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Enantioselective Catalytic Epoxidation of Cinnamate Esters

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Abstract: A broad study of the (salen)Mn(III)-catalyzed asymmetric epoxidation of cis-cinnamate esters reveals that the steric properties of the ester group have a profound influence on enantioselectivity in the epoxidation reaction, with bulkier esters affording highest ee's. The sensitivity of the reaction selectivity to the steric properties of the cis-alkene are consistent with a "skewed" side-on approach of olefin to the metal-oxo. The electronic properties of the substrate arene ring substituents do not correlate with epoxidation ee, but instead with the cis/trans partitioning of product formation. Evidence is provided for a non-polar intermediate in a stepwise oxygen-atom-transfer mechanism. The presence of pyridine *N*-oxide derivatives has a significant effect on catalysts rates and total turnovers, but negligible influence on the stereoselectivity of epoxidation. A mechanistic basis for the role of these additives is proposed. The synthetic applicability of the cinnamate epoxidation methodology is illustrated in the highly enantioselective synthesis of diltiazem.

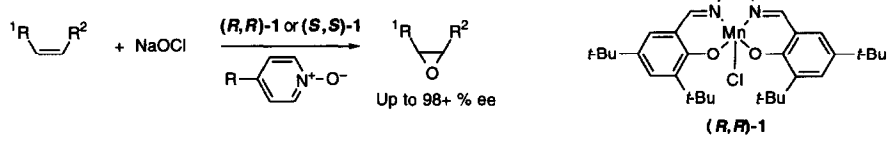
Olefin epoxidation stands as one of the most useful functional group manipulations in organic synthesis, and asymmetric epoxidation (AE) constitutes an especially powerful strategy for the synthesis of enantiomerically enriched compounds. Although this may have been well-appreciated prior to 1980, it still would have been very difficult to predict the dramatic impact that Sharpless' discovery of titanium-tartrate-catalyzed epoxidation of allylic alcohols would have not just on asymmetric synthesis, but on all of synthetic chemistry.[2] The most striking and significant feature of the Sharpless AE is its remarkable generality, as high selectivities are attainable with all allylic alcohol substitution patterns. This shattered the conventional wisdom that high catalyst selectivity demands enzyme-like substrate specificity, and laid the foundation for the current explosion of research activity in asymmetric catalysis. The subsequent development by Noyori of Ru(binap)-catalyzed directed hydrogenation reactions illustrated that a wide range of functionalized substrates could be accepted by a given asymmetric catalyst.[3]

The successful development of the Sharpless and Noyori directed reactions helped to define one of the next major challenges in asymmetric catalysis, the discovery of practical catalysis that require no directing groups on the substrate to effect high ee. In principle, this represents the ultimate solution to the issue of substrate scope. Again, Sharpless succeeded in establishing the feasibility of such a strategy, through the development of the asymmetric dihydroxylation (AD) of unfunctionalized olefins.[4] As a result of various stages of refinement and improvement, the AD is now an effective method for the enantioselective oxidation of almost all classes of prochiral olefins.[5] The utility of this method has been further enhanced by the development of simple procedures for the stereospecific conversion of 1,2-diols to epoxides.[6]

A direct and practical method for AE of unfunctionalized olefins would enjoy enormous utility, and this continues to be an important research activity in several leading laboratories. In general, a biomimetic strategy based on chiral monooxygenase models has been applied toward this goal.[7] In 1983, Groves reported the first example of asymmetric catalytic oxidation with chiral Fe and Mn porphyrin complexes,[8] and in 1990

we reported that chiral (salen)Mn complexes catalyze asymmetric epoxidation of various olefins with good-to-excellent selectivity.[9] Subsequent improvements in ligand structure and other reaction parameters have led to the development of the epoxidation process outlined in Scheme 1.[10] Both enantiomers of catalyst **1** are easily prepared from 1,2-diaminocyclohexane, and are now available commercially in both research and bulk quantities.[11]

Scheme 1



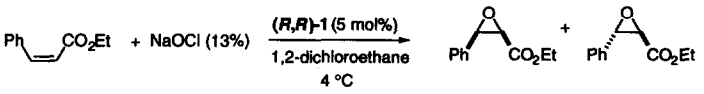
Monooxygenases and their models do not usually accept electron deficient olefins as substrates. In contrast, a remarkably wide range of electron rich to electron deficient substrates are oxidized by the (salen)Mn system, and the observation of enantioselective epoxidation of cis-cinnamate esters with (salen)Mn complexes constituted first example of epoxidation of conjugated esters via oxo transfer.[10] This reaction may be a useful probe for the study of the mechanism of epoxidation selectivity, since the cinnamate ester unit may be tuned electronically (by substitution at the arene ring) and sterically (by variation of the ester group) and these effects can be separated. The product arylglycidic esters are also extremely valuable chiral building blocks for asymmetric synthesis.[12] Herein we analyze the subtle combination of steric and electronic effects that govern enantio- and diastereoselectivity in epoxidation by (salen)Mn complexes. The utility of the cinnamate epoxidation methodology is illustrated in a highly enantioselective synthesis of diltiazem, an important commercial anti-hypertensive agent.[13]

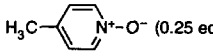
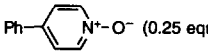
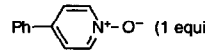
Results and Discussion

1) *Role of Additives*

For substrates such as styrene which are most reactive toward epoxidation by (salen)Mn catalysis, addition of pyridine *N*-oxide derivatives generally results in slightly increased epoxidation rates and total catalyst turnover numbers.[14] The additive effect is more pronounced in the case of relatively unreactive substrates, such as ketals of cyclic enones, simple alkyl-substituted olefins, and cinnamate esters.[15] For example, catalyst turnovers in the epoxidation of *cis*-ethyl cinnamate by 13% NaOCl are increased up to three-fold by the presence of 4-phenylpyridine *N*-oxide, and the yield of epoxide as a function of olefin consumed also improved significantly (Table 1). We have ascertained through control experiments that the *N*-oxide does not act as the oxygen atom source in the epoxidation reaction.[15] However this additive class is unique, as a wide range of other potential donor ligands were screened but found to have either no effect, or a slightly deleterious effect on catalyst turnovers.

Table 1. Additive Effects on Epoxidation of *cis* -Ethyl Cinnamate

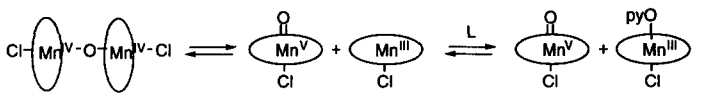


Additive	Turnover Rate (min^{-1})[a]	Turnover #[b]	Epoxide Yield (%)[c]	ee (%)[d]	cis epoxide/ trans epoxide
None	2.3	13	67	93	4-5:1
	3.3	20	82	92	4-5:1
	4.0	48	96	93	4-5:1
	7.6	43	98+	93	4-5:1

[a] Initial rate (see Experimental). [b] Total moles of reacted olefin per mole of catalyst at reaction completion, measured using 1mol% **1**. [c] Combined yield of cis and trans epoxides as a percentage of all olefin-derived products, determined by GC using an internal quantitative standard. [d] Determined by GC.

Kochi has demonstrated that pyridine *N*-oxide acts as an axial ligand in epoxidations mediated by cationic (salen)Cr complexes.[16] However, such a function is unlikely in the case of AE catalyzed by Mn complex **1** given that product ee's and cis/trans epoxide ratios are not affected by the presence of additive (Table 1).[17] Although a small or even negligible effect on enantioselectivity may be anticipated for a ligand bound axially to the metal oxo linkage, it is very unlikely that *N*-oxide complexation would have no effect on the cis/trans partitioning because the cis/trans selectivity is very sensitive to the electronic properties of the system (see below). The identical relative and absolute stereochemistry of epoxidation both in the presence and absence of additives points to a common intermediate responsible for oxo transfer (Scheme 2).

Scheme 2



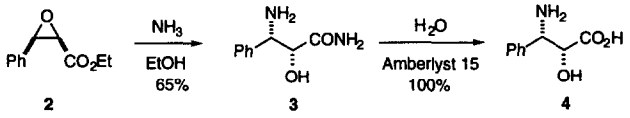
We propose that the effect of *N*-oxide additives is due to a set of equilibria, wherein the active (salen)Mn^{V}=O complex undergoes reversible coupling with a Mn^{III} complex to generate an inactive μ-oxo dimer. Kinetic evidence for an analogous achiral [(salen)Mn^{IV}]$_2$-O complex has previously been noted by Kochi.[18] In the presence of pyridine *N*-oxide derivatives, the equilibrium is shifted toward the Mn^{V} oxo intermediate as a result of additive binding to the coordinatively unsaturated Mn^{III} complex. Acceleration in the rate of epoxidation is then expected due to the increased concentration of the active Mn^{V} oxo in solution. The improvements in epoxide yield and catalyst lifetime may also be ascribed to the fact that the pyridine *N*-oxide derivative serves to protect the Lewis acidic Mn^{III} complex against irreversible reactions involving either substrate or epoxide product.

2) *Epoxidation of cis-Ethyl Cinnamate; Application to the Synthesis of the Side Chain of Taxol*

We have reported previously that the (*R,R*)-epoxide **2** derived from *cis*-ethyl cinnamate may be applied as an intermediate in the synthesis of phenylisoserine (**4**), an immediate precursor to the side chains of taxol

and taxotère.[15] This strategy has been further refined with the incorporation of a highly efficient hydrolysis of phenylisoserinamide (**3**) employing the ion exchange resin Amberlyst 15 (Scheme 3).[19] The preparation of **4** in enantiomerically pure form is therefore possible in 4 steps from commercially available ethyl phenylpropiolate via a hydrogenation/epoxidation/ammonolysis/hydrolysis sequence, employing H_2, NaOCl, NH_3, and H_2O as the only stoichiometric reagents.

Scheme 3

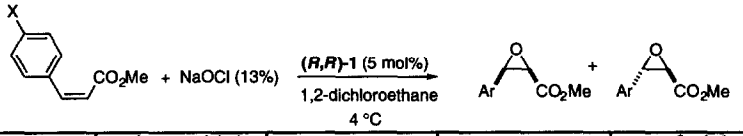


2 **3** **4**

3) *Epoxidation of Substituted Cinnamate Esters: Electronic Effects*

The simplicity of the epoxidation route to **4** suggests that a similar strategy may be applicable to the synthesis of a variety of phenylisoserine analogs, most notably those bearing aryl substitution.[20] The study of the epoxidation of substituted cinnamate esters might also provide insight into the role of substrate electronics in determining selectivity. It has previously been shown that electronic tuning of the salen catalysts can have a dramatic effect on the enantioselectivities attainable in epoxidation.[21] A series of substituted methyl cinnamates were prepared in a straightforward manner by the Still Modification of the Horner-Emmons reaction,[22] and the results of their epoxidation with **1** are summarized in Table 2. A strong relationship between the electronic properties of the substituents and the cis/trans epoxide ratio was established, with electron donating groups leading to a preference for cis epoxide formation.

Table 2. Asymmetric Epoxidation of Substituted *cis*-Methyl Cinnamate Derivatives

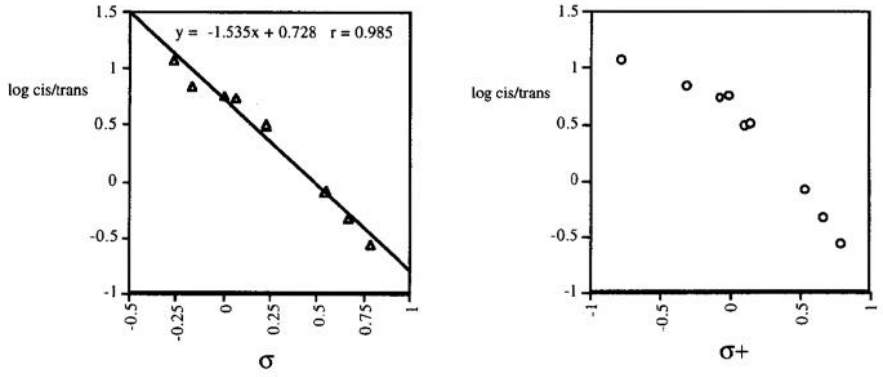


X	cis epoxide/ trans epoxide	ee_{cis} (%)	ee_{trans} (%)	facial selectivity (%)[a]
OCH_3	11.7	72	66	72
CH_3	7.0	79	41	74
H	5.7	85	62	82
F	5.4	78	50	74
Cl	3.0	80	53	73
Br	3.2	81	53	74
CF_3	0.80	79	55	65
CN	0.47	84	57	66
NO_2	0.27	91	53	61

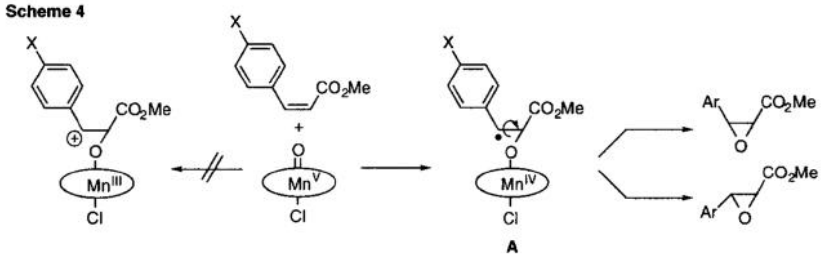
[a] Facial selectivity = (ee_{cis} x %cis) + (ee_{trans} x %trans). This number reflects the selectivity in the first C-O bond forming step. Zhang, W.; Lee, N. H.; Jacobsen, E. N. Submitted.

As shown in Figure 1, the log of the cis/trans product ratio in the epoxidation of substituted cinnamates correlates well with the σ values of the substituents, whereas the linear free energy correlation with σ^+ values is poor. This result is most consistent with the intermediacy of a non-polar species in the oxygen-atom-transfer mechanism (Scheme 4).[18] A pathway involving a cationic intermediate is unlikely not only because of the absence of correlation with σ^+, but also because of the moderate influence of the substituents on the rate of epoxidation. Epoxidation of all the substrates in Table 2 occurred within a rate window of 0.5-3 h.

Figure 1. Plots of the log of the ratio of cis and trans epoxides from Table 2 against σ and σ+.



Scheme 4



The cis/trans partitioning in epoxide formation is tied to the lifetime of intermediate **A** (Scheme 4). The increased proportion of trans product formed with substrates bearing electron withdrawing groups (EWG's) is attributable to their ability to stabilize **A** to oxidative ring closure. Conversely, such substituents are expected to have the opposite effect when located on the catalyst. Indeed, it has previously been found that EWG's on the catalyst favor high cis/trans epoxide ratios.[23]

It is significant that enantioselectivities observed in the epoxidation of *cis*-cinnamate esters do not correlate with the electronic properties of the substituents (Table 2). This was somewhat unexpected given the direct relationship previously observed between enantioselectivity and the electronic properties of catalyst.[21] However, the cis-cinnamate esters used in this study are not strictly isosteric, since their distortion from planarity is expected to vary according to substituent X. Although a complete mechanistic interpretation awaits further study, the absence of a strong dependence of substrate electronics on epoxidation selectivity has welcome synthetic implications for this process.

4) *Epoxidation of Substituted Cinnamate Esters: Steric Effects*

As illustrated in Table 2, only modest enantioselectivities are obtained in the epoxidation of *cis*-methyl cinnamate derivatives. However, selectivities may be raised above 95% ee by simple manipulation of the steric properties of ester group (Table 3). In all cases studied to date, increasing the size of the ester group has resulted in increased enantioselectivity in epoxidation.

This pronounced steric effect is noteworthy since it may shed light on the mechanism of enantiofacial selectivity. Absolute configurations of all cis- and trans-aryl glycidates described in this study have been determined either by comparison with literature assignments or by correlation. Without exception, epoxidation of cis-cinnamates by **1** obeys the same stereoselection rule as do other conjugated cis-1,2-disubstituted olefins (Figure 2).[24]

Table 3. Steric Effects on Enantioselectivity.

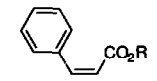
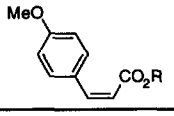
Substrate	R = Me	R = Et	R = *i*-Pr
	85% ee	92% ee	96% ee
	72% ee	86% ee	96% ee

Figure 2. Stereochemical Model for Epoxidation of Conjugated Aryl-, Alkenyl-, and Alkynyl-Substituted Olefins

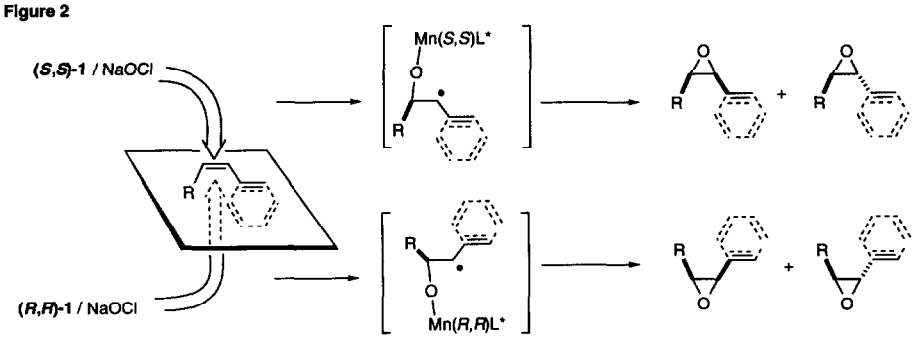
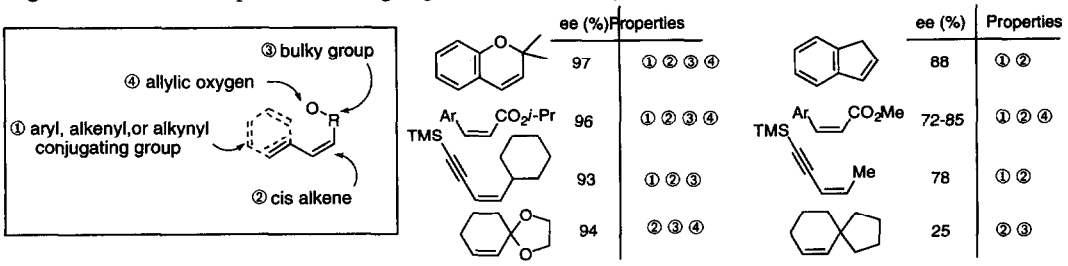


Figure 3. Substrate Properties Favoring High Enantioselectivity in Epoxidations with **1**

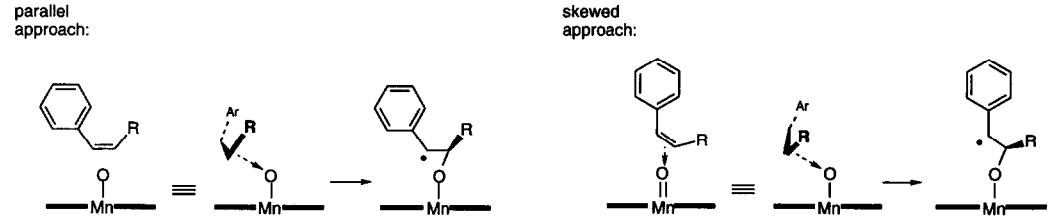


The stereochemical model that was proposed in our initial paper,[9] using *cis*-β-methyl styrene as a reference substrate, applied the common convention that the phenyl group acted as a "large" group, and the methyl as a "small" substituent. However, as shown in Figure 3, substrates that are epoxidized with very high enantioselectivity (≥96% ee), including isopropyl cinnamate esters, clearly do not obey this simplistic large/small description. In fact, the presence of bulkier substituents on the "small" side of the cis-alkene actually tends to result in higher selectivity in epoxidation. On the basis of alkenes studied to date in the AE catalyzed by **1**, substrate properties that favor high ee include: 1) an aryl, alkenyl, or alkynyl group conjugated to the alkene, 2) a cis double bond linkage, 3) a bulky R group, and 4) the presence of an allylic oxygen substituent. Combination of 3 or more of these properties results in alkenes that are excellent substrates for AE (Figure 3). In particular, 2,2-dimethylchromene derivatives and isopropyl cinnamate

derivatives combine all four characteristics, and are the best substrates uncovered thus far with respect to enantioselectivity in epoxidation.

The importance of the steric properties of R, and the relative insensitivity of selectivity to the steric properties of the aromatic, alkenyl, or alkynyl group suggest that the two cis double bond substituents interact very differently with the catalyst. This is inconsistent with the parallel side on approach originally proposed by us and others,[9,25] and suggests instead a skewed approach of olefin to the metal oxo (Figure 4).[26] The skewed approach constitutes a "least-motion" mechanism for stepwise oxygen transfer, since the orientation of the olefin relative to the metal oxo is such that the resulting radical needs to undergo minimal reorganization to achieve a stable conformation. Within the skewed approach model, *trans*-β-substituted styrene derivatives would be predicted to suffer from severe steric repulsion, and this might serve to explain why this substrate class undergoes epoxidation with generally lower rates and enantioselectivity than the related cis isomers.[27]

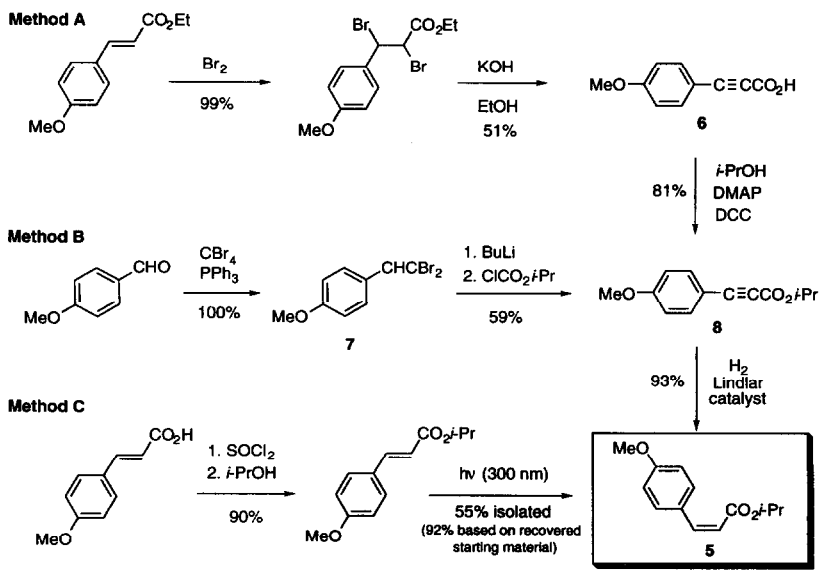
Figure 4. Possible Olefin Side-On Approach Trajectories



5) *Synthesis of Diltiazem*

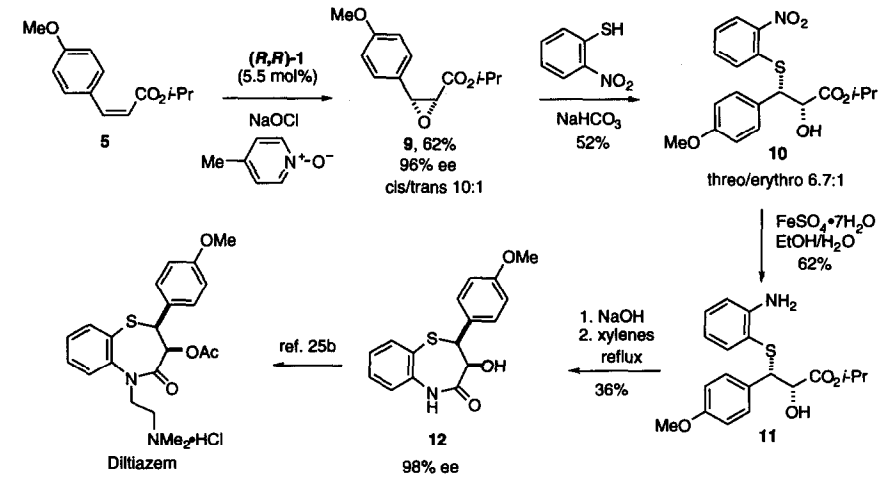
The highly enantioselective epoxidation of *cis*-isopropyl 4-methoxycinnamate (**5**) can be incorporated into a useful asymmetric synthesis of diltiazem. Currently applied commercial routes to this compound employ trans-4-(methoxyphenyl)glycidate esters due to their greater accessibility in optically active form.[28] However, synthesis of diltiazem has also been reported from the corresponding cis epoxides.[29] We examined several routes to the requisite cinnamate ester **5**; three different useful procedures are outlined in Scheme 5.

Scheme 5



Although Method C provides the shortest route, Method A is adaptable to large scale synthesis and involves no technically difficult procedures or chromatographic separations. The synthesis of diltiazem was carried out from epoxide **9** based the methods developed at Tanabe and at ICI (Scheme 6).[25b,26] The key transformation succeeding the epoxidation reaction was an invertive ring opening of **9** by 2-nitrothiophenol, which occurred stereospecifically. The enantiomeric integrity of the epoxide was maintained throughout the reaction sequence, as evidenced by the isolation of **12** in 98% ee.

Scheme 6



Concluding Remarks

As a result of the beneficial effect of bulky ester groups on enantioselectivity, cinnamate esters constitute one of the best substrate classes for the (salen)Mn-catalyzed AE reaction. Although the assignment of a precise stereochemical model for this reaction may still be premature, the skewed olefin approach provides a consistent rationalization and a useful predictive device for future catalyst and substrate design.

Acknowledgments. This work was supported by the National Institutes of Health (GM-43214). We thank the Ford Foundation for a fellowship to L. E. M. and the National Science Foundation (PYI program), the David and Lucille Packard Foundation, the Sloan Foundation, and the Camille and Henry Dreyfus Teacher Scholar Program for awards to E. N. J.

Experimental

General. Melting points were obtained in open capillary tubes with a Laboratory Devices Mel-Temp II melting point apparatus and are uncorrected. All boiling points are not corrected. The ^{1}H NMR spectra were obtained on Bruker AM250 or AM300 spectrometers. Gas chromatographic (GC) analyses were carried out on Hewlett Packard 5890 Series II instruments equipped with FID detectors and Hewlett Packard HP-5 capillary columns. Unless otherwise noted, diastereomer ratios were measured by GC. Chiral GC separations were accomplished using a commercial 20 m x 0.25 mm Astec Chiraldex G-TA (trifluoroacetyl γ-cyclodextrin) column. High pressure liquid chromatography (HPLC) was performed on a SpectraPhysics system equipped with a P100 isocratic pump and a UV100 variable wavelength detector set to λ = 225 nm. Enantiomer ratios measured by HPLC were determined using either a Daicel Chiralcel OB column (flow rate = 1 mL/min, isopropanol/hexane = 1:9), or a Regis Whelk-O column (flow rate = 1 mL/min, isopropanol/hexane = 1:99). Low resolution EI GC/MS analyses were performed on a Hewlett-Packard 5970 Mass Selective Detector coupled to a Hewlett-Packard 5890 GC. Other mass spectra were provided by the Mass Spectrometry Laboratory in Harvard University. Optical rotations were determined on a JASCO DIP-181 polarimeter. Elemental analyses were performed by the Microanalytical Laboratory of the University of Illinois. Flash chromatography was performed using E.M. 32-63 μ silica packed in glass columns, unless noted otherwise.

Complex **1** was prepared by our published method.[30] 4-Phenyl-pyridine *N*-oxide (Aldrich) was recrystallized twice from benzene. THF was distilled from sodium benzophenone ketyl. Methyl *P,P*-bis-(2,2,2 trifluoroethyl)phosponoacetate was purchased from Fluka. Sodium hypochlorite (13 % active chlorine), 1,2-dichloroethane, and methyl *t*-butyl ether (MTBE) were obtained from Jansen Chimica; all other materials were obtained from Aldrich and were used as received.

General Procedure for Epoxidation of Cinnamate Esters: (2*R*, 3*R*)-Ethyl-3-Phenylglycidate. To a solution of *cis*-ethyl cinnamate[15] (352 mg, 85% pure, 1.70 mmol) and 4-phenylpyridine-*N*-oxide (85.5mg, 29 mol%) in 1,2-dichloroethane (4.0 mL) was added the salen complex (***R***, ***R***)-**1** (38.0mg, 3.5 mol%). The resulting brown solution was cooled to 4 °C and then combined with 4.0 mL (8.9 mmol) of precooled bleach solution. The two-phase mixture was stirred for 12 h at 4 °C. The reaction mixture was diluted with methyl *t*-butyl ether (MTBE) (40 mL) and the organic phase was separated, washed with water (2x40 mL), brine (1x40 mL), and then dried over Na_2SO_4. Solvents were removed under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, pet ether/ether = 87:13, v/v) to afford a fraction of mixture enriched in cis epoxide (cis/trans = 96:4, 215 mg) and another fraction enriched in trans epoxide (cis/trans = 13:87, 54mg). The combined yield of pure epoxides was 83%. The ee of the cis epoxide was determined to be 91-93% by GC analysis, and that of the ee of the trans isomer was measured to be 65% by the same method. *cis*-Ethyl-3-phenylglycidate: ^{1}H NMR ($CDCl_3$) δ 1.02 (t, *J* = 7.2Hz, 3H), 3.83 (d, *J* = 4.8Hz, 1H), 3.9-4.1 (m, 2H), 4.27 (d, *J* = 4.8Hz, 1H), 7.2-7.5 (aromatic, 5H); *trans*-ethyl-3-phenylglycidate: ^{1}H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7.2Hz, 3H), 3.51 (d, *J* = 2.1 Hz, 1H), 4.09 (d, *J* = 1.8Hz, 1H), 4.2-4.4 (m, 2H), 7.2-7.5 (aromatic, 5H).

Measurement of turnover rates. A solution of *cis*-ethyl cinnamate (352 mg, 85% pure, 1.70 mmol), the pyridine *N*-oxide derivative, and dodecane 1,2-dichloroethane (4.0 mL) was prepared, and a 1μL aliquot was withdrawn and analyzed by GC. The catalyst (***R***, ***R***)-**1** (38.0 mg, 3.5 mol%) was added to the solution. This solution and a bleach solution (4.0 mL) were precooled to 4 °C and combined, and the two phase mixture was stirred magnetically at 4 °C. After precisely 1 min, stirring was stopped, and a 100 μL aliquot was drawn and filtered through a plug of silica gel; in all cases this work-up procedure was completed within 7 s after stirring was stopped. The plug of silica gel was washed with an additional portion of dichloroethane (0.5 mL). The extent of alkene consumption was determined by GC analysis of the combined eluents and integration relative to internal standard.

(4-Methoxyphenyl)propiolic acid (6). The literature procedure[31] was followed with minor modifications. To a solution of KOH (116 g, 1.75 mol) in 95% EtOH (490 mL) was added ethyl 2,3-dibromo-3-(4-methoxy)phenylpropiolate[32] (91.8 g 0.251 mol) and the mixture was heated to reflux for 12 h. Work-up according to the literature method afforded crude product (28.6 g, 65%) which was recrystallized from CH_2Cl_2/hexane to give the pure acid as a pale yellow crystalline solid (22.4 g, 51%): mp 132-133 °C (lit.[28] mp 135-140 °C). ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$) δ 55.4, 79.6, 90.0, 110.8, 114.4, 135.3, 158.5, 161.9.

Ethyl (4-Methoxyphenyl)propiolate. A solution of **6** (2.32g, 13.2 mmol) and *p*-toluenesulfonic acid (0.24g, 10 mol%) in EtOH (125 mL) were heated to reflux for 20 h. The reaction mixture was extracted with EtOAc (50 mL), and the organic layer was then washed with 5% Na_2CO_3 solution (3 x 25 mL), H_2O (2 x 25 mL), saturated NaCl solution (50 mL), and dried over $MgSO_4$. The resulting solution was concentrated under vacuum then distilled, yielding 2.13 g (97%) of a clear liquid, bp. 97-99 °C (0.08 mm Hg) ^{1}H NMR ($CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3 H), 3.84 (s, 3 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H).

***cis*-Ethyl 4-Methoxycinnamate.** Under an atmosphere of dry nitrogen, ethyl (4-methoxyphenyl)propiolate (1.01g, 4.94 mmol) was dissolved in a mixture of hexane and 1-hexene (2:1 v/v, 50 mL), and then quinoline (2.08 g) and palladium on calcium carbonate (Lindlar catalyst, 0.168 g) were added. The reaction vessel was then connected to a hydrogen filled balloon (1 atm) and stirred at room temperature. When GC analysis indicated complete consumption of the starting alkyne, the hydrogen atmosphere was displaced by nitrogen and the reaction mixture was filtered through a Celite pad. The filtrate was then washed with 10% acetic acid (5 x 25mL), water (3 x 25mL), and saturated $NaHCO_3$ (3 x 25mL). After the organic phase was dried over $MgSO_4$, the mixture was analyzed by GC and determined to contain 97.7% *cis*-ethyl 4-methoxycinnamate and 2.3% of the trans isomer. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 3.83 (s, 3 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 5.83 (d, *J* = 12.8 Hz, 1 H), 6.85 (d, *J* = 12.64 Hz, 1 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 8.8 Hz, 1 H).

Isopropyl (4-methoxyphenyl)propiolate (8)

Method A. A mixture containing 4-methoxyphenylpropiolic acid (17.7 g, 0.100 mol), 4-dimethylaminopyridine (1.01 g, 8.27 mmol), and isopropanol (23 mL, 0.30 mol) in CH_2Cl_2 (100 mL) was cooled in ice bath, and DCC (22.7 g, 0.110 mol) was added portionwise to the cooled solution. After the addition was complete, the mixture was allowed to warm to room temperature and then stirred for 12 h. Filtration, followed by solvent removal under vacuum, produced a brown oily residue. This material was extracted with ethyl acetate (100 mL), and the resulting suspension was filtered and concentrated under vacuum. The residue was recrystallized from pentane to afford isopropyl (4-methoxyphenyl)propiolate as pale yellow rodlike crystals (17.7 g, 81%). Mp 61-62 °C; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, *J* = 6.3 Hz, 6 H), 3.82 (s, 3 H), 5.15 (hept, *J* = 6.3 Hz, 1 H), 6.87 (d, *J* = 8.9 Hz, 2 H), 7.54 (d, *J* = 9.0 Hz, 2 H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.63; H. 6.44.

Method B. The literature procedure[33] was followed with modifications. To a stirred solution of CBr_4 (16.6 g, 50.0 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C was added triphenylphosphine (26.3 g, 100 mmol) in portions under a nitrogen counterflow. The resulting mixture was stirred 15 min at 0 °C, and then a solution of *p*-anisaldehyde (3.0 mL, 25 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 20 min. After the mixture was stirred for an additional 3 h at 0 °C, saturated $NaHCO_3$ was added until the aqueous phase reached pH 7. The organic layer was separated and dried over $MgSO_4$, and solvent was removed under vacuum to give a pale brown solid. The solid was rinsed with 5 x 25 mL portions of CH_2Cl_2, and the washings were filtered through a short silica gel column to afford 1,1-dibromo-2-(4-methoxyphenyl)ethylene (**7**) as a pale yellow solid (7.21 g, 100%). This material was used without further purification.

To a solution of **7** (300 mg, 1.03 mmol) in THF (12 mL) was added a solution of *n*-butyllithium (1.5 M in hexane, 1.40 mL, 2.24 mmol) by syringe at –78 °C under a nitrogen atmosphere. After the mixture was stirred 1 h at –78 °C, a solution of isopropyl chloroformate (1.0 M in toluene, 5.1 mL, 51 mmol) was added dropwise. The solution was stirred for 10 min at –78 °C, allowed to warm to room temperature over 30 min, then poured into a mixture of ether and saturated $NaHCO_3$. The organic layer was washed sequentially with saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. The residue obtained upon solvent removal under vacuum was purified by flash chromatography (hexane/ether = 20:1) to afford pure isopropyl 4-methoxyphenylpropiolate (133 mg, 59%), with spectral characteristics identical to those of material obtained from Method A.

***cis*-Isopropyl 4-methoxycinnamate (5).** Hydrogenation of isopropyl (4-methoxyphenyl)propiolate (6.58 g, 30.1 mmol) was carried out as described above for the corresponding ethyl ester. The reaction product residue (6.49 g) was determined by GC to consist of a mixture of 95.3 % *cis*-isopropyl 4-methoxycinnamate (93% yield), 3.7% of the trans isomer, and 1.0% over-reduction product. ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.2 Hz, 6H), 3.83 (s, 3H), 5.07 (hept, J = 6.3 Hz, 1H), 5.80 (d, J = 12.7 Hz, 1H), 6.82 (d, J = 12.7 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.99; H, 7.35. This material was used without further purification.

Method C: Photoisomerization of *trans*-4-methoxycinnamate. A mixture of 4-methoxycinnamic acid (8.97 g, 50.3 mmol) and $SOCl_2$ (20 mL, 270 mmol) was heated to reflux for 3 h under a nitrogen atmosphere. Excess $SOCl_2$ was removed under vacuum, and the residue was dissolved in a mixture of toluene (20 mL) and isopropyl alcohol (5 mL, 65 mmol). The resulting solution was heated to reflux for 1 hr, and then washed sequentially with saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, concentrated, and finally distilled under reduced pressure to give *trans*-isopropyl 4-methoxycinnamate as a pale yellow oil (9.99 g, 90%): bp 143-144 °C/0.6-0.7 mm Hg ; ^1H NMR ($CDCl_3$) δ 1.29 (d, J = 6.3 Hz, 6H), 3.81 (s, 3H), 5.12 (hept, J = 6.3 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 16.0 Hz, 1H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.93; H, 7.28.

A solution of *trans*-isopropyl 4-methoxy cinnamate (1.77 g 8.03 mmol) in 400 mL of 1,2- dichloroethane was prepared in a Pyrex tube and irradiated for 24 h using a Rayonet photoreactor (3000Å lamp) under a static nitrogen atmosphere. Analysis of the resulting solution by GC indicated the presence of cis and trans olefins in a 59:41 ratio. Solvent was removed under vacuum, and the residue was subjected to flash chromatography (silica gel, pentane/ether = 10:1). Both isomers were obtained in pure form, with *cis*-isopropyl 4-methoxycinnamate eluting first (0.98 g, 55%), and recovered *trans*-isopropyl 4-methoxycinnamate (0.71 g, 40%) being recovered from later fractions. The spectral properties of the cis isomer were identical to those of the material obtained by hydrogenation of **8**.

***cis*-Isopropyl Cinnamate (5).** A solution of ethyl phenylpropiolate (2.00g, 11.5 mmol) and a catalytic amount of conc. H_2SO_4 (1 mL) in isopropanol (25 mL) was heated to reflux for 16 h. The reaction mixture allowed to cool then extracted with MTBE (50 mL), and the resulting organic phase was washed with $NaHCO_3$ (sat.) (3 x 25 mL), H_2O (2 x 25 mL), NaCl (sat.) (50 mL) and then dried over $MgSO_4$. The yellow oil that was obtained after concentration under vacuum (2.08g) was then subjected to Lindlar hydrogenation conditions and worked up as described above. Purification by flash chromatography (hexane/ethyl acetate = 9:1) afforded 2.00 g of a clear oil which was shown by GC analysis to contain 93% *cis*-isopropyl cinnamate (86% yield), 2.5% *trans*-isopropyl cinnamate, and 4.5 % over-reduced alkane. ^1H NMR ($CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 6H), 5.05 (hept, J = 6.3 Hz, 1 H), 5.93 (d, J = 12.6 Hz, 1 H), 6.92 (d, J = 12.7 Hz, 1 H), 7.32-7.53 (aromatic m, 5 H).

(2*R*, 3*R*)-Isopropyl 3-(4-methoxyphenyl)glycidate (9). To a benzene solution of *cis*-isopropyl 4-methoxycinnamate (**5**) obtained from the hydrogenation of **8** (0.509 g, 2.31 mmol, in 5 mL) was added 4-picoline *N*-oxide (2.27 g, 20.8 mmol) and catalyst (***R*,*R*)-1** (80.5 mg, 5.5 mol %). This was combined with a precooled bleach solution (5 mL, 11 mmol), and the two-phase mixture was stirred for 24 h at 4 °C. Ether (10 mL) was then added to the solution and the organic phase was separated and filtered through a Celite® pad, washed with water (6 x 10 mL) and then dried over Na_2SO_4. The solvent was removed under vacuum and GC analysis of the residue indicated the presence of cis and trans epoxides in a 8.8:1 ratio. The ee of the cis epoxide was determined to be 95-97% ee by HPLC analysis on the Whelk-O column. The residue was purified by flash chromatography (basic alumina, hexane/EtOAc = 5:1) to afford 0.337 g (62%) of the epoxide as a 10:1 cis/trans ratio of diastereomers. ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 3.76 (d, J = 4.6 Hz, 1H), 3.79 (s, 3H), 4.20 (d, J = 4.6 Hz, 1H), 4.87 (hept, J = 6.3 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H); HRMS (EI): calcd for $C_{13}H_{16}O_4$ 236.1048, found 236.1044.

Isopropyl 2-hydroxy-3-(4-methoxyphenyl)-3-[(2-nitrophenyl)thio)]propionate (10). The literature procedure for the ring opening of ethyl 3-phenylglycidate was followed with minor modifications.[13] To a mixture of 2-nitrothiophenol[34] (449 mg, 2.89 mmol) and $NaHCO_3$ (22.2 mg, 0.264 mmol) in EtOH (2.9 mL) was added epoxide **9** (309 mg, 1.31 mmol) obtained as described above. The reaction mixture was heated to reflux for 12 h and then filtered and concentrated under vacuum. Purification by flash chromatography (hexane/EtOAc = 6:1) afforded a mixture of diastereomers as a yellow oil (267 mg, 52%). The threo/erythro ratio was determined to be 6.7:1 by ^{1}H-NMR analysis. ^{1}HNMR (major isomer, $CDCl_3$) δ 1.13 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 3.26 (d, *J* = 5.5 Hz, 1H, exchangeable), 3.79 (s, 3H), 4.52 (dd, J_1 = 5.4, J_2 = 3.5 Hz, 1H), 4.71 (d, *J* = 3.5 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.19-8.05 (aromatic m, 4H); HRMS (CI): calcd for $C_{19}H_{21}NO_6S{\bullet}NH_4$ 409.1433, found 409.1436.

(2*S*,3*S*)-Isopropyl 3-[2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionate (11). The literature procedure for the reduction of the corresponding unsubstituted ethyl ester was followed with minor modifications.[13] The mixture of diastereomeric nitro esters obtained as described above (267 mg 0.681 mmol) and $FeSO_4{\bullet}7H_2O$ (1.58 g, 5.70 mmol) in 50% (v/v) EtOH (10 mL) were heated to reflux for 30 min. Reflux was sustained as conc. NH_4OH (1.4 mL) was added dropwise over 15 min to the stirred mixture. After an additional 10 min the mixture was allowed to cool and then extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Solvent was removed under vacuum and the residue was purified by flash chromatography (petroleum ether/EtOAc = 5/1) to afford pure threo isomer (153 mg, 62%) as a yellow oil. ^{1}HNMR ($CDCl_3$) δ 1.09 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 3.79 (s, 3H), 3.83 (br, 1H, exchangeable), 4.30 (br, 2H, exchangeable), 4.38 (d, *J* = 3.4 Hz, 1H), 4.45 (br, 1H), 4.91 (hept, *J* = 6.2 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.54-7.12 (aromatic m, 4H); HRMS (FAB): calcd for $C_{19}H_{23}NO_4S{\bullet}Na$ 384.1245, found 384.1249.

(2*S*,3*S*)-3-[(2-Aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propionic acid. The literature procedure for the saponification of the corresponding 2-phenylcyclohexyl ester was followed with modifications.[25a] A mixture of aminoester **11** (146 mg 0.403 mmol) and 1N NaOH (1.2mL, 1.2mmol) in EtOH (1.6mL) was heated to reflux for 1 h. The mixture was allowed to cool to room temperature, diluted with water (3 mL), and then washed with ether (2 x 3 mL). The aqueous phase was separated and acidified with 3N H_2SO_4 to pH 4, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated under vacuum to afford 73 mg (56%) of the pure acid. A colorless solid was obtained upon trituration with acetonitrite: mp 132-134 °C (lit.[25a] 132-133 °C); ^{1}HNMR ($CDCl_3$) δ 3.76 (s, 3H), 4.50 (br, 1H), 4.51 (br, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.65-7.15 (aromatic m, 4H).

***cis*-(+)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (12).** The literature procedure was followed with minor modification.[25a] The acid prepared above (70.9 mg, 0.222 mmol) and xylenes (3 mL) were heated to reflux for 12 h. The resulting mixture was cooled to room temperature and precipitated material was collected by filtration, washed with hexane to afford **12** as pale yellow needles (42.9 mg, 64%). Recrystallization from 95% ethanol provided a colorless, analytical sample. Mp: 200-201 °C (lit.[25a] mp 201-203 °C); $[\alpha]_D$ +121.2° (*c* 0.33, EtOH) (lit.[25a] $[\alpha]_D$ +124.1° (*c* 0.3,EtOH)); ^{1}HNMR (dmso-d_6) δ 3.74 (s, 3H), 4.28 (t, *J* = 6.5 Hz, 1H), 4.76 (d, *J* = 5.5 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.13-7.60 (aromatic m, 4H), 10.30 (s, 1H).

General procedure for the synthesis of *cis*-methyl cinnamate derivatives: *cis*-methyl 4-bromocinnamate. The Still modification of the Horner-Emmons olefination[22] was followed. A solution of 18-crown-6 (5.0 g, 18.9 mmol) in THF (75 mL) was cooled to −78 °C. Methyl *P*,*P*-bis-(2,2,2 trifluoroethyl)phosphono acetate (0.8 mL ,3.78 mmol) and potassium bis-tetramethylsilylamide (7.6 mL of a 0.5 M solution in THF, 3.8 mmol) were then added via syringe, producing a golden yellow solution. Neat 4-bromobenzaldehyde (0.70 g, 3.78 mmol) was then added at once, and the solution was allowed to stir at −78 °C for 6 h. The resulting mixture was then added to a saturated NH_4Cl (50mL) solution, and the organic phase was separated and extracted again with sat. NH_4Cl (3 x 50 mL). The aqueous fractions were combined and extracted with MTBE (3 x 25 mL). The organic fractions were then combined, dried over $MgSO_4$, and concentrated under vacuum. The resulting solid residue was purified by flash chromatography (methylene chloride/hexanes 4:1) to afford 841 mg (92% yield) of *cis*-methyl 4-bromocinnamate as a crystalline solid: mp 40-42 °C ; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 5.98 (d, *J* = 12.6 Hz, 1 H), δ6.89 (d, *J* = 8.8 Hz, 2 H), δ6.88 (d, *J* = 12.6 Hz, 1 H), 7.48 (br, 4 H). The isolated cis-cinnamate derivatives listed below were all 98-99+% pure by GC analysis.

***cis*-Methyl 4-chlorocinnamate.** Colorless oil (91 % yield). ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 5.97 (d, *J* = 12.7 Hz, 1 H), 6.90 (d, *J* = 12.6 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 7.56 (d, *J* = 8.6 Hz, 2 H).

***cis*-Methyl 4-cyanocinnamate.** White solid (85 % yield). Mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 6.10 (d, *J* = 12.6 Hz, 1 H), 6.98 (d, *J* = 12.5 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.64 (s, 4 H).

***cis*-Methyl 4-fluorocinnamate.** Colorless oil (89 % yield). ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 5.94 (d, *J* = 12.7 Hz, 1 H), 6.90(d, *J* = 12.7 Hz, 1 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 7.65 (d, *J* = 8.8 Hz, 2 H).

***cis*-Methyl 4-methoxycinnamate.** Colorless oil (88 % yield). ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.84 (s, 3 H), 5.83 (d, *J* = 13.0 Hz, 1 H), 6.87 (d, *J* = 12.8 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.70 (d, *J* = 8.8 Hz, 2 H).

***cis*-Methyl cinnamate.** Colorless oil (84 % yield). ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3 H), 5.96 (d, *J* = 12.6 Hz, 1 H), 6.96 (d, *J* = 12.6 Hz, 1 H), 7.35 (d, *J* = 7.6 Hz, 2 H), 7.59 (d, *J* = 7.5 Hz, 2 H).

***cis*-Methyl 4-methylcinnamate.** Colorless oil (80 % yield). ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3 H), 3.72 (s, 3 H), 5.90 (d, *J* = 12.7 Hz, 1 H), 6.92 (d, *J* = 12.7 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H).

***cis*-Methyl 4-nitrocinnamate.** Pale yellow solid (86 % yield). Mp 91-92 °C (lit.[35] mp 91 °C); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 6.14 (d, J = 12.5 Hz, 1 H), 7.03 (d, J = 12.6 Hz, 1 H),7.68 (d, J = 8.7 Hz, 2 H), 8.22 (d, J = 8.8 Hz, 2 H).
***cis*-Methyl 4-trifluoromethylcinnamate.** Colorless oil (82 % yield). ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 6.07 (d, J = 12.6 Hz, 1 H), 7.00 (d, J = 12.5 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.65 (d, J = 8.6 Hz, 2 H).

Notes and References

1. On leave from the Daiso Chemical Company, Osaka.
2. a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.1.
3. Takaya, H.; Ohta, T.; Noyori, R. *ibid.*; Chapter 1.
4. Jacobsen, E. N.; Markó, I. E.; Mungall, W. S.; Schröder, G. W.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
5. Morikawa, K.; Park, J.; Andersson, P.G.; Hashiyama, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1993**, *115*, 8463-8464, and references therein.
6. Kolb, H.; Sharpless, K. B. *Tetrahedron* **1992**, *56*, 3177.
7. Collman, J. P.; Zhang, X.; Lee, V. J.; Uffelman, E. S.; Brauman, J. I. *Science* **1993**, *261*, 1404.
8. Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.
9. Zhang, W.; Loebach, J.L.; Wilson, S.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
10. Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
11. *Chem. Eng. News* July 19, 1993, p. 50.
12. a) Parker, R. E.; Isaacs, N. C. *Chem. Rev.* **1959**, *59*, 737. b) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67
13. Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1970**, *18*, 2284.
14. a) Ire, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, *32*, 6533. b) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2.
15. Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.
16. Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.
17. Enantioselectivity is enhanced by 5-12% by the presence of 4-phenylpyridine *N*-oxide if Clorox® is used as the terminal oxidant. This may be attributed to suppression of a non-selective pathway catalyzed by Lewis acidic Mn-containing species which result from decomposition of **1**. However, this low selectivity pathway does not appear to play a role in epoxidations using 13% NaOCl.
18. Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. We have obtained similar kinetic results using chiral (salen)Mn systems such as **1**.
19. A detailed procedure for the synthesis of phenyl isoserine using the (salen)Mn AE will be submitted shortly to *Organic Syntheses*: Martínez, L. E.; Jacobsen, E. N. Manuscript in preparation.
20. For a review on structure-activity studies pertaining to taxol, see: Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.
21. Jacobsen, E.N.; Güler, M.L.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
22. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
23. a) Ref. 18. b) Palucki, M.; Pospisil, P. J.; Jacobsen, E. N. Unpublished results.
24. Lee, N.H.; Jacobsen, E.N. *Tetrahedron Lett.* **1991**, *32*, 6533. Note that the configurations of the catalyst were inadvertedly switched in Figure 1 of that paper.
25. a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. b) Hosoya, N.; Hatayama, A.; Yanai, K.; Fujii, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 641.
26. For a related model pertaining to Rh-catalyzed cyclopropanations, see: Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.
27. In competition experiments, *trans*-ethyl cinnamate was found to undergo epoxidation with catalyst **1** 25 times more slowly than the cis isomer, and to afford epoxide in <30% ee. Katsuki has observed up to 66% ee in the epoxidation of *trans*-stilbene with chiral (salen)Mn complexes bearing stereocenters on the salicylidene portion of the ligand (ref. 25b). Although it is difficult to deduce meaningful stereochemical models from reactions that exhibit only moderate selectivity, it is apparent that the skewed approach model in Figure 4 does not apply to the epoxidation of *trans*-stilbene with Katsuki's catalyst system.
28. a) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851. b) Inoue, H.; Takeo, S.; Kawazu, M.; Kugita, H. *Yakugaku Zasshi* **1973**, *93*, 729; *Chem. Abstr.* **1973**, *79*, 66331.
29. Watson, K. G.; Fung, Y. M.; Gredley, M.; Bird, G. J.; Jackson, W. R.; Gountzos, H.; Matthews, B. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1018.
30. Both enantiomers of **1** are commercially available from Aldrich. A new, highly optimized procedure which has been adapted to large scale synthesis (> 50 kg) has been developed: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. Submitted for publication.
31. Abbott, T. W. *Org. Synth. Coll. Vol. II* **1943**, 515.
32. Abbott, T. W.; Althousen, D. *Org. Synth. Coll. Vol. II* **1943**, 270.
33. a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
34. Chrzaszczewska, A.; Bielawski, B. *Lodz. Towarz. Nauk., Wydzial III Acta Chim.* **1958**, *3*, 87; *Chem. Abstr.* **1959**, *53*, 13094a.
35. Orgura, H.; Kubo, K.; Watanabe, Y.; Itoh, T. *Chem. Pharm. Bull.* **1973**, 2026

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