D)  $^1H$  and  $^7Li$  NMR (inset) spectra of **1-Eu** treated with excess LiI in  $THF-d_8$ . EuLB (orange ●) and LiI (green ●). (E)  $^1H$  and  $^7Li$  NMR (inset) spectra in  $THF-d_8$  of independently synthesized **EuLB** (orange ●).

NMR, nor does it induce formation of multi-RE cation cluster compounds as observed with the **REMB** frameworks.

The water tolerance of **1-RE** is exceptional, especially when considering the moisture sensitivity observed for Saa and co-worker's RE-BINOLAM system (BINOLAM = 3,3'-diethylaminomethyl-1,1'-bi-2-naphthol; RE:BINOLAM = 1:3, Figure 4).<sup>17</sup> In contrast to **1-RE**, RE-BINOLAM contains neutral



**Figure 4.** Saa and co-worker's RE-BINOLAM framework (RE = Sc, Y, La-Lu; BINOLAM = 3,3'-diethylaminomethyl-1,1'-bi-2-naphthol).

intramolecular H-bonding pairs that consist of phenolic OH donors and alkyl amine acceptors. The RE-BINOLAM complexes are highly sensitive to ligand hydrolysis; synthesis of RE-BINOLAM complexes require rigorous exclusion of water, while the generation of free ligand from a hydrolysis event can be observed even in dry  $CD_3CN$ .<sup>17c</sup>

We attribute the water tolerance of **1-RE** to the strong preference for a six-coordinate geometry at the RE cation. Both RE-BINOLAM and **REMB** complexes will coordinate  $H_2O$  to adopt seven-coordinate geometries.<sup>2c,4a,17c</sup> The acidity of  $H_2O$  coordinated to RE cations is increased by  $\sim 5-6$  orders of magnitude,<sup>18</sup> resulting in enhanced rates of ligand hydrolysis.

We propose that the coordination preferences in **1-RE** arise from the unique intramolecular, ionic H-bonding interactions. The H-bond donors, H-TMG<sup>+</sup>, assume geometries in the solid state that maximize the strength of the directional H-bonding interactions. Coordination of  $H_2O$  or other Lewis bases at the RE<sup>3+</sup> cations would increase the energy of the system by weakening those intramolecular H-bonding interactions, disfavoring the seven-coordinate geometries for **1-RE**.

Encouraged by the moisture stability of **1-RE**, we pursued a modified, open-air, benchtop synthesis using inexpensive hydrated RE starting materials. Taking advantage of the rapid kinetics associated with complex formation and the low solubility of **1-RE** in polar solvents, a convenient and expedient synthetic procedure was identified. Addition of 6 equiv of TMG to concentrated stirring solutions of  $RE(NO_3)_3 \cdot 6H_2O$ /(S)-BINOL (1:3 ratio) resulted in the immediate precipitation of **1-RE**, which could be crystallized from  $CH_2Cl_2$ /pentane in 70–85% yield. Using these conditions, **1-La** was easily prepared on a 25 g scale (Figure 3A). Other early REs (La–Eu) were accessible following this procedure, with **1-Eu** reported as a representative, fully characterized example obtained in 79% crystalline yield.

The successful synthesis of **1-RE** from hydrated starting materials was surprising, because of the high hydration enthalpies associated with RE<sup>3+</sup> cations<sup>18a,19</sup> and the aqueous speciation of  $RE(NO_3)_3$  that tend to form  $RE(NO_3)_x(OH)_{y-x}$  compounds at neutral or basic pH following acid hydrolysis.<sup>20</sup> In this context, the increased Lewis acidity of the late lanthanides (Gd–Lu) and Y proved problematic for their

open-air syntheses of **1-RE**, where unlike the early lanthanides, the formation of an inseparable byproduct (~30%) was observed even upon changing the order or rate of addition of the reactants. Suppression of this byproduct, likely a mixed hydroxide species, was possible by lowering the pH of the  $\text{RE}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$  solution with 3 equiv of acetic acid. Addition of a  $\text{CH}_3\text{CN}$  solution of 3 equiv of (*S*)-BINOL and 6 equiv of TMG to the acidified  $\text{RE}(\text{NO}_3)_3 \cdot x\text{H}_2\text{O}$  solution, followed by neutralization with an additional 3 equiv of TMG resulted in the rapid formation and precipitation of **1-RE**. Crystallization from  $\text{CH}_2\text{Cl}_2$ /pentane furnished **1-RE** in similarly high yields; **1-RE**: Y = 85%, Yb = 80%, where **1-Y** was synthesized on a 10 g scale.

Notably, the synthesis of **1-RE** from either method could be carried out using technical-grade solvents without additional drying, and provided anhydrous, crystalline products following mild drying conditions (~50 °C, 200 mTorr, 2 h). Unlike the **REMB** or **RE-BINOLAM** complexes, no coordinated or interstitial  $\text{H}_2\text{O}$  crystallized with **1-RE** synthesized from benchtop methods.<sup>2c,4a,17c</sup> In addition to the strong preference for a six-coordinate geometry of the RE cation in **1-RE**, we propose that the hydrophobic methyl substituents of  $\text{TMG-H}^+$  contribute to the nonhygroscopic properties of **1-RE**.

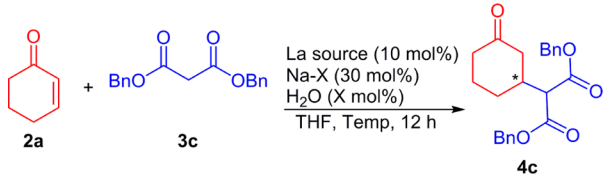
**2.2. Generation of REMB from Rare Earth BINOLate Ammonium Complexes and Catalytic Investigations.** *Generation of REMB from 1-RE.* After establishing a practical synthetic protocol for the generation of **1-RE**, we investigated methods to access Shibasaki's heterobimetallic catalysts using **1-RE** as starting materials. While the ionic H-bonding interactions in **1-RE** evidently conferred stability against hydrolysis, we envisioned that the large enthalpic contribution from forming new  $\text{M-O}_{\text{BINOLate}}$  bonds should provide a strong thermodynamic driving force for the formation of the **REMB** complexes from **1-RE**. Indeed, installation of  $\text{M}^+$  was possible through either acid-base or cation-exchange methods (Figure 3a), which produced **REMB** along with 3 equiv of TMG or  $[\text{TMG-H}^+][\text{X}^-]$  (Figure 3a and Supporting Information). A representative example is shown in Figure 3C-E, where addition of excess LiI to **1-Eu** immediately generated **EuLB** as the single observable Eu-containing product. Notably, the presence of coordinated water to the **REMB** was not observed by  $^1\text{H}$  NMR using **1-RE** synthesized from rigorously anhydrous or benchtop methods, supporting the anhydrous and nonhygroscopic nature of **1-RE** (Figure 3C-E, Supporting Information S16).

While syntheses of RE heterobimetallic frameworks have been achieved through acid-base, redox, ligand-exchange, or metathetical synthetic routes,<sup>21</sup> to the best of our knowledge, there have been no reports using cation-exchange from a RE/ammonium precursor. Our method provides a new and complementary approach that offers several potential advantages as compared to traditional synthetic strategies. A large variety of inexpensive MX salts and amine bases of varying  $\text{pK}_a$  are commercially available, which should expedite the identification of new heterobimetallic frameworks. Moreover, operational simplicity is also greatly improved by avoiding the use of strong bases that are typically moisture sensitive.

*Catalytic Investigations of 1-La/MX Precatalyst System.* Given the rapid and clean conversion of **1-RE** to various **REMB** products through cation metathesis, we turned our attention to identifying conditions where **1-RE** could be used as a general precatalyst for **REMB** reactivity. As an initial trial, the asymmetric Michael addition was chosen due to its

synthetic utility,<sup>1c,22</sup> and the sensitivity of the Lewis-acid/Bronsted-base mechanism to catalyst structure, especially in **REMB** frameworks.<sup>2c</sup> While we demonstrated **REMB** can be generated from **1-RE** and MX, the optimal combination of MX source, solvent, and additives necessary to ensure the best catalytic performance was unclear at the onset. Given the large number of available combinations of RE and the main group metal, we used microscale high-throughput experimentation (HTE) techniques<sup>7</sup> to identify conditions for **1-La/NaX** as a precatalyst for **LaNaB**. A variety of NaX sources were screened with THF or toluene as solvent using cyclohexenone (**2a**) and dibenzylmalonate (**3c**) as model substrates. The optimization results for this study are presented in Table 1.

**Table 1. Optimization of 1-La/MX in the Asymmetric Michael Addition**



entry	La source	Na-X	H <sub>2</sub> O (X mol %)	temp (°C)	ee (%)
1	<b>1-La</b>		0	25	14
2	<b>1-La</b>	Cl	0	25	8
3	<b>1-La</b>	I	0	25	42
4	<b>1-La</b>	$\text{BAr}_4^a$	0	25	33
5	<b>1-La</b>	$\text{N}(\text{SiMe}_3)_2$	0	25	50
6	<b>LaNaB</b>		0	25	62
7	<b>1-La</b>	I	10	25	70
8	<b>1-La</b>	$\text{I}^b$	10	25	69
9	<b>1-La</b>	I	20	25	75
10	<b>1-La</b>	I	30	25	78
11 <sup>c</sup>	<b>1-La</b>	I	30	0	88
12 <sup>c</sup>	<b>LaNaB</b>		30	0	88

<sup>a</sup>Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>. <sup>b</sup>60 mol % NaI was used instead of 30 mol %.  
<sup>c</sup>Malonate added portionwise over 20 min.

As a control experiment, we screened the hydrogen-bond complex **1-La** in the asymmetric Michael addition. **1-La** was not a competent catalyst for the formation of Michael adduct **4c** (entry 1). As revealed in our binding studies, **1-La** is sterically saturated and would not be expected to provide dual activation of the electrophile and nucleophile required for the Lewis-acid/Bronsted-base-mediated mechanism. Inorganic salts such as NaCl (entry 2) were ineffective in generating an active catalyst; however, use of more soluble salts provided **4c** in moderate levels of enantiomeric excess (entries 3–5). Using independently prepared **LaNaB**, we discovered that rigorously anhydrous conditions resulted in only moderate ee's, suggesting the reactions conducted in the original reports on the activity of **LaNaB** contained trace amounts of water (entry 6). Use of varying amounts of water as an additive (entries 7, 9, 10; Figure S1 and Table S2 in the Supporting Information) afforded identification of an optimal  $[\text{La}]:[\text{H}_2\text{O}]$  ratio of 1:3. Addition of excess NaI did not negatively impact selectivity (entry 8); however, selectivities were lower than the original report.<sup>2c</sup> Ultimately, we found that slow addition of malonate was critical to obtain high levels of enantioselectivity, a key observation that was made by Shibasaki and co-workers for more reactive Michael partners.<sup>23</sup> At 0 °C, the use of 10 mol % **1-La/NaI** or

LaNaB (entries 11 and 12) provided ee's identical to those observed in the original report of LaNaB.

The generality of the 1-La/NaI precatalyst system was investigated by exploring the scope of Michael donors (Table 2). While the performance of the precatalyst system, 1-La/

**Table 2. Asymmetric Michael Addition of 1,3-Dicarbonyls to Enones with the 1-La/NaI Precatalyst System**

Entry	Michael Donor	Product	x	Yield % <sup>a</sup>	ee % <sup>a</sup>
1			10 <sup>b</sup>	87 (98) <sup>c</sup>	94 (83) <sup>c</sup>
2	3a		5 <sup>d</sup>	93	90
3			2.5 <sup>d</sup>	91 <sup>e</sup>	89 <sup>e</sup>
4	3b		10 <sup>b</sup>	90 (97) <sup>c</sup>	96 (81) <sup>c</sup>
5	3c		10 <sup>b</sup>	94 (97)	88 (88)
6	3d		10 <sup>b</sup>	89 (91)	96 (92)
7	3e		5 <sup>d</sup>	87 (89)	98 (91)
8	3f		5 <sup>d</sup>	84 (98)	>99 (89)

3a	R <sup>1</sup> = Me	R <sup>2</sup> = H
3b	R <sup>1</sup> = Et	R <sup>2</sup> = H
3c	R <sup>1</sup> = Bn	R <sup>2</sup> = H
3d	R <sup>1</sup> = Bn	R <sup>2</sup> = Me

3e	
3f	

<sup>a</sup>Reactions conducted on a 1.0 mmol scale using 1 equiv of **2a** and 1 equiv of **3a–d**, or 1.2 equiv of **2b** and 1 equiv of **3e,f** unless otherwise specified. Values in parentheses are from refs 2c and 23 using LaNaB as a catalyst. Isolated yield after chromatographic purification.

<sup>b</sup>Michael donor added portionwise over ~20 min. <sup>c</sup>Reported reaction performed at room temperature. <sup>d</sup>Michael donor added slowly over 8 h. <sup>e</sup>Performed on 1 g scale. A single recrystallization furnished product in 87% yield with 94% ee.

NaI, matched LaNaB in the Michael addition of **3c** to **2a** (entry 5), examination of other symmetrical malonates (**3a**, **3b**, **3d**) resulted in improved levels of stereoselectivity (94–96% ee, entries 1, 4, 6) as compared to literature reports (Table 2, values in parentheses).<sup>2c</sup> We propose that the increased selectivity was due to the high purity of LaNaB generated from the 1-La/NaI system (Figure S5, Supporting Information).

In light of the excellent levels of activity and selectivity for 1-La in the optimized Michael addition, we sought to improve the practicality of the system by reducing catalyst loading and examining the scalability of this reaction to produce **4a** (Table 2, entries 1–3). Compound **4a** has been used as a key intermediate in the enantioselective syntheses of diverse products<sup>24</sup> including strychnine alkaloids,<sup>3d,25</sup> (–)-Gilbertine,<sup>26</sup> Haouamine B,<sup>27</sup> and (+)-2-deoxyolivin.<sup>28</sup> Decreased catalyst loadings were possible from the 1-La precatalyst (entries 2 and 3), where 2.5 mol % loading furnished **4a** on an 8.7 mmol scale under highly concentrated reaction conditions<sup>29</sup> with minimal losses in enantioselectivity (entry 3). The original levels of selectivity could be restored by a single recrystallization of **4a** in 87% isolated yield and 94% ee. While LaNaB is not as effective for this particular transformation as Shibasaki's ALB catalyst, [Li(THF)<sub>3</sub>][(BINOLate)<sub>2</sub>Al],<sup>30</sup> the 1-La/NaI system is an operationally simple complement, because no pyrophoric materials are necessary for the catalyst synthesis.

While a number of highly enantioselective catalysts for the asymmetric Michael addition of malonates to cyclic enones have been identified,<sup>22a–c,31</sup> the corresponding addition of β-ketoesters to acyclic enones still remains challenging.<sup>32</sup> Shibasaki and co-workers reported high levels of stereoselectivity for the addition of β-ketoesters to acyclic enones in CH<sub>2</sub>Cl<sub>2</sub> with as little as 5 mol % LaNaB as a catalyst.<sup>23</sup> Employing the 1-La/NaI precatalyst system under similar conditions, addition of cyclic (**3e**) and acyclic (**3f**) Michael donors to methyl vinyl ketone (**2b**) furnished Michael adducts **4e** and **4f** in 98% and 99% ee, respectively (entries 7 and 8). A similar ~10% improvement in ee was observed over the original report,<sup>23</sup> suggesting that this phenomenon could be observed in other Lewis-acid/Brønsted-base reactions.

A key attribute of the REMB system is the diversity observed in the catalytic reactions upon changing RE and M combinations. To establish that our precatalyst was amenable to different RE/M combinations, we investigated the Lewis-acid/Lewis-acid-mediated aza-Michael addition of *O*-methylhydroxylamine to α,β-unsaturated ketones.<sup>2h,27</sup> Shibasaki and co-workers accessed optically active β-amino carbonyl compounds using low catalyst loadings of YLB (0.5–3.0 mol %). In addition, β-amino carbonyl compounds are important structural motifs in many biologically active compounds.<sup>33</sup> They also demonstrated that their products could be further transformed to other useful chiral building blocks such as aziridines or β-amino alcohols with no loss in ee.<sup>2k,34</sup>

Application of the optimized 1-RE/MI precatalyst system to generate YLB from 1-Y/LiI proved general. At 3 mol % loading of 1-Y, comparable selectivities were obtained for various substitution patterns (Table 3, **7a–e**) including examples of an electron-donating group (**7b**), electron-withdrawing group (**7c**), heterocycle (**7d**), and extended conjugation (**7e**). The scalability of this reaction was also maintained, where **7a** could be obtained in 93% isolated yield and 93% ee on a 1 g scale (entry 2). Catalyst loading could be

**Table 3. Asymmetric aza-Michael Addition of *O*-Methylhydroxylamine to Chalcone Derivatives with the 1-Y/LiI Precatalyst System**

Entry	Product	x	Yield % <sup>a</sup>	ee % <sup>a</sup>
1		3	88 (97)	91 (95)
2		3	93 <sup>b</sup>	93 <sup>b</sup>
3		0.5	90 <sup>b,c</sup> (96)	88 <sup>b,c</sup> (96)
4		3	91 (96)	94 (96)
5		3	96 (96)	94 (96)
6		3	93 (96)	93 (95)
7		3	97 <sup>d</sup> (91)	91 <sup>d</sup> (94)

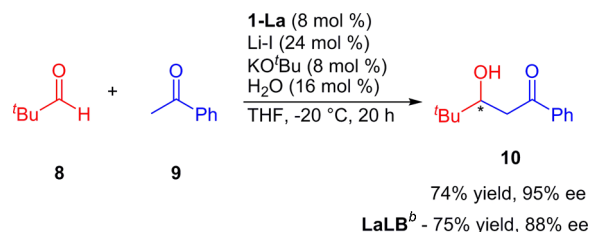
<sup>a</sup>Reactions conducted on a 0.5 mmol scale using 1 equiv of 7a–e and 1.2 equiv of 8 in THF ([enone] = 1.6 M) unless otherwise specified. Values in parentheses are from using YLB (refs 2k and 34). Isolated yield after chromatographic purification. <sup>b</sup>1 g scale. <sup>c</sup>80 h, [enone] = 2.05 M. <sup>d</sup>60 h, [enone] = 1 M.

further reduced to 0.5 mol % (entry 3), albeit with slightly decreased levels of enantioselectivity (88% versus 93% ee).

Additives have played an important, and at times poorly understood, role in improving the performance of the REMB catalysts.<sup>1a,2i,l–n,35</sup> For example, the addition of MOH and H<sub>2</sub>O to REMB solutions can generate highly active second generation catalysts for aldol and nitroaldol reactions.<sup>1a,2i</sup> To test the compatibility of additives in our precatalyst system, we chose the direct aldol reaction catalyzed by second generation LaLB (LaLB-KOH). Addition of 8 mol % KO<sup>t</sup>Bu and 16 mol % H<sub>2</sub>O to 1-La/LiI (8/24 mol %) generated LaLB-KOH, which catalyzed the direct aldol reaction between pivaldehyde (8) and acetophenone (9) to furnish 3-hydroxy-4,4-dimethyl-1-phenylpentan-1-one (10) in 74% isolated yield and 95% ee (Scheme 1). Interestingly, our preliminary results revealed an improvement (~7% ee) in enantioselectivity using our precatalyst system in a second Lewis-acid/Bronsted-base-catalyzed reaction, which supports that our system was amenable to additives similar to those of the REMB framework.

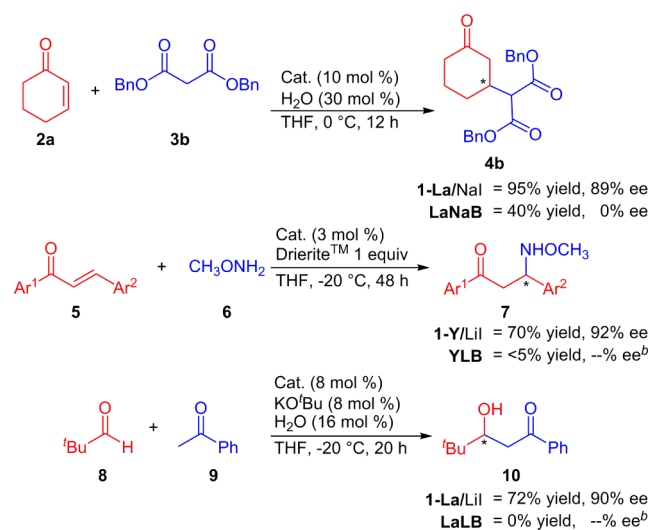
While the REMB catalysts can be stored at room temperature for extended periods of time under a dry N<sub>2</sub> atmosphere with no significant loss in catalytic activity, we were interested in performing a side-by-side comparison of the stability of 1-RE and REMB as solids stored on the benchtop. Crystals of 1-RE and REMB were stored in vials exposed to

**Scheme 1. Asymmetric Direct Aldol Reaction<sup>a</sup> of Acetophenone and Pivaldehyde Catalyzed by Second Generation LaLB, LaLB-KOH**



<sup>a</sup>Isolated yield after chromatographic purification. <sup>b</sup>Results from ref 2i.

**Scheme 2. Catalytic Activity of 1-RE and REMB Systems after Exposure to Open-Air for 6 months in the Asymmetric (1) Michael Addition, (2) aza-Michael Addition, and (3) Direct Aldol Reaction<sup>a</sup>**



<sup>a</sup>Isolated yield after chromatographic purification. <sup>b</sup>Not determined.

open air for 6 months and then employed in each of the mechanistically distinct reactions (Scheme 2). 1-RE/MX precatalysts maintained excellent catalytic activity, whereas the performance of REMB were significantly reduced due to the decomposition associated with prolonged exposure to ambient atmosphere. These experiments further supported the tolerance of 1-RE to benchtop conditions, and highlight their suitability as robust precatalysts.

### 3. CONCLUSIONS

In summary, Shibasaki's REMB catalysts are among the most enantioselective asymmetric catalysts across a broad range of mechanistically diverse reactions. The widespread utility of these catalysts, however, has been hampered by their challenging syntheses and manipulation. Even for those proficient in their use, this family of catalysts is not readily amenable to high throughput screening, because each catalyst requires independent preparation and use due to the lack of suitable precatalysts. To address these challenges, we have designed a novel class of self-assembled H-bonded RE tris(BINOLate) complexes, which have immediate application as air-stable precatalysts for Shibasaki's REMB frameworks. Incorporation of H-bonding interactions in the secondary coordination sphere resulted in improved moisture tolerance as

compared to related REMB and RE–BINOLAM systems, which facilitated the development of an operationally simple open-air synthesis of 1–RE. The 1–RE precatalysts can be synthesized using conventional benchtop methods and hydrated RE starting materials to provide high yields of crystalline, nonhygroscopic 1–RE on large scales. Use of hydrated RE sources provided a significant cost reduction; RE(NO<sub>3</sub>)<sub>3</sub>·xH<sub>2</sub>O are ~100-fold less expensive than commonly employed functionalized RE materials such as RE(O<sup>i</sup>Pr)<sub>3</sub> or RE[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub>.<sup>36</sup> Because of these properties, 1–RE were identified as excellent precursors for the generation of anhydrous heterobimetallic complexes by acid–base or cation-exchange methods with a variety of RE/M combinations.

Furthermore, we have demonstrated that 1–RE/MI could be applied as a general precatalyst system for Shibasaki's REMB framework using both traditional bench-scale and HTE techniques. This precatalyst system showed performance comparable to or improved over the reported REMB systems, and was amenable to different RE/M combinations, different reaction types (Lewis-acid/Bronsted-base, Lewis-acid/Lewis-acid), and the presence of additives. We attribute the success of this particular system to the use of MI, which cleanly generates REMB through cation-exchange while producing an innocent guanidinium iodide spectator ion. We expect that this system will provide a convenient and complementary synthetic strategy to well-known and, as of yet, unidentified heterobimetallic frameworks. Further investigations on the self-assembly of ionic H-bond pairs, identification of new heterobimetallic frameworks through cation-exchange, and their applications in catalysis are underway.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental details, NMR spectra, HPLC chromatograms of racemic and enantioenriched product, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Authors

[pwalsh@sas.upenn.edu](mailto:pwalsh@sas.upenn.edu)

[schelter@sas.upenn.edu](mailto:schelter@sas.upenn.edu)

[maericas@iciq.es](mailto:maericas@iciq.es)

### Present Address

<sup>||</sup>Batelle Memorial Institute, 2900 Fire Road, Suite 201, Egg Harbor Township, New Jersey 08234, United States.

### Notes

The authors declare the following competing financial interest(s): The authors declare competing financial interests: intellectual property pertaining to the technology described in this Report is covered by U.S. Patent Application No. 61/837,833.

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(36) As of 02/17/14, the price per gram of La (www.strem.com) was \$0.90 for La(NO<sub>3</sub>)<sub>3</sub>·6H<sub>2</sub>O (100 g quantity), as compared to \$150.23 for La(O<sup>n</sup>Pr)<sub>3</sub> (1 g quantity) or \$263.37 for La[N(SiMe<sub>3</sub>)<sub>2</sub>]<sub>3</sub> (1 g quantity). Please see Supporting Information Table S1 for a more detailed comparison.