Imprinting and locking chiral memory for stereoselective catalysis†

Jik Chin,*[a] Yong S. Chong,[b] Rhiana Bobb,[a] Lisa Studnicki[a] and Jong-In Hong*[b]

Received (in Cambridge, UK) 14th August 2006, Accepted 9th October 2006
First published as an Advance Article on the web 30th October 2006
DOI: 10.1039/b611709k

A salen ligand based Co(III) complex ±1 with imprintable chiral memory was locked-in and used for stereoselective catalysis.

In principle, achiral or racemic molecules with imprintable chiral memory could be converted to stereoselective catalysts. However, it would be difficult to design a polymer[1] or a supramolecular[2,3] structure with imprintable chiral memory that is a stereoselective catalyst. A metal complex with imprintable chiral memory that can be locked-in would stand a much better chance for such an application.[4] In the field of stereoselective catalysis, salen ligand (Schiff base formed from a 2 : 1 mixture of salicylaldehyde and ethylene diamine derivatives) based metal complexes have received considerable attention over the last couple of decades.[5] We became interested in adapting the concept of imprintable chiral memory onto a system with obvious advantages for stereoselective recognition[6] and catalysis.[7] Jacobsen,[8] Katsuki[9] and others have shown that salen based metal complexes are highly effective as stereoselective catalysts for a wide variety of important chemical reactions including (a) epoxidation of alkenes with manganese–salen complexes;[9,10] (b) hydrolysis of epoxides with cobalt–salen complexes;[8] (c) Strecker synthesis of amino acids with aluminium–salen complexes;[11] (d) Diels–Alder reaction with chromium–salen complexes;[12] (e) cyanohydrin formation with titanium–salen complexes;[13] and (f) Michael addition with aluminium–salen complexes.[14,15] We developed a salen based Co(III) complex ±**1** with imprintable chiral memory (Fig. 1) that can be locked-in and used for stereoselective catalysis.

The diimine ligand in ±**1** was synthesized from *meso*-1,2-bis(2-hydroxyphenyl)-ethylenediamine[16] and 3,5-di-*tert*-butylsalicylaldehyde.[17] The neutral ligand was reacted with cobalt acetate and air oxidized following standard procedures for making Co(III) complexes of salen ligands.[17] Although the *meso*-diamine based ligand itself is achiral, the cobalt complex derived from this ligand is chiral and is produced as a racemic mixture ±**1**. As shown in Fig. 1, only one of the two phenols can coordinate at a time to the metal. It is this coordination of the phenolic oxygen that makes the cobalt complex chiral. ^{1}H NMR of the metal complex shows four distinct *tert*-butyl group signals consistent with the proposed structure (ESI†). ^{1}H NMR reveals that addition of two equiv of (2*R*,3*S*)-2-phenyl-3-methylaziridine[18] to the racemic cobalt complex ±**1** results in complete coordination of the amine within minutes at ambient temperature (Fig. 2). One of the imine hydrogen signals of the initial cobalt complex appears as a clean singlet (Fig. 2a) while the other imine signal is buried (ESI†). Upon coordination of the aziridine, the singlet signal changes into two new singlet signals (Fig. 2b). Initially, a 1 : 1 ratio of the diastereomeric complex is formed, however after equilibration this ratio changes and stabilizes at about 2 : 1 (Fig. 2c). The rate constant at 40 °C for the equilibration reaction as measured by NMR methods is 2.4 × 10^{-4} s^{-1} ($\tau_{1/2}$ ~ 2 d at 25 °C). Thus, the chiral aziridine shifts the equilibrium in Fig. 1 by coordinating[6] and stabilizing one complex more than the other. Possible origin of the stereoselectivity is described in the ESI.†

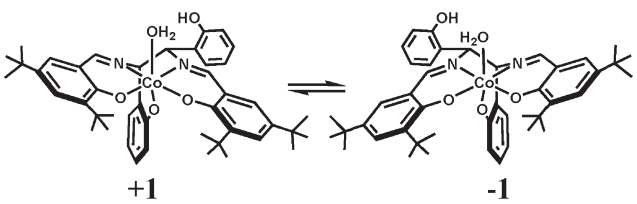

Fig. 1 Co(III)–salen ligand complex ±**1**.

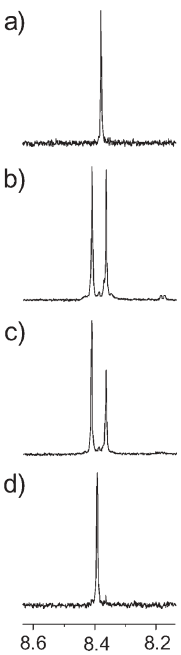

Fig. 2 ^{1}H NMR spectra in DMSO-d_6 of (a) one of the two imine signals of the initial racemic Co(III) complex ±**1**, (b) the initial diastereomeric complex formed from the addition of (2*R*,3*S*) 2-phenyl-3-methylaziridine, (c) the diastereomeric complex after equilibration by heating and (d) the complex after displacement of the coordinated aziridine with benzylamine.

[a]*Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, M5S 3H6, Canada. E-mail: jchin@chem.utoronto.ca; Fax: (+1)-416-946-7335*
[b]*Department of Chemistry, Seoul National University, Seoul, 151-747, Korea. E-mail: jihong@snu.ac.kr; Fax: (+82)-2-889-1568*
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^{1}H NMR data. See DOI: 10.1039/b611709k

The slow shift in equilibrium indicates that the rate of exchange in position of the two phenolic groups in Fig. 1 is slow. Such slow ligand exchange rates are common with octahedral Co(III) complexes and they are said to be substitutionally inert.[19] Although weakly coordinating epoxides are known to dissociate from octahedral (salen)Co(III) complexes at unusually rapid rates,[11] the strongly coordinating intramolecular phenoxy groups in ±**1** exchange slowly due to the slow dissociation rate. The coordinated aziridine can be rapidly displaced with an achiral amine such as benzylamine at ambient temperature (Fig. 2d). The chiral aziridine bound complexes are diastereomeric while the benzylamine bound complexes are enantiomeric. Thus the two imine C–H signals of the aziridine bound cobalt complexes (Fig. 2c) are replaced by a single peak (Fig. 2d) upon exchange of the aziridine with benzylamine.

The chiral aziridine cobalt complex (after equilibration of phenol coordination (Fig. 2c)) shows a distinct circular dichroism (CD) band around the absorption band for the metal complex (Fig. 3). Neither the complex by itself nor the aziridine by itself gave any CD bands (Fig. 3e and 3f). Thus the metal complex is a reporter or sensor of chirality that can generate or amplify the CD signal from a chiral guest.

Interestingly, the CD spectrum does not change appreciably when the coordinated chiral aziridine is replaced with the achiral amine (Fig. 2c and 3a to 2d and 3b). The CD spectrum in Fig. 3b was taken after confirming displacement of the aziridine and coordination of benzylamine by NMR methods (Fig. 2d). This indicates that chiral memory can be imprinted on the metal complex with the chiral aziridine. The memory effect is made possible by the slower rate of exchange of the coordinated phenol compared to the rate of exchange of the aziridine with benzylamine. We have also been able to demonstrate the chiral memory effect purely from ^{1}H NMR without the use of CD (ESI†). The chiral memory can be erased by heating the benzylamine coordinated complex. The CD bands of the imprinted complex disappear when the sample is heated at 70 °C for 30 min ($\tau_{1/2} \sim 2$ d at 25 °C). A more stable chiral memory would be desirable if we were to use the imprinted complex as a stereoselective catalyst.

In order to obtain a more lasting chiral memory, we decided to lock in the chiral memory. For the purpose of making the locked complex, phenylalanine was used as the imprinting agent rather than the chiral aziridine because the amino acid is easier to remove after imprinting. We locked in the chiral memory by acylating the free phenolic group of the imprinted complex with acetic anhydride. The amino acid was then removed by aqueous workup and the locked complex was purified by chromatography. The enantiopurity of the locked complex (36% ee) was determined by ^{1}H NMR methods using *R*-phenethylamine. We showed that although *R*-phenethylamine binds to ±**1** with no observable stereselectivity, the two diastereomeric complexes show distinct ^{1}H NMR signals (ESI†). Addition of excess *R*-phenethylamine to the locked complex results in generation of two diastereomeric complexes (Fig. 4) with distinct ^{1}H NMR signals for one of the imine C–H. As expected, the enantiopurity of the locked complex is the same when D- or L-phenylalanine is used as an imprinting agent. Opposite enantiomers of the cobalt complex are enriched depending on the chirality of the imprinting agent.

The locked complex (0.5 mol %) was used to catalyze the ring opening of styrene oxide (1 eq) with *N*-methylaniline (0.55 eq). The solvent free reaction was complete in 12 h at ambient temperature to give the amino alcohol and the unreacted epoxide (Fig. 5a). The remaining styrene oxide was isolated by fractional distillation and found to be enantioenriched.

Detection of the enantiomeric excess (ee) of styrene oxide was determined by ^{1}H NMR and by optical rotation measurements.

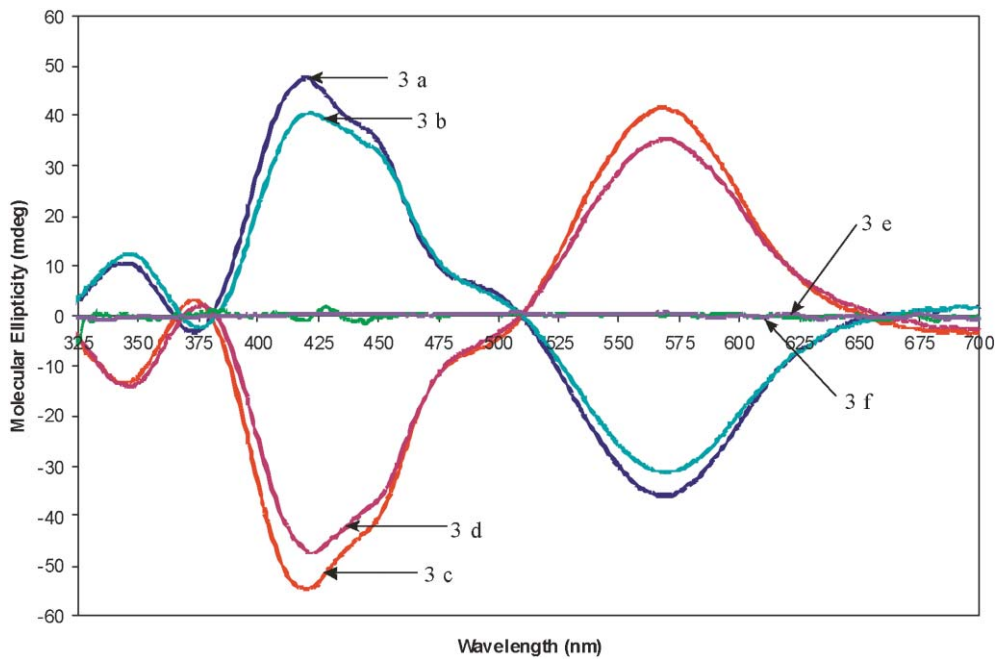

Fig. 3 Circular dichroism (CD) spectra in DMSO at 20 °C of (a) ±**1** (25 μM) + (2*R*,3*S*) 2-phenyl-3-methylaziridine (50 μM), (b) Same as (a) except after adding benzylamine (250 μM) to displace the aziridine, (c) ±**1** (25 μM) + (2*S*,3*R*) 2-phenyl-3-methylaziridine (50 μM), (d) same as (c) except after adding benzylamine (250 μM) to displace the aziridine, (e) ±**1** (25 μM), (f) (2*S*,3*R*) 2-phenyl-3-methylaziridine (50 μM).

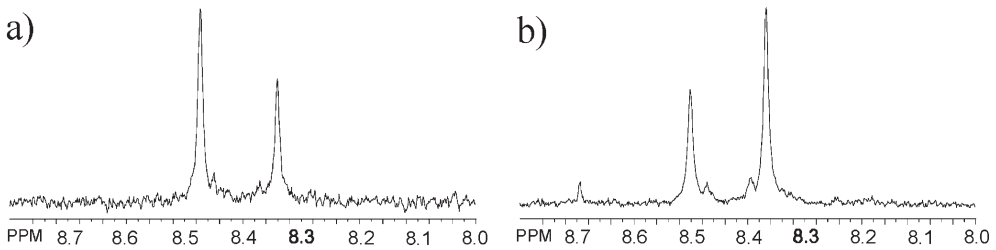

Fig. 4 ^{1}H NMR in DMSO-d_6 of one of the imine C–H signals of the locked complex after adding excess *R*-phenethylamine. Complex imprinted with (a) D-phenylalanine and (b) L-phenylalanine.

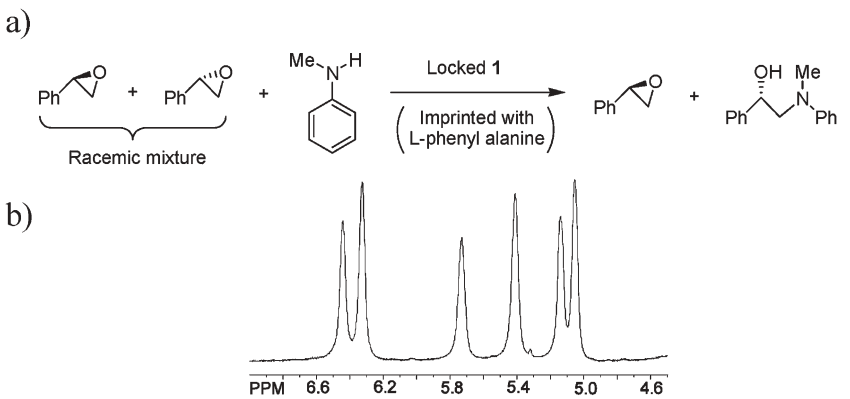

Fig. 5 (a) Schematic representation of the stereoselective ring opening reaction of styrene oxide catalyzed by locked **1** after being imprinted by L-phenyl alanine. (b) ^{1}H NMR in DMSO-d_6 of the C–H signals of the enantioenriched styrene oxide and 0.15 equiv. of NMR shift reagent, europium tris[3-(heptafluoropropylhydroxy-methylene)-(+)-camphorate].

Addition of a small amount of (0.15 eq) europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] resulted in separation of the three C–H signals of one enantiomer of styrene oxide from those of the other (Fig. 5b).[20] The unreacted styrene oxide is enriched in the S form (15% ee) if the catalyst is imprinted with L-phenylalanine. Furthermore, optical rotation studies performed on the same enantioenriched sample of styrene oxide gave a reading of +5°. This equates to an ee of 15%, based on the optical rotation value of pure styrene oxide ($\pm$34°).[17] As expected, D-phenylalanine imprinting agent gave the same value, equal in magnitude but opposite in sign. While the stereoselectivity is only modest, this study demonstrates for the first time how achiral catalysts can be easily imprinted and locked.‡

Notes and references

‡ Support of this work by NSERC of Canada and a grant from the MOCIE (Grant No. 10024945) are gratefully acknowledged. Y.S.C thanks the Korean Ministry of Education for the BK 21 postdoctoral fellowship.

1 E. Yashima, K. Maeda and Y. Okamoto, *Nature*, 1999, **399**, 449–451.
2 L. J. Prins, F. De Jong, P. Timmerman and D. N. Reinhoudt, *Nature*, 2000, **408**, 181–184.
3 T. Ishi-I, M. Crego-Calama, P. Timmerman, D. N. Reinhoudt and S. Shinkai, *J. Am. Chem. Soc.*, 2002, **124**, 14631–14641.
4 (*a*) Y. S. Chong, M. D. Smith and K. D. Shimizu, *J. Am. Chem. Soc.*, 2002, **123**, 7463–7464; (*b*) A. Sugasaki, M. Ikeda, M. Takeuchi, A. Robertson and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3259–3264; (*c*) Y. Furusho, T. Kimura, Y. Mizuno and T. Aida, *J. Am. Chem. Soc.*, 1997, **119**, 5267–5268; (*d*) Y. Kubo, T. Ohno, J. Yamanaka, S. Tokita, T. Iida and Y. Ishimaru, *J. Am. Chem. Soc.*, 2001, **123**, 12700–12701.
5 T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691–1693.
6 R. Bobb, G. Alhakimi, L. Studnicki, A. Lough and J. Chin, *J. Am. Chem. Soc.*, 2002, **124**, 4544–4545.
7 M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936–938.
8 E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421–431.
9 T. Katsuki, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, 2000, ch. 6B.
10 E. N. Jacobsen, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1st edn, 1993, ch. 4.2.
11 M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 5315–5316.
12 S. E. Schaus, J. Bränalt and E. N. Jacobsen, *J. Org. Chem.*, 1998, **63**, 403–405.
13 Y. N. Belokon, *J. Am. Chem. Soc.*, 1999, **121**, 3968–3973.
14 G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442–4443.
15 M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2003, **125**, 4442–4443.
16 F. Vögtle and E. Goldschmitt, *Chem. Ber.*, 1976, **109**, 1–40.
17 S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307–1315.
18 A. Galindo, L. Orea, D. Gnecco, R. G. Enriquez, R. A. Toscano and W. F. Reynolds, *Tetrahedron: Asymmetry*, 1997, **8**, 2877–2879.
19 C. H. Langford and H. B. Gray, *Ligand Substitution Processes*, W. A. Benjamin, New York, 1965.
20 H. J. C. Yeh, S. K. Balani, H. Yagi, R. M. E. Greene, N. D. Sharma, D. R. Boyd and D. M. Jerina, *J. Org. Chem.*, 1986, **51**, 5439–5443.

