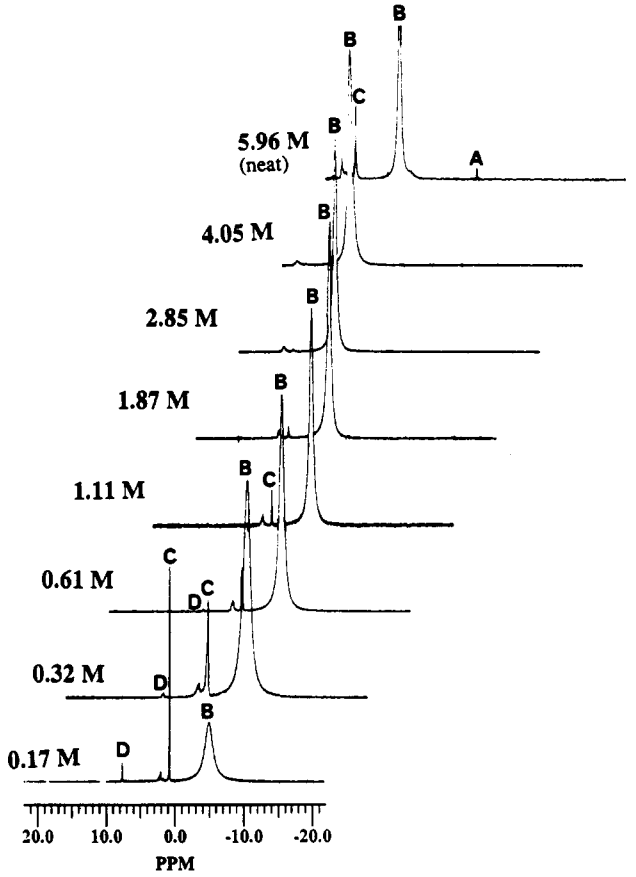


**Figure 1.** Stacked plots showing DBNO titrated into $CDCl_3$: (A) external TMS, (B) DBNO, (C) internal TMS, (D) residual $CHCl_3$. The top spectrum is neat DBNO (5.96 M) containing both internal and external TMS (C and A, respectively).

function of paramagnetic sample concentration. Therefore, *all chemical shifts of paramagnetic samples should be externally referenced.*

A hfc $a$(18 H) = +0.047 G is obtained for **2** when the same experimental approach is employed. This corresponds exactly with ESR studies and confirms our hypothesis with regards to the concentration dependence of the hfcs.[3a] The hfcs determined via ESR are not significantly concentration dependent,[7] whereas NMR $\Delta\delta$s are. Early NMR experiments were performed at very high concentrations (either neat or saturated solutions) as single point experiments and failed to properly account for the concentration dependence of the $\Delta\delta$s.[3,10] Extrapolation

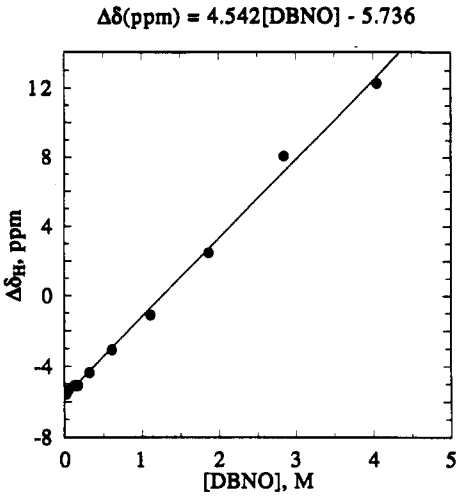


**Figure 2.** Plot of $\Delta\delta$ $^1$H chemical shift vs [DBNO] in $CDCl_3$.

of $\Delta\delta$ values measured at several concentrations to zero concentration appears to be the best approach to obtain hfcs.

The above observations are also true for $^{13}$C hfcs measured by NMR. A concentration study on the $^{13}$C resonances of **1** (at natural abundance) yielded $a$(2 C) = −4.92 G and $a$(6 C) = +4.65 G at infinite dilution. These values compare well with hfcs of $|a(2C)|$ = 4.4–5.4 G and $|a(6\ C)|$ = 4.4–4.9 G determined by ESR and represent a significant improvement in accuracy over previous NMR on neat solutions.[11] The broadening observed in $^1$H experiments occurs at a higher concentration for $^{13}$C experiments (ca. 5 mM vs 2 M). Examination of **2** by $^{13}$C proved futile since a saturated solution in $CDCl_3$ (ca. 1.5 M) showed no discernable resonances after 36 h.

NMR spectra of paramagnetic materials can be an important aid in interpreting complex ESR spectra where several small splittings are present. Given the ease with which these experiments can now be performed, and the widespread availability of NMR spectrometers, a renaissance of the use of NMR for determination of small hfcs is anticipated.

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(10) Kreilick reports that the concentration dependence does indeed exist, but he fails to comment upon its relevance with respect to the observed $\Delta\delta$s. See ref 4b.

(11) (a) Hatch, G. F.; Kreilick, R. *Chem. Phys. Lett.* **1971**, *10*, 490. (b) Hatch, G. F.; Kreilick, R. W. *J. Chem. Phys.* **1972**, *57*, 3696.

## Mechanistic Study of a Synthetically Useful Monooxygenase Model Using the Hypersensitive Probe *trans*-2-Phenyl-1-vinylcyclopropane

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*Summary:* The use of *trans*-2-phenyl-1-vinylcyclopropane as a hypersensitive probe to study the epoxidation mechanisms of monooxygenases and their models is described; the high yield epoxide formation indicates that the Mn(III) salen mediated epoxidation of unfunctionalized alkyl-substituted olefins is a concerted process. A stepwise mechanism, however, is suggested for the epoxidation of aryl-substituted olefins.

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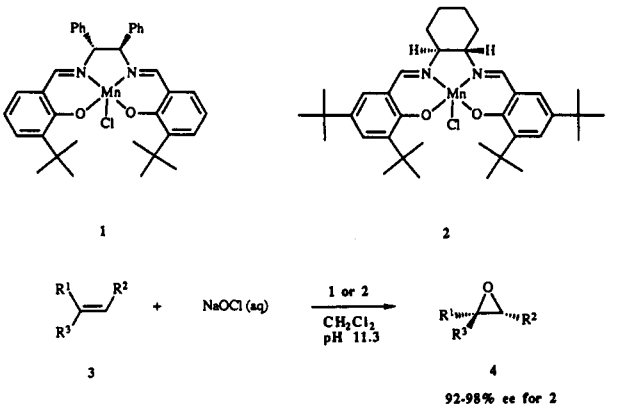
The functionalized salen (*N,N'*-bis(salicylideneamino)-ethane) Mn(III) complexes **1** and **2** have been used, in the presence of commercial bleach (NaOCl), to catalyze the enantioselective epoxidation of unfunctionalized olefins (**3** → **4**).[1,2] This method is currently the most selective asymmetric catalytic epoxidation reaction of its type developed,[3-7] with enantiomeric excesses as high as 98%.[1,2] As part of our interest in the use of monooxygenases[8,9] and their models[1,2] in organic synthesis and the investigation of their reaction mechanisms,[9] we describe herein our mechanistic studies of the epoxidation reactions mediated by **1** and **2** and some monooxygenases utilizing the hypersensitive radical probe **11**. These probes may be of general applicability to the mechanistic studies of other epoxidation catalysts.

The Mn(III) salen catalyzed epoxidation reactions proceed via discrete manganese(V)–oxo intermediates **5**,[1,2,6b] analogous to the reactive "oxygen-transfer" species of monooxygenases and their models.[7-15,16] The high stereoselectivity with *cis*-olefins is readily understood in terms

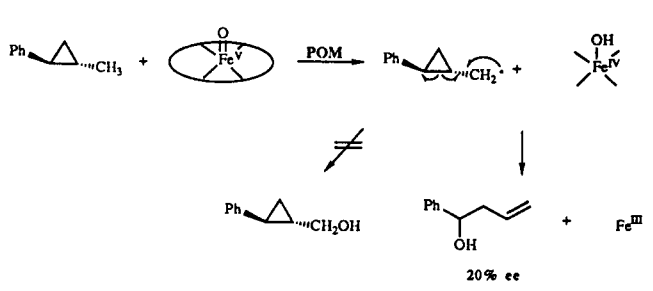



of side-on attack by the reacting olefin at the oxygen of the Mn–oxo moiety.[1,2b,6a,b] While this model generally predicts the sense and degree of enantioselectivity in alkene epoxidation, it does not distinguish between the various concerted or nonconcerted pathways that may be envisioned for oxygen atom transfer.

In general, there are four proposed mechanistic pathways for the epoxidation of olefins by the metal–oxo species (Scheme I).[10] Pathway A is a stepwise radical addition to the double bond to form **6**, followed by a ring closure to the epoxide. A concerted addition, pathway B, gives the epoxide directly. Pathway C is also a type of concerted olefin cycloaddition mechanism where a four-membered metallacycle **8** extrudes the metal. Pathway D is a stepwise mechanism where single electron transfer occurs to form the radical cation **9**, which collapses to cation **10** and is subsequently trapped by the metal alkoxide. Both pathways A and D were proposed for several Fe-containing cytochrome P-450 models,[11-13] and pathway A was proposed for Mn(III) salen mediated epoxidation of olefins.[6] Pathways B and C were suggested for other nonenzymatic epoxidation reactions.[7a-d,9,14,15]

As a probe for determining the mechanism of the Mn(III) salen epoxidation reaction, we chose the *trans*-2-phenyl-1-vinylcyclopropane (**11**), which is easily prepared.[17,18]

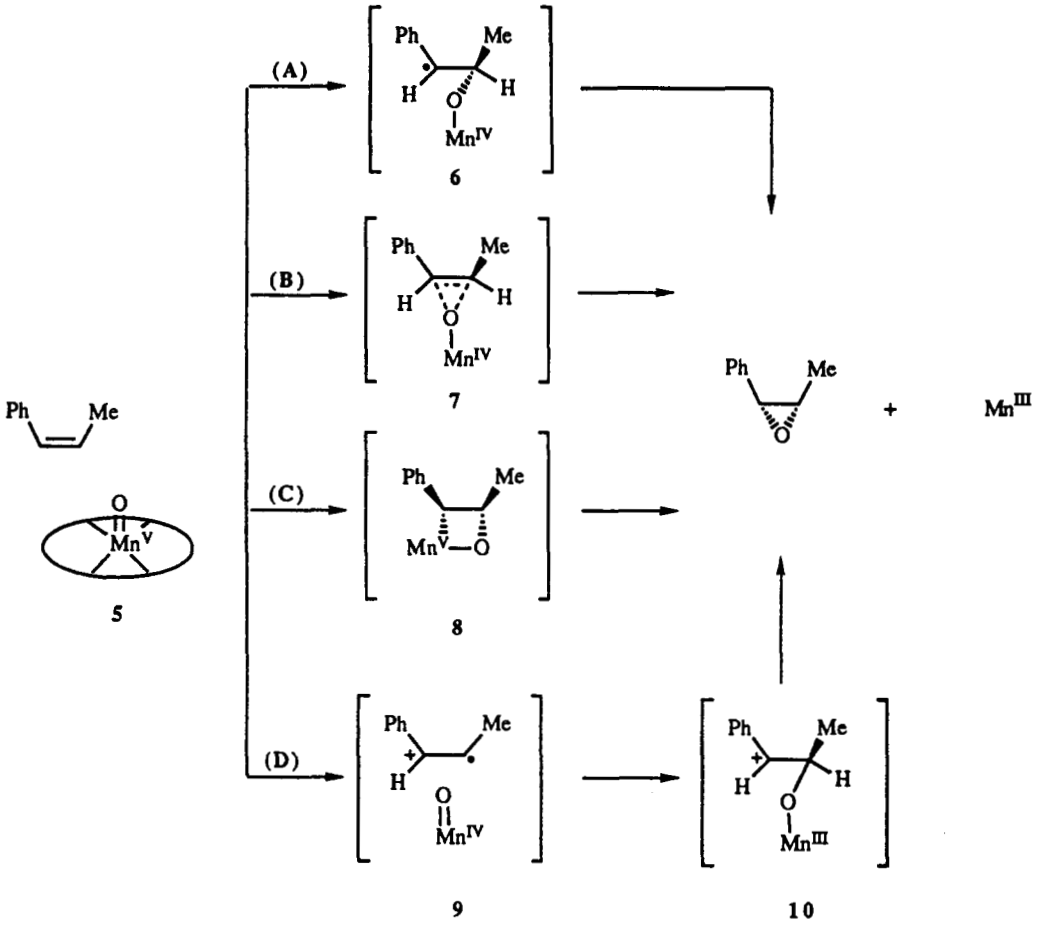
(1) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.
(2) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
(3) For a review of the asymmetric epoxidation of unfunctionalized olefins, see: Kagan, H. B.; Minoun, M.; Mark, C.; Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1979**, 485.
(4) For reviews on enantioselective catalysis, see: Brunner, H. *Synthesis* **1988**, 645. Tomioka, K. *Synthesis* **1990**, 541. Noyori, R. *Science* **1990**, *248*, 1194.
(5) For a recent study of the asymmetric catalytic epoxidation of unfunctionalized olefins, see: Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628.
(6) For additional studies of salen Mn(III) epoxidation catalysts, see: (a) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345. (b) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.
(7) For examples of manganese hydroxylation and epoxidation P-450 models, see: (a) Collman, J. P.; Hampton, P. D.; Brauman, J. I. *J. Am. Chem. Soc.* **1986**, *108*, 7861. (b) Collman, J. P.; Kodadek, T.; Raybuck, S. A.; Brauman, J. I.; Papazian, L. M. *J. Am. Chem. Soc.* **1985**, *107*, 4343. (c) Collman, J. P.; Brauman, J. I.; Meunier, B.; Hayashi, T.; Kodadek, T.; Raybuck, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 2000. (d) Collman, J. P.; Brauman, J. I.; Meunier, B.; Raybuck, S. A.; Kodadek, T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3245. (e) Hill, C. L.; Schardt, B. C. *J. Am. Chem. Soc.* **1980**, *102*, 6347. (f) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812. (g) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375. (h) Meunier, B.; Guilmet, E.; de Carvalho, M.-E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668. (i) Tabushi, I.; Yazaki, A. *J. Am. Chem. Soc.* **1981**, *103*, 7371. (j) Powell, M. F.; Pai, E. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 3277. (k) Razenberg, J. A. S. J.; Nolte, R. J. M.; Drenth, W. *J. Chem. Soc., Chem. Commun.* **1986**, 277. (l) van der Made, A. W.; Smeets, J. W. H.; Nolte, R. J. M.; Drenth, W. *J. Chem. Soc., Chem. Commun.* **1983**, 1204. (m) Renaud, J.-P.; Battioni, P.; Bartoli, J. F.; Mansuy, P. *J. Chem. Soc., Chem. Commun.* **1985**, 888.
(8) Fu, H.; Shen, G.-J.; Wong, C.-H. *Recuiel* **1991**, *110*, 167.
(9) Our mechanistic studies of the *Pseudomonas oleovorans* non-heme monooxygenase (POM) catalyzed hydroxylation of *trans*-1-methyl-2-phenylcyclopropane indicate a radical mechanism, see: Fu, H.; Newcomb, M.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 5878. This probe, however, is not a substrate for **1** or **2**.



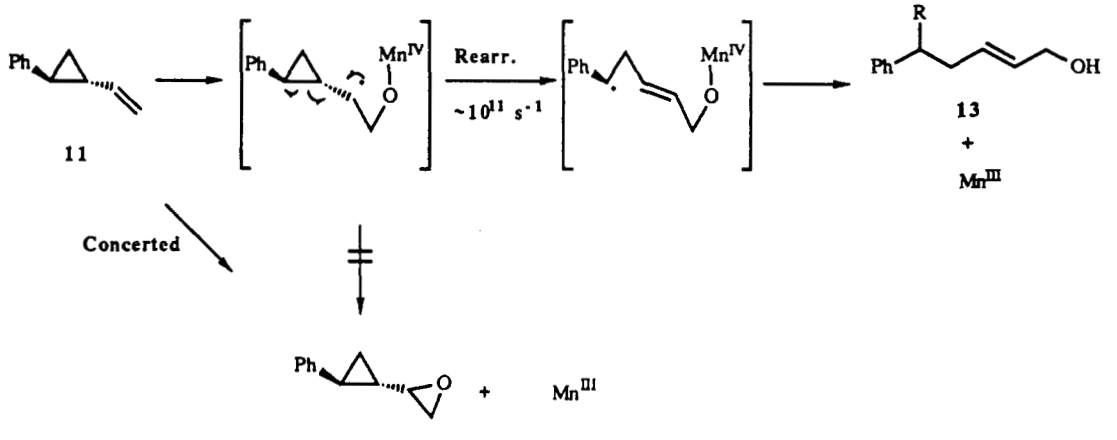

(10) Currently, there is no universal mechanism for epoxidation by metal catalysis. The nature of the epoxidation seems to vary with the metal, ligand, and sometimes substrate.

(11) de Montellano, P. R. O.; Stearns, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 3415 and refs 7e and 7g.
(12) (a) He, G.-X.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 2747 and references cited. (b) Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 7512. (c) Newcomb, M.; Manek, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 9662. (d) Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275. (e) Newcomb, M.; Manek, M. B.; Glenn, A. G. *J. Am. Chem. Soc.* **1991**, *113*, 949.
(13) Radical cation: Traylor, T. G.; Xu, F. *J. Am. Chem. Soc.* **1988**, *110*, 1953. Bruice, T. C.; Ostovic, D. *J. Am. Chem. Soc.* **1989**, *111*, 6511.
(14) Direct epoxide formation: Sugimoto, H.; Hui-Chan, T.; Sawyer, D. T. *J. Am. Chem. Soc.* **1988**, *110*, 2465.
(15) Oxa metallocycles: (a) Rappé, A. K.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1980**, *102*, 5114. (b) Groves, J. T.; Avaria-Neisser, G. E.; Fish, K. M.; Imachi, M.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 3837. (c) Groves, J. T.; Ahn, K.-H.; Quinn, R. *J. Am. Chem. Soc.* **1988**, *110*, 4217. (d) Ivin, K. J.; Reddy, B. S. R.; Rooney, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1062. (e) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
(16) Groves and Stern have determined that oxomanganese(IV) as well as oxomanganese(V) porphyrin species will epoxidize olefins, with the oxomanganese(IV) accounting for the majority of rearrangement products.[7f] However, an oxomanganese(V) salen epoxidation intermediate has been isolated.[1] Additionally, work by Kochi and co-workers[6b] *suggests* that the manganese(III) salen species undergo two-electron oxidation to afford the reactive oxomanganese(V) species.
(17) Marvell, E. N.; Lin, C. *J. Am. Chem. Soc.* **1978**, *100*, 877. Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4042.
(18) Feldman has used **11** for his studies of phenylthio and phenylseleno radical catalyzed oxygenation reactions: Feldman, K. S.; Ruckle, R. E., Jr.; Romanelli, A. L. *Tetrahedron Lett.* **1989**, *30*, 5845. Feldman, K. S.; Simpson, R. E. *Tetrahedron Lett.* **1989**, *30*, 6985. Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878.

**Scheme I**




**Scheme II**

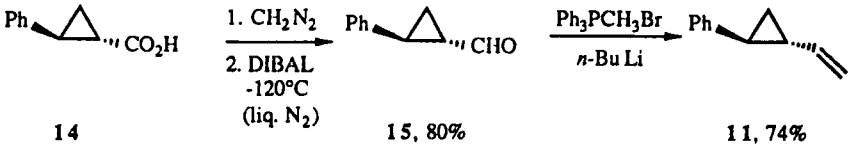



It has been determined that the rate of rearrangement of a secondary phenylcyclopropylcarbinyl radical to a secondary homoallylic radical[12a] is $\geq 10^{10}$ $s^{-1}$ and that of a primary phenylcyclopropylcarbinyl radical[12c] is $1.2 \times 10^{11}$ $s^{-1}$ at room temperature, both faster than the ring opening of cyclopropylcarbinyl ($9.4 \times 10^7$ $s^{-1}$)[12d] and bicyclo[2.1.0]pentyl ($1.5 \times 10^9$ $s^{-1}$)[12e] radicals. Similar rates have been estimated for cyclopropylcarbinyl cation rearrangements.[12a] Furthermore, Ingold has determined that the oxygen rebound rate for cytochrome P-450 models is $2 \times 10^{10}$ $s^{-1}$.[19] Therefore, with the use of the hypersensitive probe **11**, a secondary radical or cationic intermediate involved in the epoxidation reaction should rearrange at the picosecond level and afford the readily detectable product of cyclopropane cleavage **13** (Scheme II). Conversely, a concerted mechanism would exclusively afford epoxide **12**. Bruice and co-workers[12b] have successfully employed the cyclopropyl derivatives (*E*)- and (*Z*)-1,2-bis(*trans*-2,-*trans*-3-diphenylcyclopropyl)ethene as a probe for their mechanistic work with metal porphyrin epoxidation catalysts.[20] Compound **11** was chosen as our probe in an-

(19) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927.

(20) One referee has suggested that the cyclopropyl alkoxymanganese(IV) species (Scheme II) may not undergo cyclopropyl rearrangement at a sufficient rate to trap the incipient radical. This issue is being addressed by the examination of epoxidation catalysts which are known to involve radical intermediates and will be the subject of a future report.

**Scheme III**




14 15, 80% 11, 74%

ticipation of using it for delineating the mechanism of enzymatic oxidations that require terminal olefin substrates.[21]

The vinylcyclopropane probe 11 was constructed, as outlined in Scheme III, in three steps and 59% yield from commercially available 14. The probe contained ~3% of the cis cyclopropyl isomer, reflecting the ratio of cis to trans isomers in the starting acid 14.

The epoxidation reactions were performed at 0.18 mmol scale[2] and were followed by GLC using response factors determined from authentic samples using decane as an internal standard.[22] Additionally, several control experiments were performed with and without catalyst, oxidant, and substrate. After 12 h, the reactions were quenched and the mixtures were analyzed by GLC and GC/MS. The chromatograms of the reaction mixtures were compared to those of authentic products. The identity of each component of the reaction mixtures was verified by GC/MS, co-injection, thin layer chromatography (TLC), and $^1$H NMR comparison of the isolated products. The major product observed was the cyclopropane epoxide (72% yield by GLC, 83% conversion),[23] *and no products of cyclopropyl ring opening were observed by $^1$H NMR analysis of the crude reaction mixture.* An unidentified peak on the GLC was determined as having arisen from the decomposition of the product epoxide as evidenced by the observation of this peak when an authentic sample of epoxide was subjected to the reaction conditions.

The formation of the epoxides in lieu of the cyclopropyl radical or cation rearrangement products strongly supports a concerted mechanism of epoxidation for 11 in which C–O bond formation occurs in a concerted manner at both ends of the olefin. This conclusion is consistent with observations we have made with aliphatically substituted internal *cis*-alkenes such as *cis*-2-octene and *cis*-2,2-dimethyl-3-hexene, which are epoxidized stereospecifically, with the corresponding cis epoxides as sole products. In contrast, aryl-substituted acyclic *cis*-alkenes always provide measurable (3–20%) amounts of the corresponding trans epoxides as byproducts.[1,6] Since neither the *cis*-alkenes nor the cis epoxides isomerize under the reaction conditions, the trans epoxides are primary products.[24] This strongly suggests that aryl-substituted alkenes may proceed by a different, nonconcerted mechanism (e.g. pathways A or D in Scheme I), with benzylic stabilization of the intermediate radical or with stepwise formation of the two C–O bonds in the product epoxide. This is supported by the fact that aryl-substituted olefins react much faster than aliphatically substituted olefins ($k_{rel}$ = 30:1 in sterically similar cases). Enantioselectivities are also very different for these two substrate classes.[25]

In summary, with the use of a hypersensitive probe as a substrate, the Mn(III) salen mediated epoxidation of unfunctionalized alkyl-substituted olefins indicates a concerted process (pathway B or C), and a stepwise process is suggested for the epoxidation of aryl-substituted olefins. Given the ease with which 11 is prepared, this radical probe should prove to be invaluable in the mechanistic evaluation of other monooxygenases and their models.

**Supplementary Material Available:** Experimental procedures and characterization data for compounds 11, 12, and 15 and GLC data for catalyzed and control reactions (4 pages). Ordering information is given on any current masthead page.

(21) Bruice's (*Z*)-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical probe[12a,b] would not be a substrate for monooxygenases such as that from *P. oleovorans* since these enzymes are specific for terminal olefins. 11 was not a substrate for *P. oleovorans* monooxygenase, chloroperoxidase, horseradish peroxidase, and cytochrome *c* oxidase. Reaction with other monooxygenases is under investigation.

(22) For these studies, racemic catalyst 1 was employed. Similar results were observed with 2.

(23) Only one epoxide is formed from the reaction as evidenced by GLC and $^1$H NMR analyses. Efforts are currently underway to determine the stereochemistry of this compound. The reactions were stopped after 12 h and 83% conversion due to the gradual decomposition of epoxide 12 under the reaction conditions. Taking into account the epoxide decomposition product, total mass recovery is estimated to be ~96%.

(24) No isomerization of *cis*-β-methylstyrene oxide is observable when the epoxide is stirred with either 1 or 2 in the presence or in the absence of NaOCl, or if authentic pure cis epoxide is added to an ongoing catalytic epoxidation reaction. These control experiments rigorously rule out the possibility of epoxide cis–trans isomerization to account for the observed trans epoxide byproducts with aryl olefins.

(25) Groves has reported that styrene derivatives and *tert*-butylethylene display opposite facial selectivity in asymmetric epoxidation.[5]

(26) This research was supported by the NSF (CHE-8996249) to C. H.W. and an American Cancer Society Postdoctoral Fellowship (PF-3525, to G.C.L.). E.N.J. acknowledges a NSF Presidential Young Investigator Award (CHE-9057740) and support from the NIH (GM-4314-01A1).

# An Efficient Synthesis of Hydroxyethylene Dipeptide Isosteres: The Core Unit of Potent HIV-1 Protease Inhibitors

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*Summary:* An efficient and stereocontrolled synthesis of hydroxyethylene dipeptide isosteres 1 from commercially available, optically pure D-mannose is described. This synthesis represents a practical and enantioselective entry to a range of other dipeptide isosteres, which are not limited to amino acid derived substituents.

Since the advent of acquired immunodeficiency syndrome (AIDS) and the discovery of its causative agent, human immunodeficiency virus (HIV-1),[1] the design and

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