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A New Class of Ligands for Aqueous, Lanthanide-Catalyzed, Enantioselective Mukaiyama Aldol Reactions

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Abstract

The development of aqueous methods to generate enantiopure β -hydroxy carbonyl compounds is an important goal because these subunits compose many bioactive compounds, and the ability to synthesize these groups in water has environmental and cost benefits. In this communication, we report a new class of ligands for aqueous, lanthanide-catalyzed, asymmetric Mukaiyama aldol reactions to synthesize chiral β -hydroxy ketones. Furthermore, we use luminescence-decay measurements to unveil mechanistic information regarding the catalytic reaction via changes of water-coordination number. The precatalysts presented here yielded β -hydroxy carbonyls from aliphatic and aryl substrates with outstanding *syn:anti* ratios and enantiometric excesses of up to 49:1 and 97%.

The enantioselective Mukaiyama aldol reaction is one of the most useful protocols to synthesize optically active β -hydroxy carbonyl moieties that are subunits of many bioactive compounds.¹ Lanthanide triflate-catalyzed versions of this reaction have gained prominence in the last decade because they are water tolerant and, consequently, have the benefits associated with not rigorously excluding water, including being more environmentally-benign and less expensive.² However, few examples exist of enantioselective, lanthanide-catalyzed Mukaiyama aldol reactions in aqueous media.³ These reactions use chiral crown ether-based ligands and result in moderate to good enantiomeric excesses, *ee*'s, with aromatic aldehydes and poor *ee*'s for alkyl aldehydes. The lack of a thorough mechanistic understanding of these complexes in the presence of water has hindered the improvement of stereoselectivity and the widespread use of these catalysts. Additionally, the multidentate chiral ligands necessary to chelate lanthanide ions are often difficult to synthesize and purify. Here, we report the facile synthesis of a new class of C_2 -symmetric lanthanide-containing complexes that were designed using insight gained from water-coordination-number measurements. We also report the excellent enantioselectivity of these new precatalysts in the aqueous Mukaiyama aldol reaction and the structure–activity relationships obtained using our recently reported use of luminescence decay to study bond formation.⁴

Our ligand design was inspired by macrocyclic gadolinium-containing contrast agents for magnetic resonance imaging.⁵ These complexes were chosen as our starting point because they are water tolerant, and we hypothesized that the multidenticity of these ligands would allow for facile incorporation of chiral centers (Figure 1). However, we modified the ligands because the contrast agents have only one open coordination site and our previous studies showed that a larger number of coordination sites is associated with higher turnover frequencies.⁴ To increase the number of open coordination sites, we replaced two of the

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Supporting Information Available: Synthetic methods, experimental details, and tables of *q* values (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

aminocarboxylic acid arms with ethers to yield a hexadentate C_2 -symmetric system. The resulting ligands have three sites for substrate to coordinate: two “side” positions near the ethers in the macrocycle that are equivalent by symmetry and one “top” site between the two side sites. Our new class of ligands takes advantage of the low degree of conformational flexibility and water-tolerance of lanthanide complexes of macrocyclic polyaminopolycarboxylate-based ligands. Additionally, we stereospecifically introduced methyl groups onto the methylene positions of the two remaining arms with the goal of imparting chirality. Furthermore, by converting the carboxylic acids into esters, we aimed to control the possible binding sites for substrate molecules through changing the size of the R groups of the esters. We hypothesized that this feature would be a powerful tool to study structure–activity relationships of our ligands with the goal of improving enantioselectivity.

The new C_2 -symmetric ligands (*R,R*) were prepared in 97–98% yields by a simple two-step protocol starting from commercially-available (*S*)-2-bromopropanoic acid (95% ee) (Scheme 1). No chromatographic purification was needed, and none of the opposite enantiomer (*S,S*) was observed in preparing ligands **I–VI**. Ligand **VII** was synthesized by saponification of **I**. The ligands were complexed with $\text{Eu}(\text{OTf})_3$ in situ prior to catalysis. Eu^{3+} was chosen because it is an effective promoter for the activation of aldehydes in aqueous media^{2,6,7} and because it enables luminescence-decay measurements.^{4,8}

Initially, we examined the structure–activity relationships of chiral ligands with different R groups. The results demonstrated that the size of the R group has a direct effect on the catalytic rate (based on yield in a set time) and enantioselectivity of the precatalyst: linear substituents generated excellent yields and enantioselectivities (Table 1, ligands **I–IV**), and bulky substituents dramatically reduced yields and enantioselectivities (Table 1, ligands **V** and **VI**). The exception to this trend was with ligand **VII**, and this difference is likely due to differences in hydrogen bonding ability, charge, and Lewis acidity of the Eu^{3+} ion in the presence of carboxyl groups in place of esters.² Furthermore, we hypothesized that enantioselectivity could be improved by increasing the *syn:anti* ratio of the ligand. We increased this ratio to 5:1 for ligand **I** by performing the last step in Scheme 1 at 0°C instead of ambient temperature. The resulting ligand was used to achieve an increase in ee to 89%. We then chromatographically isolated a single *syn* isomer of **I**, which provided product **9** in 93% ee.

To explore the mechanistic reasons for our observations, we used luminescence-decay measurements to study the water-coordination numbers, q , of Eu^{3+} complexes of ligands **I–VII** in the presence and absence of benzaldehyde.⁴ Eu^{3+} complexes of each ligand had water-coordination numbers between two and three prior to the addition of benzaldehyde.⁶ This range is expected for a hexadentate ligand. Upon addition of benzaldehyde, a decrease of water-coordination number was observed for each precatalyst. The change in water-coordination number is listed as Δq in Table 1. A negative Δq value implies displacement of water by benzaldehyde (Scheme 2) and thus a shift in equilibrium from the hydrated precatalyst toward coordinated (activated) benzaldehyde (eq in Scheme 2). Therefore, larger absolute values of Δq can be used to account for increased yields in a set time. For linear R groups (ligands **I–IV**), we observed a displacement of 0.40–0.68 water molecules upon addition of benzaldehyde. These Δq values are larger than the Δq values observed for unchelated Eu^{3+} .⁵ This observation suggests that the ligands induce an interaction with the aldehyde, potentially hydrophobic or non-classical hydrogen bonding,⁹ that causes a favorable binding of aldehyde to metal. Much smaller Δq values were observed for bulkier R groups (ligands **V** and **VI**) suggesting that the steric bulk hinders the binding of substrate and leads to lower yields.

The proposed transition state in Figure 2 accounts for our observed (*R,R*) product. In this model, benzaldehyde coordinates to the metal on the top position based on the Δq data in Table 1, bulky R groups would block this position. When the aldehyde is coordinated in this position, the silyl enol ether can only attack from the side coordination site because the opposite face is blocked by an ester. Benzaldehyde is unlikely to bind with the H and Ph groups reversed from the arrangement in Figure 2 because of unfavorable steric interactions between the phenyl ring and the macrocycle. This model also accounts for the racemic product observed with ligand **VII** because there are no ester groups to hinder the approach of the silyl enol ether from either side. If benzaldehyde were bound to the side positions, contradicting our Δq data, attack of the silyl enol ether would be blocked by the methyl group at the chiral center or by the ester.

To explore the substrate scope of our best ligand, **I**, we used the aldehydes and silyl enol ethers listed in Table 2. All of these reactions gave excellent ee's (84–97%) and high diastereoselectivities (11:1–49:1). To the best of our knowledge, these values are the highest stereoselectivities reported in the presence of water with any Lewis acid-based catalyst. With aromatic aldehydes, electron-donating and withdrawing substitutions had negligible influence on stereoselectivity (Table 2, entries 1–3). The results in Table 2 are particularly outstanding because the stereoselectivity observed with α,β -unsaturated and aliphatic aldehydes (entries 4–8). In addition to changes in aldehydes, we tested ligand **I** with a silyl enol ether derived from an aliphatic ketone (Table 2, entry 9), and the desired product was obtained in high ee and diastereoselectivity. Furthermore, the reactivity of aliphatic aldehydes supports our proposed transition state model because as the bulkiness of the aldehydes increases (Table 2 entries 4–8), the observed yields in a set time decrease. This trend associated with the steric bulk of the substrates is similar to the trend observed with change in steric bulk of the ligand (Table 1): the steric nature of the aliphatic aldehydes influences the efficiency of the Mukaiyama aldol reaction but has minimal impact on diastereoselectivity and enantioselectivity.

The findings presented here provide insight into the synthesis of potent chiral precatalysts for carbon–carbon bond-forming reactions in aqueous media. This work also introduces a new class of lanthanide-based chiral precatalysts for aqueous carbon–carbon bond-forming reactions that is easy to synthesize and offers excellent enantioselectivity and diastereoselectivity. Studies exploring the optimization of other aspects of the ligand design and the application of this new class of chiral ligands and luminescence-decay measurements to the study of other important lanthanide-catalyzed transformations are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Structures of (left) a common gadolinium-containing polyaminopolycarboxylate-based contrast agent and (right) our ligands with two types of water-binding sites labeled.

Figure 2.
Proposed transition state in the asymmetric Mukaiyama aldol reaction using new ligands I–VI.

Scheme 1.
Synthesis of chiral ligands.

Scheme 2.

(Left) Proposed equilibrium leading to **8** being activated for nucleophilic attack by **7**; (Right) equation for equilibrium constant based on q measurements.

Table 1

Relationships among yield, enantioselectivity, and water-coordination number.^a

Ligand	R	yield (%) ^b	Δq	K^c	<i>syn:anti</i> ^d	ee (% <i>, syn</i>) ^d
I ^e	CH ₃	85	-0.62	0.38	26:1	86
I ^f	CH ₃	88	-0.56	0.36	26:1	89
I ^g	CH ₃	92	-0.68	0.40	32:1	93
II	C ₂ H ₅	82	-0.40	0.29	20:1	85
III	<i>n</i> -C ₃ H ₇	83	-0.45	0.31	21:1	86
IV	<i>n</i> -C ₄ H ₉	83	-0.49	0.33	22:1	87
V	<i>i</i> -Pr	20	-0.19	0.16	18:1	80
VI	<i>t</i> -Bu	18	-0.14	0.12	8:1	51
VII	H	8	-0.09	0.08	1:1	0

^a Reaction conditions: To a mixture of ligand (48 mol%) and Eu(OTf)₃ (20 mol%), which was stirred at 50 °C for 2 h then cooled to -25 °C, was added **7** (48.8 μmol, 1.5 equiv) and **8** (32.5 μmol, 1.0 equiv);

^b isolated yields;

^c based on the eq in Scheme 2;

^d determined by chiral HPLC analysis;

^e ligand *syn:anti* = 4:1;

^f ligand *syn:anti* = 5:1;

^g ligand *syn:anti* >99:1, purified by chromatography.

Table 2

Substrate scope of ligand **1**.^a

$ \begin{array}{c} \text{OSi(CH}_3)_3 \\ \\ \text{R}^1-\text{C}=\text{C}-\text{R}^2 \\ \\ \text{R}^3 \end{array} + \begin{array}{c} \text{O} \\ \\ \text{R}^4-\text{C}-\text{H} \end{array} \xrightarrow[\text{-25 } ^\circ\text{C, 168 h}]{\text{[1] (48 mol\%)} + \text{Eu(OTf)}_3 \text{ (20 mol\%)}, \text{EtOH/H}_2\text{O (0.4 mL, 9:1 v/v)} $					
Entry	Enolate	R ⁴	product	yield (%) ^c	syn:anti ^d ee (%), syn ^d
1	7	Ph	9a	92	32:1 93
2	7	<i>p</i> -ClPh	9b	75	21:1 91
3	7	<i>p</i> -CH ₃ Ph	9c	73	24:1 90
4	7	CH ₃ CH=CH ^e	9d	65	21:1 93
5	7	CH ₃	9e	32	22:1 ^f 97 ^g
6	7	CH ₃ (CH ₂) ₅	9f	22	23:1 96
7	7	<i>c</i> -C ₆ H ₁₁	9g	12	49:1 ^f 95 ^g
8	7	(CH ₃) ₃ C	9h	trace	nd ^h
9	R ¹ = C ₂ H ₅ , R ² = CH ₃ , R ³ = H		Ph	61	11:1 84

^aReaction conditions: Unless specified, see footnote *a* in Table 1;

^bligand *syn:anti* >99:1;

^cisolated yields;

^ddetermined by chiral HPLC analysis;

^e*trans*;

^f*anti:syn*;

^g*anti*;

^hnot determined.