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Synthesis, Spectroscopic Characterization, and Reactivity of Water-Tolerant Eu^{3+}-Based Precatalysts

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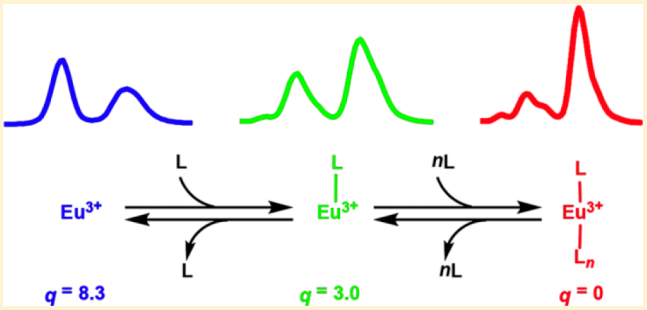
Supporting Information

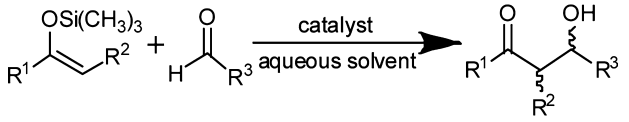
ABSTRACT: We report the synthesis, spectroscopic characterization, and reactivity of Eu^{3+} in the presence of a new set of chiral ligands designed for the aqueous, enantioselective Mukaiyama aldol reaction. Luminescence and NMR measurements were used to characterize the coordination environments of the Eu^{3+}-based precatalysts, and this data is compared with yields and stereoselectivities. In addition to structure–function relationships, we found that, in the presence of excess hexadentate ligands, Eu^{3+} is coordinatively saturated, and subsequently, the reactivity of the precatalysts is reduced. These findings are helpful for the design of new ligands that bind Eu^{3+} without saturating the Eu^{3+} coordination sphere.



INTRODUCTION

Many pharmaceuticals and natural products contain β-hydroxy carbonyl moieties, making the synthesis of this functional group an active area of research.[1−7] The Mukaiyama aldol reaction is a Lewis-acid-catalyzed, carbon–carbon bond-forming reaction that produces β-hydroxy carbonyls (Scheme 1), and this

Scheme 1. Aqueous Mukaiyama Aldol Reaction



reaction requires chiral precatalysts to induce stereoselectivity. Due to precatalyst instability toward hydrolysis, anhydrous solvents are used commonly,[8−10] but recent efforts have focused on aqueous versions of the enantioselective Mukaiyama aldol reaction because of the financial and environmental benefits of using aqueous media.[11] Several examples of enantioselective precatalysts that function in the presence of water exist: $Cu(OTf)_2$, $Pb(OTf)_2$, and $Ln(OTf)_3$ with crown ethers, where OTf^- is trifluoromethanesulfonate;[12−16] Trost-type semicrowns with $Ga(OTf)_3$;[17,18] and $Zn(OTf)_2$ and $FeCl_2$ with pybox-type ligands.[19−22]

Previously, we reported the synthesis and application of water-tolerant Eu^{3+}-based precatalysts for aqueous, enantioselective Mukaiyama aldol reactions using ligands **1** and **2** shown in Figure 1.[23,24] The use of ligand **1** with $Eu(OTf)_3$ at a ligand-to-metal ratio of 2.4:1 resulted in high enantiomeric ratios (95:5–99:1) for Mukaiyama aldol reaction products but required long (168 h) reaction times. The excess of ligand was required to achieve high stereoselectivity, but reaction times were slower in the presence of excess ligand, suggesting

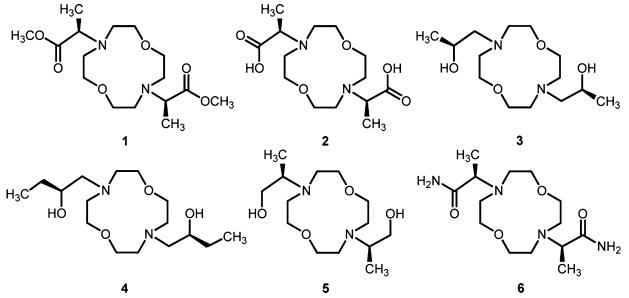


Figure 1. C_2-symmetric ligands used to prepare Eu^{3+}-based precatalysts.

that excess ligand slows the reaction. Because of these observations, we hypothesized that equilibria exist between uncomplexed Eu^{3+} (racemic precatalyst), ligand-bound Eu^{3+} (stereoselective precatalyst), and Eu^{3+} encapsulated by more than one ligand (deactivated precatalyst) and that an understanding of the ligand features that influence this equilibrium would enable rational ligand variations to improve reactivity and selectivity.

To test our hypothesis, a variety of ligand features that we suspected could affect reactivity and selectivity were studied. Ligands **3**–**6** were synthesized and combined with Eu^{3+} to investigate the influence of ligand donor type, chiral center location, and chiral center bulk on reactivity. Eu^{3+} was chosen over other trivalent lanthanides because it can act as an optical probe to provide feedback regarding its coordination environment via luminescence-decay and steady-state luminescence measurements. Additional information about the Eu^{3+} coordi-

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nation environment was obtained from NMR spectroscopy, and the enantioselectivities and diastereoselectivities of reaction products formed in the presence of ligands **3**–**6** with Eu^{3+} were determined using chiral columns with high-performance liquid chromatography (HPLC) for the aqueous, enantioselective, Mukaiyama aldol reaction. In this Article, we describe the relationships between ligand structure and precatalyst activity with regard to efficiency and coordination.

EXPERIMENTAL SECTION

Materials. Commercially available chemicals were used without further purification. Water was purified using a PURELAB Ultra Mk2 (ELGA) water purification system. (2*R*,2′*R*)-Dimethyl-2,2′-(1,7-dioxa-4,10-diazacyclododecane-4,10-diyl)dipropanoate (**1**),[23] (2*R*,2′*R*)-2,2′-(1,7-dioxa-4,10-diazacyclododecane-4,10-diyl)dipropanoic acid (**2**),[24] and (*Z*)-trimethyl(1-phenylpropyl-1-enyloxy)-trimethylsilane (**7**) (*Z*/*E* = 12:1)[18] were synthesized according to previously published procedures.

Characterization. Flash chromatography was performed using silica gel 60, 230–400 mesh.[25] Analytical thin-layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F_{254} (250 μm layer thickness). TLC visualization was accomplished using a UV lamp. NMR spectra were obtained in the Lumigen Instrumentation Center at Wayne State University. ^{1}H NMR and correlation spectroscopy (COSY) spectra were obtained using a Varian Mercury 400 (400 MHz) spectrometer, a Varian MR400 (400 MHz) spectrometer, or a Varian 500-S (500 MHz) spectrometer. ^{13}C NMR, distortionless enhancement by polarization transfer (DEPT) and heteronuclear multiple quantum coherence (HMQC) spectra were obtained using a Varian Mercury 400 (100 MHz) spectrometer, a Varian MR400 (100 MHz) spectrometer, or a Varian 500-S (125 MHz) spectrometer. DEPT, COSY, and HMQC spectra were used to assign spectral peaks. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) or CHD_2OD in CD_3OD (3.31 ppm); multiplicity ("s" = singlet, "d" = doublet, "t" = triplet, "q" = quartet, "m" = multiplet, and "brs" = broad singlet); coupling constant, *J* (Hz); assignment (italicized elements are responsible for the shifts); and integration. Data for ^{13}C NMR spectroscopy are reported as ppm relative to $CDCl_3$ (77.23 ppm) or CD_3OD (49.15 ppm) followed by assignment (italicized elements are responsible for the shifts). High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on a Waters Micromass LCT Premier XE mass spectrometer electrospray time-of-flight high-resolution mass spectrometer. HPLC analyses were carried out on a Shimadzu instrument equipped with a Chiralpak AS-H column (Chiral Technologies Inc., 250 mm × 4.6 mm) using a binary isocratic method (pump A, 2-propanol; pump B, hexanes; flow rate 1.0 mL/min, isocratic, 90% A, 10% B, λ = 254 nm). Luminescence-decay measurements[26−28] for the determination of water-coordination number, *q*, and steady-state luminescence measurements were performed using a HORIBA Jobin Yvon Fluormax-4 spectrofluorometer. Titration mixtures were vortexed using a Fisher Scientific vortex mixer before each measurement. Centrifugation was performed using a Centrific Centrifuge at 7000 rotations per minute (04-978-50, Fisher Scientific). Optical rotations were recorded using an Autopol III automatic polarimeter.

Synthesis and Characterization of Chiral Ligands 3–6. *(2S,2′S)-1,1′-(1,7-Dioxa-4,10-diazacyclododecane-4,10-diyl)bis-(propan-2-ol) (**3**).* To a stirring solution of 1,7-dioxa-4,10-diazacyclododecane (**8**) (0.040 g, 0.23 mmol) in methanol (2 mL) was added (*S*)-(−)-propylene oxide (**9**) (0.41 g, 7.0 mmol) at ambient temperature. After 12 h, the reaction mixture was filtered and concentrated under reduced pressure to yield a clear, colorless oil. Yield 61 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.33 (brs, O*H*, 2H), 3.78–3.67 (m, C*H*, 2H), 3.58–3.47 (m, CH_2, ring, 4H), 3.43–3.33 (m, CH_2 ring, 4H), 2.79–2.66 (m, CH_2 ring, 4H), 2.60–2.50 (m, CH_2 ring, 4H), 2.44–2.35 (m, CH_2 arm, 2H), 2.31–2.19 (m, CH_2 arm, 2H), 1.05 (d, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 69.5 (CH_2 ring), 64.3 (CH_2 arm) 64.2 (CH), 55.3 (CH_2 ring), 19.8 (CH_3). HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{31}N_2O_4$, 291.2284; found 291.2289. $[\alpha]_D^{23}$ +1.48 (*c* 1.35, CH_3OH).

*(2S,2′S)-1,1′-(1,7-Dioxa-4,10-diazacyclododecane-4,10-diyl)bis-(butan-2-ol) (**4**).* To a stirring solution of 1,7-dioxa-4,10-diazacyclododecane (**8**) (0.040 g, 0.23 mmol) in methanol (2 mL) was added (*S*)-(−)-1,2-epoxybutane (**10**) (0.51 g, 7.0 mmol) at ambient temperature. After 12 h, the reaction mixture was filtered and concentrated under reduced pressure to yield a clear, colorless oil. Yield 64 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.30 (s, O*H*, 2H), 3.61–3.37 (m, C*H* and CH_2, 10H), 2.83–2.71 (m, CH_2, 4H), 2.59–2.50 (m, CH_2, 4H), 2.48–2.40 (m, CH_2, 2H), 2.36–2.26 (m, CH_2, 2H), 1.51–1.28 (m, CH_3CH_2, 4H), 0.96 (t, *J* = 7.3 Hz, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 70.0 (CH), 69.5 (CH_2), 62.6 (CH_2), 55.5 (CH_2), 27.5 (CH_3CH_2), 10.5 (CH_3). HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{35}N_2O_4$, 319.2597; found 319.2596. $[\alpha]_D^{23}$ +1.28 (*c* 1.34, CH_3OH).

*(2R,2′R)-2,2′-(1,7-Dioxa-4,10-diazacyclododecane-4,10-diyl)bis-(propan-1-ol) (**5**).* To a stirring solution of **1** (0.038 g, 0.11 mmol) in tetrahydrofuran (1 mL) was added lithium aluminum hydride in tetrahydrofuran (0.27 mL, 2.0 M, 0.54 mmol) at ambient temperature. After 20 min of stirring, methanol (5 mL) was added followed by water (5 mL). The mixture was washed with CH_2Cl_2 (3 × 15 mL). Volatiles were removed under reduced pressure; water was added; the mixture was filtered; and water was removed under reduced pressure to yield a clear, colorless oil. Yield 28 mg, 91%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.01–4.90 (m, O*H*, 2H), 3.60–3.52 (m, CH_2 ring, 4H), 3.45–3.24 (m, CH_2 ring and HOCH_2, 8H), 2.98–2.87 (m, C*H*, 2H), 2.83–2.74 (m, CH_2, ring, 4H), 2.56–2.47 (m, CH_2 ring, 4H), 0.82 (d, *J* = 6.5 Hz, CH_3, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 69.9 (CH_2 ring), 64.1 ($HOCH_2$), 56.9 (CH), 49.5 (CH_2 ring), 9.34 (CH_3). HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{31}N_2O_4$, 291.2284; found 291.2275. $[\alpha]_D^{23}$ +0.881 (*c* 0.267, CH_3OH).

*(2R,2′R)-2,2′-(1,7-Dioxa-4,10-diazacyclododecane-4,10-diyl)-dipropanamide (**6**).* To a mixture of 1,7-dioxa-4,10-diazacyclododecane (**8**) (0.050 g, 0.29 mmol) and Cs_2CO_3 (1.0 g, 3.1 mmol) in acetonitrile (4 mL) was added (*S*)-amino-1-oxypropan-2-yl-4-methylbenzenesulfonate (**11**) (0.21 g, 0.86 mmol), and the resulting mixture was stirred for 72 h at ambient temperature and then centrifuged for 10 min. The supernatant was concentrated under reduced pressure and washed with diethyl ether (6 × 15 mL) to yield a white solid. Yield 67 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.16 (brs, NH_2, 2H), 5.44 (brs, NH_2, 2H), 3.70 (t, CH_2 *J* = 11.3 Hz, 4H), 3.44–3.31 (m, CH_2, C*H*, 6H), 2.94–2.80 (m, CH_2, 4H), 2.60–2.48 (m, CH_2, 4H), 1.25 (d, CH_3, *J* = 7.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 177.7 ($CONH_2$), 68.0 (CH_2), 59.1 (CH), 49.9 (CH_2), 8.6 (CH_3). HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{29}N_4O_4$, 317.2189; found 317.2198. $[\alpha]_D^{23}$ +0.349 (*c* 1.16, CH_3OH).

*(S)-Amino-1-oxypropan-2-yl-4-methylbenzenesulfonate (**11**).* To a stirring solution of (*S*)-2-hydroxypropanamide (1.00 g, 0.0112 mol) in a mixture of triethylamine and dichloromethane (1:5 v/v, 10 mL) was added 4-methylbenzene-1-sulfonyl chloride (2.35 g, 0.0123 mol) at ambient temperature. After 96 h, the crude reaction mixture was concentrated under reduced pressure and purified using flash chromatography (1:1 ethyl acetate/hexanes) to afford a fluffy white solid. Yield 704 mg, 26%. TLC R_f = 0.2 (1:1 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, CD_3OD, δ): 7.83 (d, *J* = 8.3 Hz, C*H*, 2H), 7.45 (d, *J* = 8.3 Hz, C*H*, 2H), 4.82–4.73 (m, C*H*, 1H), 2.46 (s, CH_3, 3H), 1.39 (d, *J* = 6.9 Hz, CH_3, 3H). ^{13}C NMR (100 MHz, CD_3OD, δ): 174.2 ($CONH_2$), 147.1, 134.7, 131.3 (CH), 129.3 (CH), 77.4 (CH), 21.8 (CH_3), 19.4 (CH_3). HRESIMS (*m*/*z*): $[M + H]^+$ calcd for $C_{10}H_{14}NO_4S$, 244.0599; found 244.0644.

Titration Experiment General Procedure. Ligand-to-metal titrations were performed in a cuvette by adding solutions of ligand (11.0 mM in 9:1 EtOH/H_2O) to solutions of $Eu(OTf)_3$ (0.834 mM in 9:1 EtOH/H_2O). The resulting solutions were vigorously shaken using a vortex mixer for 20 s and then allowed to stand for 5 min before acquiring emission spectra. Emission spectra were obtained by exciting at 395 nm (excitation and emission slit widths were set to 5 nm).

Mukaiyama Aldol Reaction General Procedure. To a mixture of ligand and $Eu(OTf)_3$ in 9:1 ethanol/water (0.4 mL) that was stirred

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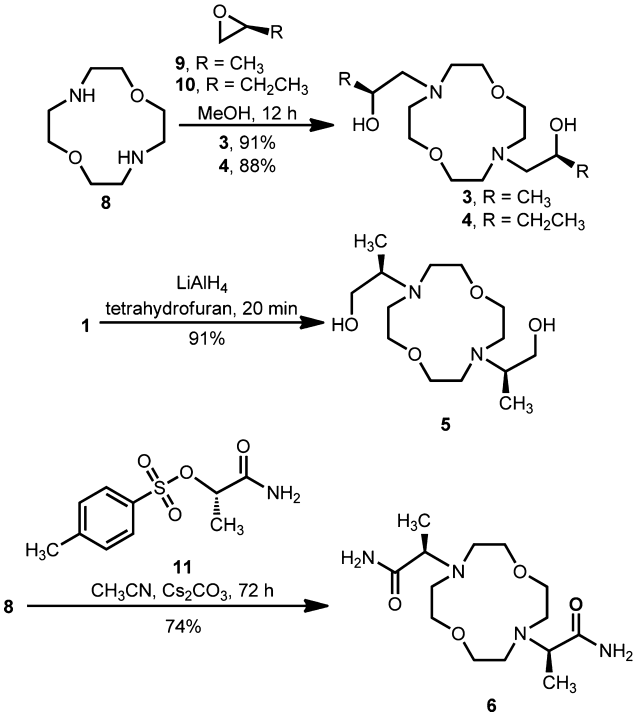
for 5 min at ambient temperature and then cooled to −25 °C was added benzaldehyde (**12**) (3.2 μL, 32 μmol, 1.0 equiv) followed by (*Z*)-trimethyl-(1-phenylpropyl-1-enyloxy)trimethylsilane (**7**) (11 μL, 48 μmol, 1.5 equiv). The mixture was stirred for 168 h at −25 °C. Silyl enol ether **7** hydrolyzes throughout the course of the reaction as observed by TLC, but it is not completely consumed until 168 h. The mixture was then purified using silica gel chromatography (1:9 ethyl acetate/hexanes, R_f = 0.2), and volatiles were removed under reduced pressure. The enantiomeric and diastereomeric ratios of the products were determined by HPLC.[8]

RESULTS AND DISCUSSION

Ligands 1−6. With ligands **1**−**6** and Eu^{3+}, we were able to study the influence of ligand structure on reactivity, selectivity, and complex formation. The functional groups that bind to the metal were changed as part of this strategy to incorporate esters (**1**), carboxylic acids (likely carboxylates under reaction conditions) (**2**), alcohols (**3**, **4**, and **5**), and amides (**6**). These functional groups were chosen because esters, carboxylic acids, alcohols, and amides have different Lewis basicities that affect the ability of ligands to bind Eu^{3+}. In addition to functional groups, the location and size of the chiral center on the ligand side arms were investigated with ligands **3**, **4**, and **5** to study the influence of structural features on reactivity and selectivity.

The syntheses of ligands **3**−**6** are shown in Scheme 2. Briefly, **3** and **4** were synthesized by the ring-opening of epoxides with

Scheme 2. Syntheses of Ligands 3−6



macrocycle **8** in MeOH. Ligand **5** was prepared by reducing **1** with lithium aluminum hydride. The reduction of **1** to produce **5** was chosen instead of preparing a chiral-alcohol side arm to react with **8** because the stereoisomers of starting material **1** can be readily purified by HPLC. Ligand **6** was synthesized by functionalizing **8** using (*S*)-amino-1-oxypropan-2-yl-4-methylbenzenesulfonate (**11**). Ligands **3**−**6** were all synthesized in good yields (74−91%) in one step from commercially available or reported starting materials.

Luminescence Measurements for the Study of Eu^{3+} Coordination Environment. Luminescence measurements were performed to study the interaction of Eu^{3+} with ligands **1**−**6**. Eu^{3+} is a useful optical probe for studying coordination environments because of its coordination-environment sensitive luminescence-lifetime[26−30] and the hypersensitivity of the $^5D_0 \rightarrow {}^7F_2$ transition (emission at ∼616 nm) to perturbations of symmetry.[31−33] Consequently, luminescence-lifetime measurements were used to determine water-coordination numbers (q), and steady-state luminescence measurements were used to monitor changes in the crystal field of Eu^{3+}during ligand-to-metal titrations.

To calculate q for Eu^{3+} in each mixture, we used eq 1, where 1.2, 0.23, 0.44, and 0.075 are empirically derived constants. The value of 1.2 is independent of the solvent system, and the correction factor of 0.23 was used because our solvent systems were composed of EtOH/H_2O (9:1) and not water.[34] The terms *n*OH and *n*NH are the number of non-water-based inner-sphere alcohol (O−H) or amide (N−H) oscillators, respectively.[29,34] The terms $\tau^{-1}_{H_2O}$ and $\tau^{-1}_{D_2O}$ are the measured luminescence-decay rates of Eu^{3+} in EtOH/H_2O and EtOD/D_2O, respectively (decay rates are in the Supporting Information). Water-coordination numbers of Eu^{3+} were measured in mixtures of EtOH/H_2O 9:1 (v/v) with ligand-to-Eu^{3+} ratios of 1:1, 2:1, and 6:1 (Table 1). This solvent

Table 1. Water-Coordination Numbers for Eu^{3+} with Ligands 1−6

ligand	$q^{a,d,g}$	$q^{a,e,g}$	$q^{b,d,g}$	$q^{b,e,g}$	$q^{c,d,g}$	$q^{c,e,g}$
1[f]	3.5	3.5	2.1	2.1	1.4	1.4
2[f]	2.2	2.2	0.8	0.8	0.0	0.0
3	2.2	1.1	2.0	1.0	1.1	0.0
4	1.9	0.8	1.8	0.8	nd	nd
5	2.1	1.0	2.1	1.0	0.5	0.0
6	3.8	3.4	3.0	2.6	1.7	1.3

[a]Ligand-to-metal ratio of 1:1. [b]Ligand-to-metal ratio of 2:1. [c]Ligand-to-metal ratio of 6:1. [d]Calculated for complexes with Eu^{3+} coordination by one ligand. [e]Calculated for complexes with Eu^{3+} coordination by two ligands. [f]Ligands **1** and **2** do not have chelator-based inner-sphere O−H or N−H oscillators; therefore, $q^d = q^e$. nd = not determined. [g]The error associated with water-coordination number determination is ±0.1 water molecules.[29]

composition was chosen because it is commonly used for lanthanide-catalyzed Mukaiyama aldol reactions.[13,23,24] Also, ligand-to-Eu^{3+} ratios of 1:1, 2:1, and 6:1 were chosen to determine if more than 1 equiv of ligand can bind Eu^{3+}. Due to the possibility of more than 1 equiv of ligand being coordinated to Eu^{3+}, we calculated q values for both 1 and 2 equiv of ligand bound to Eu^{3+} (we did not calculate q values for greater than 2 equiv of ligand bound to Eu^{3+} because this type of binding is unlikely to occur based on steric interactions and entropy) assuming that all N−H or O−H oscillators on each ligand would be in the inner sphere of the metal ion. This assumption allowed us to obtain maximum and minimum q values with ratios of 1:1 ligand-to-Eu^{3+} (maximum) and 2:1 ligand-to-Eu^{3+} (minimum). For example, maximum and minimum q values for Eu^{3+} with ligand **6** were calculated for 1 equiv of ligand (2 amides or 4 N−H oscillators) for a maximum q value and for 2 equiv of ligand (4 amides or 8 N−H oscillators) for a minimum q value.

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$$q = 1.2[(\tau_{H_2O}^{-1} - \tau_{D_2O}^{-1}) - 0.23 - 0.44nOH - 0.075nNH] \quad (1)$$

Eu^{3+} usually has a coordination number between 8 and 9; therefore, because q determinations represent the average of all species in solution, water-coordination numbers greater than 3 in the presence of hexadentate ligands suggest the presence of uncomplexed Eu^{3+} (Figure 2) or incomplete coordination by

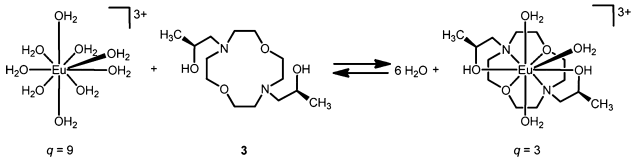

Figure 2. Representation of unchelated Eu^{3+} and a Eu^{3+}-containing complex of **3** with q values of 9 and 3, respectively (counteranions have been omitted for clarity). One complex is shown on the right of the equilibrium to demonstrate the point of the figure, but multiple species are likely in the actual solution including sandwich-type structures that involve incomplete chelation from more than one multidentate ligand.

the ligands. By measuring the water-coordination numbers of Eu^{3+} at different ligand-to-metal ratios, we were able to monitor the complexation of Eu^{3+} with ligands **1**–**6**. Mixtures of Eu^{3+} with ligands **1** and **6** at ligand-to-metal ratios of 1:1 have Eu^{3+} water-coordination numbers greater than 3, indicating incomplete complexation of Eu^{3+}. This observation suggests that ligands **1** and **6** form labile complexes with Eu^{3+} under these conditions. Ligands **2**–**5** with Eu^{3+} at ligand-to-metal ratios of 1:1 have q values between 0.8 and 2.2. These values of q suggest that ligands **2**–**5** (ligands with side arms that have functional groups with the ability to become deprotonated) chelate Eu^{3+} more strongly than **1** and **6** (ligands with side arms that have functional groups that lack the ability to become deprotonated).

Average values of q are lower at ligand-to-metal ratios of 2:1 compared to 1:1 mixtures prepared from the same ligands. This observation is a demonstration of Le Chatelier's principle where the equilibrium system shown in Figure 2 can be driven to the right (increased chelation of Eu^{3+}) in the presence of excess ligand. Water-coordination numbers were lower than 3 at ligand-to-Eu^{3+} ratios of 6:1 in the presence of ligands **1**–**3**, **5**, and **6** indicating that Eu^{3+} can be bound by more than one ligand at a time. Mixtures of **4** and Eu^{3+} at a ligand-to-Eu^{3+} ratio of 6:1 became turbid in $EtOD/D_2O$; therefore, we did not calculate q for Eu^{3+} with **4** at this ratio. Interestingly, Eu^{3+} in the presence of 6 equiv of ligand **2** had a q value of 0.0; the most reasonable explanation for such a low q is complete encapsulation of Eu^{3+} by 2 or more equiv of ligand **2**. These observations of q at different ligand-to-Eu^{3+} ratios support our hypothesis that an equilibrium system with multiple species occurs with ligands **1**–**6** and Eu^{3+}. We suspect that there are multiple equilibria in solution but that the predominant species are unbound Eu^{3+}, a single multidentate ligand coordinated to Eu^{3+}, and two multidentate ligands coordinated to Eu^{3+} (Eu^{3+} is potentially moving between the macrocycles of each ligand while being coordinated by the appendages of both ligands).

To gain a better understanding of the Eu^{3+} equilibrium system, we titrated solutions of ligand into solutions containing Eu^{3+} and monitored the changes in coordination by steady-state luminescence measurements. Monitoring changes in steady-state luminescence intensity as a function of ligand-to-Eu^{3+} ratio allows the determination of end points for ligand-to-Eu^{3+} binding stoichiometries for ligands **1**–**6** with Eu^{3+}. To monitor changes in luminescence intensities, we compared the $^5D_0 \rightarrow {}^7F_1$ and $^5D_0 \rightarrow {}^7F_2$ transitions of Eu^{3+}. Figure 3 illustrates the

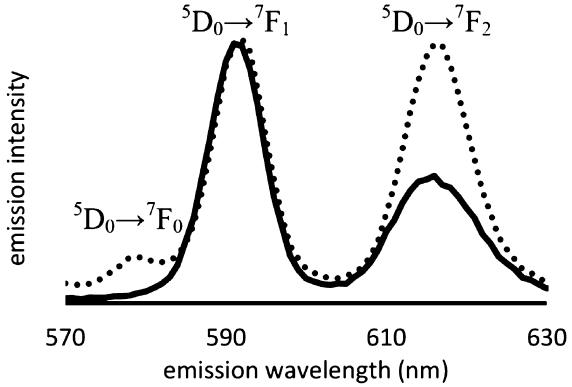

Figure 3. Normalized emission spectra (λ_{ex} = 395 nm) of $Eu(OTf)_3$ in $EtOH/H_2O$ 1:9 with (dotted line) and without (solid line) 0.6 equiv of ligand **3**. The bands at 577, 591, and 616 nm arise from the $^5D_0 \rightarrow {}^7F_0$, $^5D_0 \rightarrow {}^7F_1$, and $^5D_0 \rightarrow {}^7F_2$ transitions, respectively. Similar spectra were observed for the other ligands in this Article. The sensitivity of the $^5D_0 \rightarrow {}^7F_2$ transition combined with the less sensitive $^5D_0 \rightarrow {}^7F_1$ transition makes Eu^{3+} a useful ratiometric sensor for concentration-independent sensing of changes in coordination [$(^5D_0 \rightarrow {}^7F_2)/(^5D_0 \rightarrow {}^7F_1)$ emission intensity ratios are independent of concentration]. The intensity ratio increase is expected upon ligand coordination to Eu^{3+} because the $^5D_0 \rightarrow {}^7F_2$ emission intensity is highly sensitive to perturbations of the Eu^{3+} crystal field by coordinated ligands.[32,33,35,36]

sensitivity of the $^5D_0 \rightarrow {}^7F_2$ transition to changes in coordination environment (with and without 0.6 equiv of multidentate ligand **3**). The emission spectrum of Eu^{3+} in the presence of ligand **3** was normalized to the magnetic-dipole ($^5D_0 \rightarrow {}^7F_1$) band at 591 nm (relatively insensitive to changes in coordination environment) for visual comparison of the $^5D_0 \rightarrow {}^7F_2$ emission intensities.

Compared to $Eu(OTf)_3$ in the absence of hexadentate ligands, the intensity of the $^5D_0 \rightarrow {}^7F_2$ transition relative to the $^5D_0 \rightarrow {}^7F_1$ transition increased in the presence of every hexadentate ligand in this study. Changes in Eu^{3+} coordination environments were monitored by plotting the emission intensity ratios versus ligand-to-Eu^{3+} ratios (Figure 4). Ligand-to-Eu^{3+} titrations with **1**–**6** caused an increase in the intensity ratio of the $^5D_0 \rightarrow {}^7F_2$ to $^5D_0 \rightarrow {}^7F_1$ transitions of Eu^{3+} between 1 and 3 equiv of ligand (indicating change in Eu^{3+} coordination). Ester functionalized ligand **1** does not have titration end points in the range studied, indicating weak interactions between ligand and Eu^{3+}. Lastly, the titration of ligand **6** and Eu^{3+} has an apparent end point near 6 equiv of ligand, which indicated weak interactions between ligand and Eu^{3+}. On the basis of the titration data in Figure 4, ligand donor type affects coordination more than chiral center location and size. The relative strength of interactions with Eu^{3+} for these ligands is carboxylate > alcohol > amide > ester. Alcohol-based ligands might appear out of order, but if they are at least partially deprotonated when coordinated to Eu^{3+}, then they would be expected to bind more tightly than amides or esters. This stability trend is in agreement with other studies of macrocyclic ligands with Eu^{3+}.[37–40]

^{1}H NMR Characterization of Ligands with Eu^{3+}. In addition to luminescence measurements, NMR spectroscopy

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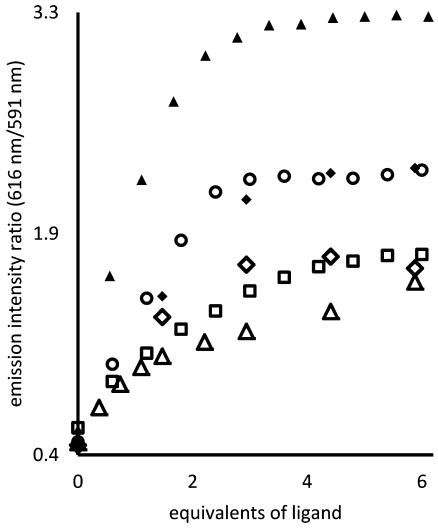

Figure 4. Emission intensity ratios of Eu^{3+} (616 nm/591 nm) versus equiv of ligand for Eu^{3+} with **1** (Δ), **2** (▲), **3** (♦), **4** (◊), **5** (○), and **6** (□). Increases in magnitude of the emission intensity quotient (616 nm/591 nm) arise from increases in crystal field splitting of Eu^{3+}.[33]

was used to investigate the interactions between ligands and Eu^{3+}. By monitoring changes in the ^1H NMR spectra of ligands in the presence of Eu^{3+} at different ligand-to-Eu^{3+} ratios, we found that at least three different species can exist in solution. Figure 5 contains ^1H NMR spectra of ligand **3** that were acquired at ligand-to-Eu^{3+} ratios of 1:0, 4:1, and 0.5:1. These ligand-to-Eu^{3+} ratios were chosen because they allowed us to investigate **3** without Eu^{3+} (1:0), with an excess of ligand (4:1), and with an excess of Eu^{3+} (0.5:1). The NMR spectra were different at each ratio, indicating the presence of different ligand environments. With a ligand-to-Eu^{3+} ratio of 4:1 and an acquisition temperature of −40 °C, we observed new signals downfield from the signals arising from only ligand. We attribute the downfield signals to a Eu^{3+}−L_n ($n > 1$) species because an excess of ligand increases the probability for multiple ligands to bind Eu^{3+}. The NMR spectral evidence for the presence of a Eu^{3+}−L_n ($n > 1$) species is also consistent with q measurements for Eu^{3+} in the presence of excess **3**. Although these experiments were performed at different temperatures that likely influence the rates associated with ligand binding (−40 °C for NMR spectroscopy to avoid coalescence and ambient temperature for luminescence measurements because of instrument capabilities), the conclusions with respect to precatalyst structure are consistent because the luminescence values represent an average of all species in solution, and this value changes as a function of the stoichiometry. At a ligand-to-metal ratio of 0.5:1, we observed signals upfield relative to signals arising from the ligand. We attribute the upfield signals to a 1:1 Eu^{3+}-to-ligand complex because an excess of metal will shift the equilibrium toward 1:1 ligand-to-metal complexes and unchelated Eu^{3+}, or possibly a $Eu^{3+}{}_n$−L ($n \geq 1$) species. From the ^1H NMR spectra of ligands **1**−**6** with Eu^{3+} at different ligand-to-metal ratios, we found that at least three different species of Eu^{3+} exist depending on the ligand-to-Eu^{3+} ratio, and these findings corroborate our luminescence observations.

Testing of Precatalyst Reactivity and Selectivity in the Aqueous Enantioselective Mukaiyama Aldol Reaction. We tested the reactivity and selectivity of mixtures of Eu^{3+} with ligands **1**−**6** in the aqueous Mukaiyama aldol reaction shown in Scheme 3. We chose the reaction in Scheme 3 because it has been previously used for testing of precatalysts for Mukaiyama aldol reactions;[41−44] therefore, our results can be compared to results obtained using other precatalysts. Because reactivity and

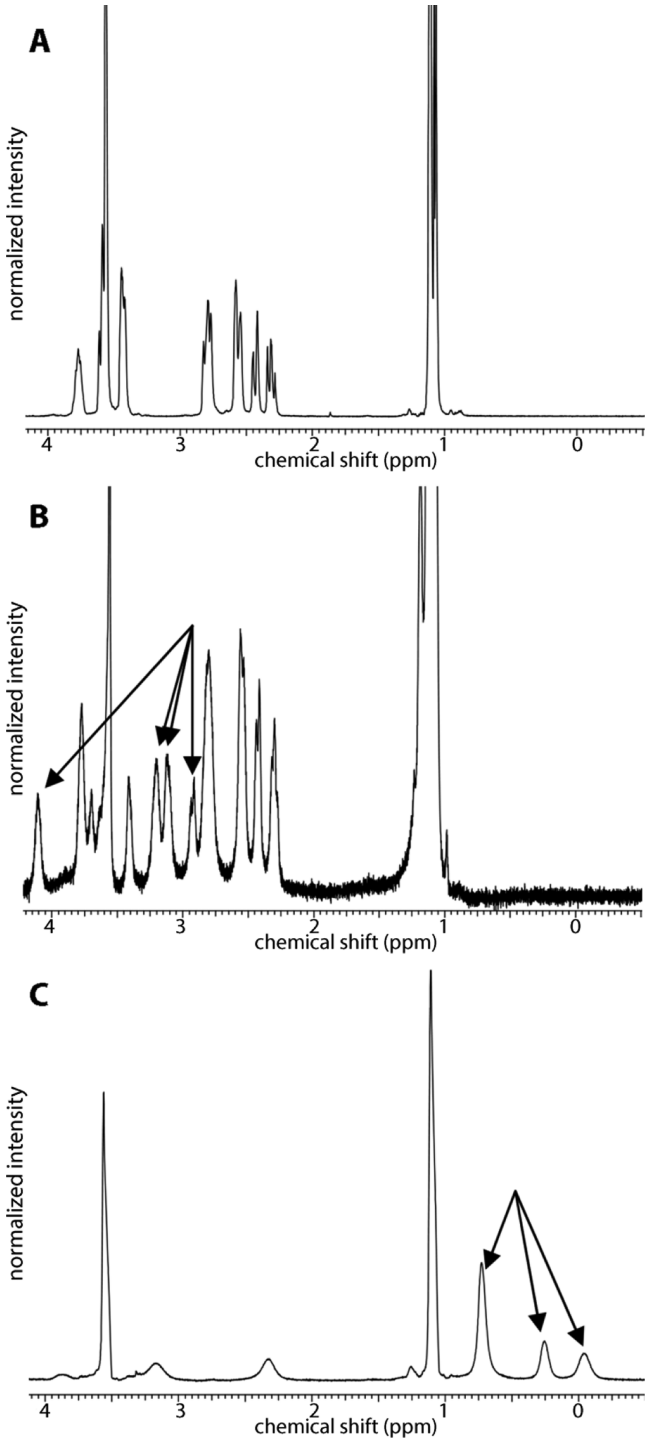

Figure 5. (A) ^1H NMR spectrum of **3** in 9:1 EtOD/D_2O. (B) ^1H NMR spectrum of **3** in 9:1 EtOD/D_2O at −40 °C with 0.25 equiv of $Eu(OTf)_3$. Arrows point to signals observed in the presence of excess ligand (the temperature of −40 °C was required to resolve the signals between 4 and 2 ppm). We attribute these new signals to a Eu^{3+}−L_n ($n > 1$) species. (C) ^1H NMR spectrum of **3** in 9:1 EtOD/D_2O with 2 equiv of $Eu(OTf)_3$. Arrows point to signals observed in the presence of excess Eu^{3+}. We attribute the new upfield signals to a $Eu^{3+}{}_n$−L ($n \geq 1$) species.

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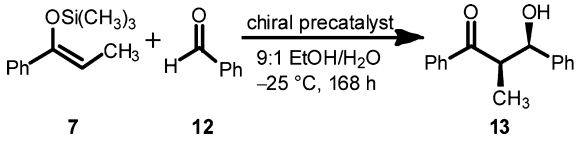
Scheme 3. Aqueous Mukaiyama Aldol Reaction Performed with Ligands 1–6



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selectivity of Mukaiyama aldol reactions depend on ligand-to-metal ratios,[14,23,24] the reactions in this study were performed at ligand-to-Eu^{3+} ratios of 1.2:1 and 2.4:1 (Table 2) to enable comparison to published values.[18,23]

Table 2. Aqueous Mukaiyama Aldol Yields and Selectivities Catalyzed by $Eu(OTf)_3$ with Ligands 1–6

	1	2	3	4	5	6
yield[a,b] (%)	96[c]	8	17	12	5	20
yield[b,d] (%)	92[e]	0	0	0	0	6
dr[a,f] (syn:anti)	2.1:1[c]	0.72:1	1.3:1	1.1:1	1.1:1	0.93:1
dr[d,f] (syn:anti)	32:1[e]	nd	nd	nd	nd	0.55:1
er[a,f] (syn)	2:1[c]	1.03:1	1.2:1	1:1	1:1	0.78:1
er[d,f] (syn)	96:1[e]	nd	nd	nd	nd	0.66:1

[a]24 mol % ligand, 20 mol % $Eu(OTf)_3$. [b]Isolated yield. [c]Reference 18. [d]48 mol % ligand, 20 mol % $Eu(OTf)_3$. [e]Reference 23. [f]Determined by chiral HPLC analysis; nd = not determined.

Ligand **1** with Eu^{3+} was previously reported to give 96% and 92% yields at ligand-to-Eu^{3+} ratios of 1.2:1 and 2.4:1 with respective diastereomeric ratios of 2.1:1 and 32:1 and enantiomeric ratios of 2:1 and 96:1.[23,24] In this study, ligand **2** with Eu^{3+} gave an 8% yield at a ligand-to-Eu^{3+} ratio of 1.2:1 with a diastereomeric ratio of 0.72:1 and an enantiomeric ratio of 1.03:1 with no products being formed at the 2.4:1 ligand-to-Eu^{3+} ratio. We hypothesize that, in the presence of excess **2**, the inner-coordination sphere of Eu^{3+} nears saturation and cannot act as a precatalyst for Mukaiyama aldol reactions, which is consistent with observed *q* numbers for Eu^{3+} in the presence of excess **2**. Chiral alcohol ligands **3**–**5** with Eu^{3+} gave low yields (5–17%) and low diasteriomeric (1.1:1–1.3:1) and enantiomeric (1:1–1.2:1) ratios at ligand-to-Eu^{3+} ratios of 1.2:1. The low selectivity is likely due to the lack of steric bulk on the ligand side arms. A lack of steric bulk near the coordinated atom might not allow the ligand to block nucleophilic attack at either the *re* or *si* face of the aldehyde from the incoming silyl enol ether (Figure 6, left). This blocking is the suspected mechanism that imparts selectivity.[24] No products were observed for mixtures of 2.4:1 ligand-to-Eu^{3+} with ligands **3**–**5**, and this lack of reactivity is likely due to an equilibrium system that involves displacement of inner-sphere water by a second equivalent of ligands **3**–**5** (Figure 7). Saturation of Eu^{3+} by more than 1 equiv of ligand could inhibit the reaction by preventing aldehyde coordination to Eu^{3+} to become activated for nucleophilic attack. The *q* data for Eu^{3+} with ligands **3**–**5** support our hypothesis that excess ligand prevents the aldehyde from becoming activated for nucleophilic attack.

Amide functionalized ligand **6** with $Eu(OTf)_3$ at ligand-to-Eu^{3+} ratios of 1.2:1 and 2.4:1 gave low yields (20 and 6%, respectively) and low diasteriomeric and enantiomeric selectivity. It is likely that excess **6** slowed the Mukaiyama aldol reaction by decreasing the Lewis acidity at the metal center. These findings suggest that amide side arms deactivate the metal center compared to ester side arms. The reduced

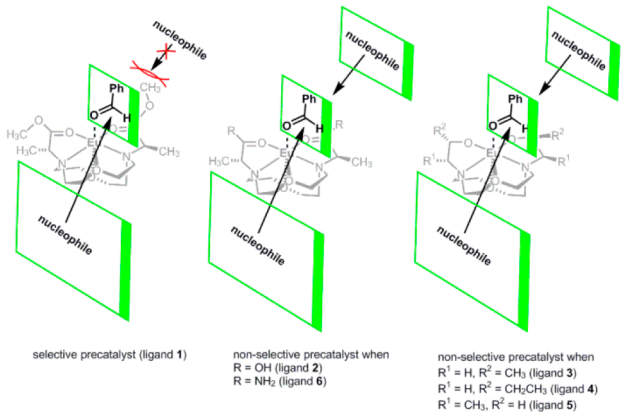

Figure 6. (left) Proposed selective nucleophilic attack at the *si* face of benzaldehyde (high selectivity and reactivity is observed). (middle) Precatalysts are nonselective when R is OH or NH_2. (right) Ligands **3**–**5** with Eu^{3+} are unable to block nucleophilic attack at either face of benzaldehyde likely due to the stereochemistry at the position of R^2 causing less blocking than with ligand **1**. Coordinated water has been omitted for clarity; additionally, ligand **2** has been drawn in the carboxylic acid form although it likely exists in the deprotonated state while coordinated to Eu^{3+} in aqueous media.

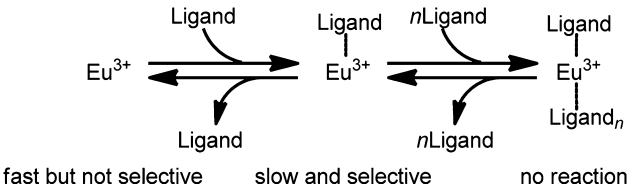

Figure 7. Proposed equilibria involving multiple Eu^{3+} species with reactivity summarized under the species. These equilibria are based on luminescence-decay, steady-state luminescence measurements, and ^1H NMR data with reactivity and selectivity from Mukaiyama aldol reaction results.

reactivity of Eu^{3+} in the presence of **6** is likely explained by the resonance structure of amides that place electron density on the carbonyl oxygen, lowering the Lewis acidity of Eu^{3+}. Because low selectivity was observed with $Eu(OTf)_3$ in the presence of **6**, we hypothesize that the steric bulk of the primary amide ligand is not large enough to selectively block the nucleophilic attack by the incoming silyl enol ether (Figure 6).

From Mukaiyama aldol reactions, we found that substitution at the carbonyl carbon and the carbon adjacent to the macrocycle nitrogen is required for high stereoselectivity in the products (Figure 7). Finally, we found that carboxylic acid, alcohol, and amide functionalized ligands (**2**, **3**–**5**, and **6**, respectively) cause a reduction in reactivity compared to **1**. We hypothesize that ligand **1** likely donates the lowest amount of electron density to Eu^{3+} out of all of the ligands studied, resulting in the strongest Lewis acid precatalyst (most reactive) of the series when combined with Eu^{3+}. This result suggests that improvements to reactivity would need to include donors that are weaker bases than esters.

■ CONCLUSION

We synthesized a series of new, chiral, Eu^{3+}-binding ligands. By spectroscopically characterizing the ligands and Eu^{3+} interactions using luminescence-decay, steady-state luminescence, and NMR spectroscopies, we found evidence suggesting that saturation of the Eu^{3+} coordination sphere by multiple

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hexadentate ligands occurs in the presence of excess ligand. A comparison of ligand functional groups and chiral center location and bulk provided insight into the factors that affect reactivity and selectivity of water-tolerant chiral precatalysts. We found that the reactivity of Eu^{3+}-based precatalysts depends on the type of coordinating functional groups on the ligands, and that the selectivity of Eu^{3+}-based precatalysts depends on chiral center location and functional group size. The selectivity, reactivity, and spectroscopic characterizations described here contribute to the understanding of lanthanide-based precatalysts, and we expect these findings to be useful in the design of new precatalysts with high activity and selectivity for asymmetric carbon−carbon bond-forming reactions in aqueous media.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for ligands **3**−**6**, ^1H and ^{13}C NMR spectra for **11**, chiral HPLC chromatograms for Mukaiyama aldol products, tabulated emission intensity ratios from titrations, tabulated luminescence-decay rates, and ^1H NMR spectra of ligands **1**−**6** with and without Eu^{3+}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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