Solutions. All solutions were prepared in 50% Me_2SO–50% water (v/v) with potassium chloride added as a compensating electrolyte in order to maintain a constant ionic strength of $\mu = 0.50$ M. The solutions were purged with nitrogen or argon before adding the thiol. All pH measurements were performed on an Orion Research 611 digital pH meter calibrated for 50% Me_2SO–50% water (v/v) with buffers described by Hallé et al.[43]

Synthesis of $Ph(HOCH_2CH_2S)CHCH(Ph)(NO_2)$. To a solution of 0.345 g (1.55×10^{-3} moles) of α-nitrostilbene in 5 mL of acetonitrile were added, with stirring, 0.242 g (0.217 mL, 3.10×10^{-3} mol) of 2-mercaptoethanol and 0.433 mL (0.314 g, 3.10×10^{-3} mol) of triethylamine, whereupon a color change from pale yellow to bright yellow-orange was observed. The color change presumably corresponds to the formation of T_{SR}^-. To this solution was added 0.931 g (0.887 mL, 1.55×10^{-2} mol) of acetic acid, and the solution became colorless. The solution was poured into 25 mL of dichloromethane and washed with 3 × 20 mL of water. The dichloromethane layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was recrystallized from 95% ethanol to give a white solid: mp 103–105 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 7.4 (b, 10 H, Ar H), 5.78, 4.85 (AB, $J = 12$ Hz, 2 H), 3.54 (t, 2 H, $J = 6$ Hz, the OCH_2 signal was obscured by the OH signal; the triplet becomes observable when D_2O is added to exchange the OH), δ 2.30 (t, 2 H, $J = 6$ Hz, SCH_2); MS, m/e 303 (M^+).

Kinetics. All rate constants were measured in a Durrum-Gibson stopped-flow spectrophotometer with computerized data acquisition and analysis. Rate constants in the forward direction were measured by mixing a 5×10^{-5} M solution of the substrate in 0.5 M KCl, 50% Me_2SO–50% water with a solution of the thiol in a 50% Me_2SO–50% water solution buffered at pH 7.56 with *N*-methylmorpholine; $\mu = 0.50$ M (KCl). The thiolate concentration was calculated from the known thiol concentration, the pK_a of the thiol, and the measured pH. Pseudo-first-order conditions were maintained by keeping the thiol in excess over the substrate. The decrease in absorbance vs time was monitored at the λ_{max} of the substrate, and first-order rate constants were calculated by using a computerized data acquisition and analysis system.

Generation of Thiol Adducts and pH-Jump Experiments. A stock solution of the thiol adduct T_{SR}^- was generated in situ by preparing a solution of 0.05 M of the respective α-nitrostilbene in 0.1 M triethylamine, 0.1 M thiol, in acetonitrile. Solutions of T_{SR}^- for the pH-jump experiments were prepared by diluting 100 μL of the 0.05 M T_{SR}^- stock solution into 100 mL of 0.01 M KOH, 50% Me_2SO-50% water, $\mu = 0.50$ (KCl). The thiol adduct could be distinguished from the hydroxy adduct by their characteristic UV–vis spectra.[44] In pH-jump experiments, the solution of the T_{SR}^- adduct in 0.01 M KOH, 50% Me_2SO–50% water, $\mu = 0.50$ M (KCl), was mixed in the stopped-flow apparatus with various concentrations of acetic acid buffers to give a final pH of 5.78 and a final total thiol concentration of 5×10^{-5} M. The thiolate adducts derived from methyl mercaptoacetate and methyl-3-mercaptopropionate were unstable if kept for long periods of time, but the pH-jump experiments were successful if performed within ca. 10 min upon dilution of the 0.05 M T_{SR}^- stock solution into 0.01 M KOH.

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Registry No. S (Z = 4-Me), 116467-17-5; S (Z = H), 1215-07-2; S (Z = 4-Br), 40770-84-1; S (Z = 3-NO_2), 116467-18-6; S (Z = 4-NO_2), 116467-19-7; T_{SR}^- (Z = 4-Me; R = $(CH_2)_2OH$), 116467-20-0; T_{SR}^- (Z = H; R = $(CH_2)_2OH$), 116467-21-1; T_{SR}^- (Z = 4-Br; R = $(CH_2)_2OH$), 116467-22-2; T_{SR}^- (Z = 3-NO_2; R = $(CH_2)_2OH$), 116467-23-3; T_{SR}^- (Z = 4-NO_2; R = $(CH_2)_2OH$), 116467-24-4; T_{SR}^- (Z = H; R = CH_2CH_3), 116467-25-5; T_{SR}^- (Z = H; R = $(CH_2)_2CO_2Me$), 116467-26-6; $CH_3CH_2S^-$, 20733-13-5; $HO(CH_2)_2S^-$, 57966-62-8; $CH_3OCO(CH_2)_2S^-$, 59177-13-8; $CH_3OCOCH_2S^-$, 64743-45-9; $Ph(HO(CH_2)_2S)CHCH(Ph)NO_2$, 116467-27-7; $HO(CH_2)_2SH$, 60-24-2.

Supplementary Material Available: Kinetic data, Tables S1–S4 (6 pages). Ordering information is given on any current masthead page.

(43) Hallé, J. C.; Gaboriaud, R.; Schaal, R. *Bull. Soc. Chim. Fr.* **1970**, 2047.

(44) Bernasconi, C. F.; Fassberg, J., unpublished results.

Intermediates in the Epoxidation of Alkenes by Cytochrome P-450 Models. 2. Use of the *trans*-2,*trans*-3-Diphenylcyclopropyl Substituent in a Search for Radical Intermediates

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Abstract: (*Z*)-1,2-Bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (**1-Z**) has been used to search for radical intermediates in the epoxidation reactions of cytochrome P-450 model systems. The studied systems used the following as catalysts: (*meso*-tetrakis(pentafluorophenyl)porphinato)iron(III) chloride [$(F_{20}TPP)Fe^{III}(Cl)$], (*meso*-tetrakis(2,6-dichlorophenyl)-porphinato)iron(III) chloride [$(Cl_8TPP)Fe^{III}(Cl)$], and (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)manganese(III) hydroxide [$(Cl_8TPP)Mn^{III}(OH)$] in CH_2Cl_2 with C_6F_5IO as oxidant. All investigated systems gave *cis*-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)oxirane (**2-c**), the *cis*-epoxide corresponding to **1-Z**, in high yield (>80% based on reacted **1-Z**). Stereoisomerization products (**2-t** and **1-E**) could not be detected. The remaining reaction products were found as very nonpolar (non-oxygen containing) components and are interpreted in terms of the radical cation intermediate A which has been intercepted by a cyclopropylcarbinyl to homoallyl radical rearrangement (CPCRR). In order to discuss the mechanistic position of A (on the pathway to epoxide vs formation in a parallel reaction) the rate constant for CPCRR of the secondary (*trans*-2,-*trans*-3-diphenylcyclopropyl)carbinyl radical (D) was determined. For this purpose *trans*-2,*trans*-3-diphenyldicyclopropyl ketone (**3**) was treated with the known radical reductants *n*-$Bu_3SnH/h\nu$ and $Li/NH_3(l)$. Product analyses showed that *trans*-2,-*trans*-3-diphenyl substitution increases the CPCRR rate constant by a factor $\geq 10^3$. From this value the rate constant for CPCRR of D may be calculated as $\geq 2 \times 10^{10}$ s^{-1}. This rate constant in conjunction with the yields of very nonpolar products obtained from the cytochrome P-450 model systems would require the radical cation A, as an intermediate, to proceed to epoxide with a rate constant of $\geq 1 \times 10^{11}$ to 2×10^{11} s^{-1}. Such a rate constant is not unreasonable. No products from the neutral radical C were detected. From the preceding considerations, C, as an intermediate, is required to proceed to epoxide with a rate constant $\geq 10^{12}$ s^{-1}. Such a rate constant would argue against C as a discrete intermediate.

It has been proposed,[1] in analogy to catalase and horseradish peroxidase, that the oxidant of cytochrome P-450 is an iron oxo porphyrin π-cation radical ($^{+\bullet}P)Fe^{IV}(O)$. The two cytochrome P-450 oxidations of principal interest to organic chemists are

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epoxidation and hydroxylation. Evidence has accumulated which supports substrate-derived radicals (SDRs) as intermediates in alkane hydroxylation.[2] Our interests concern such intermediates in the epoxidation of alkenes.

The cyclopropyl- to homoallylcarbinyl radical rearrangement (CPCRR) has been shown to be an effective radical trap in enzymic[3] and nonenzymic[4] systems. Studies of alkane hydroxylation by cytochrome P-450 using the CPCRR[3b] have demonstrated that the rate constant for disappearance of SDRs to hydroxylated products is "in excess of 1×10^9 s^{-1}".[3b] For the study of alkene epoxidation we have conceived of the *trans*-2,*trans*-3-diphenylcyclopropyl substituent as a radical trap.[5b] The CPCRR rate constant that we have determined for the secondary (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical (D) is $\geq 2 \times 10^{10}$ s^{-1} (30 °C). The radical trap was incorporated into the alkene substrate **1-Z** which was subjected to epoxidation by C_6F_5IO with (*meso*-tetrakis(pentafluorophenyl)porphinato)iron (III) chloride [$(F_{20}TPP)Fe^{III}(Cl)$], (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)iron(III) chloride [$(Cl_8TPP)Fe^{III}(Cl)$], and (*meso*-tetrakis(2,6-dichlorophenyl)porphinato)manganese(III) hydroxide [$(Cl_8TPP)Mn^{III}(OH)$] as catalysts in CH_2Cl_2 solvent. Product analyses by HPLC with UV detection allows for the determination of individual product yields which are ≥0.1% of the total product yield. This limit and the CPCRR rate constant for D permits the detection of SDRs that have rate constants for disappearance to epoxides approaching 10^{12} s^{-1}. The determination of the CPCRR rate constant for D and the mechanistic implications derived from the epoxidation of **1-Z** are presented within.

(1) (a) *Cytochrome P-450: Structure, Mechanism, and Biochemistry*, Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986. (b) Guengerich, F. P.; Macdonald, T. C. *Acc. Chem. Res.* **1984**, *17*, 9.

(2) (a) White, R. E.; Miller, J. P.; Faveau, L. V.; Bhattacharyya, A. *J. Am. Chem. Soc.* **1986**, *108*, 6024. (b) Groves, J. T.; Subramanian, D. V. *Ibid.* **1984**, *106*, 2177. (c) Shapiro, S.; Piper, J. U.; Caspi, E. *Ibid.* **1982**, *104*, 2301. (d) Gelb, M. H.; Heimbrook, D. C.; Malkonen, P.; Sligar, S. G. *Biochemistry* **1982**, *21*, 370. (e) Groves, J. T.; McClusky, G. A. *Acta Biol. Med. Ger.* **1979**, *38*, 475. (f) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154. (g) Hjelmeland, L. M.; Arnow, L.; Trudell, J. R. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 541. (h) Groves, J. T.; McClusky, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 859.

(3) (a) Livingston, D. J.; Shames, S. L.; Gennis, R.; Walsh, C. T. *Bioorg. Chem.* **1987**, *15*, 358. (b) Ortiz de Montellano, P. R.; Stearns, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 3415. (c) Houghton, J. D.; Beddows, S. E.; Suckling, K. *Tetrahedron Lett.* **1986**, *27*, 4655. (d) Silverman, R. B.; Zieske, P. A. *Biochemistry* **1985**, *24*, 2128. (e) Fitzpatrick, P. F.; Villafranca, J. J. *J. Am. Chem. Soc.* **1985**, *107*, 5022. (f) Silverman, R. B.; Yamasaki, R. B. *Biochemistry* **1985**, *24*, 6543. (g) Silverman, R. B.; Vazquez, M. L. *Ibid.* **1985**, *24*, 6538. (h) Silverman, R. B.; Zieske, P. A. *Ibid.* **1985**, *24*, 2128. (i) Sherry, B.; Abeles, R. H. *Ibid.* **1985**, *24*, 2594. (j) Silverman, R. B.; Yamasaki, R. B. *Ibid.* **1984**, *23*, 1322. (k) Guengerich, F. P.; Willard, R. J.; Shea, J. P.; Richards, L. E.; Macdonald, T. L. *J. Am. Chem. Soc.* **1984**, *106*, 6446. (l) van Niel, J. C. G.; Pandit, U. K. *J. Chem. Soc., Chem. Commun.* **1983**, 149. (m) Wiseman, J. S.; Nichols, J. S.; Kolpak, M. X. *J. Biol. Chem.* **1982**, *257*, 6328. (n) Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2050. (o) Hanzlik, R. P.; Tullman, R. H. *Ibid.* **1982**, *104*, 2048. (p) MacInnes, I.; Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *J. Chem. Soc., Chem. Commun.* **1982**, 121. (q) Nonhebel, D. C.; Orszulik, S. T.; Suckling, C. J. *Ibid.* **1982**, 1146. (r) Paech, C.; Salach, J. I.; Singer, T. P. *J. Biol. Chem.* **1980**, *255*, 2700. (s) Hanzlik, R. P.; Kishore, V.; Tullman, R. *J. Med. Chem.* **1979**, *22*, 759.

(4) (a) Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1984**, *106*, 8319. (b) Nishida, S.; et al. *J. Org. Chem.* **1984**, *49*, 496. (c) Darmon, M. J.; Schuster, G. B. *J. Org. Chem.* **1982**, *47*, 4658. (d) McCormick, J. P.; Fitterman, A. S.; Barton, D. L. *Ibid.* **1981**, *46*, 4708. (e) Marino, P. S.; Bay, E.; Watson, D. G.; Rose, T.; Bracken, C. *J. Org. Chem.* **1980**, *45*, 1753. (f) Lubbe, F.; Sustmann, R. *Chem. Ber.* **1979**, *112*, 57. (g) Takakis, I. M.; Agosta, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2383. (h) Krusic, P. J.; Fagan, P. J.; San Filippo, J., Jr. *Ibid.* **1977**, *99*, 250. (i) Law, K. Y.; de Mayo, P.; Wong, S. K. *Ibid.* **1977**, *99*, 5813. (j) Hall, S.; Sha, C.-K. *Chem. Ind. (London)* **1976**, 216. (k) House, H. O.; Week, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2778. (l) Jenkins, C. L.; Kochi, J. K. *Ibid.* **1972**, *94*, 856. (m) Monti, S. A.; Bucheck, D. J.; Shepard, J. C. *J. Org. Chem.* **1969**, *34*, 3080. (n) Dauben, W. G.; Wolf, R. E. *Ibid.* **1970**, *35*, 374. (o) Fraisse-Jullien, R.; Frejaville, C. *Bull. Soc. Chim. Fr.* **1968**, 4449. (p) Zimmerman, H. E.; Hancock, K. G; Licke, G. C. *J. Am. Chem. Soc.* **1968**, *90*, 4892. (q) Zimmerman, H. E.; Rieke, R. D.; Scheffer, J. R. *Ibid.* **1967**, *89*, 2033. (r) Fraisse-Jullien, R.; Frejaville, C.; Toure, V. *Bull. Chem. Soc. (Fr.)* **1966**, 3725. (s) Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794.

(5) (a) Castellino, A. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1988**, *110*, 158 and references therein. (b) Castellino, A. J.; Bruice, T. C. *Ibid.* **1988**, *110*, 1313.

Materials and Methods

General Procedures. Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Infrared (IR) spectra were obtained in $CHCl_3$ on a Perkin-Elmer monochromator grating spectrometer (Model 1330) or a Bio-Rad Fourier transform spectrometer (Model FTS-60). IR data are given in cm^{-1} with intensities s, m, w, v, and b signifying strong, moderate, weak, very, and broad. Low-resolution and high-resolution mass spectra (LRMS and HRMS) were recorded on a VG Analytical spectrometer (Model VGII-250) by electron impact (EI), chemical ionization (CI) with CH_4, or fast atom bombardment (FAB) in a *m*-nitrobenzyl alcohol matrix. ^1H NMR spectra were obtained in $CDCl_3$ with Varian CFT-20, Nicolet NT-300, and General Electric GN-500 spectrometers. Chemical shifts are reported in δ relative to Me_4Si with s, d, t, q, and m signifying singlet, doublet, triplet, quartet, and multiplet; coupling constants (J) are reported in hertz. High-pressure liquid chromatography (HPLC) used two Perkin-Elmer Series 10 pumps, a Perkin-Elmer Series 10 LC Controller, a Schoeffel Spectroflow Monitor (Model SF770) at 254 nm, and a Hewlett-Packard Integrator (Model 3392A). Chromatographic conditions are given in the following order: column, solvent system, solvent composition, and flow rate (as subscript). Altex columns 4.6 × 250 mm 5 μm Ultrasphere C_8-SiO_2 (col A), 4.6 × 250 mm 5 μm LiChrosorb SiO_2 (col B), 10 × 250 mm 5 μm LiChrosorb SiO_2 (col C), 10 × 250 mm 10 μm RSil-CN (col D), 5 × 250 mm 5 μm RSil-CN (col E), and Whatman column 10 × 500 mm 10 μm Partisil SiO_2 (col F) eluted with the solvent systems hexanes–EtOAc (sys A), CH_3CN–H_2O (0.1 M KBr) (sys B), and hexanes–CH_2Cl_2 (sys C) were employed. Flash chromatography was performed on silica gel 60 (230–400 mesh) from Fluka. Thin-layer chromatography (TLC) was performed on aluminum-backed plates with 0.2-mm silica gel 60-F_{254} (Merck). All reactions were conducted under N_2 atmosphere. Sodium acetylide used in the Wittig condensation was obtained from the Aldrich Chemical Co. Photochemical experiments were conducted in Pyrex vessels placed 10 cm from a 450-W Hg-arc lamp which provided an internal temperature of 60 °C. Organic extracts were dried by washing with brine and standing over $MgSO_4$. The catalysts $(F_{20}TPP)Fe^{III}(Cl)$, $(Cl_8TPP)Fe^{III}(Cl)$, and $(Cl_8TPP)Mn^{III}(OH)$ and the oxidant C_6F_5IO were prepared by previously described procedures.[5a]

***trans*-2,*trans*-3-Diphenylcyclopropanecarboxaldehyde (8).** To a mechanically stirred solution of 0.38 mL of oxalyl chloride (4.4 mmol) in 10 mL of CH_2Cl_2 at −60 °C was added a solution of 0.48 mL of DMSO (6.8 mmol) in 2 mL of CH_2Cl_2. After 2 min a solution of 896 mg of (4 mmol) (*trans*-2,*trans*-3-diphenylcyclopropyl)methanol[6] (**5**) in 4 mL of CH_2Cl_2 was added over a 5-min period. Stirring was continued for another 15 min whereupon 2.8 mL of Et_3N (20 mmol) was added. After 5 min the reaction mixture was allowed to reach room temperature, and then equal volumes (100 mL) of CH_2Cl_2 and water were added. The organic layer was washed with 50 mL each of 1% HCl, water, 5% Na_2CO_3, water, and brine. The residue obtained after concentration was flash chromatographed (sys A, 3:1) to give 783 mg, 88% yield, of **8**: mp 56–57 °C (ligroin); TLC (sys A, 3:1) R_f 0.41; ^1H NMR δ 2.8–2.9 (m, 1 H), 3.17 (d, 2 H, J = 5), 7.0–7.2 (m, 10 H), 8.50 (1 H). Anal. Calcd for $C_{16}H_{14}O$: C, 86.5; H, 6.3. Found: C, 86.4; H, 6.4.

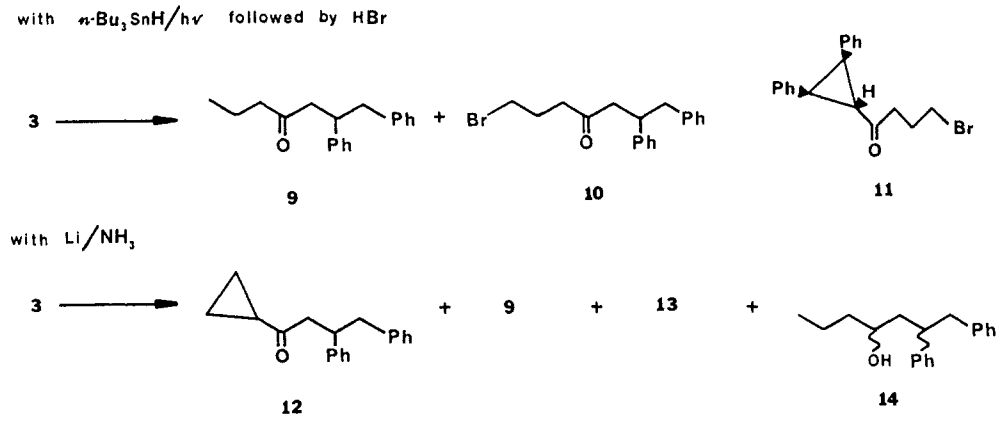
(*trans*-2,*trans*-3-Diphenylcyclopropyl)methyl Bromide (6). To a solution of 896 mg of **5** (4 mmol) in 4 mL of THF at −78 °C was added 0.14 mL of PBr_3 (1.5 mmol). After reaching room temperature, the reaction mixture was stirred for 2 h and then quenched with saturated $NaHCO_3$ (4 mL). The resulting solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried and concentrated, and the resulting residue was flash chromatographed (sys A, 3:1) to give 796 mg, 69% yield, of **6**: mp 58.0–58.5 (ligroin); TLC (sys A, 3:1) R_f 0.60; ^1H NMR δ 2.0–2.3 (m, 1 H), 2.47 (d, 2 H, J = 6), 3.61 (d, 2 H, J = 7), 7.0–7.2 (m, 10 H). Anal. Calcd for $C_{16}H_{15}Br$: C, 66.9; H, 5.3; Br, 27.8. Found: C, 67.2; H, 5.3; Br, 28.0.

[(*trans*-2,*trans*-3-Diphenylcyclopropyl)methyl]triphenylphosphonium Bromide (7). A solution of 684 mg of **6** (2.4 mmol) and 936 mg of PPh_3 (3.6 mmol) in 20 mL of diglyme was refluxed for 8 h. The precipitate was collected, thoroughly washed with hexanes, and dried ($h\nu$, P_2O_5, 80 °C) to give in high purity (by HPLC) 1.15 g, 87% yield, of **7**: mp (water) >200 °C; HPLC (col A; sys B, $3:1_{1.0}$) t_R 7.2 min; ^1H NMR δ 1.5–1.7 (m, 1 H), 2.93 (d, 2 H, J = 6), 4.50 (dd, 2 H, J = 7, 12), 6.6–7.1 (m, 10 H), 7.5–8.0 (m, 15 H). Anal. Calcd for $C_{34}H_{30}PBr$: C, 74.3; H, 5.5; Br, 14.5. Found: C, 74.8; H, 5.3; Br, 14.6.

(*E*)- and (*Z*)-1,2-Bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (1-E and 1-Z). A 18% sodium acetylide slurry (67 mg, 0.25 mmol of

(6) Breslow, R.; Lockhardt, J.; Small, A. *J. Am. Chem. Soc.* **1962**, *84*, 2793.

Scheme I



NaCCH) was washed with hexanes (2 × 1 mL), and the remaining solid was dried over a N_2 stream. Directly to the solid was added 137 mg of **7** (0.25 mmol) and 56 mg of **8** (0.25 mmol) in the minimum amount of DMF. After stirring for 0.5 h at room temperature, the reaction mixture was poured into cold water (20 mL) and extracted with Et_2O (4 × 20 mL). The combined organic solutions were dried and concentrated, giving a residue which was purified by low-pressure Al_2O_3 chromatography (neutral activity II, 100% CCl_4) to give 63 mg, 60% yield, **1-E** and **1-Z**. The pure isomers were obtained by semipreparative HPLC (col F; sys C, $9{:}1_{6.0}$). **1-E**: mp 201–202 °C ($EtOH–CHCl_3$); HPLC (col B; sys C, $9{:}1_{1.0}$) t_R = 37.5 min; IR 1603 (vs), 1497 (s), 1456 (w), 1446 (m), 1027 (m), 974 (bm), 916 (bw) cm^{-1}; ^1H NMR δ 2.3–2.4 (m, 2 H), 2.49 (d, 4 H, J = 6), 5.64 (dd, 2 H, J = 2, 5), 6.90 (m, 8 H), 7.1 (m, 12 H). **1-Z**: mp 95–96 °C (MeOH); HPLC (col B, sys C, $9{:}1_{1.0}$) t_R 32.7 min; IR 1603 (vs), 1497 (s); 1456 (m), 1446 (m), 1360 (m), 1313 (w), 1026 (m), 968 (m), 906 (vbm), 843 (m) cm^{-1}; ^1H NMR δ 2.55 (d, 4 H, J = 6), 2.6–2.7 (m, 2 H), 5.42 (dd, 2 H, J = 2, 5), 6.9 (m, 8 H), 7.1 (m, 12 H). Anal. Calcd for $C_{32}H_{28}$: C, 93.2; H, 6.8. Found: C, 93.0; H, 7.0.

***trans*-2,*trans*-3-Diphenyldicyclopropyl Ketone (3) or *trans*-2,*trans*-3-Diphenylcyclopropyl *n*-Propyl Ketone (4).** To 2 mmol of cyclopropylmagnesium bromide[7] or *n*-propylmagnesium bromide in 8 mL of Et_2O at 0 °C was added 444 mg **8** (2 mmol). After 0.5 h, the reaction mixture was refluxed for 15 min and then quenched with saturated NH_4Cl. The organic solution was dried, concentrated, and flash chromatographed (sys A, 3:1) to give (*trans*-2,*trans*-3-diphenyldicyclopropyl)methanol or (*trans*-2,*trans*-3-diphenylcyclopropyl)*n*-propylmethanol (80–100% yield). To 264 mg of the alcohol (1 mmol) in 80 mL of acetone was added Jones reagent. The precipitate that formed upon dilution of the reaction mixture with water (80 mL) was flash chromatographed (sys A, 9:1) to give **3** or **4** in variable yield (50–100%). Ketone **3**: mp (hexanes) 93–95 °C; HPLC (col B, sys A, $80{:}1_{1.5}$) t_R 23.4 min; ^1H NMR δ 0.96–1.00 (m, 2 H), 1.16–1.19 (m, 2 H), 2.20–2.25 (m, 1 H), 2.93 (t, 1 H, J = 5), 3.11 (d, 2 H, J = 5), 6.8–7.2 (m, 10 H). Anal. Calcd $C_{19}H_{18}O$: C, 87.0; H, 6.9. Found: C, 86.9; H, 7.0. Ketone **4**: mp (hexanes) 104–105 °C; HPLC (col B, sys A, $80{:}1_{1.5}$) t_R 15.0 min; ^1H NMR δ 0.98 (t, 3 H, J = 7), 1.74 (m, 2 H, J = 7), 2.71 (t, 2 H, J = 7), 2.81 (t, 1 H, J = 5), 3.07 (d, 2 H, J = 5), 6.9–7.1 (m, 10 H). Anal. Calcd for $C_{19}H_{20}O$: C, 86.3; H, 7.6. Found: C, 86.4; H, 7.8.

***n*-Bu_3SnH Reduction of Alkene 1.** A heterogeneous mixture of 0.15 g of **1** (0.36 mmol) in 1 mL of *n*-Bu_3SnH was photolyzed for 5 h. To the reaction mixture at 0 °C was added 1 mL of CCl_4 (O_2-free). The resulting solution was flash chromatographed (sys C, 7:3) to give 0.19 g, 75% yield, of **16a** and **16b** [TLC (sys C, 7:3) R_f 0.60]. The tin adducts were separated by semipreparative HPLC (col C; sys C, $9{:}1_{3.5}$) t_R (**16a**) 30.3 min; t_R (**16b**) 33.3 min.

***n*-Bu_3SnH Reduction of Ketone 3.** A solution of 33 mg of **3** (0.125 mmol) in 1 mL of *n*-Bu_3SnH was photolyzed for 6 h. To the reaction mixture at 0 °C was added 1 mL of CCl_4 (O_2-free). After dilution with 10 mL of cyclohexane, HBr(g) was passed through the solution at room temperature. After concentration, the residue was Kugelrohr distilled (high vacuum) to remove unreacted *n*-Bu_3SnH and then flash chromatographed (sys A, 9:1) to give a mixture of **3**, **9**, **10**, and **11**. The components were separated by semipreparative HPLC (col C, sys A, $40{:}1_{3.0}$). **9**: HPLC (col B, sys A, $40{:}1_{1.0}$) t_R 12.6 min; ^1H NMR δ 0.77 (t, 3 H, J = 7), 1.45 (m, 2 H, J = 7), 2.17 (m, 1 H, J = 7, 15), 2.23 (m, 1 H, J = 7, 15), 2.67 (m, 1 H, J = 7, 16), 2.73 (m, 1 H, J = 7, 16), 3.47 (m, 1 H, J = 7), 7.1–7.3 (m, 10 H); IR 1710 (s) cm^{-1}; HRMS(CI) Calcd for $C_{19}H_{22}O$: $(M + H)^+$, 267.1750. Found: 267.1720. **11**: HPLC (col B, sys A, $40{:}1_{1.0}$) t_R 16.8 min; ^1H NMR δ 2.24 (m, 2 H, J = 7), 2.83 (t, 1 H, J = 5), 2.97 (t, 2 H, J = 7), 3.10 (d, 2 H, J = 5), 3.50 (t, 2 H, J = 7), 7.1–7.3 (m, 10 H); IR 1695 (s) cm^{-1}. HRMS(CI) Calcd for $C_{19}H_{19}OBr$: $(M + H)^+$, 343.0698; $(M + H)^+ + 2$, 345.0678. Found: $(M + H)^+$, 343.0681; $(M + H)^+ + 2$, 345.0669. **10**: HPLC (col C, sys A, $40{:}1_{1.0}$) t_R 22.2 min; ^1H NMR δ 1.95 (m, 2 H, J = 7), 2.35 (m, 1 H, J = 7, 18), 2.45 (m, 1 H, J = 7, 18), 2.71 (m, 1 H, J = 7, 16), 2.77 (m, 1 H, J = 7, 16), 2.86 (m, 1 H, J = 7, 14), 2.90 (m, 1 H, J = 7, 14), 7.1–7.3 (m, 10 H); IR 1710 (s) cm^{-1}. HRMS(CI) Calcd for $C_{19}H_{21}OBr$: $(M + H)^+$, 345.0854; $(M + H)^+ + 2$, 347.0834. Found: $(M + H)^+$, 345.0856; $(M + H)^+ + 2$, 347.0837.

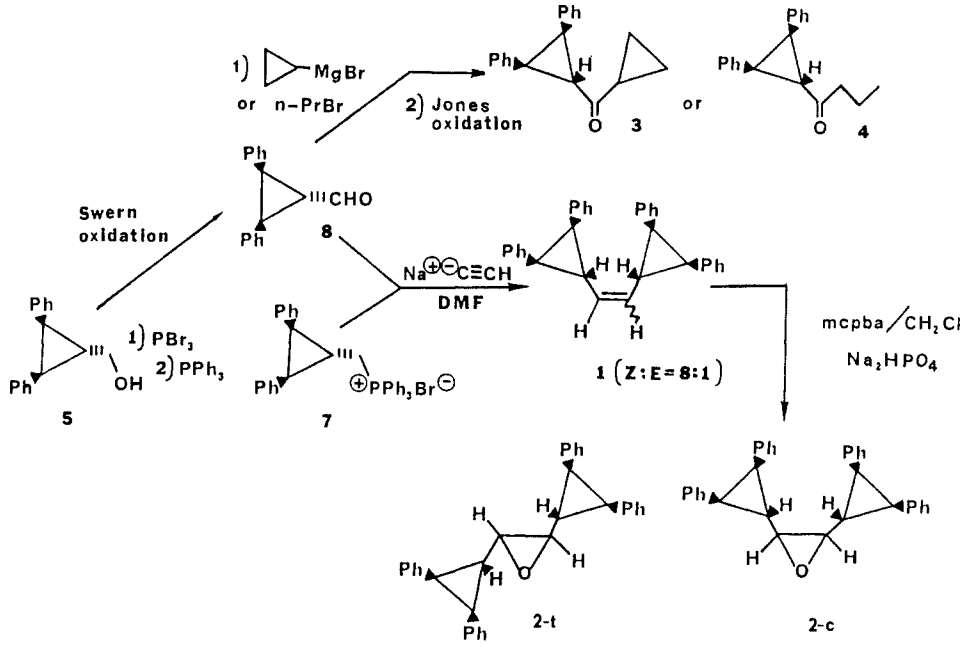
Lithium Metal Reduction of Ketone 3. To 15 mL of NH_3 was added 0.6 cm of 3.2 mm o.d. Li wire (45 mg cm^{-1}, 4 mmol). To the refluxing solution was added 52 mg of **8** (0.2 mmol) in 2 mL of Et_2O. The reaction was quenched after 0.5 h with 430 mg of NH_4Cl (8 mmol). The residue remaining after solvent evaporation was partitioned between water (50 mL) and Et_2O (50 mL). The organic solution was washed with 1% HCl (25 mL) and water (25 mL) and then dried and concentrated to give a mixture of **9**, **12**, **13**, **14a**, and **14b**. The components were separated into mixtures consisting of **9**, **12**, and **13** and **14a** and **14b** by flash chromatography (sys A, 9:1). The purified components were obtained by semipreparative HPLC (col C, sys A, $80{:}1_{3.5}$ and $9{:}1_{3.0}$). **12**: HPLC (col B, sys A, $80{:}1_{1.5}$) t_R 16.3 min; ^1H NMR δ 0.63 (m, 2 H, J = 4, 6), 0.79 (m, 2 H, J = 3, 4), 1.63 (m, 1 H, J = 3, 6), 2.74 (dd, 2 H, J = 6, 14), 2.98 (dd, 2 H, J = 8, 14), 7.1–7.3 (m, 10 H); IR 1690 (s) cm^{-1}; HRMS(CI) Calcd for $C_{19}H_{20}O$: $(M + H)^+$, 265.1593. Found: 265.1615. **13**: HPLC (col B, sys A, $80{:}1_{1.5}$) t_R 27.5 min; ^1H NMR δ 0.7–0.9 (m, 4 H), 1.82 (m, 1 H, J = 3, 6), 2.89 (m, 4 H), 3.50 (m, 1 H, J = 7), 7.1–7.3 (m, 10 H); IR 1690 (s) cm^{-1}. HRMS Calcd for $C_{19}H_{20}O$: $(M + H)^+$, 265.1593. Found: 265.1593.

Epoxidation of Alkene 1 with *m*-Chloroperbenzoic Acid. To 90 mg of **1** (0.22 mmol) and 187 mg of Na_2HPO_4 (1.3 mmol) in 2.5 mL of CH_2Cl_2 at 0 °C was added 71 mg of 85% mcpba (0.22 mmol). After 2.5 h the reaction mixture was partitioned between water (25 mL) and CH_2Cl_2 (25 mL). The organic solution was extracted with 0.5 N NaOH (3 × 10 mL), dried, and concentrated to give a mixture of **2-c** and **2-t**. The components were separated by semipreparative HPLC (Col. D, sys C, $6{:}1_{3.5}$). **2-t**: HPLC (col E, sys C, $6{:}1_{2.0}$) t_R 9.7 min; ^1H NMR δ 1.98 (m, 2 H, J = 4, 6), 2.52 (m, 2 H, J = 6, 10), 2.56 (m, 2 H, J = 6, 10), 3.20 (d, 2 H, J = 4), 6.9–7.2 (m, 20 H); IR 1604 (vs), 1498 (s), 1448 (m), 1453 (m), 1024 (w), 899 (bm); cm^{-1}; HRMS(CI) Calcd for $C_{32}H_{28}O$: 429.2220. Found: 429.2219. **2-c**: HPLC (col E, sys C, $6{:}1_{2.0}$) t_R 15.3 min; ^1H NMR δ 2.00 (m, 2 H, J = 5, 6), 2.60 (m, 2 H, J = 6, 10), 2.74 (m, 2 H, J = 6, 10), 3.14 (d, 2 H, J = 5), 6.8–7.2 (m, 20 H); IR 1604 (vs), 1498 (s), 1448 (s), 1459 (s), 1360 (bm), 1167 (bw), 1076 (m), 1026 (m), 978 (bm), 838 (m) cm^{-1}. HRMS(CI) Calcd for $C_{32}H_{28}O$: 429.2220. Found: 429.2219.

Epoxidation of Alkene 1-Z with Cytochrome P-450 Model Sysytems. In a typical oxidation run, C_6F_5IO (0.05 mmol) was added in one portion to a 0.5-mL CH_2Cl_2 solution of catalyst (10^{-3} M) and **1-Z** (0.25 mmol) at room temperature in a N_2 glovebox. After 0.5 h the reaction was

(7) Von Hanack, M.; Eggensperger, H. *Liebigs Ann. Chem.* **1963**, 31.
(8) For example, the $\nu_{C=O}$ for cyclopropyl methyl ketone is 1690 cm^{-1}. *Coblentz Society Spectra*; Sadtler Research Laboratories: Philadelpha; No. 5339.
(9) Curtin, D. Y.; Gruen, H.; Hendrickson, Y. G.; Knipmeyer, H. E. *J. Am. Chem. Soc.* **1961**, *83*, 4838.
(10) (a) Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2270. (b) Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1967. (c) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (d) Groves, J. T.; Kruper, W. J., Jr.; Haushalter, R. C. *Ibid.* **1980**, *102*, 6377.
(11) (a) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981. (b) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1473. (c) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.

Scheme II



quenched with aqueous Na_2SO_3. The organic solution was analyzed by HPLC for **1-Z** and **1-E** (col B, sys C, $9{:}1_{1.0}$) and **2-c** and **2-t** (col E, sys C, $6{:}1_{2.0}$).

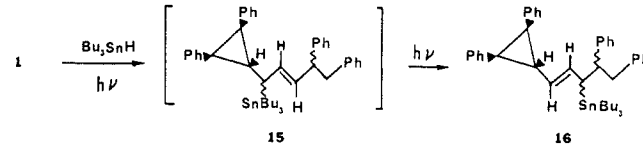
Results

Reduction of *trans*-2,*trans*-3-Diphenyldicyclopropyl Ketone (3). Photolysis of **3** in neat *n*-Bu_3SnH (Scheme I) for 6 h provided a mixture of educt and tin adducts. Treatment with HBr(g) removed the stannyl substituents[12a] to give **9**, **10**, and **11** (**11**:**10**:**9** = 2.5:1.6:1.0 at 70% conversion of **3**). The purified components (by HPLC) were analyzed by IR, ^1H NMR, and mass spectroscopy. Ketone **11** results from HBr cleavage of the unsubstituted cyclopropyl ring in **3**. The IR spectrum shows a carbonyl stretch (1695 cm^{-1}) indicative of a ketone adjacent to a cyclopropyl ring.[8] The ^1H NMR spectrum shows the A_1X_2 spin system characteristic of *trans*-2,*trans*-3-diphenyl substitution.[6,9] ^1H NMR homonuclear decoupling experiments also reveals a $A_2M_2X_2$ system. Low-resolution mass spectroscopy (LRMS) gives a base peak at 193 consistent with a diphenylcyclopropyl cation. High-resolution mass spectroscopy (HRMS) gives the molecular formula $C_{19}H_{19}OBr$, which indicates incorporation of the atoms of HBr into **3**.

Ketone **9** results from double reduction of **3**. The IR spectrum shows a $V_{C=O}$ (1710 cm^{-1}) for a unperturbed ketone. ^1H NMR homonuclear decoupling experiments show isolated $A_3M_2X_2$ and $AA'B_2X$ spin systems. The LRMS spectrum has its base peak at m/z 181, which is consistent with a diphenylethyl cation. HRMS gives the molecular formula $C_{19}H_{22}O$, which indicates the loss of two degrees of unsaturation from **3**.

Ketone **10** results from a single reduction of **3**. The IR spectrum again has $V_{C=O}$ = 1710 cm^{-1}. ^1H NMR homonuclear decoupling experiments show isolated $A_2MM'X_2$ and $AA'BB'X$ systems. The latter is similar to the $A'AB_2X$ system of ketone **9** and is due to a 1,2-diphenylethyl group. This is confirmed by LRMS, which gives a base peak at 181. HRMS gives a molecular formula of $C_{19}H_{21}OBr$, indicating the incorporation of the atoms of H_2 and HBr into **3**. Therefore, ketone **10** must result from reduction of the *trans*-2,*trans*-3-diphenylcyclopropyl ring in **3** followed by HBr cleavage of the unsubstituted ring.

Scheme III



Ketone **4** is expected to be the initial product from reduction of the *trans*-2,*trans*-3-diphenylcyclopropyl ring, but use of an authentic sample did not reveal the presence of this ketone. A detection limit of 0.1% was established by doping the product mixture with 0.1 mol% of **4**. The possibility that **4** had also undergone HBr cleavage and was responsible for the 4% of reaction products which could not be identified was investigated by subjecting an authentic sample of **4** to the workup conditions. HPLC analysis showed no reaction products and complete recovery of **4**.

Lithium metal reduction of **3** (Scheme I) gave a mixture of three ketones, **9**, **12**, and **13** (**9**:**12**:**13** = 1.6:1.3:1.0), and two alcohols, **14a** and **14b** (**14a**:**14b** = 1:1), with ketone: alcohol = 1.8:1 at 100% conversion of **3**. Both **14a** and **14b** provided **9** upon oxidation. Therefore, the alcohol products are diastereomers which resulted from triple reduction of **3**. Ketone **12** resulted from single reduction of **3**. The IR spectrum shows $V_{C=O}$ = 1690 cm^{-1}, which is consistent with a cyclopropyl ketone. ^1H NMR homonuclear decoupling experiments revealed a A_2B_2X spin system expected for an unsubstituted cyclopropyl ketone and inconsistent with *trans*-2,*trans*-3-diphenyl substitution. The remaining spin system, $AA'BB'$, is consistent with a 1,2-diphenylethyl group. HRMS gives the molecular formula $C_{19}H_{20}O$, indicating the incorporation of the atoms of H_2 into **3**.

A positive identification of **13** was not possible. The presence of a cyclopropyl ketone is indicated by the IR spectrum ($V_{C=O}$ = 1690 cm^{-1}). The ^1H NMR spectrum did not show an A_2X splitting pattern. This spin system exists in all compounds containing a *trans*-2,*trans*-3-diphenylcyclopropyl group that have been studied. Thus, the diphenyl-substituted cyclopropyl group has undergone the CPCRR. This is confirmed by LRMS, which shows a m/z 181 base peak due to the diphenylethyl cation. HRMS give the molecular formula $C_{19}H_{20}O$. Therefore, **13** is isomerically related to **12**.

Synthesis of Alkene 1. (*Z*)- and (*E*)-1,2-bis(*trans*-2,*trans*-3-diphenylcyclopropyl)ethene (**1-Z** and **1-E**) were synthesized by

(12) (a) Ratier, M.; Pereyre, M.; Davies, A. G.; Sutcliff, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907. (b) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 589. (c) Davies, A. G.; Muggleton, B.; Godet, J.-Y.; Pereyre, M.; Pommier, J.-C. *Ibid.* **1976**, 1719. (d) Davies, A. G.; Godet, J.-Y.; Muggleton, B.; Pereyre, M. *J. Chem. Soc., Chem. Commun.* **1976**, 813. (e) Blum, P.; Davies, A. G.; Pereyre, M.; Ratier, M. *Ibid.* **1976**, 814. (f) Godet, J.-Y.; Pereyre, M. *J. Organomet. Chem.* 1972, *40*, C23. (h) Pereyre, M.; Godet. J.-Y. *Tetrahedron Lett.* **1970**, 3653.

(13) For review of electrophillic addition to cyclopropanes, see: De Puy, C. H. *Top. Curr. Chem.* **1973**, *40*, 73.

Witting condensation (NaCCH in DMF) of aldehyde **8** and phosphonium salt **7** (Scheme II). Aldehyde **8** was obtained by Swern oxidation of (*trans*-2,*trans*-3-diphenylcyclopropyl)methanol (**5**).[6] The phosphonium salt was obtained by treatment of **8** with PBr_3 (to give **6**) followed by Ph_3P in Δ_x diglyme. The diastereomers **1-Z** and **1-E** were purified by semipreparative HPLC (**1-Z**:**1-E** = 8.1:1). The stereochemistry was assigned from IR data. In the 1500–800-cm^{-1} region the isomer assigned the *E* configuration showed stronger absorbances (relative to the strongest absorbance at 1603 cm^{-1}) than the isomer assigned the *Z* configuration.

Reduction of Alkene 1. Treatment of **1** with *n*-Bu_3SnH (Scheme III) gave a mixture of tin adducts, **16a**, and **16b** (75% yield; **16a**:**16b** = 2.1:1). ^1H NMR homonuclear decoupling experiments on **16a** revealed a complex spin system partially characterized by $A_2MXX'Y$ with the following: cyclopropane C(Ph)*H* δ 2.96, d, 2 H, J_{am} = 8; cyclopropane C*H* δ 3.57 dd, 1 H, J_{am} = 8, J_{mx} = 6. The second coupling constant is due to a C=C*H* which is in a 2 H multiplet. Decoupling of δ 3.57 reduces this multiplet to δ 5.55, d, 1 H, $J_{xx'}$ = 15 and δ 5.63 dd, 1 H, $J_{xx'}$ = 15, $J_{x'y}$ = 7. These values are consistent with a *trans*-alkene having a cyclopropane and a methine carbon as the substituents. The remainder of the complex spin system consists of a multiplet due to magnetically nonequivalent hydrogens that have identical coupling constants (PhCH_2 δ 2.13, dd, 1 H, *J* = 5, 10; 2.19, dd, 1 H, *J* = 5, 10) and a multiple due to two magnetically nonequivalent hydrogens with nonidentical coupling constants. Interpretation of the latter multiplet is aided by examination of the ^1H NMR spectrum of **16b**. The spectra of **16a** and **16b** are similar and suggest a diastereomeric relationship. For **16b** the benzyl methylene (PhCH_2 δ 2.22, dd, 1 H, *J* = 5, 10; 2.28, dd, 1 H, *J* = 5, 10) and vinyl hydrogens (C=C*H* δ 5.52 dd, 1 H, *J* = 7, 15; 5.66 dd, 1 H, *J* = 6, 15) provided the same multiplets as for **16a**. However, the complex multiplet in **16a** is now separated in **16b** into two interpretable multiplets (δ 2.08, m, 1 H, *J* = 5, 10; 1.89, dd, 1 H, *J* = 6, 10). The multiplet of δ 2.08 is consistent with PhC*H* except the benzyl methylene and methine hydrogens are in reverse order from normal expectations. This is explained by a deshielding atom (Sn) nearby the PhC*H*. It is therefore concluded that a methine SnC*H* is responsible for the δ 1.89 multiplet and is coupled to PhC*H* and a C=C*H*. The latter is confirmed by homonuclear decoupling of the vinyl hydrogens.

Epoxidation of (*Z*)-1,2-Bis(*trans*-3-diphenylcyclopropyl)ethene (1-*Z*). The possible epoxide products *cis*- and *trans*-1,2-bis-(*trans*-2,*trans*-3-diphenylcyclopropyl)oxirane (**2-c** and **2-t**) were synthesized by treating alkene **1** with *m*-chloroperbenzoic acid in the presence of Na_2HPO_4. The epoxides **2-c** and **2-t** were purified to homogeneity by semipreparative HPLC. The cis and trans isomers are distinguished by differences in their IR spectra. In the 1500–800-cm^{-1} region the isomer assigned the cis configuration showed stronger absorbances (relative to the strongest absorbance at 1604 cm^{-1}) than the isomer assigned the trans configuration. The stereochemical assignments are confirmed by the ^1H NMR spectra. For both epoxides the cyclopropyl ring system appears as a ABX pattern. For **2-t** the chemical shifts for the benzyl protons, which comprise the AB portion of the spin system, are at δ 2.52 and 2.56. However, for **2-c** the benzyl protons appear at δ 2.74 and 3.14. The vicinal coupling constant is 10 Hz for both compounds. The magnetic nonequivalence of the benzyl protons in **2-c** and **2-t** may be explained by restricted rotation about the oxirane carbon to cyclopropyl carbon bond.[9] The greater $\Delta\nu/J$ in **2-c** for the benzyl protons is due to the greater rotational restriction which results from steric interactions between the two cyclopropyl groups.

The results from epoxidation of **1-Z** with $(F_{20}TPP)Fe^{III}(Cl)$, $(Cl_8TPP)Fe^{III}(Cl)$, and $(Cl_8TPP)Mn^{III}(OH)$ in CH_2Cl_2 with C_6F_5IO as oxidant are presented in Table I. Yields of **2-c** decrease in the order $(F_{20}TPP)Fe^{III}(Cl)$ > $(Cl_8TPP)Fe^{III}(Cl)$ > $(Cl_8TPP)Mn^{III}(OH)$. Epoxide **2-t** and alkene **1-E** could not be detected. These stereoisomerization products would result if an acyclic intermediate with free rotation about the central carbon–carbon bond were formed. A detection limit of 0.1% was established by adding 0.1 mol % of **2-t** and **1-E** to the product mixture. Control reactions established that C_6F_5IO alone cannot epoxidize **1-Z**. All model systems showed no catalyst degradation and provided products that are lower in polarity compared to that of **2-c** and **2-t**. For $(Cl_8TPP)Mn^{III}(OH)$ the fewest and greatest yield of nonpolar products were obtained. Analytical HPLC analysis (col E, sys C, $6{:}1_{1.0}$; experimental Section) shows a major (t_R 5.9 min) and a minor (t_R 4.7 min) nonpolar product. After semipreparative HPLC purification (col D, sys C, $6{:}1_{3.5}$) the fractions were reanalyzed on the analytical column. The results show that both major and minor components are interconvertible on SiO_2 and must therefore be regarded as isomers. A sufficient quantity of the isomer mixture was obtained only for mass spectral analysis. The LRMS spectrum given in Figure 1 has *m*/*z* 193, 181, and 167, which are diagnostic for diphenylcyclopropyl, diphenylethyl, and diphenylmethyl cations, respectively. Also present are clusters centered at *m*/*z* 205 (206), 219, 231 (232), and 245, which indicate the presence of four contiguous CH groups. The highest observed *m*/*z* is 412. HRMS for this fragment gives a molecular formula of $C_{32}H_{28}$ (calcd, 412.2220; found, 412.2192). The mass spectral data is consistent with a mixture of two compounds which have the generalized structures of **17** and **18** (Figure 2), where X is a labile substituent. Loss of HX (as $H^\bullet$ and X^-), under the mass spectrometer conditions, from **17** and **18** would give the radical ions I and H, which are both responsible for the *m*/*z* 412 fragment. From I, fragmentation of *m*/*z* 412 gives *m*/*z* 321, 231, and 205 from sequential loss of $PhCH_2$, PhCH, and CH_2CH_2. Radical ion I is also responsible for *m*/*z* 193 and 181 due to the diphenylcyclopropyl and diphenylethyl cations. From H, fragmentation of *m*/*z* 412 gives *m*/*z* 245, 232, 219, and 206 from sequential loss of Ph_2CH and four CH groups. Radical ion H is also responsible for *m*/*z* 193 and 167 due to the diphenylcyclopropyl and diphenylmethyl cations. Thus, **17** and **18** show that one cyclopropyl group in **1-Z** has undergone rearrangement while the other has remained intact.

Table I. Epoxidation of Alkene **1-Z** with C_6F_5IO and Several Metalloporphyrins as Catalysts

catalyst	% yield[a] of epoxide **2-c**
$(F_{20}TPP)Fe^{III}(Cl)$	95
$(Cl_8TPP)Fe^{III}(Cl)$	89
$(Cl_8TPP)Mn^{III}(OH)$	84

[a] Yield based on reacted **1-Z**.

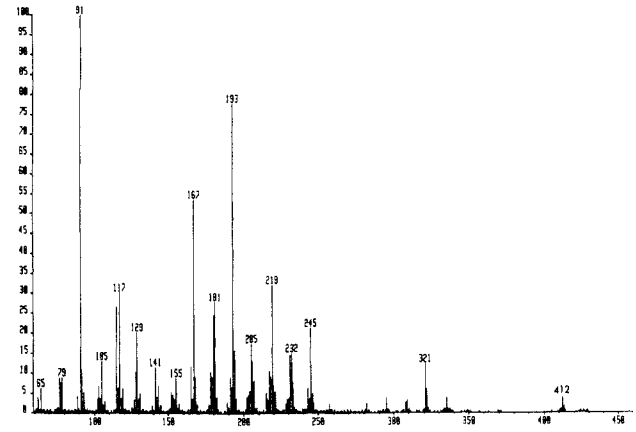
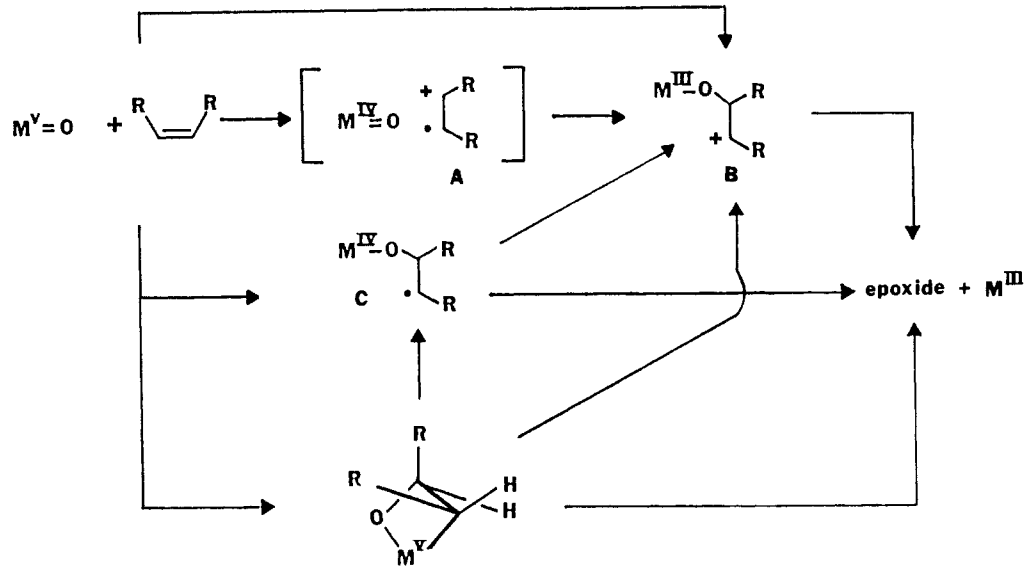


Figure 1. Low-resolution mass spectrum of nonpolar product derived from oxidation of **1-Z** using $(Cl_8TPP)Mn^{III}(OH)$ as catalyst.

Discussion

Intermediates proposed[1,10] for the epoxidation of alkenes by cytochrome P-450 model systems and their possible interrelationships are given in Scheme IV. In a previous report[5a] *cis*-stilbene was used as a mechanistic probe. The results are as follows: (1) *trans*-stilbene and *trans*-stilbene oxide, which result from stereoisomerization of educt, are found as products, (2) diphenylacetaldehyde and deoxybenzoin, which result from Ph and H migration, respectively, are primary reaction products, (3)

Scheme IV



the amount of *cis*-stilbene consumed in excess of oxidant employed is sensitive to the presence of nucleophiles and O_2, and (4) yields of *cis*-stilbene oxide, *trans*-stilbene, and PhCHO are sensitive to O_2. Result 2 is best explained with the carbocation B. Results 3 and 4 are consistent with either the radical cation A or the neutral radical C, while result 1 can be accommodated by either A, B, or C.

To explore the intermediacy of the radical species A and C in alkene epoxidation, a special substrate was required. The cyclopropyl substituent has been used in many chemical and enzymatic reactions as a radical trap.[3,4] Rate constants determined[11] for the cyclopropylcarbinyl to homoallyl radical rearrangement (CPCRR) are in the range of 10^7–10^8 s^{-1} (30 °C). For example, the CPCRR rate for rearrangement of a primary to a primary radical[11c] is 1.6×10^8 s^{-1}, while the rearrangement of a secondary

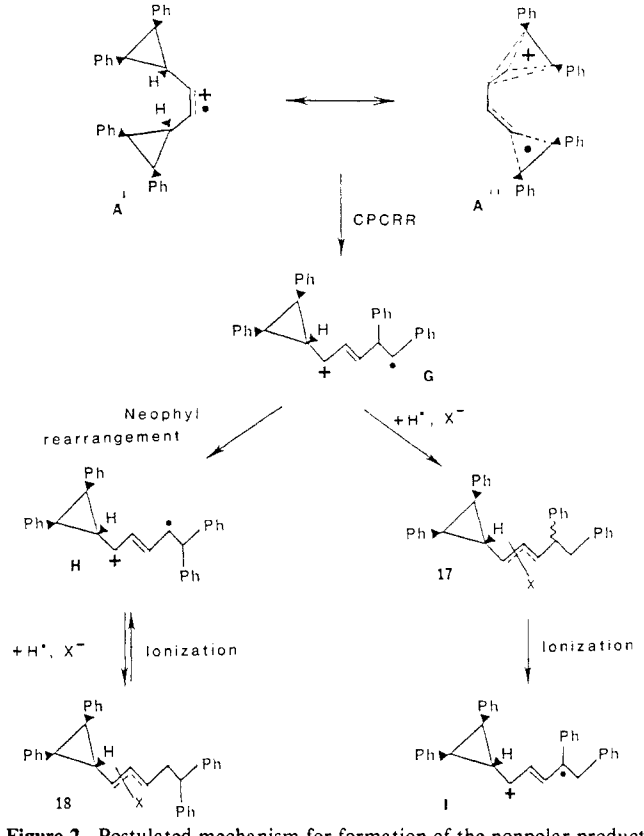
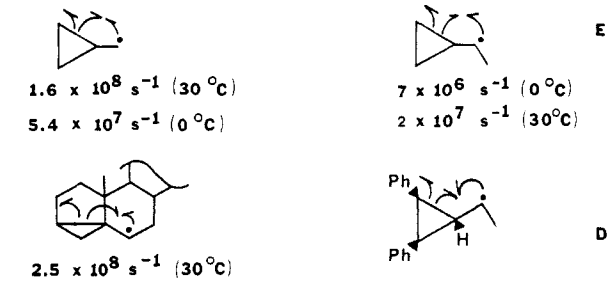


Figure 2. Postulated mechanism for formation of the nonpolar product derived from oxidation of **1-Z** using $(Cl_8TPP)Mn^{III}(OH)$ as catalyst.

Scheme V



to a primary radical[11b,14] is 2×10^7 s^{-1} (Scheme V). Such rate constants are too small to allow for the detection of rearrangement products if A or C disappear to epoxide with rate constants $>10^{10}$ s^{-1}. In order for the CPCRR to effectively trap radical intermediates which may be on the pathway to epoxidation, the rate constant for the CPCRR reaction must be much larger. Alkene **1** was designed so that a CPCRR would be induced upon generation of A or C. CPCRR from a radical intermediate generated from **1-Z** would involve the conversion of a secondary radical to a secondary benzyl radical.

The rate constant for the secondary to secondary benzyl radical CPCRR involving ring opening of the *trans*-2,*trans*-3-diphenylcyclopropyl ring was determined in competitive experiments (Figure 3). Thus, secondary to secondary benzylic (pathway a) and secondary to primary (pathway b) radical rearrangements may compete in the ring-opening reactions of F. The intermediate F was generated from *trans*-2,*trans*-3-diphenyldicyclopropyl ketone (**3**) by reaction with two different radical reductants. The first involved photocatalytic reduction of **3** by *n*-$Bu_3SnH/h\nu$[12b–h] and the second a dissolving metal reduction with Li in liquid NH_3.[4m–o] The use of two vastly different methods to generate F gave qualitatively the same results (Scheme I).

Ketone **12** obtained by Li metal reduction of **3** results from the secondary to secondary benzylic CPCRR. Ketone **10** from *n*-Bu_3SnH reduction results from **12** after HBr cleavage of the cyclopropane ring.[13] The structure of ketone **13** from Li metal reduction is unknown; however, it is isomerically related to **12**. It does not contain an intact *trans*-2,*trans*-3-diphenylcyclopropyl ring, but it does retain the unsubstituted cyclopropyl ring. Thus, the origin of **13** must be from the secondary to secondary benzylic CPCRR. Ketone **9** obtained from both reductions is more problematic, since it results from a double reduction of **3**. Therefore,

(14) Reference 12b reports the rate constant for secondary to primary radical rearrangement as 7×10^6 s^{-1} at 0 °C. From the rate dependence of CPCRR given in ref 12c, this rate is expected to be $\geq 2 \times 10^7$ s^{-1} at 30 °C.

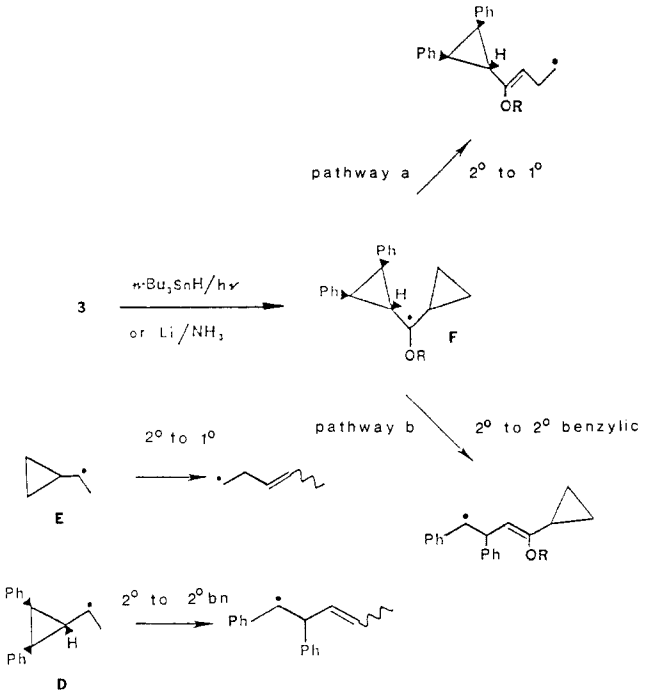


Figure 3. Competitive cyclopropylcarbinyl to homoallyl radical rearrangements induced by Li metal and *n*-Bu_3SnH reduction of ketone **3**.

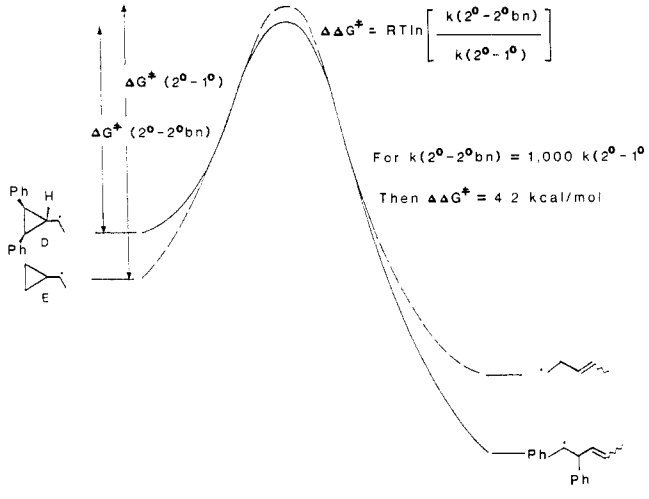


Figure 4. Reaction coordinate diagram for CPCRR of the cyclopropylcarbinyl and (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radicals D and E.

the possibility exists that reduction proceeded through the secondary to 1° CPCRR in F to give **4** followed by the secondary to secondary benzylic CPCRR to give **9**. If this were the case, ketone **4**, in addition to **12** (or its progeny **10**), should be present. However, use of an authentic sample did not reveal **4** as ≥0.1% (detection limit) of the reaction products. If **4** were the source of **9**, the carbonyl in **4** would have to be much more susceptible to reduction than the carbonyl in **12** in order to escape detection.

The rate constant for secondary to primary CPCRR is $\sim 2 \times 10^7$ s^{-1} (30 °C).[14] Since no rearrangement products involving CPCRR with the unsubstituted cyclopropyl ring were found in the above competition experiment at a detection limit of 0.1%, then the rate constant for the secondary to secondary benzyl CPCRR must be $\geq 2 \times 10^{10}$ s^{-1}. The 10^3-fold increase in the CPCRR rate constant on going from ring opening of an unsubstituted cyclopropyl ring to ring opening of the *trans*-2,*trans*-3-diphenylcyclopropyl ring is not unreasonable when differences in ground-state and transition-state energies for the two CPCRR's (i.e, D and E) are considered (Figure 4). The differences in the ground-state energies of the products are an important consideration. The difference in stability of secondary benzyl and

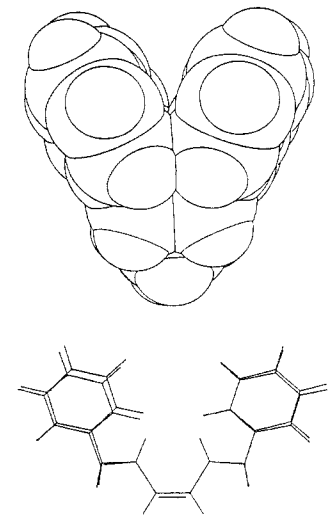


Figure 5. CPK model of the *trans*-2,*trans*-3-diphenylcyclopropyl ring system and alkene **1-Z** generated from computer graphics construction.

primary alkyl radicals (calculated from $\Delta H°$ values)[15] is 15 kcal mol^{-1}. Reactant ground-state destabilization for D relative to E is also expected. This is based on computer graphic construction of the *trans*-2,*trans*-3-diphenylcyclopropyl ring system,[16] which shows that the phenyl rings are parallel to each other and bisect the plane defined by the cyclopropane carbon atoms (Figure 5). Thus, the phenyl substituents are not in resonance with the cyclopropyl ring bonds and will be acting only as electron-withdrawing groups. Electrostatic repulsion between the π-systems of the two phenyl rings would raise the ground-state energy of D as compared to E (Figure 5). To the extent that differences in the $\Delta H°$ of the reactions for D and E contribute to differences in the ΔG^*, a larger CPCRR rate constant for D is expected. A 4.2 kcal mol^{-1} $\Delta\Delta G^*$ is required for the observed 10^3-fold increase in the CPCRR rate constant for D as compared to that of E. From the preceding discussion this seems most reasonable.

The alkene **1-Z** incorporates the *trans*-2,*trans*-3-diphenylcyclopropyl group as a hypersensitive radical trap into a suitable substrate for epoxidation.[17] To establish that a CPCRR will proceed from **1-Z**, the alkene was subjected to photocatalytic reduction with *n*-Bu_3SnH (Scheme III). ^1H NMR analysis of the two resulting tin adducts showed they were diastereomers and were composed of a cyclopropylvinyl and a 1,2-diphenylethyl spin system connected via a Sn*CH* methine hydrogen (vide supra). Thus, one *trans*-2,*trans*-3-diphenylcyclopropyl group remained intact while the other had undergone a CPCRR to give **15**. Subsequent allyl tin rearrangement[18] produced **16a** and **16b**.

With C_6F_5IO as oxidant, the catalysts employed in the epoxidation of **1-Z** were $(F_{20}TPP)Fe^{III}(Cl)$, $(Cl_8TPP)Fe^{III}(Cl)$, and $(Cl_8TPP)Mn^{III}(OH)$. Reactions were carried out under anaerobic conditions in CH_2Cl_2 (experimental section). The results presented in Table I show all systems giving high yields of the *cis*-epoxide **2-c** (>80%). Neither *trans*-alkene (**1-E**) nor *trans*-epoxide (**2-t**) could be found as ≥0.1% yield (detection limit) of the reaction products in any of the reactions investigated. The remaining reacted **1-Z** was found as very nonpolar products (8–16% yield

(15) Calculated from thermodynamic data given in: (a) Benson, S. W.; et al. *Chem. Rev.* **1969**, *69*, 279. (b) O'Neal, J. K.; Benson, S. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, pp 338–340.

(16) Computer graphics and calculations were performed with the Tripos Co. software package Sybil.

(17) Alkene **1-Z** was chosen for study over **1-E**, because *cis*-alkenes are more reactive than *trans*-alkenes to metalloporphyrin-catalyzed epoxidation. For example, see: Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.

(18) For examples of allylic rearrangements of allyltins, see: (a) Gambaro, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1981**, *210*, 57. (b) Matarasso-Tchiroukhine, E.; Cadiot, P. *Ibid.* **1976**, *121*, 169. (c) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M. *J. Am. Chem. Soc.* **1975**, *97*, 843. (d) Matarasso-Tchiroulchine, E.; Cadiot, P. *C. R. Seances Acad. Sci., Ser. E* **1972**, *274*, 2118.

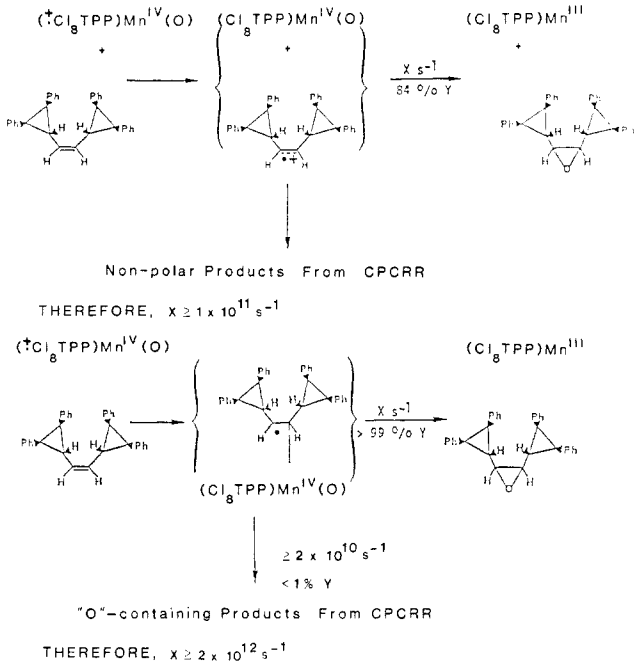


Figure 6. Kinetic analyses for reactions of the radical cation A and the neutral radical C.

dependent upon catalyst). In this respect $(Cl_8TPP)Mn^{III}(OH)$ was of particular interest, because it provided the fewest nonpolar products (two) and the highest combined yield (16%) of such products. Mass spectral analysis showed that the two nonpolar products from $(Cl_8TPP)Mn^{III}(OH)$ are isomers and have one intact *trans*-2,*trans*-3-diphenylcyclopropyl group (vide supra). The structures of the nonpolar components were found to be **17** and **18** after examination of the fragmentation pattern from the mass spectrum (Figure 1). The identity of the substituent X could not be established, but it is most likely Cl, since chloride ions are generated from oxidation of the reaction solvent (CH_2Cl_2). Pathways that would explain the formation of **17** and **18** from a common intermediate (A) are given in Figure 2. CPCRR of A gives G, which then abstracts a hydrogen atom and captures X^- to give **17**. Alternatively, G may undergo a neophyl rearrangement[19] to provide the more resonantly stabilized radical cation I, which then adds $H^\bullet$ and X^- to give **18**.

Knowing from the competitive reactions of Figure 3 that the rate constant for CPCRR of the (*trans*-2,*trans*-3-diphenylcyclopropyl)carbinyl radical D is $\geq 2 \times 10^{10}$ s^{-1} (30 °C) and the yields of nonpolar products derived from the radical cation A are 5–16% (Table I), we may conclude that the rate constant for conversion of A to epoxide is required to be $\geq 1 \times 10^{11}$ to 2×10^{11} s^{-1} (Figure 6). A rate constant between 1×10^{11} to 2×10^{11} s^{-1} for the recombination of a solvent-caged pair involving A to provide epoxide is not unreasonable. A rate constant $\geq 10^{12}$ s^{-1} would prevent its detection as a discrete intermediate. This analysis, of course, is only appropriate if A is an intermediate to the formation of epoxide. It is quite possible that the products **17** and **18** are formed from the radical ion A in a reaction that is parallel to that of epoxidation.

It may be argued that the CPCRR rate constant obtained in the competitive experiments of Figure 3 cannot apply to the radical cation due to resonance stabilization from A′ (Figure 2). However, A may be viewed as if it were composed of a cyclopropylcarbinyl radical and a cyclopropylcarbinyl cation with minimal interaction between the two systems. This simplification may be justified by considering the extensive delocalization of the radical and cation sites due to resonance interactions with the cyclopropyl rings (A″ in Figure 2). Therefore, it is expected that, acting independently of the cyclopropylcarbinyl cation,[20] the cyclopropylcarbinyl radical will undergo the CPCRR.

The inability to detect the stereoisomerization products **1-E** and **2-t** may also argue against A. However, this result would still be consistent with A as an intermediate if the intimate pair of $[(Porph)M^{IV}{=}O{\cdot}A]$ is tight enough so that steric interactions from the bulky cyclopropyl groups hinder rotation about the central C–C bond of A. Formation of A results from approach of **1-Z** to the epoxidizing agent, $(^{+\bullet}Porph)M^{IV}{=}O$, from the unsubstituted edge of the double bond.[17] The resulting radical ion A, existing in an intimate ion pair, will therefore have its diphenylcyclopropyl substituents directed from its ion partner, $(Porph)M^{IV}{=}O$. Rotation about the central C–C bond of A (formerly the C=C bond of **1-Z**) requires a bulky diphenylcyclopropyl substituent to project into the hindered porphyrin ring system of $(Porph)M^{IV}{=}O$. This most unfavorable intermolecular interaction would overwhelm the effect from relieving the intramolecular interaction between the two diphenylcyclopropyl substituents within A. The net effect would decrease the rate constant for rotation to the extent that it cannot compete with the rate constant for the disappearance to epoxide.

No products other than **2-c**, **17**, and **18** were found with $(Cl_8TPP)Mn^{III}(OH)$. Therefore, if products attributable to the neutral radical C were formed, their yields must fall below the 0.1% detection limit. Thus, the rate constant for formation of epoxide from $(Cl_8TPP)Mn^{III}(OH)$ is required to be $\geq 2 \times 10^{12}$ s^{-1}. On this basis the neutral radical species C cannot be a discrete intermediate to epoxide formation with $(Cl_8TPP)Mn^{III}(OH)$ as catalyst. This same analysis applies for $(F_{20}TPP)Fe^{III}(Cl)$ and $(Cl_8TPP)Fe^{III}(Cl)$ as catalysts, because neither provided an oxygen-containing product other than **2-c**.

The multitude and low individual yields of the nonpolar products from $(F_{20}TPP)Fe^{III}(Cl)$ and $(Cl_8TPP)Fe^{III}(Cl)$ make their complete characterization impossible. It is plausible that they may arise from direct oxidation of the cyclopropane ring, since the potentials for $1e^-$ oxidation of diphenylcyclopropanes[21] and the $1e^-$ oxidations of iron(III) oxo porphyrins[22] are comparable. Direct $1e^-$ oxidation of the *trans*-2,*trans*-3-diphenylcyclopropyl ring would result in cleavage of the C(2)–C(3) cyclopropane bond in **1-Z** (in contrast, the CPCRR in **1-Z** results in cleavage of the C(1)–C(2,3) bond). To explore this possibility, the electrochemical behavior of alkene **1** is currently being examined.

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(19) For a review of the neophyl rearrangement, see: Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. I, pp 346–367.

(20) Products arising from a cyclopropylcarbinyl cation to homoallyl cation are not expected. Rather, any rearrangement product from this system will proceed through a cyclobutyl cation (for review, see: H. Richey In *Carbonium Ions*; Olah, G., Schleyer, P. v. R., Eds.; Wiley: New York, 1972; Vol. 3, pp 1201–1294.) The spectral evidence which is presented for the nonpolar products derived from A is inconsistent with structures anticipated for the cyclopropylcarbinyl cation to cyclobutyl cation rearrangement.

(21) Wong, P. C.; Arnold, D. R. *Tetrahedron Lett.* **1979**, 2101.

(22) (a) Calderwood, T. S.; Lee, W. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 8272. (b) Lee, W. A.; Calderwood, T. S.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 4301. (c) Groves, J. T.; Gilbert, J. A. *Inorg. Chem.* **1986**, *25*, 125.