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Transition metal-mediated reactions of diazo reagents: cyclopropanation and insertion into benzylic C-H bonds

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Transition metal-mediated reactions of diazo reagents:
Cyclopropanation and insertion into benzylic C-H bonds

by

Christopher G. Hamaker

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Inorganic Chemistry

Major Professor: L. Keith Woo

Iowa State University

Ames, Iowa

1999

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LIST OF ABBREVIATIONS

acac	acetyl acetonate anion, $[\text{CH}_3\text{C}(\text{O})\text{CHC}(\text{O})\text{CH}_3]^-$
Ar	generic aryl group
av	average
bipymox	5,5'-bis(oxazoliny)-2,2'-bipyridine
ⁱ Bu	<i>sec</i> -butyl
^t Bu	<i>tert</i> -butyl
^t BuPc	dianion of tetra-4- <i>tert</i> -butylphthalocyanine
Cp	cyclopentadienyl
DMF	<i>N,N</i> -dimethylformamide
ee	enantiomeric excess
eq	equation
EDA	ethyl diazoacetate
Et	ethyl
EtOH	ethanol
GC	gas chromatography
GC-MS	gas chromatography coupled to mass spectrometry
IR	infrared
Me	methyl
MeOH	methanol
Mes	mesityl, (2,4,6-trimethylphenyl)

mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimole
mol	mole
MS{CI}	mass spectrometry by chemical ionization
MS{EI}	mass spectrometry by electron impact
MS{ESI}	mass spectrometry by electrospray ionization
MS{FAB}	mass spectrometry by fast atom bombardment
NMR	nuclear magnetic resonance
OAc	acetate anion, $[\text{CH}_3\text{C}(\text{O})\text{O}]^-$
OEP	dianion of 2,3,7,8,12,13,17,18-octaethylporphyrin
PFP	dianion of <i>meso</i> -tetra(pentafluorophenyl)porphyrin
Ph	phenyl
PhCN	benzonitrile
Por	general porphyrin dianion
ppm	parts per million
Pr	<i>n</i> -propyl
^t Pr	isopropyl
py	pyridine
pybox	2,6-bis(oxazoliny)pyridine
R	generic alkyl group

s	seconds
saldach	dianion of <i>trans</i> -1,2-bis(salicylidene)cyclohexanediamine
salen	dianion of a generic bis(salicylidene)diamine
THF	tetrahydrofuran
TMP	dianion of <i>meso</i> -tetramesitylporphyrin
tmtaa	dianion of dibenzotetramethyltetraaza[14]annulene
TMS	trimethylsilyl
TOHDMAP	dianion of <i>meso</i> -tetra(1,2,3,4,5,6,7,8-octahydro-1:4,5:8-dimethanoanthracenyl)porphyrin
tolyl	<i>p</i> -C ₆ H ₄ CH ₃
t.o.n.	turnover number
TPP	dianion of <i>meso</i> -tetraphenylporphyrin
TPP- <i>p</i> -OMe	dianion of <i>meso</i> -tetra(<i>p</i> -methoxyphenyl)porphyrin
TPrPyc	dianion of 2,7,12,17-tetra- <i>n</i> -butylporphycene
TTP	dianion of <i>meso</i> -tetratolylporphyrin
Ts	<i>p</i> -toluenesulfonyl, [-SO ₂ -(<i>p</i> -C ₆ H ₄ CH ₃)]
UV-vis	ultraviolet-visible

GENERAL INTRODUCTION

Dissertation organization

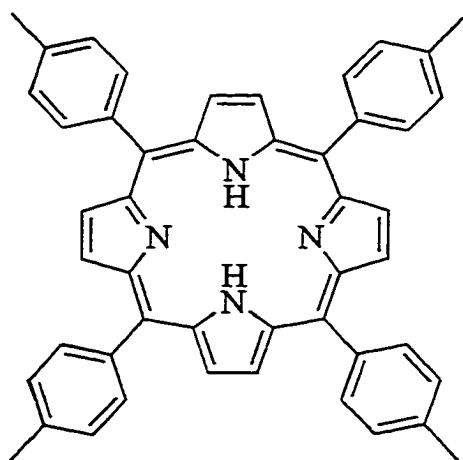
The first chapter of this dissertation is a literature review of methods for catalytic cyclopropanation and insertion of diazo compounds into C-H bonds using either metalloporphyrin or group 8 metal catalysts. The remaining chapters are papers which have either been published or are being prepared for submission. General conclusions follow the last chapter. All of the work in chapter 2 using iron(III) porphyrins was performed by Dr. Jennifer Robbins Wolf at the University of Texas at Austin. Approximately 40% of the work in chapter 4 was performed by Jean-Pierre Djukic or Daniel Smith. .

Porphyrin and dibenzotetraaza[14]annulene ligands

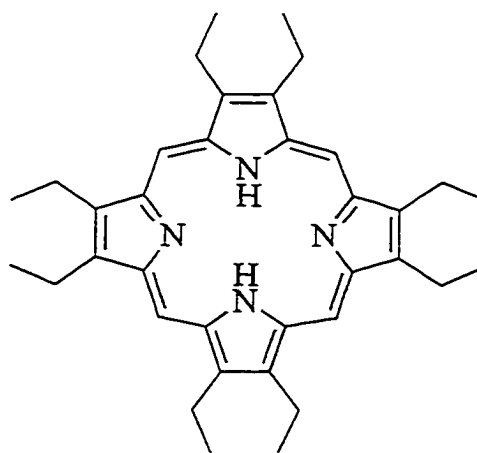
Porphyrins are widely used ligands in organometallic and coordination chemistry. These macrocyclic ligands contain nitrogen donor atoms from four pyrrole units as donors. Porphyrins contain 11 π -bonds in the macrocyclic core. In any one continuous path, nine of these π -bonds form a conjugated ring in an aromatic ($4n + 2$ π electrons) system. The commonly used *meso*-tetra-*p*-tolylporphyrin (TTP) and octaethylporphyrin (OEP) both have high symmetry (Figure 1). Consequently, these ligands have simple NMR spectra. For example, the TTP ligand gives rise to only four resonances in the ^1H NMR (β -pyrrole, *m*-tolyl, *o*-tolyl, and methyl) in most metal complexes. Another advantage of porphyrins is their rigidity. This rigidity is due to their macrocyclic and aromatic nature. Rearrangement of the axial ligands within the metal coordination sphere in metalloporphyrin complexes is rare.

Most transition metals fit within the N_4 -core of the macrocycle, leading to a *trans*-configuration of the axial ligands on the metal.

Dibenzotetraaza[14]annulenes (Figure 2) are related macrocyclic N_4 -donor ligands. However, there are several important differences between porphyrins and dibenzotetraaza[14]annulenes. The macrocyclic core of the ligand contains 6 π -bonds and 2 lone pairs and therefore is formally anti-aromatic (16π -electrons, $4n$). Consequently the benzo rings are not conjugated with the diazadiene fragments. This results in a saddle-shaped conformation for the dibenzotetraaza[14]annulene. Additionally, the 1.9 Å diameter N_4 -cavity of dibenzotetraaza[14]annulenes is approximately 0.1 Å smaller than that of porphyrins. Thus, metal ions in dibenzotetraaza[14]annulene complexes reside above the N_4 -plane of the ligand. This forces bis-ligand adducts of dibenzotetraaza[14]annulene complexes to adopt a *cis* geometry.



meso-tetra-*p*-tolylporphyrin



octaethylporphyrin

Figure 1. Two commonly used porphyrin ligands.

3

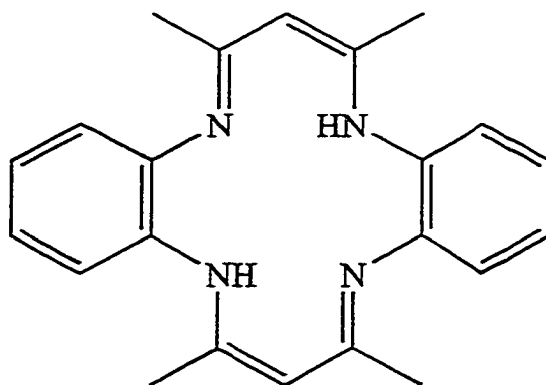


Figure 2. Structure of tetramethyldibenzotetraaza[14]annulene.

Metalloporphyrins and related complexes as catalysts

Metalloporphyrins have long been used as catalysts due to their robust nature and their ability to impart unique stereoselectivity to the products. Manganese, iron, and ruthenium porphyrins have been used extensively as oxidation catalysts. Also, rhodium(III) porphyrins are active cyclopropanation catalysts. In fact, rhodium(III) porphyrins generally yield the less thermodynamically stable *cis*-cyclopropanes. This is in contrast to the more commonly employed non-porphyrin copper and rhodium complexes used as catalysts where *trans*-cyclopropanes are the primary products. The work presented in chapters 2-4 focuses on the catalytic cyclopropanation of olefins with diazo reagents catalyzed by iron(II) and osmium(II) porphyrins.

CHAPTER 1: CATALYTIC CYCLOPROPANATION AND C-H INSERTION WITH
DIAZO REAGENTS USING METALLOPORPHYRIN OR GROUP 8 METAL
CATALYSTS

Introduction

The catalytic production of cyclopropanes is an important synthetic goal. The cyclopropyl group is a common functionality in natural products,¹ many of which have or are being investigated for medicinal properties.² For example, the natural, cyclopropane-containing antibiotic (+)-ambruticin (Figure 1) showed excellent *in vitro* and oral *in vivo* activity against fungal infections.³ Cyclopropanes are also valuable synthetic intermediates.⁴ Corey and coworkers used diethyl-2-phenylcyclopropane-1,1-dicarboxylate as an intermediate in the synthesis of Sertraline (Zoloft ®), an important antidepressant drug (Scheme I).⁵

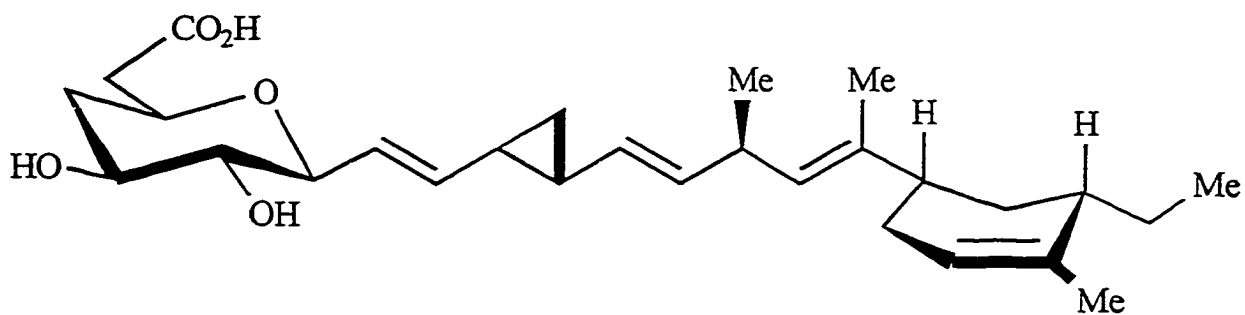
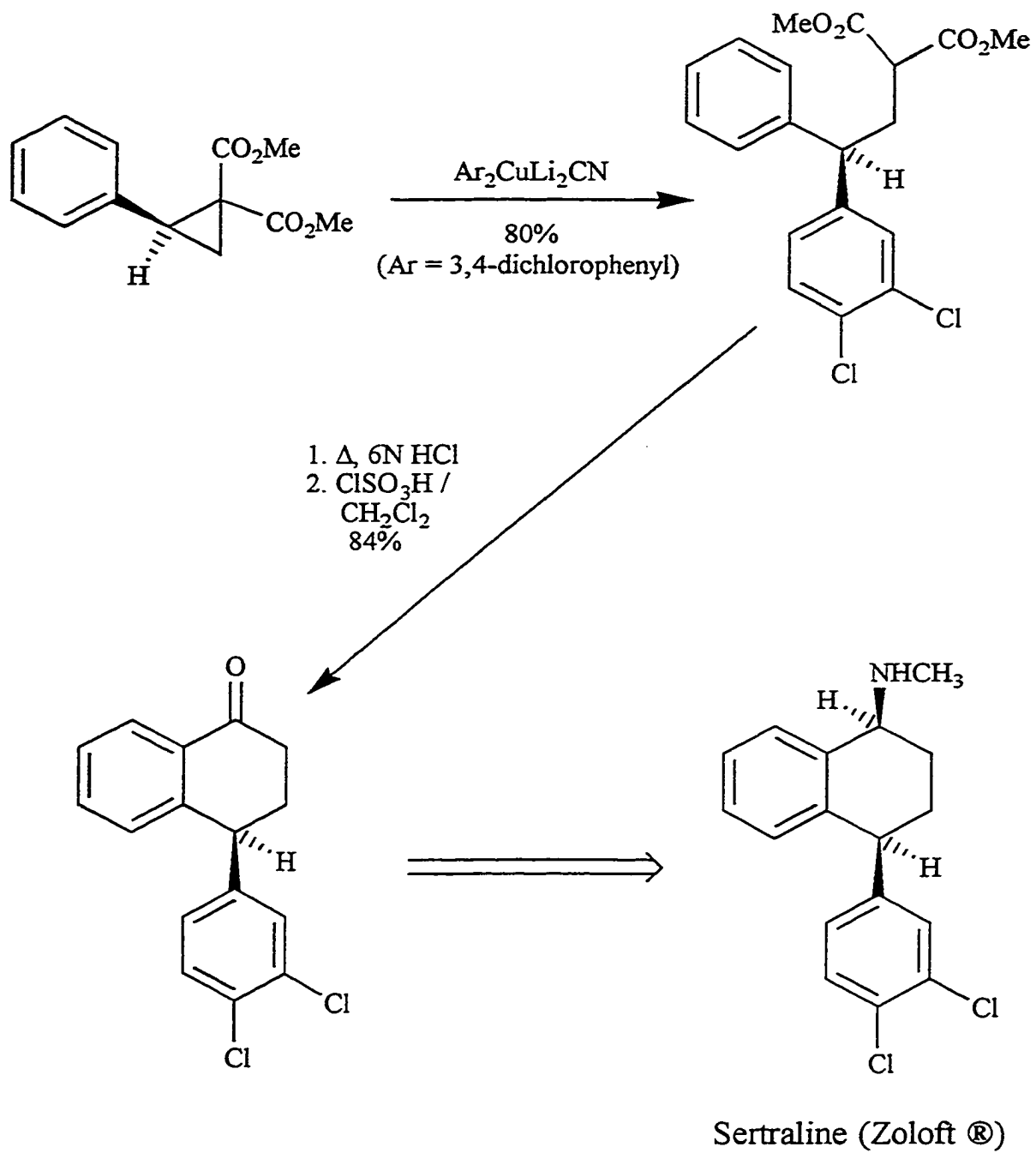


Figure 1. Structure of (+)-ambruticin.

A variety of metal complexes have been employed as catalysts for cyclopropanation reactions. Although copper complexes are among the oldest cyclopropanation catalysts known,⁶ complexes of rhodium, iron, ruthenium, osmium, cobalt, palladium, and platinum are also efficient cyclopropanation catalysts.^{7,8,9} Some results from early reports on catalytic

Scheme I

cyclopropanation with non-porphyrin catalysts are presented in Table I. Since a number of reviews of catalytic cyclopropanation have appeared recently,¹⁰ this chapter will discuss cyclopropanation reactions mediated only by metalloporphyrin complexes, related macrocyclic catalysts, and non-porphyrin catalysts containing group 8 metals.

Table I: Cyclopropanation of styrene with ethyl diazoacetate using various catalysts.

catalyst	% yield	<i>trans/cis</i>	ref	catalyst	% yield	<i>trans/cis</i>	ref
Mo ₂ (OAc) ₄	5	NR	8	Cu(OAc) ₂	71 [†]	2.6 [†]	9
Ru ₂ (OAc) ₄ Cl	38	1.8	8	Cu bronze	53 [†]	1.9 [†]	9
Rh ₂ (OAc) ₂	93	1.6	9	Cu(acac) ₂	65	2.1	8
Rh ₆ (CO) ₁₆	86	1.7	9	PdCl ₂ (PhCN) ₂	65	2.3	8
RhCl(PPh ₃) ₃	12	NR	8	Pd(OAc) ₂	98	2.0	8

All reactions conducted at room temperature except [†] performed at 80°C. NR = not reported.

Metalloporphyrin and related catalysts for cyclopropanation

Metalloporphyrin cyclopropanation catalysts are well studied. The first metalloporphyrin catalyst for the cyclopropanation of olefins with diazo reagents was a rhodium example reported by Callot and coworkers in 1980.¹¹ The cyclopropanation of styrene with ethyl diazoacetate using (TPP)RhI (see Figure 2 for structures of porphyrins)¹² produced primarily *cis*-ethyl-2-phenylcyclopropane carboxylate (*cis/trans* = 1.13, 71% yield). However, when the porphyrin was changed to the more bulky tetramesitylporphyrin, the *cis/trans* ratio decreased to 1.02:1¹³ (Table II). Nonetheless, rhodium(III) porphyrins are among the few catalysts that gave primarily *cis*-cyclopropane products.

Table II: Cyclopropanation of styrene with ethyl diazoacetate using metalloporphyrin and metallophthalocyanine catalysts.

catalyst	% yield	<i>trans/cis</i>	ref
(TTP)RhI	71	0.88	9
(TMP)RhI	78	0.98	11
(^t BuPc)Co	100	1.2	13
(^t BuPc)Fe(py) ₂	52	3.0	13
[(TTP)Os] ₂	79	10.2	14
(TPP)Ru(CO)	93	13.1	15
(TMP)Ru(CO)(EtOH)	68	7.7	16
(OEP)Ru(CO)(EtOH)	25	12.0	16
(TTP)Ru[=C(CO ₂ Et) ₂](MeOH)	85	14.0	18

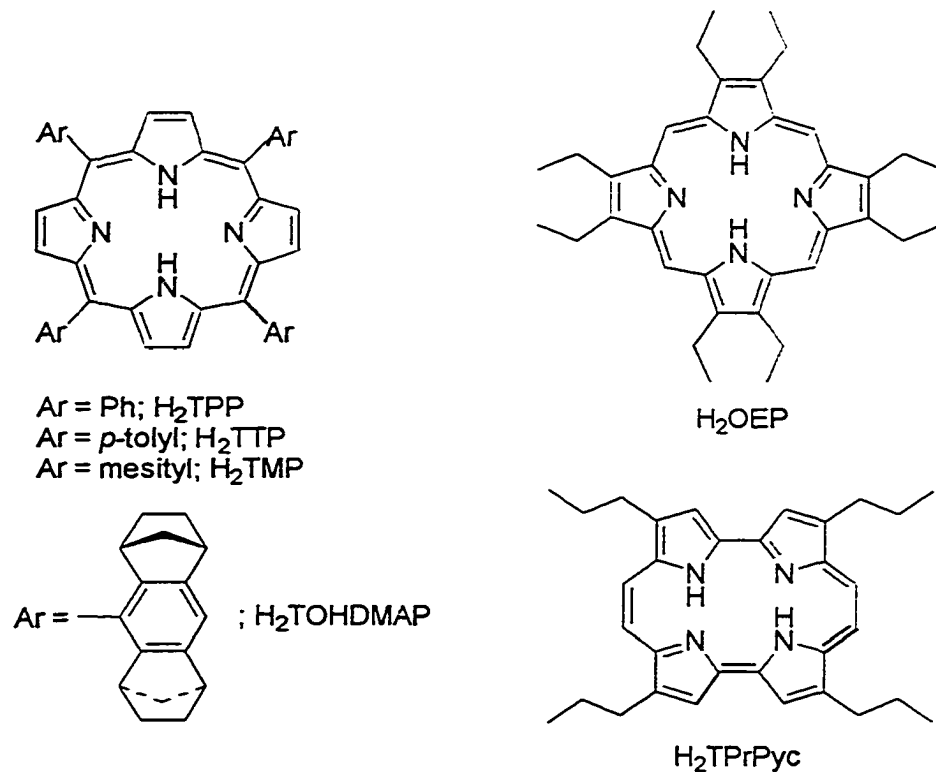


Figure 2. Structures of porphyrin and porphycene ligands discussed in this chapter. For full nomenclature, see endnote 12.

Porphyrinato rhodium(III) catalysts are useful for the cyclopropanation of several olefins including cyclohexene, norbornene, styrene, and hexene. Kodadek and co-workers investigated the substrate profile for the rhodium(III) porphyrin-catalyzed cyclopropanation reaction with ethyl diazoacetate.¹⁴ Generally, as the number of substituents on the alkene increased, the rate of cyclopropanation decreased. For example, 1-hexene reacted 1.6 times faster than *cis*-3-heptene. The exception was for trisubstituted alkenes which reacted at about the same rate as monosubstituted alkenes. Additionally, *cis*-1,2-alkenes reacted faster than *trans*-1,2-alkenes. With the more sterically encumbered (TMP)RhI, similar reactivity trends were observed, except that trisubstituted alkenes reacted more slowly than monosubstituted alkenes but still faster than disubstituted alkenes. The substrate discrimination by (TMP)RhI was greater than that exhibited by (TTP)RhI. Also, rhodium(III) porphyrins showed no electronic preference for substrates. Styrene and *p*-methoxystyrene were cyclopropanated at the same rate. Therefore, it was concluded that the substrate preferences were based on steric aspects, not electronic factors. Although rhodium(III) porphyrins generally gave primarily *cis*-cyclopropanes, the diastereoselectivities were quite low.

Shortly after Callot's report of rhodium(III) porphyrin-catalyzed cyclopropanation, Pazykina, *et al.*, reported the use of tetra-4-*tert*-butylphthalocyanine (Figure 3) complexes of several metals as cyclopropanation catalysts.¹⁵ Among the metals investigated, it was found that tetra-4-*tert*-butylphthalocyanine complexes of iron(II), cobalt(II) and rhodium(III) were efficient catalysts for the cyclopropanation of styrene with ethyl diazoacetate. The complexes (tBuPc)Co and (tBuPc)RhCl gave *trans/cis* product ratios of nearly 1:1, compared to a

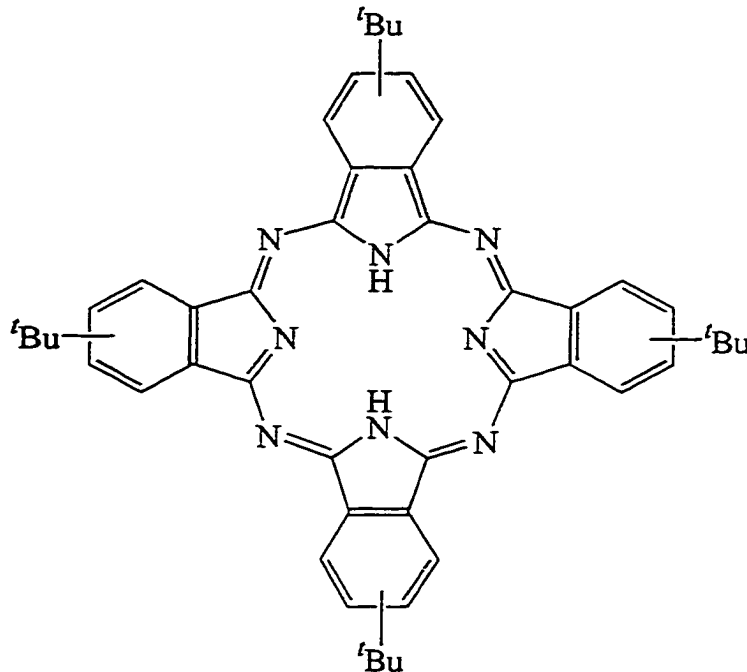


Figure 3. Structure of tetra-4-*tert*-butylphthalocyanine.

trans/cis ratio of 2.0:1 for the uncatalyzed thermal reaction. The iron complex (*t*BuPc)Fe(py)₂ gave a the highest *trans/cis* product ratio of 3.0:1 for this class of catalysts.

The next metalloporphyrin cyclopropanation catalyst was reported by Woo and co-workers in 1993.¹⁶ The osmium(II) complex [(TTP)Os]₂ was a very efficient catalyst for cyclopropanation. The reaction of styrene with ethyl diazoacetate catalyzed by [(TTP)Os]₂ (less than 0.5 mole %) gave ethyl-2-phenylcyclopropane carboxylate in 79% yield with a *trans/cis* ratio of 10.2:1. Other osmium complexes were investigated, including (TTP)Os(CO)(py) and the isolated carbene complex (TTP)Os=CHCO₂Et, which were both efficient catalysts. The osmium(II) porphyrin complexes were found to exhibit a pronounced substrate selectivity. Only 1- and 1,1-substituted alkenes were cyclopropanated; 1,2-

substituted alkenes were unreactive. This was quite different than the rhodium(III) porphyrin catalyzed reactions in which only tetrasubstituted alkenes were poor substrates.

In 1997, two separate groups reported using ruthenium(II) porphyrins as cyclopropanation catalysts. Simonneaux and co-workers showed that using catalytic amounts of (TTP)Ru(CO), ethyl-2-phenylcyclopropane carboxylate could be obtained from ethyl diazoacetate and excess styrene in 93% yield with a *trans/cis* ratio of 13.1:1. The remaining 7% of the ethyl diazoacetate was converted to diethyl maleate and fumarate.¹⁷ Using the bulkier complex (TMP)Ru(CO), the *trans/cis* ratio decreased to 7.7:1 but less of the diethyl maleate and fumarate byproducts were produced. Interestingly, the Ru(VI) compound (TMP)Ru(O)₂ was also an efficient catalyst giving a yield similar to that obtained using (TMP)Ru(CO). However, a slightly lower diastereoselectivity (*trans/cis* = 7.1:1) was obtained. Using these ruthenium porphyrins, α -methylstyrene and *p*-chlorostyrene were also converted to cyclopropanes, but cyclohexene and β -methylstyrene were unreactive towards cyclopropanation. This substrate selectivity was similar to that reported for the (TTP)Os-catalyzed cyclopropanation reaction.¹⁶ Later in 1997, Lo *et al.* reported the use of several complexes of the type (L)Ru(CO)(EtOH) (L = TPP, TMP, OEP, TPrPyc, and TOHDMAP) as cyclopropanation catalysts.¹⁸ Using (TPP)Ru(CO)(EtOH) as the catalyst for the cyclopropanation of styrene with ethyl diazoacetate, the product ethyl-2-phenylcyclopropane carboxylate was obtained in 45% yield with a *trans/cis* ratio of 9.2:1. This value is less than the value of 13.1:1 reported by Simonneaux¹⁷ and is presumably due to slightly different experimental conditions.¹⁹ Using (TMP)Ru(CO)(EtOH), a *trans/cis* ratio of 7.7:1 was obtained (this is the same as that reported by Simonneaux for (TMP)Ru(CO)). The complex

(OEP)Ru(CO)(EtOH) gave a *trans/cis* ratio of 12:1; and (TPrPyc)Ru(CO)(EtOH) gave a *trans/cis* ratio of 11:1. For the other olefins investigated, (TPP)Ru(CO)(EtOH) gave the highest diastereoselectivity and (TMP)Ru(CO)(EtOH) gave the lowest diastereoselectivity. The chiral complex (TOHDMAP)Ru(CO)(EtOH) was also tested as a cyclopropanation catalyst. At room temperature, a *trans/cis* ratio of 17.8:1 was obtained for the cyclopropanation of styrene with EDA with an 86.5% ee for the *trans*-cyclopropane isomer (the ee for the *cis*-cyclopropane was 3.8%). At 0°C, the *trans/cis* ratio increased to 23.6:1 with a 90.8% ee for the *trans*-cyclopropane isomer (4.0% ee for the *cis* isomer).

In 1998, Simonneaux reported using the isolated ruthenium(II) carbene complex (TPP)Ru[=C(CO₂Et)₂](MeOH) as a cyclopropanation catalyst.²⁰ With EDA, this complex converted styrene to ethyl-2-phenylcyclopropane carboxylate in 85% yield with a *trans/cis* ratio of 14.0:1. Simonneaux speculated that the catalytic cycle proceeded through the bare, 14-electron complex [(TPP)Ru]. The original complex (TPP)Ru[=C(CO₂Et)₂](MeOH) was isolated after the reaction was complete. No evidence for transfer of the diethoxycarbene ligand to styrene was observed.

Non-porphyrin group 8 metal complexes for cyclopropanation

Iron cyclopropanation catalysts. Although many iron complexes have been used as *stoichiometric* cyclopropanation reagents,²¹ their use as catalysts is less common. Hossain's group reported using the iron Lewis acid [CpFe(CO)₂(THF)]⁺BF₄⁻ as a catalyst for the cyclopropanation of olefins with EDA.²² Treatment of five equivalents of styrene with EDA in the presence of 10 mole % [CpFe(CO)₂(THF)]⁺BF₄⁻ at 40°C gave cyclopropane product in

68±3% yield after 12 hours with a *cis/trans* ratio of 5.7±1.1. Lowering the temperature to 4°C increased the *cis/trans* ratio to 32:1 but the yield dropped to only 10% after 24 hours. Performing the reaction at room temperature lowered the yield to 40% with little gain in diastereoselectivity. Other aromatic olefins were investigated but all had lower *cis/trans* product ratios. For example, using *p*-methylstyrene as the substrate, a 66% yield of cyclopropane with a *cis/trans* ratio of 1.5:1 was obtained. Also, 2-methoxypropene was cyclopropanated in 66% yield with a *cis/trans* ratio of 1.2:1. Aliphatic olefins (cyclohexene and 2-methyl-2-butene) afforded no cyclopropane products. Hossain believes the mechanism involved a transient iron-carbene intermediate, which could not be detected spectroscopically. Support for the mechanism is based upon analogy with isolated iron-carbene complexes which yield cyclopropanes *stoichiometrically* in the presence of olefins²² and the fact that *cis*-cyclopropanes are produced. In the uncatalyzed thermal reaction, *trans*-cyclopropanes are the primary products.¹⁵

Hossain also investigated the use of phenyldiazomethane as the carbene source in the cyclopropanation reaction catalyzed by $[\text{CpFe}(\text{CO})_2(\text{THF})]^{-}\text{BF}_4^{-}$.²³ Using styrene as the substrate, 1,2-diphenylcyclopropane was obtained in 80% yield with a *cis/trans* ratio of 24:1 at room temperature. Using either *p*-methylstyrene or vinyl acetate, the product cyclopropanes were obtained in 51% yield with only the *cis*-cyclopropane isomers produced. Cyclopentene and 2-methyl-2-butene were also cyclopropanated with high diastereoselectivities but low yields (25% and 20%, respectively).

Ruthenium(II) bis(oxazoline) catalysts. In 1994, Nishiyama's group reported using chiral bis(oxazolanyl) ligands (Figure 4) in ruthenium-catalyzed asymmetric cyclopropanation

reactions.^{24,25} The first ligand Nishiyama investigated was the bis(oxazoliny) bipyridine (bipymox) ligand. The complex (bipymox-^{*i*}Pr)RuCl₂ catalyzed the cyclopropanation of styrene with EDA in 54% yield with a *trans/cis* ratio of 2.6:1. However, the ee's obtained were less than 10%.²⁴ Nishiyama refined the ligand by removing one of the pyridines to give the bis(oxazoliny)pyridine (pybox) ligands also shown in Figure 4. Using the achiral complex (pybox-H)RuCl₂(CH₂=CH₂) as the catalyst, Nishiyama obtained ethyl-2-phenyl-cyclopropane carboxylate in 54% yield with a *trans/cis* ratio of 8.1:1.²⁶ However, using the bulkier, chiral pybox-^{*i*}Pr ligand, cyclopropane was obtained in 73% yield with a *trans/cis* ratio of 10.1:1. The ee for the *trans*-cyclopropane was 89% and the ee for the *cis*-cyclopropane was 79%.²⁵ Table III summarizes some of the results obtained in Nishiyama's group.

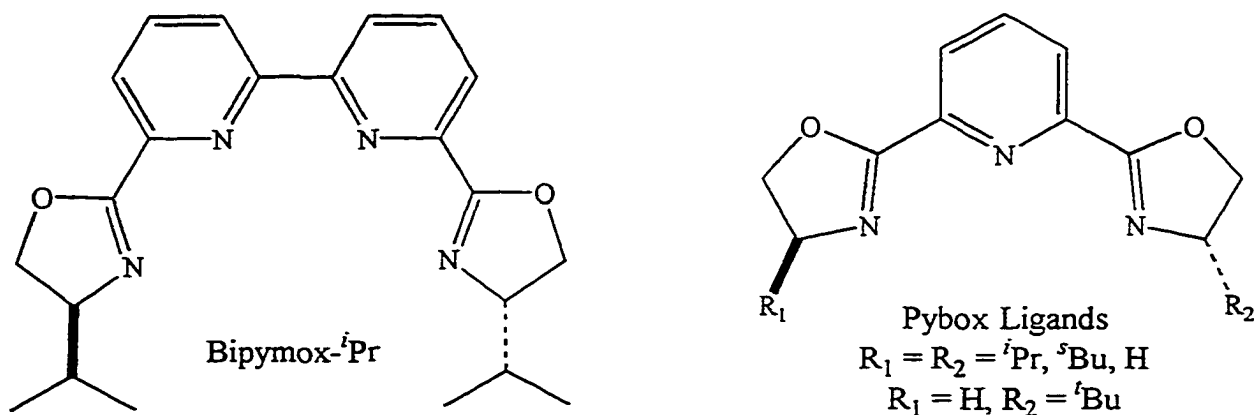


Figure 4. Structure of Nishiyama's bipymox-^{*i*}Pr and pybox ligands.

Table III: Cyclopropanation of styrene with ethyl diazoacetate using bis(oxazolinyl) ruthenium(II) complexes.

catalyst	% yield	<i>trans/cis</i>	% ee	ref
(bipymox- ^t Pr)RuCl ₂	54	2.6	< 10	24
(pybox- ^t Pr)RuCl ₂ (CH ₂ =CH ₂)	73	10.1	89 (<i>trans</i>), 79 (<i>cis</i>)	25
(pybox- ^t Bu)RuCl ₂ (CH ₂ =CH ₂)	82	15.7	91 (<i>trans</i>), 79 (<i>cis</i>)	26
(pybox-H)RuCl ₂ (CH ₂ =CH ₂)	54	8.1	-----	26
(pybox-H, ^t Bu)RuCl ₂ (CH ₂ =CH ₂)	93	8.1	90 (<i>trans</i>), 66 (<i>cis</i>)	27

When the complex (pybox-H,^tBu)RuCl₂(CH₂=CH₂), possessing only one stereogenic center, was used as the catalyst, a 93% yield of cyclopropane with a *trans/cis* ratio of 8.1:1 was obtained for the cyclopropanation of styrene with EDA.²⁷ The *trans/cis* ratio was slightly lower than that observed with the pybox-^tPr ligand which contains two stereogenic centers but the ee's were comparable (*trans*-cyclopropane: 90% ee; *cis*-cyclopropane: 66% ee for the pybox-H,^tBu complex). The enantioselectivities for these reactions can be increased by using chiral diazo esters. Using *d*-menthyl diazoacetate increased the enantiomeric excess for the *cis*-cyclopropane and *l*-menthyl diazoacetate increased the enantiomeric excess for the *trans*-cyclopropane. The *trans/cis* ratio was also increased to greater than 32:1 when menthyl diazoacetate was used as the carbene source.²⁵

Carbene complexes of the type (pybox-^tPr)RuCl₂(=CHCO₂Ar) (Ar = mesityl or 2,6-diisopropylphenyl) can be isolated when bulky diazoesters are used.²⁸ Both of these carbene complexes generated cyclopropanes *stoichiometrically* in the presence of styrene with yields, enantioselectivities, and rates which were the same as the corresponding catalytic reaction using (pybox-^tPr)RuCl₂(CH₂=CH₂). This observation led Nishiyama to conclude that the

active carbene transfer reagent was the carbene complex, (pybox-^{Pr})RuCl₂(=CHCO₂R).

Other ruthenium and osmium complexes. Demonceau investigated a number of monomeric ruthenium(II) and osmium(II) complexes for cyclopropanation activity. A few examples of these results are shown in Table IV. Simple complexes with the general formula MCl₂L₃ where M is either ruthenium or osmium and L is triphenylphosphine, triphenylarsine, or triphenylstibine were examined..^{29,30} Using RuCl₂(PPh₃)₃, the cyclopropanation of styrene with EDA was sluggish at 20 °C (37% cyclopropane yield) but was faster at 60 °C (93% yield). However, raising the temperature resulted in decreased diastereoselectivities (*trans/cis* = 2.0 at 20 °C and 1.25 at 60 °C). Substituting the phosphine ligands with heavier analogs gave higher *trans/cis* ratios at similar temperatures. For example, at 60 °C the complex RuCl₂(AsPh₃)₃ gave a *trans/cis* ratio of 1.4:1 and RuCl₂(SbPh₃)₃ gave a 2.4:1 *trans/cis* ratio.²⁹ The heavier congener, OsCl₂(PPh₃)₃, produced a lower yield of cyclopropane (52%) with a modest gain in diastereoselectivity to a *trans/cis* ratio of 2.2:1.³⁰ The activity of the related

Table IV: Cyclopropanation of styrene with ethyl diazoacetate using monomeric ruthenium(II) and osmium(II) catalysts.

catalyst	% yield	<i>trans/cis</i>	ref	catalyst	% yield	<i>trans/cis</i>	ref
RuCl ₂ (PPh ₃) ₃ /20 °C	37	2.0	29	OsH ₄ (PPh ₃) ₃ /60 °C	40	2.5	31
RuCl ₂ (PPh ₃) ₃ /60 °C	93	1.25	29	OsH ₄ (PPh ₃) ₃ /100 °C	91	2.1	31
RuCl ₂ (AsPh ₃) ₃ /60 °C	92	1.4	29	[(<i>p</i> -cymene)OsCl ₂] ₂ /60 °C	59	1.8	32
RuCl ₂ (SbPh ₃) ₃ /60 °C	94	2.4	29	RuH(PPh ₃) ₂ L [†] /100 °C	96	1.6	33
OsCl ₂ (PPh ₃) ₃ /60 °C	52	2.2	30	(<i>p</i> -cymene)RuCl ₂ - (TsN(CH ₂) ₃ NH ₂)/60 °C	94	1.7	34

[†]L is *exo*-7-diphenylphosphino-8-methyl-7,8-dicarba-*nido*-undecaborate(1-).

osmium(IV) hydride complex $\text{OsH}_4(\text{PPh}_3)_3$ was also investigated.³¹ At 60°C, styrene was cyclopropanated with EDA in 40% yield with a *trans/cis* ratio of 2.5:1 after 24 hours.

Increasing the temperature to 80°C increased the yield to 73% after 24 hours with a *trans/cis* ratio of 2.2:1. The reaction was rapid at 100°C yielding 91% cyclopropane in 8 hours with a *trans/cis* ratio of 2.1:1.

The π -arene complex $[\text{OsCl}_2(p\text{-cymene})]_2$ also catalyzed the cyclopropanation of styrene with EDA.³² The yield of cyclopropane was 59% with a *trans/cis* ratio of 1.8:1 at 60°C. Increasing the temperature to 80°C increased the yield to 78% with only a slight loss in diastereoselectivity. All of the aforementioned complexes exhibited a substrate selectivity reminiscent of the ruthenium(II) and osmium(II) porphyrin-catalyzed reactions. Aliphatic and cyclic olefins were poor substrates (cyclopropane yields were generally less than about 20%) while terminal and 1,1-substituted olefins with aromatic substituents were excellent substrates.

Demonceau investigated the scope of two ruthenium carborane complexes which were able to cyclopropanate simple aliphatic olefins.³³ The complexes have the formula $\text{RuH}(\text{PPh}_3)_2\text{L}$, where L is *exo*-7-diphenylphosphino-8-R-7,8-dicarba-*nido*-undecaborate(1-) and R is either H or methyl (Figure 5). Coordination of the carborane ligand to ruthenium involves an η^3 linkage through the phosphine and two B-H→Ru bonds. At 100°C, the cyclopropanation of styrene with EDA occurred in 96% yield with a *trans/cis* product ratio of 1.6:1. In the cyclopropanation of 1-undecene with EDA, cyclopropane was obtained in 60% yield with a *trans/cis* ratio of 1.4:1. These catalysts, while able to cyclopropanate aliphatic and conjugated double bonds, have a large preference for conjugated olefins. In a competitive cyclopropanation reaction, styrene reacted about ten times faster than 1-octene when EDA

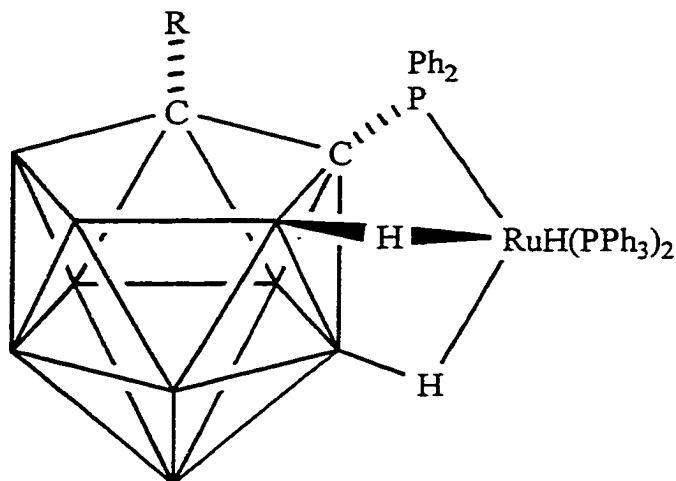


Figure 5. The complex bis(triphenylphosphine)(η^3 -*exo*-7-diphenylphosphino-8-R-7,8-dicarba-*nido*-undecaborate)ruthenium(II) hydride. R on the carborane ligand is either H or methyl. Each unlabeled vertex represents a boron atom. Unless shown, terminal hydrides have been omitted.

was used as the carbene source. Finally, Demonceau investigated a series of π -arene complexes with the general formula (*p*-cymene)RuCl[TsN(CH₂)_xNR₂] or (*p*-cymene)RuCl[TsN(CH₂)_xpy], where $x = 1, 2,$ or 3 .³⁴ All of the complexes gave similar yields and diastereoselectivities regardless of the structure of the amido-amine ligand. The highest yields (94%) for the cyclopropanation of styrene with EDA were produced when the amido-amine ligand was TsN(CH₂)₃NH₂. The *trans/cis* ratio was 1.7:1.

The cyclopropanation of olefins catalyzed by some iron(II) and osmium(II) complexes with macrocyclic and chelating ligands is discussed in the following three chapters.

Catalytic intermolecular insertion of diazo reagents into C-H bonds

While there are many examples of intramolecular insertion of diazo reagents into C-H bonds,³⁵ the analogous intermolecular reaction has received much less attention. Noels and coworkers reported the use of rhodium(II) carboxylate complexes for the insertion of EDA into the C-H bonds of alkanes and cycloalkanes.³⁶ All of the catalysts investigated preferentially mediated C-H insertion at the C₂ position. However, the use of more sterically encumbered catalysts enhanced attack at the C₁ position. For example, rhodium(II) acetate gave only 3% ethyl nonanate from the insertion of EDA into the C₁ position of *n*-octane while rhodium(II) (9-triptycenyloxy)carboxylate yielded 19% ethyl nonanate (Table V).

Table V. Product distribution for the insertion of ethyl diazoacetate into the C-H bonds of *n*-octane catalyzed various by rhodium catalysts.

Catalyst	Percent attack at				Reference
	C ₁	C ₂	C ₃	C ₄	
Rh ₂ (OAc) ₄	3	47	25	25	36b
Rh ₂ [O ₂ C(9-triptycenyloxy)] ₄	19	53	14	14	36b
(TPP)RhI	6	52	22	20	37
(TMP)RhI	21	52	14	13	37

In 1982, Callot and Metz reported using rhodium(III) porphyrins for the insertion of EDA into the C-H bonds of alkanes.³⁷ As observed in the rhodium carboxylate system, insertion occurred primarily at the C₂ position. However, use of the sterically hindered (TMP)RhI for the insertion of EDA into the C-H bonds of *n*-octane afforded 21% ethyl nonanate compared to 6% ethyl nonanate for (TPP)RhI.

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12. Ligand abbreviations used: TPP = dianion of *meso*-tetraphenylporphyrin; TTP = dianion of *meso*-tetra-*p*-tolylporphyrin; TMP = dianion of *meso*-tetramesitylporphyrin; TOHDMAP = dianion of *meso*-tetra(1,2,3,4,5,6,7,8-octahydro-1:4,5:8-dimethanoanthracenyl)porphyrin; OEP = dianion of 2,3,7,8,12,13,17,18-octaethylporphyrin; TPrPyc = dianion of 2,7,12,17-tetra-*n*-butylporphycene; ^tBuPc = dianion of tetra-4-*tert*-butylphthalocyanine.
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CHAPTER 2. SHAPE AND STEREOSELECTIVE CYCLOPROPANATION OF
ALKENES CATALYZED BY IRON PORPHYRINS

A paper published in the *Journal of the American Chemical Society*[†]

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Thomas Kodadek^{†*}, and L. Keith Woo^{‡*}

Abstract

Iron porphyrin complexes are active catalysts for the cyclopropanation of alkenes by ethyl diazoacetate. Fe(TTP) (TTP = *meso*-tetra-*p*-tolylporphyrin), an isolated iron(II) porphyrin complex, can be used as the catalyst, or the iron(III) complexes of several porphyrins can be reduced in situ. The reactions produce synthetically useful excesses of the *trans* cyclopropyl ester products. This stereoselectivity exhibits a modest solvent dependence, with donor solvents giving higher ratios of the *trans* cyclopropane products. The diastereoselectivity exhibits only a modest dependence on the steric bulk of the porphyrin. The reactions are selective for 1-alkenes and 1,1-disubstituted alkenes. Conjugated substrates and enol ethers react more rapidly than simple aliphatic alkenes. A mechanistic model for the iron-mediated reactions is proposed which is consistent with the data presented herein.

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Introduction

The metal-catalyzed cyclopropanation of substituted olefins by diazo esters is a reaction commonly employed in organic synthesis.² Chiral copper,³⁻⁵ and rhodium,^{6,7} catalysts have recently been reported to effect cyclopropanation with high enantioselectivity. However, the diastereoselectivities obtained in these reactions are generally poor. Mixtures of the *trans* and *cis* cyclopropyl esters are produced, with the *trans* isomer obtained in only a slight excess. A notable exception is a recently reported ruthenium catalyst⁸ which provided high enantioselectivities and *trans/cis* ratios of 10:1 using ethyl diazoacetate (EDA) as the carbene source.

We are interested in the development of metalloporphyrin cyclopropanation catalysts, since such reactions often exhibit unique stereoselectivities and exceedingly high catalyst turnover numbers. For example, rhodium(III) porphyrin-catalyzed cyclopropanation reactions using EDA as the carbene source produced the *cis* cyclopropyl ester as the major product when bulky ligands such the tetramesityl porphyrin (TMP) (see Figure 1) were employed.⁹⁻¹² To the best of our knowledge, this is the only example of a catalyst that produces synthetically useful excesses of *cis* cyclopropyl esters.

More recently, osmium(II) porphyrins have been shown to catalyze the cyclopropanation of alkenes with diazoesters. These reactions also exhibit good diastereoselectivity, but of the opposite sense. Using styrene as the substrate and EDA as the carbene source, catalysts such as the osmium(II) tetra-*p*-tolylporphyrin (TTP) dimer, (TTP)Os(pyridine)₂, and (TTP)Os(CO)(pyridine) provided the *trans* product in up to a 10-fold excess over the *cis* cyclopropyl ester.^{13,14} The divergent stereoselectivities observed in

these reactions is curious, since investigations of stoichiometric osmium and rhodium porphyrin-catalyzed cyclopropanation reactions have suggested that the active species are the isoelectronic Os(II) and Rh(III) carbenes, respectively. Thus, it would appear that subtle factors have a profound effect on the stereochemical outcome of the reaction with these two metals.

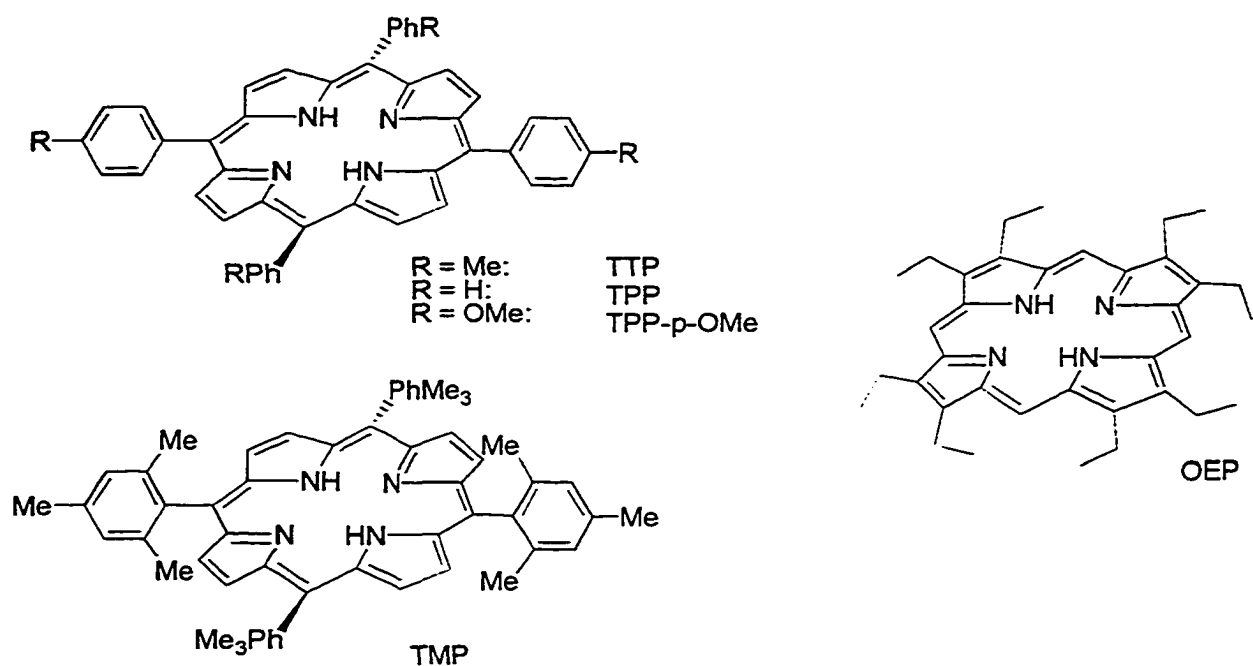


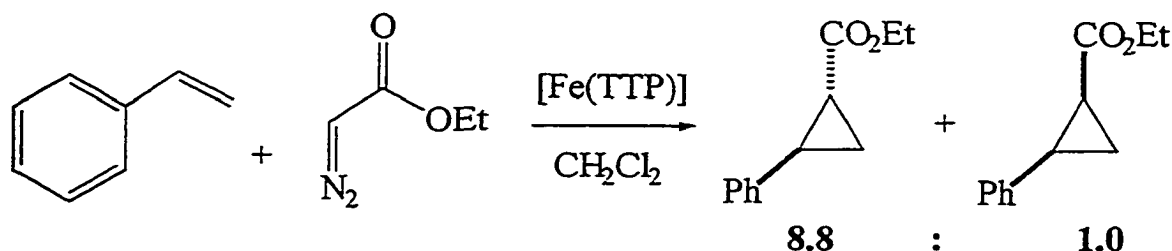
Figure 1. Structures of porphyrins used in this study.

In this paper, we describe studies of iron porphyrin-catalyzed alkene cyclopropanations. First, we hoped that the analysis of a third type of porphyrin catalyst would shed light on the unusual metal-dependence of the product stereochemistry. Second, while the osmium and rhodium porphyrins and the ruthenium tripyridyl complex are efficient catalysts, they are expensive and are not currently commercially available. If an efficient and

stereoselective catalyst containing a more inexpensive metal could be devised, this might be more practical for use in large-scale organic synthesis. We find that iron porphyrins are excellent catalysts for the cyclopropanation of some alkenes by diazoesters. The reactions produce synthetically useful excesses of the *trans* cyclopropyl ester. The iron porphyrin catalysts exhibit pronounced substrate selectivities that may be useful in the selective cyclopropanation of polyolefins. A model for carbene transfer from the metal to the alkene is proposed that is consistent with all of the data regarding porphyrin-based catalysts reported to date. This model will be of great utility in designing chiral metalloporphyrins for asymmetric cyclopropanation reactions.

Results

Fe(II) porphyrins catalyze the cyclopropanation of styrene. Iron(II) porphyrins are isoelectronic with Os(II) and Rh(III) porphyrins and so were examined for cyclopropanation activity. It was found that Fe(II)(TTP) was quite active in the presence of styrene and EDA. Approximately 1300 catalyst turnovers were observed over an hour and an 8.8 to 1 ratio of *trans* to *cis* cyclopropyl esters was produced, comparable to the best results obtained with other types of catalysts. This *trans*-selective reaction appears to be more closely related to the osmium-catalyzed process than the rhodium-mediated reaction and



suggests that for the iron triad, the transition state for carbene transfer favors the thermodynamically more stable stereochemical arrangement of the ester and the alkene substituent.

In situ reduction of Fe(III) porphyrins provides highly active cyclopropanation catalysts. Given this encouraging result, we wished to examine the scope of the iron porphyrin-catalyzed cyclopropanation reaction. However, because of their air-sensitivity, isolated Fe(II) porphyrins are easily handled only in an inert atmosphere box and are generally not convenient reagents for organic synthesis. In order to devise a more practical process, we examined the *in situ* reduction of air-stable iron(III) porphyrins under argon as a means to generate an active catalyst. Since EDA is known to be a mild reducing agent,¹⁵ we mixed the chloroiron(III) derivative of tetraphenylporphyrin (TPP) with styrene and EDA in dichloromethane. Neither the production of cyclopropanes nor the decomposition of EDA was observed at room temperature. However, heating the solution to reflux was sufficient to initiate a reaction that was dependent on the presence of the catalyst. The ratio of stereoisomeric products was 5.5:1 with the *trans* cyclopropyl ester predominating. When the argon blanket was removed, the reaction proceeded very sluggishly. This supports the contention that the active species is the air-sensitive Fe(II) porphyrin.

Since it seemed likely that higher stereoselectivities would be obtained at reduced temperatures, we explored other protocols for the *in situ* reduction of iron(III) porphyrins. It was found that the one-electron reductant cobaltocene is a superior reagent for this purpose. In the presence of cobaltocene and the Fe(TPP)Cl precatalyst, the reaction proceeded to completion in a short period of time and excellent turnover numbers were

Table I. Catalytic cyclopropanation of olefins with ethyl diazoacetate using iron porphyrin complexes as catalysts.

Olefin	Catalyst ^a	Reaction Time (h)	t.o.n. ^b	<i>trans/cis</i> ratio ^d	Cyclopropane/ diethyl maleate
styrene	Fe(PFP)Cl	6	4200	6.0	75:25
styrene	Fe(TPP)Cl/40°C	10	400	5.5	76:24
styrene	Fe(TPP)Cl/CoCp ₂	2	910	8.7	80:20
styrene	Fe(TTP)	1	1300	8.8	<i>e</i>
styrene	Fe(TPP- <i>p</i> -OMe)Cl/CoCp ₂	3	730	9.0	<i>e</i>
styrene	Fe(TMP)Cl/CoCp ₂	2	890	13	<i>e</i>
styrene	Fe(OEP)Cl/CoCp ₂	4	300	10	<i>e</i>
α -methylstyrene	Fe(PFP)Cl	3	4300	1.1	67:33
α -methylstyrene	Fe(TPP)Cl/40°C	18	250	3.4	70:30
α -methylstyrene	Fe(TMP)Cl/CoCp ₂	8	900	3.0	97:3
α -methylstyrene	Fe(OEP)Cl/CoCp ₂	4	1800	3.7	85:15
α -methylstyrene	Fe(TTP)	1	1700	4.2	<i>e</i>
<i>p</i> -MeO-styrene	Fe(PFP)Cl	7	2000	5.8	<i>e</i>
<i>p</i> -MeO-styrene	Fe(TPP)Cl/40°C	5	73	5.5	<i>e</i>
<i>p</i> -MeO-styrene	Fe(TMP)Cl/CoCp ₂	3	1400	11	<i>e</i>
ethyl vinyl ether	Fe(PFP)Cl	4	1800 ^c	3.3	67:33
ethyl vinyl ether	Fe(TMP)Cl/CoCp ₂	4	550 ^c	4.1	82:18
ethyl vinyl ether	Fe(OEP)Cl/CoCp ₂	4	250 ^c	4.5	34:66
2-ethyl-1-butene	Fe(PFP)Cl	2	390	–	30:70

(a) 0.02-0.05% catalyst. (b) T.o.n. = turnover number, based on equivalents of cyclopropyl ester produced. Determined by G.C. unless noted otherwise. (c) Determined by ¹H NMR. (d) Determined by G.C. (e) Trace diethyl maleate observed.

observed. For example, more than 900 equivalents of styrene with respect to catalyst were cyclopropanated in two hours at room temperature. The diastereoselectivity was identical, within experimental error, to that observed using preformed Fe(II)TTP (8.7 to 1 ratio of *trans* to *cis* cyclopropanes). Although cobaltocene itself is air-sensitive, its oxidation is very slow and reactions can be set up conveniently without the use of a glove box. Cobaltocene alone also mediated cyclopropanation under these conditions, but the rate was so low that this reaction did not contribute significantly to product accumulation and had no effect of the stereochemical outcome. For example, only four turnovers per cobalt in a 4-hour period were observed when cobaltocene alone was used to catalyze the cyclopropanation of *p*-methoxystyrene.

Influence of porphyrin structure and solvent on product stereochemistry. Using this more convenient system, we explored the effect of changing the peripheral substituents on the porphyrin ligand. In rhodium porphyrin-catalyzed cyclopropanations, bulkier, more bowl-shaped ligands provide higher ratios of *cis* to *trans* cyclopropyl ester products. However, as shown in Table I, a variety of porphyrins with very different steric environments around the catalytic iron atom produced similar ratios of cyclopropyl ester stereoisomers. For example, in the iron-catalyzed reaction between EDA and styrene, the crowded tetramesityl porphyrin (TMP) ligand and the unencumbered octaethylporphyrin (OEP) ligand (Figure 1) supported reactions that provided 13:1 and 10:1 ratios of *trans* to *cis* cyclopropyl esters, respectively. This modest difference was not part of a trend. The TTP ligand, which is intermediate in bulk between the OEP and TMP ligands, supported a product ratio of 8.8 to 1. The addition of an electron-donating *p*-methoxy group to the porphyrin arene rings also had essentially no effect.

We conclude that the substrate and the porphyrin substituents do not interact significantly.

The stereoselectivities exhibit a modest solvent dependence. Higher *trans* selectivities are observed with donor solvents (Table II). For example, cyclopropanation of styrene catalyzed by Fe(II)TTP yields a *trans/cis* ratio of 13:1 and 12:1 in THF and acetonitrile, respectively, whereas in dichloromethane the ratio of isomers is 8.8:1 and in toluene it is 8.0:1.

Table II. Effect of solvent on cyclopropyl ester product isomer ratio in cyclopropanation reactions of styrene with EDA using [Fe(TTP)] as the catalyst.

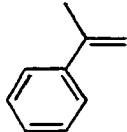
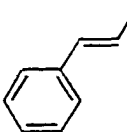
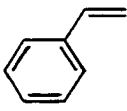
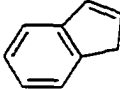
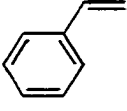

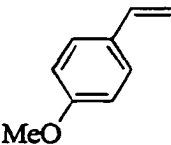
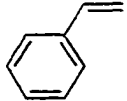
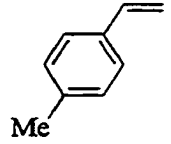
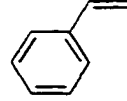
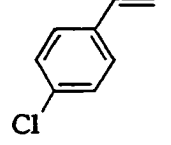
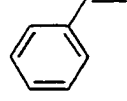
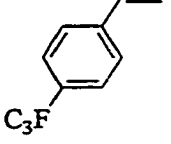
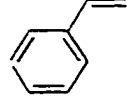
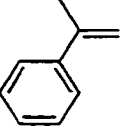
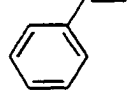
Solvent	Ratio of <i>trans/cis</i> products
toluene	8.0
benzene	8.3
styrene	8.3
dichloromethane	8.8
diethyl ether	9.3
acetonitrile	12
THF	13

Cyclopropanation using Fe(PFP)Cl. In order to simplify the system even further, we examined the cyclopropanation activity of iron *meso*-tetrakis(pentafluorophenyl)-porphyrin chloride (Fe(PFP)Cl) in the absence of cobaltocene. We reasoned that if common porphyrins could be reduced by EDA at elevated temperatures, then perhaps this much more electron-deficient porphyrin would be transformed in situ to the Fe(II) species even at room temperature. Indeed, Fe(PFP)Cl catalyzed the cyclopropanation of various olefins by EDA

efficiently at room temperature without the need for added cobaltocene. For example, over 4000 catalyst turnovers were observed in 6 hours using styrene as the substrate (Table 1). This contrasts with Fe(TPP)Cl-catalyzed reactions which needed to be heated to 40°C to effect reduction and subsequent cyclopropanation, or Fe(TMP)Cl-mediated reactions, which proceeded only at 80°C (data not shown). In both cases, catalyst efficiency was much lower than that obtained with the Fe(PFP)Cl catalyst at room temperature. Although the stereoselectivity for the *trans* isomer (6:1 for styrene in dichloromethane) is slightly lower than that observed using conventional porphyrins in the cobaltocene-initiated reaction, it is still very good compared to commonly employed cyclopropanation catalysts. Moreover, Fe(PFP)Cl is commercially available.

Iron porphyrin-catalyzed cyclopropanation reactions exhibit pronounced shape and electronic substrate preferences. The iron porphyrins catalyzed the cyclopropanation of 1-alkenes and 1,1-disubstituted olefins very efficiently, but alkenes with other substitution patterns were poor substrates. Styrene, α -methylstyrene, and ethyl vinyl ether were cyclopropanated with reasonable to high efficiencies (Table I), but only very low yields (less than 5%) of cyclopropane products were observed for *cis*- or *trans*- β -methylstyrene, indene, and 1-methylcyclohexene using Fe(PFP)Cl as the catalyst precursor (data not shown). This selectivity is borne out in competition studies. For example, when equal amounts of styrene and indene were mixed with limiting EDA in the presence of 0.035% Fe(PFP)Cl, a 26:1 ratio of styrene-derived to indene-derived cyclopropyl esters was obtained (Table III). This is a remarkable example of shape selectivity in that these substrates differ by only a single methylene group. *Trans*-1,2-disubstituted alkenes are also poor substrates. Using Fe(TTP) as

Table III. Competition experiments reveal significant electronic and shape preferences in the iron porphyrin-catalyzed cyclopropanation reactions.

Olefin A	Olefin B	Catalyst	Ratio of Products Derived From A/B
		Fe(TTP)	only reaction of A observed
		Fe(PFP)Cl	26
	$\text{CH}_3(\text{CH}_2)_7$ 	Fe(PFP)Cl	74
		Fe(TTP)	2.50
		Fe(TTP)	1.85
		Fe(TTP)	1.33
		Fe(TTP)	0.62
		Fe(TTP)	3.00

the catalyst, no detectable cyclopropanation products from *trans*- β -methylstyrene were detected in a competition experiment when equal amounts of *trans*- β -methylstyrene and α -methylstyrene were used as the substrates (Table III). When *trans*- β -methylstyrene or cyclohexene alone was the substrate, diethyl maleate and fumarate were the only detectable products (data not shown). This shape selectivity is reminiscent of that observed for Os(TTP)-catalyzed cyclopropanation,¹² but contrasts with the much broader substrate compatibility of rhodium porphyrin-catalyzed reactions.¹¹ In the latter case, only tetrasubstituted alkenes are sluggish substrates.

The iron porphyrin catalysts also exhibit pronounced preferences based on the electronic nature of the alkene. In general, olefins with aromatic or π -donating heteroatoms are better substrates. For example, 1,1-disubstituted alkenes with two alkyl substituents, such as 2-ethyl-1-butene, could be cyclopropanated, but yields were low due to a competitive reaction which formed diethyl maleate in high yield (Table I). This product is presumably formed by the attack of EDA on the iron carbene, which will be favored if carbene transfer to the alkene is sluggish. The preference for aromatic substituents was also reflected in a competitive experiment in which equal amounts of styrene and 1-decene were present. Using Fe(PFP)Cl as the catalyst, styrene was cyclopropanated at least 74 times more rapidly (Table III).

A linear free energy relationship was derived from relative rate studies. Four cyclopropanation competition experiments were conducted with equimolar amounts of styrene and 4-X-styrene (X = OCH₃, CH₃, Cl, CF₃) and limiting quantities of EDA. Electron-donating substituents increased the rate of cyclopropanation, while electron-withdrawing

substituents resulted in slower rates (Table III). The data were fit to a Hammett plot (Figure 2) with $\rho = -0.68 \pm 0.07$. Analogous electronic preferences were not observed in the corresponding rhodium porphyrin-catalyzed cyclopropanation reactions,¹⁷ suggesting that there is some buildup of electron deficiency on the alkene carbons in the transition state for carbene transfer from iron to the substrate, whereas this is not the case when rhodium porphyrins are employed. The electronic preferences exhibited by the iron porphyrin catalysts are similar to those observed for cyclopropanations catalyzed by $\text{Os}_2(\text{TTP})_2$, again demonstrating the similarity between the iron and osmium-based systems.

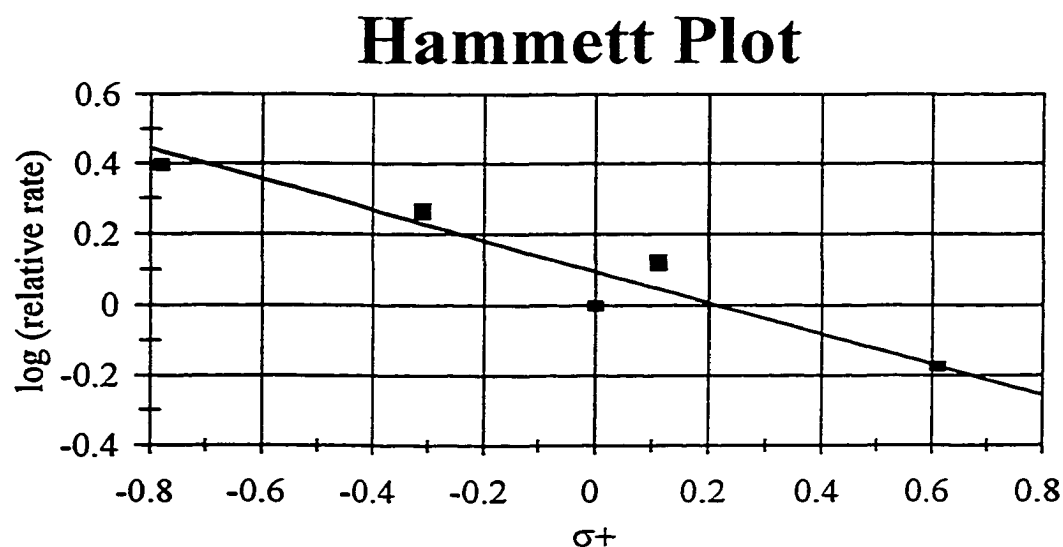


Figure 2. Hammett plot for the cyclopropanation of styrenes with EDA using $\text{Fe}(\text{TTP})$ as the catalyst.

Isotope Effects. In order to probe the nature of the transition state of the iron-mediated cyclopropanation, the secondary kinetic isotope effect was determined in a competitive reaction between styrene and styrene- d_8 using Fe(PFP)Cl as the catalyst. A modest, but significant, inverse isotope effect of 0.87 ± 0.07 was observed. This suggests that there is some rehybridization of the olefin in the transition state of the iron-mediated reaction. In an analogous study using Rh(TMP)Me as the catalyst, no kinetic isotope effect was observed ($k_H/k_D = 1.0 \pm 0.07$).¹⁷ Therefore, the transition state of the iron porphyrin-catalyzed reaction is later and more product-like than that of the rhodium-mediated reaction (see Discussion below).

Discussion

We have demonstrated that iron porphyrins can efficiently catalyze the cyclopropanation of alkenes. Exceedingly high turnover numbers have been observed and synthetically useful ratios of *trans* to *cis* cyclopropyl ester products were obtained. The *trans* to *cis* product ratios are comparable to the highest ratios observed for styrene, and those observed for α -methylstyrene and ethyl vinyl ether are the highest such ratios reported to date. The reaction also exhibits novel substrate preferences that depend on both the shape and electronic nature of the alkene. A variety of iron porphyrins, many of which are commercially available, have been shown to be effective catalysts.

Preformed iron(II) porphyrins are highly active catalysts, but are less convenient for use in most laboratories since they are extremely air-sensitive. Stable, easily handled iron(III) porphyrins can be employed as precatalysts if reduced in situ to generate the catalytically

active iron(II) species. EDA, the carbene source, can itself act as the reductant. For common porphyrins, this requires that the solution be heated to 40 °C-80 °C, which reduces the level of *trans* selectivity. This can be avoided by the addition of cobaltocene, which smoothly effects reduction of the precatalysts even at room temperature. Alternatively, Fe(PFP)Cl may be employed in the absence of cobaltocene at room temperature. Presumably, the electron-withdrawing pentafluorophenyl groups render the iron porphyrin more easily reduced by EDA. Very high turnover numbers and useful diastereoselectivities are observed using Fe(PFP)Cl as the precatalyst. Furthermore, this complex is commercially available, making the Fe(PFP)Cl-based system perhaps the most convenient for synthetic purposes.

We presume that the active intermediate in the iron porphyrin-catalyzed reactions is an iron-carbene species formed by reaction of the iron(II) porphyrin with EDA. This is by analogy to earlier work in which we demonstrated that isolated, isoelectronic Os(II) porphyrin carbene complexes are catalytically active.¹⁴ In addition, we have presented evidence that rhodium porphyrin-catalyzed reactions proceed via an isoelectronic, cationic Rh(III) carbene complex, although this species has eluded direct detection.¹² Although Fe(II) carbene complexes have been reported previously,¹⁶ one have been reported to be catalytically active for cyclopropanation. However, all of these isolated iron porphyrin carbene complexes were disubstituted, many with heteroatoms attached directly to the carbene carbon, and thus do not closely resemble the iron carbene complex relevant to our system.

The results presented here, combined with those obtained previously using osmium and rhodium porphyrin catalysts, illustrate the strong metal-dependence of the diastereoselectivity and substrate preferences exhibited in porphyrin-mediated

cyclopropanation reactions. The neutral osmium(II) and iron(II) catalysts provide the *trans* cyclopropyl ester as the major product and the influence of the groups appended to the porphyrin macrocycle is quite modest. Aryl or heteroatom-substituted alkenes are cyclopropanated much more efficiently than aliphatic alkenes, and only monosubstituted and 1,1-disubstituted alkenes are good substrates. The rhodium porphyrin-catalyzed reaction has strikingly different properties. Almost equal amounts of the *cis* and *trans* products are obtained with sterically unencumbered porphyrin ligands, but when bowl-shaped ligands such as TMP are employed, synthetically useful excesses of the *cis* product are produced. Furthermore, these reactions exhibit a very broad substrate compatibility. The electronic nature of the alkene substituent has little or no effect and only bulky-tetrasubstituted alkenes are cyclopropanated inefficiently. The only exception is when the alkene substituents are very large. In these cases, monosubstituted alkenes are the preferred substrates.

These very significant differences are somewhat surprising in light of the fact that the putative osmium, iron, and rhodium carbene intermediates are isoelectronic. We propose here a model to reconcile these facts. The central tenet of this model is that transfer of the carbene ligand from the metal to the alkene proceeds along a similar reaction coordinate in each case, but that the transition state is very early in the rhodium-catalyzed reaction, but relatively late in the iron and osmium-mediated reactions.

We have previously proposed the scheme for carbene transfer from rhodium porphyrins to an alkene shown in Figure 3.¹⁷ The substrate is envisioned to approach the metallocarbene in a roughly perpendicular orientation relative to the metal-carbon axis and then to rotate either clockwise (Figure 3, top pathway) or counterclockwise (Figure 3, bottom

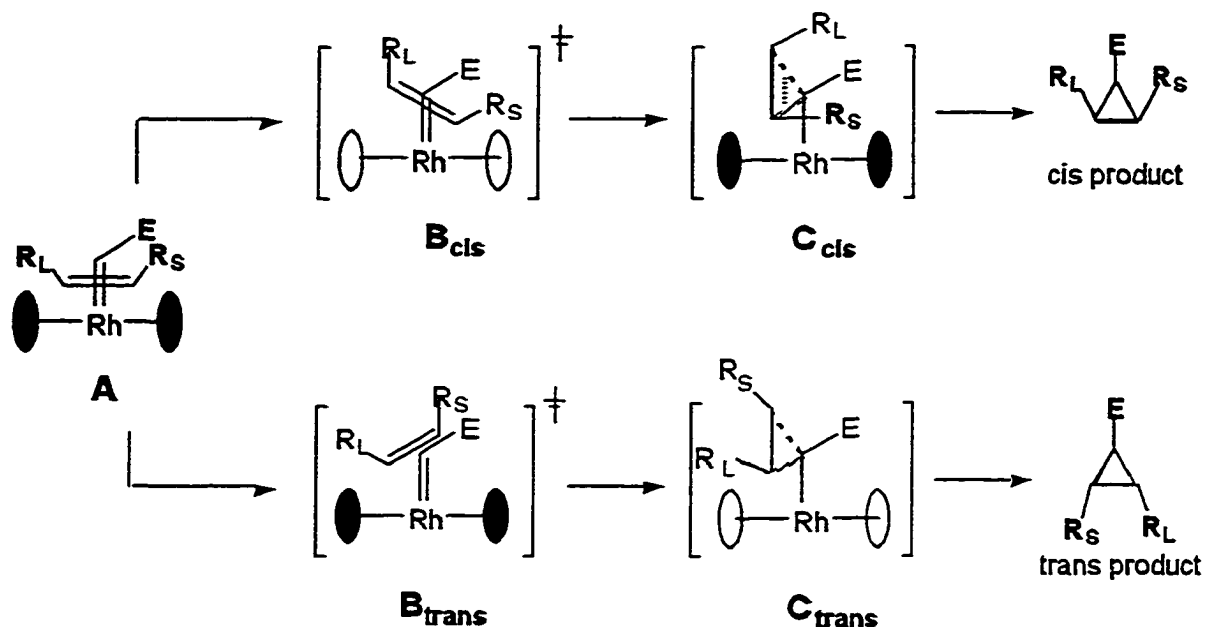


Figure 3. Proposed mechanism for the rhodium porphyrin-catalyzed cyclopropanation of alkenes. The porphyrin macrocycle is represented by the horizontal line, and meso-aryl substituents are represented by stipled ovals. R_L = larger olefin substituent, R_S = smaller olefin substituent. An early transition state (structures B) is proposed. For steric reasons, B_{cis} is proposed to be preferred over B_{trans} when porphyrins with bulky meso substituents are employed.

pathway), eventually reaching the arrangement of atoms found in the product. These pathways would eventually lead to the *cis* and *trans*-cyclopropyl esters, respectively. We assume that the largest alkene substituent would approach so as to avoid the ester group. Since the Rh(III)-carbene complex is exceedingly electrophilic and because the reaction does not display a detectable secondary isotope effect, the transition state for carbene transfer (B_{cis} and B_{trans} in Figure 3) is likely to be very early. This is consistent with the absence of a secondary isotope effect and also rationalizes the observed substrate selectivity. Only in cases of extremely bulky substituents or tetrasubstituted alkenes do the substrates suffer severe

steric interactions with the catalyst. Furthermore, if there is no significant polarization of the olefinic carbons, then substituent effects should be very modest, which is the case. Finally, as the porphyrin becomes more bowl-shaped, the transition state leading to the *trans* product will be increasingly destabilized relative to that leading to the *cis* product, since R_L , the larger substituent, must rotate towards the peripheral porphyrin substituent (stipled oval). Many other observations are also consistent with this model.

In contrast, we propose that in the iron and osmium systems, the transition state for carbene transfer is reached later and resembles species C in Figure 4. This seems reasonable based on the fact that the iron(II) and osmium(II) carbenes should be less electrophilic than the Rh(III) species. Indeed, Os(II) carbenes are isolable at room temperature, while Rh(III) carbenes are highly reactive even at low temperatures. The later transition state postulated in Figure 4 implies that the alkene carbons should have significant carbocationic (or radicaloid) character and should no longer be completely sp^2 -hybridized, though it is far from a full-blown carbonium ion. This is consistent with the observation of a modest negative ρ value in the Hammett plot and the small inverse secondary deuterium isotope effect. It also rationalizes why aromatic alkenes and enol ethers are superior substrates. In addition, the orientation of the alkene with respect to the porphyrin plane would strongly select against the presence of substituents on the carbon closest to the macrocycle, thus explaining the pronounced shape selectivity observed. Finally, since the alkene substituents R_L and R_S project up and out of the porphyrin pocket one would not predict that the groups appended to the porphyrin would have a large effect on the stereochemical outcome of the reaction. Rather, this would be

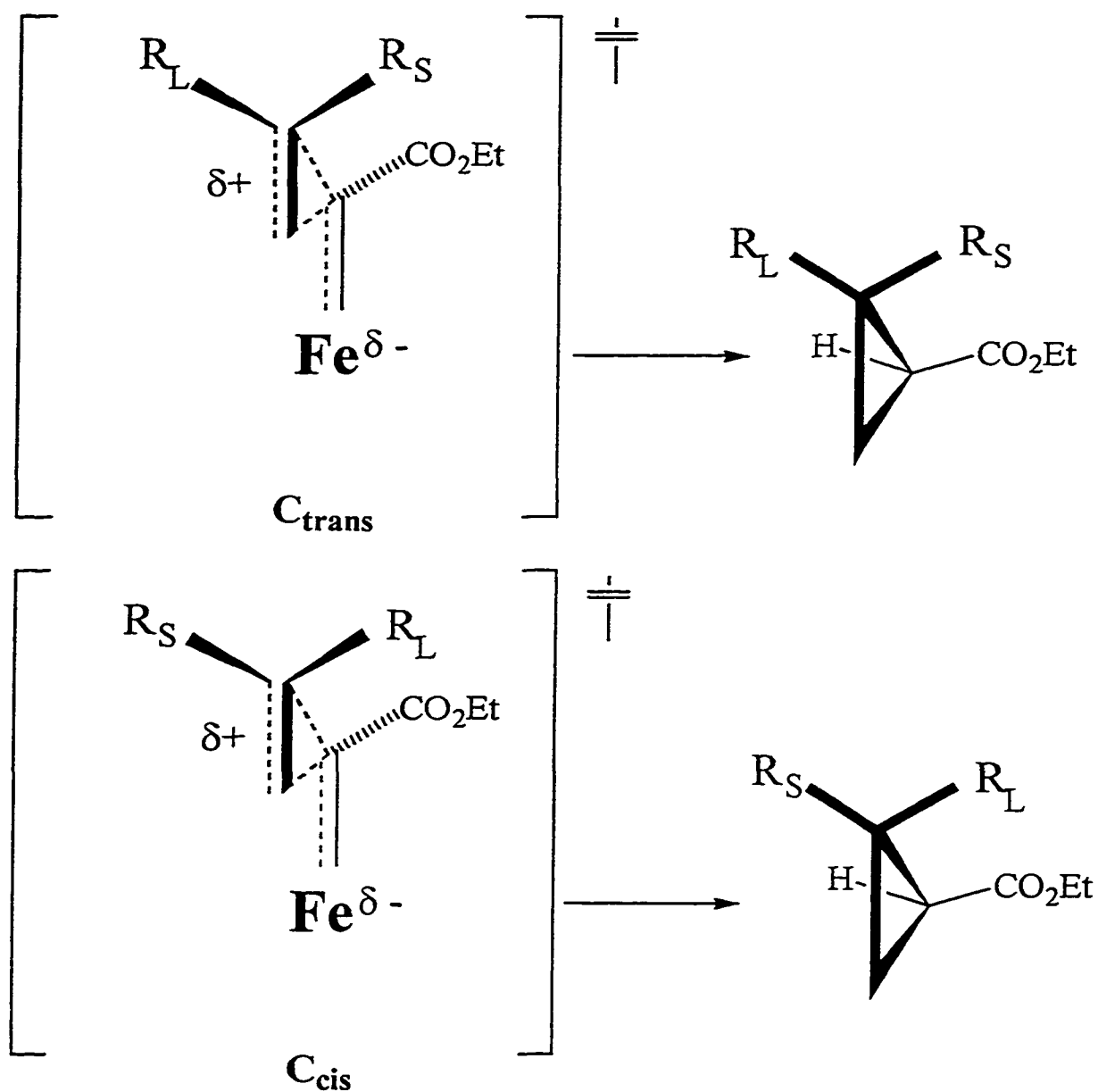


Figure 4. Proposed transition state for iron porphyrin-catalyzed cyclopropanation reactions. The porphyrin meso substituents were omitted for clarity. R_L = larger olefin substituent, R_S = smaller olefin substituent. A later transition state than in the rhodium porphyrin-catalyzed reaction is proposed in which the olefin is parallel to the metallocarbene and significant bond forming has occurred (structures **C** which are analogous to the corresponding structures **C** in Fig. 3). This geometry rationalizes why 1,2-disubstituted alkenes are poor substrates, since one of the alkene substituents would suffer severe steric interactions with the porphyrin macrocycle. C_{trans} is proposed to be preferred over structure C_{cis} since this minimizes steric interactions between the carbene ester and the larger alkene substituent.

dominated by the interaction between R_L and the ester, leading to the *trans* product. This is in agreement with the observation that many different porphyrins provide similar *trans/cis* product ratios for a given alkene, and that the modest differences observed do not correlate with the steric bulk of the porphyrin substituents (Table I). Another appealing aspect of the model is that it rationalizes why donor solvents slightly increase the *trans* to *cis* product ratio. If the *trans* preference is the result of a late transition state, which in turn is due to the relatively modest electrophilicity of the metallocarbene, then an axially ligated donor solvent should make the carbene even less electrophilic. This model will be employed as the basis for the rational design of enantioselective porphyrin cyclopropanation catalysts.

Acknowledgments

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Experimental

General procedures. Dichloromethane and acetonitrile were distilled from calcium hydride suspension before use. THF, diethyl ether, benzene, and toluene were distilled from sodium benzophenone ketyl. Olefins, decane, and tridecane were purchased from Aldrich and were passed through a plug of alumina and degassed with argon before use. Ethyl diazoacetate, Fe(PFP)Cl, Fe(TPP)Cl, and Fe(TPP-*p*-MeO)Cl were purchased from Aldrich and used as received. Tetramesitylporphyrin was prepared according to the method of

Lindsey.¹⁷ Fe(TMP)Cl was prepared by reaction of TMP with excess FeCl₂ in refluxing DMF for 12 h, followed by precipitation into 1 M HCl according to the procedure of Kobayashi.¹⁹

All reactions with Fe(TTP) were carried out under a nitrogen atmosphere using a Vacuum/Atmospheres glove box equipped with a model MO40DH DriTrain gas purification system. Solvents and reagents used in the Fe(TTP) reactions were degassed by three freeze-pump-thaw cycles. Fe(TTP) was synthesized using the procedure of Reed by reduction of either Fe(TTP)Cl or [Fe(TTP)]₂(μ-O) with Zn/Hg amalgam in THF for 12 hours.²⁰ The UV/vis spectrum for Fe(TTP) was analogous to that of other iron(II) porphyrins.²¹

The stereochemistry of the cyclopropyl ester products was assigned by ¹H NMR spectroscopy by comparison with published data.^{13,22} Once the major isomer was assigned by ¹H NMR, product ratios were determined by G.C.

Cyclopropanation reactions using Fe(TTP). In a typical experiment, 2.9 mg (4.0 μmol) of Fe(TTP), 8.7 mmol of olefin, and 22.5 μL (16.8 mg) of dodecane (internal GC standard) were placed into a roundbottom flask and dissolved in 3 ml of solvent. A solution of ethyl diazoacetate (90 μL, 860 μmol) in 12 ml of solvent was added dropwise over approximately 1 hour to the solution of catalyst and olefin with vigorous stirring. After the addition was finished, an aliquot of the reaction mixture was taken and diluted four-fold with fresh solvent. The solution was analyzed by gas chromatography to determine the yield of the reaction. To achieve maximum turnover numbers, aliquots of EDA were added to the porphyrin and substrate-containing solution (10 ml of toluene with dodecane as an internal standard) until no further reaction was observed.

Cyclopropanation reactions using Fe(III) porphyrins reduced in situ. In a typical reaction, the iron(III) porphyrin complex (1.8 μmol) and cobaltocene (2 mmol) were placed in a round bottom flask which was then evacuated and back-filled with argon. Dichloromethane (5 mL) was then added, followed by degassed olefin (9.4 mmol) and decane (0.200 mL, 1.0 mmol) or (0.200 mL, 820 μmol) tridecane as an internal GC standard. The flask was placed in a room temperature water bath. An oil bubbler line was attached to the flask and the argon line removed. The first aliquot of EDA (0.10 mL, 950 μmol) was added to initiate the reaction. In the cases of high catalyst activity, vigorous bubbling was observed within 2 minutes, additional aliquots of EDA was added at approximately 15 minute intervals until bubbling ceased. In the cases where no reaction was observed immediately, the water bath was replaced with a heating mantle and the reactions were heated to reflux temperature (no additional EDA was added). In all cases cyclopropane formation was monitored by GC.

Competition studies using Fe(PFP)Cl. These experiments were performed in a manner analogous to those described above, using equimolar amounts of each olefin (ca. 9.4 mmol each) and 0.035% Fe(PFP)Cl (based on total olefin) in a room temperature water bath. The product ratios listed in Table 3 were determined at early time points in the reaction (15 minutes, 0.2 equiv EDA added based on total olefin).

Competition studies using Fe(TTP). In a typical experiment Fe(TTP) (2.0 mg, 2.8 μmol), 7.6 mmol of each olefin and dodecane (0.0225 mL, 9.86 mmol) were placed in a roundbottom flask and dissolved in 15 mL toluene. EDA (0.040 mL, 380 μmol) was added with vigorous stirring. GC analysis was then performed to determine yields.

Determination of the secondary kinetic isotope effect k_H/k_D . Equimolar amounts of styrene and styrene- d_8 (0.050 mL, 440 μ mol each) and Fe(PFP)Cl (2.0 mg, 1.8 μ mol) were dissolved in dichloromethane (3 mL) in a round bottom flask. The solution was deoxygenated by three freeze-pump-thaw cycles, and was backfilled with argon. The flask was placed in a room temperature water bath. An oil bubbler line was attached to the flask and the argon line removed. EDA (0.035 mL, 280 μ mol) was added over a period of 20 min, after which time the solution was allowed to stir for an additional 0.5 h. The reaction mixture was analyzed by GC-MS (Finnegan 4500 ITD) in selected ion monitoring mode (detecting masses 190 and 198), and the peak areas were integrated and corrected for the k_H/k_D of ionization. The observed secondary kinetic isotope effect was 0.87 ± 0.07 and represents the average of at least 5 GC-MS runs each of 3 reactions.

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CHAPTER 3. CATALYTIC CYCLOPROPANATION WITH IRON(II) COMPLEXES:
ENHANCED CONTROL OF CYCLOPROPANE STEREOSELECTIVITY

A paper to be submitted to *Organometallics*

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Abstract

Iron(II) complexes of *meso*-tetra-*p*-tolylporphyrin (TTP), tetramethyldibenzotetraaza-[14]annulene, and *trans*-1,2-bis(salicylidene)cyclohexanediamine catalyzed the cyclopropanation of styrene with aryl diazomethanes. When *p*-tolyl diazomethane was used as the carbene source, *trans*-cyclopropanes were the major products. *Trans/cis* ratios up to 17:1 were obtained. However, using mesityl diazomethane resulted in a reversal of stereoselectivity, giving *cis*-cyclopropanes as the major product (*cis/trans* ratios of up to 10:1). The stereoselectivity of iron(II) porphyrin-catalyzed cyclopropanation reactions was enhanced by performing the reactions at low temperature or by using bulky porphyrin ligands. Using trimethylsilyl diazomethane as the carbene source, trimethylsilylcyclopropanes were produced in excellent yields with (TTP)Fe. Carbene complexes of (TTP)Fe were observed spectroscopically. These complexes transferred their carbene ligand to styrene to produce cyclopropanes stoichiometrically.

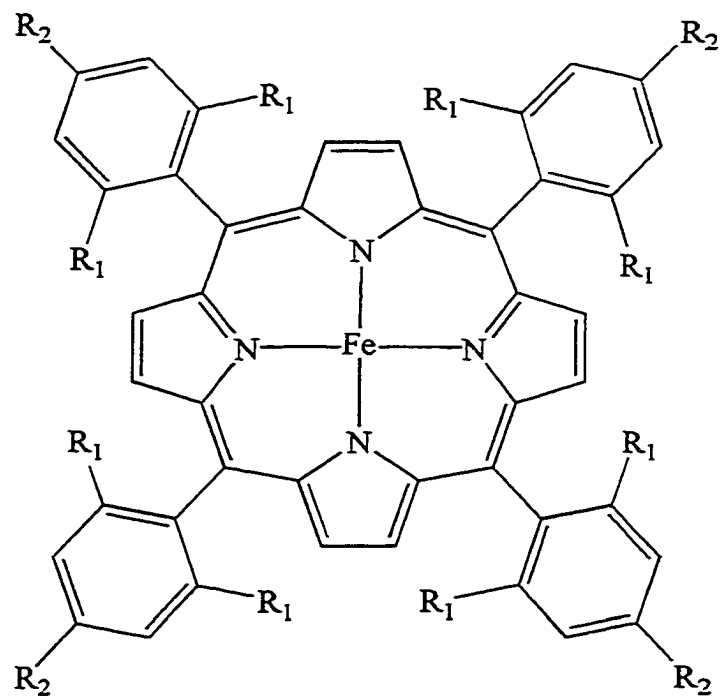
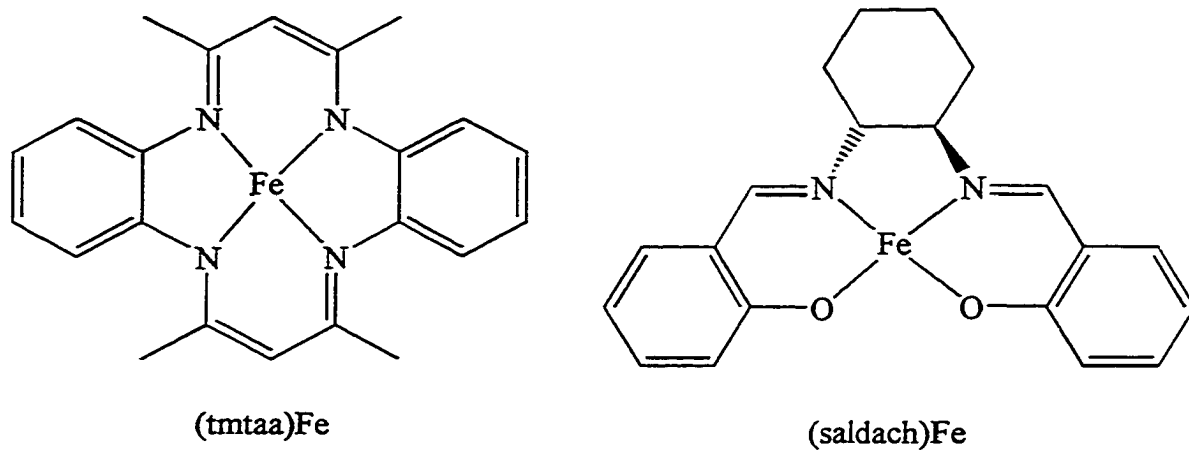
Introduction

Transition metal mediated cyclopropanation has received much attention recently.¹ The majority of catalytic studies employ diazocarbonyl compounds as the carbene source. Despite numerous reports of *stoichiometric* cyclopropanation with transition metal benzyldiene complexes,² few reports exist on transition metal catalyzed cyclopropanation using aryldiazomethanes.^{3,4} Moreover, production of arylcyclopropanes from mixtures of aryldiazomethanes and olefins is typically achieved by treatment with zinc halides⁵ or by photolysis.⁶

Arylcyclopropanes are reactive molecules and valuable synthetic intermediates. For example, they have been used as starting materials in the synthesis of 1,3-dihalo-1,3-diarylpropanes,⁷ 1,3-dimethoxy-1,3-diarylpropanes,⁸ 3,5-diaryl-1,2-dioxolanes,⁹ 3,5-diaryl-2-isoxazolines,¹⁰ and cyclopropanecarboxylic acids.¹¹ In addition, arylcyclopropanes also possess useful photochemical properties.¹² Thus the catalytic production of arylcyclopropanes is an important synthetic goal.

Although silylcyclopropanes are also versatile synthetic intermediates,¹³ very few reports exist on cyclopropanation reactions employing trimethylsilyldiazomethane as the carbene source.^{14,3c} Trimethylsilyldiazomethane is one of the most robust diazo compounds¹⁵ and is available commercially,¹⁶ making it an attractive reagent.

We recently reported that iron(II) porphyrin complexes are efficient catalysts for the formation of cyclopropyl esters.¹⁷ Other related complexes containing the readily derivatized salen¹⁸ and tmtaa ligand systems seemed like a logical extension to our cyclopropanation studies (Figure 1). Jacobsen and others have used (salen)Mn(III) complexes extensively as



$R_1 = \text{H}, R_2 = \text{Me}; (\text{TTP})\text{Fe}$
 $R_1 = R_2 = \text{Me}; (\text{TMP})\text{Fe}$
 $R_1 = \text{OMe}, R_2 = \text{H}; (\text{TDMPP})\text{Fe}$

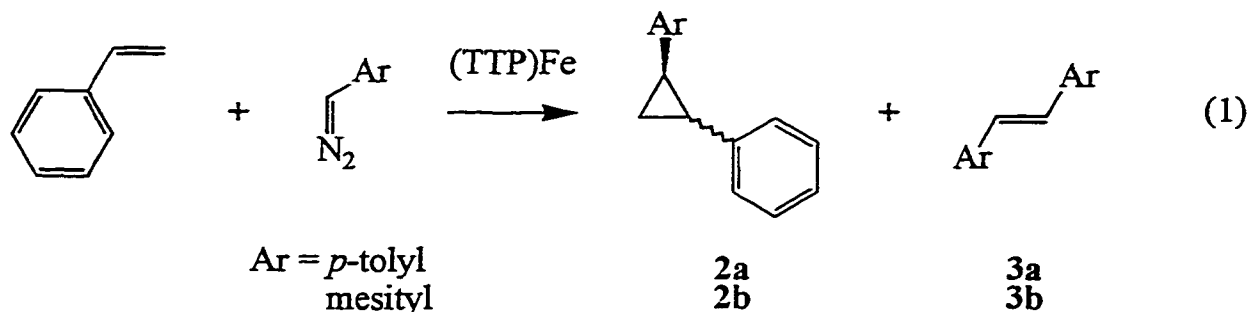
Figure 1. Iron complexes used in this study.¹⁸

epoxidation catalysts.¹⁹ Moreover, chiral salen ligands have been used in highly enantioselective Mn(III)-catalyzed epoxidation¹⁹ and in Co(III)-catalyzed cyclopropanation reactions.²⁰ While no reports exist, to our knowledge, on reactions between (salen)Fe(II) complexes and diazo reagents, Floriani and co-workers recently reported the isolation of (tmtaa)Fe=CPh₂ by treatment of (tmtaa)Fe(II) with diphenyldiazomethane.²¹ Floriani also demonstrated that (tmtaa)Fe reacts with phenyldiazomethane to yield a carbene complex which is only observable at low temperature. At room temperature, the benzyldiene complex decomposed to give (tmtaa)Fe and a mixture of *cis*- and *trans*-stilbene.

Results

Catalytic production of arylcyclopropanes using (TTP)Fe. Since iron(II) porphyrins are efficient catalysts for the production of cyclopropyl esters from ethyl diazoacetate and olefins,¹⁷ an investigation of the catalytic production of diarylcyclopropanes using (TTP)Fe was undertaken. Indeed, (TTP)Fe, **1**, was an excellent catalyst for the cyclopropanation of olefins with aryldiazomethanes. Dropwise addition of a hexanes solution of *p*-tolylidiazomethane to a THF solution containing styrene (14 equiv) and (TTP)Fe (< 1 mole %) produced 1-(4-methylphenyl)-2-phenylcyclopropane, **2a**, in 79% yield (*trans/cis* = 14 ± 1) as shown in equation 1. A side product, 4,4'-dimethylstilbene, **3a**, was obtained in 21% yield (Table I). When the *p*-tolylidiazomethane was added as a solution in diethyl ether, the *trans/cis* ratio for cyclopropane **2a** increased slightly to 17:1. This increase in *trans/cis* ratio is consistent with previous observations.¹⁷

Interestingly, when mesityldiazomethane was used as the carbene source, the *cis*



cyclopropane isomer became the major product (*cis/trans* = 7.7 ± 0.9). The yield of 1-mesityl-2-phenylcyclopropane, **2b**, was 51% and the yield of 2,2',4,4',6,6'-hexamethylstilbene, **3b**, was 49% using a 20 minute slow addition of a 48 mM hexanes solution of mesityldiazomethane (Table II). Increasing the addition time of the diazo solution from 20 to 30 minutes increased the cyclopropane/olefin ratio to 60:40 and increased the *cis/trans* ratio of cyclopropane **2b** to 10.1 ± 0.2. Additionally, *trans*- β -methylstyrene was converted to 1-mesityl-2-methyl-3-phenylcyclopropane, **2c**, in the presence of (TTP)Fe and mesityldiazomethane. Compound **2c** was obtained in ca. 35% yield (unoptimized) and was detected by GC/MS ($m/z = 250 [M]^+$). Using other diazo reagents such as ethyl diazoacetate (EDA) and trimethylsilyldiazomethane, *trans*- β -methylstyrene was not converted to the corresponding cyclopropane when (TTP)Fe was used as the catalyst.

Table I: Synthesis of 1-*p*-tolyl-2-phenylcyclopropane from styrene and N₂CH(*p*-tolyl).

Entry	Catalyst	Addition Time	Olefin % Yield ^a	Cyclopropane	
				% Yield ^a	<i>trans/cis</i> ^a
1	(saldach)Fe(II) ^b	50 min	33(4) ^c	18(4)	4.0(4)
2	(tmtaa)Fe(II) ^b	2 h	84(7)	16(7)	1.9(4)
3	(TTP)Fe(II) ^d	25 min	21(5)	79(4)	14(1)

^aDetermined by GC analysis. ^b1.5 - 1.7 mol % catalyst. ^cValues in parentheses are standard deviations based on at least three catalytic runs. ^d0.8 - 0.9 mol % catalyst.

Table II: Synthesis of 1-mesityl-2-phenylcyclopropane from styrene and N₂CH(mesityl).

Entry	Catalyst	Addition Time	Olefin % Yield ^a	Cyclopropane	
				% Yield ^a	<i>cis/trans</i> ^a
1	(tmtaa)Fe(II) ^b	1.5 hr	57(4) ^c	43(4)	5.3(9)
2	(TTP)Fe(II) ^d	20 min	49(4)	51(4)	7.7(9)
3	(TTP)Fe(II) ^d	30 min	40(3)	60(3)	10.1(2)

^aDetermined by GC analysis. ^b1.6 – 2.0 mol % catalyst. ^cValues in parentheses are standard deviations based on at least three catalytic runs. ^d0.6 – 0.9 mol % catalyst.

Catalytic cyclopropanation with (tmtaa)Fe. The scope of cyclopropanation with catalytic amounts of (tmtaa)Fe, **4**, was also examined. Results using EDA as the carbene source were poor. Generally, less than 20% of EDA was converted to products in the presence of complex **4** and an excess of styrene. However, complex **4** was an efficient catalyst for the decomposition of aryldiazomethanes. Dropwise addition of a 39 mM pentane/THF solution of *p*-tolylidiazomethane over 2 hours to a solution containing 14 equivalents of styrene and (tmtaa)Fe (1.5 mole %) in THF produced cyclopropane **2a** in 16% yield. The remaining *p*-tolylidiazomethane was converted to olefin **3a** (84% yield). However, the *trans/cis* ratio for cyclopropane **2a** was 4.0 ± 0.4 , significantly lower than the 14:1 ratio obtained using (TTP)Fe as the catalyst. When mesityldiazomethane was used as the diazoalkane, the yield of cyclopropane **2b** was 46% and the yield of olefin **3b** was 54% using a 1.5 hour slow addition of diazo reagent. As with (TTP)Fe, the major isomer was *cis*-**2b** (*cis/trans* = 5.3 ± 0.9).

Catalytic cyclopropanation using (saldach)Fe. An iron(II) salen complex, (saldach)Fe, **5**, was also investigated as a cyclopropanation catalyst. Cyclopropanation of

styrene using EDA and catalytic amounts of **5** gave less than 30% yield of diethyl maleate, diethyl fumarate, and ethyl-2-phenylcyclopropane carboxylate, **6**, combined. Unlike (tmtaa)Fe, changing the diazo reagent to *p*-tolyl diazomethane did not improve product yields. Only about 50% of the *p*-tolyl diazomethane was converted to cyclopropane **2a** and olefin **3a** in the presence of excess styrene.

Temperature effects in the cyclopropanation of styrene with EDA catalyzed by (TTP)Fe. In our studies of catalytic cyclopropanation reactions, it was possible to vary slightly the stereoselectivity by changing the solvent. Additionally, the reaction temperature had a dramatic effect on the *trans/cis* ratio. When a solution of (TTP)Fe and excess styrene in dichloromethane was treated with EDA at -78°C , cyclopropane **6** was obtained in $92 \pm 7\%$ with a *trans/cis* ratio of 29 ± 2 . This is significantly greater than the 8.8:1 ratio for the same reaction in dichloromethane at 25°C .¹⁷

Effect of porphyrin structure in iron(II) porphyrin-catalyzed cyclopropanation. The structure of the porphyrin also had an effect on the diastereoselectivity of iron(II) porphyrin-catalyzed cyclopropanation reactions. At ambient temperature in toluene, the cyclopropanation of styrene with EDA produced primarily *trans*-**6**. When the porphyrin was TTP, the *trans/cis* ratio was 8.0:1. However, using the bulky TDMPP ligand, the *trans/cis* ratio was 15:1 (Table III).

Catalytic synthesis of 1-phenyl-2-trimethylsilylcyclopropane, **7.** Since trimethylsilyl diazomethane is commercially available, its use as a carbene source in catalytic cyclopropanation reactions was also investigated. Using 0.6 mole % of (TTP)Fe and approximately a 10-fold excess of styrene, 1-phenyl-2-trimethylsilylcyclopropane, **7**, was

Table III: Effect of porphyrin structure in the cyclopropanation of styrene with EDA.

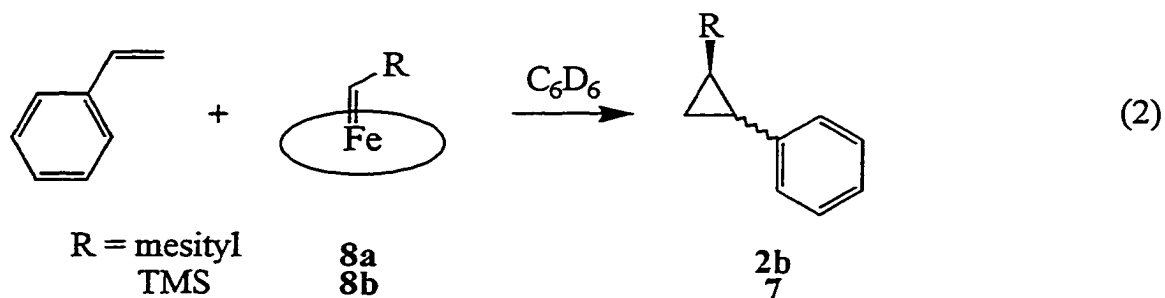
Entry	catalyst	solvent	<i>trans/cis</i>	reference
1	(TTP)Fe	toluene	8.0:1	17
2	(TTP)Fe	THF	13:1	17
3	(TMP)Fe	toluene	13:1	a
4	(TDMPP)Fe	toluene	15:1	a
5	(TDMPP)Fe	THF	21:1	a

^aThis work.

obtained in $89 \pm 4\%$ yield with trimethylsilyl diazomethane as the carbene source. Unlike previously reported cyclopropanations using trimethylsilyl diazomethane, no evidence for formation of 1,2-bis(trimethylsilyl)ethene byproducts from carbene coupling was observed. The *trans/cis* ratio for cyclopropane **7** was 10 ± 1 when the reaction was performed in toluene and 13 ± 1 when the reaction was performed in THF. Neither (tmtaa)Fe or (saldach)Fe produced any detectable quantities of cyclopropane **7** under similar conditions.

Spectroscopic identification of carbene complexes of (TTP)Fe. Treatment of a solution of (TTP)Fe with a solution of N_2CHR (R = mesityl, trimethylsilyl) led to the formation of carbene complexes (TTP)Fe=CHR (R = mesityl, **8a**; R = trimethylsilyl, **8b**). Samples of the carbene complexes were usually contaminated with ca. 5% of unreacted (TTP)Fe as evidenced by 1H NMR. Unlike (TTP)Fe, the iron carbene complexes are diamagnetic and have NMR spectra that are similar to the known osmium(II) complexes, (TTP)Os=CHR.²² The α -protons of the carbene ligands show large downfield shifts ($\delta = 19.71$ ppm for **8a** and $\delta = 24.86$ ppm for **8b** in C_6D_6) while the protons on the R groups show large upfield shifts, consistent with their position above the porphyrin ligand. Complexes **8a**

and **8b** slowly decomposed during recrystallization, preventing isolation of pure samples. However, both complexes generated cyclopropanes from a *stoichiometric* reaction in the presence of excess styrene (eq 2).



The stoichiometric reaction between (TTP)Fe=CH(mesityl) and styrene was followed by ^1H NMR spectroscopy. The reaction was monitored by following the disappearance of the β -pyrrole signal of the porphyrin and the *ortho*-methyl signal of the mesityl group. In the presence of excess styrene, the reaction followed pseudo-first order kinetics. The half-life was approximately 41 minutes in the presence of 12 equivalents of styrene and approximately 17 minutes in the presence of 18 equivalents of styrene.

Discussion

Ligand effects in iron(II) catalyzed cyclopropanation. Given the success of iron(II) porphyrins as cyclopropanation catalysts, iron(II) complexes of the related *saldach* and *tmtaa* ligand systems were investigated. Both (TTP)Fe and (tmtaa)Fe were efficient catalysts for the catalytic cyclopropanation of olefins with aryldiazomethanes. The cyclopropane stereoselectivities derived from (TTP)Fe were greater than those obtained using (tmtaa)Fe, **4**. Steric factors may influence these observed stereoselectivities. The iron atom in

complex **4** lies 0.114 Å above the N₄ plane of the tmtaa ligand²³ while the iron atom in (TTP)Fe is situated within the N₄ plane of the porphyrin ligand.²⁴ In fact, in the structurally characterized complex (tmtaa)Fe=CPh₂, the iron atom lies 0.355(1) Å above the N₄ plane towards the carbene ligand.²¹ As a result, the carbene ligand encounters little steric encumbrance from the benzo rings of the tmtaa ligand. Presumably, the carbene carbon in (tmtaa)Fe=CHR is more accessible compared to the carbene carbon of (TTP)Fe=CHR. Thus, the less crowded environment at the active site in (tmtaa)Fe=CHR leads to lower stereoselectivities compared to that of (TTP)Fe=CHR. Further evidence for the steric influence of the macrocyclic ligand on diastereoselectivities was derived from studies in which the size of the *o*-substituents of the tetraarylporphyrin was varied. This served to modify the size of the pocket around the active site. As the *ortho*-group increased in steric bulk [R = H (TTP), Me (TMP), and OMe (TDMPP)], the *trans/cis* ratio for cyclopropane **6** increased sequentially from 8.0:1, to 13:1, and to 15:1 respectively (Table III).

The complex (saldach)Fe was not an efficient catalyst for cyclopropanation. This may be due to activation of the imine bonds of the salen ligand²⁵ and complications arising from side reactions involving these functional groups.

Effect of diazo reagent structure on cyclopropane stereoselectivity. Catalytic production of *cis*-substituted cyclopropanes is rare. Rhodium(III) porphyrins give slight excesses of *cis*-substituted cyclopropanes using diazo esters as the carbene source.²⁶ Doyle and co-workers showed that catalysis using rhodium(II) acetate gave primarily *cis*-substituted cyclopropanes when phenyldiazomethane was used as the carbene source (*cis/trans* = 3.3 for 1,2-diphenylcyclopropane), but the yields are often low (38% for 1,2-diphenylcyclopropane).^{3b}

Additionally, Seitz and Hossain reported that 10 mole % of the iron complex $[(\eta^5\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2(\text{THF})][\text{BF}_4]$ catalyzed the production of *cis*-substituted cyclopropanes (*cis/trans* \geq 24:1) using phenyl diazomethane as the carbene source.^{3c}

Using either ca. 0.8 mole % (TTP)Fe, **1**, or ca. 1.8 mole % (tmtaa)Fe, **4**, and *p*-tolylidiazomethane, primarily *trans*-cyclopropanes were obtained with styrene (*trans/cis* = 14:1 for **1** and 4.0:1 for **4**). However, by changing the diazo reagent to mesityldiazomethane, *cis*-cyclopropanes became the major product. A mechanistic analysis rationalizes this phenomenon. As proposed previously for (TTP)Fe,¹⁷ the preferred olefin approach for cyclopropanation arises from a parallel, side-on orientation of the C=C-C alkene plane relative to the Fe=CHC_α plane (Figure 2). However, when the substituent on the carbene ligand is 2,4,6-mesityl, this side-on approach is impeded by the methyls in the 2,6-positions of the mesityl group (Figure 3). Consequently, the only available product-forming olefin approach with the mesitylmethylidene intermediate is from above the iron mesitylmethylidene complex. This change in olefin approach with the mesityldiazomethane system is supported by the observation that *trans*-β-methylstyrene was converted to cyclopropane **2c** using mesityldiazomethane as the carbene source and (TTP)Fe as the catalyst. In comparison, *trans*-β-methylstyrene was not cyclopropanated when EDA, *p*-tolylidiazomethane, or trimethylsilyldiazomethane were used as the carbene source. The side-on approach shown in Figure 2 is not available to 1,2-substituted olefins due to unfavorable steric interactions with the bulky porphyrin (or tmtaa) ligand.

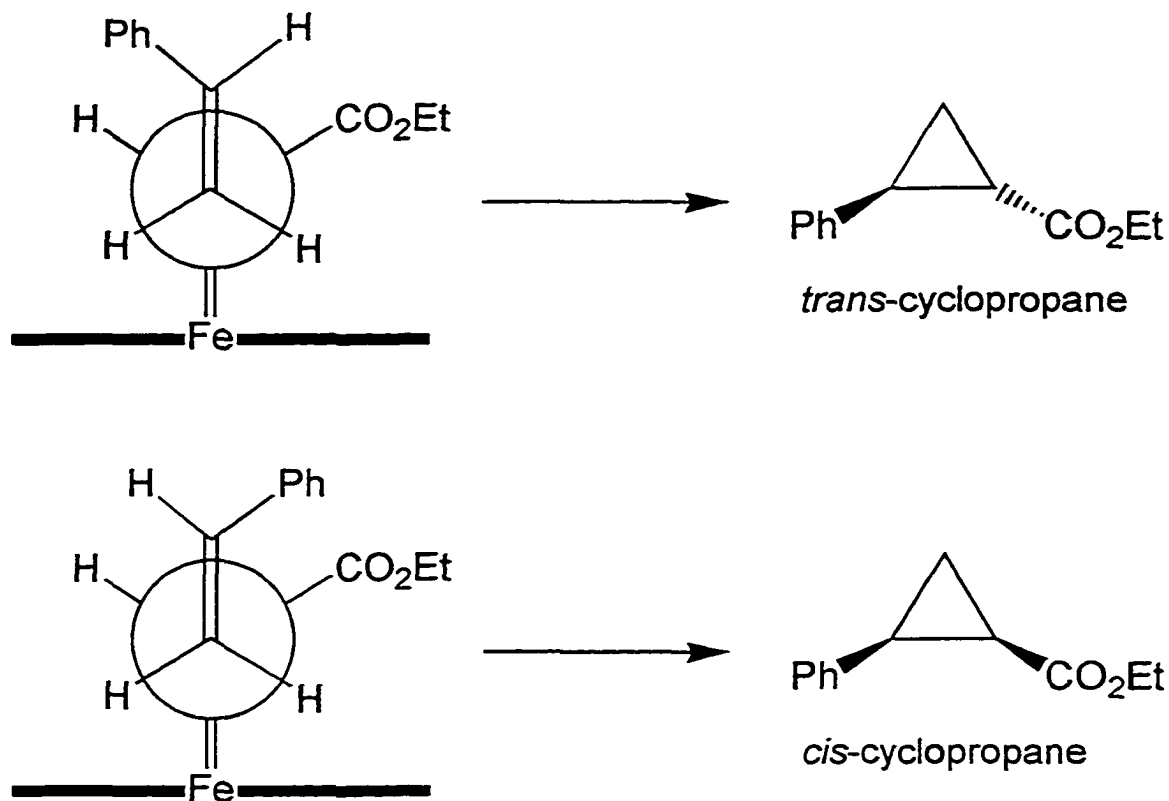


Figure 2. Olefin approach to the iron carbene intermediate when the carbene substituent is small. The *trans/cis* ratio of the product cyclopropane is determined by the approach of the styrene molecule and the late transition state along the reaction path.

Use of low temperature to improve stereoselectivity in (TTP)Fe catalyzed cyclopropanation reactions. A common method used to increase the *trans/cis* ratio for catalytic cyclopropanation of olefins with diazo esters is to increase the size of the alkyl group on the diazo ester.²⁷ However, most diazo reagents are not commercially available. Consequently, it would be synthetically useful to improve diastereoselectivities with commercially available reagents. At ambient temperature in methylene chloride solvent, catalytic amounts of (TTP)Fe produce cyclopropane from EDA and styrene with a *trans/cis*

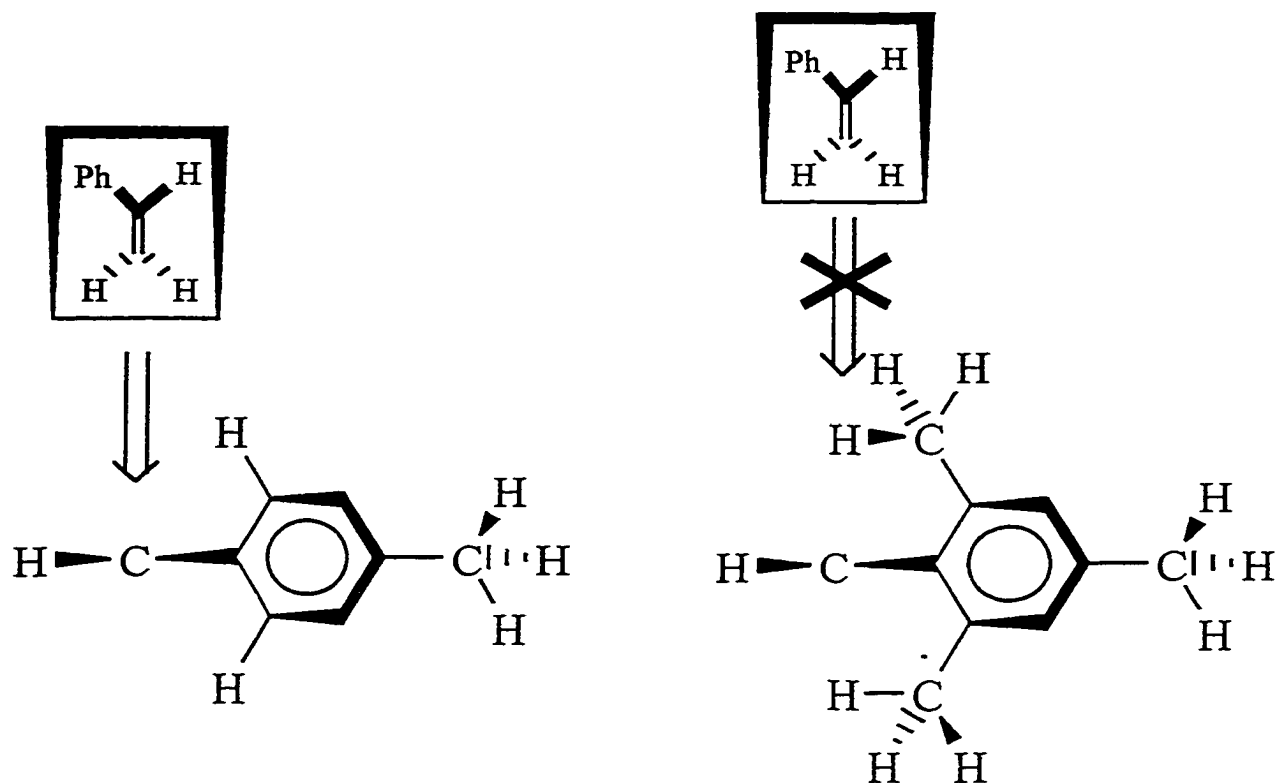


Figure 3. Olefin approach to the iron carbene intermediate when R is either *p*-tolyl (left) or mesityl (right) as viewed down the C=Fe bond (Fe atom not shown beneath the carbene carbon). The plane of the olefin is parallel to the plane defined by the Fe=CH fragment. When R is mesityl, the *ortho*-methyl groups prevent the olefin from approaching from the same direction as when R is *p*-tolyl.

ratio of 8.8:1.¹⁷ By lowering the reaction temperature to -78°C , the *trans/cis* ratio for cyclopropane **6** was dramatically increased to 29 ± 2 when methylene chloride was used as the solvent. This increase in stereoselectivity is consistent with the late transition state for (TTP)Fe-catalyzed cyclopropanation reactions proposed previously.¹⁷

Cyclopropanation using trimethylsilyldiazomethane as the carbene source. In the few documented cases of cyclopropanation using trimethylsilyldiazomethane as the carbene source, yields were generally low. A 46% yield of cyclopropane **7** with a *trans/cis* ratio of 4.8

was obtained using catalytic amounts of copper(I) chloride^{14c} and only a 2% yield of cyclopropane **7** was obtained using a ruthenium(II) carbene complex as the catalyst.^{3c} Also, significant amounts of bis(trimethylsilyl)ethene were produced. When (TTP)Fe was used as the catalyst, styrene was converted to cyclopropane **7** in 89 ± 4% yield with no bis(trimethylsilyl)ethene production. Additionally, the stereoselectivity for the reaction was excellent, providing up to a 13-fold excess of *trans*-**7**.

Conclusions

Iron(II) porphyrins are among the most efficient catalysts reported for the catalytic cyclopropanation of olefins with diazo reagents. Using iron(II) complexes of tmtaa and porphyrins, the stereochemistry of product cyclopropanes can be controlled by varying the reaction temperature, solvent, macrocyclic substituents, or diazo reagent. For example, at -78°C, *trans/cis* ratios of up to 29:1 were possible in the cyclopropanation of styrene with EDA using (TTP)Fe. The complex (TDMPP)Fe gave higher *trans/cis* ratios than (TTP)Fe. Additionally, (TTP)Fe and (tmtaa)Fe were efficient catalysts for the production of diarylcyclopropanes from aryldiazomethanes and styrene. Significantly, a reversal of stereoselectivity was observed with mesityldiazomethane. Cyclopropane *cis/trans* ratios as high as 10:1 were achieved using mesityldiazomethane. Few catalysts are capable of producing such high excesses of *cis*-cyclopropane isomers. The complex (TTP)Fe was also an excellent catalyst for the production of silylcyclopropanes using trimethylsilyldiazomethane as the carbene source. When styrene was employed as the olefin, 1-phenyl-2-trimethylsilylcyclopropane was obtained in 89% yield.

Experimental

General. All reactions were carried under dry nitrogen or argon using a Vacuum/Atmospheres glove box equipped with a MO40H DriTrain gas purification system or on a vacuum line using standard Schlenk techniques. All solvents were dried using standard methods.²⁸ Olefins were dried over activated 4Å molecular sieves and degassed prior to use. ¹H NMR spectra were recorded on Varian VXR300 or Bruker DRX400 spectrometers. ¹H NMR peak positions were referenced against residual proton resonances of deuterated solvents (δ , ppm: CDCl₃, 7.24; C₆D₆, 7.15). Gas chromatography was performed using a HP 5890 Series II²⁹ and GC/MS data was obtained from a Finnegan Magnum GC-MS.³⁰ Electrospray mass data was obtained on a Finnigan TSQ 700 in the positive ion mode. Elemental analyses (C, H, N) were performed by Iowa State University Instrument Services. Hexamethylbenzene was used as the internal standard for all GC yield determinations. Aryldiazomethanes were prepared from the corresponding tosylhydrazones according to a literature procedure,³¹ except that di(ethylene glycol) methyl ether was used rather than tri(ethylene glycol) as the solvent. The ligand H₂tmtaa was synthesized using the literature procedure.³² The ligand H₂(saldach) was synthesized by treating 2 equivalents of salicylaldehyde with *trans*-1,2-diaminocyclohexane in refluxing ethanol for 1 hour.³³ The disodium salt, Na₂(saldach) was synthesized according to the literature procedure.³² A procedure published by Reed on the reduction of either (TTP)FeCl or [(TTP)Fe]₂(μ -O) with Zn/Hg amalgam in THF for 12 hours was used to synthesize (TTP)Fe.³⁴ Modified procedures as described below were used for the preparation of (tmtaa)Fe³⁵ and (saldach)Fe.³⁶

Synthesis of (tmtaa)Fe, 4. In a round bottom flask, 271 mg (0.790 mmol) of H_2tmtaa and 474 mg (2.20 mmol) of FeBr_2 were dissolved in ca. 5 mL of 2:1 (v/v) toluene/THF. To the stirred reaction was added approximately 1 mL of triethyl amine, and the reaction mixture changed from orange to red-purple in color. After 19 hours, the solvent was removed *in vacuo* and the product dissolved in 5 mL of toluene. The mixture was filtered through a pad of Celite to remove excess FeBr_2 and triethyl ammonium bromide. Recrystallization at $-25\text{ }^\circ\text{C}$ from toluene/hexanes (1:5 v/v) afforded 213 mg (68 %) of complex 4 as a purple solid in two crops. The complex (tmtaa)Fe was paramagnetic with no observable signals in the ^1H NMR. However, sharp signals for the complex (tmtaa)Fe(py) $_2$ were observed upon addition of an excess of pyridine. ^1H (C_6D_6 , 300 MHz): 7.03 (m, 12 H, $\text{H}_{\text{Ar}} + \text{H}_{\text{py-3,5}}$); 6.56 (d, 4H, $\text{H}_{\text{py-2,6}}$); 4.27 (s, 2H, methine); 2.42 (s, 12H, H_{Me}). The pyridine H-4 triplet was not observed. These data match the literature values in which (tmtaa)Fe was synthesized from H_2tmtaa and $\text{Fe}(\text{py})_4(\text{NCS})_2$.

Synthesis of (saldach)Fe, 5. A round bottom flask was charged with $\text{Na}_2(\text{saldach})$ (440 mg, 1.20 mmol), FeBr_2 (270 mg, 1.25 mmol), and 12 mL of toluene. THF (3 mL) was added to the brown-orange slurry which immediately changed color to a bright purple. The reaction was stirred for 10 minutes and then filtered over a pad of Celite. The solvent was removed *in vacuo* and then the product was dissolved in a minimum of toluene and recrystallized from toluene/hexanes (4:1 v/v) at $-25\text{ }^\circ\text{C}$. The yield of 6 was 230 mg (51%). The complex (saldach)Fe was paramagnetic with no observable signals in the ^1H NMR spectrum. Addition of pyridine or *tert*-butylisocyanide did not yield any species observable by ^1H NMR. The UV/vis data was similar to that reported for the complex (salen)Fe which was

synthesized from either H₂salen and iron(II) sulfate or iron(II) acetate in DMF or ethanol or from H₂(salen) and Fe₃(CO)₁₂ in DMF. UV/vis (toluene): 350, 533 nm. Anal. Calcd (found) for C₂₀H₂₀FeN₂O₂: C, 63.85 (63.40); H, 5.36 (5.65); N, 7.45 (6.59). MS{ESI}: m/z = 376 [M]⁺.

Catalytic cyclopropanation reactions using aryldiazomethanes. To a round bottom flask was added 1.0 mL (8.70 mmol) styrene, a known amount (typically on the order of 30 mg) of hexamethylbenzene (internal standard for GC), the appropriate iron catalyst, and 5 mL THF. To the stirred reaction mixture was slowly added a solution of aryldiazomethane in 15 mL 2:1 (v/v) petroleum ether/THF (ca. 580 μmol for reactions using *p*-tolylidiazomethane and ca. 600 μmol for reactions using mesityldiazomethane). The reaction was analyzed by GC to determine product yields. Products were identified by coinjection with authentic samples.

Independent synthesis of 1-mesityl-2-phenylcyclopropane, 2b. An authentic sample of compound 2b was synthesized using the method of Applequist and Gdanski from mesitaldehyde and acetophenone.³⁷ The yield was 900 mg (12.2%) of a tan, viscous oil having a *trans/cis* ratio of 1.5:1. ¹H NMR (CDCl₃, 400 MHz) *cis*-isomer, 5c: 7.02 (m, 3H, C₆H₅), 6.72 (s, 2H, C₆H₂(CH₃)₂), 6.44 (m, 2H, C₆H₅), 2.66 (s, 6H, CH₃), 2.54 (s, 3H, CH₃), 2.02 (m, 1H, C₃H₄), 1.97 (m, 1H, C₃H₄), 1.40 (m, 1H, C₃H₄), 1.04 (m, 1H, C₃H₄). ¹H NMR (CDCl₃), 5c, *trans* isomer: 7.32 (t, 2H, C₆H₅, J_{HH} = 7.6 Hz), 7.20 (m, 3H, C₆H₅), 6.86 (s, 2H, C₆H₂(CH₃)₂), 2.50 (s, 3H, CH₃), 2.45 (s, 6H, CH₃), 1.84 (m, 1H, C₃H₄), 1.76 (m, 1H, C₃H₄), 1.17 (m, 1H, C₃H₄), 1.02 (m, 1H, C₃H₄). ¹³C NMR (CDCl₃, 100.8 Mhz) *trans*- and *cis*-isomers: 143.23, 141.03, 138.95, 138.62, 135.85, 135.52, 135.28, 130.78, 128.72, 128.70,

128.34, 127.29, 126.31, 125.53, 125.42, 124.93, 25.85, 24.86, 23.42, 22.90, 20.82, 20.81, 20.79, 20.67, 19.50, 17.77.³⁸ MS{EI} m/z (rel. intensity): 236 ($[M]^+$, 100), 222 (24), 133(24), 117(20), 63(70), 53(31).

Low temperature preparation of ethyl-2-phenylcyclopropanecarboxylate, 3. In the glovebox, 18 mg (25 μ mol) (TTP)Fe, 22 μ L dodecane (GC standard), and 9.13 mmol styrene were placed into a round bottom flask and dissolved in 15 mL of dichloromethane. The flask was capped with a rubber septum and removed from the glove box. The flask was cooled to -78°C with a dry ice/acetone bath and EDA (108 μ mol) was added via syringe. The reaction was stirred at -78°C for 3 hours and then allowed to warm to room temperature. The reaction was analyzed by gas chromatography. The yield of cyclopropane was $92 \pm 7\%$ with a *trans/cis* ratio of 29:1.

1-Phenyl-2-(trimethylsilyl)cyclopropane, 7. In a typical reaction, 8.5 mmol styrene, 3.5 mg (TTP)Fe (4.8 μ mol, 0.6 mole %), and 20 μ L dodecane (GC standard) were dissolved in 3 mL of solvent. Trimethylsilyldiazomethane (400 μ L of a 2.0 M solution in hexanes, 800 μ mol) in 12 mL of solvent was added dropwise over approximately 1 hour. The reaction mixture was stirred vigorously, and analyzed by GC after ca. 18 hours. Unlike cyclopropanation with other diazo reagents, the slow addition was not necessary, as no carbene dimer, 1,2-bis(trimethylsilyl)ethene, was ever detected in the reactions performed using (TTP)Fe as a catalyst. Therefore, subsequent reactions were performed by adding all of the trimethylsilyldiazomethane at once, rather than dropwise. The yield of cyclopropane was $89 \pm 4\%$. The *trans/cis* ratio was 10 ± 1 using toluene as the solvent and 13 ± 1 using THF as the solvent. The cyclopropane could be isolated by removing all of the solvent and excess

styrene *in vacuo*, dissolving the residue in hexanes, passing the solution through a plug of neutral alumina (2 x 5 cm), and washing the alumina with hexanes. The cyclopropane was isolated after removal of the hexane from the combined filtrate and washings by rotary evaporation. ^1H (C_6D_6 , 300 MHz) *trans*-isomer: 7.13 (m, 2H, C_6H_5), 7.03 (m, 3H, C_6H_5), 1.74 (m, 1H, C_3H_4), 0.89 (m, 1H, C_3H_4), 0.77 (m, 1H, C_3H_4), -0.03 (m, 10H, C_3H_4 + $\text{Si}(\text{CH}_3)_3$). *Cis*-isomer: 0.85 (m, 1H, C_3H_4), -0.19 (s, 9H, $\text{Si}(\text{CH}_3)_3$), all other signals for the *cis*-cyclopropane were obscured by those of the *trans*-isomer.

(TTP)Fe=CH(mesityl), 8a. A round bottom flask was charged with 9 mg (13 μmol) (TTP)Fe and ca. 2 mL of THF. To this was added 120 μL of a 136 mM solution of $\text{N}_2\text{CH}(\text{mesityl})$ (16.3 μmol) in pentane. The reaction mixture was stirred vigorously for 3 minutes and then the solvent was removed *in vacuo*. The resulting complex was dissolved in C_6D_6 and its ^1H NMR spectrum was recorded. ^1H (C_6D_6 , 400 MHz): 19.71 (s, 1H, =CHAr), 8.72 (s, 8H, $\beta\text{-H}$), 7.84 (br, 8H, $\text{C}_6\text{H}_4\text{CH}_3$), 7.23 (d, 8H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.6$ Hz), 5.54 (s, 2H, $\text{C}_6\text{H}_2(\text{CH}_3)_3$), 2.34 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$), 1.70 (s, 3H, *p*- $\text{C}_6\text{H}_2(\text{CH}_3)_3$), -1.12 (s, 6H, *o*- $\text{C}_6\text{H}_2(\text{CH}_3)_3$). Contamination of the sample with varying amounts of (TTP)Fe precluded the isolation of pure material for elemental analysis.

(TTP)Fe=CH(TMS), 8b. To a solution of 24 mg (TTP)Fe (33 μmol) in 5 mL of toluene was added 51.5 μL of a 2.0 M solution of $\text{N}_2\text{CH}(\text{TMS})$ (1.0×10^2 μmol) in hexanes. The mixture was stirred for 3 hours and the solvent was removed at reduced pressure. The residue was dissolved in C_6D_6 and its ^1H NMR spectrum was recorded. ^1H (C_6D_6 , 300 MHz): 24.86 (s, 1H, =CHTMS), 8.69 (s, 8H, $\beta\text{-H}$), 7.92 (d, 8H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8$ Hz), 7.17 (d, 8H, $\text{C}_6\text{H}_4\text{CH}_3$, partially obscured by C_6D_6), 2.31 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$), -1.80 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

Contamination of the sample with varying amounts of (TTP)Fe precluded the isolation of pure material for elemental analysis.

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CHAPTER 4. MECHANISM OF CYCLOPROPANATION REACTIONS MEDIATED BY
(5,10,15,20-TETRA-*PARA*-TOLYLPORPHYRINATO)OSMIUM(II) COMPLEXES¹

A paper to be submitted to the *Journal of the American Chemical Society*

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Abstract

Group 8 metalloporphyrins complexes are excellent precatalysts for cyclopropanation reactions. 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 monocarbene 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 towards transfer to an olefin. Labeling studies with (TTP)Os=CHX and N₂CHY and substrate reactivity profiles are consistent with a *trans*-osmium(II) biscarbene species as the active catalyst.

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Introduction

Based on the volume of publications, one can place cyclopropanation of alkenes with diazo alkanes, carbon-hydrogen bond insertion, and olefin formation among the most studied metal-mediated organic transformations.³ 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 diazoalkane reagent with the active metal center of the catalyst.⁴ The nature of the resulting organometallic species has been ascertained only in rare cases as being a metal-carbene, metal-diazoalkyl or metal-ylide complex. Due to the transient nature of these intermediates, spectroscopic detection has been achieved in few cases.⁵ Recent spectroscopic studies of (porphyrinato)rhodium(III)-catalyzed cyclopropanation reactions provided evidence for the formation of a (porphyrinato)rhodium-diazoalkyl complex when the former complex was treated with ethyl diazoacetate at low temperature.⁶ In our recent reports we described the efficiency of osmium(II) porphyrin complexes, such as (TTP)OsLL' (L = L' = py, **1a**; L = py, L' = CO, **1b**) and [Os(TTP)]₂,⁷ **2**, and iron (II) porphyrin complexes, Fe(TTP), **3**, for the catalysis of olefin formation from diazoalkanes and for the stereoselective cyclopropanation of alkenes with diazoalkanes.⁸ We demonstrated that neutral monoalkylidene species form upon treatment of [Os(TTP)]₂ by diazoalkanes. Two examples of these monoalkylidene complexes have been characterized by X-ray crystallography.⁹ These isolable monoalkylidene complexes can act as catalysts or stoichiometric reagents in cyclopropanation reactions. Preliminary studies showed that (TTP)Os=CH(CO₂Et), **4a**, used

stoichiometrically or catalytically, can promote stereoselectively the cyclopropanation of styrene giving similar yields of products in both cases. However, monoalkylidene 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.

Experimental Section

General Methods. All manipulations of reagents and products were carried out under a dry nitrogen atmosphere using a Vacuum/Atmospheres glove box equipped with a model MO40H DriTrain 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. ^1H NMR and ^{13}C NMR spectra were recorded on Nicolet NT300, Varian VXR300, Bruker DRX400, and Unity 500 spectrometers. ^1H NMR peak positions were referenced against residual proton resonances of deuterated solvents (δ ppm: CDCl_3 , 7.24; C_6D_6 , 7.15). ^{13}C NMR signals were referenced against the center line of the deuterated solvent resonance (δ ppm: CDCl_3 , 77.10; C_6D_6 , 128.00). ^2H NMR experiments were performed with a Bruker DRX400 spectrometer using CDCl_3 as an internal standard. UV-visible spectra were obtained using a Hewlett-Packard HP8452A diode array spectrometer. IR spectra were recorded using a FTS-7 BioRad Fourier transform spectrometer. Gas chromatographic analyses were performed with a HP 5890 Series II¹⁰ or a Finnigan Magnum GC-MS.¹¹ Dodecane or hexamethylbenzene was used as an internal standard. High resolution mass spectroscopy for exact mass determination was performed on a Kratos MS50 spectrometer using electron

impact {EI} ionization. Ethyl diazoacetate, trimethylsilyldiazomethane, and olefins (Aldrich Chemical Co.) were dried over molecular sieves, degassed by three or more freeze-pump-thaw cycles, and passed through a plug of alumina (1 × 2 cm). Aryldiazomethanes were prepared by oxidation of hydrazones with yellow mercury(II) oxide in toluene or hexane¹² or by solution pyrolysis of the corresponding tosyl hydrazone.¹³ Diester or β-ketoester diazo reagents were prepared by transferring a diazo group to the corresponding diester or β-ketoester α-carbon from CH₃SO₂N₃ under basic conditions.¹⁴ Propyl diazoacetate was made by diazo transfer to propyl acetoacetate from CH₃SO₂N₃ followed by acetyl group cleavage under basic conditions in a manner similar to the preparation of other diazo reagents.¹⁴ Propyl acetoacetate was made by acetoacetylation of 1-propanol with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (diketene-acetone adduct) in refluxing xylenes.¹⁵ A literature procedure was used in the preparation of *trans*-β-deutereostyrene.¹⁶ Bis[(5,10,15,20-tetra-*p*-tolylporphyrinato)osmium(II)], [Os(TTP)]₂, was prepared from (TTP)Os(py)₂, according to a published procedure.¹⁷ The bispyridine complex, (TTP)Os(py)₂, was prepared from either (TTP)Os(CO)(py), or (TTP)OsO₂ by using reported methods.¹⁸ Literature procedures were used to prepare (TTP)Os=CHCO₂Et^{8a}, **4a**; (TTP)Os=C(*p*-tolyl)₂, **4b**; and (TTP)Os=CHTMS, **4c**.⁹ Authentic samples of ethyl-2-(4-methylphenyl)cyclopropanecarboxylic acid ester, **5d**, and ethyl-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxylic acid ester, **5f**, were gifts from Thomas Kodadek of the University of Texas at Austin.

(TTP)Os=CH(Mes), **4d**. In a glovebox, [Os(TTP)]₂ (53 mg, 31 μmol) was dissolved in toluene (6 mL). A solution of mesityldiazomethane (35 mL, 6.6 mM, 230 μmol) in toluene was added over a period of 5 hours. The resulting mixture was concentrated to ca. 20 mL

and the product was eluted as a red-brown band on a 1 cm x 10 cm Florisil column (toluene/THF:10/1). The red-brown fraction was taken to dryness under reduced pressure to afford an orange-brown solid (50.6 mg, 84% yield). $^1\text{H NMR}$ (C_6D_6): 20.78 (s, =CHMes), 8.19 (s, 8H, H- β), 7.99 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 7.89 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 7.25 (m, 8H, $\text{C}_6\text{H}_4\text{CH}_3$), 5.59 (s, 2H, *m*- C_6H_2), 2.36 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$), 1.77 (s, 3H, *p*- CH_3), -0.39 (s, 6H, *o*- CH_3). $^{13}\text{C NMR}$ (C_6D_6): 248 (d, $J_{\text{CH}} = 141.1$ Hz, Os=C). UV-vis (C_6H_6): 418 (Soret), 518, 550 nm.

(TTP)Os=CHCO₂CH₂CH₂CH₃, **4e**. In a glovebox, 44 mg (26 μmol) of [Os(TTP)]₂ was dissolved in ca. 5 mL benzene. A solution of propyl diazoacetate (22 mg, 170 μmol , 3.3 equiv per Os) in 5 mL of benzene was added dropwise over a period of 5 minutes. The solution was vigorously stirred for 2 hours after which the solvent was removed *in vacuo*. The crude residue was purified by chromatography on a Florisil column (1 x 10 cm), eluting first with toluene to remove organic impurities and then with 10:1 (v/v) toluene/THF to elute a red-brown band. Removal of solvents from the red-brown fraction under reduced pressure afforded approximately 29 mg (59.1%) of a brownish-red waxy solid contaminated with approximately 1 equivalent of dipropyl maleate. $^1\text{H NMR}$ (C_6D_6): 21.82 (s, 1H, CHCO₂Pr); 8.36 (s, 8H, H- β); 8.03 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.5, 1.8$ Hz); 7.97 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.5, 1.8$ Hz); 7.28 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.5$ Hz); 7.19 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.5$ Hz); 2.61 (t, 2H, CO₂CH₂CH₂CH₃, $J_{\text{HH}} = 6.9$ Hz); 2.34 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$); 0.67 (m, 2H, CO₂CH₂CH₂CH₃); 0.07 (t, 3H, CO₂CH₂CH₂CH₃, $J_{\text{HH}} = 7.2$ Hz). $^1\text{H NMR}$ data for maleate: 5.73 (s, 2H, C=C-H), 3.94 (t, 4H, CO₂CH₂CH₂CH₃, $J_{\text{HH}} = 6.6$ Hz), 1.39 (m, 4H, CO₂CH₂CH₂CH₃), 0.68 (br t, 6H, CO₂CH₂CH₂CH₃, $J_{\text{HH}} = 7.2$ Hz).

(TTP)Os=CH(*p*-tolyl), 4f. A hexanes solution of $\text{N}_2\text{CH}(\textit{p}\text{-tolyl})$ (97 mM, 2.1 mL, 200 μmol) was added to a vigorously stirred solution of 62 mg (36 μmol) of $[\text{Os}(\text{TTP})]_2$ in 10 mL of a 1:1 (v/v) mixture of toluene and THF. After 30 minutes, the solvents were removed *in vacuo*. The crude residue was purified by chromatography on a Florisil column (1 x 10 cm), eluting first with hexanes and then 50:1 (v/v) hexanes/toluene to remove organic impurities. Complex **4f** was eluted as a red band using toluene. The red fraction was taken to dryness to yield ca. 10 mg (14%) of complex **4f**. $^1\text{H NMR}$ (C_6D_6): 19.85 (s, $=\text{CHC}_6\text{H}_4\text{CH}_3$), 8.21 (s, 8H, H- β), 8.01 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8, 1.2$ Hz), 7.89 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8, 1.2$ Hz), 7.27 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8$ Hz), 7.14 ($\text{C}_6\text{H}_4\text{CH}_3$, partially obscured by $\text{C}_6\text{D}_5\text{H}$), 5.68 (d, 2H, $=\text{CHC}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8$ Hz), 4.77 (d, 2H, $=\text{CHC}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 8.6$ Hz), 2.34 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$), 0.41 (s, 3H, $=\text{CHC}_6\text{H}_4\text{CH}_3$).

(TTP)Os=CH(*p*-ethylphenyl), 4g. Into a round bottom flask was placed 98 mg (57 μmol) of $[\text{Os}(\text{TTP})]_2$ and 15 mL of a 7:2 (v/v) mixture of toluene and THF. To the vigorously stirred solution was added 5.0 mL of 42 mM solution of $\text{N}_2\text{CH}(\textit{p}\text{-ethylphenyl})$ (210 μmol) in hexanes. After 45 minutes, the solvents were removed *in vacuo*. The crude residue was purified by chromatography on a Florisil column (1 x 10 cm), eluting first with hexanes (ca. 400 mL) and then 50:1 (v/v) hexanes/toluene (ca. 400 mL) to remove organic impurities. Complex **4g** was eluted as a red band using toluene. The red fraction was taken to dryness to yield ca. 15 mg (13%) of complex **4g**. $^1\text{H NMR}$ (C_6D_6): 19.93 (s, $=\text{CHC}_6\text{H}_4\text{Et}$), 8.21 (s, 8H, H- β), 8.02 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.6, 1.2$ Hz), 7.88 (dd, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.6, 1.2$ Hz), 7.27 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 8.4$ Hz), 7.14 ($\text{C}_6\text{H}_4\text{CH}_3$, partially obscured by $\text{C}_6\text{D}_5\text{H}$), 5.74 (d, 2H, $\text{C}_6\text{H}_4\text{Et}$, $J_{\text{HH}} = 8.4$ Hz), 4.85 (d, 2H, $\text{C}_6\text{H}_4\text{Et}$, $J_{\text{HH}} = 8.4$ Hz), 2.34 (s,

12H, C₆H₄CH₃), 0.99 (q, 2H, C₆H₄CH₂CH₃, J_{HH} = 7.6 Hz), 0.52 (t, 3H, C₆H₄CH₂CH₃, J_{HH} = 7.6 Hz).

(TTP)Os=C(CO₂Et)(C(=O)CH₂CH₂CH=CH₂), 4h. To a solution of [Os(TTP)]₂ (15 mg, 9 μmol) in toluene (5 mL) was added a solution of N₂C(CO₂Et)(C(=O)CH₂CH₂CH=CH₂) (70 mg, 360 μmol) in toluene (15 mL) over 2 hours. The mixture was stirred for 20 minutes, at which time the solution had changed from brown to red-orange, and the solvents removed *in vacuo*. The crude residue was eluted down a 1 x 10 cm Florisil column as a red-brown band and complex **4h** was recovered quantitatively as an orange waxy solid after evaporation of solvents from the red-brown fraction. ¹H NMR (C₆D₆): 8.40 (s, 8H, H-β), 8.27 (d, 4H, C₆H₄CH₃, J_{HH} = 6.4 Hz), 8.03 (d, 4H, C₆H₄CH₃, J_{HH} = 6.4 Hz), 7.26 (m, 8H, C₆H₄CH₃), 5.17 (m, 1H, CH₂CH₂CH=CH₂), 4.65 (d, 1H, CH₂CH₂CH=CH₂, J_{HH} = 9.6 Hz), 4.55 (dd, 1H, CH₂CH₂CH=CH₂, J_{HH} = 17.2, 1.6 Hz), 2.85 (q, 2H, CO₂CH₂CH₃, J_{HH} = 7.2 Hz), 2.42 (s, 12H, C₆H₄CH₃), 1.31 (m, 2H, CH₂CH₂CH=CH₂), 0.34 (t, 3H, CO₂CH₂CH₃, J_{HH} = 7.2 Hz), -0.37 (m, 2H, CH₂CH₂CH=CH₂). UV-vis (toluene): 398 nm (Soret), 420 (sh), 432 (sh), 518, 572 nm. IR (KBr): ν 1704-1674 cm⁻¹ (broad band, C=O). MS{FAB⁺}: m/z 1028 [M]⁺, 953 [M-CO₂C₂H₅]⁺, 943 [M-C₅H₇O]⁺, 873 [M-CO₂C₂H₅-C₅H₇O]⁺, 858 [M-{C(CO₂C₂H₅)(C₅H₇O)}]⁺.

(TTP)Os=CMePh, 4i. To a solution of [Os(TTP)]₂ (16 mg, 9 μmol) in 6 mL of benzene, an excess of N₂CMePh in 5 mL of benzene was added dropwise over a period of 8 minutes. The resulting mixture became orange and was stirred for 1 hour. The solution was placed onto a neutral alumina column. Olefins were removed by elution with benzene and complex **4i** was eluted using 10% THF in benzene. The solvent was removed under vacuum

to yield complex **4i**. ^1H NMR (C_6D_6): 8.16 (s, 8H, H- β), 8.00 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.5$ Hz), 7.93 (d, 4H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 7.26 (m, 8H, $\text{C}_6\text{H}_4\text{CH}_3$), 6.54 (t, 1H, *p*- C_6H_5 , $J_{\text{HH}} = 7.5$ Hz), 6.26 (t, 2H, *m*- C_6H_5 , $J_{\text{HH}} = 7.5$ Hz), 4.10 (d, 2H, *o*- C_6H_5 , $J_{\text{HH}} = 7.5$ Hz), 2.35 (s, 12H, $\text{C}_6\text{H}_4\text{CH}_3$), -4.36 (s, 3H, = CCH_3). ^{13}C NMR (C_6D_6): 263.9 (d, $^2J_{\text{CH}} = 7.87$ Hz, Os=C). UV-vis (C_6H_6): 410 (Soret), 424 (sh), 516, 540 nm.

Ethyl-2-phenylcyclopropanecarboxylic acid ester, 5a. Method A. In a typical experiment, (TTP)Os(CO)(py) (3 mg, 3 μmol), styrene (0.220 mL, 1.90 mmol), and dodecane (internal standard) were vigorously stirred in toluene (3 mL). A toluene solution (12 mL) of $\text{N}_2\text{CHCO}_2\text{Et}$ (0.100 mL, 952 μmol) was added dropwise over one hour. GC analysis: $14 \pm 3\%$ yield of olefin, $54 \pm 8\%$ yield of cyclopropane **5a** (*trans/cis* = 8.9 ± 0.5). *trans*-**5a**: ^1H NMR (CDCl_3): 7.3-7.0 (m, C_6H_5 , partially obscured by CHCl_3), 4.15 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.1$ Hz), 2.49 (m, 1H, C_3H_4), 1.87 (m, 1H, C_3H_4), 1.58 (m, 1H, C_3H_4), 1.30 (m, 1H, C_3H_4), 1.23 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.1$ Hz). *cis*-**5a**: ^1H NMR (CDCl_3): 7.3-7.0 (m, C_6H_5 , partially obscured by CHCl_3), 3.85 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.1$ Hz), 2.50 (m, 1H, C_3H_4), 2.05 (m, 1H, C_3H_4), 1.71 (m, 1H, C_3H_4), 1.30 (m, 1H, C_3H_4), 0.95 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.1$ Hz). Proton assignments for the major cyclopropane isomer were made by comparison to the ^1H NMR spectrum of an authentic sample. MS{EI}: m/z 190 $[\text{M}]^+$, 162 $[\text{M-Et+H}]^+$, 144, 127, 117 $[\text{M-CO}_2\text{Et}]^+$, 115.

Method B. In a typical experiment, $[\text{Os}(\text{TTP})]_2$ (3.0 mg, 1.7 mmol) and styrene (0.110 mL, 961 μmol) were vigorously stirred in toluene (3 mL). A toluene solution (12 mL) of $\text{N}_2\text{CHCO}_2\text{Et}$ (0.100 mL, 952 μmol) was added dropwise over one hour. GC analysis revealed only a trace of olefin and $79 \pm 2\%$ yield of cyclopropane **5a** (*trans/cis* = 10.2 ± 0.1).

Method C. In a typical experiment, (TTP)Os=CHCO₂Et, **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 N₂CHCO₂Et (0.100 mL, 952 μmol) was added dropwise over one hour. 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) (TTP)Os=CHCO₂Et and 0.4 mL C₆D₆. 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 hours, the reaction was 96% complete. GC analysis indicated a *trans/cis* ratio of 11.5 ± 0.4.

Method E. A mixture of (TTP)Os(CO) (3 mg, 3 μmol), styrene (0.980 mL, 7.90 mmol) and 22.5 μL dodecane was dissolved in 5 mL toluene. A solution of ethyldiazoacetate (88 μL, 840 μmol) in 10 mL toluene was added dropwise over five minutes. After two hours, 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 [Os(TTP)]₂ (ca. 2 mg, 0.3 mol % Os), 1-octene (1.40 mL, 8.92 mmol), and 21 μL dodecane was dissolved in 5 mL toluene. Ethyl diazoacetate (100 μL, 951 μmol) in 10 mL toluene was added either all in one aliquot or dropwise over a period of ca. 7 minutes. The reaction 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_2 (33 x 3.8 cm) using hexanes/ethyl acetate (25:1 v/v). The *cis* isomer eluted with diethyl maleate fumarate and could not be isolated in pure form. The *trans* isomer eluted as a wider band, and could be isolated cleanly by collecting the latter portion of the band (222 mg, 43%). ^1H NMR (*trans*, CDCl_3): 4.09 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$); 1.31 (m, 15H, $n\text{-(CH}_2)_5\text{CH}_3 + 2 \text{C}_3\text{H}_4 + \text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz); 1.12 (m, 1H, C_3H_4); 0.86 (approx. t, 3H, $n\text{-(CH}_2)_5\text{CH}_3$, $J_{\text{HH}} = 6.8$ Hz); 0.65 (m, C_3H_4). MS{CI}: m/z 198 $[\text{M}]^-$.

Ethyl-2-(4-methoxyphenyl)cyclopropanecarboxylic acid ester, 5c. Using method B, cyclopropane 5c was prepared by treating a toluene (2 mL) mixture of $[\text{Os}(\text{TTP})]_2$ (12 mg, 7 μmol) and 4-methoxystyrene (536 mg, 3.98 mmol) with a toluene (25 mL) solution of $\text{N}_2\text{CHCO}_2\text{Et}$ (456 mg, 4.00 mmol). The addition of the diazoalkane was carried out over 4 hours and the resulting mixture was allowed to stir overnight. The solvent was removed *in vacuo* and the brown residue was dissolved in diethyl ether. The resulting solution was passed through a silica gel column in order to remove porphyrinic 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 5a and 9. ^1H NMR (CDCl_3): 7.00 (d, 2H, $\text{C}_6\text{H}_4\text{OCH}_3$, $J_{\text{HH}} = 8.7$ Hz), 6.78 (d, 2H, $\text{C}_6\text{H}_4\text{OCH}_3$, $J_{\text{HH}} = 8.7$ Hz), 4.12 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 3.75 (s, 3H, OCH_3), 2.44 (m, 1H, C_3H_4), 1.78 (m, 1H, C_3H_4), 1.51 (m, 1H, C_3H_4), 1.24 (t + m, 4H, $\text{C}_3\text{H}_4 + \text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz). MS{EI}: m/z 220 $[\text{M}]^+$, 191 $[\text{M}-\text{C}_2\text{H}_5]^+$, 147 $[\text{M}-\text{C}_3\text{H}_5\text{O}_2]^+$, 131, 115, 103.

Ethyl-2-(4-chlorophenyl)cyclopropanecarboxylic acid ester, 5e. In a glovebox, $[\text{Os}(\text{TTP})]_2$ (2 mg, 2 μmol) and 4-chlorostyrene (2.30 mL, 44.1 mmol) were dissolved in 5 mL of THF. A solution of EDA (770 μL , 7.32 mmol) in 20 mL of THF was added dropwise over a period of 15 hours. The THF was removed by rotary evaporation and the residue chromatographed on neutral alumina (3.5 \times 35 cm) using 50:1 (v/v) hexanes/ethyl acetate. The first band off the column was excess 4-chlorostyrene followed by cyclopropane **5e** and then diethyl maleate and fumarate. The fractions containing only **5e** were combined and the solvent removed by rotary evaporation to yield 1.26g (77%) of cyclopropane **5e**. *trans-5e*: ^1H NMR (C_6D_6): 6.96 (d, 2H, $\text{C}_6\text{H}_4\text{Cl}$, $J_{\text{HH}} = 8.4$ Hz), 6.39 (d, 2H, $\text{C}_6\text{H}_4\text{Cl}$, $J_{\text{HH}} = 8.4$ Hz), 3.97 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 2.39 (m, 1H, C_3H_4), 1.68 (m, 1H, C_3H_4), 1.49 (m, 1H, C_3H_4), 0.95 (t, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 0.78 (m, 1H, C_3H_4). *cis-5e*: ^1H NMR (C_6D_6): 7.07 (d, 2H, $\text{C}_6\text{H}_4\text{Cl}$, $J_{\text{HH}} = 8.4$ Hz), 6.92 (d, 2H, $\text{C}_6\text{H}_4\text{Cl}$, $J_{\text{HH}} = 8.4$ Hz), 3.69 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 1.88 (m, 1H, C_3H_4), 1.73 (m, 1H, C_3H_4), 1.49 (m, 1H, C_3H_4), 0.75 (t, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 0.70 (m, 1H, C_3H_4).

1-Mesityl-2-phenylcyclopropane, 5g. A procedure similar to method A was used to prepare cyclopropane **5c** from complex $(\text{TTP})\text{Os}(\text{CO})(\text{py})$ (2 mg, 2 μmol), styrene (0.100 mL, 874 μmol), and $\text{N}_2\text{CH}(\text{Mes})$ (20 mL, 0.033 M in toluene, 660 μmol). GC analysis revealed less than 1% olefin and 99% yield of cyclopropane **5g** (*trans/cis* = 0.4). Assignment of the cyclopropane major isomer was made by 2D-NOESY ^1H NMR (500 MHz) correlation. ^1H NMR (CDCl_3), *cis*-isomer, **5g**: 7.02 (m, 3H, C_6H_5), 6.72 (s, 2H, $\text{C}_6\text{H}_2(\text{CH}_3)_2$), 6.44 (m, 2H, C_6H_5), 2.66 (s, 6H, CH_3), 2.54 (s, 3H, CH_3), 2.02 (m, 1H, C_3H_4), 1.97 (m, 1H, C_3H_4), 1.40 (m, 1H, C_3H_4), 1.04 (m, 1H, C_3H_4). ^1H NMR (CDCl_3), **5g**, *trans* isomer: 7.32 (t, 2H, C_6H_5 ,

$J_{\text{HH}} = 7.6 \text{ Hz}$), 7.20 (m, 3H, C_6H_5), 6.86 (s, 2H, $\text{C}_6\text{H}_2(\text{CH}_3)_2$), 2.50 (s, 3H, CH_3), 2.45 (s, 6H, CH_3), 1.84 (m, 1H, C_3H_4), 1.76 (m, 1H, C_3H_4), 1.17 (m, 1H, C_3H_4), 1.02 (m, 1H, C_3H_4).

MS{EI}: m/z 236 $[\text{M}]^+$, 221 $[\text{M}-\text{Me}]^+$, 143, 132, 115, 91 $[\text{C}_7\text{H}_7]^+$.

Propyl-2-phenylcyclopropanecarboxylic acid ester, 5h. In a typical experiment, 2 mg (1 mmol, 0.3 mole % Os) of $[\text{Os}(\text{TTP})]_2$ was dissolved in 5 mL toluene. Styrene (1.00 mL, 906 mg, 8.70 mmol) and 21 μL dodecane (internal standard) were added. A solution of propyl diazoacetate (109 mg, 851 μmol) was added dropwise over a period of ca. 25 minutes. The solution was allowed to stir an additional 15 hours. GC analysis of the reaction mixture indicated that the yield of cyclopropane was $100 \pm 3\%$ with a *trans/cis* ratio of 11.5:1. ^1H NMR (*trans*, CDCl_3): 7.26 (t, 2H, C_6H_5 , $J_{\text{HH}} = 5.4 \text{ Hz}$); 7.18 (t, 1H, C_6H_5 , $J_{\text{HH}} = 5.4 \text{ Hz}$); 7.08 (d, 2H, C_6H_5 , $J_{\text{HH}} = 5.7 \text{ Hz}$); 4.06 (t, 2H, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 5.1 \text{ Hz}$); 2.50 (m, 1H, C_3H_4); 1.89 (m, 1H, C_3H_4); 1.65 (sextet, 2H, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 5.4 \text{ Hz}$); 1.58 (m, 1H, C_3H_4); 1.30 (m, 1H, C_3H_4); 0.94 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 5.4 \text{ Hz}$).

***endo,endo*-2,4-Di(ethoxycarbonyl)-1-phenyl[1.1.0]bicyclobutane, 6a.** Using method A, compound 6a was prepared from $(\text{TTP})\text{Os}(\text{CO})(\text{py})$ (4 mg, 4 μmol), 50 μL (460 μmol) phenylacetylene, and $\text{N}_2\text{CHCO}_2\text{Et}$ (0.100 mL, 952 μmol). GC analysis indicated major formation of olefin ($41 \pm 1\%$ yield) along with bicyclobutane 6a ($11 \pm 1\%$ based on starting alkyne). ^1H NMR and GC analysis indicated that only one bicyclobutane isomer formed. The stereochemistry of compound 6a was established as the *endo-endo* configuration on the basis of its 2D NOESY and 1D ^1H NMR spectra. ^1H NMR (C_6D_6): 7.66 (m, 2H, C_6H_5), 7.06 (m, 3H, C_6H_5), 3.7 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.41 (s, 1H, C_4H_3), 1.71 (s, 2H, C_4H_3), 0.70 (t, 6H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2 \text{ Hz}$). MS{EI}: m/z 274 $[\text{M}]^+$, 229 $[\text{M}-\text{C}_2\text{H}_5\text{O}]^+$, 201 $[\text{M}-\text{C}_3\text{H}_5\text{O}_2]^+$,

183, 173, 155, 144, 127, 115. Using method B, compound **6a** was prepared from $[\text{Os}(\text{TTP})]_2$ (4.1 mg, 2.4 μmol), 0.50 mL (4.56 mmol) phenylacetylene in 6 mL toluene, and $\text{N}_2\text{CHCO}_2\text{Et}$ (1.00 mL, 9.52 mmol) in 24 mL toluene. GC analysis indicates the formation of olefin (21% yield) and bicyclobutane **6a** (46%).

endo-exo-2,4-Di(mesityl)-1-phenyl[1.1.0]bicyclobutane, 6b. Using method A, bicyclobutane **6b** was prepared from $(\text{TTP})\text{Os}(\text{CO})(\text{py})$ (4 mg, 4 μmol), 0.100 mL (912 μmol) phenylacetylene, and $\text{N}_2\text{CH}(2,4,6\text{-(CH}_3)_3\text{C}_6\text{H}_2)$ (31.6 mL, 0.045 M in toluene, 1.4 mmol). GC analysis indicated formation of bicyclobutane **6b** ($77 \pm 4\%$ yield) along with a trace of olefin ($2 \pm 1\%$ yield). $^1\text{H NMR}$ (CDCl_3): 7.09 (m, 3H, C_6H_5), 6.97 (dd, 2H, C_6H_5 , $J_{\text{HH}} = 7.8, 1.8$ Hz), 6.84 (s, 2H, C_6H_2), 6.77 (s, 2H, C_6H_2), 3.39 (d, 1H, C_4H_3 , $J_{\text{HH}} = 3.2$ Hz), 2.65 (dd, 1H, C_4H_3 , $J_{\text{HH}} = 3.2, 1.8$ Hz), 2.56 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.39 (br-s, 1H, C_4H_3), 2.26 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.22 (s, 6H, CH_3). A 2D COSY experiment 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 $^1\text{H NMR}$ studies. High resolution MS{EI}: m/z found (calc.) 366.23454 (366.23475).

1,1-Di-(*p*-tolyl)-2-phenylcyclopropane, 7a. $[\text{Os}(\text{TTP})]_2$ (1 mg, 0.6 μmol), styrene (0.200 mL, 1.75 mmol), and $\text{N}_2\text{C}(\text{tolyl})_2$ (20 mg, 90 μmol) were vigorously stirred in THF (3 mL). After 4 days the solvent was removed under reduced pressure. The yield was determined by $^1\text{H NMR}$ peak integration analysis of porphyrin β -pyrrole proton (8.18 ppm) to cyclopropane derivative, **7a**, signal at 2.78 ppm, and confirmed by integration of styrene resonances at 5.6 and 5.1 ppm. GC analysis indicated the formation of only one cyclopropane

derivative **7a** (39% yield). $^1\text{H NMR}$ (C_6D_6): 7.20 (d, 2H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 8.1$ Hz), 7.02 (d, 2H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 8.1$ Hz), 7.0-6.8 (m, 7H, $\text{C}_6\text{H}_5 + \text{C}_6\text{H}_4\text{CH}_3$), 6.78 (d, 2H, $\text{C}_6\text{H}_4\text{CH}_3$, $J_{\text{HH}} = 7.8$ Hz), 2.78 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 8.7, 6.6$ Hz), 2.11 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 1.83 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 6.6, 5.4$ Hz), 1.60 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 9.0, 5.4$ Hz). MS{EI}: m/z 298 $[\text{M}]^+$.

Dimethyl-2-phenylcyclopropane-1,1-dicarboxylic acid diester, 7b. In a typical reaction, 3 mg (0.4 mole % Os) $[\text{Os}(\text{TTP})]_2$ styrene (890 mg, 8.53 mmol) and dodecane (21 μL) were dissolved in 15 mL of benzene. Dimethyl diazomalonate (150 mg) was added to the reaction. The solution was stirred and yields determined periodically by gas chromatography. The reaction takes ca. 7 hours to complete, significantly longer than with monoester diazo reagents. The yield was $100 \pm 4\%$ by GC analysis. $^1\text{H NMR}$ (CDCl_3): 7.30-7.15 (m, 5H, C_6H_5), 3.79 (s, 3H, CO_2CH_3), 3.36 (s, 3H, CO_2CH_3), 3.23 (t, 1H, C_3H_3 , $J_{\text{HH}} = 8.7$ Hz), 2.20 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 8.1$ Hz, 5.2 Hz), 1.74 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 9.3$ Hz, 5.1 Hz). MS{EI}: m/z 235 $[\text{M}+\text{H}]^+$, 202 $[\text{M}-\text{OMe}-\text{H}]^+$, 170 $[\text{M}-2\text{OMe}-2\text{H}]^-$, 121, 115.

Diethyl-2-phenylcyclopropane-1,1-dicarboxylic acid diester, 7c. To 15 mL of benzene was added 900 mg (8.7 mmol) styrene, 4 mg (0.5 mol %) $[\text{Os}(\text{TTP})]_2$ and dodecane (internal standard). Diethyl diazomalonate (176 mg, 946 μmol) was added. The reaction was allowed to stir vigorously and monitored periodically by GC. The reaction was complete in ca. 8 hours. Yield was $100 \pm 7\%$ by GC analysis. $^1\text{H NMR}$ (CDCl_3): 7.21 (m, 5H, C_6H_5), 4.22 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.82 (q, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 3.20 (t, 1H, C_3H_3 , $J_{\text{HH}} = 8.4$ Hz), 2.15 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 8.0, 5.2$ Hz), 1.68 (dd, 1H, C_3H_3 , $J_{\text{HH}} = 9.2, 5.2$ Hz), 1.28 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz), 0.84 (t, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J_{\text{HH}} = 7.2$ Hz). MS{EI}: m/z

262 [M⁺], 216 [M-OEt+H]⁺, 170 [M-2OEt+2H]⁺, 135, 115.

Ethyl-2-oxo[3.1.0]bicyclohexanecarboxylic acid ester, 8. **Method A.** To a solution of [Os(TTP)]₂ (4 mg, 2 μmol) in toluene (20 mL) was added 270 μL (1.4 μmol) of N₂C(CO₂Et)[C(=O)CH₂CH₂CH=CH₂]. The solution was refluxed for 2 days. Solvent was removed under reduced pressure. The mixture was taken up in pentane and purified by chromatography over Al₂O₃ (2 × 20 cm) using pentane as the eluent. The fractions containing **8** were combined and the pentane removed by rotary evaporation. ¹H NMR (C₆D₆): 4.03 (m, 2H, CO₂CH₂CH₃), 2.00 (m, 1H), 1.72 (m, 1H), 1.66 (m, 1H), 1.48 (m, 1H), 1.27 (m, 1H), 1.06 (m, 1H), 1.01 (t, 3H, CO₂CH₂CH₃, J_{HH} = 7.8 Hz), 0.57 (br t, 1H, J_{HH} = 5.0 Hz). MS{EI}: m/z 168 [M]⁺, 139 [M-C₂H₅]⁺, 123 [M-OC₂H₅]⁺, 95 [M-CO₂C₂H₅]⁺, 85, 67, 55.

Method B. A frozen benzene-*d*₆ or toluene-*d*₈ solution of complex **4h** in an NMR tube was pressured to less than one atmosphere of carbon monoxide. The tube was flame sealed, the frozen solid was thawed, and the reaction monitored by ¹H 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, ca. 4 mg (0.5 mole % Os) [Os(TTP)]₂ was dissolved in 5 mL of toluene. Dodecane (18 μL, internal GC standard) and α-methylstyrene (1.00 mL, 7.62 mmol) were added. A solution of ethyl diazoacetate (89 mg, 780 μmol) in 10 mL toluene was added dropwise over ca. 10 minutes. The reaction was stirred for approximately 3 hours 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 ¹H NMR correlation, had the ethyl carboxylate group *trans* to the phenyl group. Compound **9**, *trans* isomer: ¹H NMR (CDCl₃):

7.3-7.1 (m, C_6H_5 , partially obscured by $CHCl_3$), 4.15 (m, 2H, $CO_2CH_2CH_3$, $J_{HH} = 7.1$ Hz), 1.92 (m, 1H, C_3H_3), 1.49 (s, 3H, CH_3), 1.40 (m, 1H, C_3H_3), 1.37 (m, 1H, C_3H_3), 1.26 (t, 3H, $CO_2CH_2CH_3$, $J_{HH} = 7.1$ Hz). Compound 9, *cis* isomer: 1H NMR ($CDCl_3$): 7.3-7.1 (m, C_6H_5 , partially obscured by $CHCl_3$), 3.8 (m, 2H, $CO_2CH_2CH_3$, $J_{HH} = 7.1$ Hz), 1.86 (m, 1H, C_3H_3), 1.74 (m, 1H, C_3H_3), 1.43 (s, 3H, CH_3), 1.10 (m, 1H, C_3H_3), 0.90 (t, 3H, $CO_2CH_2CH_3$, $J_{HH} = 7.1$ Hz). MS{EI}: m/z 204 $[M]^+$, 189 $[M-CH_3]^+$, 175 $[M-C_2H_5]^+$, 159 $[M-C_2H_5O]^+$, 147, 131 $[M-C_3H_5O_2]^+$, 115.

Ethyl-*cis*-2-methyl-*trans*-3-phenylcyclopropanecarboxylic acid ester, 10. Using method A, cyclopropane 10 was prepared from 4 mg (4 μ mol) of (TTP)Os(CO)(py), 0.120 mL (926 μ mol) *trans*- β -methylstyrene and N_2CHCO_2Et (0.100 mL, 952 μ mol). GC analysis indicated major formation of olefin ($43 \pm 2\%$ yield) and minor formation of cyclopropane 10 ($13 \pm 2\%$ yield). 1H NMR ($CDCl_3$): 7.3-7.1 (m, 5H, C_6H_5), 3.99 (m, 2H, $CO_2CH_2CH_3$), 2.61 (~ t, 1H, C_3H_3 , $J_{HH} = 9.0$ Hz), 2.05 (dd, 1H, C_3H_3 , $J_{HH} = 9.0, 17$ Hz), 1.38 (m, 1H, C_3H_3), 1.27 (d, 3H, CH_3 , $J_{HH} = 6.6$ Hz), 0.97 (t, 3H, $CO_2CH_2CH_3$, $J_{HH} = 7.1$ Hz). MS{EI}: m/z 204 $[M]^+$, 189 $[M-CH_3]^+$, 175 $[M-C_2H_5]^+$, 158, 131 $[M-C_3H_5O_2]^+$, 115, 103, 91.

Reaction of (TTP)Os=CHCO₂Et, 4a, with styrene and ethyl diazoacetate. To a solution of complex 4a (4 mg, 4 μ mol) in toluene (3 mL) was added styrene (100 μ L, 874 μ mol). Ethyl diazoacetate (100 μ L, 952 μ mol) 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, $65 \pm 4\%$ yield (*trans/cis* = 9) with traces of diethyl maleate/diethyl fumarate.

Reaction of (TTP)Os=CH(Mes), 4d, with N_2CHCO_2Et and styrene. Complex 4d (10 mg, 11 μ mol) 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. Only cyclopropane **5a** was detected (20% overall yield, *trans/cis* = 10.2) along with diethyl maleate (60% yield).

Reaction of (TTP)Os=CHCO₂Et, 4a, with N₂CH(Mes) and styrene. To a solution of complex **4a** (28 mg, 30 μmol) in ca. 1 mL of toluene was added a mixture of styrene (50 mg, 30.6 μmol) and N₂CH(Mes) (1.26 mL, 0.026 M, 31 μmol). GC analysis followed immediately and indicated the formation of cyclopropane **5a** ($28 \pm 3\%$ yield, *trans/cis* = 14 ± 1) and cyclopropane **5g** ($37 \pm 3\%$ yield, *trans/cis* = 0.54 ± 0.04).

Competitive cyclopropanation of two olefins with [Os(TTP)]₂. In a typical experiment, 2 mg (1 μmol) of [Os(TTP)]₂, 7.6 mmol of each olefin (styrene and a substituted styrene), and dodecane (internal GC standard) were placed in a round bottom flask and dissolved in 3 mL toluene. A solution of 41.5 μL (400 μmol) of ethyl diazoacetate in 12 mL toluene was dropwise for approximately 20-30 minutes with vigorous stirring. GC analysis was performed to determine product ratios. Products were identified by GC using coinjection of authentic samples with the reaction mixtures.

Competitive cyclopropanation of styrene and α -methylstyrene using (TTP)Os(CO). A mixture of styrene (980 μL , 8.53 mmol), α -methylstyrene (1.11 mL, 8.46 mmol), 23 μL dodecane, and (TTP)Os(CO) (4 mg, 4 μmol) was dissolved in 10 mL toluene. Ethyl diazoacetate (87 μL , 830 μmol) was added in one aliquot and the reaction was stirred for at least 10 hours. GC analysis showed $14 \pm 2\%$ olefin, $24 \pm 3\%$ ethyl-2-phenylcyclopropane carboxylic acid ester, **5a**, (*trans/cis* = 8.1 ± 0.9), and $66 \pm 4\%$ ethyl-2-methyl-2-phenylcyclopropane carboxylic acid ester, **9**, (*trans/cis* = 2.4 ± 0.1). The ratio of

9:5a was 2.7 ± 0.4 .

Competitive catalytic cyclopropanation of α -methylstyrene and *trans*- β -methylstyrene with (TTP)Os=CHCO₂Et. To a solution of (TTP)Os=CH(CO₂Et), **4a**, (5 mg, 5 μ mol) in toluene (2.5 mL) was added dropwise for 0.5 h a mixture of α -methylstyrene (103.5 μ L, 789 μ mol), *trans*- β -methylstyrene (103.5 μ L, 789 μ mol) and ethyl diazoacetate (10 mg, 88 μ mol). The resulting mixture was stirred for 6 h and analyzed. GC analysis: cyclopropane **9**, 100%, *trans/cis* = 2.5.

Competitive stoichiometric cyclopropanation of styrene and α -methylstyrene with (TTP)Os=CHCO₂Et. To an equimolar amount of styrene and α -methylstyrene was added 1.0 mL of a toluene solution containing 6.5 μ mol (< 0.1 equiv) of (TTP)Os=CHCO₂Et. The reaction mixture was stirred for ca. 18 hours and dodecane (3.2-6.6 μ L) added. The reactions were then analyzed by gas chromatography to determine product ratios.

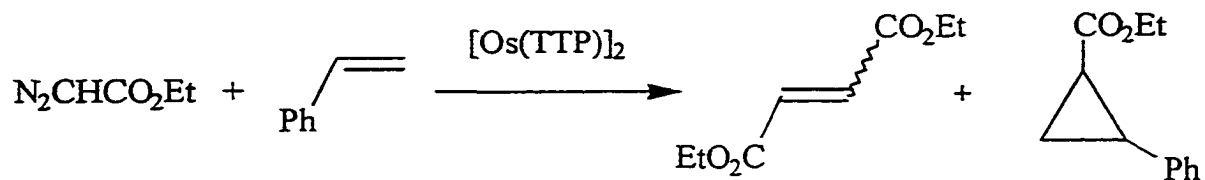
Labeling experiments at -78 °C. A stock solution of osmium carbene complex in toluene was prepared in a 5 mL volumetric flask with concentrations in the range 1 - 4 mM. Concentrations were determined by ¹H NMR using triphenylmethane as an internal standard. A second toluene stock solution containing styrene, diazo reagent, and the internal GC standard (dodecane for diazoesters or hexamethylbenzene or fluorene for aryldiazomethanes) was prepared in a 10 mL volumetric flask. In a glovebox, a 5 mL round bottom flask was charged with ca. 800 μ L of carbene complex solution and a stir bar. The flask was capped with a rubber septum and sealed with parafilm. The flask was removed from the glovebox, placed in a -78 °C dry ice/acetone slurry bath, and stirred to allow the solution to reach thermal equilibrium (ca. 5 minutes). Approximately 25 - 30 μ L of the second stock solution

(1 equivalent diazo reagent and 5 equivalents styrene with respect to carbene complex) were added by syringe into the cold reaction flask. The initial concentrations of carbene complex and diazoacetate were 1 - 3 mM. These initial concentrations were chosen so that reasonable GC detection of products could be accomplished. The mixture was analyzed by GC as fast as mechanically possible (2 - 10 sec) to determine product ratios.

Results

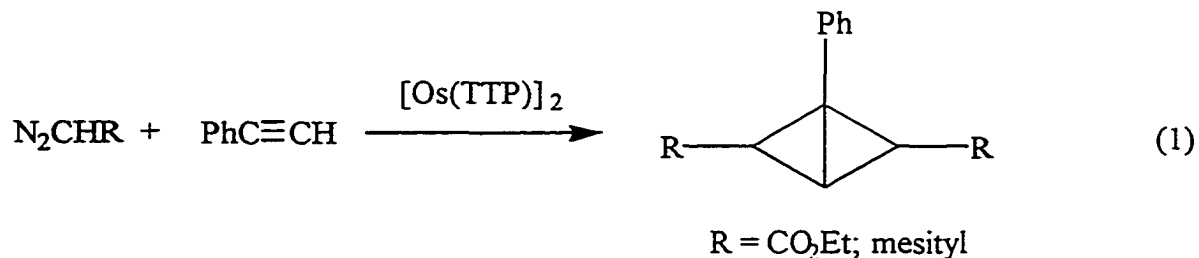
Osmium Catalyzed Cyclopropanation. The catalytic cyclopropanation of styrene with ethyl diazoacetate mediated by $[\text{Os}(\text{TTP})]_2$, **2**, is a relatively rapid process. At ambient temperature with 0.5 mol % $[\text{Os}(\text{TTP})]_2$, 100 μM styrene, and 100 μM ethyl diazoacetate, reactions 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. In fact, maleates and fumarates were the major product and were formed in approximately 70% yield if all reagents were present prior to addition of the $[\text{Os}(\text{TTP})]_2$. The cyclopropane yields were typically 30%. However, the unwanted self-condensation reaction was minimized by using an excess of styrene (Scheme I) 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 two hours to 960 μmol of styrene and 0.2 mol % $[\text{Os}(\text{TTP})]_2$ 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.

Scheme I



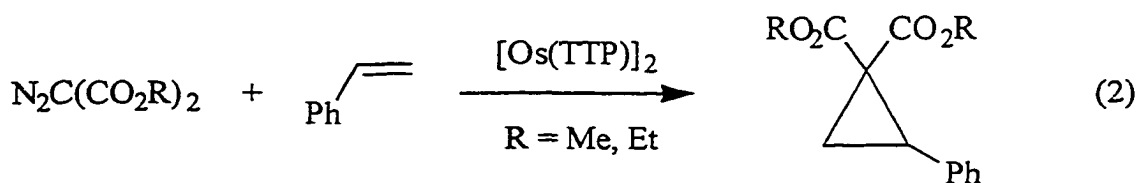
<u>styrene / EDA</u>	<u>olefin / cyclopropane</u>
1	70:30
2	62:38
5	40:60
10	28:72

Non-activated linear and cyclic olefins were less reactive than styrene. For example, dropwise addition of ethyl diazoacetate to a solution of 1-octene and $[\text{Os}(\text{TTP})]_2$ (0.3 mol %) produced ethyl-2-*n*-hexylcyclopropane carboxylic acid ester, **5b**, in 66% yield with 34% diethyl maleate and fumarate present. In contrast, phenylacetylene was a particularly active substrate. Both π -bonds undergo cyclopropanation to afford *endo,endo*-2,4-di(ethoxycarbonyl)-1-phenyl-[1.1.0]bicyclobutane, **6a**, in 46% yield using ethyl diazoacetate (eq 1). When mesityldiazomethane was used, the yield of *endo,exo*-2,4-di(mesityl)-1-phenyl[1.1.0]bicyclo-butane, **6b**, was 77%.



Qualitative Effect of Diazo Substituents. Qualitatively, 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=CHTMS, **4c**. In a qualitative sense, steric and electronic properties of the substituents on the α-carbon of the diazo reagent significantly influence cyclopropanation.

Diazomalonates, 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 2). For example, the cyclopropanation of styrene (10 equivalents) with approximately 850 μmol ethyl diazoacetate was complete in less than one minute using [Os(TTP)]₂ as a catalyst. However, under similar conditions, the reaction took 7-8 hours when diethyl or dimethyl diazomalonate was used as the carbene source. The yield of diester cyclopropanes was quantitative with no olefin byproducts from carbene coupling.



Relative Rate Studies. In a typical competition experiment, a 1:1 mixture of styrene and *p*-methylstyrene containing 0.3 mole % $[\text{Os}(\text{TTP})]_2$ in toluene was treated dropwise with a solution of ethyl diazoacetate for ca. 30 minutes (Scheme II). GC analysis of the product mixture gave a reactivity ratio of 1.66:1 for *p*-methylstyrene/styrene (Table I). The data for five substrates (*p*-OMe, *p*-Me, *p*-H, *p*-Cl, and *p*-CF₃ styrenes) yielded a Hammett plot (Fig. 1), with a slope of -0.80 ± 0.09 ($R^2 = 0.926$), indicating a modest electronic effect.

Scheme II

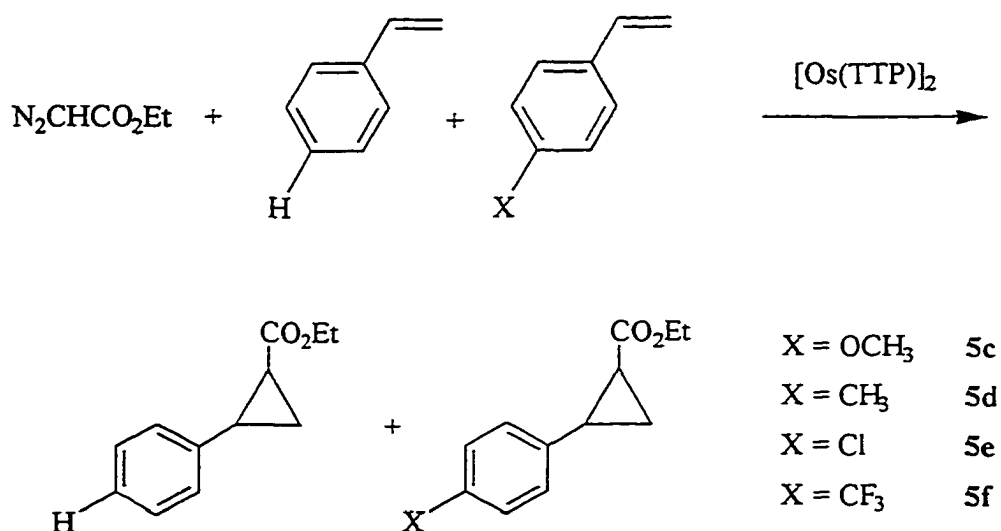


Table I. Competition reactions catalyzed by $[\text{Os}(\text{TTP})]_2$.

Olefin A	Olefin B	Ratio of Products Derived from A/B
4-methoxystyrene	styrene	2.24 ± 0.03
4-methylstyrene	styrene	1.66 ± 0.06
4-chlorostyrene	styrene	0.83 ± 0.02
4-methoxystyrene	4-trifluorostyrene	4.8 ± 1.1
α -methylstyrene	styrene	2.39 ± 0.06
α -methylstyrene	<i>trans</i> - β -methylstyrene	only A reacts

Hammett Plot

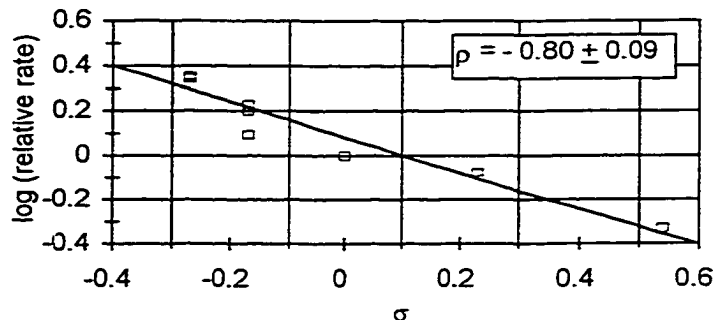
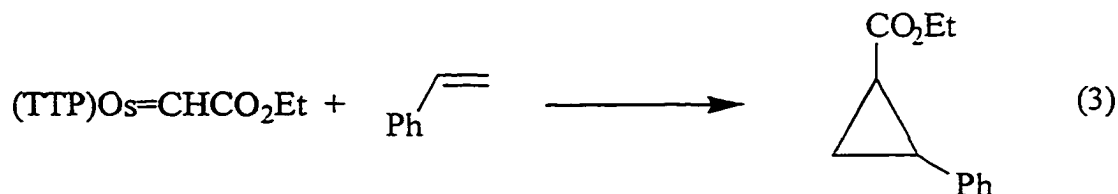


Figure 1. Hammett plot for the cyclopropanation of styrenes with EDA using $[\text{Os}(\text{TTP})_2]$ as the catalyst.

Catalytic and Stoichiometric Cyclopropanation with $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$.

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 $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ can be isolated and purified, it was examined for its ability to promote stoichiometric cyclopropanation. On treatment of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ with a 3-fold excess of styrene at ambient temperature in toluene, ethyl-2-phenylcyclopropane carboxylic acid ester formed slowly in 96% yield after 4 hours (eq 3). In contrast, when $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ was used in catalytic amounts with styrene and ethyl diazoacetate, the

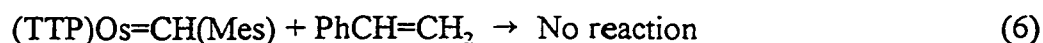
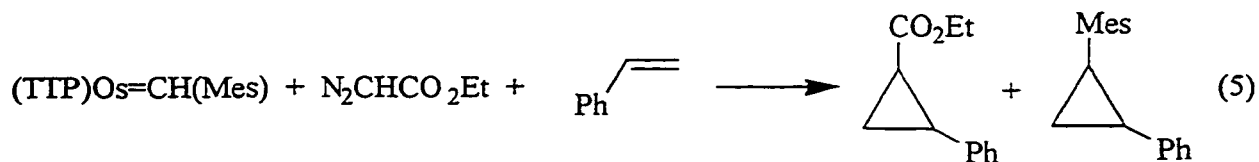
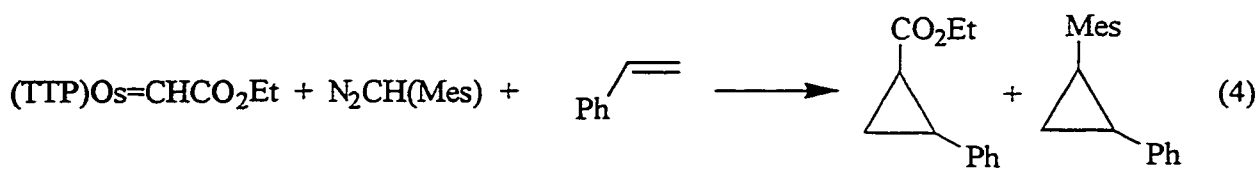


cyclopropanation reaction was complete in seconds - a rate that was qualitatively comparable to the $[\text{Os}(\text{TTP})]_2$ -catalyzed reaction.

σ -Donor Ligand Additives. Based on the stoichiometric study described above, it was apparent that a monocarbene complex could not be the active catalyst in this system. A possible alternative was that the carbene ligand is activated towards transfer by coordination of an additional axial ligand. Ligands such as PPh_3 or THF did bind to the carbene complex as observed by ^1H NMR studies. For example, treatment of $(\text{TTP})\text{Os}=\text{C}(p\text{-tolyl})_2$, **4b**, with excess THF in C_6D_6 produced new upfield resonances for a single 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 PPh_3 or THF in a catalytic reaction inhibited 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.¹⁹ Cyclopropanation of styrene with these ylide complexes occurred slowly over a period of days.

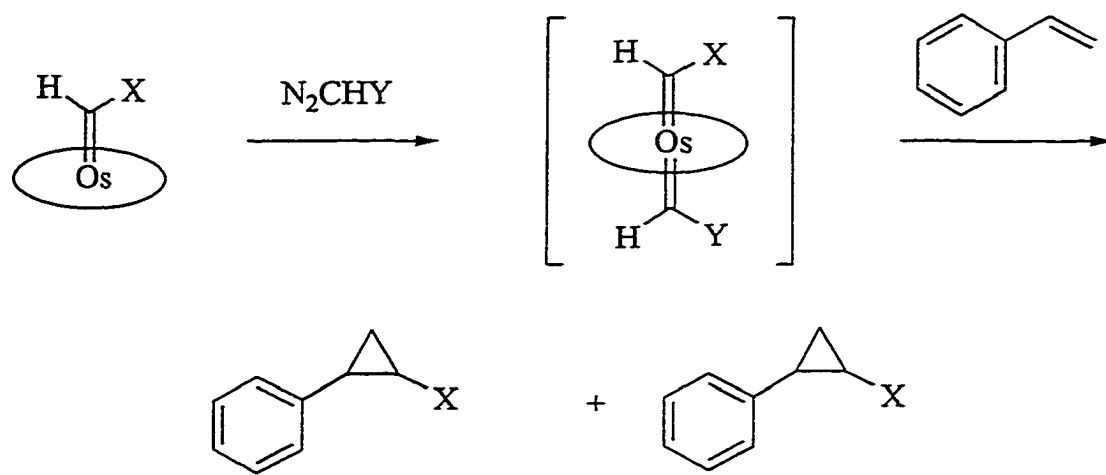
Biscarbene Intermediates. Since biscarbene complexes of $\text{Os}(\text{TTP})$ were observed when $[\text{Os}(\text{TTP})]_2$ was treated with $\text{N}_2\text{C}(p\text{-tolyl})_2$,^{8a} experiments to test for a catalytically active biscarbene species were undertaken. When 1 equivalent of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ was treated with a mixture of 1 equivalent of mesityldiazomethane and 10 equivalents of styrene in toluene at ambient temperature (eq 4), a rapid reaction ensued which produced cyclopropane 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 (eq 5). 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 mesitylmethylidene ligand from (TTP)Os=CH(Mes), **4d**, did not occur until a diazo reagent was added.



Labeling Experiments. To help gain further insight into the mechanism of [Os(TTP)]₂-catalyzed cyclopropanation, a series of labeling studies was undertaken as illustrated in Scheme III. In order to test the viability of a transient mixed biscarbene species in which both carbene ligands have identical or nearly identical tendencies for transfer, ester groups were initially chosen on both the starting monocarbene 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, biscarbene

Scheme III



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. This undesirable symmetric bis-carbene species, $(\text{TTP})\text{Os}[\text{=CHY}]_2$ would form from the remaining diazo reagent and result in over-incorporation of the Y label into the product mixture. Since the catalytic cyclopropanation reaction was complete in about 25 seconds with 0.5 mol % of the osmium precatalyst at ambient temperature, it was apparent that labeling experiments would be too fast to monitor at this temperature. As a consequence, 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 one equivalent $\text{N}_2\text{CHCO}_2\text{Pr}$, five equivalents styrene, and dodecane as an internal standard in toluene was added to a stirred toluene solution of one equivalent of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ 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 to 6 seconds) to determine product ratios. Complementary experiments with $\text{N}_2\text{CHCO}_2\text{Et}$ and $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Pr}$, **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 unreliable. Conversions were still variable and ranged from 10 - 50%. Additionally, it was found that the monoester carbene complexes in several samples decomposed to give $(\text{TTP})\text{Os}(\text{CO})$, which is also an active cyclopropanation catalyst (*vide infra*). Contamination with small amounts of the carbonyl complex would result in overincorporation of the diazo label into the products.

The collective data from the labeling studies allowed an extrapolation of the product ratios at low conversions. The product ratio from this data, extrapolated to zero conversion, is 1.07 ± 1.00 . This suggests that the two carbene fragments have similar transfer rates. However, because of the scatter in the data (product ratios ranged from 0.17 to 5.88), as reflected in the large error in extrapolated the product ratio, a carbene-diazo adduct could not be ruled out as the active species in the catalytic reaction. The data were scattered equally above and below the best fit line, implying that no systematic error occurred in this experiment. The large scatter in the data is due to the inability to sample the product ratios at low conversions because of the rapid rate of reaction, even at $-78\text{ }^\circ\text{C}$. The presence of varying amounts of $(\text{TTP})\text{Os}(\text{CO})$ from the decomposition of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{R}$ also contributed to the scatter in the data.

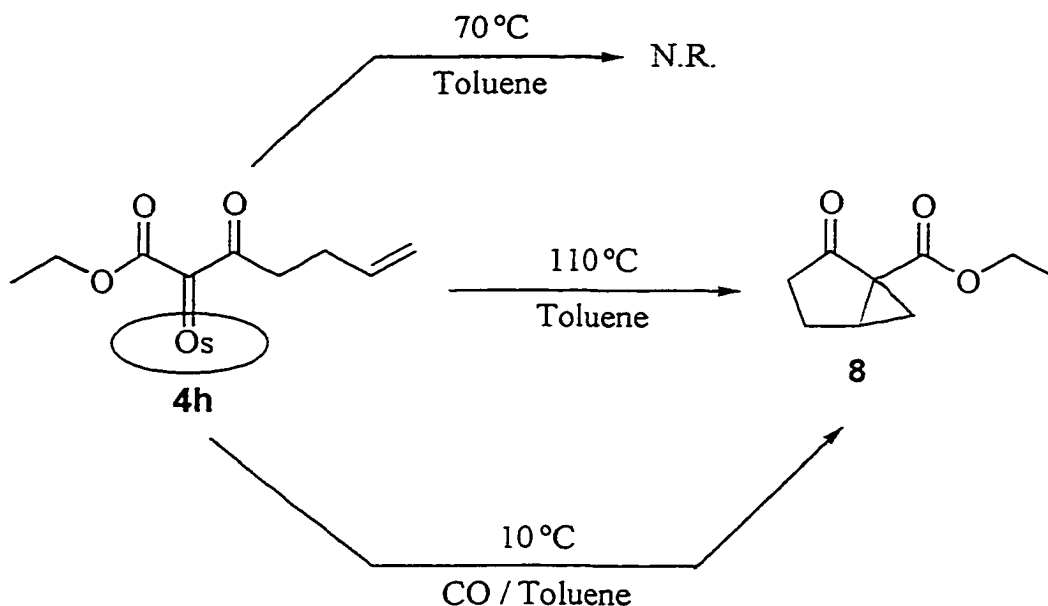
Because of the difficulty encountered due to the decomposition of the monoester carbene complexes, a series of labeling studies using aryl rather than ester diazo reagents was undertaken. Thus *p*-tolyl and *p*-ethylphenyl labels were used. Conditions analogous to the experiments with the ester labels were used, except that hexamethylbenzene 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, lower 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 seconds), the product ratio for the two labels is near one at low conversions. 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*-tolyl diazomethane), the ratio of *p*-tolyl to *p*-ethylphenyl products was 0.99 ± 0.11 . All of the data points were within the range of 0.70 to 1.20, a much narrower range than the experiments using ester labels. 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.²⁰ Thus a strong π -acid ligand such as CO may also activate monocarbene complexes towards transfer. To test this hypothesis, a monocarbene complex containing an appended olefin, (TTP)Os=C(CO₂Et)[C(O)CH₂CH₂CH=CH₂], **4h**, was prepared. At 70°C in toluene, complex **4h** showed no evidence of cyclopropanation after 2 hours. However, at 110°C, intramolecular cyclopropanation was observed with the formation of ethyl-2-oxo[3.1.0]bicyclohexanecarboxylic acid ester, **8**, (Scheme IV). 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 $(TTP)Os(CO)$ was used as the catalyst, results similar to those in the $[Os(TTP)]_2$ -catalyzed reactions were obtained. Using a ten-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 seconds. When the diazo reagent was added slowly over 5 minutes, only 2% of the olefin byproduct was observed.

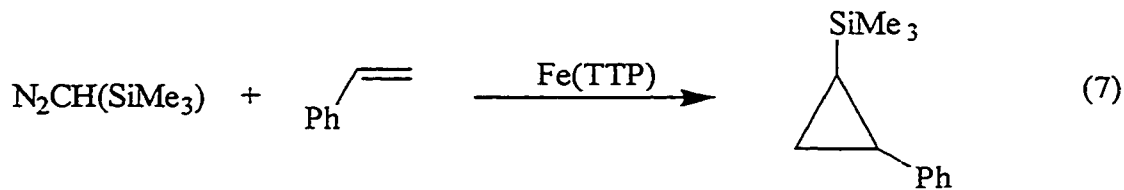
Scheme IV



Stoichiometric Competition Reactions. Upon treatment of $(TTP)Os=CHCO_2Et$, **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 $[\text{Os}(\text{TTP})]_2$ -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 metalloporphyrin complexes. In line with this observation, iron(II) porphyrins were also potent cyclopropanation catalysts.^{8c} Further evidence for the effectiveness of Fe(TTP) was derived from the cyclopropanation of styrene with trimethylsilyldiazomethane (eq 7). The cyclopropane product yield was 90% (*trans/cis* = 10 in toluene) at ambient temperature.²¹ Under the same conditions, $[\text{Os}(\text{TTP})]_2$ did not produce any observable cyclopropane.

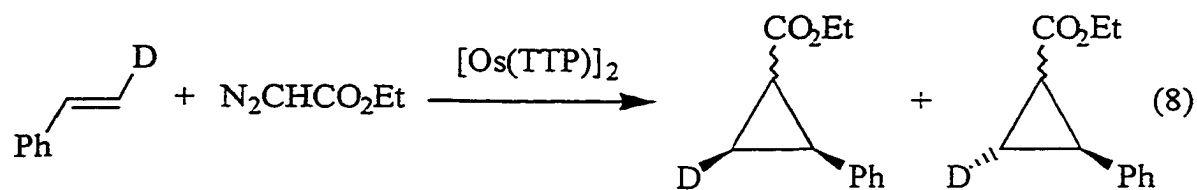


Reactivity Profile. Several substituted olefins were tested as substrates for the $[\text{Os}(\text{TTP})]_2$ -catalyzed cyclopropanation with ethyl diazoacetate. Mono- and 1,1-disubstituted styrenes were excellent substrates for the $[\text{Os}(\text{TTP})]_2$ -mediated cyclopropanation reactions. Phenylacetylene was also a good substrate, yielding bicyclobutanes. This is in contrast to Rh_2L_4 -catalyzed reactions which produced cyclopropenes.²² Monosubstituted olefins such as 1-octene could be cyclopropanated, 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 -methyl styrene was cyclopropanated 2.4 times faster than styrene, showing the preference of the osmium catalyst for electron-rich olefins. However, α -methyl styrene 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 cyclopropanated, 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 $87 \pm 4\%$ retention of stereochemistry. In the complimentary experiment, using *cis*- β -deuteriostyrene as the substrate, the retention of deuterium to phenyl stereochemistry was $92 \pm 4\%$.



Discussion

Cyclopropanation reactions mediated by transition metal complexes generally can be divided into two categories: stoichiometric and catalytic. In stoichiometric reactions, a reactive carbene complex is typically generated *in situ* as the active carbene transfer reagent. In contrast, isolable carbene complexes do not cyclopropanate olefins under mild conditions.²³ 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 $(\text{CO})_5\text{W}=\text{CHPh}$ relative to the $\text{Rh}_2(\text{OAc})_4$ -catalyzed cyclopropanation reaction with N_2CHPh .²⁴ Similar stereoselective correlations, as a function of olefin, were observed for ethyl diazoacetate with other catalysts.^{25,26} Also, the observation of enantiomeric excesses in chiral copper- and rhodium-catalyzed^{27,3e} cyclopropanation processes suggested that the metal complex was intimately involved in the product forming step. Moreover, production of free carboethoxy carbene from EDA does not result in the formation of diethyl maleates or fumarates.²⁸ The results observed in the $[\text{Os}(\text{TTP})]_2$ system are inconsistent with free carbenes.²⁸

Recently, however, Nishiyama and co-workers have isolated trimethylsilylmethylidene and aryloxycarbonylmethylidene complexes of a bis(oxazolinyl)pyridine ruthenium complex by

treatment of an active cyclopropanation catalyst with bulky diazo reagents.²⁹ 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.

Kodadek and coworkers observed a rhodium(III) porphyrin adduct with ethyl diazoacetate at low temperature by treatment of (TTP)RhI with EDA at -40 °C.^{6a} The EDA adduct lost N₂ above -20°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.^{6d} Kodadek ruled out participation of the iodoalkyl fragment in cyclopropanation by using an ethoxycarbonyl iodoalkyl rhodium(III) porphyrin complex as a catalyst for cyclopropanation with *tert*-butyl diazoacetate. At the end of the reaction, only *tert*-butyl-2-phenylcyclopropane carboxylic acid ester had been produced. In addition, the final iodoalkyl rhodium(III) complex was the ethyl ester derivative, (TTP)Rh-CH[C(O)OEt]I.

Our ability to isolate carbene complexes from osmium porphyrin-catalyzed cyclopropanation reactions suggested 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*-methoxystyrene reacted 4.8 times faster than *p*-trifluoromethylstyrene. This observation is inconsistent with prior coordination of the olefin to osmium followed by nucleophilic attack on the π -bound olefin by the α -carbon of the diazo reagent. The most likely mechanism involves formation of a carbene complex and subsequent nucleophilic 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*-tolyl)diazomethane than it was with ethyl diazoacetate. Moreover, when trimethylsilyldiazomethane was used as the carbene source, no cyclopropanation was observed. 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. Isolation of a 1-phenylethylidene complex, (TTP)Os=CMePh, **4i**, was possible. If dissociation of the carbene ligand occurs, rearrangement of the free carbene to styrene would occur with a rate constant of 10^6 s^{-1} .³⁰ However, solutions of (TTP)Os=CMePh did not produce any detectable amounts of styrene at ambient temperature.

As further evidence for the involvement of carbene complexes, (TTP)Os=CHCO₂Et was examined as a cyclopropanation catalyst. Under similar conditions, both [Os(TTP)]₂ and the monocarbene complex produced similar yields and stereoselectivities of cyclopropane products from styrene and ethyl diazoacetate in qualitatively similar rates. However, in the stoichiometric reaction between (TTP)Os=CHCO₂Et and an excess of styrene, the production

of cyclopropane occurred over a time span of hours. Consequently, the monocarbene complex could not be the active catalytic species. Additionally, activation of the carbene towards transfer could not be achieved through addition of σ -donor ligands. Thus, the presence of THF, 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 biscarbene complex. Carbene ligands are typically electron withdrawing in character,²⁰ thus a biscarbene intermediate would be more susceptible towards nucleophilic attack. In addition, biscarbene complexes of osmium porphyrins have been observed and isolated with di(*p*-tolyl)diazomethane and 1-phenyldiazoethane. We have not been able to observe a biscarbene complex by low temperature spectroscopic techniques when ethyl diazoacetate was used as the carbene source. Presumably this is due to the strongly electron withdrawing nature of the ester functionality and relative accessibility of the carbene carbon. If any biscarbene formation occurs from the reaction between (TTP)Os=CHCO₂Et and ethyl diazoacetate, build up of the biscarbene intermediate is prevented by a rapid reaction with additional ethyl diazoacetate to form diethyl maleates, diethyl fumarates, and (TTP)Os=CHCO₂Et.

Recently, Simonneaux and co-workers used (Por)Ru(CO) complexes as catalysts for the cyclopropanation of styrene with ethyl diazoacetate.³¹ A carbene-carbonyl complex, (Por)Ru(=CHCO₂Et)(CO) was detected spectroscopically. This species, with an electron-withdrawing carbon monoxide ligand *trans* to the carbene ligand is related to our proposed biscarbene osmium intermediate. Che and Cheng also recently reported using carbonyl

ruthenium porphyrin and porphycene complexes as cyclopropanation catalysts.³²

Key evidence for a biscarbene intermediate was derived from a series of experiments which compare the carbene transfer abilities of isolated carbene complexes in the presence and absence of diazo reagents. For example, the monocarbene complex, $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$, slowly produced cyclopropane from styrene over a period of hours in a stoichiometric reaction at ambient temperature. However, addition of mesityldiazomethane to a mixture of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{Et}$ and styrene in toluene resulted in the rapid formation of cyclopropanes containing the ester group or the mesityl substituent. More compelling was the complementary experiment using $(\text{TTP})\text{Os}=\text{CH}(\text{mesityl})$. As shown in equation 6, this monocarbene complex was unable to produce, stoichiometrically, cyclopropane on treatment with styrene over the course of days. However, addition of ethyl diazoacetate to the mixture resulted in rapid cyclopropane production over a period of minutes. Although the major product was ethyl-2-phenylcyclopropane carboxylic acid ester, approximately 10% of the product was 1-mesityl-2-phenylcyclopropane. Clearly, addition of the diazo reagent resulted in activation of the mesityl carbene ligand.

In order to investigate the mechanism of $[\text{Os}(\text{TTP})]_2$ catalyzed cyclopropanation, a series of labeling experiments was undertaken to address the formation of a biscarbene intermediate. Initial studies utilized alkyl diazoacetates and alkoxycarbonylcarbene complexes because substitution of the alkyl groups on the ester moieties provided a simple means of labeling the different carbene sources. The rapid rate of cyclopropanation in this system at $-78\text{ }^\circ\text{C}$ prevented sampling at low conversions. For example, after 3 - 10 s of reaction time at $-78\text{ }^\circ\text{C}$, conversions as high as 80% were observed. Attempts to quench the reaction at low

conversions also proved to be limited in determining product ratio measurements at low conversions. A further complication arose from the decomposition of $(\text{TTP})\text{Os}=\text{CHCO}_2\text{R}$ to $(\text{TTP})\text{Os}(\text{CO})$. The carbonyl complex was an efficient cyclopropanation catalyst and artificially increased the diazo label incorporation. Consequently, a series of labeling experiments using aryl labels was also undertaken. The labeling studies using *p*-tolyl and *p*-ethylphenyl labels were also consistent with a biscarbene intermediate. The average ratio of cyclopropane products from the diazo reagent to the cyclopropane products from the initial osmium carbene fragment for all of the labeling experiments was 0.97 ± 0.17 . The aryl labeling data taken at early times during the reaction were much less scattered than the data from the ester labeling experiments. The fact that the relative transfer rate for both the initial carbene on the osmium and the carbene derived from the diazo reagent were similar suggested that a biscarbene was the active catalytic species.

Alternative intermediates, osmium(II) carbene-diazoalkane adducts, were also considered. Figure 2 shows the structures of some possible intermediates. Both N-bound³³ and C-bound^{6a} diazo adducts of EDA are known. A large number of N-bound diazo adducts, showing both η^1 - and η^2 -binding modes, exist. However, these complexes tend to be stable towards loss of N_2 .³³ Moreover, the chemistry of a series of molybdenum η^1 -N-bound diazo adducts employing aryl and alkyl diazoalkanes showed Wittig-type reactivity. These complexes yielded olefins with loss of N_2 upon treatment with simple phosphoranes, Ph_3PCHR ($\text{R} = \text{H}, \text{tBu}, \text{Ph}$).³⁴

A C-bound diazoacetate adduct was also a possibility, as proposed by Kodadek and co-workers for the rhodium porphyrin system.^{6a} However, the rhodium C-bound

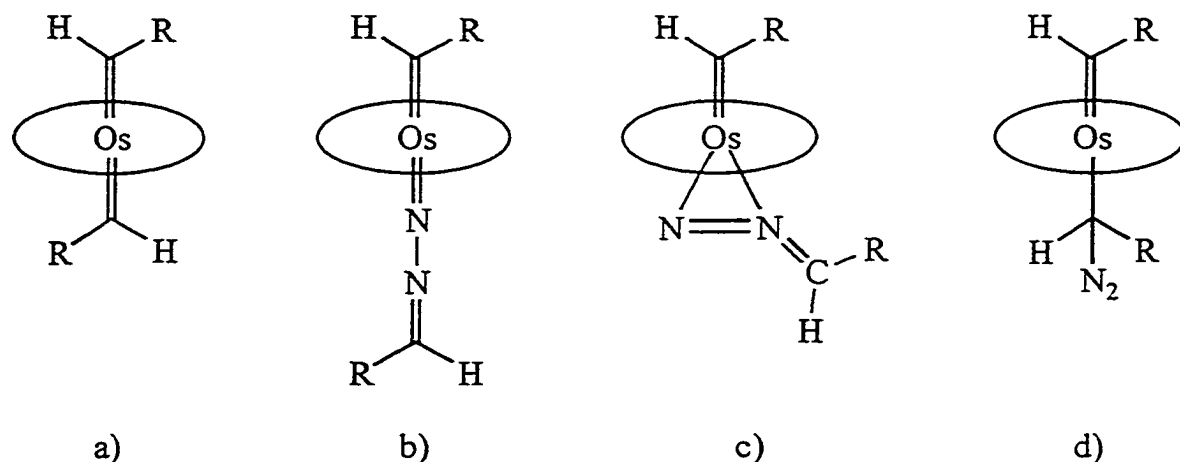


Figure 2. Possible active intermediates in the $[\text{Os}(\text{TTP})]_2$ -catalyzed cyclopropanation reaction. a) An Os(II) biscarbene. b) An Os(II) carbene- η^1 -N-bound diazo adduct. c) An Os(II) carbene- η^2 -N,N-bound diazo adduct. d) An Os(II) carbene-C-bound diazo adduct.

intermediate was not thermally stable and lost N_2 above $-20\text{ }^\circ\text{C}$. The only other examples of C-bound metal complexes of diazo reagents were not relevant to the osmium porphyrin system since these involve the replacement of an α -H with a metal, yielding a metal-substituted diazo alkane $[\text{N}_2=\text{C}(\text{R})(\text{M})]$.³⁵

If the carbon fragment transferred to the olefin originates from the C-bound diazo intermediate, *trans*-(TTP)Os=CHR[CH(N₂)R], it is likely that the substrate selectivities of the catalytic and stoichiometric processes would differ. This was not observed. The catalytic and stoichiometric substrate selectivities were found to be indistinguishable within experimental error. Thus, the most viable intermediate in the Os porphyrin system is a biscarbene species. The presence of two electron withdrawing carbene ligands on a single metal center should result in a higher susceptibility towards nucleophilic attack by an olefin. In essence, the

second carbene ligand serves to activate the complex towards cyclopropanation. To provide further support for this activation mechanism, the internal cyclopropanation of $(\text{TTP})\text{Os}=\text{C}(\text{CO}_2\text{Et})[\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2]$, **4h**, was investigated. As shown in Scheme III, 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 towards nucleophilic attack and promotes cyclopropanation.

The importance of the electrophilicity of the metal complex was supported by studies with $(\text{TTP})\text{Os}(\text{CO})$ and $\text{Fe}(\text{TTP})$. Both complexes are extremely effective cyclopropanation catalysts. The *trans/cis* cyclopropane ratio and rate of reaction for $(\text{TTP})\text{Os}(\text{CO})$ are comparable to the $[\text{Os}(\text{TTP})]_2$ -catalyzed reactions. In addition, $\text{Fe}(\text{TTP})$ was more active than $[\text{Os}(\text{TTP})]_2$, as the iron complex was capable of catalyzing cyclopropanation of styrene with N_2CHTMS . 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.

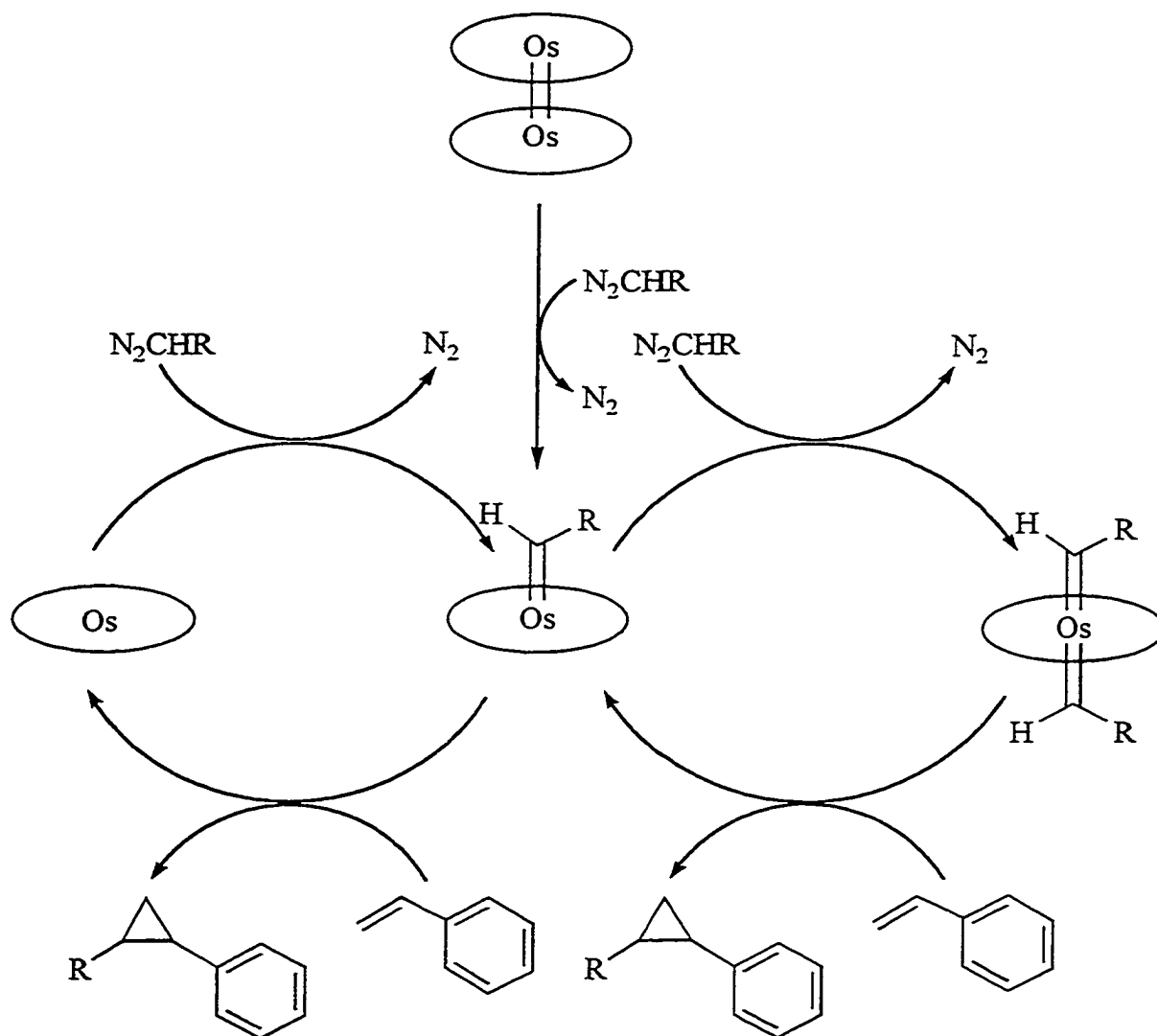
Conclusions

Osmium porphyrins are excellent catalysts for the stereoselective cyclopropanation of olefins with diazo reagents. Chemical and mechanistic investigations are consistent with a biscarbene osmium(II) porphyrin as the active catalytic species (Scheme V). For example, biscarbene species could be isolated using diaryldiazomethanes. In addition, stoichiometric cyclopropanation by isolated monocarbene osmium(II) porphyrins was much slower than the catalytic process. Although a *trans*-osmium(II) carbene-diazo adduct cannot be explicitly ruled out, substrate selectivity profiles are more consistent with a biscarbene intermediate.

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Scheme V



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CHAPTER 5: INSERTION OF DIMETHYL DIAZOMALONATE INTO C-H BONDS
CATALYZED BY (CARBONYL)(TETRA-*P*-TOLYLPORPHYRINATO)OSMIUM(II)

A paper to be submitted to *Organometallics*

Christopher G. Hamaker and L. Keith Woo*

Abstract

Facile insertion of dimethyl diazomalonate into benzylic C-H bonds was achieved using (TTP)Os(CO) (TTP = dianion of *meso*-tetra-*p*-tolylporphyrin) as a catalyst. The reaction between toluene and dimethyl diazomalonate led to multiple products from insertion of one and two dimethoxycarbonylcarbene fragments into benzylic positions. Products were identified by GC/MS. Insertion into aromatic C-H bonds was not observed.

Introduction

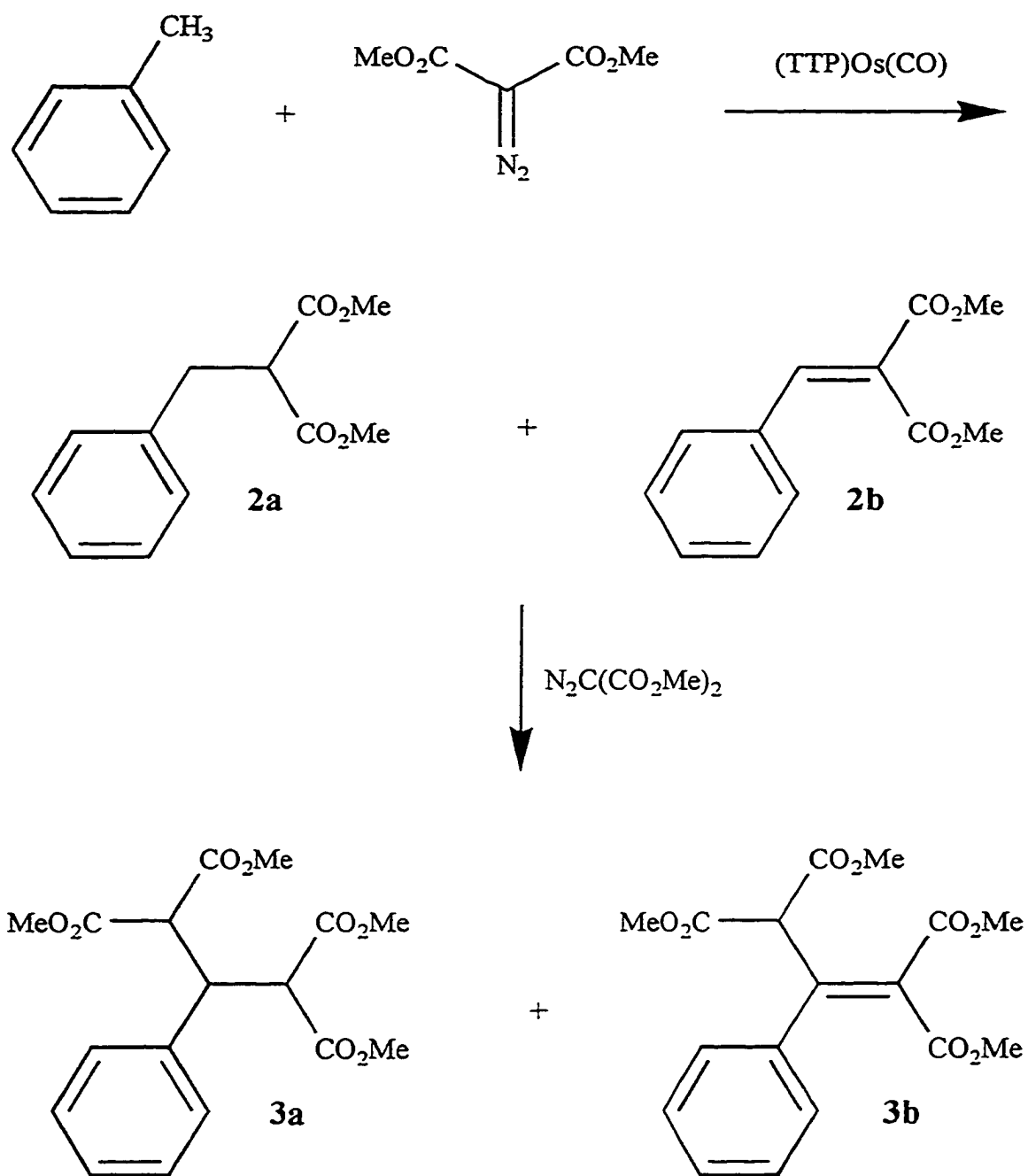
The transition metal-catalyzed intramolecular insertion of diazo compounds into C-H bonds is a well investigated phenomenon in organic chemistry.¹ However, catalytic intermolecular C-H bond insertion processes are much less studied.² The major problem with the intermolecular reaction is low selectivity. Regiocontrol is difficult to achieve and mixtures of products result. Noels and co-workers have investigated several rhodium(II) carboxylates as catalysts for the insertion of ethyl diazoacetate into C-H bonds of alkanes. All of the complexes investigated preferentially inserted the carboethoxycarbene fragment at the C₂

position of *n*-alkanes (47 - 57 % of the products arose from C₂ insertion with 0.5 - 23% from C₁ insertion). However, catalysts with bulkier ligands generally afforded a higher percentage of C₁ insertion.^{2c} Callot and Metz noted similar trends for (porphyrinato)rhodium(III) iodide catalyzed insertion of ethyl diazoacetate into alkane C-H bonds. Using (TPP)RhI,³ attack was mostly at the C₂ position (6% C₁ insertion and 52% C₂ insertion) but (TMP)RhI resulted in increased attack at the C₁ position (21% C₁ insertion and 52% C₂ insertion).

Results and Discussion

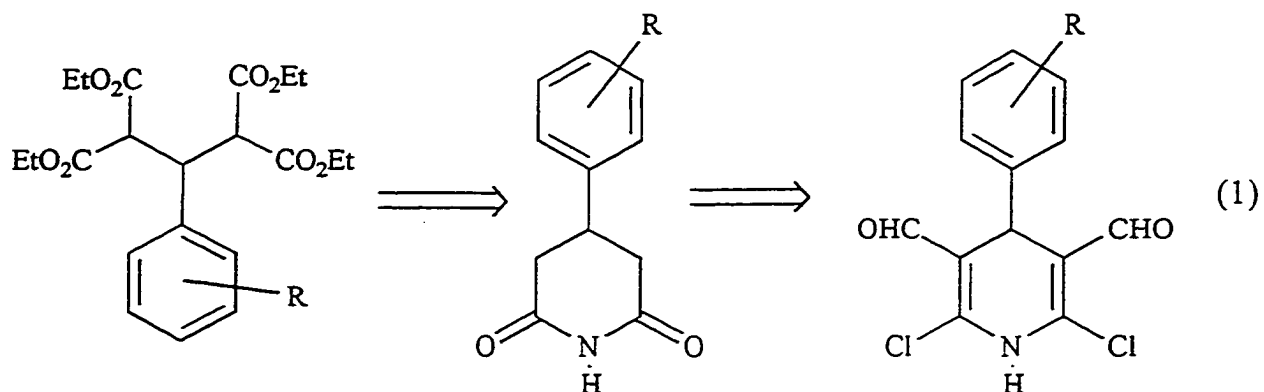
The complex (TTP)Os(CO), **1**, is an effective catalyst for the insertion of dimethyl diazomalonate into benzylic C-H bonds. Treatment of 55 equivalents of toluene with dimethyl diazomalonate in the presence of 0.7 mole % complex **1** afforded multiple insertion products as identified by GC/MS analysis (Scheme I). Along with products from insertion of one carbene fragment (**2a** and **2b**), products from insertion of a second dimethoxycarbonylcarbene fragment were also formed (**3a** and **3b**). For compound **2a**, a signal corresponding to [M+H]⁺ at *m/z* = 223 was observed by electron impact MS. For compound **2b**, the molecular ion peak at *m/z* = 220 was observed. Both products gave the expected fragmentation patterns (see experimental section). The ratio of **2a** to **2b** was approximately 8:1 as determined by ¹H NMR. The products derived by insertion of two carbene fragments gave very weak molecular ion peaks using electron impact, but were readily identified using chemical ionization with methane. Compound **3a** yielded a peak at *m/z* = 353 corresponding to [M+H]⁺. Compound **3b** was identified by a peak at *m/z* = 379 for [M+C₂H₅]⁺. The relative ratio of compound **3b** to compound **3a** was approximately 2:1 by GC (assuming the same FID response for

Scheme I



compounds **3a** and **3b**). However, while toluene was readily functionalized using dimethyl diazomalonate and (TTP)Os(CO), no insertion into the C-H bonds of diphenylmethane or triphenylmethane was observed.

Derivatives of compound **3a** with substituted benzene rings and ethyl rather than methyl esters have been used in the synthesis of 2,6-dichloro-1,4-dihydropyridine-3,5-dicarboxaldehydes (eq 1). These compounds are an important class of drugs used to treat



cardiovascular diseases.⁴ The tetraethyl ester derivative of **3a** has also been used in the synthesis of bis(crown ethers).⁵ Additionally, derivatives of compound **3a** could be used as synthons for dendrimers after saponification.

Experimental

General. All reactions were carried under dry nitrogen using a Vacuum/Atmospheres glove box equipped with a MO40DH DriTrain gas purification system or on a vacuum line using standard Schlenk techniques. All solvents were dried using standard methods.⁶ ¹H NMR were recorded on Varian VXR300, Varian VXR400, or Bruker DRX400

spectrometers and referenced against residual proton resonances of the deuterated solvents (δ (ppm) CDCl_3 : 7.24; C_6D_6 : 7.15). Gas chromatographic analyses were performed with a HP 5890 Series II.⁷ GC/MS analyses was performed on either a Finnigan Magnum GC-MS (electron impact, positive ion mode) or a Finnigan TSQ 700 (chemical ionization using methane, positive ion mode). Diethyl diazomalonate was prepared by diazo group transfer to dimethylmalonate from $\text{CH}_3\text{SO}_2\text{N}_3$ under basic conditions.⁸ The complex $(\text{TTP})\text{Os}(\text{CO})$ was prepared according to the literature procedure.⁹

Insertion of dimethyl malonate into benzylic C-H bonds of toluene. Into a round bottom flask was placed 8 mg (9 μmol) $(\text{TTP})\text{Os}(\text{CO})$ and 4 mL of toluene. A solution of 190 mg (1.20 mmol) of dimethyl diazomalonate in 3 mL of toluene was added at once. The reaction was stirred at 25°C and analyzed by GC and GC/MS. The excess toluene was removed *in vacuo* and the mixture of products analyzed by ^1H NMR.

Mass spectral data for compound 2a. MS{EI⁺}: $m/z = 223$ $[\text{M}+\text{H}]^+$, 191 $[\text{M} - \text{OCH}_3]^+$, 162 $[\text{M} - \text{CO}_2\text{CH}_3 + \text{H}]^+$, 131 $[\text{M} - \text{CO}_2\text{CH}_3 - \text{OCH}_3]^+$, 103 $[\text{M} - 2(\text{CO}_2\text{CH}_3)]^+$, 91 $[\text{M} - \text{CH}(\text{CO}_2\text{CH}_3)_2]^+$.

Mass spectral data for compound 2b. MS{EI⁺}: $m/z = 220$ $[\text{M}]^+$, 205 $[\text{M} - \text{CH}_3]^+$, 189 $[\text{M} - \text{OCH}_3]^+$, 160 $[\text{M} - \text{CO}_2\text{CH}_3 - \text{H}]^+$, 102 $[\text{M} - 2(\text{CO}_2\text{CH}_3)]^+$, 91 $[\text{M} - \text{C}(\text{CO}_2\text{CH}_3)_2 + \text{H}]^+$.

Mass spectral data for compound 3a. MS{CI⁺}: $m/z = 353$ $[\text{M} + \text{H}]^+$, 321 $[\text{M} - \text{OCH}_3]^+$, 261 $[\text{M} - \text{CO}_2\text{CH}_3 - \text{OCH}_3]^+$, 221 $[\text{M} - \text{CH}(\text{CO}_2\text{CH}_3)_2]^+$, 189 $[\text{M} - \text{CH}(\text{CO}_2\text{CH}_3)_2 - \text{OCH}_3 - \text{H}]^+$.

Mass spectral data for compound 3b. MS{Cl⁻}: m/z = 379 [M + C₂H₅]⁻, 221 [M - CH(CO₂CH₃)₂]⁺, 189 [M - CH(CO₂CH₃)₂ - OCH₃ - H]⁺, 91 [M - CH(CO₂CH₃)₂ - C(CO₂CH₃)₂ + H]⁺.

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GENERAL CONCLUSIONS

This dissertation focuses on the use of osmium and iron porphyrin complexes as catalysts for the production of cyclopropanes from diazo reagents and olefins. Also investigated was the insertion of dimethyl diazomalonate into benzylic C-H bonds.

Iron(II) and osmium(II) porphyrins are some of the most efficient catalysts reported for the cyclopropanation of olefins with diazo reagents. A wide variety of diazo reagents can be used as the carbene source, including diazo esters, aryldiazomethanes, diazomalonates, and trimethylsilyldiazomethane. The diastereoselectivity of the product cyclopropane can be controlled by the choice of catalyst, temperature, diazo reagent, and/or solvent.

At room temperature, (TTP)Fe catalyzed the production of ethyl-2-phenylcyclopropane carboxylate in high yield with excellent diastereoselectivity. *Trans/cis* ratios of up to 13:1 were obtained at ambient temperature using (TTP)Fe. However, by lowering the reaction temperature to -78°C , *trans/cis* ratios of 29 ± 2 could be achieved. These are among the best selectivities achieved for catalytic cyclopropanation using ethyl diazoacetate. A modest solvent dependence was also observed. Donor solvents and polar solvents gave higher *trans/cis* product ratios.

Additionally, (TTP)Fe is also an active catalyst for cyclopropanation using trimethylsilyldiazomethane. 1-Phenyl-2-trimethylsilylcyclopropane was obtained in 89% yield from styrene and trimethylsilyldiazomethane with no observable byproducts. This is in contrast to other catalysts which generally give low yields of cyclopropanes contaminated with 1,2-bis(trimethylsilyl)ethylene byproducts.

The synthesis of diaryl cyclopropanes from styrene and aryldiazomethanes was achieved using both iron(II) porphyrins and iron(II) tetramethyldibenzotetraaza[14]annulene. Diastereoselectivities were higher with (TTP)Fe compared to those for (tmtaa)Fe. Interestingly, while *p*-tolylidiazomethane gave primarily *trans*-cyclopropane products, mesityldiazomethane gave primarily *cis*-cyclopropanes. This difference in diastereoselectivity was rationalized by a change in the mechanism of the reaction. The orientation of the olefin as it approaches the intermediate carbene complex is altered when mesityldiazomethane is used. The *o*-methyl groups shield the carbene α -carbon and prevent a side-on approach. The reversal of diastereoselectivity with a change in diazo reagent is unique. Consequently, the (TTP)Fe system provides a simple synthetic route to both *cis*- and *trans*-cyclopropanes.

The scope and mechanism of the [Os(TTP)]₂-catalyzed cyclopropanation reaction was investigated. Ethyl diazoacetate, dialkyl diazomalonates, and mesityldiazomethane were used for the production of cyclopropanes with [Os(TTP)]₂. The most likely active intermediate in the [Os(TTP)]₂-catalyzed reaction is either a *trans*-osmium(II) biscarbene or *trans*-carbene-diazo adduct. Labeling studies utilizing either ester- or aryl-labeled diazo reagents and osmium carbene were performed and were consistent with a biscarbene intermediate. Also, addition of carbon monoxide serves to activate intramolecular cyclopropanation.

The complex (TTP)Os(CO) was an active catalyst for the insertion of dimethyl diazomalonate into the benzylic C-H bonds toluene. Products arising from insertion of one and two carbene fragments were observed.

There are two extensions of the research presented here with merit further study: modification of the tmtaa ligand and the use of chiral salen complexes of the heavier group 8

metals ruthenium and osmium.

The first area modification of the tmtaa ligand is the synthesis of chiral derivatives for enantioselective catalysis. The second is the addition electron withdrawing groups at the methine positions of the ligand could enhance catalytic activity. Iron(II), ruthenium(II), and osmium(II) complexes of the modified dibenzotetraaza[14]annulene ligands could serve as cyclopropanation catalysts.

Preliminary results using ruthenium(II) salen complexes are promising. The use of chiral salen ligands in ruthenium(II)-catalyzed cyclopropanation has great potential. Additionally, osmium(II) salen complexes could also yield some interesting chemistry.

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