Highly Enantioselective, Catalytic Epoxidation of Trisubstituted Olefins

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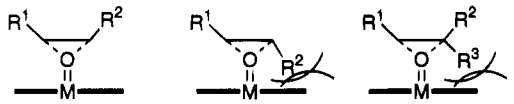
Summary: Chiral (salen)Mn(III) complexes have been found to be highly selective catalysts for the asymmetric epoxidation of several cyclic and acyclic trisubstituted olefins. These results are interpreted with a transition-state model for epoxidation involving a skewed, side-on approach of olefin to a (salen)Mn(oxo) intermediate.

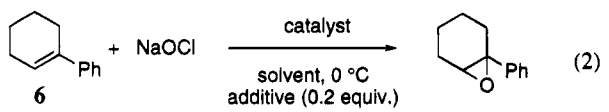
Chiral (salen)manganese(III) complexes have been demonstrated to be highly enantioselective catalysts for the epoxidation of conjugated cis disubstituted olefins.[1] In contrast, slow reaction rates and low enantioselectivities (<65% ee) are obtained with analogous trans-disubstituted olefins using these and related catalysts.[2] Transition-state geometries involving side-on approach of olefin in either a parallel or a skewed orientation relative to the ligand plane have been proposed to account for observed enantioselectivities, and these models also account for the observed rate differences (eq 1).[3] By



(1)

analogy, this model might also be used to predict that trisubstituted olefins should be poor substrates in epoxidation by oxo transfer catalysts, and this may explain why this important substrate class has remained essentially unstudied in asymmetric epoxidation.[1b,4] We report here that trisubstituted alkenes are in fact excellent substrates for the (salen)Mn-catalyzed epoxidation reaction, with high enantioselectivity attainable even with very bulky alkene substrates. We also address the implications of this unexpected, synthetically useful observation on the mechanism of epoxidation by metal oxo complexes.

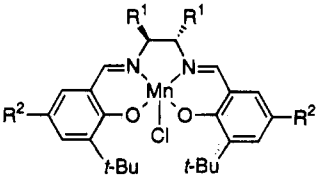
Epoxidation of 1-phenylcyclohexene was examined under a variety of conditions in order to identify the optimal catalysts and reaction protocol for this representative trisubstituted olefin (eq 2).[5] As illustrated in Table



(2)

1, high enantioselectivity was obtained using several different 1,2-diaminocyclohexane and 1,2-diphenylethanediamine-derived catalysts, with the former exhibiting

Table 1. Enantioselective Epoxidation of 1-Phenylcyclohexene



1: R^1,R^1 = -$(CH_2)_4$-, R^2 = *t*-Bu
2: R^1,R^1 = -$(CH_2)_4$-, R^2 = O*t*-Bu
3: R^1,R^1 = -$(CH_2)_4$-, R^2 = OSi*i*-Pr_3
4: R^1 = Ph, R^2 = Me
5: R^1 = Ph, R^2 = O*t*-Bu

entry	catalyst	solvent	additive	ee (%)
1	**1**	CH_2Cl_2	none	89
2	**1**	CH_2Cl_2	4-*t*-BuC_5H_4NO	92
3	**1**	TBME	4-PhC_5H_4NO	93
4	**1**	CH_2Cl_2	4-PhC_5H_4NO	92
5	**1**	$ClCH_2CH_2Cl$	4-PhC_5H_4NO	86
6	**1**	EtOAc	4-PhC_5H_4NO	92
7	**2**	CH_2Cl_2	4-PhC_5H_4NO	91
8	**3**	CH_2Cl_2	4-PhC_5H_4NO	92
9	**4**	CH_2Cl_2	4-PhC_5H_4NO	86
10	**5**	CH_2Cl_2	4-PhC_5H_4NO	86

slightly higher selectivity. As is the case for cis-disubstituted olefins, the most selective catalysts for epoxidation of 1-phenylcyclohexene were **1** and **3**,[6] which bear bulky, electron-donating substituents at the 5 and 5′ positions of the salicylide ligand. High enantioselectivity was observed in epoxidations using a variety of nonprotic solvents (entries 3–6), with *tert*-butyl methyl ether (TBME) and CH_2Cl_2 proving particularly effective. The addition of catalytic levels of pyridine *N*-oxide derivatives had a slight, yet consistently beneficial effect on enantioselectivity, reaction rate, and product yield (e.g., entries 1–3).[3b,7]

Table 2 summarizes results obtained in the epoxidation of a series of different trisubstituted olefins under optimized conditions. In most cases, the readily available complex **1**[8] proved to be most effective with regard to product enantioselectivity. For all reactions shown, epoxide was the dominant or exclusive product detected by GC analysis of crude reaction mixtures. Under the conditions of catalysis, the coordinatively unsaturated (salen)Mn(III)Cl complexes did not promote Lewis acid-

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(2) (a) Sakaki, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 300. (b) Halterman, R. L.; Jan, S.-T. *J. Org. Chem.* **1991**, *56*, 5253. (c) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (d) Collman, J. P.; Lee, V. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1993**, *115*, 3834.

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(5) General Procedure for Epoxidation. A solution of olefin (1.0 mmol) in solvent (1.25 mL), dodecane (internal quantitative standard), catalyst (0.03 mmol), and pyridine *N*-oxide derivative (0.2 mmol) was cooled to 0 °C. Buffered bleach (1.5 mmol, pH = 11.3) precooled to 0 °C was added to the solution, and the reaction was stirred at 0 °C. When complete disappearance of starting olefin was ascertained by TLC or GC analysis, the phases were separated, the organic layer was washed with distilled water, the aqueous phases were extracted CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4. Purification was effected by flash column chromatography using pentane/CH_2Cl_2 as eluent.

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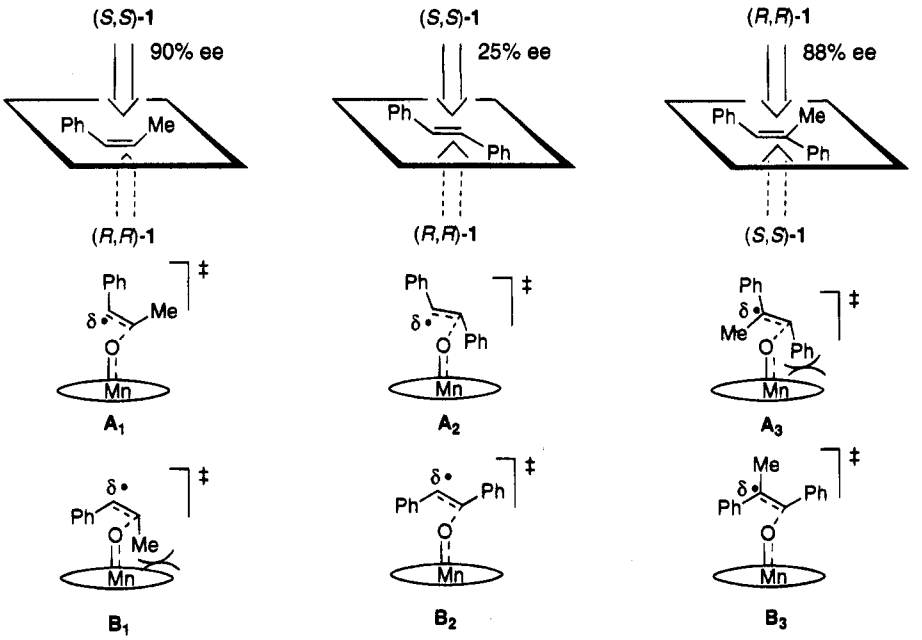
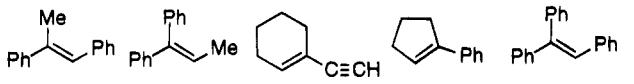


Figure 1.

Table 2. Enantioselective Epoxidation of Trisubstituted Olefins[a]



7 8 9 10 11

entry	substrate	catalyst	isolated yield (%)	ee (%), config[b]
1	**6**	(*R,R*)-**1**	69	93 (−)-(*S,S*)
2	**7**	(*R,R*)-**1**	87	88 (−)-(*S,S*)
3	**8**	(*R,R*)-**1**	91	95 (−)-(*S*)
4	**9**	(*R,R*)-**4**	61[c]	86[d]
5	**10**	(*R,R*)-**3**	75	86 (−)-(*S,S*)
6	**11**	(*R,R*)-**1**	97	92 (+)-(*S*)

[a] Reactions were carried using the conditions shown in ref 5 with CH_2Cl_2 as solvent and 4-PhC_5H_4NO as additive. [b] Methods employed for determination of epoxide ee and absolute configuration are described in detail in the supplementary material. [c] GC yield. [d] Absolute configuration not determined.

mediated epoxide ring-opening reactions, even with highly reactive epoxides such as 1-phenylcyclopentene oxide and triphenylethylene oxide. As has been noted previously with other olefin substitution patterns,[1d] nonconjugated trisubstituted olefins underwent epoxidation with low-to-moderate enantioselectivity (e.g., 40% ee with 1-methylcyclohexene using catalyst **2**).

Important insight into the factors controlling stereoinduction in the epoxidation of trisubstituted olefins was provided by the observed sense of absolute asymmetric induction with these substrates, which was opposite to that predicted based on previous results obtained with cis-disubstituted and trans-disubstituted olefins. This is illustrated specifically in Figure 1 in the comparison of the epoxidation of *cis*-β-methylstyrene, *trans*-stilbene, and *trans*-1,2-diphenylpropene by catalyst **1**. All other di- or trisubstituted olefinic substrates for which epoxide absolute configuration has been determined also follow the general selectivity patterns outlined in Figure 1.

Although these results at first seem to render unlikely any mechanism for stereoinduction that is common to all three substrate classes, the enantioselectivity in epoxidation can in fact be evaluated according to a general, skewed side-on approach transition-state model.[3b] Epoxidation of conjugated olefins has been shown previously to proceed via a stepwise mechanism involving radical intermediates.[3b] If the assumption is made that the dissymmetry of the chiral salen ligand in (*S,S*)-**1** can effectively orient the radical selectively to the left in the schematic shown in Figure 1 (conversely, the ligand in (*R,R*)-**1** would position the radical to the right),[9] then *cis*-β-methylstyrene would be subject to epoxidation via transition states $\mathbf{A_1}$ and $\mathbf{B_1}$. Clearly, transition state $\mathbf{B_1}$ suffers from severe steric interactions between olefin and ligand and is expected to be significantly higher in energy than $\mathbf{A_1}$. If the same analysis is applied to *trans*-stilbene, the resulting competing transition states $\mathbf{A_2}$ and $\mathbf{B_2}$ are subject to similar steric interactions between olefin and the essentially flat[10] ligand plane. Thus, the low enantioselectivity that is observed in the epoxidation of *trans*-stilbene may be attributed to the participation of both of these competing pathways, with the $\mathbf{A_2}$ pathway predominating slightly. In the case of trisubstituted olefins, the corresponding transition state $\mathbf{A_3}$ leads now to severe steric repulsion between ligand and olefin. Such interactions are avoided in competing transition state $\mathbf{B_3}$, so once again high enantioselectivity is predicted. This highly simplified and qualitative model thus provides a unified explanation for both the magnitude and the sense of enantioselection with these three substrate classes.

The synthetic utility of these highly enantioselective epoxidations of trisubstituted olefins may be realized immediately. For example, epoxidation of 1-phenylcyclohexene was applied to the synthesis of the extremely useful Whitesell auxiliary *trans*-2-phenylcyclohexanol (**12**) (eq 3).[11,12] Similarly, the chiral auxiliary **13** was prepared in two steps from triphenylethylene in excellent overall yield (eq 4).[13]

(9) The designations of "left" and "right" are intended solely for the purposes of illustration. The critical assumption in this discussion is simply that the dissymmetric ligand influences olefin attack at the oxo through steric or stereoelectronic control such that the radical intermediate is positioned selectively.

(10) X-ray crystal structure analysis of **3** reveals that the ligand adopts a nearly planar conformation: Pospisil, P. J.; Carsten, D. H.; Jacobsen, E. N., work in progress. The ligand conformation in the active Mn(oxo) intermediate is likely to be similar.

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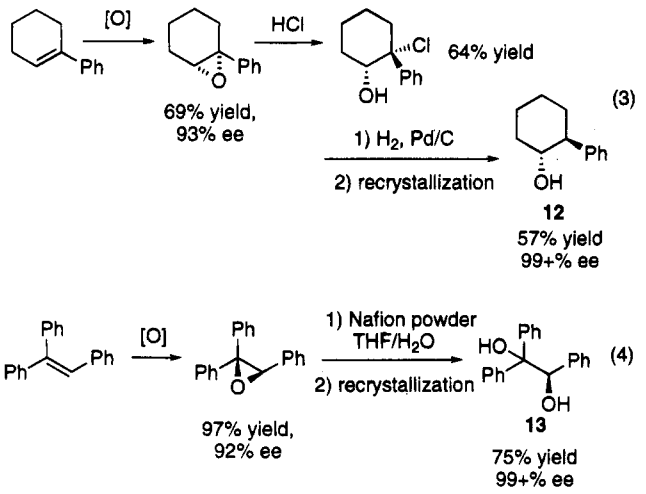

In summary, the synthetic scope of the (salen)Mn-catalyzed asymmetric epoxidation reaction is expanded significantly by the inclusion of trisubstituted olefins into the pool of successful substrates. Perhaps more important, these results demonstrate that oxo transfer via (salen)Mn catalysis is not limited to cis-disubstituted olefin substitution patterns, but rather that it is compatible with a wide range of substrate structures.

Acknowledgment. Preliminary studies on epoxidation of trisubstituted olefins by Mr. R. M. Heid, Dr. J. W. Young, and Mr. D. S. Nirschl and helpful discussions with Dr. N. S. Finney are gratefully acknowledged. This work was supported by the National Institutes of Health (GM-43214). We thank the Packard Foundation, the National Science Foundation (PYI Program), the Camille and Henry Dreyfus Teacher–Scholar program, and the Sloan Foundation for awards to E.N.J.

Supplementary Material Available: Chromatographic and/or spectral analyses of all racemic and enantiomerically enriched epoxides from Table 2; procedures used for the assignment of epoxide absolute configurations; experimental procedures employed for the synthesis of **12** and **13** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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