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Highly Active Oligomeric (salen)Co Catalysts for Asymmetric Epoxide Ring-Opening Reactions

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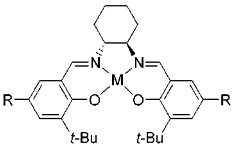
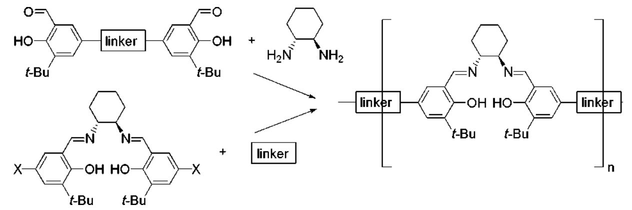
Cooperative bimetallic catalysis has been documented in several recently reported asymmetric epoxide opening reactions that display second-order kinetic dependence on catalyst, specific requirements for multiple metal ions, and/or pronounced catalyst nonlinear effects.[1] In such systems, one metal is proposed to serve as Lewis acid for epoxide activation and another as counterion for the nucleophile. In this mechanistic context, complexes that contain multiple metal centers in appropriate relative proximity and orientation can provide improved reactivity relative to monometallic catalysts. For example, chiral metal salen complexes such as **1** are effective catalysts for asymmetric epoxide ring-opening reactions, and operate by a second-order mechanism.[2] Linking these catalysts as dimers[3] or to polymeric[4] or dendrimeric[5] frameworks leads to catalytic systems with similar enantioselectivity and substantially enhanced reactivity relative to **1**. The synthetic utility of multimeric catalysts prepared in this manner is limited, however, by the inefficiency of their syntheses.[6] We report here new, easily synthesized oligomeric analogues of **1** that exhibit not only remarkably enhanced reactivity, but also significantly higher enantioselectivity relative to **1**.



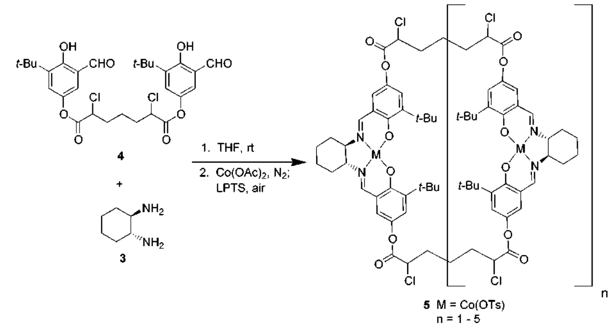
(*R,R*)-1: R = *t*-Bu
(*R,R*)-2: R = OC(O)CH(Cl)CH$_3$
a: M = Co
b: M = Co(OAc)
c: M = Co(OTs)

The construction of oligomers or polymers consisting of repeating C_2 symmetric salen units would circumvent the problems associated with the preparation of unsymmetrical salen derivatives (Scheme 1).[7] Extensive studies were carried out to establish the optimal strategy for oligomerization of C_2-symmetric salen units, with evaluation of not only the two condensation strategies outlined in Scheme 1, but also of such variables as linker identity, use of endcaps, and reaction solvent and temperature. Ultimately, it was found that oligomerization could be effected cleanly by condensation of (*R,R*)-diaminocyclohexane (**3**) and dialdehyde **4** in solvents such as THF (Scheme 2).[8,9] Subsequent metal insertion and air oxidation in the presence of lutidinium *p*-toluenesulfonate (LPTS) afforded a mixture of oligo-(salen)Co(OTs) complexes (**5**). Mass spectral (FAB$^+$-TOF) and ^{13}C NMR data indicated the exclusive formation of cyclic oligomers containing 2−6 metal-(salen) units.[10]

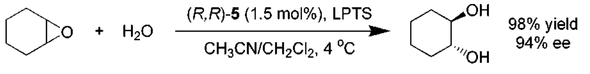
Scheme 1. Strategies for Polymerization of C_2 Symmetric Salen Ligands



Scheme 2. Preparation of the Cyclic Oligosalen Catalysts



Asymmetric hydrolysis of cyclohexene oxide (eq 1) was selected as a challenging test of the reactivity of **5**, as this reaction has proven to be very difficult to catalyze with monomeric (salen)-Co complexes.[11] At a catalyst loading of 1.5 mol % with respect to Co (i.e. 1.5/*n* mol % with respect to the oligmer mixture **5**),[12] hydrolysis of cyclohexene oxide was complete within 11 h providing the corresponding *trans*-1,2-diol in 94−96% ee. As reflected by the data in Figure 1, significant enhancements in both rate and enantioselectivity were observed relative to monomeric catalysts.



(1)

The catalytic asymmetric ring-opening of epoxides with alcohols as nucleophiles is a second reaction class that has proven particularly difficult to effect, with no examples reported to date.[13] In the context of kinetic resolution of terminal epoxides, alcoholic

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(1) (a) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924−10925. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen. E. N. *Science* **1997**, *277*, 936−938. (c) McCleland, B. W.; Nugent, W. A.; Finn, M. G. *J. Org. Chem.* **1998**, *63*, 6656−6666. (d) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252−2260. (e) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.

(2) For reviews, see: (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; pp 1309−1326. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431.

(3) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780−10781.

(4) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147−4154.

(5) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604−3607.

(6) This inefficiency stems from the absence of local C_2 symmetry in the individual salen units, as present in **1**. The condensation of two different salicylaldehyde derivatives with 1,2-diaminocyclohexane provides a statistical mixture of desired unsymmetrical and undesired symmetrical salen ligands that are readily separable only by chromatography.

(7) For recent examples of polymeric catalysts, see: (a) Rossi, P.; Felluga, F.; Tecilla, P.; Foermaggio, F.; Crisma, M.; Toniolo, C.; Scrimin, P. *J. Am. Chem. Soc.* **1999**, *121*, 6948−6949. (b) Fan, Q.; Ren, C.; Yeung, C.; Hu, W.; Chan, A. S. C. *J. Am. Chem. Soc.* **1999**, *121*, 7407−7408. (c) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500−6501.

(8) The importance of chlorine substituents on the linker was established through studies on the model monomer catalyst **2**, which was found to display reactivity and enantioselectivity similar to **1**. Dialdehyde **4** was synthesized as a mixture of diastereomers in two steps from pimelic acid via the corresponding α,α′-dichlorodiacid chloride (see Supporting Information). Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.

(9) Full experimental details, spectral data for new compounds and ee determinations are presented in the Supporting Information.

(10) For previous examples of cyclic disalen derivatives, see: (a) Huck, W. T. S.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 273−276. (b) Li, Z.; Jablonski, C. *Chem. Commun.* **1999**, 1531−1532.

(11) For asymmetric ring-opening of meso epoxides with other oxygen nucleophiles, see ref 1d and: (a) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, 773−776. (b) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 11008−11009. (c) Weijers, C. A. G. M. *Tetrahedron: Asymmetry* **1997**, *8*, 639−647.

(12) The MW/Co of **5** is independent of *n*.

10.1021/ja005867b CCC: $20.00

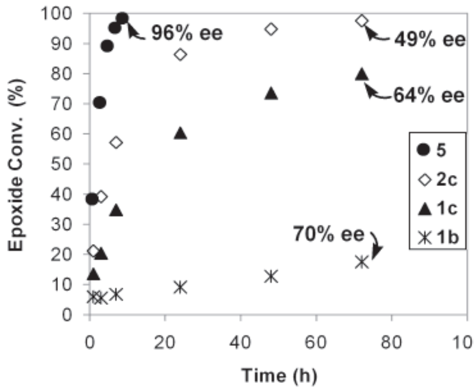
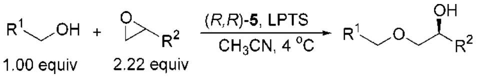


Figure 1. Asymmetric hydrolysis of cyclohexene oxide catalyzed by (salen)Co complexes. Reactions were carried out with $[\text{epoxide}]_0 = 2.5$ M in 1:1 CH_3CN:CH_2Cl_2 at 4 °C. Conversion was determined by GC analysis relative to an internal standard.

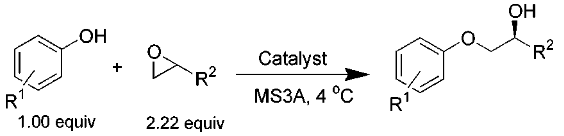
Table 1. Kinetic Resolution of Epoxides with Alcohols Catalyzed by **5**[a]



entry	R^1	R^2	Co (mol %)[b]	yield (%)[c]	ee (%)[d]
1	C_6H_5	$(CH_2)_3CH_3$	2.0	87	98
2	(TMS)CH_2	$(CH_2)_3CH_3$	0.2	97	99
3	H	$(CH_2)_3CH_3$	0.1	96	94
4	2-BrC_6H_4	$(CH_2)_3CH_3$	0.1	99	>99
5	4-(OMe)C_6H_4	$(CH_2)_3CH_3$	2.0	62	94
6	2-(NO_2)C_6H_4	$(CH_2)_3CH_3$	0.5	98	99
7	$CH_2{=}CH$	$(CH_2)_3CH_3$	0.5	87	97
8	C_6H_5	CH_2Cl	2.0	91	98
9	C_6H_5	CH_2O(allyl)	2.0	95	98

[a] Reactions were carried out with $[\text{epoxide}]_0 = 5$ M in CH_3CN for 3−24 h. See Supporting Information for details. [b] Catalyst loading on a per Co basis relative to alcohol. [c] Isolated yields based on alcohol. [d] Determined by chiral HPLC or GC analysis.

Table 2. Preparation of α-Aryloxy Alcohols by Kinetic Resolution of Terminal epoxides with phenols catalyzed by (salen)Co Complexes[a]



entry	R^1	R^2	catalyst	Co (mol %)[b]	yield (%)[c]	ee (%)[d]
1	H	CH_2Cl	monomer (**1c**)	4.0[e]	96	99
			oligomer (**5**)	0.25	99	99
2	*o*-O(allyl)	CH_2Cl	**1c**	4.4	48	84
			5	0.25	99	98
3	H	C_6H_5	**1c**	4.0	[f]	n.d.
			5	1.0	60	97
4	H	*c*-hexyl	**1c**	8.0	89	94
			5	0.5	99	98
5	*o*-Cl	*n*-butyl	**1c**	4.0	80[g]	68
			5	0.8	98	99

[a] Reactions were carried out with $[\text{epoxide}]_0 = 5$ M in TBME (**1c**) or CH_3CN (**5**) for 4−24 h unless indicated otherwise. See Supporting Information for details. [b] Catalyst loading on a per Co basis relative to phenol. [c] Isolated yields based on phenol. [d] Determined by chiral HPLC or GC analysis. [e] Reference 17. [f] After 10 d, the reaction had proceeded to 63% conversion of phenol to afford a 2:3 mixture of regioisomeric products favoring internal attack. [g] 72 h reaction time.

ring opening provides an attractive strategy for the direct preparation of optically active monoprotected 1,2-diols. The model reaction of benzyl alcohol and (±)-1,2-epoxyhexane was catalyzed by **5** with complete regioselectivity to afford 1-benzyloxy-2-hexanol in highly enantioenriched form, while monomeric catalysts displayed very low levels of reactivity. A variety of alcohols and epoxides were found to participate effectively in the ring opening reaction catalyzed by **5** (Table 1). Thus, 1,2-diols bearing benzyl, substituted benzyl,[14] allyl, and SEM protection on the primary alcohol were synthesized in high yield and enantioselectivity, and with complete regioselectivity.

The enhanced reactivity displayed by **5** prompted us to evaluate its activity in the hydrolytic kinetic resolution (HKR) of terminal epoxides.[1b] Using conditions optimized for isolation of either epoxide or diol, the use of **5** allowed a 10- to 50-fold decrease in Co concentration, with a simultaneous decrease in reaction time by a factor of up to 16.[15] The results with epichlorohydrin highlight the practical potential of the new catalyst in the HKR: under solvent-free conditions, 0.5 mol were resolved in 11 h at room temperature using only 50 mg of catalyst, providing 23 g of recovered epoxide in >99% ee.

Similar improvements in reactivity relative to monomeric complexes were observed in the kinetic resolution of terminal epoxides with phenols (Table 2). Use of **5** allows substantial decreases in catalyst loading and provides improved enantioselectivity in many cases (entries 1, 4, and 5). More striking, perhaps, are the epoxide−phenol combinations that were unreactive with catalyst **1c**, but that provide the α-aryloxy alcohols in high yield, ee, and regioselectivity in the presence of the oligosalen catalyst **5** (entries 2 and 3).

Analysis of the addition of *o*-chlorophenol to (±)-1,2-epoxyhexane in the presence of **5** revealed a first-order kinetic dependence on catalyst,[16] consistent with an intramolecular ring-opening event. This stands in contrast to the second-order dependence observed with monomeric catalysts, and provides a compelling indication that epoxide ring-opening with **5** takes place via cooperative reactivity of two (or possibly more)[2b] metal sites within the cyclic framework. Whereas the act of oligomerizing Co(salen) units was expected to lead to catalysts with enhanced reactivity relative to monomeric analogues, the observed improvements in enantioselectivity were unanticipated. The latter cannot be ascribed to perturbations to the local coordination environment of the catalysts, since monomer **2c** is effectively identical to **5** in that respect yet it displays enantioselectivities more akin to those of **1**. Instead, the cyclic architecture of **5** appears to constrain the salen units in relative orientations that lead to enhanced stereochemical communication in epoxide ring-opening reactions. A fuller understanding of the origin of this improvement is the focus of ongoing studies.

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Supporting Information Available: Experimental details of the catalyst synthesis, the epoxide ring-opening reactions, and the kinetic studies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA005867B

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(13) Racemic opening of epoxides with alcohols: Iranpoor, N.; Shekarriz, M.; Shiriny, F. *Synth. Commun.* **1998**, *28*, 347−366.

(14) For the use of 2-bromobenzyl ethers as protecting groups, see: Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148−7149.

(15) A table of specific examples is provided as Supporting Information.

(16) Initial rates were determined over a 10-fold concentration range of catalyst ([Co] = 0.93−9.3 mM). Reactions were performed at 30 °C with $[\text{epoxide}]_0 = 2.96$ M and $[\text{phenol}]_0 = 1.33$ M.

(17) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086−6087.