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Catalytic asymmetric cyclopropanation at a chiral platform†‡

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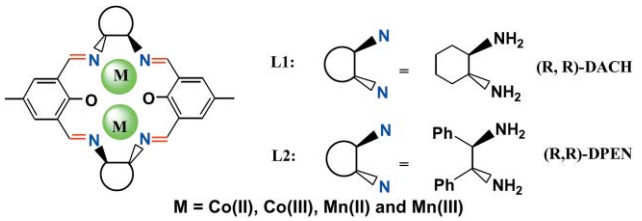
Novel chiral Robson-type macrocyclic complexes M_2–**L** [where M = Mn(II), Mn(III), Co(II) and Co(III) and **L** denotes tetra-Schiff base chiral ligands, **L1** or **L2**] have been synthesized by metal template condensation of 2,6-diformyl-4-methyl-phenol, with 1*R*,2*R*-diaminocyclohexane (**L1**) or 1*R*,2*R*-diphenylethylenediamine (**L2**). The dinuclear Co(II) and Co(III) complexes catalyze asymmetric cyclopropanation of styrene with diazoacetate cooperatively and with high enantioselectivity.

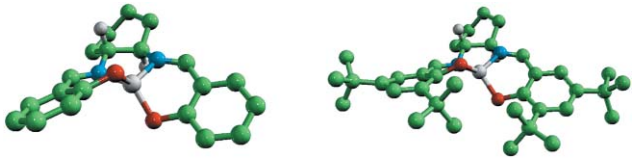
Schiff base Robson-type macrocycles containing two bridging phenol groups have been widely used to synthesize homo- and heterodinuclear complexes.[1] Detailed investigations in this area have provided valuable insight into bioinorganic and catalytic chemistry.[2] However, chiral Robson-type macrocyclic complexes, such as M_2–**L** (M = Mn(II), Mn(III), Co(II) or Co(III), **L** = **L1** or **L2**; Scheme 1) have rarely been investigated to date.[3] Our interest in such complexes centers on their potential application in metal ion-mediated asymmetric catalytic reactions.



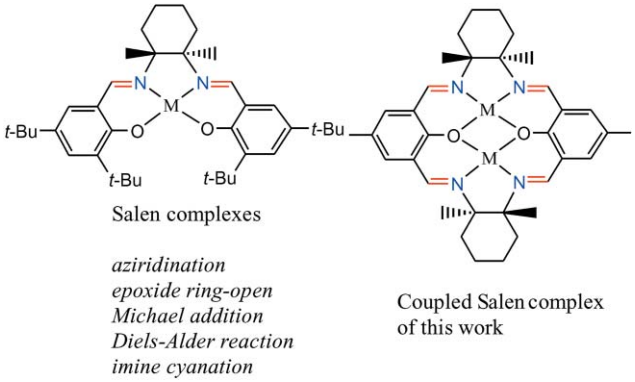
Scheme 1

Chiral Salen-complex catalysts containing 1*R*,2*R*-diaminocyclohexane moieties and various metals have being used in the promotion of numerous catalytic asymmetric reactions such as the asymmetric epoxidation,[4] aziridination,[5] nucleophilic epoxide ring opening,[6] Michael addition,[7] Diels–Alder reaction[8] and cyanide addition to aldehydes and imines[9] These catalyst molecules incorporate a single chirality and a single metal ion (Scheme 2). The molecular structure can be described as a 4-coordinated metal adjacent to a chiral diaminocyclohexanal backbone. The enantioselectivity for the formation of a given product is governed at the metal center, as a result of the presence of the stereogenic carbon. It is noteworthy that, in such complexes, the effect of approaching reactants can occur, not only in the axial direction, but also in the planar direction, opposite to the cyclohexyl ring. Such actions are substantiated by the observation of improved enantioselectivity when *t*-Bu groups are integrated with the "Salen" ligand.

However, chiral Robson-type dinuclear complexes which are "coupled-Salen" complexes (Scheme 3) may represent a new type of effective catalysts in asymmetric synthesis. This is due to the fact that the substrate molecules will invariably be subjected



Scheme 2



Scheme 3

to chiral induction by the chiral backbone as they approach the complex platform. Other than the geometric interaction occurring in multi-chiral complexes, the potential synergism between the metal centers should improve the enantioselectivity of the product. The chiral di- and multi-nuclear complex catalysts we have employed[10–13] along with other researchers[14–16] have received substantial attention due to their unique nature and potential for developing entirely new areas of investigation in synthetic chemistry.

A review of the literature indicates that transition metal-catalyzed asymmetric cyclopropanation has been an area of intense study for several years.[17] Some of the most efficient catalysts include the following complexes, Cu(I)/Cu(II)–bis(oxazoline),[18] Ru(II),[19] Co(II)/Co(III)–Salen[20] and Fe(II)/(Fe(III).[21] Despite the presence of a wide variety of mononuclear complexes and their high enantioselectivity, there appear to be limited publications which deal with dimetallic complexes. The research reported herein deals with enantioselective catalysis and is focused on the development of dinuclear complex catalysts, which can function cooperatively within complexes having enzyme-like active centers.

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‡ Electronic supplementary information (ESI) available: experimental procedures. See http://www.rsc.org/suppdata/ob/b5/b503971a/

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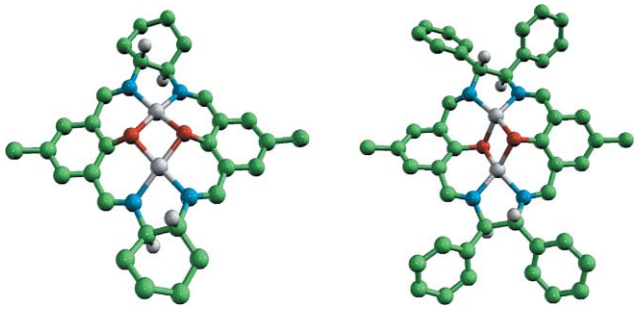
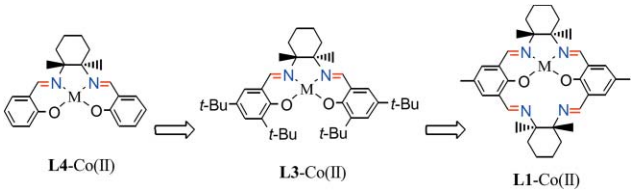
The dinuclear Mn(II) and Co(II) complexes of **L1** and **L2** were successfully prepared by direct template condensation (refer to the supplementary information). The molecular structures of the Co(II) complexes of **L1** and **L2** were defined by electro spray ionization (ESI) and elemental analyses. Molecular modeling indicates that the energy-minimized conformations of the complexes are basically planar (Scheme 4), providing sufficient new information to begin a mechanistic analysis of the subject reaction. The dimanganese (III) and dicobalt(III) complexes were prepared by oxidation of the corresponding Mn(II) or Co(II) complex by air in the presence of acetic acid. A tetranuclear Co(III) complex $[\mathbf{L1}_2Co_4(III)(OH)_2(OAc)_2](ClO_4)_4{\cdot}4CH_3OH$ has been defined by X-ray studies.[3]



Scheme 4

With the structurally defined catalysts in hand, we proceeded to investigate the catalytic asymmetric cyclopropanation of styrene with diazoacetic ester. Using 4.0 mmol of styrene and 5.0 mol% catalyst in 10 ml of CH_2Cl_2 at 25 °C as standard conditions, the results are shown in Table 1. The product yields were good to excellent (70–94%) for Mn(II), Mn(III), Co(II) and Co(III) complexes. For the **L1**–Co_2(III) complex, a *trans*-to-*cis* ratio of 74 : 26 was observed with an enantiomeric excess (ee) of 88.4 and 94.2% for *trans* and *cis* cyclopropane isomers, respectively. Investigation of the dinuclear Co(II) complexes indicated that the stereo- and enantioselectivity are similar to the corresponding dinuclear Co(III) complexes, which implies that the underlying mechanism is the same. However when employing the dinuclear Mn(III) complex of **L1**, the stereo- and enantioselectivities were found to be comparatively lower with *trans*-to-*cis* ratios of 68 : 32 and an ee of 56.0 and 58.2% for the *trans* and *cis* isomer respectively. Solvent effects were also investigated by changing the reaction medium, and demonstrated a corresponding yield and selectivity (entry **9**–**12**). The use of alcohol solvent was found to decrease the stereoselectivity by more than 30% based on the ee. This is likely to be the result of a subtle interaction between the complex and the diazo reagent.

To gain a greater understanding of the underlying mechanisms, three other complexes (Scheme 5) were tested. As shown in Table 2, **L4**–Co(II) produces very little catalytic activity. Catalyst **L3**–Co(II) affords a somewhat improved yield (48%) and an ee of 57% for the *cis* enantiomer. This may be due to the substituent effect of *t*-Bu groups on **L3**. Further improvement in stereo- (*cis* : *trans*, 69 : 31) and enantioselectivity (*cis* enantiomer ee = 80.4%) were observed for the mononuclear **L1**–Co(II) complex, indicating the combined effects of asymmetric induction and steric hindrance from the proximal chiral cyclohexyl moiety.



Scheme 5 Introducing of the steric barrier on the molecular plan.

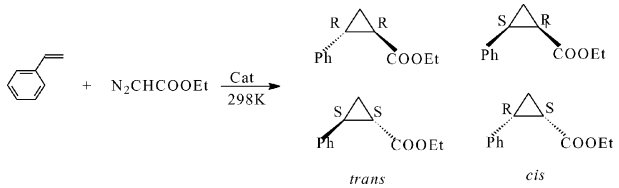
A probable mechanism for the transition metal complex-catalyzed cyclopropanation may be the following: a transition metal complex reacts with diazoacetates to generate a metal–carbene intermediate. The intermediate then reacts with the alkene to produce cyclopropane.[20a] In our catalysts, two carbene

Table 2 Yields and enantioselectivities of different Co(II) complex as a control

Entry	Catalysts	Yield (%)	*trans* : *cis*	ee (*trans*, %)[b]	ee (*cis*, %)[c]
1	**L1**–Co(II)	74	69 : 31	78.0	80.4
2	**L3**–Co(II)	48	62 : 38	47.2	57.0
3	**L4**–Co(II)	25	45 : 55	14.3	15.2

[a] The solvent was added in preparing the reaction mixture. [b] 1*R*,2*R* as the major enantiomer; [c] 1*S*,2*R* as the major enantiomer.

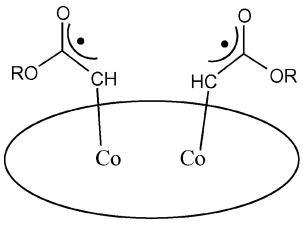
Table 1 Dimetallic Mn(II), Mn(III), Co(II) and Co(III) complexes showing catalyzed cyclopropanation



Entry	Catalyst	Solvent	Yield (%)	*trans* : *cis*	ee (*trans*, %)[a]	ee (*cis*, %)[b]
1	**L1**–Mn_2(II)	CH_2Cl_2	70	64 : 36	51.3	57.0
2	**L1**–Mn_2(III)	CH_2Cl_2	62	68 : 32	56.0	58.2
3	**L1**–Co_2(II)	CH_2Cl_2	90	72 : 28	86.2	91.5
4	**L1**–Co_2(III)	CH_2Cl_2	92	74 : 26	88.4	94.2
5	**L2**–Mn_2(II)	CH_2Cl_2	84	67 : 33	82.4	86.2
6	**L2**–Mn_2(III)	CH_2Cl_2	69	69 : 31	77.6	69.7
7	**L2**–Co_2(II)	CH_2Cl_2	93	70 : 30	89.0	92.0
8	**L2**–Co_2(III)	CH_2Cl_2	94	76 : 24	94.3	90.6
9	**L2**–Co_2(III)	EtOH	72	66 : 34	58.3	60.9
10	**L2**–Co_2(III)	*t*-BuOH	65	62 : 38	47.2	52.1
11	**L2**–Co_2(III)	Ph–CH_2OH	49	49 : 51	35.0	40.4
12	**L2**–Co_2(III)	MeCN	85	71 : 29	60.9	68.3

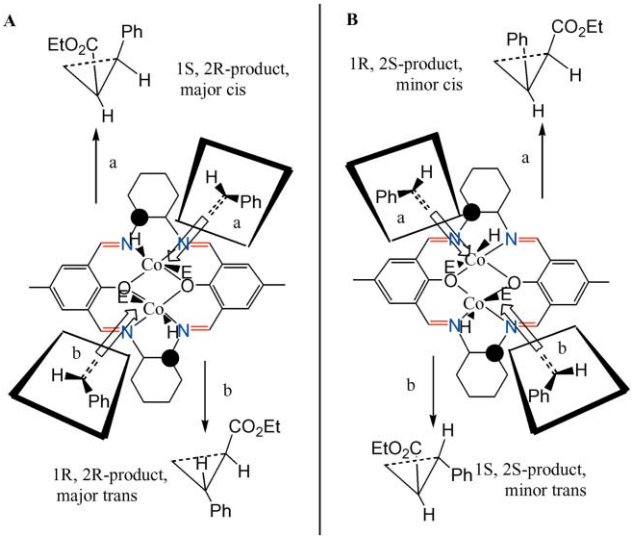
[a] 1*R*,2*R* as the major enantiomer. [b] 1*S*,2*R* as the major enantiomer.

intermediates might have been held by a single complex molecule and were subsequently re-oriented as a result of interaction (Scheme 6). The enantioselectivity occurring in these cyclopropanation reactions can be correlated with the orientation of the carbene ligand and the approach of the incoming olefins.



Scheme 6

The favorable orientation of the carbene intermediates in the **L1**–Co_2(II) catalyzed reaction is shown in Scheme 7. One carbene-plane is parallel to the other, but the planes are perpendicular to the complex platform. This arrangement minimizes the steric interactions between the ester groups as well as their interaction with the axial hydrogen atoms on the sterogenic centers. As demonstrated in a prior investigation of cyclopropanation by 8 group transition metal metalloporphyrin carbene complexes, the approach of olefin with its C=C axis parallel to the M=C bonds is strongly preferred.[21] The approach of a styrene along path *a* can minimize the steric interaction of axial hydrogen atoms with the olefin phenyl group. This produces the desired *cis* product with a 1*S*,2*R* configuration. The major *trans* enantiomer results from an approach along path *b*, which is consistent with the observed stereochemistry. After numerous efforts to obtain a crystal structure of the bis-carbene complexes, we remain unsuccessful with our available equipment and techniques. Although the carbene intermediate was difficult to isolate, this mechanistic analysis is critical and may shed light on the future design of highly selective catalysts in other asymmetric syntheses.



Scheme 7 The possible mechanism that will lead to four different isomers (E denotes the ester groups bound with the Co(II) centers).

References

1 (*a*) N. H. Pilkington and R. Robson, *Aust. J. Chem.*, 1970, **23**, 2225; (*b*) R. Das and K. Nag, *Inorg. Chem.*, 1991, **30**, 2831; (*c*) B. Bosnich, *Inorg. Chem.*, 1999, **38**, 2554.

2 (*a*) R. C. Long and D. N. Hendrickson, *J. Am Chem. Soc.*, 1983, **105**, 1513; (*b*) A. Atkins, D. Black, A. J. Blake, A. Marin-Becerra, S. Persons, L. Ruiz-Ramirez and M. Schroder, *Chem. Commun.*, 1996, 457; (*c*) M. Yonemura, N. Usuki, Y. Nakamura, M. Ohba and H. Okawa, *J. Chem. Soc., Dalton Trans.*, 2000, 3624.

3 J. Gao, J. H. Reibenspies, R. A. Zingaro, F. Ross Woolley, A. E. Martell and A. Clearfield, *Inorg. Chem.*, 2005, **44**, 232–241.

4 (*a*) S. Cheng, N. H. Lee and E. N. Jacobsen, *J. Org. Chem.*, 1993, **58**, 6939; (*b*) P. J. Pospisil, D. H. Carsten and E. N. Jacobsen, *Chem. Eur. J.*, 1996, **2**, 974; (*c*) T. Flessner and S. Doye, *J. Prakt. Chem./Chem.-Ztg.*, 1999, **341**, 436; (*d*) Z. Li and C. Jablonski, *Chem. Commun.*, 1999, 1531.

5 Z. Li, K. R. Conser and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1993, **115**, 5326.

6 (*a*) L. E. Martinez, J. A. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897; (*b*) J. F. Larrow, S. E. Schaus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420; (*c*) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

7 J. K. Myers and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1999, **121**, 8959.

8 (*a*) D. A. Evans, T. Lectka and S. J. Miller, *Tetrahedron Lett.*, 1993, **34**, 7027; (*b*) S. E. Schaus, J. Branalt and E. N. Jacobsen, *J. Org. Chem.*, 1998, **63**, 403.

9 (*a*) M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 5315; (*b*) V. I. Tararov, D. E. Hibbs, M. B. Hursthouse, N. S. Ikonnikov, K. M. A. Malik, M. North, C. Orizu and Y. N. Belokon, *J. Chem. Soc., Chem. Commun.*, 1998, 387.

10 J. Gao, R. A. Zingaro, J. H. Reibenspies and A. E. Martell, *Org. Lett.*, 2004, **14**, 2453.

11 J. Gao, J. H. Reibenspies and A. E. Martell, *Angew. Chem., Int. Ed.*, 2003, **42**, 6008–6012.

12 J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2801.

13 J. Gao and A. E. Martell, *Org. Biomol. Chem.*, 2003, **1**, 2795.

14 (*a*) B. M. Trost and L. R. Terrell, *J. Am. Chem. Soc.*, 2003, **125**, 338; (*b*) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 5; (*c*) B. M. Trost, E. R. Silcoff and H. Ito, *Org. Lett.*, 2001, **3**, 2497.

15 (*a*) M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187–2209; (*b*) M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem., Int. Ed.*, 1997, **36**, 1236.

16 (*a*) T. P. Yoon and E. N. Jacobson, *Science*, 2003, **299**, 1691; (*b*) J. M. Ready and E. J. Jacobsen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1374.

17 (*a*) M. P. Doyle, M. A. Mckervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylids*, John Wiley and Sons, New York, 1998; (*b*) T. Ye and M. A. Mckervey, *Chem. Rev.*, 1994, **94**, 1091; (*c*) M. P. Doyle, D. C., *Chem. Rev.*, 1998, **98**, 911; (*d*) J. Gao and S. H. Zhong, *J. Mol. Catal.*, 2003, **191**, 23; (*e*) A. M. Harm, J. G. Knight and G. Stemp, *SYNLETT*, 1996, 677.

18 (*a*) R. J. Clarke and I. J. Shannon, *Chem. Commun.*, 2001, 1936; (*b*) M. I. Burguete, J. M. Fraile, J. I. Garcia, E. G. Verdugo, S. V. Luis and J. A. Mayoral, *Org. Lett.*, 2000, **24**, 3905; (*c*) R. Boulch, A. Scheurer, P. Mosset and R. W. Saalfrank, *Tetrahedron Lett.*, 2001, **41**, 1023; (*d*) R. E. Lowenthal, A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1990, **31**, 6005; (*e*) D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726.

19 (*a*) Z. Zheng, X. Yao, C. Li, H. Chen and X. Hu, *Tetrahedron Lett.*, 2001, **42**, 2847; (*b*) X. Yao, M. Qiu, W. Lu, H. Chen and Z. Zheng, *Tetrahedron: Asymmetry*, 2001, **12**, 197; (*c*) H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park and K. Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2232; (*d*) S. B. Park, N. Sakata and H. Nishiyama, *Chem. Eur. J.*, 1996, **2**, 303; (*e*) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park and K. Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2223.

20 (*a*) T. Ikeno, I. Iwakura and T. Yamada, *J. Am. Chem. Soc.*, 2002, **124**, 15152; (*b*) T. Fukuda and T. Katsuki, *SYNLETT*, 1995, 825; (*c*) T. Niimi, T. Uchida, R. Irie and T. Katsuki, *Adv. Synth. Catal.*, 2001, **343**, 79.

21 (*a*) C. G. Hamaker, G. A. Mirafzal and L. K. Woo, *Organometallics*, 2001, **20**, 5171; (*b*) G. Du, B. Andrioletti, E. Rose and L. K. Woo, *Organometallics*, 2002, **21**, 4490.