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

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Abstract: The development of aqueous methods for generating 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 for the synthesis of chiral β-hydroxy ketones. Furthermore, we have used luminescence-decay measurements to unveil mechanistic information regarding the catalytic reaction via changes in 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%, respectively.

The enantioselective Mukaiyama aldol reaction is one of the most useful protocols for synthesizing optically active β-hydroxy carbonyl moieties, which are subunits of many bioactive compounds.[1] Lanthanide triflate-catalyzed versions of this reaction have gained prominence in the past decade because they are water tolerant and consequently have the benefits associated with not having to rigorously exclude water, including being more environmentally benign and less expensive.[2] However, few examples of enantioselective, lanthanide-catalyzed Mukaiyama aldol reactions in aqueous media exist.[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 with 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, whereas 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 aminocarboxylic acid arms with ethers to yield a hexadentate C_2-symmetric system. The
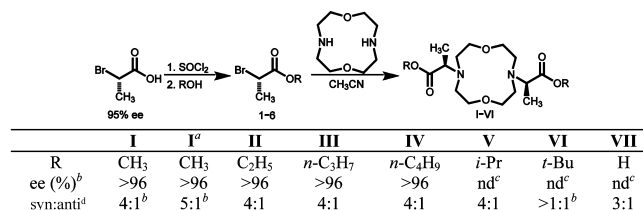
resulting ligands have three sites at which the substrate can coordinate: two "side" positions near the ethers in the macrocycle that are equivalent by symmetry and one "top" site between the two side sites. Our new class of ligands takes advantage of the low degree of conformational flexibility and the water tolerance of lanthanide complexes of macrocyclic polyaminopolycarboxylate-based ligands. Additionally, we stereospecifically introduced methyl groups at 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 for studying structure−activity relationships of our ligands with the goal of improving the enantioselectivity.
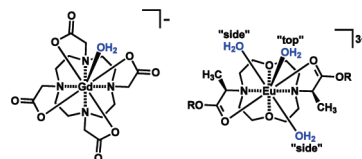
Figure 1. Structures of (left) a common gadolinium-containing polyaminopolycarboxylate-based contrast agent and (right) our ligands with two types of water-binding sites labeled.

The new C_2-symmetric ligands (*R,R*)-**I**−**VI** 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 (*S,S*) enantiomer was observed in preparing ligands **I**−**VI**. Ligand **VII** was synthesized by saponification of **I**. The ligands were complexed with Eu(OTf)$_3$ in situ prior to catalysis. Eu^{3+} was chosen because it is an effective promoter of the activation of aldehydes in aqueous media[2,6,7] and because it enables luminescence-decay measurements.[4,8]

Scheme 1. Synthesis of Chiral Ligands

	I	I[a]	II	III	IV	V	VI	VII
R	CH₃	CH₃	C₂H₅	n-C₃H₇	n-C₄H₉	i-Pr	t-Bu	H
ee (%)[b]	>96	>96	>96	>96	>96	nd[c]	nd[c]	nd[c]
syn:anti[d]	4:1[b]	5:1[b]	4:1	4:1	4:1	4:1	>1:1[b]	3:1

[a] The last step was stirred at 0 °C for 240 h. [b] Determined by chiral high-performance liquid chromatography (HPLC) analysis. [c] Not determined. [d] Determined by ¹H NMR spectroscopy.

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 enantioselectivies (Table 1, ligands **I−IV**), whereas bulky substituents afforded dramatically reduced yields and enantioselectivities (Table 1, ligands **V** and **VI**). The exception to this trend was 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 the 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.

**Table 1.** Relationships among Yield, Enantioselectivity, and Water-Coordination Number[a]

ligand	R	yield (%)[b]	Δq	K^c	syn:anti[d]	ee (%, syn)[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_2H_5	82	−0.40	0.29	20:1	85
III	$n\text{-}C_3H_7$	83	−0.45	0.31	21:1	86
IV	$n\text{-}C_4H_9$	83	−0.49	0.33	22:1	87
V	$i\text{-}Pr$	20	−0.19	0.16	18:1	80
VI	$t\text{-}Bu$	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 and 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 equation 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.

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 2 and 3 prior to the addition of benzaldehyde.[6] This range is expected for a hexadentate ligand. Upon addition of benzaldehyde, a decrease in 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 the equilibrium from the hydrated precatalyst toward coordinated (activated) benzaldehyde (see the equation 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 displacements of 0.40−0.68 water molecules upon addition of benzaldehyde. These Δq values are larger than those observed for unchelated Eu^{3+}.[5] This observation suggests that the ligands induce an interaction with the aldehyde, potentially hydrophobic or nonclassical hydrogen bonding,[9] that causes a favorable binding of aldehyde to the 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 at the top position on the basis of the Δq data in Table 1 (bulky R groups would block this position). When the aldehyde

Scheme 2. (left) Proposed Equilibrium Leading to Activation of **8** for Nucleophilic Attack by **7**; (right) Equation for the Equilibrium Constant Based on q Measurements

$$K = \frac{-\Delta q}{\Delta q + 1}$$
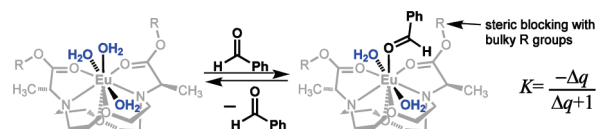
is coordinated in this position, the silyl enol ether can attack only from the side coordination site because the opposite face is blocked by an ester. Benzaldehyde is unlikely to bind with the H and Ph groups reversed from the arrangement in Figure 2 because of unfavorable steric interactions between 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.
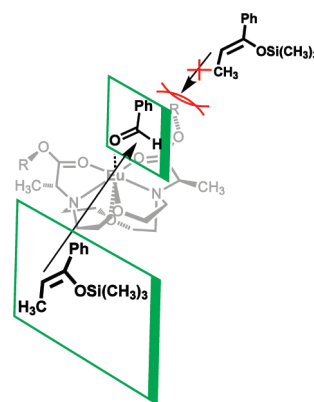
Figure 2. Proposed transition state in the asymmetric Mukaiyama aldol reaction using the new ligands **I−VI**.

Table 2. Substrate Scope of Ligand **I**[a]

entry	enolate	R^4	product	yield (%)[c]	syn:anti[d]	ee (%, syn)[d]
1	**7**	Ph	**9a**	92	32:1	93
2	**7**	$p\text{-}ClPh$	**9b**	75	21:1	91
3	**7**	$p\text{-}CH_3Ph$	**9c**	73	24:1	90
4	**7**	$CH_3CH=CH$[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**	$c\text{-}C_6H_{11}$	**9g**	12	49:1[f]	95[g]
8	**7**	$(CH_3)_3C$	**9h**	trace	nd[h]	nd[h]
9	$R^1 = C_2H_5,$ $R^2 = CH_3, R^3 = H$	Ph	**9i**	61	11:1	84

[a] Reaction conditions were the same as in footnote a of Table 1, unless otherwise specified. [b] Ligand syn:anti > 99:1. [c] Isolated yields. [d] Determined by chiral HPLC analysis. [e] Trans isomer. [f] Anti:syn. [g] Anti. [h] Not determined.

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 substituents had negligible

influence on the stereoselectivity (Table 2, entries 1−3). The results in Table 2 are particularly outstanding because of the stereoselectivity observed with α,β-unsaturated and aliphatic aldehydes (entries 4−8). In addition to changes in the aldehyde, 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 aldehyde increases (Table 2, entries 4−8), the observed yield in a set time decreases. 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 aldehyde influences the efficiency of the Mukaiyama aldol reaction but has minimal impact on the 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.

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

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