Mechanism of Cyclopropanation Reactions Mediated by (5,10,15,20-Tetra-p-tolylporphyrinato)osmium(II) Complexes

Christopher G. Hamaker
Illinois State University

Jean-Pierre Djukic
Universite Louis Pasteur

Daniel A. Smith
Goshen College

L. Keith Woo
Iowa State University, kwoo@iastate.edu

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Abstract
Catalytic systems derived from [Os(TTP)]2 or Fe(TTP) (TTP = 5,10,15,20-tetra-p-tolylporphyrinato) are extremely efficient at converting styrenes and diazo reagents to cyclopropanes in high yields and high stereoselectivity. A number of mechanistic studies have been undertaken to elucidate the catalytic pathway. A mono(carbene) complex, (TTP)OsCHCO2Et, has been isolated but is not the catalytically active species. An electron-withdrawing ligand trans to the carbene in (TTP)OsCHCO2Et activates the carbon fragment toward transfer to an olefin. Labeling studies with (TTP)OsCHX and N2CHY and substrate reactivity profiles are consistent with a trans-osmium(II) bis(carbene) species as the active catalyst.

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Mechanism of Cyclopropanation Reactions Mediated by (5,10,15,20-Tetra-p-toly lpor phyrinato)osmium(II) Complexes

Christopher G. Hamaker,† Jean-Pierre Djukic,‡ Daniel A. Smith,§ and L. Keith Woo*†

Department of Chemistry, Campus Box 4160, Illinois State University, Normal, Illinois 61790-4160, Laboratoire de Syntheses Metallo-induite–UMR 7513 CNRS, Universite Louis Pasteur, 4, rue Blaise Pascal, 67070 Strasbourg, France, Department of Chemistry, Goshen College, Goshen, Indiana 46526, and Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111

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Catalytic systems derived from [Os(TTP)]2 or Fe(TTP) (TTP = 5,10,15,20-tetra-p-tolylpor phyrinato) are extremely efficient at converting styrenes and diazo reagents to cyclopropanes in high yields and high stereoselectivity. A number of mechanistic studies have been undertaken to elucidate the catalytic pathway. A mono(carbene) complex, (TTP)-Os=CHCO2Et, has been isolated but is not the catalytically active species. An electron-withdrawing ligand trans to the carbene in (TTP)Os=CHCO2Et activates the carbon fragment toward transfer to an olefin. Labeling studies with (TTP)Os=CHX and N2CHY and substrate reactivity profiles are consistent with a trans-oximino(II) bis(carbene) species as the active catalyst.

Introduction

On the basis of the volume of publications, one can place cyclopropanation of alkenes with diazalkanes, carbon–hydrogen bond insertion, and olefin formation among the most studied metal-mediated organic transformations. Although a good understanding of the factors influencing the stereochemistry and chemoselectivity has been obtained from systematic studies, the nature of the actual intermediates involved in these processes, often called “carbenoids,” is still the subject of speculation. Most of the above-mentioned transformations involve interaction of the diazalkane reagent with the active metal center of the catalyst.2 The nature of the resulting organometallic species has been ascer-

1 Illinois State University.
2 University Louis Pasteur.
3 Goshen College.
4 Iowa State University.


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similar to the preparation of other diazo reagents.²⁸ Propyl acetoacetate was made by acetoacetylation of 1-propanol with 2,2,6-trimethyl-4H-1,3-dioxin-4-one (diketene–acetic adduct) in refluxing xylene.²⁶ A literature procedure was used in the preparation of trans-β-deuteriostyrene.²⁷ Bis[5,10,15,20-tetra-p-tolylporphyrinato]osmium(II), [Os(TPP)], was prepared from (TPP)Os(py)₂, according to a published procedure.²⁸ The bis(pyridine) complex, (TPP)Os(py)₂, was prepared from either (TPP)Os(CO)(py) or (TPP)OsO₂ by using reported methods.²⁷ Literature procedures were used to prepare (TPP)O₂⁻CH₂⁻CH₂⁻CH₃ (4a), (TPP)O₂⁻C⁻(p-toly) (4b), and (TPP)O₂⁻CH₃TS (4c).²⁹ Authentic samples of ethyl 2-(4-methylphenyl) cyclopropanecarboxylic acid ester (5d) and ethyl 2-(4-fluorophenyl) cyclopropanecarboxylic acid ester (5f) were gifts from Thomas Kodak of the University of Texas at Austin.

**Experimental Section**

**General Methods.** All manipulations of reagents and products were carried out under a dry nitrogen atmosphere using a Vacuum Atmospheres glovebox equipped with a Model MO-40H DryTrain gas purification system or on a vacuum line using Schlenk techniques. All solvents were dried and distilled from purple solutions of sodium benzophenone ketyl radical.³⁰ Products were carried out under a dry nitrogen atmosphere in the catalysis of olefin formation from diazoalkanes and diazoalkanes.⁹ We demonstrated that neutral mono-(alkylidene) species form upon treatment of [Os(TPP)]₂⁺ by diazoalkanes. Two examples of these monomono(alkylidene) complexes have been characterized by X-ray crystallography.¹⁰ These isolable mono(alkylidene) complexes can act as catalysts or stoichiometric reagents in cyclopropanation reactions. Preliminary studies showed that (TPP)Os⁻⁻⁻=CH₂⁻⁻⁻CO₂⁻⁻⁻Et (4a), used stoichiometrically or catalytically, can promote stereoselectively the cyclopropanation of styrene, giving similar yields of products in both cases. However, mono(alkylidene) complexes react slowly with alkenes compared to the analogous catalytic reaction. Herein, we bring further insight into the mechanism of osmium(II) porphyrin catalyzed cyclopropanation of alkenes by diazoalkanes.

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(11) DB-5 capillary column (30 m, 0.32 mm i.d., 0.25 µm film thickness).

(12) Varian gas chromatograph coupled to an IRTS 40 ion trap mass spectrometer (capillary column DB-5MS (30 m, 0.25 mm i.d., 0.25 µm film thickness).


Method A. In a typical experiment, (TTP)Os(CO)(py) (3 mg, 2 μmol) and styrene (0.110 mL, 961 μmol) were vigorously stirred in toluene (3 mL). A toluene solution (12 mL) of N\textsubscript{2}HCHO\textsubscript{2}Et (0.100 mL, 952 μmol) was added dropwise over 1 h. GC analysis revealed only traces of olefin and 79 ± 2% yield of cyclopropane 5a (trans/cis = 10.2 ± 0.1).

Method C. In a typical experiment, (TTP)Os=CH\textsubscript{2}CO\textsubscript{2}Et (4a, 4 mg, 4 μmol) and styrene (0.100 mL, 874 μmol) were vigorously stirred in toluene (3 mL). A toluene solution (12 mL) of N\textsubscript{2}HCHO\textsubscript{2}Et (0.100 mL, 952 μmol) was added dropwise over 1 h. GC analysis revealed only traces of diethyl maleate and diethyl fumarate and 66 ± 4% yield of cyclopropane 5a (trans/cis = 8.9 ± 0.6).

Method D. An NMR tube was loaded with 3 mg (3 μmol) of (TTP)Os=CH\textsubscript{2}CO\textsubscript{2}Et and 0.4 mL of C\textsubscript{6}D\textsubscript{6}. After an initial 1H NMR spectrum was taken, 1 μL (9 μmol) of styrene was added via syringe and the tube was shaken vigorously. The reaction was monitored by 1H NMR spectroscopy. After 4 h, the reaction was 96% complete. GC analysis indicated a trans/cis ratio of 3.3 ± 0.3.

Method E. A mixture of (TTP)OsCO (3 mg, 3 μmol), styrene (0.980 mL, 7.90 mmol), and 22.5 μL of dodecane was dissolved in 5 mL of toluene. A solution of ethyl diazoacetate (88 μL, 840 μmol) in 10 mL of toluene was added dropwise over 5 min. After 2 h, the GC analysis of the product mixture showed 2 ± 2% diethyl maleate and 100 ± 8% cyclopropane (trans/cis = 8.4 ± 0.2).

Ethyl 2-n-Hexylcyclopropanecarboxylic Acid Ester (5b). A mixture of (TTP)\textsubscript{2}Co (ca. 2 mg, 1 μmol), 1-octene (1.40 mL, 8.92 mmol), and 21 μL of dodecane was dissolved in 5 mL of toluene. Ethyl diazoacetate (100 μL, 951 μmol) in 10 mL of toluene was added either all in one aliquot or dropwise over a period of ca. 7 min. The reaction mixture was analyzed by GC. For the one-aliquot addition of EDA, the yields of cyclopropane and diethyl maleate fumarate were 11 ± 1% and 89 ± 4%, respectively. Using a slow addition, the cyclopropane and diethyl maleate fumarate yields were 66 ± 3% and 34 ± 2%, respectively. The cyclopropane trans/cis ratio was 4.8 ± 0.2. The cis and trans isomers have very similar 1H NMR spectra. Purification of the cyclopropane was accomplished by column chromatography on SiO\textsubscript{2} (33 × 3.8 cm) using hexanes/ethyl acetate (25/1 v/v). The cis isomer was eluted with diethyl maleate and the band containing the cis isomer was eluted as a wider band and could be isolated cleanly by collecting the latter portion of the band (222 mg, 43%). 1H NMR (trans, C\textsubscript{6}D\textsubscript{6}): δ 4.09 (q, 2H, CH\textsubscript{2}CHO\textsubscript{2}CH\textsubscript{3}), 1.31 (m, 15H, n-(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3} + 2 CH\textsubscript{2}H\textsubscript{4} + CO\textsubscript{2}CH\textsubscript{3}), J\textsubscript{HH} = 7.2 Hz), 1.12 (m, 1H, CH\textsubscript{2}H\textsubscript{4}), 0.86 (approximately t, 3H, n-(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}, J\textsubscript{HH} = 6.8 Hz), 0.65 (m, 1H, CH\textsubscript{2}H\textsubscript{4}), MS (Cl\textsubscript{3}): m/z 198 [M\textsuperscript{+}].

Ethyl 2-(4-Methoxyphenyl)cyclopropanecarboxylic Acid Ester (5c). Using method B, cyclopropane 5c was prepared by treating a toluene (2 mL) mixture of (Os[TTP])\textsubscript{2} (12 mg, 7.0 μmol) and 4-methoxy styrene (536 mg, 3.98 mmol) with a toluene (25 mL) solution of N\textsubscript{2}HCHO\textsubscript{2}Et (456 mg, 4.00 mmol). The addition of the diazoketone was carried out over 4 h, and the resulting mixture was stirred overnight. The solvent was removed in vacuo, and the crude residue was dissolved in diethyl ether. The resulting solution was passed through a silica gel column in order to remove porphyrin compounds. The solvent was removed under reduced pressure, and 5c precipitated as pure white crystals (647 mg, 70%). Only one isomer was isolated, and it was identified as having trans stereochemistry by comparison of NMR data with those of 5a and 9. 1H NMR (CDCl\textsubscript{3}): δ 7.00 (d, 2H, CH\textsubscript{2}OHCH\textsubscript{3}), J\textsubscript{HH} = 8.7 Hz), 6.78 (d, 2H, CH\textsubscript{2}CH\textsubscript{2}OCH\textsubscript{3}), J\textsubscript{HH} = 8.7 Hz), 4.12 (q, 2H, CO\textsubscript{2}CH\textsubscript{3}CH\textsubscript{3}), J\textsubscript{HH} = 7.2 Hz), 3.75 (s, 3H, OCH\textsubscript{3}), 2.44 (m, 1H, J = 7.8 Hz).
C₃H₄), 1.78 (m, 1H, C₃H₄), 1.51 (m, 1H, C₃H₄), 1.24 (t + m, 4H, C₃H₄ + CH₂CO₂CH₃), 1.14 (s, 1H, C₃H₄), 3.41 (s, 1H, C₃H₄), 1.71 (s, 2H, C₃H₄), 0.70 (t, 6H, CO₂CH₃), Jₙₗₙ = 5.7 Hz, MS (EI): m/z 274 [M⁺], 229 [M − CO₂H]⁺, 201 [M − C₃H₄O₂]⁺, 183, 173, 155, 144, 127, 115. Using method B, compound 6a was prepared from [Os(TTP)]⁺ (4.1 mg, 2.4 mmol), 0.50 mL (4.56 mmol) of phenylacetylene in 6 mL of toluene, and N₂CHCO₂Et (1.00 mL, 9.52 mmol) in 24 mL of toluene. GC analysis indicates the formation of olefin (21% yield) and bicyclobutane 6a (46%).

**endo-exo-2,4-Dimethyl-1-phenyl[1,1,1,10]bicyclo[8.3.3]octane (6b).** Using method A, bicyclobutane 6b was prepared from [OsCl(ppy)] (4 mg, 4 μmol), 0.100 mL (912 μmol) of phenylacetylene, and N₂CH(2,4,6-(CH₃)₃C₆H₃) (31.6 mL, 0.045 M in toluene, 1.4 mmol). GC analysis indicated formation of bicyclobutane 6b (77 ± 4% yield) along with a trace of olefin (2 ± 1% yield). ¹H NMR (CDCl₃): δ 7.09 (m, 3H, C₃H₄), 6.97 (dd, 2H, C₃H₄, Jₙₗₙ = 7.8, 1.8 Hz), 6.84 (s, 2H, C₃H₄), 6.77 (s, 2H, C₃H₄), 3.39 (m, 1H, CD₃CH₂CH₃), 3.25 (m, 1H, CH₃CH₂CH₃), 2.48 (s, 3H, CH₉), 2.39 (br-s, 1H, C₃H₄), 2.26 (s, 3H, CH₉), 2.24 (s, 3H, CH₉), 2.23 (s, 3H, CH₉), 1.15 (1D COSY spectra that showed cross-peaks between both the doublet at 3.39 ppm and the broad singlet at 2.39 ppm with the doublet of doublets at 2.65 ppm. The product was assigned to have endo,exo stereochemistry on the basis of 1D and 2D (H)NMR studies. High-resolution MS (EI): m/z found (calcld) 366.2345 (346.2345).
Cyclopropanation Mediated by Os(II) Porphyrins

**Method A.** A frozen benzene-δ₉ or toluene-δ₉ solution of complex 4h in an NMR tube was pressured to less than 1 atm of carbon monoxide. The tube was flame-sealed, the frozen solid was thawed, and the reaction was monitored by H NMR spectroscopy in a cooled NMR probe. Formation of cyclopropane 8 was rapid, even at 10 °C.

Ethyl 2-Methyl-2-phenylcyclopropanecarboxylic Acid Ester (9). In a typical reaction, 4 mg (2 μmol) of Os(II) porphyrins was dissolved in 5 mL of toluene. Dodecane (18 μL, internal GC standard) and 2-methylstyrene (0.16 mL, 7.62 mmol) were added. A solution of ethyl diazoacetate (89 mg, 780 μmol) in 10 mL of toluene was added dropwise over ca. 10 min. The reaction mixture was stirred for approximately 3 h and analyzed by gas chromatography. The yield of cyclopropane 9 was 100 ± 5% (trans/cis ratio of 2.5 ± 0.1). The major isomer, as determined by 500 MHz NOESY H NMR correlation, had the ethyl carbonyl group trans to the phenyl group. Compound 9, trans isomer: δ H NMR (CDCl₃) 0.7–3.1 (m, 18 H, CH₂CH₃, partially obscured by CHCl₃), 1.45 (m, 2 H, CO₂CH₂C₃H₃), 1.86 (m, 1 H, CH₃), 1.74 (m, 1 H, CH₃), 1.37 (m, 1 H, CH₃), 2.63 (t, 3 H, CO₂CH₃, Jnmr = 7.1 Hz). Compound 9, cis isomer: δ H NMR (CDCl₃) 0.7–3.1 (m, 18 H, CH₂CH₃, partially obscured by CHCl₃), 1.38 (m, 2 H, CO₂CH₃, Jnmr = 7.1 Hz), 1.49 (m, 1 H, CH₃), 1.40 (m, 1 H, CH₃), 1.27 (m, 2 H, CH₃), 1.14 (m, 1 H, CH₃), 0.90 (t, 3 H, CO₂CH₃, Jnmr = 7.1 Hz). MS (EI): m/z 204 [M⁺], 189 [M – CH₃⁺], 175 [M – CH₃O₂⁺], 147, 131 [M – CH₃O₂⁺], 115.

Ethyl cis-2-Methyl-trans-3-phenylcyclopropanecarboxylic Acid Ester (10). Using method A, cyclopropane 10 was prepared from 2 mg (4 μmol) of [TTP(OCO)(py)] in 0.120 mL (926 μmol) of trans-β-methylstyrene, and N₂CH₃CH₂CO₂Et (0.100 mL, 952 μmol). GC analysis indicated major formation of olefin (43 ± 2% yield) and minor formation of cyclopropane 10 (13 ± 2% yield). H NMR (CDCl₃): δ 0.7–3.1 (m, 18 H, CH₂CH₃, 3.99 (m, 2 H, CO₂CH₂C₃H₃), 2.61 (~t, 1 H, CH₃), Jnmr = 9.0 Hz, 2.05 (dd, 1 H, CH₃, Jnmr = 0.17 Hz), 1.38 (m, 1 H, CH₃, 1.27 (d, 3 H, CH₃), Jnmr = 6.6 Hz), 0.97 (t, 3 H, CO₂CH₃, Jnmr = 7.1 Hz). MS (EI): m/z 204 [M⁺], 189 [M – CH₃⁺], 175 [M – CH₃O₂⁺].

Reactions of [TTP]₆–CH₃C₆H₄CO₂Et with Styrene and Ethyl Diazoacetate. To a solution of complex 4a (4 mg, 4 μmol) in toluene (3 mL) was added styrene (100 μL, 0.874 μmol). Ethyl diazoacetate (100 μL, 0.952 μmol) in toluene (12 mL) was added dropwise for 50 min. The resulting solution was stirred overnight and analyzed by GC-MS. GC analysis: cyclopropane 5a, 65 ± 4% yield (trans/cis = 9) with traces of diethyl maleate/ethyl fumarate.

Reaction of [TTP]₆–CH₃C₆H₄CO₂Et with Styrene and Ethyl Diazoacetate. To a solution of complex 4d (10 mg, 11 μmol) was stirred in 0.5 mL of toluene. A toluene mixture (0.5 mL) of ethyl diazoacetate (1.1 μL, 9.6 μmol) and styrene (10.9 mg, 0.105 μmol) was injected. GC analysis followed immediately. Cyclopropane 5a was detected as the major product (20% overall yield, trans/cis = 10:2) along with diethyl maleate (60% yield).

**Results**

Osmium-Catalyzed Cyclopropanation. The catalytic cyclopropanation of styrene with ethyl diazoacetate mediated by [Os(TTP)]₄ (2) is a relatively rapid process. At ambient temperature with 0.5 mM Os(TTP)]₄ (200 mM of styrene, and 100 mM of ethyl diazoacetate, reactions were typically complete after 25 s. A competing side reaction, self-condensation of the diazo reagent to form fumarates and maleates, was also catalyzed by the osmium porphyrin complex (eq 1). In fact, maleates and fumarates were the major products and were
formed in approximately 70% yield if all reagents were present prior to addition of [Os(TTP)]₂. The cyclopropane yields were typically 30%. However, the unwanted self-condensation reaction was minimized by using an excess of styrene or by slowly adding the diazo reagent to the reaction mixture. For example, slow addition of a toluene solution of ethyl diazoacetate (960 μmol) over 2 h to 960 μmol of styrene and 0.2 mol % [Os(TTP)]₂ in toluene produced 79(2)% (GC yield) ethyl-2-phenylcyclopropane carboxylic acid ester (5a; trans/cis = 10.2). Only traces of diethyl maleate were observed by GC.

Nonactivated linear and cyclic olefins were less reactive than styrene. Dropwise addition of ethyl diazoacetate to a solution of 1-octene and [Os(TTP)]₂ (0.3 mol %) produced ethyl 2-n-hexylcyclopropane carboxylic acid ester (5b) in 66% yield with 34% diethyl maleate and furamate present. With phenylacetylene as a substrate, both π-bonds undergo cyclopropanation to afford endo-endo-2,4-bis(ethoxycarbonyl)-1-phenyl[1.1.1]bicyclobutane (6a) in 46% yield using ethyl diazoacetate (eq 2).

When methyldiazomethane was used, the yield of endo-exo-2,4-dimesityl-1-phenyl[1.1.1]bicyclobutane (6b) was 77%.

**Qualitative Effect of Diazot Substituents.** Catalytic cyclopropanation reactions of styrene were slower when di-p-tolyl Diazomethane was used as the carbene source compared to using EDA. Only a 3% yield of 1,1-di-p-tolyl-2-phenylcyclopropane (7a) was obtained from a reaction mixture containing [Os(TTP)]₂ (2 mg, 0.4 mol %), di-p-tolyl diazomethane (143 mg, 640 μmol), and styrene (680 mg, 6.6 mmol) after 23 h at 19 °C. When (trimethylsilyl)diazomethane was the carbene source, no cyclopropanation products were produced in the presence of styrene and [Os(TTP)]₂. The only observed species were unreacted styrene and (TTP)Os=CHCO₂Et.

In a qualitative sense, steric and electronic properties of the substituents on the α-carbon of the diazo reagent significantly influence cyclopropanation. Diazalones, N₂C(CO₂R)₂ (R = Me, Et), were also effective as carbene sources. The reaction proceeded more slowly with diester diazo reagents than with monoester diazo reagents (eq 3).

\[
N₂C(CO₂R)₂ + Ph ≈ \frac{[Os(TTP)]_2}{-3 N₂} \xrightarrow{\text{R = Me, Et}} \text{Ph} \quad \text{with} \quad \text{N₂C(CO₂R)} \xrightarrow{\text{R = Ph}} \text{Ph} \quad \text{with \ N₂} \tag{3}
\]

cyclopropanation of styrene (10 equiv per diazo reagent) with approximately 850 μmol of ethyl diazoacetate was complete in less than 1 min using [Os(TTP)]₂ as a catalyst. However, under similar conditions, the reaction took 7–8 h when diethyl or dimethyl diazomalonate was used as the carbene source. The yield of diester cyclopropanes was quantitative, with no olefin byproducts from carbene dimerization.

**Relative Rate Studies.** In a typical competition experiment, a 1/1 mixture of styrene and p-X-styrene containing 0.3 mol % [Os(TTP)]₂ in toluene was treated dropwise with a solution of ethyl diazoacetate for ca. 30 min. GC analysis of the product mixture gave relative rate ratios. The k₆/₄ values were 2.24 ± 0.03 (p-OMe), 1.66 ± 0.06 (p-CH₃), and 0.83 ± 0.02 (p-Cl). A competition between p-CF₃-styrene and p-methoxystyrene produced the ratio k₆/₄ = 4.8 ± 1.1. These relative rates yielded a Hammett plot with a slope of 0.80 ± 0.09 (R² = 0.926), indicating a modest electronic effect. In a competition reaction of α-methylstyrene and trans-β-methylstyrene, only α-methylstyrene reacted to form cyclopropane. α-Methylstyrene was also found to react 2.39 ± 0.06 times faster than styrene.

**Catalytic and Stoichiometric Cyclopropanation with (TTP)Os=CHCO₂Et.** Mechanistically, a carbene complex may be involved in the catalytic cycle for cyclopropanation. If so, it should also serve as a stoichiometric reagent for cyclopropanation. Since (TTP)Os=CHCO₂Et can be isolated and purified, it was examined for its ability to promote stoichiometric cyclopropanation. On treatment of (TTP)Os=CHCO₂Et with a 3-fold excess of styrene at ambient temperature in toluene, ethyl 2-phenylcyclopropane carboxylic acid ester formed slowly in 96% (trans/cis = 3.3) yield after 4 h. In contrast, when (TTP)Os=CHCO₂Et was used in catalytic amounts with styrene and ethyl diazoacetate, the cyclopropanation reaction was complete in seconds—a rate that was qualitatively comparable to the [Os(TTP)]₂-catalyzed reaction.

**α-Donor Ligand Additives.** On the basis of the stoichiometric study described above, it was apparent that a mono(carbene) complex could not be the active catalyst in this system. A possible alternative was that the carbene ligand is activated toward transfer by coordination of an additional axial ligand. Ligands such as PPh₃ and THF did bind to the carbene complex, as observed by ¹H NMR studies. For example, treatment of (TTP)Os=CHCO₂Et with excess THF in C₆D₆ produced new upfield resonances for a singly bound THF at 2.91 and 1.07 ppm. In comparison, free THF exhibits resonances at 3.55 and 1.41 ppm. However, the presence of α-donor ligands such as PPh₃ did not inhibit the cyclopropanation reaction. Similarly, 4-picoline and other pyridine derivatives also bind to osmium carbene complexes. These ligands produced six-coordinate ylides in which one pyridine was bound to the α-carbon of the carbene ligand and a second pyridine was bound to the trans position on osmium.

**Bis(carbene) Intermediates.** Since bis(carbene) complexes of Os(TTP) were observed when [Os(TTP)]₂ was treated with N₂C(p-tolyl)₂,¹⁰ experiments to test for a catalytically active bis(carbene) species were under-
taken. When 1 equiv of (TTP)Os=CHCO₂Et was treated with a mixture of 1 equiv of mesityldiazomethane and 10 equiv of styrene in toluene at ambient temperature (eq 4), a rapid reaction ensued which produced cyclo-

\[
\text{(TTP)Os=CHCO₂Et} + \text{N₂CH(Mes)} + 2 \text{Ph} \rightarrow \text{2N₂} \rightarrow \text{CO₂Et} + \text{Mes} \quad (4)
\]

propane products resulting from the transfer of the ester carbene (37%, trans/cis = 10) and the mesityl carbene (28%, trans/cis = 0.4). When the substituents were interchanged on the carbene complex and the diazo reagent, the same products and stereoselectivities were observed, but much less mesitylcyclopropane was formed. In eq 5, 10 times more ester cyclopropane was produced, relative to the mesityl product. In an important control experiment, the mesityl carbene complex did not undergo stoichiometric cyclopropanation with styrene at ambient temperature (eq 6). Thus, the mesitylmethylidene ligand, relative to the ethyl carboxyl carbene ligand, had a much lower propensity for transfer to an olefin. Moreover, transfer of the mesitylmethylene ligand from (TTP)Os=CH(Mes) (4d) did not occur until a diazo reagent was added.

**Labeling Experiments.** In hopes of gaining further insight into the mechanism of [Os(TTP)]₂-catalyzed cyclopropanation, a series of labeling studies was undertaken, as illustrated in Scheme 1, in which ester groups were initially used on both the starting mono(carbene) complex and the diazo reagent. For ease of synthesis and purification of the diazo reagents, ethyl and n-propyl labels were used. Note that for all monoester carbene sources used in this work, bis(carbene) complexes have not been isolated or spectroscopically observed. Labeling experiments were repeated several times using carbene complexes that were purified by column chromatography. Ideally, a single turnover experiment is preferred so that no dilution of the mixed bis(carbene) transient with a homoleptic bis(carbene) intermediate occurs. The undesirable symmetric bis(carbene) species (TTP)Os=CHY₂ would form from the remaining diazo reagent and result in overincorporation of the Y label into the product mixture. Since the catalytic cyclopropanation reaction was complete in about 25 s with 0.5 mol % of the osmium precatalyst at ambient temperature, labeling experiments were too fast to monitor at this temperature. Consequently, labeling studies were performed at −78 °C in toluene so that product ratios could be monitored at the lowest possible conversions. In a typical run, a mixture of 1 equiv of N₂CHCO₂Pr, 5 equiv of styrene, and dodecane as an internal standard in toluene was added under N₂ and a stirred toluene solution of 1 equiv of (TTP)Os=CHCO₂Et at −78 °C. The excess amount of styrene was optimized to minimize the olefin-forming side reaction but not speed up the rate of cyclopropanation too much. The reaction was sampled as quickly as mechanically possible (3–8 s) to determine product ratios. Complementary experiments with N₂CHCO₂Et and (TTP)Os=CHCO₂Pr (4e) were also examined. Under these conditions, conversions were as low as 20% but were typically about 50%. Attempts to quench the reaction with dioxygen to destroy the osmium catalyst did not completely stop cyclopropanation activity. Quenching the reaction with excess picoline was also undependable. Conversions were still variable and ranged from 10 to 50%. Additionally, it was found that the monoester carbene complexes in several samples decomposed to (TTP)Os(CO), which is also an active cyclopropanation catalyst (vide infra). A similar decomposition of (TTP)-Ru=CHCO₂Et to (TPP)Ru(CO) (21) Galardon, E.; Le Maux, P.; Toupet, L.; Simonneaux, G. Organometallics 1998, 17, 505. was reported by Simonneaux. Contamination with small amounts of the carbonyl complex resulted in overincorporation of the diazo label into the products. Product ratios were scattered over a range of 1.1–3.8. As a result of the problems described above, the ester labeling experiments were erratic and unreliable.

A series of labeling studies using aryl diazo reagents was subsequently undertaken, using p-tolyl and p-ethylphenyl labels. Conditions analogous to the experiments with the ester labels were employed, except that hexamethylenbenzene or fluorene was used as the internal GC standard. The rate of cyclopropanation reactions with aryl diazo reagents was slower than that for diazo esters. Thus, low conversions were more readily achieved. Results using (TTP)Os=CH(p-tolyl) (4f) and (p-ethylphenyl)diazomethane have shown that at early times (3–8 s), the product ratio for the two labels is near 1 at low conversions (5–20%). The data gave an average p-ethylphenyl to p-tolyl product ratio of 0.96 ± 0.20. When the labels were reversed [(TTP)Os=CH(p-ethylphenyl) (4g) and p-tolylidiazomethane], the ratio of p-tolyl to p-ethylphenyl products was 0.99 ± 0.11. The aryl labeling studies also suggest that both carbene fragments have similar transfer rates.

**Activation by CO.** A carbene ligand, with its π-acid character, is generally an electron-withdrawing species. Thus, a strong π-acid ligand such as CO may also activate mono(carbene) complexes toward transfer. To test this hypothesis, a mono(carbene) complex containing an appended olefin, (TTP)Os=CH(CO)CH₂CH₂CH₂(CO)₂ (4h), was prepared. At 70 °C in toluene, complex 4h showed no evidence of cyclopropanation after 2 h. However, at 110 °C, intramolecular cyclopropanation was observed with the formation of ethyl 2-oxo[3.1.0]bicyclohexanecarboxylic acid ester (8) (Scheme 2). In contrast, at 10 °C under an atmosphere of CO,
complex 4h underwent rapid intramolecular cyclopropanation. The reaction was approximately 50% complete in 6 min.

In addition, when (TTP)Os(CO) as the catalyst, results similar to those in the [Os(TTP)]2-catalyzed reactions were obtained. Using a 10-fold excess of styrene and adding ethyl diazoacetate in one portion, a 76% yield of cyclopropane with a trans/cis ratio of 8.4 ± 0.2 and a 24% yield of olefin was obtained in less than 60 s. When the diazo reagent was added slowly over 5 min, only 2% of the olefin byproduct was observed.

Stoichiometric Competition Reactions. Upon treatment of (TTP)Os-CHCO2Et (4a) with an excess of styrene and α-methylstyrene, cyclopropanes 5a and 9 were both formed. The ratio of cyclopropane products 9/5a was 2.3 ± 0.2. This is the same, within experimental error, as the product ratio from catalytic reactions using [Os(TTP)]2. However, the trans/cis ratio for cyclopropane 5a was 3.3 ± 0.3 in the stoichiometric reaction, compared to 10.2 in the [Os(TTP)]2-catalyzed reaction. The trans/cis ratio for compound 9 was 5.8 ± 0.5 in the stoichiometric competition reaction, compared to 2.5 in the catalytic reaction.

Iron(II) Porphyrin Precatalysts. The CO activation experiments indicated that reducing the electron density of the metal center facilitated cyclopropanation mediated by metallloporphyrin complexes. In line with this observation, iron(II) porphyrins were also potent cyclopropanation catalysts. Further evidence for the effectiveness of Fe(TTP) was derived from the cyclopropanation of styrene with (trimethylsilyl)diazomethane (eq 7). The cyclopropane product yield was 90% (trans/cis = 10 in toluene) at ambient temperature. Under the same conditions, [Os(TTP)]2 did not produce any observable cyclopropane.

Reactivity Profile. Several substituted olefins were tested as substrates for the [Os(TTP)]2-catalyzed cyclopropanation with ethyl diazoacetate. Monosubstituted and 1,1-disubstituted styrenes were excellent substrates for the [Os(TTP)]2-mediated cyclopropanation reactions. Phenylacetylene was also a good substrate, yielding bicyclobutanes. This is in contrast to Rh2L4-catalyzed reactions which produced cyclopropenes. Monosubstituted olefins such as 1-octene could be cyclooctaned, but carbene coupling was a competitive side reaction (66% yield of ethyl 2-n-hexylcyclopropanecarboxylic acid ester and 34% yield of diethyl maleate and fumarate). Additionally, 1,2-substituted olefins (cis or trans) were generally poor substrates and led to large amounts of olefin side products. For example, when trans-β-methylstyrene was the substrate, ethyl 2-methyl-3-phenylcyclopropane carboxylic acid ester (10) was formed in only 13% yield. The major products of the reaction were diethyl maleate and fumarate.

Interestingly, α-methylstyrene was cyclopropanated 2.4 times faster than styrene, showing the preference of the osmium catalyst for electron-rich olefins. However, α-methylstyrene led to a lower trans/cis ratio in the cyclopropane product than that observed for styrene (2.5:1 versus 10:1). Not surprisingly, in a competition reaction between α-methylstyrene and trans-β-methylstyrene, only α-methylstyrene reacted.

When trans-β-deuteriostyrene was the substrate, a mixture of cyclopropanes with cis and trans deuterium labels (with respect to the phenyl group) was detected by 2H NMR. The trans/cis product ratio (deuterium relative to the phenyl group) was 6.7:1 (eq 8), corresponding to an 87 ± 4% retention of stereochemistry. In the complementary experiment, using cis-β-deuteriostyrene as the substrate, the retention of deuterium to phenyl stereochemistry was 92 ± 4%.

Discussion

Cyclopropanation reactions mediated by transition-metal complexes can be divided into two categories: stoichiometric and catalytic. Isolable carbene complexes generally do not cyclopropanate olefins under mild conditions. In stoichiometric reactions, a reactive carbene complex is typically generated in situ as the active carbene transfer reagent. Catalytic processes typically involve Lewis acidic transition-metal complexes which mediate carbene transfer from a diazo reagent to an olefin. The commonly accepted mechanism in the diazo-based system involves formation of a transient carbene complex as the active cyclopropanation species. The primary basis for the involvement of transition-metal carbene species in catalytic cyclopropanation processes is derived mainly from indirect evidence. This includes asymmetric induction and reactivity correlations between catalytic and stoichiometric reactions. The trans/cis product ratios, as a function of olefin, correlate well in a comparison of the stoichiometric cyclopropanation with (CO)5W=CHPh relative to the Rh2(OAc)4-catalyzed cyclopropanation reaction with N2CHPh.

(23) Hamaker, C. G.; Mirafzhal, G. A.; Woo, L. K. Organometallics, in press.
with other catalysts.\textsuperscript{27,28} Also, the observation of enantio-meric excesses in chiral copper- and rhodium-catalyzed\textsuperscript{29,30} cyclopropanation processes suggested that the metal complex was intimately involved in the product-forming step. Moreover, production of free carbo-ethoxy carbene from EDA does not result in the formation of diethyl maleates or fumarates.\textsuperscript{30} The results observed in the [Os(TTP)]\textsubscript{2} system are inconsistent with free carbones.\textsuperscript{28,30}

Recently, Nishiyama and co-workers have isolated (trimethylsilyl)methylidene and (aryloxy carbonyl)meth-ylidene complexes of a bis(oxazolyl)pyridine ruthenium complex by treatment of an active cyclopropana-tion catalyst with bulky diazo reagents.\textsuperscript{7} These carbene complexes stoichiometrically cyclopropanated styrene with the same selectivity observed in the corresponding catalytic system. Moreover, the ruthenium carbene complexes were also cyclopropanation catalysts. The rates for stoichiometric and catalytic reactions were similar in the Nishiyama system.

Kodake and co-workers observed a rhodium(III) porphyrin adduct with ethyl diazoacetate at low tem-perature by treatment of (TTP)RhI with EDA at \(-40^\circ\text{C}\.\textsuperscript{4a} The EDA adduct lost N\textsubscript{2} above \(-20^\circ\text{C}\), forming a transient carbene complex which underwent nucleophilic attack by iodide to give a rhodium(III) iodoalkyl porphyrin complex. This iodoalkyl species was believed to be the active catalyst in rhodium porphyrin catalyzed cyclopropanation reactions. Presumably, the rhodium(III) alkyl complex reacted with EDA to yield a trans-alkyl rhodium(III) carbene complex. However, the trans-alkyl rhodium(III) carbene complex was not observed spectroscopically. Subsequent nucleophilic attack of olefin on the carbene ligand afforded cyclopropane and the steady-state rhodium(III) iodoalkyl complex.\textsuperscript{4d}

Kodake ruled out participation of the iodoalkyl fragment in cyclopropanation by using an ethoxy carbonyl iodoalkyl rhodium(III) porphyrin complex as a catalyst for cyclopropanation with tert-butyl diazoacetate. At the end of the reaction, only tert-butyl 2-phenoxylo-panocarbonylic acid ester had been produced. In addition, the final iodoalkyl rhodium(III) complex was the ethyl ester derivative, (TTP)RhCH\textsubscript{2}C(O)OEt\textsubscript{1}.

Our ability to isolate carbene complexes from osmium porphyrin catalyzed cyclopropanation reactions sug-gested that a study of this system would provide important mechanistic insight into this process. Experiments utilizing diazo and olefin substituent effects both supported a mechanism which involves formation of an osmium carbene complex. For example, as more electron-rich olefins were used, the catalytic production of cyclopropanes increased in rate. Thus, p-methoxy styrene reacted 4.8 times faster than p-(trifluoromethyl)-styrene. This observation is inconsistent with prior coordination of the olefin to osmium followed by nucleo-

[Philipic attack on the \(\pi\)-bound olefin by the \(\alpha\)-carbon of the diazo reagent. The most likely mechanism involves formation of a carbene complex and subsequent nucleo-philic attack of the olefin at the carbene carbon. In support of this pathway is the qualitative decrease in rate of cyclopropanation as the substitution about the incipient carbene carbon is changed. Hence, the cyclopropanation of styrene was much slower with di-p-tolyldiazomethane than it was with ethyl diazoacetate. Moreover, when (trimethylsilyl)diazomethane was used as the carbene source, no cyclopropanation was ob-served. The reaction stopped at the formation of (TTP)-Os=CH(TMS). It was also possible to rule out a pathway involving a free carbene species. The 1-phenylethylidene complex (TTP)OS=CM\textsubscript{E}Ph (41) can be isolated. If disso-ociation of the carbene ligand occurs, rearrangement of the free 1-phenylethylidene to styrene would occur with a rate constant of \(10^6\ s^{-1}\.\textsuperscript{31}\) However, solutions of (TTP)OS=CM\textsubscript{E}Ph did not produce any detectable amounts of styrene at ambient temperature.

As further evidence for the involvement of carbene complexes, (TTP)OS=CHCO\textsubscript{2}Et was examined as a cyclopropanation catalyst. Under similar conditions, both [Os(TTP)\textsubscript{2}] and the mono(carbene) complex produced similar yields of cyclopropane products from styrene and ethyl diazoacetate in qualitatively similar rates. However, in the stoichiometric reaction between (TTP)OS=CHCO\textsubscript{2}Et and an excess of styrene, the produc-tion of cyclopropane occurred over a time span of hours. In addition, the stereoselectivities differed. In the catalytic process, the trans/cis ratio was 10.2/1, whereas for the stoichiometric reaction the ratio was 3.3/1. Consequently, the mono(carbene) complex could not be the active catalytic species. Additionally, activation of the carbene toward transfer could not be achieved through addition of \(\sigma\)-donor ligands. Thus, the presence of triphenylphosphine or pyridine ligands inhibited the cyclopropanation reaction.

Under catalytic conditions in the presence of excess diazo reagent, a likely alternative for activation of the carbene ligand toward transfer is through formation of a bis(carbene) complex. Carbene ligands are typically electron withdrawing in character,\textsuperscript{22} thus, a bis(carbene) intermediate would be more susceptible toward nucleo-philic attack. In addition, bis(carbene) complexes of osmium porphyrins have been observed and isolated with di-p-tolyldiazomethane and 1-phenyl diazoe-thane.\textsuperscript{5a} We have not been able to observe a bis(carbene) complex by low-temperature spectroscopic techniques when ethyl diazoacetate was used as the carbene source. Presum-ably this is due to the strongly electron withdrawing nature of the ester functionality and relative accessibility of the carbene carbon. If any bis(carbene) formation occurs from the reaction between (TTP)OS=CHCO\textsubscript{2}Et and ethyl diazoacetate, build up of the bis(carbene) intermediate is prevented by a rapid reaction with additional ethyl diazoacetate to form diethyl maleates, diethyl fumarates, and (TTP)OS=CHCO\textsubscript{2}Et.

Recently, Simonneaux and co-workers used (Por)Ru-(CO) complexes as catalysts for the cyclopropanation of styrene with ethyl diazoacetate.\textsuperscript{32} A carbene carbonyl...
A recent communication by Che34 provides additional evidence that a bis(carbene) porphyrin complex is an active intermediate in the stoichiometric cyclopropanation of styrene. The mono(carbene) complex (TPFPPP)-Os=CH(CH3)2 (TPFPPP = meso-tetakis(pentafluorophenyl)porphyrinato) did not undergo stoichiometric cyclopropanation with styrene at 80 °C. However, treatment of the bis(carbene) complex trans-(TPFPPP)Os=CH(CH3)2 with styrene at 80 °C produced 1,1,2-triphenylcyclopropane (70%) and (TPFPPP)Os=CH2.

The higher reactivity and more transient nature of bis(carbene) osmium porphyrin complexes can be attributed to the electron-withdrawing nature of carbene ligands in general.22 Thus, a bis(carbene) complex would be more susceptible to nucleophilic attack than the related mono(carbene) complex. Consistent with this rationale is the demonstration that CO will activate a mono(carbene) complex toward cyclopropanation. This was cleanly demonstrated with the internal cyclopropanation of (TTP)Os-CH2CH=CH2 (4h). As shown in Scheme 2, complex 4h did not produce any cyclopropane at 70 °C. However, at 10 °C under an atmosphere of carbon monoxide, cyclopropane formation was relatively rapid. Presumably, the CO binds trans to the carbene ligand. The strong π-acceptor character of CO activates the carbene toward nucleophilic attack and promotes cyclopropanation.

A single-crystal X-ray structure of trans-(TPFPPP)Os- (=PH2)2 also provides an explanation of the higher reactivity of bis(carbene) complexes. The Os=C distances in (TPFPPP)Os- (=CPh2)2 are substantially longer (2.035(2) and 2.027(3) Å)34 compared to the Os=C distance in the mono(carbene) complex (TPP)Os-=CPh2 (1.856(8) Å).10 Thus, the longer, weaker Os=C bonds in the bis(carbene) complex account for the dramatic increase in cyclopropanation activity.

The importance of the electrophilicity of the metal complex was supported by studies with (TTP)Os(CO) and Fe(TTP). Both complexes are extremely effective cyclopropanation catalysts. The trans/cis cyclopropane ratio and rate of reaction for (TTP)Os(CO) are comparable to those for the [Os(TTP)]2-catalyzed reactions. In addition, Fe(TTP) was more active than [Os(TTP)]2, as the iron complex was capable of catalyzing the cyclopropanation of styrene with N2CHTMS. This latter reaction was not observed with osmium porphyrins.

Additional mechanistic insights were obtained from deuterium labeling studies using cis- and trans-β-deuteriostyrene. Some scrambling of the deuterium labels was observed, implying that carbon–carbon bond...
formation proceeds along a stepwise rather than a concerted pathway. However, since the level of scrambling was low, ring closure must be rapid compared to rotation about the C–C bond.

Conclusions

Osmium porphyrins are excellent catalysts for the stereoselective cyclopropanation of olefins with diazo reagents. Isolated carbene complexes of osmium porphyrins have allowed a systematic mechanistic study. Although a mono(carbene) complex, (TTP)Os=CHCO₂Et, is able to mediate the stoichiometric cyclopropanation of styrene, this reaction is much slower than the catalytic process. Chemical and mechanistic investigations are consistent with a bis(carbene) osmium(II) porphyrin as the active catalytic species (Scheme 3). Activation of ligand transfer by formation of a bis-(carbene) intermediate is a new mechanism for the cyclopropanation process.

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