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Enantioselective Intramolecular Openings of Oxetanes Catalyzed by (salen)Co(III) Complexes: Access to Enantioenriched Tetrahydrofurans

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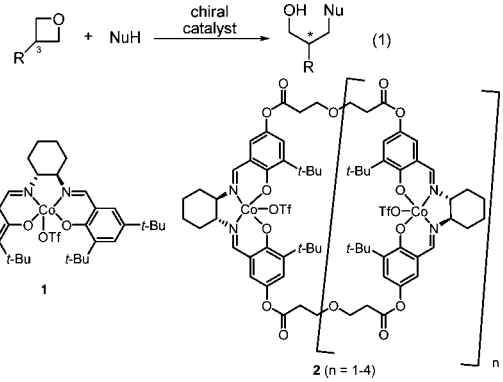
Oxetanes are receiving increased attention as intermediates in organic synthesis and drug discovery, thanks in part to the development of new methods for their preparation.[1,2] At this stage, few enantioselective reactions of oxetanes have been realized; these include ring expansions catalyzed by chiral copper complexes[3] and ring openings with organolithium reagents promoted by a chiral boron reagent.[4] We became intrigued by the possibility of activating oxetanes with (salen)Co(III) complexes for enantioselective ring opening (e.g., eq 1), given the successful application of these catalysts in the asymmetric ring-opening of epoxides.[5,6] Herein, we describe intramolecular openings of oxetanes catalyzed by (salen)Co(III) complexes **1** and **2** to afford functionalized tetrahydrofurans in high yields and enantioselectivities.

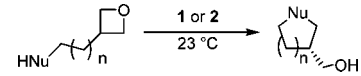


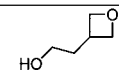
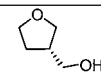
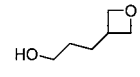
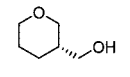
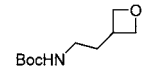
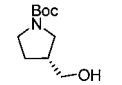
Lewis acid catalysis represents a viable approach to enantioselective ring opening of oxetanes, given that oxetanes possess lower ring strain[7] but superior Lewis basicity[8] relative to epoxides. Mechanistic studies of (salen)Co(III)-catalyzed reactions have established that epoxide ring openings occur through cooperative bimetallic mechanisms involving simultaneous activation of nucleophile and Lewis acid activation of epoxide.[9] By enforcing cooperative interactions between (salen)Co units, oligomeric catalysts such as **2** have been shown to provide greatly enhanced reactivity compared with monomeric catalysts.[10]

We chose to examine achiral 3-substituted oxetanes as potential reacting partners, as these substrates are readily accessed from malonate esters or 3-oxetanone[11] and are susceptible, in principle, to enantioselective ring opening with nucleophiles other than water. Intermolecular additions to 3-butyloxetane were studied using nucleophiles proven effective in (salen)Co(III)-catalyzed epoxide ring-opening reactions, such as methanol,[10c,e] 4-methoxyphenol,[10c,e,12] and *tert*-butyl carbamate.[13,10e] However, no desired ring-opened product was obtained in any case using either 10 mol% monomeric (salen)Co(III) complex **1** or 2 mol% of the oligomeric complex **2**.

Encouraged by the excellent reactivity and enantioselectivity obtained in intramolecular epoxide openings with alcohols using monomeric (salen)Co(III),[14] we examined intramolecular opening of oxetanes as a potential route to pharmacologically active and synthetically useful 3-substituted heterocycles (Table 1).[15−17] A variety of oxetane-containing tethered nucleophiles were prepared and treated with catalytic levels of (salen)Co(III) complexes **1** and **2**. Cyclization to provide tetrahydrofuran **4a** proceeded in excellent enantioselectivity and yield using either the monomeric or oligomeric catalyst. Cyclization of **5** to tetrahydropyran **6** proceeded substantially more slowly, yet with high enantioselectivity and yield using oligomeric catalyst **2**, whereas cyclizations to provide seven-membered ring oxepanes were unsuccessful. Oxetane **7** bearing a carbamate nucleophilic component underwent ring opening with diminished yield and enantioselectivity.

Table 1. Representative Intramolecular Oxetane Ring Openings



entry	substrate	product	catalyst (mol%)	time (h)	yield[a]	ee[b] (%)
1			**1** (1)	1	92[d]	98[e]
2			**2** (0.01)	2	93[e]	96[c]
	3a	**4a**				
3			**1** (10)	96	38[d]	7
4			**2** (0.1)	96	89[e]	96
	5	**6**				
7			**1** (10)	72	72[f]	50[c]
8			**2** (10)	72	70[e]	10[c]
	7	**8**				

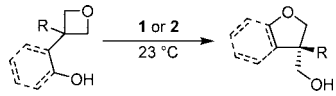
[a] Isolated yield after flash chromatography on SiO_2. [b] Determined by chiral HPLC analysis of the benzoylated product unless noted otherwise. [c] Determined by chiral GC analysis of the trifluoroacetylated product. [d] Reaction carried out in the absence of solvent. [e] Reaction carried out in MeCN (6 M). [f] Reaction carried out in TBME (6 M).

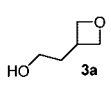
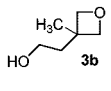
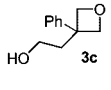
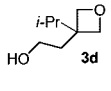
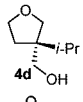
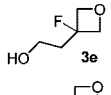
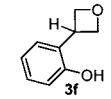
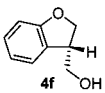
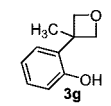
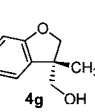
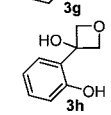
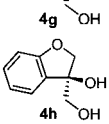
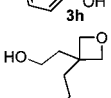
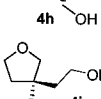
The scope of the intramolecular opening of oxetanes with *O*-centered nucleophiles was examined with a variety of achiral oxetane substrates bearing nucleophilic appendages (Table 2). A series of substituted ethanol derivatives underwent ring opening with high enantioselectivity and yield (entries 3−10). Alkyl (**3b−c, 3i**) and phenyl (**3d**) substitution at the 3-position of the oxetane was tolerated, affording products bearing quaternary stereocenters.[18] Incorporation of a fluorine substituent in the substrate provided tetrahydrofuran **4e**, which contains an interesting fluorine-bearing stereocenter. Ring opening of phenolic substrates (**3f−h**) provided enantioenriched dihyrobenzofurans; however, higher catalyst loadings were required to attain high levels of enantioselectivity.

Both monomeric and oligomeric complexes proved to be efficient catalysts for the enantioselective ring opening of oxetanes, providing

10.1021/ja809176m CCC: $40.75

Table 2. Enantioselective Tetrahydrofuran and Benzodihydrofuran Synthesis



entry	substrate	product	catalyst (mol%)	time (h)	yield[a] (%)	ee[b] (%)
1			**1** (1.0)	1	92[c]	98[h]
2	**3a**	**4a**	**2**(0.01)	2	93[d]	96[h]
3			**1** (1.0)	6	87[c]	99
4	**3b**	**4b**	**2**(0.01)	6	88[d]	96
5			**1** (1.0)	24	96[e]	98
6	**3c**	**4c**	**2**(0.01)	24	98[d]	99
7			**1** (1.0)	2	93[c]	99
8	**3d**	**4d**	**2**(0.01)	12	97[d]	99
9			**1** (1.0)	7	87[c]	97[h]
10	**3e**	**4e**	**2**(0.01)	7	76[d]	98[h]
11			**1** (5)	8	94[c]	93
12	**3f**	**4f**	**2** (0.01)	6	89[d]	98
13			**1** (10)	8	77[e]	96
14	**3g**	**4g**	**2** (1)	8	95[d]	98
15			**1** (10)	96	79[f]	84
16	**3h**	**4h**	**2** (1)	6	94[g]	88
17			**1** (1)	5	88[c]	97
18	**3i**	**4i**	**2** (0.01)	5	98[d]	99

[a] Isolated yield, after flash chromatography on SiO_2. [b] Determined by chiral HPLC analysis of the benzoylated product unless noted otherwise. [c] Reaction carried out in the absence of solvent. [d] Reaction carried out in MeCN (6 M). [e] Reaction carried out in TBME (6 M). [f] TBME (1 M). [g] MeCN (1 M). [h] Determined by chiral GC analysis of the trifluoroacetylated product.

access to a wide variety of tetrahydrofurans in high enantioselectivity and yield. Monomeric catalyst **1** is easily accessed from the commercially available (salen)Co(II) complex by treatment with TfOH.[19] Reactions using this catalyst can be carried out either solvent-free or with small amounts of TBME and with catalyst loadings as low as 1 mol%. Oligomeric catalyst **2** displays enhanced efficiency and can be used in loadings as low as 0.01 mol%, often with improved enantioselectivity. We are now pursuing synthetic applications and mechanistic studies of the oxetane ring-opening reaction.

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Supporting Information Available: Representative experimental procedures, characterization data, chiral chromatographic analyses of racemic and enantiomerically enriched products, and complete refs 15a,b. This material is available free of charge via the Internet at http://pubs.acs.org

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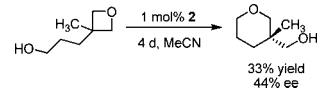
(18) Ring-opening reactions affording tetrahydropyrans bearing quaternary centers proceeded in low yield and enantioselectivity.



(19) For details of catalyst synthesis, see Supporting Information. For a similar procedure to make the (salen)CoOTs analogue of **1**, see: Stevenson, C. P.; Nielsen, L. P. C.; Jacobsen, E. N. *Org. Synth.* **2006**, *83*, 162−169.

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