

## Oligometallic Template Strategy for Ring-Closing Olefin Metathesis: Highly Cis- and Trans-Selective Synthesis of a 32-Membered Macrocylic Tetraoxime

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An oligometallic template effect was observed on the cis/trans selectivity of a 32-membered macrocyclic tetraoxime in ring-closing olefin metathesis of an acyclic diallyl derivative  $H_4L$ ; the metathesis of heterotrinnuclear complex  $LZn_2M$  ( $M = Ca^{2+}, La^{3+}$ ) afforded the cis isomer, whereas uncomplexed  $H_4L$  gave the trans isomer.

Recently, ring-closing olefin metathesis by Grubbs catalysts<sup>1</sup> has been frequently utilized for the synthesis of cyclic compounds. In the synthesis of five-, six-, and seven-membered ring compounds, the *cis*-olefin is known to be exclusively formed.<sup>2</sup> Olefin metathesis is also useful for the synthesis of medium- or large-sized cyclic compounds,<sup>3</sup> including a number of interesting interlocked compounds containing a macrocyclic component.<sup>4</sup> However, such macrocyclization generally gives a mixture of *cis* and *trans* isomers that are difficult to separate. There are a few reports of selectivity in the synthesis of *cis* or *trans* isomers changing with the reaction conditions<sup>5</sup> because it is usually under thermodynamic control, meaning that the *trans* isomer is preferred.<sup>5,6</sup> Nevertheless, it is important to develop a strategy to selectively obtain both *cis* and *trans* isomers, especially of macrocyclic ligands, because they are expected to show very different complexation ability.<sup>7</sup> In general, macrocyclization proceeds efficiently in the presence of an appropriate template metal ion,<sup>8</sup> which restricts orientation of the

reactants or reaction intermediates in such a way that the final step of the macrocyclization is entropically favorable.<sup>9</sup> Such a restriction of the reacting olefin moieties may cause not only preferential intramolecular cyclization but also *cis*/*trans*-selective metathesis.<sup>5,9a</sup>

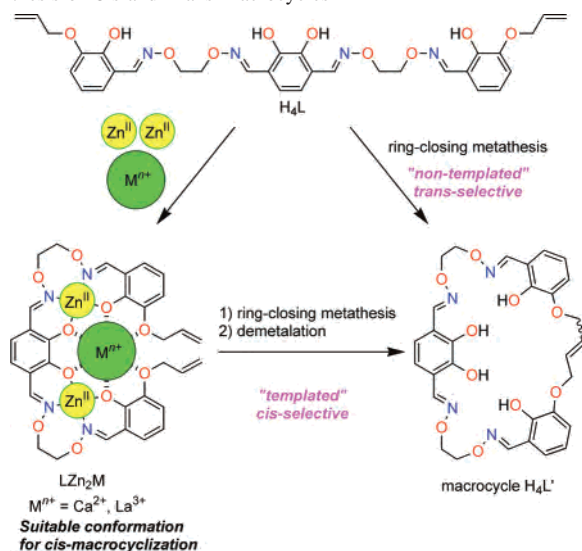
We have recently reported that a linear tetraoxime ligand forms C-shaped homo- and heterotrinnuclear complexes on complexation with appropriate metal ions.<sup>10</sup> If olefinic units are introduced into the termini of the C-shaped complex, the spatial arrangement and the distance of the units should be suitable for cyclization. Thus, the metal ions are expected to act as an oligometallic template<sup>11</sup> to give the *cis* isomer because the olefin metathesis results in the ring-closure reaction of a seven-membered atomic array including the central metal. Here, we report the synthesis of the allylated tetraoxime ligand  $H_4L$ , which was converted to the corresponding  $LZn_2M$  ( $M = Ca^{2+}, La^{3+}$ ) complexes with a helical conformation suitable for the *cis* macrocyclization. The ring-closing metathesis of  $H_4L$  and  $LZn_2M$  selectively afforded *trans* and *cis* isomers, respectively, of a 32-membered macrocyclic tetraoxime (Scheme 1).

The allylated ligand  $H_4L$  was prepared by the reaction of 1,2-bis(aminooxy)ethane<sup>12</sup> with 3-(allyloxy)-2-hydroxybenzaldehyde,<sup>13</sup> followed by reaction with 2,3-dihydroxyben-

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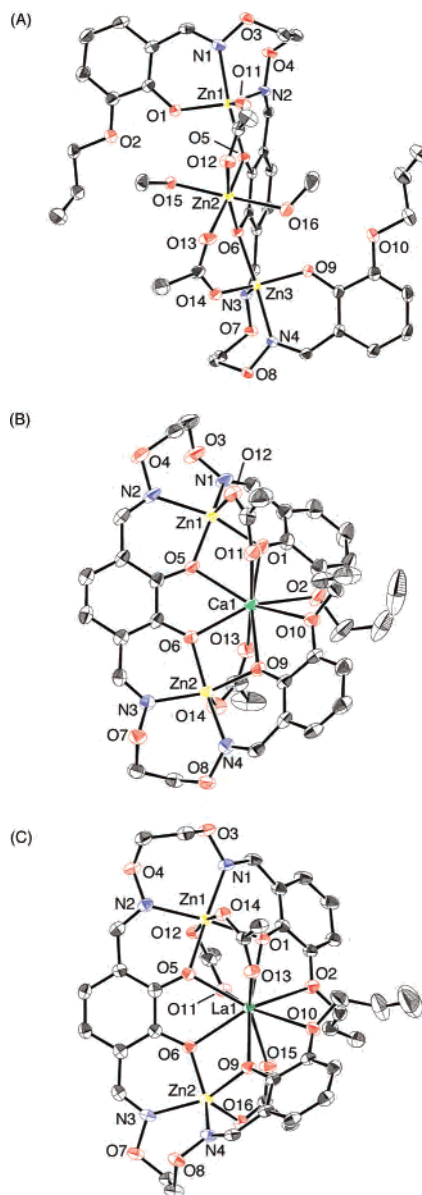
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**Scheme 1.** Oligometallic Template Strategy for the Selective Synthesis of Cis and Trans Macrocycles

zene-1,4-dicarbaldehyde,<sup>10e</sup> using a procedure analogous to that for the methoxy derivative.<sup>10e</sup> The complexation of  $H_4L$  with zinc(II) acetate (3 equiv) gave homotrimeric complex  $[LZn_3(OAc)_2(MeOH)_2]$  in 73% yield. Heterotrimeric complexes  $[LZn_2Ca(OAc)_2]$  and  $[LZn_2La(OAc)_3]$  were prepared by the reaction of  $H_4L$  with zinc(II) acetate and calcium or lanthanum(III) acetates, respectively, in 80 and 88% yields. The structures of these complexes were determined by X-ray crystallography (Figure 1).<sup>14–16</sup> The homotrimeric complex  $[LZn_3(OAc)_2(MeOH)_2]$  adopts an S-shaped conformation in which the two terminal allyl groups point in opposite directions (the distance between two allylic carbons is 12.31 Å). Neither allyloxy (O2 and O10) nor phenoxo groups (O1 and O9) coordinate to the  $Zn^{2+}$  ion at the central O<sub>6</sub> site. In contrast, heterotrimeric complexes  $[LZn_2Ca(OAc)_2]$  and  $[LZn_2La(OAc)_3]$  adopt a C-shaped helical conformation in which the distances between the two allylic carbons are 4.06 and 3.91 Å, respectively. Coordination of the allyloxy groups to the  $Ca^{2+}$  or  $La^{3+}$  ion at the central O<sub>6</sub> site fixes the two allyl groups close to each other.

- (14) Crystallographic data for  $[LZn_3(OAc)_2(MeOH)_2] \cdot CHCl_3$ :  $C_{39}H_{45}Cl_3N_4O_{16}Zn_3$  (1128.25), yellow crystal ( $0.4 \times 0.25 \times 0.2$  mm<sup>3</sup>) triclinic,  $P1$ ,  $a = 13.350(6)$  Å,  $b = 14.073(4)$  Å,  $c = 14.187(4)$  Å,  $\alpha = 83.293(12)^\circ$ ,  $\beta = 68.602(15)^\circ$ ,  $\gamma = 70.833(14)^\circ$ ,  $V = 2344.0(14)$  Å<sup>3</sup>,  $Z = 2$ ,  $T = 120$  K,  $D_{calc} = 1.599$  g cm<sup>-3</sup>,  $\mu(Mo K\alpha) = 1.765$  mm<sup>-1</sup>,  $F(000) = 1152$ , 22 345 reflections measured (Rigaku R-Axis Rapid), 10 150 unique ( $R_{int} = 0.0313$ ),  $R1 = 0.0523$  [ $I > 2\sigma(I)$ ],  $wR2 = 0.1666$  (all data).<sup>21</sup>
- (15) Crystallographic data for  $[LZn_2Ca(OAc)_2] \cdot 0.5CHCl_3 \cdot 0.75H_2O$ :  $C_{36.5}H_{38}CaCl_{1.5}N_4O_{14.75}Zn_2$  (992.70), orange crystal ( $0.25 \times 0.25 \times 0.2$  mm<sup>3</sup>), triclinic,  $P1$ ,  $a = 13.791(3)$  Å,  $b = 15.788(4)$  Å,  $c = 20.439(4)$  Å,  $\alpha = 84.018(10)^\circ$ ,  $\beta = 81.632(10)^\circ$ ,  $\gamma = 73.877(11)^\circ$ ,  $V = 4220.1(17)$  Å<sup>3</sup>,  $Z = 4$ ,  $T = 120$  K,  $D_{calc} = 1.562$  g cm<sup>-3</sup>,  $\mu(Mo K\alpha) = 1.424$  mm<sup>-1</sup>,  $F(000) = 2034$ , 40 444 reflections measured (Rigaku R-Axis Rapid), 18 349 unique ( $R_{int} = 0.0676$ ),  $R1 = 0.0632$  [ $I > 2\sigma(I)$ ],  $wR2 = 0.1809$  (all data).<sup>21</sup>
- (16) Crystallographic data for  $[LZn_2La(OAc)_3] \cdot CHCl_3$ :  $C_{39}H_{40}Cl_3LaN_4O_{16}Zn_2$  (1196.75), yellow crystal ( $0.4 \times 0.2 \times 0.2$  mm<sup>3</sup>), triclinic,  $P1$ ,  $a = 12.836(5)$  Å,  $b = 13.302(5)$  Å,  $c = 14.564(5)$  Å,  $\alpha = 115.026(14)^\circ$ ,  $\beta = 94.160(17)^\circ$ ,  $\gamma = 93.458(17)^\circ$ ,  $V = 2236.0(14)$  Å<sup>3</sup>,  $Z = 2$ ,  $T = 120$  K,  $D_{calc} = 1.778$  g cm<sup>-3</sup>,  $\mu(Mo K\alpha) = 2.256$  mm<sup>-1</sup>,  $F(000) = 1196$ , 21 394 reflections measured (Rigaku R-Axis Rapid), 9716 unique ( $R_{int} = 0.0297$ ),  $R1 = 0.0472$  [ $I > 2\sigma(I)$ ],  $wR2 = 0.1431$  (all data).<sup>21</sup>

**Figure 1.** Crystal structures of (A)  $[LZn_3(OAc)_2(MeOH)_2]$ , (B)  $[LZn_2Ca(OAc)_2]$ , and (C)  $[LZn_2La(OAc)_3]$ .

Olefin metathesis of free ligand  $H_4L$  in dichloromethane (1 mM) using a first-generation Grubbs catalyst afforded the corresponding monomeric macrocycle  $H_4L'$  in addition to a small amount of oligomeric products. The crude product contained cis and trans isomers (7:93) of  $H_4L'$  (Table 1), from which pure *trans*- $H_4L'$  was obtained in 68% yield by recrystallization. For  $H_4L$ , the cis/trans ratio did not depend significantly on the catalysts (*cf.* 6:94 for second generation). On the other hand, ring-closing metathesis of the metal complexes of  $H_4L$  proceeded only with the catalyst of second generation. The product of the metathesis reaction of  $[LZn_3(OAc)_2(MeOH)_2]$  in tetrahydrofuran (THF) was analyzed after demetalation.<sup>17</sup> Macrocycle  $H_4L'$  was obtained through the intramolecular cyclization, although the two allyl groups are apart from each other in the crystal structure of  $[LZn_3(OAc)_2(MeOH)_2]$ . The bound zinc centers are probably sufficiently

- (17) The zinc(II) complex of the cyclic product  $H_4L'$  was observed in the mass spectrum of the reaction mixture before demetalation.

**Table 1.** Ring-Closing Metathesis of H<sub>4</sub>L and Its Metal Complexes<sup>a</sup>

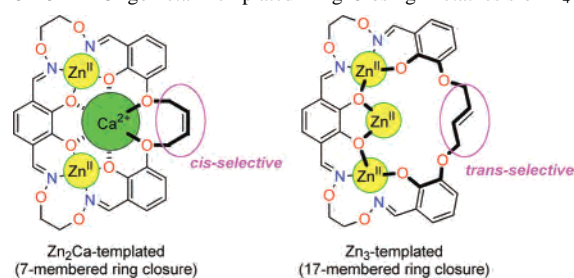
substrate	yield (%)				H <sub>4</sub> L recovery
	H <sub>4</sub> L'	cis/trans <sup>b</sup>	A	B	
H <sub>4</sub> L <sup>c</sup>	94 <sup>d</sup> [68, trans]	7:93	0	0	0
[LZn <sub>3</sub> (OAc) <sub>2</sub> (MeOH) <sub>2</sub> ] <sup>e</sup>	58	32:68	12	4	16
[LZn <sub>2</sub> Ca(OAc) <sub>2</sub> ] <sup>e</sup>	77 [64, cis]	100:0	4	0	16
[LZn <sub>2</sub> La(OAc) <sub>3</sub> ] <sup>e</sup>	5	100:0	58	5	26

<sup>a</sup> Yields were determined from <sup>1</sup>H NMR spectra of the crude reaction mixture. Isolated yields after recrystallization are given in brackets. <sup>b</sup> Cis/trans ratios of macrocycle H<sub>4</sub>L'. <sup>c</sup> In dichloromethane, 1 mM, 30 h, room temperature, Grubbs catalyst of the first generation (5 mol %). <sup>d</sup> This contains a small amount of oligomeric products. <sup>e</sup> In THF, 5 mM, 9 h, reflux, Grubbs catalyst of the second generation (10 mol %); followed by demetalation with 1 M HCl. **A**: mono-deallylated product. **B**: bis-deallylated product.

labile for the ligand to rearrange during the reaction to a conformation better suited to ring closure. The cis/trans ratio (32:68) in H<sub>4</sub>L' from the zinc complex was greater than that (7:93) for the uncomplexed ligand.

In contrast, the ring-closing metathesis of heterotrinnuclear complex [LZn<sub>2</sub>Ca(OAc)<sub>2</sub>] exclusively afforded the cis isomer of the macrocyclic product. No trans isomer was detected in the reaction mixture. Pure *cis*-H<sub>4</sub>L' was easily isolated (yield 64%) by recrystallization of the crude product. Obviously, the cis/trans ratio depends on the combination of the metals employed, as well as the absence/presence of the metals. The Zn<sub>2</sub>Ca core tightly fixes the allyl groups so that the macrocyclization produces a seven-membered metallacycle (Scheme 2). The exclusive formation of the cis isomer could be due to such small ring formation. On the other hand, the Zn<sub>3</sub> metal center loosely restricts the spatial arrangement of the allyl groups. In this case, the olefin metathesis leads to a 17-membered metallacycle (Scheme 2) because the oxygen donors of the terminal salicylidene moieties do not coordinate to the central zinc (Zn<sub>2</sub> in Figure 1A). Consequently, the valency and size of the central ion is important to determine cis/trans selectivity.

The ring-closing metathesis of the lanthanum complex [LZn<sub>2</sub>La(OAc)<sub>3</sub>] also afforded macrocycle H<sub>4</sub>L' with excellent cis/trans selectivity (100:0), but the yield for the macrocycle was only 5%. Instead, a considerable amount of

**Scheme 2.** Oligometal-Templated Ring-Closing Metathesis of H<sub>4</sub>L

deallylated products (**A** and **B**)<sup>18</sup> was obtained. Grubbs catalysts cleave *N*-allyl groups in some cases,<sup>19</sup> but the cleavage of an allyl ether has rarely been reported.<sup>20</sup> This unexpected deallylation may be relevant to effective coordination of allyloxy groups to a Lewis acidic La<sup>3+</sup> ion. The coordination might activate the reactivity of the allylic carbon to promote isomerization to vinyl ether, which would be readily hydrolyzed to phenol derivatives in the demetalation procedure with HCl.

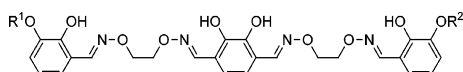
In conclusion, we have established a new strategy to obtain cis and trans isomers of a macrocycle H<sub>4</sub>L' using oligometallic template and nontemplated conditions, respectively, without employing laborious chromatographic separation. A preliminary complexation study showed that the macrocycles obtained also form a heterotrinnuclear complex with Zn<sup>2+</sup> and Ca<sup>2+</sup> ions. It will be interesting to investigate the memory effect to see if the macrocycle remembers the template metal combination employed in the macrocyclization. Further investigation of the complexation ability of the macrocycles with the metal ions is in progress.

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**Supporting Information Available:** Synthetic procedures for ligands and metal complexes in pdf format and X-ray crystallographic data for [LZn<sub>3</sub>(OAc)<sub>2</sub>(MeOH)<sub>2</sub>]·CHCl<sub>3</sub>, [LZn<sub>2</sub>Ca(OAc)<sub>2</sub>]·0.5CHCl<sub>3</sub>·0.75H<sub>2</sub>O, and [LZn<sub>2</sub>La(OAc)<sub>3</sub>]·CHCl<sub>3</sub> in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Deallylated products **A** and **B** were characterized by spectroscopic analyses.



**A**: R<sup>1</sup> = H, R<sup>2</sup> = allyl  
**B**: R<sup>1</sup> = R<sup>2</sup> = H

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