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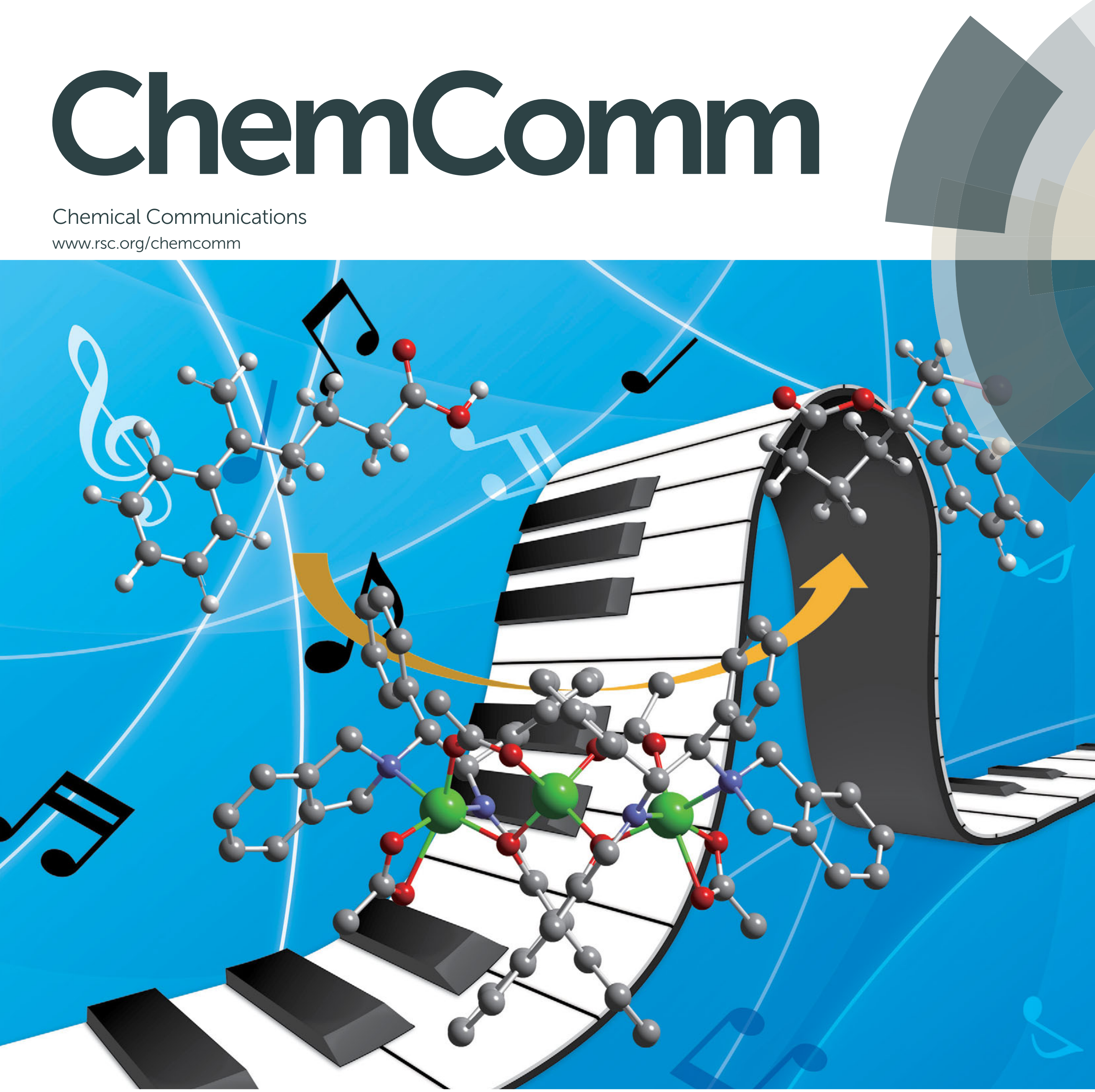

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A trinuclear $Zn_3(OAc)_4$-3,3′-bis(aminoimino)-binaphthoxide complex for highly efficient catalytic asymmetric iodolactonization†

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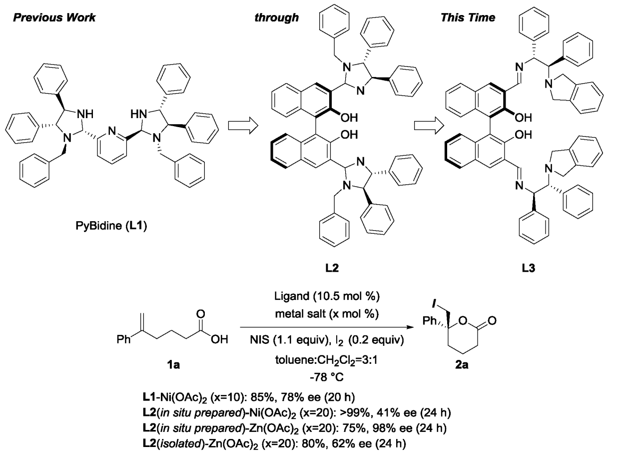
A 3,3′-bis(aminoimino)BINOL ligand was newly designed and synthesized for the formation of a trinuclear Zn complex upon reaction with $Zn(OAc)_2$. Using the harmony of the tri-zinc atoms, 1 mol% $Zn_3(OAc)_4$-3,3′-bis(aminoimino)binaphthoxide catalyzed asymmetric iodolactonization in up to 99.9% ee.

In nature, many metalloenzymes containing multiple metal centers show remarkable catalytic activity not observed in non- or mono-metallic active sites. The multiple metal ions in the multinuclear metalloenzymes act cooperatively to produce maximum activity. For 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, and the multiple zinc atoms are bridged by Asp122 and a water (or hydroxide) molecule.[1] Employing multi-nuclear cooperative effects also becomes an important concept for the design of artificial "catalysts",[2] after pioneering works on the development of lanthanide-containing heterobimetallic asymmetric catalysts.[3] While the bimetallic system in asymmetric catalyses has typically been produced using the force of self-assembly, the rational design of tri- or higher multinuclear complexes is still difficult even in cutting-edge chemistry. Here, we report a designer *multinuclear* metal catalyst for catalyzed asymmetric iodolactonization.

Iodolactonization,[4–10] a type of halolactonization,[11–13] 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] Within the limited examples of 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 are prepared to form a *multinuclear* metal catalyst for use in asymmetric iodolactonization, through the story described in Scheme 1.

Based on the mononuclear **L1**–Ni$(OAc)_2$ catalyst, the imidazolidine ligand **L2**, with a chiral BINOL-backbone, was designed for a dinuclear metal complex. 3,3′-bis(imidazolidine)BINOL **L2**, prepared *in situ* by the condensation of monobenzyl (*R*,*R*)-diphenylethylenediamine with (*R*)-3,3′-formylbinaphthol, was applied to complex formation using 2 equiv. of metal acetate. In the asymmetric iodolactonization of



Scheme 1 The development of the chiral ligand of the multinuclear metal catalyst for use in asymmetric iodolactonization, and preliminary results on asymmetric iodolactonization using **L1** and **L2**.

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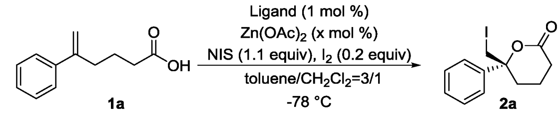
5-phenylhex-5-enoic acid (**1a**), although the **L2**–Ni(OAc)$_2$ 1 : 2 complex gave iodolactone **2a** with 41% ee, the **L2**–Zn(OAc)$_2$ 1 : 2 complex drastically improved the optical yield of **2a** to 98% ee. The diastereomeric 3,3′-bis(imidazolidine)BINOL, derived from (*S*,*S*)-diphenylethylenediamine with (*R*)-3,3′-formylbinaphthol, gave a 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.

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 using 1 : 2 or 1 : 3 ratios. The catalytic activity of several analogs was also investigated in Table 1. The diastereomer of **L3** (**L4**) only gave 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 the appropriate position, harmonizes cooperatively to produce iodolactones in a highly enantioselective manner.

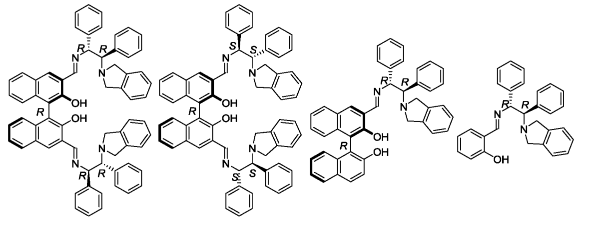
Results of investigations into the scope and generalization of the catalytic asymmetric iodolactonization are shown in Table 2.

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 was also transformed successfully with 99.3% ee (entry 12). It should be emphasized that only 0.1 mol% **L3**–Zn$_3$(OAc)$_4$ catalyst gave 98% ee of **2a** with a quantitative yield (entry 2).

Table 1 The effect of the **L3** : Zn(OAc)$_2$ ratio and the analogs on catalytic activity

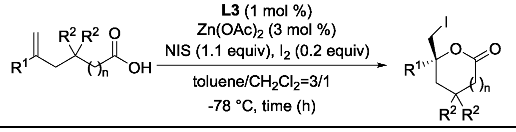


Entry	Ligand	*X* (mol%)	Time (h)	Yield (%)	ee (%)
1	**L3**	1	2	19	99
2	**L3**	2	2	64	99.6
3	**L3**	3	2	69	99.6
4	**L4**	3	2	9	68
5	**L5**	2	24	34	89
6	**L6**	1	24	Trace	—



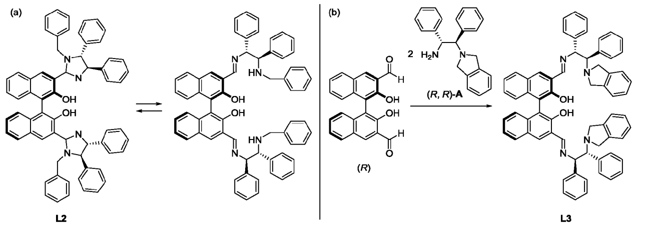
L3 L4 L5 L6

Table 2 Results for catalytic asymmetric iodolactonization using a **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 was used. [b] 5 mol% catalyst was used. [c] The solvent was toluene : CH_2Cl_2 = 4 : 1.



L2 L3

Scheme 2 (a) The equilibrium of **L2** between the imidazolidine and aminoimino forms. (b) The design and synthesis of the 3,3′-bis(*tert*-aminoimino)BINOL ligand (**L3**).

For accessing the catalytic structure of the **L3**–Zn(OAc)$_2$ complex, ESI-MS analysis of the catalyst solution suggested the presence of a multi-nuclear zinc complex (Fig. 1). An ion peak at *m*/*z* = 1028.3031 attributed to [$L3_2$–Zn_3]$^{2+}$ was observed,

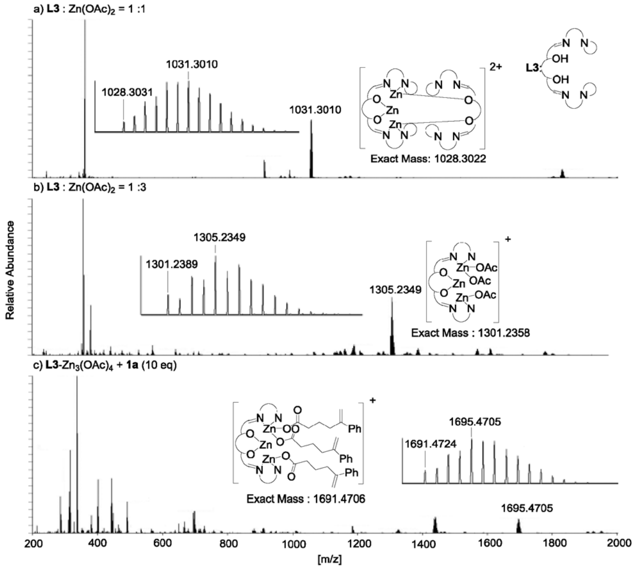


Fig. 1 ESI-MS spectra of (a) **L3** + $Zn(OAc)_2$ (1 : 1), (b) **L3** + $Zn(OAc)_2$ (1 : 3), and (c) **L3**–$Zn_3(OAc)_4$ + **1a** (1 : 10).

even when 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 showed a new peak at m/z = 1301.2389, which suggested the formation of a trinuclear zinc complex with **L3**.

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 Fig. 2.

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 formed 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 (Fig. 3) and 1 mol% catalyst promoted the asymmetric iodolactonization to give **2a** with 99% ee.

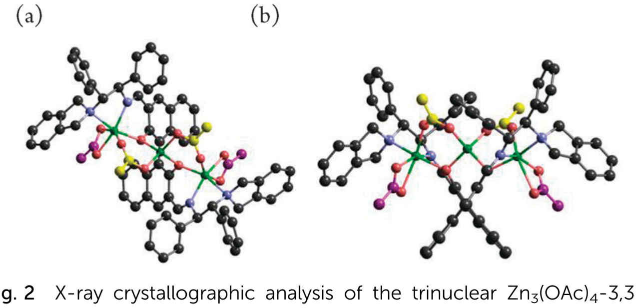


Fig. 2 X-ray crystallographic analysis of the trinuclear $Zn_3(OAc)_4$-3,3′-bis(aminoimino)binaphthoxide complex (**L3**–$Zn_3(OAc)_4$): (a) the side view, and (b) the front view of the complex. Yellow and purple colored atoms are coordinated acetyl carbons. Hydrogen atoms and solvent molecules are omitted for clarity.

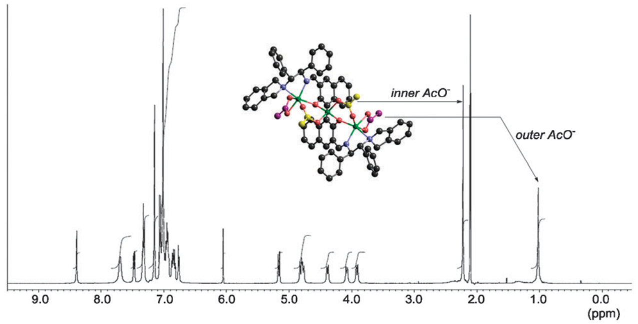


Fig. 3 ^{1}H-NMR spectrum of the **L3**–$Zn_3(OAc)_4$ complex in toluene-d_8 at −40 °C.

Regarding the catalytic 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 $[\mathbf{L3}\text{–}Zn_3(CO_2(CH_2)_3C(CH_2)Ph)_3]^+$ (Fig. 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 of **L3**–$Zn_3(OAc)_4$ with **1a**, a plausible transition state for the **L3**–$Zn_3(OAc)_4$-catalyzed iodolactonization is proposed by DFT computed molecular modeling (Fig. 4).[17]

The zinc-carboxylate of **1a** is generated on the outer zinc atom. In the cyclic transition state of the iodolactonization, the benzene ring of **1a** keeps away from the naphthyl ring of **L3** to avoid the steric repulsion observed in **TS2** (the red curves in Fig. 4). From the **TS1** depicted in Fig. 4, the stereoselective formation of (*R*)-iodolactone **2a** is explained well. Because multiple zinc atoms are important for getting high catalytic

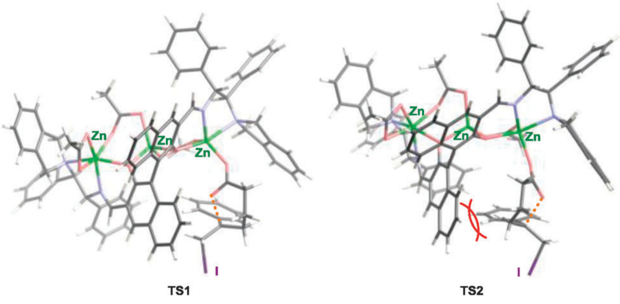


Fig. 4 A plausible transition state of **L3**–$Zn_3(OAc)_4$-catalyzed iodolactonization: **TS1** for (*R*)-iodolactone **2a**, **TS2** for (*S*)-**2a**.

activity as shown in Table 1, the central zinc atom would also contribute to enhancing the zinc-carboxylate formation of **1a** and/or to accelerating the nucleophilic cyclization of the zinc-carboxylate.

In conclusion, using a newly designed 3,3′-bis(aminoimino)-BINOL ligand, the trinuclear $Zn_3(OAc)_4$-3,3′-bis(aminoimino)-binaphthoxide complex (**L3**–$Zn_3(OAc)_4$) was prepared. The harmony of the tri-Zn centers in **L3**–$Zn_3(OAc)_4$ showed outstanding catalytic activity for the iodolactonization reaction to yield products in quantitative yields with excellent enantioselectivity.[18]

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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.

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