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

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Abstract

The catalytic enantioselective intramolecular ring-opening of oxetanes with alcohols is catalyzed by (salen)Co(III) complexes. Either a monomeric or oligomeric catalyst can be used successfully in this transformation, providing 3-substituted tetrahydrofurans in both high yield and enantioselectivity. This methodology extends the range of electrophiles that can be activated toward highly enantioselective addition reactions by (salen)metal catalysts to an important new class.

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 complexes³ 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.

(1)

Lewis acid catalysis represents a viable approach to enantioselective ring opening of oxetanes, given that oxetanes possess lower ring strain⁷ but superior Lewis basicity⁸ 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 carbamate nucleophilic component underwent ring-opening with diminished yield and enantioselectivity.

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 dihydrobenzofurans; 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 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

catalyst (mol%)		time (h)	yield ^a (%)	ee ^b (%)
1	(1)	1	92 ^d	98
		2	93 ^e	96

product

4a

catalyst (mol%)time (h)yield ^a (%)ee ^b (%)		
1 (10)	96	38 ^d
2 (0.1)	96	89 ^e

product

catalyst (mol%) time (h) yield^a (%) ee^b (%)

1 (10) 72 72^f 50^c
2 (10) 72 70^e 10^c

product

f Reaction carried out in TBME (6 M).

Table 2
ofuran Synthesis

catalyst (mol%)time (h)yield ^a (%)ee ^b (%)
	1 (1.0)	1	92 ^c	98 ^h
		2 (0.01)	2	93 ^d	96 ^h

catalyst (mol%)time (h)yield^a (%)ee^b (%)

1 (1.0) 6 87^c 99
2 (0.01) 6 88^d 96

product

catalyst (mol%)		time (h)	yield ^a (%)	ee ^b (%)
1	(1.0)	24	96 ^c	98
	2 (0.01)	24	98 ^d	99
1	(1.0)	2	93 ^c	99
	2 (0.01)	12	97 ^d	99

product

product				catalyst (mol%)time (h)yield ^a (%)ee ^b (%)	
				1 (1.0)	7
				2 (0.01)	7
					87 ^c
					97 ^h
					76 ^d
					98 ^h

catalyst (mol%) time (h) yield^a (%) ee^b (%)

1 (5) 8 94^c 93

2 (0.01) 6 89^d 98

product

4f

product			catalyst (mol%)time (h)yield ^a (%)ee ^b (%)	
			1 (10)	8
			2 (1)	8
				77 ^c
				95 ^d
				96
				98

4a

product			
catalyst (mol%)time (h)yield ^a (%)ee ^b (%)			
1	(10)	96	79 ^f
2	(1)	6	94 ^g
			84
			88

4h

catalyst (mol%)time (h)yield^a (%)ee^b (%)

1 (1)	5	88 ^c	97
2 (0.01)	5	98 ^d	99

product

catalyst (mol%)time (h)yield^a (%)ee^b (%)

product