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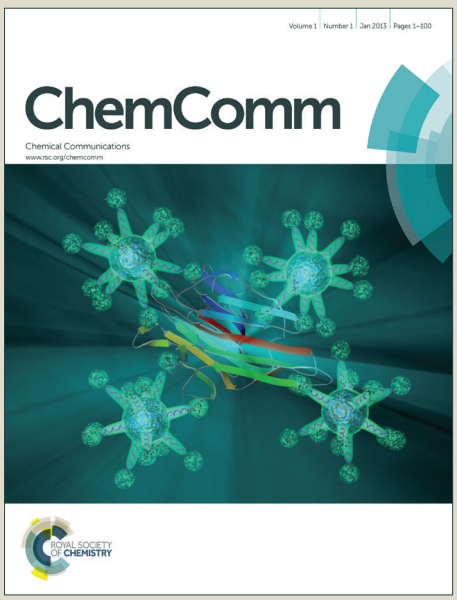

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Trinuclear $Zn_3(OAc)_4$-3,3'-bis(aminoimino)binaphthoxide Complex for Highly Efficient Catalytic Asymmetric Iodolactonization

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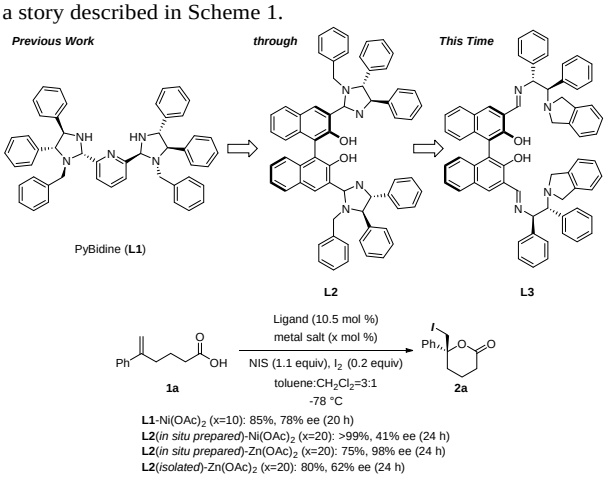
A 3,3'-bis(aminoimino)BINOL ligand was newly designed and synthesized for providing a trinuclear Zn complex upon reaction with $Zn(OAc)_2$. Using the harmony of tri-zinc atoms, 1 mol % $Zn_3(OAc)_4$-3,3'-bis(aminoimino)binaphthoxide catalyzed the asymmetric iodolactonization in up to 99.9% ee.

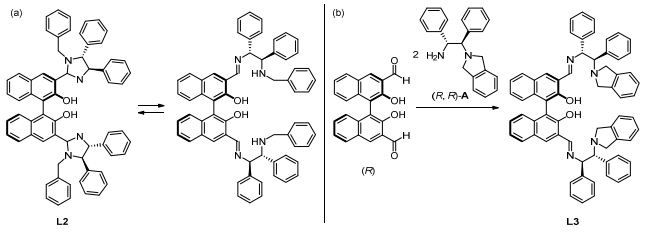
In nature, many metalloenzymes containing multiple metal centers show remarkable catalyst activities, not observed in the non- or monometallic active site. The plural metal ions in the multinuclear metalloenzymes act cooperatively to garner the full activities. For the example, phosphatidylcholine-preferring phospholipase C from Bacillus cereus (PC-PLCBc) catalyzes the hydrolysis of phospholipids. The active site of PC-PLCBc contains three Zn^{2+} ions, wherein the plural zinc atoms are bridged by Asp122 and a water (or hydroxide) molecule.[1] Employing the multi-nuclear cooperative effects becomes also an important concept for the design of artificial "catalyst",[2] after pioneering works on the development of lanthanide-consisting heterobimetallic asymmetric catalysts.[3] While the bimetallic system in asymmetric catalyses has been typically produced using a force of a self-assembly, the rational design of tri or more multinuclear complex is still difficult even in the cutting-edge chemistry. Here, we report a designer *multinuclear* metal-catalyst for the catalyzed asymmetric iodolactonization.

Iodolactonization,[4-10] a type of halolactonization,[11] represents a powerful synthetic tool for generating iodine-functionalized cyclic compounds in a single reaction. The resulting iodolactones are both versatile and useful, and have applications as synthetic intermediates in the total synthesis of natural products as well as in the production of biologically significant pharmaceutical compounds and agricultural chemicals. Jacobsen pioneered an organo-catalytic version of a useful asymmetric iodolactonization reaction using an urea catalyst.[4] More recently, Johnston reported an asymmetric iodolactonization catalyzed by a bis(amidine) (BAM)-based Brønsted acid.[5] For the limited examples of the metal-catalyzed asymmetric iodolactonization, Gao reported the use of a mononuclear Co-salen complex as a Lewis acid catalyst for asymmetric iodolactonization.[8,9] We have also reported an asymmetric iodolactonization strategy using a newly developed PyBidine(**L1**)-$Ni(OAc)_2$ catalyst.[10] The designer chiral ligands is renovated for the *multinuclear* metal-catalyst in the asymmetric iodolactonization through a story described in Scheme 1.



Scheme 1. Odyssey of chiral ligand development of multinuclear metal catalyst for asymmetric iodolactonization, and primitive results on asymmetric iodolactonization using **L1** and **L2**.

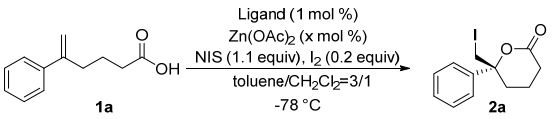
Based on the mononuclear **L1**-Ni(OAc)$_2$ catalyst, the imidazolidine ligand **L2**, with a chiral BINOL-backbone was designed for dinuclear metal complex. The 3,3'-bis(imidazolidine)BINOL **L2**, prepared *in situ* by condensation of monobenzyl (*R*,*R*)-diphenylethylenediamine with (*R*)-3,3'-formylbinaphthol, was applied to the complex formation using 2 equiv of metal acetate. In the asymmetric iodolactonization of 5-phenylhex-5-enoic acid (**1a**), although the **L2**-Ni(OAc)$_2$ 1:2 complex gave iodolactone **2a** with 41% ee, the **L2**-Zn(OAc)$_2$ 1:2 complex drastically improved the optical yield of **2a** to 98% ee. The diasteromeric 3,3'-bis(imidazolidine)BINOL, derived from (*S*,*S*)-diphenylethylenediamine with (*R*)-3,3'-formylbinaphthol, gave 92% yield of **2a** with 85% ee. The successful development of an efficient asymmetric catalyst encouraged further study to determine the structure of the **L2**-Zn(OAc)$_2$ complex. The ^{1}H-NMR study revealed that both **L2** and the **L2**-Zn(OAc)$_2$ 1:2 complex existed as complex mixtures. The isolation of pure **L2** required great effort, but using the 1:2 Zn(OAc)$_2$ catalyst with isolated **L2** gave **2a** with a significantly lower selectivity of 62% ee compared to that obtained using the catalyst generated *in situ*. The imidazolidine ring of **L2** prepared *in situ* was hypothesized to be in equilibrium with the opened aminoimino-form as shown in Scheme 2a, meaning that the 3,3'-bis(aminoimino)BINOL is a promising candidate for providing an effective Zn(OAc)$_2$ catalyst.



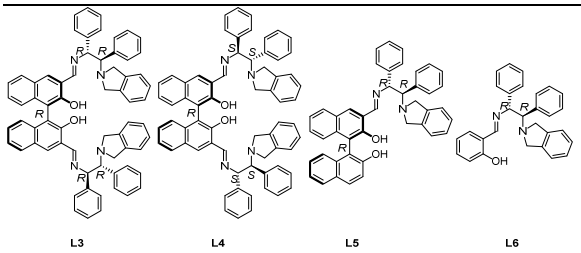
Scheme 2. (a) Equilibrium of **L2** between the imidazolidine and aminoimino forms. (b) Design and synthesis of 3,3'-bis(tert-aminoimino)BINOL ligand (**L3**).

To eliminate the cyclized imidazolidine from the equilibrium, the 3,3'-bis(*tert*-aminoimino)BINOL ligand (**L3**) in Scheme 2b was redesigned. The newly designed **L3** can capture two or three metals in the flexible bis(aminoimino)binaphthol pocket.[14] Reaction of (*R*)-3,3'-formylbinaphthol and (1*R*,2*R*)-2-(isoindolin-2-yl)-1,2-diphenylethan-1-amine (**A**)[15] in ethanol proceeded smoothly at 80 °C to form the imine, and a cold ethanol wash of the resulting precipitate gave **L3** as the sole product.[16] The effect of changing the ratio of Zn(OAc)$_2$ to **L3** on catalyst performance was examined in Table 1. With an **L3**:Zn(OAc)$_2$ ratio of 1:1 to 1:3, the iodolactone **2a** was produced with 99% ee (entries 1-3). However, stopping the reaction within 2 h revealed that a 1:1 **L3**:Zn(OAc)$_2$ ratio resulted in a slower reaction than those using 1:2 or 1:3 ratios. The catalyst activity of the several analogs was also investigated in Table 1. The diastereomer of **L3** (**L4**) gave only 68% ee of **2a** (entry 4). When one aminoimino functional group was eliminated from **L3**, the **L5**-Zn(OAc)$_2$ catalyst yielded a product with 89% ee, although catalytic activity was significantly reduced (entry 5). Removal of the axial chirality of the binaphthyl skeleton resulted in a trace amount of **2a** (entry 6). These results suggest that at least one set of zinc atoms existing at appropriate position harmonizes cooperatively to produce iodolactones in a highly enantioselective manner.

Table 1. Effect of the **L3**:Zn(OAc)$_2$ ratio and the analogs on catalyst activity.

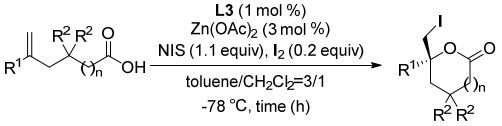


entry	Ligand	X (mol %)	Time (h)	Yield (%)	ee (%)
1	**L3**	1	2	19	99
2	**L3**	2	2	64	99.6
3	**L3**	3	2	69	99.6
4	**L4**	3	2	9	68
5	**L5**	2	24	34	89
6	**L6**	1	24	trace	-



Results of investigations into the scope and generalization of the catalytic asymmetric iodolactonization are shown in Table 2.

Table 2. Catalytic asymmetric iodolactonization using **L3**-Zn$_3$(OAc)$_4$ catalyst.



entry	R^1	R^2	n	Time (h)	Yield (%)	ee (%)
1	C_6H_5	H	1	20	>99	99.5
2[a)]	C_6H_5	H	1	20	>99	98
3	*p*-BrC_6H_4	H	1	6	>99	99.8
4	*p*-ClC_6H_4	H	1	16	>99	99.8
5	*p*-FC_6H_4	H	1	15	>99	94
6	*p*-$CF_3C_6H_4$	H	1	12	>99	99.9
7	*p*-MeC_6H_4	H	1	17.5	>99	93
8	*m*-MeC_6H_4	H	1	8	>99	99.7
9[b)]	*o*-MeC_6H_4	H	1	18	>99	99.4
10	*p*-$MeOC_6H_4$	H	1	12	>99	82
11[c)]	C_6H_5	H	0	9	96	87
12	*c*-C_6H_{11}	H	1	4	>99	99.3
13	Me	H	1	20	92	94
14	C_6H_5	Me	1	24	74	99

a) 0.1 mol % catalyst were used. b) 5 mol % catalyst were used. c) solvent was toluene/CH_2Cl_2 = 4/1.

Using 1 mol% **L3**-Zn$_3$(OAc)$_4$ catalyst, a variety of 5-arylhex-5-enoic acid substrates were converted quantitatively to the corresponding chiral gluconolactones with excellent enantioselectivity. For example, the *p*-trifluoromethyl-substituted compound was obtained in 99.9% ee (entry 6). The relatively less reactive substrate having an *o*-substituent on the benzene ring was used with 5 mol% catalyst to give the product in >99% yield with 99.4% ee (entry 9). The reaction of 4-phenylpent-4-enoic acid gave the γ-butyrolactone with 87% ee (entry 11). 5-Cyclohexylhex-5-enoic acid also was transformed successfully with 99.3% ee (entry 12). It should be emphasized only 0.1 mol % **L3**-Zn$_3$(OAc)$_4$ catalyst gave 98% ee of **2a** with quantitative yield (entry 2).

For accessing the catalyst structure of **L3**-Zn(OAc)$_2$ complex, the ESI-MS analysis of the catalyst solution suggested the presence of a multi-nuclear zinc complex (Figure 1). An ion peak at *m*/*z*=1028.3031 attributed to [**L3**$_2$-Zn$_3$]$^{2+}$ was observed even by mixing **L3** and Zn(OAc)$_2$ in a 1:1 ratio. When **L3** and Zn(OAc)$_2$ were mixed in a 1:3 ratio, ESI-MS analysis provided a new peak at *m*/*z*=1301.2389, which suggested the formation of a trinuclear zinc complex with **L3**.

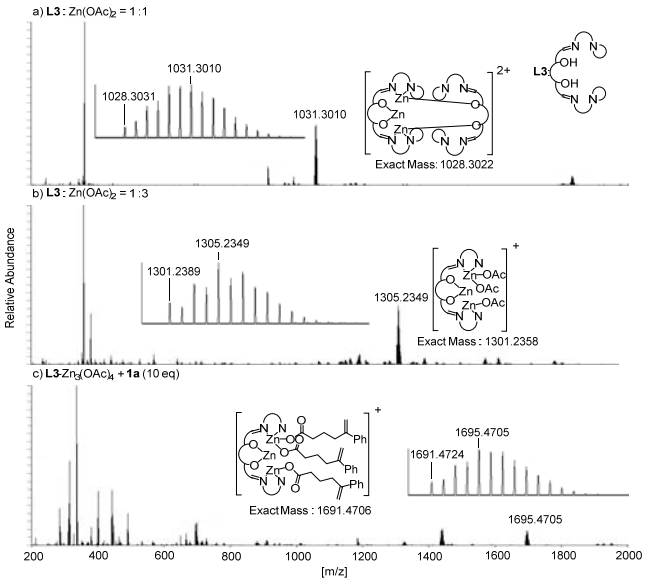


Figure 1. ESI-MS spectra of (a) **L3**+Zn(OAc)$_2$ (1:1), (b) **L3**+Zn(OAc)$_2$ (1:3), and (c) **L3**-Zn$_3$(OAc)$_4$ + **1a** (1:10).

A single crystal was obtained from the reaction of the 1:3 mixture of **L3** and Zn(OAc)$_2$ in methanol, and X-ray crystallographic analysis revealed the structure of the complex to be trinuclear Zn$_3$(OAc)$_4$-3,3'-bis(aminoimino)binaphthoxide as shown in Figure 2.

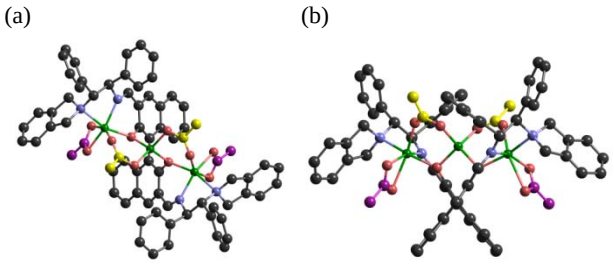


Figure 2. X-ray crystallographic analysis of trinuclear Zn$_3$(OAc)$_4$-3,3'-bis(aminoimino)binaphthoxide complex (**L3**-Zn$_3$(OAc)$_4$): (a) side view and (b) front view of the complex. Yellow and purple colored atoms are coordinated acetyl carbons. Hydrogen atoms and solvent molecules were omitted for clarity.

In **L3**-Zn$_3$(OAc)$_4$, the two end zinc atoms make the complex hexa-coordinated, and the central zinc atom is part of a tetrahedral coordination sphere. For complex formation, one Zn(OAc)$_2$ reacted with **L3** to give the central zinc binaphthoxide, and the two remaining Zn(OAc)$_2$ were coordinated, one at each end, by the aminoimino functionality of **L3**. Alternatively, both end zinc atoms form a mixed acetoxy-binaphthoxide, and the central zinc remained as Zn(OAc)$_2$. Because X-ray crystallography and DFT calculations of **L3**-Zn$_3$(OAc)$_4$ suggest σ-bond characteristics of the central zinc with phenolic oxygens, complex formation could be explained *via* zinc-binaphenoxide [Zn-O: 1.949(3) or 1.962(3) Å]. In the **L3**-Zn$_3$(OAc)$_4$ complex, each of the acetoxy anions bridges the central zinc and the end zinc atoms, which restricts the conformation of the **L3**-Zn$_3$ complex. The isolated crystalline Zn$_3$(OAc)$_4$-3,3'-bis(aminoimino)binaphthoxide produced a clean ^{1}H-NMR spectrum at -40 °C (Figure 3) and 1 mol % catalyst promoted the asymmetric iodolactonization to give **2a** with 99% ee.

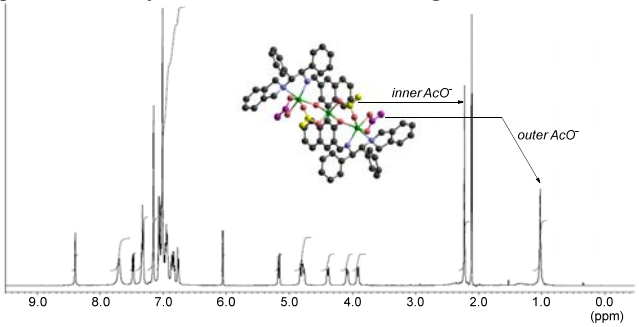


Figure 3. ^{1}H-NMR spectrum of **L3**-Zn$_3$(OAc)$_4$ complex in toluene-d$_8$ at -40 °C.

Regarding the catalyst role of **L3**-Zn$_3$(OAc)$_4$, after mixing **L3**-Zn$_3$(OAc)$_4$ and 10 equiv of **1a**, all acetoxy anions of **L3**-Zn$_3$(OAc)$_4$ were replaced with **1a** to give the ion peak at m/z=1691.4724 corresponding to [**L3**-Zn$_3$(CO$_2$(CH$_2$)$_3$C(CH$_2$)Ph)$_3$]$^+$ (Figure 1c). This exchange suggests that the zinc-carboxylate of **1a** is generated by the **L3**-Zn$_3$(OAc)$_4$ catalyst as a vital intermediate in the highly enantioselective iodolactonization reaction. However, two types of acetoxy anions were observed in the ^{1}H-NMR spectrum of **L3**-Zn$_3$(OAc)$_4$, at 1.02 and 2.22 ppm. The up-field peak was assigned by the DFT-GIAO calculation to the outer acetoxy anions indicated in purple. Because the peak at 1.02 ppm becomes broader than the peak at 2.22 ppm, the outer acetoxy anions would smoothly accept the exchange with substrate **1a**. Based on these experimental analyses on the interaction **L3**-Zn$_3$(OAc)$_4$ with **1a**, a plausible transition state for the **L3**-Zn$_3$(OAc)$_4$-catalyzed iodolactonization is proposed by the DFT computed molecular modeling (Figure 4) [17].

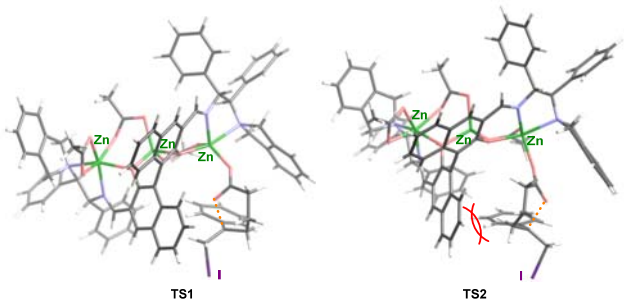


Figure 4. Plausible transition state of the **L3**-Zn$_3$(OAc)$_4$-catalyzed iodolactonization: **TS1** for (*R*)-iodolactone **2a**, **TS2** for (*S*)-**2a**.

The zinc-carboxylate of **1a** is generated on the outer zinc atom. In the cyclic transition state of iodolactonization, the benzene ring of **1a** keeps away from the naphthyl ring of **L3** to avoid the steric repulsion observed in **TS2** (red curves in Figure 4). From the **TS1** depicted in Figure 4, the stereoselective formation of (*R*)-iodolactone **2a** is well explained. Because plural zinc atoms are important for getting high catalyst activity as shown in Table 1, the central zinc-atom would also contribute to enhance the zinc-carboxylate formation of **1a** and/or to accelerate the nucleophilic cyclization of the zinc-carboxylate.

In conclusion, using a newly designed 3,3'-bis(aminoimino)BINOL ligand, the trinuclear Zn3$(OAc)_4$-3,3'-bis(aminoimino)binaphthoxide complex (**L3**-$Zn_3(OAc)_4$) was prepared. The harmony of tri-Zn centers in **L3**-$Zn_3(OAc)_4$ showed outstanding catalytic activity in the iodolactonization reaction to yield products in quantitative yield with excellent enantioselectivity.

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17. The transition structure was partially optimized with the B3LYP method using 631LAN basis set consisting of LANL2DZ for Zn and 6-31G* for the rest. The **L3**-$Zn_3(OAc)_3$ moiety was only fully optimized while the iodolactone **2a** was frozen at the transition structure model of the Zn cation catalyzed iodolactonization.

