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Enantiotopic Discrimination by Coordination-Desymmetrized *meso*-Ligands

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Abstract: The first examples of enantiopure catalysts that are chiral merely due to coordination of different metal ions at enantiotopic positions of an achiral *meso*-ligand are reported. These catalysts exhibit a pseudo-C_s symmetry and are able to catalyze reactions demanding simultaneous involvement of two catalytic sites. The latter was demonstrated by application in the asymmetric ring-opening of *meso*-epoxides.

Molecular chirality and symmetry have inspired advances in chemistry for over a century.[1] Chirality remains an important tool in topics ranging from elucidation of reaction mechanisms,[2] to synthesis of new enantioenriched compounds[3] and the fundamental understanding of life.[4] It has even motivated synthesis for aesthetic purposes.[5] Efficient breaking of molecular mirror-symmetry by enantiomorphic or enantiotopic discrimination has been accomplished by numerous methods. Commonly, asymmetric catalysis[3a-b,6] and chiral chromatography are used,[7] but more esoteric methods have also been reported such as the use of circularly polarized light,[8] crystallization,[9] sublimation[10] and absolute asymmetric catalysis.[11]

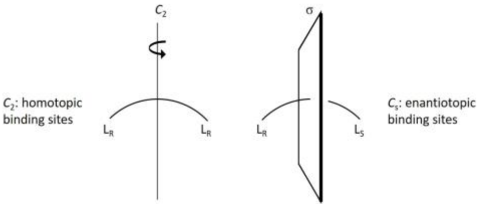

Figure 1. In a C_2-symmetric ligand containing two binding sites (L), the binding sites are homotopic (left) (previous work[15]). In a *meso*-ligand containing two binding sites, the binding sites are enantiotopic (right) (this work).

Asymmetric catalysis using chiral ligands coordinated to Lewis acidic metal ions has been an active research area for the past decades with great importance for the development of reactions such as asymmetric cycloadditions, carbonyl-ene, aldol, Mannich, Michael, Friedel-Crafts, hydogenations, hydrosilyations of ketones, reductions and allylic oxidations.[12] Commonly, the ligands are designed around privileged motives based on C_2 symmetry such as Jacobsen's salens,[13a] boronic acids,[13b] oxazolines,[13c] and 1,1'-binaphthyl-2,2'-diols.[13d] A less-developed approach is to use achiral ligands that are desymmetrized by coordination of catalytically active metal ions.[14] This concept would be particularly attractive in bimetallic catalysis but no examples of such structures have been reported to date.

In a C_2-symmetric bi-functional ligand with binding sites related by the two-fold symmetry axis, the sites are homotopic (Figure 1, left). In principle, enantiopure hetero-bimetallic complexes (pseudo-C_2-symmetric complexes) can thus be readily accessed by sequential coordination of two different metal ions.[15] On the other hand, formation of the corresponding enantioenriched hetero-bimetallic complexes of homologous C_s-symmetric ligands (pseudo-*meso* complexes) where the binding sites are instead related by a plane of symmetry[16] is more challenging as such sites are enantiotopic (Figure 1, right). Sequential coordination of different metal ions would thus, absent external chiral influence, lead to a racemic product (Figure 2).

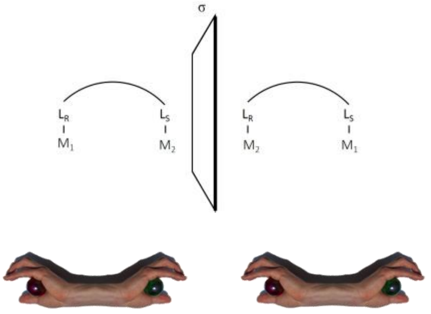

Figure 2. Two enantiomeric bimetallic complexes based on one (prochiral) *meso*-ligand (L_R L_S) (top). A macroscopic analogy (bottom): An enantiomeric pair is created by interchanging the position of the red and the green balls of the *meso*-hands.

Contingent that no metal-ion exchange occurs, one possible tactic to solve this problem is to join two ligand-metal moieties step-wise. That is, starting with an enantiopure ligand, inserting the first metal ion, introducing another ligand, then inserting the second metal ion. Using this approach, we here report the first enantiopure hetero-bimetallic complexes with a *meso*-ligand backbone,[17] and the *proof-of-principle* that such pseudo-*meso* complexes can perform enantiotopic discrimination in *meso*-substrates to induce substantial *ee*'s in the product of useful catalytic processes.

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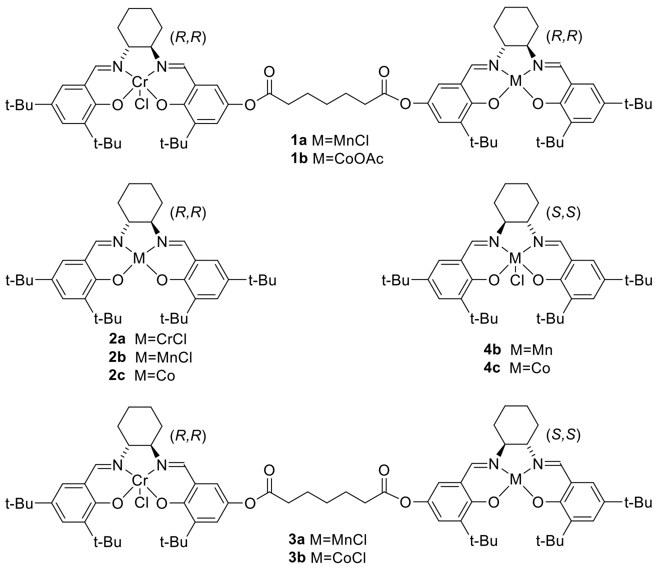
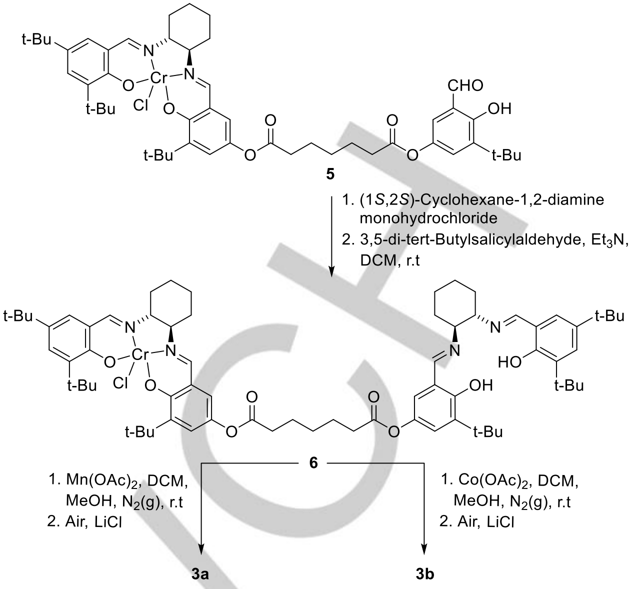


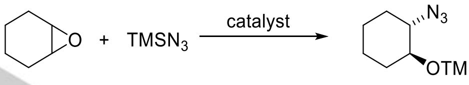
Figure 3. Structures of pseudo-C_2 symmetric bimetallic bissalen complexes (top), C_2-symmetric monometallic monosalen complexes (middle), and pseudo-*meso* bimetallic bissalen complexes (bottom).

Drawing from Jacobsen's C_2-symmetric homo-bimetallic bissalen catalysts,[18] we recently reported a study of hetero-bimetallic bissalen catalysts.[15] In this study, the bimetallic pseudo-C_2 catalysts **1a** and **1b** (Figure 3, top) displayed significantly increased reaction rates and enantioselectivies in the ring opening of *meso*-epoxides compared the corresponding 1:1 mixtures of monometallic monosalen catalysts **2a** and **2b** or **2a** and **2c**, respectively (Figure 3, middle),[15,18] and even higher yields and *ee*'s were obtained compared to using Jacobsen's parent bimetallic C_2 symmetric catalyst for the ring opening of cyclohexene oxide.[15,18] The different metal ions in **1a** and **1b** enable an efficient intramolecular activation of both the epoxide and the nucleophile.[15,18,19] The success of this system suggests that a bimetallic catalyst with a *meso*-backbone could also provide an efficient entry to chiral discrimination. For such a study, pseudo-*meso* complexes **3a** and **3b** (Figure 3, bottom) were targeted. The principal design elements of **3a** and **3b** (metal ions, tether length etc.) draws from prior work on the optimization of pseudo-C_2 symmetric catalysts **1a** and **1b**.[15]



Scheme 1. The synthesis of the pseudo-*meso* bissalen complexes **3a** and **3b**.

Table 1. Ring-opening of cyclohexene oxide with $TMSN_3$ catalyzed by pseudo-C_s-bissalen complexes or a 1:1 mixture of mono-metallic mono-salen complexes.[a]



Entry	Catalyst (mol%)	Solvent[b]	TOF[c] (h^{-1})	Yield [d] (%)	*ee*[e,j] (%)
1[15]	**1a**(0.01)	None	76	96[f]	66
2[15]	**1b**(0.01)	None	23	> 99[g]	94
3	**3a**(1)	THF	2.9	49[h]	62
4	**3a**(0.1)	None	120	> 99[i]	50
5	**3a**(0.01)	None	118	> 99[i]	32
6	**3b**(1)	THF	0.7	35[h]	36
7	**3b**(0.1)	None	97	> 99[i]	57
8	**3b**(0.01)	None	144	> 99[i]	35
9	**2a**(1)+**4b**(1)	THF	0.61	24[h]	7
10	**2a**(0.01)+**4b**(0.01)	None	7.2	22[i]	4
11	**2a**(1)+**4c**(1)	THF	0.52	24[h]	4
12	**2a**(0.01)+**4c**(0.01)	None	10.6	31[i]	4

[a] Reaction conditions: r.t, cyclohexene oxide (0.5 mmol), $TMSN_3$ (0.6 mmol). [b] Reaction in THF (270 μL) or solvent-free. [c] Calculated as (initial rate)/[catalyst]. [d] Determined by GC using 1,2,4,5-tetramethylbenzene as internal standard. [e] The absolute configuration was determined by comparison with the optical rotation reported in the literature. [f] Measured after 72 h. [g] Measured after 108 h. [h] Measured after 24h. [i] Measured after 120 h. [j] The major configuration is (*S*,*S*).

Synthetically, catalysts **3a** and **3b** were readily prepared in enantiopure form starting by the condensation of (1*S*,2*S*)-cyclohexane-1,2-diamine mono-hydrochloride and (*R*,*R*)-

[Cr(III)Cl]salen complex **5** (Scheme 1).[15] Triethylamine was added to deprotonate the ammonium group which was then reacted with 3,5-di-*tert*-butyl-2-hydroxy-benzaldehyde to give the monometallic bissalen complex **6**. Insertion of Mn(II) or Co(II) followed by air oxidation quantitatively furnished the respective analytically pure pseudo-*meso* bimetallic complexes [Cr(III)-Mn(III)]bissalen **3a** and [Cr(III)-Co(III)]bissalen **3b**. The complexes were characterized by HRMS and elemental analysis. Both structures **3a** and **3b**, and their common precursor **6** were found stable and do not undergo metal-ion scrambling,[18,19] as confirmed by ESI-MS and CD spectroscopy (Figure S18-19).

The catalytic properties of the pseudo-*meso* complexes were first investigated in the ring opening of cyclohexene oxide with $TMSN_3$ in THF (Table 1, entry 3 and 6). Both **3a** and **3b** gave moderate to good conversions into product with moderate to low enantioselectivities (62% *ee* for **3a** and 36% *ee* for **3b**). All reactions gave higher yields and higher turn-over frequencies (TOFs) under solvent-free conditions compared to THF (Table 1, entry 4, 5, 7 and 8). When compared to the pseudo-C_2 catalysts, the *ee*'s of the ring-opened products were however lower for the pseudo-*meso* catalysts under identical conditions (Table 1, entry 1 *vs.* 5, entry 2 *vs.* 8). The performances of the bimetallic complexes **3a** and **3b** were also compared to 1:1 mixtures of (*R*,*R*)-salen **2a** and (*S*,*S*) salen **4b**[20] or (*S*,*S*)-salen **4c.**[21] Notably, both **3a** and **3b** gave better yields, TOFs and *ee*'s than the corresponding mixtures of monometallic catalysts in each case (Table 1, entry 3 vs. 9, 5 vs. 10, 6 vs. 11, and 8 vs. 12). This is in agreement with what was observed in a similar comparison for pseudo-C_2 catalysts **1a** and **1b**.[15]

The lower performance in terms of both reaction rate and enantioselectivity for pseudo-*meso* **3a** and **3b** compared to that of pseudo-C_2 **1a** and **1b**[15] under otherwise identical conditions, is indicative of a less favored bimetallic transition state in the pseudo-*meso* case. We thus conclude that it is the relative stereochemistry of the pseudo-C_2 system rather than the pseudo-*meso* system that constitutes the matched case in this reaction.

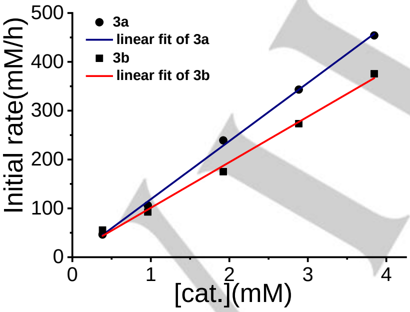
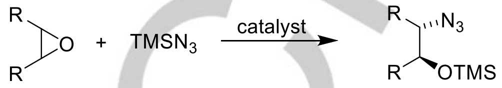


Figure 4. Fitting of a first order kinetic model to the observed kinetic data for the ring-opening of cyclohexene oxide with pseudo-C_s complexes **3a** and **3b** under solvent-free conditions.

The initial reaction rates for catalysis with **3a** and **3b** under solvent-free conditions were then investigated with catalyst concentrations varying from 0.01 to 0.1 mol%. The rates fit a first-order kinetic model with respect to the concentration of the catalyst, which is in agreement with a dominating bimolecular transition state (Figure 4).[15,18] In contrast to the bimetallic pseudo-*meso* catalysts **3a** and **3b**, the corresponding mixtures of monosalen catalysts follow a second order kinetic model with respect to the catalyst.[15,18] From Fig. 4 it is clear that complex **3a** catalyzes the reaction faster than **3b**. The Cr-Mn is thus a more efficient combination than Cr-Co in the pseudo-meso-case, which is in good agreement with both the C_2- and pseudo-C_2 systems.[18-19]

Table 2. Ring-opening of various *meso*-epoxides with $TMSN_3$ catalyzed by pseudo-*meso* bissalen complexes under solvent-free conditions.[a]



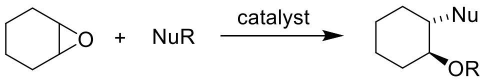
Entry	R	Catalyst (mol%)	Yield[b] (%)	*ee*[c][d][e] (%)	t(d)
1	$-CH_3$	**3a**(0.1)	50	23	5
2	$-CH_3$	**3b**(0.1)	35	17	5
3	$-(CH_2)_3-$	**3a**(0.1)	> 99	63	5
4	$-(CH_2)_3-$	**3b**(0.1)	> 99	76	5
5	$-(CH_2)_5-$	**3a**(0.1)	50	10	7
6	$-(CH_2)_5-$	**3b**(0.1)	11	14	7

[a] Reaction conditions: r.t, *meso*-epoxide (0.5 mmol), $TMSN_3$ (0.6 mmol). [b] Determined by ^1H NMR with 1,2,4,5-tetramethylbenzene as internal standard. [c] Determined by GC. [d] The absolute configuration was determined by comparison of the optical rotation with the literature value. [e] The major configuration is (*S*,*S*).

The substrate scope was also explored. The ring-opening reaction of cyclopentene oxide with $TMSN_3$ as the nucleophile gave the highest observed selectivities for the pseudo-*meso* system with 76% and 63% *ee* for **3b** and **3a**, respectively (Table 2, entries 4 and 3). The acyclic *meso*-butene oxide gave moderate *ee*'s of 23% with **3a** and 17% with **3b** (Table 2, entries 2 and 1**)**. With cycloheptene oxide, the *ee*'s dropped to around 10% for both catalysts (Table 2, entries 5 and 6).

Other nucleophiles than $TMSN_3$ were also investigated. Within all the entries, the asymmetric ring opening using **3a** as catalyst and water as the nucleophile gave the highest *ee* of 57% (Table 3, entry 1). The same reaction catalyzed by **3b** (Table 3, entry 2), gave both a low enantioselectivity and yield. For the other nucleophiles studied (PhSH, TMSCN and TMSCl), both catalysts **3a** and **3b** gave low *ee's* in the resulting products (Table 3, entries 3-8). In terms of absolute configuration, for most nucleophiles studied, the major enantiomers follows that of the ring opening of epoxides by $TMSN_3$, i.e. (*S*,*S*). In contrast, when H_2O was employed as the nucleophile and **3a**/**3b** as the catalyst, the opposite major absolute configuration of the product, i.e. (*R*,*R*), was favored.

Table 3. Ring-opening of cyclohexene oxide with various nucleophiles catalyzed by pseudo-C_s bissalen complexes under solvent-free conditions.[a]



Entry	NuR	Catalyst (mol%)	Yield[b] (%)	*ee*[e] (%)	t(d)
1	H_2O	**3a**(0.1)	5	57[c][g]	5
2	H_2O	**3b**(0.1)	31	17[c][g]	5
3	PhSH	**3a**(0.1)	> 99	15[d][h]	7
4	PhSH	**3b**(0.1)	> 99	17[d][h]	7
5	TMSCN	**3a**(0.1)	10	4[c][f]	6
6	TMSCN	**3b**(0.1)	11	4[c][f]	6
7	TMSCl	**3a**(0.1)	> 99	4[c][h]	1
8	TMSCl	**3b**(0.1)	> 99	6[c][h]	1

[a] Reaction conditions: r.t, cyclohexene oxide (0.5 mmol), NuR (0.6 mmol). [b] Determined by ^{1}H NMR spectroscopy with 1,2,4,5-tetramethylbenzene as internal standard. [c] Determined by GC. [d] Determined by HPLC. e] The absolute configuration was determined by comparison with that reported in the literature. [f] The major configuration is (*S*,*R*) [g] The major configuration is (*R*,*R*). [h] The major configuration is (*S*,*S*).

In summary, for the first time chiral bimetallic bis-salen catalysts, based on the desymmetrization of *meso*-ligands containing two enantiotopic coordination sites by the coordination of two different metal ions, have been designed, synthesized and evaluated in catalysis. The system was shown capable of enantiotopic discrimination in asymmetric nucleophilic ring opening of *meso*-epoxides with up to quantitative yields, and with up to 76% *ee*. As such, the study touches upon how seemingly small modifications that break the symmetry of a *meso*-ligand can be used to induce substantial *ee*'s in the products of catalytic reactions. Beyond synthetic considerations, we envision that catalysts of the described type could find applications as mechanistic probes: The two metal ions are surrounded by complimentary chiral environments, thus the enantiomeric outcome of a reaction should reflect the role of each metal ion in the stereo-discriminating step. Finally, a molecular equivalent to a structure that is chiral merely through the presence of two different spheres at positions related by a mirror plane is not without a certain aesthetic appeal (Figure 2, bottom). Further investigation of this catalytic system in other contexts as well as applications in synthesis are under way and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: pseudo-meso • bissalen • asymmetric ring opening

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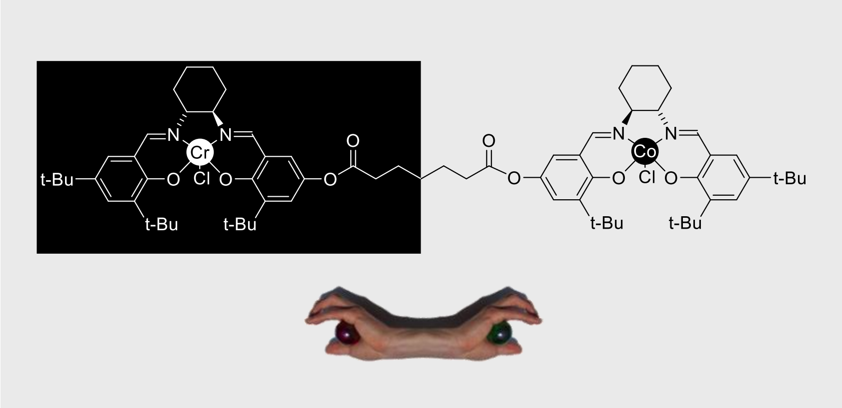
COMMUNICATION



Just barely chiral: A meso-ligand, desymmetrized by coordination of two different metal ions, gives a pseudo-meso catalyst. This catalyst system mediates opening of meso-epoxides in moderate ee's and excellent yields.

Yutang Li, Anna Lidskog, Helena Armengol-Relats, Thanh Huong Pham, Antoine Favraud, Maxime Nicolas, Sami Dawaigher, Zeyun Xiao, Dayou Ma, Emil Lindbäck, Daniel Strand, Kenneth Wärnmark**

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Title
Enantiotopic Discrimination by Coordination-Desymmetrized meso-Ligands