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[9] Crystal structure analyses: STOE-IPDS area detector, $Mo_{K\alpha}$ radiation, graphite monochromator, $T = 193(2)$ K, The structures were solved by direct methods and refined by full-matrix least-squares techniques against F^2.[10] Hydrogen atoms were placed in calculated positions and refined with anisotropic temperature factors; all other atoms were refined anisotropically. In all structures one of the *para*-isopropyl groups was disordered and was refined on two positions with the occupancy factors of 0.5 each. **5**: $C_{90}H_{138}SSi_4 \cdot 2C_7H_8$, triclinic, space group $P\bar{1}$, $a = 1421.59(6)$, $b = 1672.47(12)$, $c = 2291.20(15)$ pm, $\alpha = 69.142(8)$, $\beta = 72.451(7)$, $\gamma = 81.476(7)^\circ$, $Z = 2$, $V = 4848.5(5) \times 10^6$ pm^3, $\rho_{calcd} = 1.061$ g cm^{-3}, $2\theta_{max} = 52^\circ$; of 59638 measured reflections, 17716 were independent and 11548 observed with $I > 2\sigma(I)$, $R1 = 0.063$, w$R2$ (all data) $= 0.1671$ for 817 parameters. **6**: $C_{90}H_{138}SeSi_4 \cdot 2C_7H_8$, triclinic, space group $P\bar{1}$, $a = 1433.48(6)$, $b = 1674.36(10)$, $c = 2300.24(12)$ pm, $\alpha = 68.812(6)$, $\beta = 71.954(5)$, $\gamma = 81.111(6)^\circ$, $Z = 2$, $V = 4888.9(4) \times 10^6$ pm^3, $\rho_{calcd} = 1.084$ g cm^{-3}, $2\theta_{max} = 52^\circ$; of 60128 measured reflections, 17891 were independent and 12099 observed with $I > 2\sigma(I)$. $R1 = 0.0526$, w$R2$ (all data) $= 0.1459$ for 817 parameters. **7**: $C_{90}H_{138}Si_4Te \cdot 2C_7H_8$, triclinic, space group $P\bar{1}$ $a = 1453.30(8)$, $b = 1697.00(9)$, $c = 2029.62(15)$ pm, $\alpha = 95.390(8)$, $\beta = 90.089(8)$, $\gamma = 100.912(6)^\circ$, $Z = 2$, $V = 4892.4(5) \times 10^6$ pm^3, $\rho_{calcd} = 1.116$ g cm^{-3}, $2\theta_{max} = 52^\circ$; of 60004 measured reflections, 17885 were independent and 8548 observed with $I > 2\sigma(I)$. $R1 = 0.0548$, w$R2$ (all data) $= 0.0985$ for 879 parameters. Crystallogaphic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-116 227 (**5**), CCDC-116 228 (**6**), and CCDC-116 229 (**7**) Copies of the data can be obtained free of charge on application to CCDC, 12 Union Raod, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Regio- and Enantioselective Cyclization of Epoxy Alcohols Catalyzed by a [Co^{III}(salen)] Complex**

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The construction of substituted oxygen heterocycles stands as a significant target for synthetic methodology, mainly as a consequence of the abundance of interesting natural products that contain this structural unit.[1] One of the most important approaches to cyclic ether synthesis involves the intramolecular cyclization of epoxy alcohols, whereby stereospecific epoxide opening offers a stereocontrolled route to these targets.[2] An inherent challenge to this strategy is the control of the regioselectivity of the ring opening of epoxy alcohols. Our own interest in intermolecular asymmetric ring opening (ARO) reactions[3] led us to the question of whether chiral catalysts might influence the regiochemical outcome of intramolecular cyclizations of epoxy alcohol. Such regiocontrol would be rendered even more powerful if accompanied by enantiocontrol, so that racemic or prochiral substrates could be cyclized to produce enantioenriched oxygen heterocycles. Herein we disclose the first intramolecular ARO reaction catalyzed by a chiral [Co^{III}(salen)] complex, with the successful attainment of both regio- and stereochemical elements of control (H_2salen = bis(salicylidene)ethylenediamine).

To date, terminal epoxides represent the most successful substrate class identified in Co-catalyzed ARO reactions. While products arising from *exo* attack are favored under either acidic or basic conditions for epoxides such as 4,5-epoxypentanol (**2**)[4], we were quite surprised to observe that (*R*,*R*)-**1** catalyzed the *endo*-selective ring closure of **2** to afford the tetrahydropyranol **5** as the major cyclization product (12:1) in 46% yield (by GC). Equally impressive was the remarkable enantiodiscrimination displayed in this reaction. Racemic **2** underwent efficient kinetic resolution to afford the *endo* product in 95% *ee*,[5] which was isolated in 41% yield following benzoylation of the crude reaction mixture and subsequent purification by flash chromatography (Table 1). The [Co^{III}(salen)] complex **1** also catalyzed the *endo*-selective kinetic resolution of racemic 5,6-epoxyhexan-1-ol (**3**) to afford the hydroxyoxepane **6** in 47% yield (39% yield of isolated product) and 94% *ee*. A dramatic decrease in the reaction rate was observed with the homologous substrate **4** containing seven carbon atoms; no detectable cyclization products were observed after 48 hours. Nonetheless, the ability of (*R*,*R*)-**1** to override the inherent stereoelectronic preference for *exo* attack in the ring opening of epoxides **2** and

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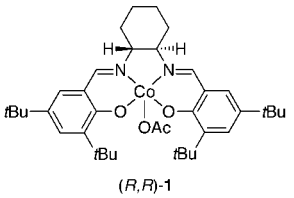
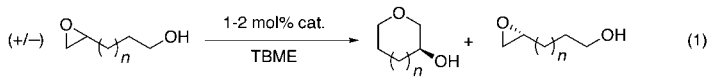
Table 1. Intramolecular kinetic resolution of epoxy alcohols catalyzed by (*R*,*R*)-**1** [Eq. (1)].



(*R*,*R*)-**1**



2-4 **5**: *n*=1 **6**: *n*=2 (1)

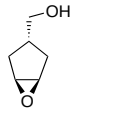
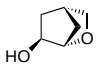
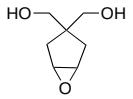
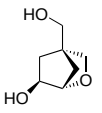
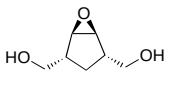
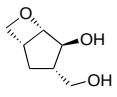
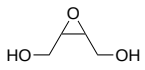
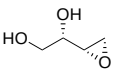
Epoxide	*T* [°C]	*t* [h]	*ee* (product)[a] [%]	Yield[b] [%]	*ee* (epoxide)[c] [%]	Yield[b] [%]
2 (*n* = 1)	0	1	95	46 (41)	93	50
3 (*n* = 2)	0	7	94	47 (39)	98	50
4 (*n* = 3)	23	48	n.r.[d]	n.r.	n.r.	n.r.

[a] Determined by chiral HPLC (Chiracel AD) of the benzoate esters. [b] GC yields. The yields of the isolated benzoate esters of **5** and **6** are given in parenthesis. [c] The

3[6] coupled with the high enantioselectivity associated with this mode of cyclization was noteworthy.

Having established the viability of intramolecular cyclization[7] to effect the kinetic resolution of terminal epoxy alcohols, we next turned our attention to the enantioselective cyclization of *meso* substrates. Despite the fact that disubstituted epoxides have proven generally unreactive under hydrolytic conditions with catalyst **1**, good reactivity was observed in the cyclization of 1,2-disubstituted epoxy diols (Table 2). For example, epoxy alcohol **7** cleanly cyclized under

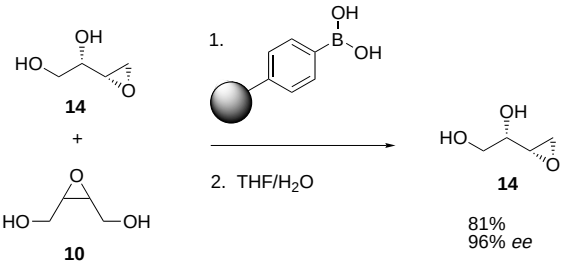
Table 2. Intramolecular desymmetrization of *meso* epoxy alcohols catalyzed by (*R*,*R*)-**1**.

Substrate	Product	*ee* [%][a]	Yield [%][b]
 **7**	 **11**	98	96
 **8**	 **12**	95	86
 **9**	 **13**	99	45[c]
 **10**	 **14**	96[d]	81

[a] Determined by chiral GC or HPLC. See the supporting information for details. [b] Yields of isolated product. [c] Isolated as the mono-TIPS ether (TIPS = triisopropylsilyl). [d] Absolute configuration established by comparison of optical rotation to literature values. All other assignments are made by analogy.

the influence of Co catalysis to afford the desymmetrized bicyclic ether **11** in 96% yield and 98% *ee*. Similarly, the *gem*-bishydroxymethylcyclopentene oxide **8**[8] also underwent highly enantioselective ring closure to afford the bicyclic ring system **12** in 86% yield and 95% *ee*. An interesting regiochemical issue was presented by the *meso* epoxy diol **9**, which can potentially cyclize in either a 4-*exo* or 5-*endo* fashion to yield novel bicyclic structures. In the event, substrate **9** underwent exclusive 4-*exo* ring closure to afford oxetane **13** as the sole product, which was isolated from the recovered starting material (50%, GC) in 45% yield and 99% *ee*.[9]

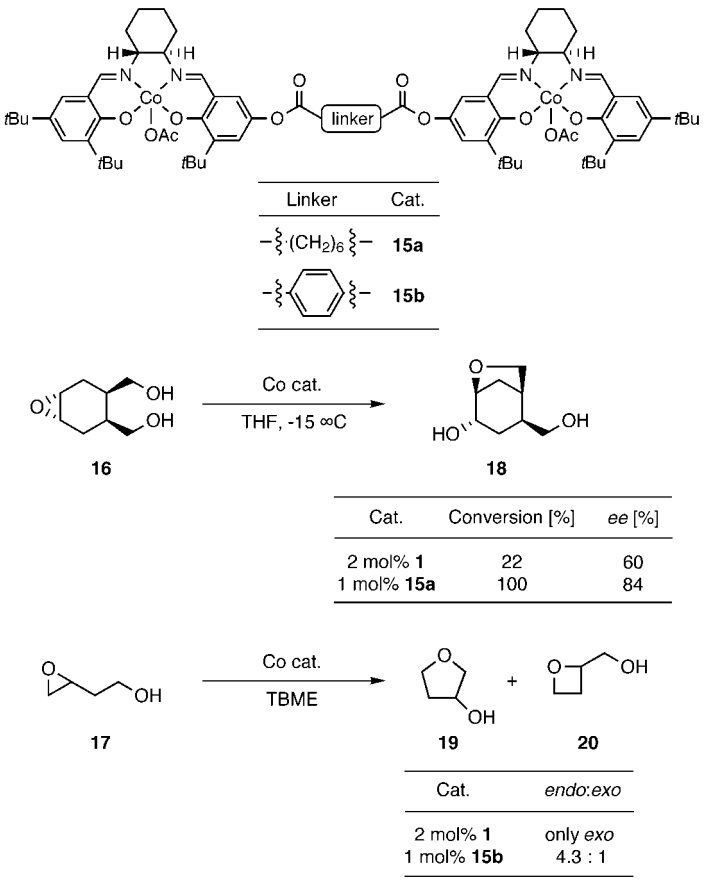
The *meso* epoxy diol **10**, readily prepared as a white crystalline solid by epoxidation of *cis*-2-buten-1,4-diol with *m*-chloroperbenzoic acid (*m*CPBA), was a particularly interesting substrate in the intramolecular ring opening reaction. Diol **10** underwent [Co(salen)]-catalyzed Payne rearrangement[10] to afford the 1,2-anhydrothreitol product **14**.[11] GC analysis of this reaction indicated incomplete conversion of **10**, and efforts to drive the rearrangement to completion were unsuccessful. In order to isolate the desired 1,2-diol product from the unchanged 1,4-diol **10**, a resin capture strategy utilizing polystyryl boronic acid[12] was successfully applied.[13] Following hydrolysis of the immobilized boronate ester the epoxy diol **14** was isolated in 81% yield and 96% *ee* (Scheme 1).



Scheme 1. Resin capture strategy for isolation of **14**.

Preliminary evidence suggests a preferred bimetallic cyclization step for these ring-closure reactions of epoxy alcohols wherein Co^{III} complexes serve dual roles of activating both epoxide and alcohol.[14] In the ring closure of **3**, for instance, a dramatic rate enhancement is observed with the dimeric [Co^{III}(salen)] catalyst **15a** in which two [Co(salen)] units are covalently tethered through an aliphatic diester chain.[15] Moreover, results obtained in the cyclization of two substrates which proved problematic with catalyst **1** provided additional support for a favored bimetallic pathway.

The outcome of the enantioselective desymmetrization of **16** was significantly improved when dimeric catalyst **15a** was used in place of monomeric catalyst **1**. Cooperative reactivity of the [Co(salen)] units not only increased the reaction rate relative to that with the monomeric catalyst, but also improved enantioselection in the formation of **18** from 60% *ee* (with **1**) to 84% *ee* (Scheme 2). It appears likely that the higher enantioselectivity with **15a** might originate from enhanced stereochemical communication between the two tethered chiral Co catalysts relative to a less-selective mono-



Scheme 2. Cyclization with dimeric [Co(salen)] complexes. TBME = *tert*-butyl methyl ether.

metallic pathway that is more easily accessed with monomeric catalyst **1**.

The effect of enhanced cooperative catalysis was manifested in a dramatic way in the regioselectivity of the cyclization of epoxy alcohol **17**. With monomeric catalyst **1** only the *exo* cyclization product **20** was obtained, whereas cyclization under the influence of dimeric catalyst **15b** led to preferential formation of the *endo* tetrahydrofuran product **19**. A monometallic Lewis acid mechanism might explain the exclusive *exo* selectivity shown by catalyst **1**, while dual activation of both the epoxide and hydroxyl groups by dimeric **15b** may create a sterically more-demanding transition state assembly that now favors the *endo* product **19** as the major cyclic product.

The [Co(salen)]-catalyzed intramolecular ARO reaction thus allows the synthesis of novel cyclic and bicyclic ethers ranging from three- to seven-membered rings in good yields and high enantiopurity. This methodology can be applied effectively to the kinetic resolution of racemic epoxy alcohols as well as to the desymmetrization of *meso* substrates, in which the [Co^{III}(salen)] catalyst exhibits exceptional regio- and enantiocontrol. Exploration of the synthetic utility of the cyclization products as well as elucidation of the reaction mechanisms of these [Co(salen)]-catalyzed processes remain important goals in our research.

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