ORGANIC
LETTERS

2004
Vol. 6, No. 14
2453−2455

Direct Observation of Enantioselective Synergism at Trimetallic Centers

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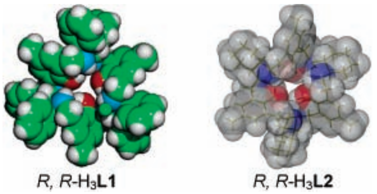
Received May 9, 2004

ABSTRACT



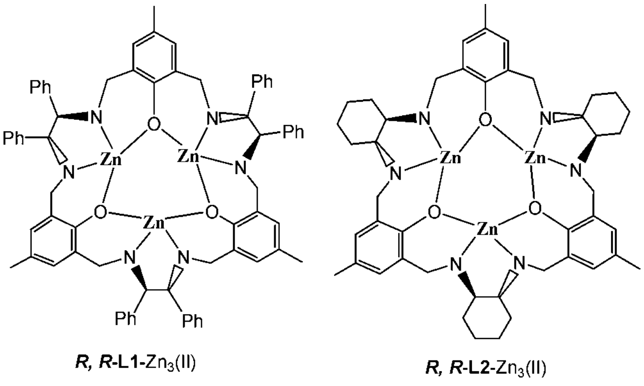
New oligomeric chiral macrocyclic ligands have been synthesized using an efficient self-assembly method. High enantioselective cooperativity in the catalytic asymmetric aldol reactions was directly observed using the conceptually novel chiral multinuclear complex catalysts.

The last two decades have witnessed the development and application of multinuclear complexes in bioinorganic catalytic chemistry.[1] Compared with this, the synthesis and utilization of *chiral multinuclear complexes* in enantioselective catalysis and the discovery of enzymelike catalytic asymmetric reactions are still in their infancies. The vast majority of many useful chiral ligands and their corresponding metal catalysts thus far developed have incorporated only one chiral-metal center.[2] Recently, several groups have investigated chiral catalysts containing two or more metal sites.[3] The synergistic cooperation between metal centers has been found to play an important role in the realization of high enantioselectivity.[4]

Review of the literature indicates that organic chemists have recognized chiral multinuclear complex catalysis longer than have inorganic chemists. One possible reason for this is that it is usually difficult to construct structure-defined chiral multinuclear complexes. Another factor that merits consideration is the recognization of the synergism in enantioselectivity for catalytic reactions that require more catalytic centers.[5]

We have been studying macrocyclic chemistry for several decades, focusing on multinuclear complex-catalyzed enzy-

Scheme 1. Molecular Structures of Trinuclear Zn(II) Complexes of H_3L1 and H_3L2.



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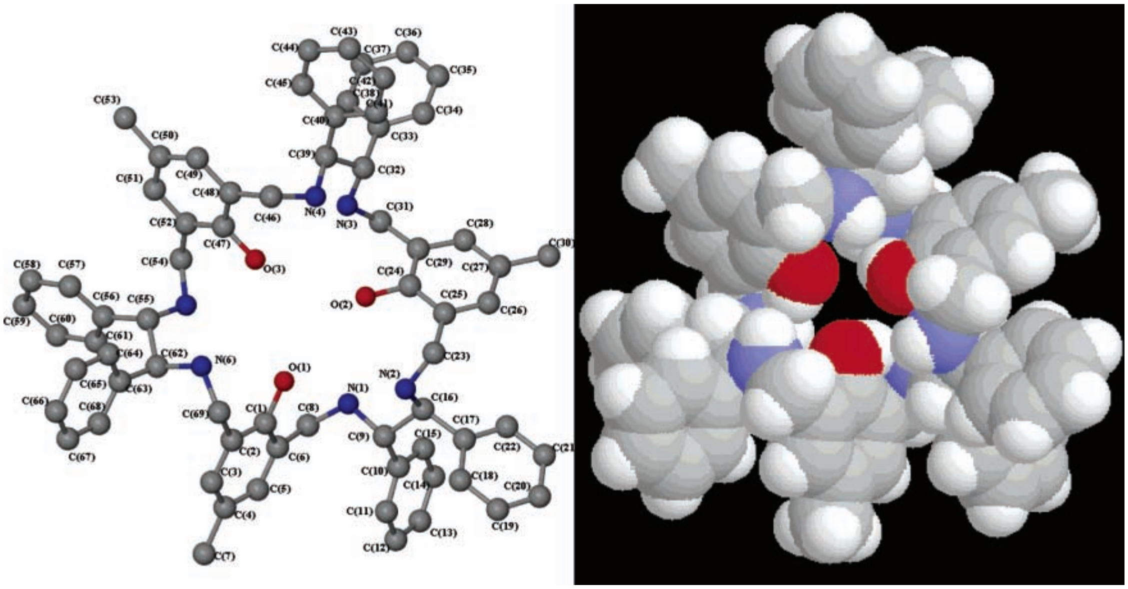


Figure 1. X-ray crystal structure of (R,R)-H_3**L1**.

matic reactions.[6] Recently, we have initiated a study of the chemistry of chiral macrocycles, seeking reliable routes for the synthesis of novel chiral macrocyclic complexes to serve as biofunctional catalysts.[7] To achieve this goal, the macrocyclic ligands must contain special chiral moieties and other donor groups having special affinities to host multimetal centers. The designed oligomeric salen complex (Scheme 1) was derived from a practical consideration of the salen−metal complexes of Jacobsen that have been shown to be useful catalysts.[8]

(R,R)-H_3**L1** (**1**) and (R,R)-H_3**L2** (**2**) were synthesized via an efficient self-assembly of the corresponding oliogomeric Schiff base macrocycles. The availability of such ligands demonstrates their potential as a class of useful chiral ligands. From a practical standpoint, any chiral ligand that can be utilized in asymmetric catalysis should be easily synthesized.

The trimeric structure of **1** was established by X-ray analysis. The most striking structural feature of **1** (Figure 1) is the cyclic helix conformation, which is unusual in this group of compounds. The C_3-symmetric neutral macrocycle contains three chiral-diamino backbones arranged in the form of an equilateral triangle, and the N_2O_2 cavities are proximal to each other. The specific coordination environment of (R,R)-H_3**L1** and (R,R)-H_3**L2** may allow for the formation of the oligomeric *multinuclear chiral complexes*. The X-ray structure of a trinuclear zinc complex, $[Zn_3(II)$**L2**$](ClO_4)_3$ (**3**), is shown in Figure 2.

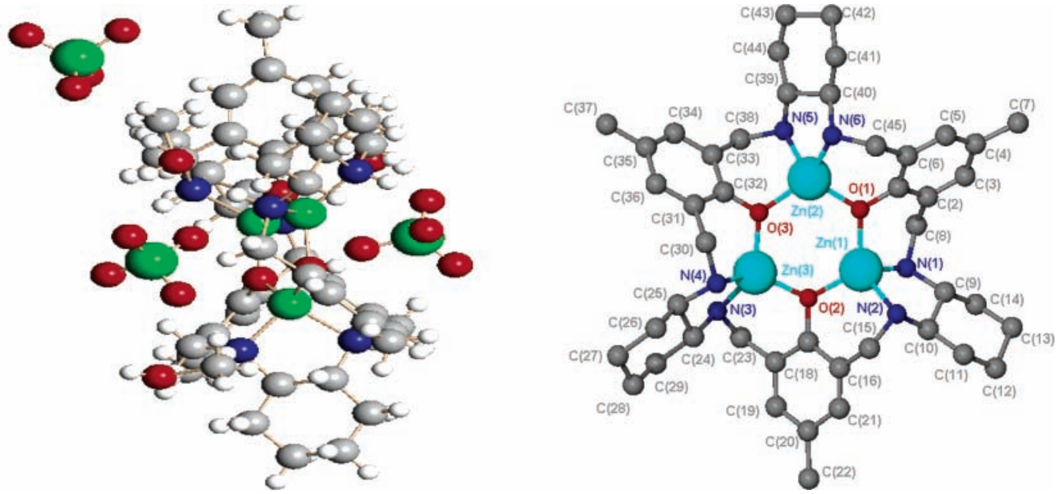
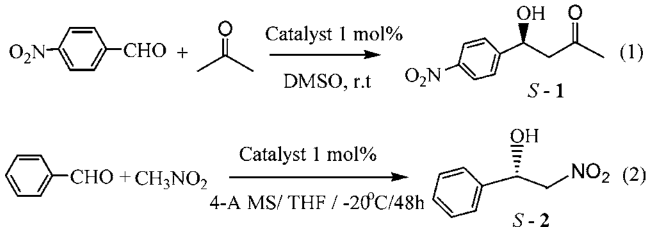


Figure 2. X-ray crystal structure of $[(R,R)$-**L2**$-Zn_3(II)](ClO_4)_3$.

Table 1. Cooperative Effects of Catalytic Asymmetric Aldol (**1**) (Entries 1−10) and Henry (**2**) (Entries 11−20) Reaction



entry	catalyst	L2:ZnEt$_2$	yield %[a]	ee %[b]	entry	catalyst	L1:ZnEt$_2$	yield %[a]	ee %[b]
1	1% L2	1:0.5	36	25	11	1% L1	1:0.5	28	29
2	1% L2	1:1.0	57	39	12	1% L1	1:1.0	44	42
3	1% L2	1:1.5	72	57	13	1% L1	1:1.5	51	65
4	1% L2	1:2.0	86	86	14	1% L1	1:2.0	67	84
5	1% L2	1:2.5	94	92	15	1% L1	1:2.5	80	90
6	1% L2	1:3.0	95	94	16	1% L1	1:3.0	84	92
7	1% L2	1:3.5	95	95	17	1% L1	1:3.5	86	92
8	1% L2	1:4.0	95	95	18	1% L1	1:4.0	89	92
9	2% L2	1:1.0	68	42	19	2% L1	1:10	52	43
10	3% L2	1:1.0	74	41	20	3% L1	1:1.0	63	45

[a] Isolated after column chromatography. [b] Enantionmeric excess determined by chiral column.

The availability of the structurally defined chiral ligands and their metal complexes have made possible the direct observation of a cooperative effect in a catalytic asymmetric reaction. Initially, a series of (*R*,*R*)-**L2**−Zn(II)*n* (*n* denotes the ratio of Zn(II) to the ligand, $n = 1{-}3$) complexes were investigated as mimics of a class II zinc-containing aldolase. This study received impetus from the success of Trost's[9] and Shibasaki's[10] catalysts. In comparison with those catalysts, (*R*,*R*)-**L2**−Zn$_3$(II) contains three totally equal subunits in a unique chemical and steric environment. The simple adjustment of the *n* value allows for the direct observation of an intramolecular cooperative effect. By employing the optimal reaction conditions derived from our former investigation,[7] (*R*,*R*)-**L2**−Zn$_3$(II) was found to effectively promote the direct aldol reaction of 4-nitrobenzaldehyde with acetone. As is shown in Table 1, increasing the ratio of diethylzinc to (*R*,*R*)-**L2** (0.5−3.0) resulted in an increased conversion and ee within the same time period (entries 1−6). Using 1 mol % (*R*,*R*)-**L2** and 3 mol % Et$_2$Zn, the product was obtained in high yield (up to 95%), as well as an excellent enantiomeric excess of up to 94%. The use of more than three portions of ZnEt$_2$ had little effect on the ee. In justifying the synergistic effect, the catalytic efficiency of 2 and 3 mol % mononuclear catalysts (entries 9 and 10) was tested. The enantioselectivity of 3 mol % mononuclear catalyst is much lower than that of 1 mol % trinuclear catalyst, thus clearly demonstrating the existence of an intramolecular cooperativity between the metallic centers. The cooperative phenomenon was further proved by investigating a nitroaldol (Henry) reaction using the (*R*,*R*)-**L1**−Zn$_3$(II) system. As indicated in Table 1 (entries 11−20), the dinuclear and trinuclear Zn(II) complexes display dramatically enhanced reactivity and enantioselectivity when compared with the mononuclear counterpart, which is lacking in intramolecular cooperation.

In summary, we report a class of new chiral macrocyclic ligands. An enantioselective synergism has been observed in several catalytic asymmetric reactions. Modification of the macrocyclic donor set from N_2O_2 to N_2P_2 or N_2S_2 may be expected to bind to more active metal centers. Additional studies on the synthesis and application of these ligands are under way in our laboratories. It is believed that *chiral multinuclear complex* catalysts will be of use in future catalytic investigation.

Acknowledgment. This work was supported by Welch Foundation (Grants A-0259 and A-084).

Supporting Information Available: Detailed experimental procedures, full characterization of the compound **1**−**3** and CIF files for **1** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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