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Enantioselective Epoxidation of Cyclic 1,3-Dienes Catalyzed by a Sterically and Electronically Optimized (Salen)Mn Complex

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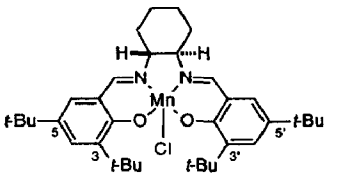
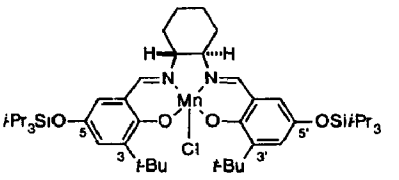
Summary: Chiral (salen)Mn(III)Cl complexes catalyze epoxidation of cyclic 1,3-dienes with moderate-to-good enantioselectivity. A new catalyst (**2**), bearing sterically hindered and electron donating OSi(*i*Pr)$_3$ (OTIPS) substituents, induces up to 12% higher selectivity than the previously-reported *tert*-butyl substituted analog **1**.

Cyclic vinyl epoxides serve as building blocks for the synthesis of a variety of biologically important structures.[1,2] While access to these epoxides in enantiomerically enriched form would clearly be valuable, no effective direct methods for their asymmetric synthesis have been developed to date. Conjugated cis-disubstituted alkenes constitute the best substrate class for asymmetric epoxidations catalyzed by chiral (salen)Mn complexes,[3] so cyclic 1,3-dienes might be predicted to be excellent candidates for this process. However, in the single reported example of asymmetric epoxidation of a cyclic diene,[4] we noted that 1,3-cyclooctadiene underwent epoxidation with only 45% ee employing (salen)Mn(III) catalyst **1**. Because of the potential importance of this class of alkenes in asymmetric epoxidation, we selected cyclic 1,3-dienes as model substrates for our studies of catalyst ligand optimization. The results of this investigation are outlined herein, including the report of a new chiral (salen)Mn complex **2** which affords slightly higher enantioselectivity than **1** with all alkenes studied to date.



(*R,R*)-1



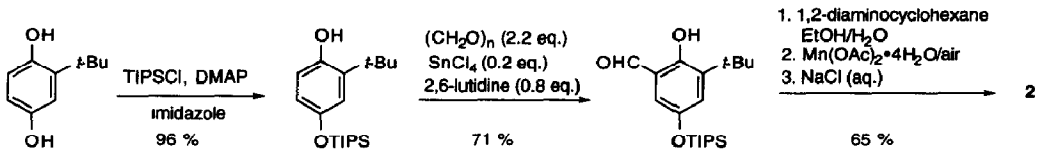
(*R,R*)-2

Both the steric and the electronic properties of substituents on the salen ligand have been shown to influence the enantioselectivity attainable in epoxidation with (salen)Mn(III) catalysts. The presence of bulky groups on the 3,3'- and 5,5'-positions of the salicylidene units leads to improved selectivity in the epoxidation of almost all olefin classes. This is attributable to steric inhibition of competing side-on approaches of the substrate to the putative Mn(V) oxo intermediate, with resulting substrate approach occurring near the

dissymmetric diimine bridge.[5] The electronic properties of the substituents on the 5 and 5' positions also play a significant role in determining enantioselectivity, with catalysts bearing electron-donating groups affording better selectivities than sterically similar electron withdrawing substituents.[6] Electron donating substituents attenuate the reactivity of the catalyst, resulting in a milder, more selective oxidant.[3]

Taken together, these observations suggest that salicylidene substituents that are both sterically bulky and electron-donating might effect a superimposition of beneficial properties on catalyst selectivity. In order to assess this possibility, a series of catalysts bearing bulky alkoxide or siloxide substituents at the 5 and 5' positions (e.g. R^2 = O*i*-Pr, O*t*-Bu, OTMS, OTES, OTIPS) were prepared and screened. Although good enantioselectivity was exhibited by all catalysts in epoxidation of model substrates, only the OTIPS-substituted catalyst **2** exhibited the desired combination of high selectivity and acceptable catalytic activity. Preparation of **2** was effected in a straightforward manner from *t*-butylhydroquinone (Scheme 1).

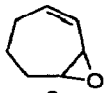
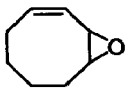
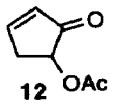
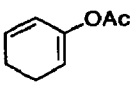
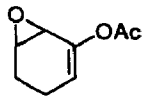
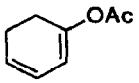
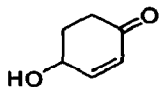
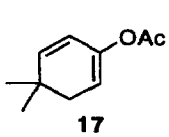
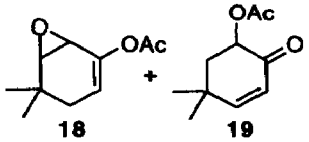
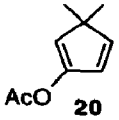
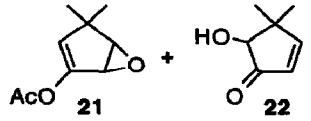
Scheme 1



Epoxidation of a variety of cyclic dienes was carried out at room temperature or at 4 °C with commercial bleach as oxidant and 4-5 mol% of **1** or **2** as catalyst.[7] In general, 2-3% better selectivities were obtained at the lower temperature. With excess bleach solution (1.2-1.5 eq. relative to substrate) and 5 mol% catalyst, complete diene conversions were obtained within 3-5 hours at 4 °C. The product vinylepoxides were found to be resistant to a second epoxidation, even upon exposure to excess oxidant. However, prolonged reaction led to gradual decomposition of the monoepoxides and reductions in yield. In most cases, GC analysis of crude reaction mixtures indicated that the reactions led to clean conversion to product. However, the isolated yields were diminished because of the sensitivity of the products to typical chromatographic supports. Solvent effects on stereoselectivity and conversion were small, with reactions run in ethyl ether generally affording higher ee's but lower catalyst turnover numbers compared to ethyl acetate or dichloromethane. Addition of 4-phenyl pyridine *N*-oxide (20 mol %) to the reaction media led to measurable increases in epoxide yield and rate.[8]

Results of epoxidation of cyclic 1,3-dienes mediated by catalysts **1** and **2** are summarized in Table 1. Consistently higher enantioselectivities were obtained with catalyst **2**, with differences in ee ranging from 1 to 12% depending on the diene. Epoxidation of the parent cyclic 1,3-dienes (**3**, **5**, **7**, **9**) occurred with modest selectivity (57-70% ee with catalyst **2**). In the case of 1,3-cyclohexadiene, epoxide **6** and benzene were generated in nearly equimolar amounts. Similar aromatization pathways were also observed in the oxidations of the substituted cyclohexadienes **13** and **15**. As of yet, effective protocols have not been found for uncoupling epoxidation pathways from aromatization in the oxidation of cyclohexadienes by the (salen)Mn complexes.

Table 1. Asymmetric Epoxidation of Cyclic 1,3-dienes[a]

Olefin	Major Product(s)	Catalyst	Solvent[b]	ee (%)[c]	Isolated Yield (%)
 3	 4	1	Me_3COMe	63[c]	40
		2	Et_2O	64[d]	45
 5	 6[e]	1	Et_2O	61	33
		2	Et_2O	65	30
 7	 8	1	EtOAc	64	73
		2	EtOAc	70	49
 9	 10	1	Et_2O	52	58
		2	Et_2O	57	55
 11	 12	1	EtOAc	69	40
		2	EtOAc	71	35
 13	 14	1	Et_2O	85	30
		2	Et_2O	90	32
 15	 16[f]	1	EtOAc	63	30
		2	EtOAc	68	47
 17	 18 + 19	1	EtOAc	**18**: 80 **19**: 77	**18**: 40 **19**: 20
		2	EtOAc	**18**: 91 **19**: 85	**18**: 39 **19**: 15
 20	 21 + 22	1	EtOAc	**21**: 67 **22**: 4	**21**: 30 **22**: 40
		2	EtOAc	**21**: 79 **22**: 4	**21**: 30 **22**: 42

[a] All reactions were carried out as described in footnote 7. [b] For each entry, the solvent shown led to highest enantioselectivity in the epoxidation reaction. [c]Unless noted otherwise, ee's were determined by GC on a commercial column (γ-cyclodextrin, trifluoroacetyl, 20 m x 0.25 mm, compounds **6**, **10**, **12**, **21**, **22**), or by ^1H NMR using Eu(hfc)3 as chiral shift reagent (compounds **8**, **14**, **16**, **18**, **19**). [d] Ee determined by GC (Cyclodex B 30 m capillary column) after hydrolysis to 1,4-cyclopentendiol and silylation. [e] The absolute configuration of the major enantiomer was determined to be (3*R*,4*S*)-(+).[9] [f] The absolute configuration of the major enantiomer was determined to be (4*S*)-(–).[10]

In general, higher enantioselectivity was attained in the oxidation of substituted cyclic 1,3-dienes.[11,12] Dienes **17** and **20** afforded mixtures of chiral oxidation products as a result of oxidation at either of the two diene double bonds. Oxidation at the acetate-bearing double bond in **20** lead to the hydroxy enone **22** in racemic form. A similar pathway was observed in the oxidation of **17**, although the less-hindered six-membered ring acetate **19** was stable to hydrolysis and did not undergo epimerization.

The high selectivity displayed in the epoxidation of cyclic 1,3-diene derivatives such as **13** demonstrates the utility of the (salen)Mn-catalyzed epoxidation in the preparation of highly oxygenated, cyclic chiral building blocks. Although the slightly higher enantioselectivity exhibited by **2** may not justify its use over the more readily available catalyst **1**, it reinforces the significant notion that both steric and electronic effects are important in determining asymmetric induction with salen ligand templates.

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6. Jacobsen, E.N.; Güler, M.L.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
7. The following epoxidation procedure is representative. To a solution of **7** (140 mg, 1.49 mmol), (*R,R*)-Mn complex **1** (47 mg, 0.074 mmol) and 4-phenyl pyridine *N*-oxide (51 mg, 0.29 mmol) in 15 ml of solvent was added 1.3 ml of 13% NaOCl solution. The reaction mixture was stirred at 4 °C and disappearance of starting material was monitored by TLC (product $R_f = 0.6$, hexane/ethyl acetate = 2:1). After 4 hours, the reaction mixture was extracted with ethyl acetate, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/ethyl acetate = 4/1) provided pure monoepoxide **8** (120 mg, 73%).
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11. Dienes **11**, **13**, **15**, **17**, and **20** were prepared by literature methods and purified by flash chromatography: a) House, H.O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362 b) Matty, J.; Trampe, G.; Runsink, J. *Chem. Ber.* **1988**, *121*, 1991. c) The acetates **11** and **20** were very unstable to purification on silica gel, and were isolated instead by chromatography on basic alumina.
12. All oxidation products were fully characterized by NMR and HRMS.

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