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Iron(II) porphyrin catalyzed olefination reactions

by

Guilong Cheng

A thesis submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Organic Chemistry

Program of Study Committee:
L. Keith Woo, Major Professor
William S. Jenks
John D. Corbett

Iowa State University

Ames, Iowa

2002

Graduate College
Iowa State University

This is to certify that the master's thesis of

Guilong Cheng

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy

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LIST OF ABBREVIATIONS

EDA	ethyl diazoacetate
GC	gas chromatography
GC-MS	gas chromatography coupled to mass spectrometry
IR	infrared
mg	milligram
mol	mole
mmol	millimole
mL	milliliter
min	minute
MHz	megahertz
NMR	nuclear magnetic resonance
MS{EI}	mass spectrometry by electron impact
Ph	phenyl
ppm	parts per million
TPP	dianion of meso-tetraphenylporphyrin
TTP	dianion of meso-tetratolylporpyrin
tolyl	p-$C_6H_4CH_3$

CHAPTER 1.

GENERAL INTRODUCTION

Thesis organization:

This thesis includes four chapters. Chapter one summarizes the field of metalloporphyrin catalysis and an overview of metal-catalyzed olefination reactions. Chapter two is a communication published in the *Journal of the American Chemistry Society* on an iron porphyrin-catalyzed olefination reaction and a preliminary mechanistic study. Chapter three is an expansion of chapter two to a full paper for submission to the *Journal of Organic Chemistry*. Chapter four gives general conclusions.

Porphyrin ligands:

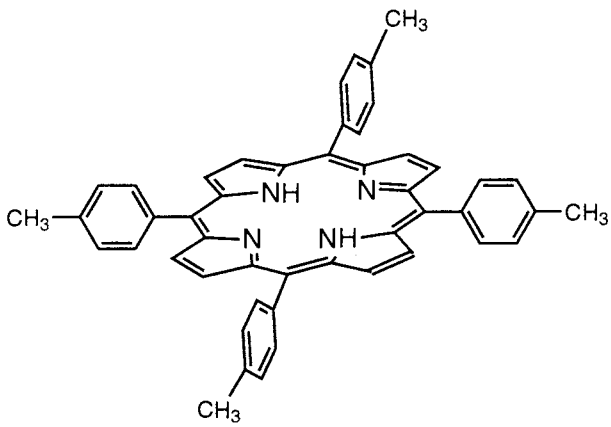
Porphyrins are highly conjugated macrocyclic molecules with four nitrogen donor atoms and twenty sp^2 carbons in the core. Due to its aromatic nature, the porphyrin skeleton is often planar. However, studies reported by Fleisher *et al.* showed that porphyrin ligands can deviate from planarity. For example, Nickel etioporphyrin-I has a saddle-shaped distortion in which the pyrrole rings alternately tilt upward and downward. The average displacement of the β-carbon atoms from the plane defined by the four meso carbons is about 0.25 Å.[1]

The most commonly used synthetic porphyrins are *meso*-tetra-*p*-tolylporphyrin (TTP), *meso*-tetraphenylporphyrin (TPP) and octaethylporphyrin (OEP) (Figure 1). The high symmetry of these molecules produces useful properties, involving a simple NMR spectra.

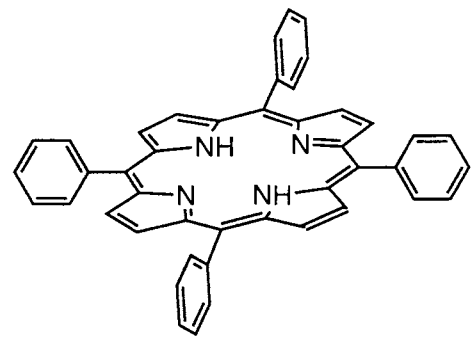
The TPP ligand gives rise to only four proton resonances in the ^{1}H NMR spectrum (ß-pyrrole, *o*-phenyl, *m*-phenyl, and *p*-phenyl).

Metalloporphyrin catalysis:

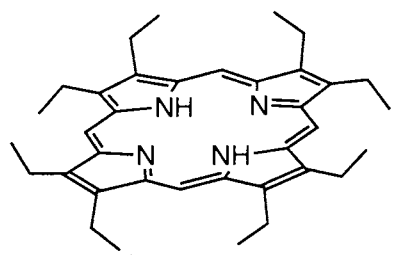
Porphyrins have been widely used as ligands in organometallic chemistry. Many transition metals, such as rhodium, osmium, iron, manganese, titanium, etc. bind in the porphyrin cavity. These metallophyrins have been successfully used as catalysts in a variety of reactions, such as oxidation, cyclopropanation, insertion,[2] and polymerization reactions.[3]



meso-tetra-*p*-tolylporphyrin (H_2TTP)



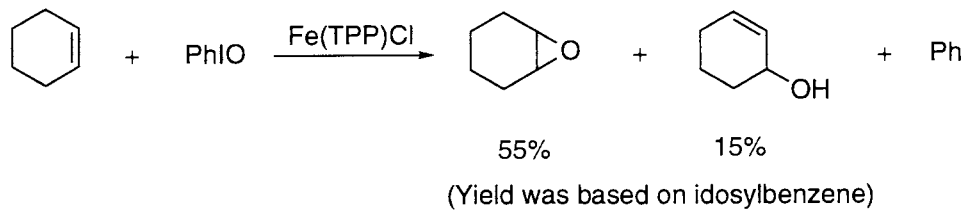
meso-tetraphenylporphyrin (H_2TPP)



octaethylporphyrin (OEP)

Figure 1 Commonly used synthetic porphyrins.

Olefin epoxidation is the first area in which metalloporphyrins were successfully used as catalysts. In fact, this is now the most widely used reaction catalyzed by synthetic porphyrin complexes.[4] In 1979, Groves and co-workers reported the use of iodosylbenzene as a simple oxygen atom source in epoxidation reactions catalyzed by Fe(TPP)Cl (Equation 1).[5] With cyclohexadiene, the reaction gave a 74% yield of the corresponding monoepoxide. Interestingly, the PhIO-epoxidation of olefins catalyzed by Fe(TPP)Cl was stereospecific. *Cis*-stilbene was converted to *cis*-stilbene oxide while *trans*-stilbene was inert. To rationalize this result, Groves proposed a mechanism that involved an electrophilic high-valent iron-oxo



Equation 1

species. Due to steric hinderance, *cis*-styrene would have a greater accessibility to the active iron-oxo porphyrin than *trans*-styrene. Two years later, John *et al.* reported a more detailed study to support Groves' mechanism.[6] Results reported in this paper showed that as the number of substituents on the double bond increased, the rate of epoxidation increased. For example, 2,3-dimethyl-2-butene, reacted 200 times faster than 1-octene. Furthermore, a series of 3- and 4-substituted styrenes was examined. As expected, electron-donating substituents enhanced the reaction rate of epoxidation. A Hammett treatment of these data gave a ρ value of -0.93, consistent with nucleophilic attack of the olefin on an electron-poor intermediate.

At the same time, studies reported by Chang and co-workers showed that the catalytic activity of the iron(III) porphyrin could been greatly improved when the macrocycle was replaced by *meso*-tetrakis(pentafluorophenyl)porphyrin (TPFPP).[7] With cyclohexene, the yield for cyclohexene oxide improved from 55% to 95% when Fe(TPP)Cl was replaced by (TPFPP)FeCl. This increase in catalytic efficiency was explained by an increase in resistance to porphyrin ring oxidation when TPP was replaced by the more electron deficient TPFPP.

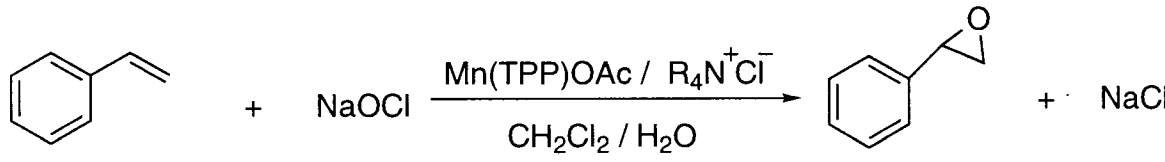
A more robust catalyst, 5,10,15,20-tetra(2,6-dichlorophenyl)porphyrinatoiron(III) chloride Fe(TDCPP)Cl, was reported by Traylor *et al.* in a 1984 epoxidation study.[8] The bulk and electron-withdrawing nature of chloride substituents made Fe(TDCPP)Cl even less vulnerable to dimerization. In fact, studies reported in Traylor's work showed that Fe(TDCPP)Cl is a much more efficient catalyst than those discussed above. When iodosylpentaflurobenzene was used as an oxidant, up to 10,000 turnovers of norbene oxide could be produced for every molecule of Fe(TDCPP)Cl.

Besides iron(III) porphyrin complexes, other metalloporphyrin species also catalyzed the epoxidation reaction. In 1979, Groves and co-workers reported the use of a chromium(III) porphyrin complex as a catalyst for epoxidation.[9] Like Fe(TPP)Cl, the epoxidation of olefins catalyzed by Cr(TPP)Cl was also stereospecific. *Cis*- and *trans*-stilbene were converted to *cis*- and *trans*-stilbene oxide respectively during catalysis. However, with cyclohexene, allylic oxidation was the main reaction product (2-cyclohexenol : 2-cyclohexenone : cyclohexene oxide = 75 : 21 : 4).

Mn(TPP)Cl was another metalloporphyrin complex that could be used in catalytic oxidation reactions. In 1980, Hill *et al.*[10] and Groves *et al.*[11] reported Mn(TPP)Cl-catalyzed oxidation reactions at the same time. In contrast to the Fe(TPP)Cl and Cr(TPP)Cl,

Mn(TPP)Cl-catalyzed epoxidation gave a mixture of *cis* and *trans* products from *cis*-stilbene (*cis/trans* ratio = 1:1.6). The loss of stereochemistry was explained by a radical pathway.[11] Studies reported by Groves showed that a carbon-centered radical was the reaction intermediate. The lifetime of this radical was sufficient to allow isomerization by a carbon-carbon bond rotation, accounting for the loss of stereochemistry.

In 1980, Meunier reported the first use of dilute sodium hypochlorite solution, NaOCl, as the oxygen source in the epoxidation of styrene catalyzed by Mn(TPP)OAc (Equation 2).[12] Sterically hindered manganese porphyrins were widely used in this reaction and good yields were generally achieved[13], including reactions of non-reactive substrates

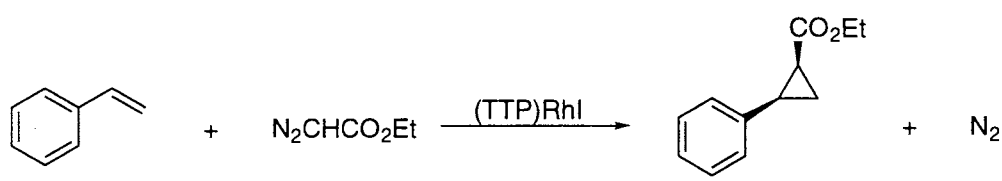


Equation 2

such as terminal olefins. In 1986, Suslick and co-workers reported the use of an extremely hindered manganese complex based on the *meso*-tetrakis-(2,4,6-triphenyl-phenyl)porphyrin ligand in the epoxidation of the exocyclic double bond of 4-vinylcyclohexane and limonene.[14] An enhanced selectivity due to size exclusion was observed.

Besides iodosylbenzene and sodium hypochlorite, a variety of other oxygen atom sources have been tried. For each reagent, different metalloporphyrin complexes have been employed as catalysts.[15] The area of oxidation reactions catalyzed by metalloporphyrin complexes is still an active area, with more than 100 articles published every year.[16]

Cyclopropanation of olefins is another area where metalloporphyrins gained extensive application. In 1980, Callot and co-workers reported the first use of a metalloporphyrin complex as a cyclopropanation catalyst for olefins with diazo reagents.[17] The cyclopropanation of styrene with ethyl diazoacetate using (TPP)RhI produced primarily *cis*-ethyl 2-phenylcyclopropanecarboxylate (*cis/trans* = 1.13, 71% yield, Equation 3). This result is quite unique when compared to the cases in which non-porphyrin copper and rhodium complexes were used as catalysts. In the latter cases the thermodynamically preferred *trans*-cyclopropanes are the major products.



Equation 3

In 1992, Kodadek and co-workers reported an investigation of the substrate profile for the rhodium(III) porphyrin-catalyzed cyclopropanation reaction with ethyl diazoacetate.[18] Generally, as the number of substituents on the double bond increased, the rate of cyclopropanation decreased. The exception was for trisubstituted alkenes, which reacted at about the same rate as monosubstituted alkenes. Also, *cis*-1,2-alkenes reacted faster than *trans*-1,2-alkenes.

One year later, our group reported that an osmium(II) complex, $[(TTP)Os]_2$ was an efficient catalyst for cyclopropanation.[19] The reaction of styrene with ethyl diazoacetate catalyzed by $[(TTP)Os]_2$ gave ethyl 2-phenylcyclopropanecarboxylate in 79% yield with a

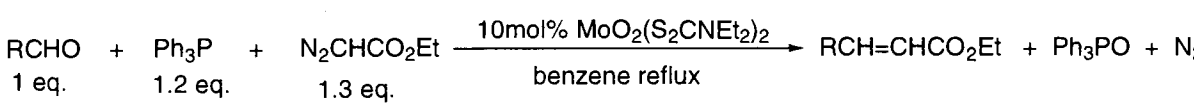
trans/cis ratio of 10.2:1. Other osmium complexes, including (TTP)Os(CO)(py) and the carbene complex (TTP)Os=$CHCO_2Et$ were tried and both found to be efficient catalysts. The osmium(II) porphyrin complexes were found to exhibit pronounced substrate selectivity. Only 1-substituted and 1,1-disubstituted alkenes were cyclopropanated. *Cis*- or *trans*-1,2-disubstituted alkenes were unreactive. Following the research on $[(TTP)Os]_2$, our group reported another group 8 metal porphyrin complex, Fe(TTP), was an efficient cyclopropantion catalyst.[20] The reaction of styrene with ethyl diazoacetate catalyzed by Fe(TTP) gave primarily *trans* cyclopropyl ester (*trans/cis* = 8.8) with a catalyst turnover number of 1300. This stereoselectivity exhibited a modest solvent dependence, with donor solvents such as THF giving higher ratios of the *trans* cyclopropane products. Similar to osmium porphyrin complexes, Fe(TTP) catalyzed the cyclopropanation of 1-substituted alkenes and 1,1-disubstituted alkenes very efficiently, but alkenes with 1,2-substitution patterns were poor substrates. Later research showed that changing the diazo reagent to a bulky diazo reagent such as mesityldiazomethane resulted in a reversal of stereoselectivity, giving *cis*-cyclopropane as the major product (*cis/trans* ratio up to 2.9).[21]

As a result of the high synthetic utility of metalloporphyrins with diazo compounds, we extended the scope of this activity by employing an iron(II) porphyrin complex as a catalyst for efficient and selective olefination of aldehydes. This is the first use of an iron(II) porphyrin complex as an olefination reaction catalyst and the detailed work will be discussed in chapters two and three.

Olefination of carbonyl compounds:

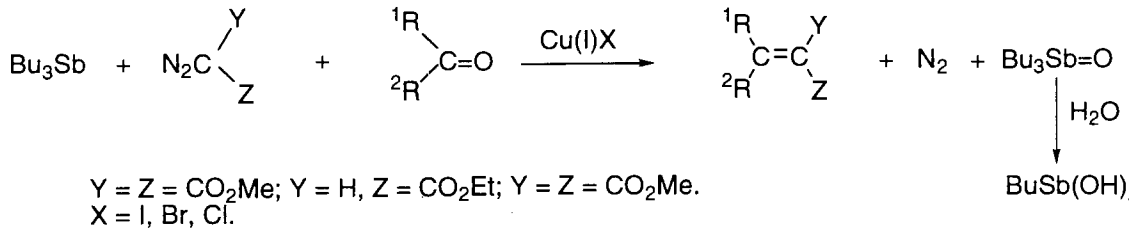
The generation of a carbon-carbon double bond is one of the important synthetic transformations in organic chemistry, especially in the areas of natural products and polymer

synthesis. Commonly used procedures include the Wittig reaction and its modified versions, the Peterson reaction and the Julia reaction.[22] Organometallic variants for this transformation have also been investigated in the past two decades and some have achieved significant success.[23] Another alternative is the olefination of carbonyl compounds by suitable diazo reagents in the presence of transition metal catalysts and triphenylphosphine or trialkylstibines as reducing agents. In 1989, Lu and co-workers published the first paper in this area.[24] A molybdenum complex, $MoO_2(S_2CNEt_2)_2$ was used as a catalyst for the olefination of aldehydes (Equation 4). In the next two years, two other catalytic systems

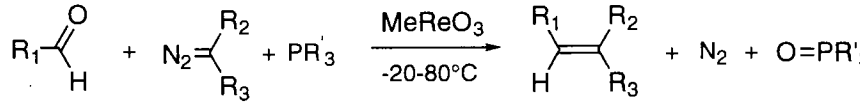


Equation 4

were reported by Huang, *et al.*[25] (Equation 5) and Herrmann, *et al.*[26] (Equation 6). In these approaches, olefins are generally produced in simple one-pot reactions. However, several drawbacks are apparent. These include a) high reaction temperatures that increase safety hazards when diazo compounds are used,[24,25] b) high catalyst loading (>5 mol%),[24,25,26] c) stereoselectivities[26] often highly dependent on the choice of the aldehydes and d) low yields.[24,26] In 1998, Fujimura[27] reported a one-pot olefination method using a ruthenium(II) complex as the catalyst (Equation 7). In this methodology, the amount of catalyst was

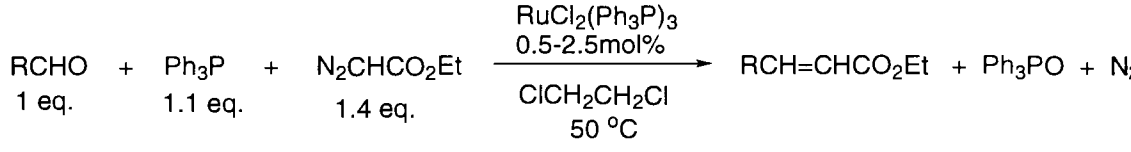


Equation 5



Equation 6

reduced to 2.5 mol% and a temperature of 50 °C was employed. For some aldehyde substrates, the isolated yields were not particularly high.



Equation 7

The work presented in chapters two and three describes a new catalytic method for the olefination of aldehydes and ketones using an iron(II) complex as the catalyst. High stereoselectivities and high yields of olefins are generally produced from a variety of aldehydes with ethyl diazoacetate in our method. Our reaction conditions are the mildest among all the catalytic olefination methods reported.

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CHAPTER 2.

A NEW AND EFFICIENT METHOD FOR THE SELECTIVE OLEFINATION OF ALDEHYDES WITH ETHYL DIAZOACETATE CATALYZED BY AN IRON(II) PORPHYRIN COMPLEX

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Gholam A. Mirafzal,[‡] Guilong Cheng, and L. Keith Woo*

Transition metal complexes based on porphyrins and a variety of ancillary ligands have been used extensively by this group[2] and others[3] to catalyze the cyclopropanation of alkenes using ethyl diazoacetate and other suitable diazo reagents. In this communication, we describe an extension of the catalytic activity of metalloporphyrins and its applications with the first use of an iron(II) metalloporphyrin complex as a catalyst for an efficient and selective olefination of aldehydes. The generation of a carbon-carbon double bond is one of the important synthetic transformations in organic chemistry, especially in the areas of natural products and polymer synthesis. Although other metal complexes can catalyze this reaction,[4] the iron system is especially proficient and cost effective.

Olefination of aromatic and aliphatic aldehydes (Table 1) was achieved in excellent yield at ambient temperature using 2 eq of ethyl diazoacetate, N_2CHCO_2Et, (EDA) and 1.1 eq triphenylphosphine, Ph_3P, in the presence of catalytic amounts of iron(II) meso-tetra(p-tolyl)porphyrin, Fe^{II}(TTP), (1-2 mol%), in toluene (eq 1). Ratios of reagents were selected for

convenient reaction times, high yields, and ease of purification. Ehyl maleate and fumarate were also observed as side products, but were readily removed by chromatography.

$$RCHO + N_2CHCO_2Et + Ph_3P \xrightarrow[-\,N_2]{Fe^{II}(TTP)} RCH{=}CHCO_2Et + Ph_3P{=}O \quad (1)$$

$$R = Ph\text{-},\ p\text{-}CH_3C_6H_4\text{-},\ p\text{-}NO_2C_6H_4\text{-},\ p\text{-}ClC_6H_4\text{-},\ PhCH_2\text{-},\ (Ph)_2CH\text{-}$$

Treatment of benzaldehyde, **1**, with EDA/Ph3P/Fe^{II}(TTP) in toluene at ambient temperature resulted in 98% conversion to ethyl cinnamate after 6 hours of reaction time. Both GC and ^{1}H-NMR analysis confirmed a high selectivity for *trans* to *cis* olefin products (24:1).[5] Purification of the trans-olefin product by silica gel column chromatography using hexane:ethyl acetate (20:1 v/v) afforded a 94% yield for olefination of **1** (Table 1). The reaction is catalytic as no olefination products were formed without Fe^{II}(TTP). In the absence of the catalyst, the azine, PhCH=N-N=$CHCO_2Et$ (m/z = 204, 131(base), 104, 77), was produced when the reaction mixture was allowed to stir for a period of 2 days. The reaction in the absence of Ph_3P also produced no olefination product. We found that this reaction requires a stoichiometric amount of Ph_3P to that of the aldehydes in order to give a high conversion to olefination products. The aldehyde oxygen is transferred to Ph_3P, producing 1 equiv of Ph_3P=O. GC and GC-MS analysis confirmed formation of Ph_3P=O (m/z = 278).

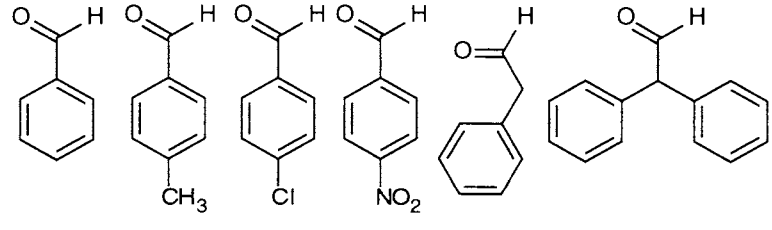


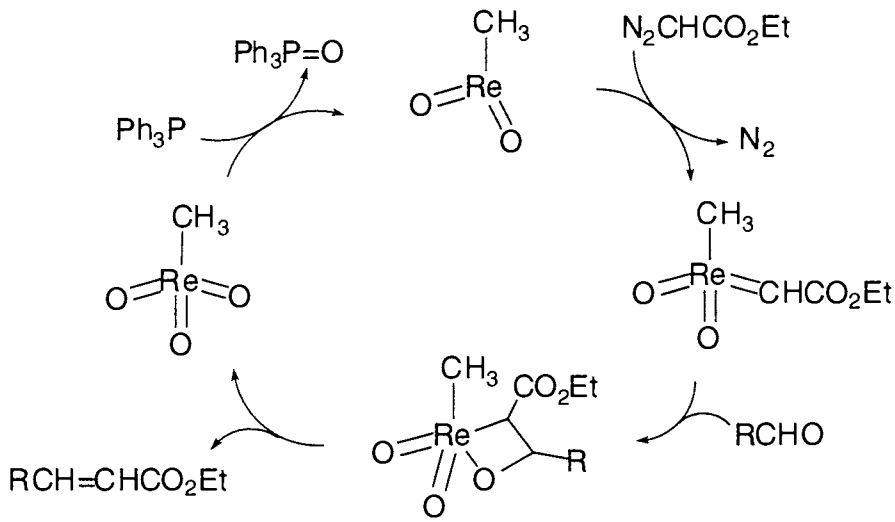
Table 1. Olefination of Aldehydes Using EDA/Ph_3P/Fe^{II}(TTP) System[a]

aldehyde	reaction time (h)	yield (%)[b]	turnover number	trans/cis selectivity[c]
1	6	94	128	24:1
2	12	99	119	24:1
3	3	95	98	13:1
4	2	90	80	24:1
5	23	85	95	10:1
6	12	93	64	49:1

[a] Typical procedure: To a stirred solution of 1-2 mol% Fe^{II}(TTP), 0.94 mmol (1 eq) aldehyde, and 1.04 mmol (1.1 eq) of Ph_3P in 10 mL toluene at room temperature under an inert atmosphere, was added dropwise a solution of 1.88 mmol (2 eq) of EDA in 3 mL of toluene. The progress of reaction was monitored by GC. [b] Isolated yield. [c] *Trans/cis* selectivity was determined by GC and ^{1}H-NMR. In our GC analysis, the *cis* isomer appeared at a shorter retention time versus the trans-isomer. ^{1}H-NMR analysis showed a $^3J_{HH}$ of 15.9 Hz for *trans*-hydrogens and a $^3J_{HH}$ of 12.6 Hz for *cis*-hydrogens.

Preliminary studies were undertaken to probe the mechanism for this olefination process. A catalytic cycle (Scheme 1) proposed for the analogous methyltrioxorhenium (MTO) catalyzed reaction[4e,6] involves oxygen atom abstraction from MTO by phosphine. The resultant Re(V) dioxo complex reacts with a diazo reagent to produce a carbene complex that subsequently forms a metallaoxetane species in the presence of aldehydes. Fragmentation of the metallaoxetane produces the new olefin and regenerates MTO. We presume that the active

Scheme 1



species in the iron porphyrin catalyzed reactions is an iron-carbene complex formed by reaction of the iron(II) porphyrin with EDA. Related complexes prepared from mesityl diazomethane and trimethylsilyl diazomethane are readily observed by ^{1}H NMR spectroscopy.[2c,d] However, (TTP)Fe=$CHCO_2Et$ is too reactive to isolate or detect spectroscopically. The more electron rich osmium analogue, (TTP)Os=$CHCO_2Et$, has been isolated and is well characterized.[2a,b] If a metallaoxetane intermediate is involved, the iron-carbene complex may serve as a nucleophile[7] that attacks the carbonyl functional group of aldehydes. This is consistent with the higher reactivity of electron poor aldehydes (vide infra). Subsequent ring opening of the metallaoxetane would produce an olefin and an oxoiron porphyrin complex. Regeneration of Fe(TTP) would occur by oxidation of phosphine to phosphine oxide.

For this mechanism to be viable, the inner sphere reaction between unencumbered oxoiron(IV) and iron(II) porphyrins, producing a μ-oxo Fe(III) dimer,[8] must be minimal. Formation of the Fe(III) dimer would serve to quickly inactivate the catalyst. However, rapid deactivation was not observed[9] and attempts were made to test for the presence of the iron(IV) oxo complex with other oxygen atom acceptors. Olefins were chosen since oxoiron(IV)

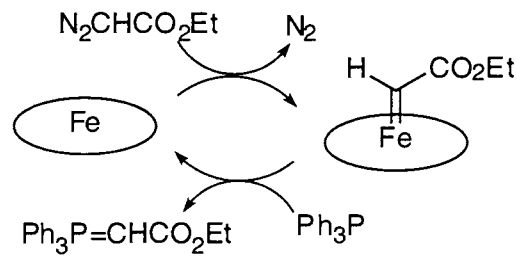
porphyrin complexes effectively epoxidize the double bond.[10] When an Fe(TTP)-catalyzed reaction of benzaldehyde and EDA was run with styrene substituted as the reductant in place of Ph_3P, no ethyl cinnamate was observed. The only product was ethyl 2-phenylcyclopropylcarboxylate (100%), indicating that styrene was much more efficient in reacting with the carbene complex than was the aldehyde. An alternative oxygen atom acceptor, cyclohexene, was subsequently employed. 1,2-Substituted olefins are poor cyclopropanation substrates,[2c] but readily undergo epoxidation.[10] However, using cyclohexene in place of Ph_3P under catalytic conditions resulted in neither olefination of the aldehyde nor epoxidation of the alkene. The organic products were ethyl maleate and fumarate produced by carbene dimerization. These studies indicated that an iron carbene complex was involved but that the oxoiron(IV) species was an unlikely intermediate.

The reactivity profile of the Fe(TTP)-catalyzed olefination reaction differs significantly from the $MoO(S_2CNEt_2)_2$-mediated process.[4h] The catalytic cycle for the Mo system purportedly involves metalloazines,[11] $(Et_2NCS_2)_2OMo{=}N{-}N{=}CHCO_2Et$, and phosphazines, $Ph_3P{=}N{-}N{=}CHCO_2Et$.[4h] The phosphazine is presumably responsible for the formation of large amounts of azines with electron poor aldehydes in this system.

On the basis of the above data, the most likely mechanism for the Fe(TTP) olefination reaction is shown in Scheme 2. In this process, the Fe complex serves to catalytically convert the diazo reagent and phosphine to phosphorane. The phosphorane in turn produces a new olefin and phosphine oxide on reaction with the aldehyde. Evidence for this mechanism is derived from two key control experiments. The production of phosphorane, $Ph_3P{=}CHCO_2Et$, was independently established in a reaction of Ph_3P, EDA, and Fe(TTP) (1 mol%). The phosphorane was clearly identified by ^1H and ^{31}P NMR spectroscopy.[12,13] Particularly diagnostic is the coupling constant J = 21 Hz between the phosphorous and the methine proton.[13a] In addition, the stoichiometric reaction of $Ph_3P{=}CHCO_2Et$ and benzaldehyde produced ethyl cinnamate in high yields and high stereoselectivity.

The proposed catalytic cycle in Scheme 2 suggests that an increased phosphine concentration should enhance the rate of reaction. However, phosphine can bind to Fe(TTP)[14] and may inhibit the formation of the carbene complex. These competing factors were observed. Qualitatively, the rate of reaction with 2 equiv of Ph_3P was faster than when 1 equiv was used, with no noticeable change in yields. Above 2 equiv of Ph_3P the rate appeared to saturate.

Scheme 2



$$Ph_3P{=}CHCO_2Et + RCH{=}O \longrightarrow RCH{=}CHCO_2Et + Ph_3P{=}O$$

Tolualdehyde, **2**, was converted to olefin after 12 hours of reaction time, with a high *trans/cis* selectivity of 24:1. Purification of the product by silica gel column chromatography gave 99% of the *trans*-olefin product (Table 1). The reaction is slower for substrate **2** compared to benzaldehyde due to the presence of the electron donating methyl group.

Olefination of *p*-Cl and *p*-NO_2 substrates, **3** and **4**, both containing electron withdrawing groups resulted in 100% conversion to olefin in much shorter reaction times. Olefination of **3** was complete after 3 hours and resulted in a *trans/cis* ratio of 13:1 in 95% isolated yield after purification. Furthermore, the olefination of **4** was complete after 2 hours, producing a high selectivity of *trans* -to *cis*-olefins (24:1) with an isolated yield of 90% after purification. Electron poor aldehydes are more susceptible to nucleophilic attack by the phosphorane.

We also examined two aliphatic aldehydes substrates, phenylacetaldehyde, **5**, and diphenylacetaldehyde, **6**. Olefination of **5** was slow and after 23 hours of reaction time resulted in 91% conversion and 85% isolated yield after purification. A high *trans* to *cis*

selectivity (10:1) was also achieved for olefination of **5**. Olefination of aliphatic aldehyde, **6** resulted in 95% conversion after 12 hours and produced a *trans* to *cis* selectivity of 49:1. Purification of the reaction mixture from substrate **6** with column chromatography, produced a 93% isolated yield of the *trans*-olefin product.

We have reported here the first application of a Fe(II) metalloporphyrin catalyst for the olefination of carbonyl compounds with EDA and Ph_3P. Both aromatic and aliphatic aldehydes were efficiently converted to olefin products in excellent yields (>85%) with high selectivity for the *trans*-olefin isomer (>90%). Further mechanistic studies, application of Fe(II) porphyrin complexes as a catalyst for the olefination of ketones, and the use of other diazo reagents in this system are currently under investigation.

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[5] In a control experiment with ethyl cinnamate (*trans/cis* = 6) and Fe(TTP) in toluene, no change in the *trans/cis* ratio was observed over 4 days in either the presence or absence of ethyl diazoacetate. Thus, olefin isomerization does not occur under catalytic conditions.

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[12] ^{1}H NMR (300 MHz, $CDCl_3$, -30 °C) cisoid isomer: δ 7.59 (m, C_6H_5), 7.38 (m, C_6H_5), 3.99 (2H, q, J = 7.1 Hz, CH_2), 2.94 (1H, d, J_{P-H} = 21.3 Hz, P=C*H*), 1.19 (3H, t, J = 7.1 Hz, CH_3); transoid isomer: δ 7.47 (m, C_6H_5), 7.38 (m, C_6H_5), 3.78 (2H, q, J = 7.1 Hz, CH_2), 2.76 (1H, d, J_{P-H} = 21.9 Hz, P=C*H*), 0.60 (3H, t, J = 7.1 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) cisoid isomer: δ 18.8; transoid isomer: δ 17.3.

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CHAPTER 3.

IRON(II) PORPHYRIN-CATALYZED OLEFINATION OF CARBONYL COMPOUNDS WITH ETHYL DIAZOACETATE

A paper to be submitted to the *Journal of Organic Chemistry*

Guilong Cheng, Gholam A. Mirafzal and L. Keith Woo*

Abstract

Iron(II) *meso*-tetraphenylporphyrin was an efficient catalyst for selective olefination of a variety of aromatic and aliphatic aldehydes. These reactions gave high *E*-selectivities in excellent yields. For the olefinations of ketones, the reactions were generally slow and the selectivities were low compared to aldehydes. Iron(III) *meso*-tetraphenylporphyrin chloride was also examined as an olefination catalyst, but proved to be less potent as the iron(II) porphyrin complex. The mechanism of this reaction was investigated and the likely pathways are discussed.

Introduction

Transition metal complexes have been used extensively by this group[1] and others[2] to catalyze the cyclopropanation of alkenes using ethyl diazoacetate and other suitable diazo reagents. In this paper, we describe an extension of the catalytic activity of metalloporphyrins and its applications with the first use of an iron(II) metalloporphyrin complex as a catalyst for an efficient olefination of carbonyl compounds. The generation of a carbon-carbon double bond is one of the important synthetic transformations in organic

chemistry, especially in the areas of natural products and polymer synthesis. Commonly used procedures include the Wittig reaction and its modified versions, the Peterson reaction and the Julia reaction.[3] Organometallic variants for this transformation have also been investigated in the past two decades and some achieved great success.[4] Another alternative is the olefination of carbonyl compounds by suitable diazo reagents in the presence of transition metal catalysts and reducing agents such as triphenylphosphine or trialkylstibines.[5] In contrast to the conventional two-step Wittig method, the metal-mediated syntheses are streamlined into one simple reaction. However, several drawbacks are apparent. These include a) high reaction temperatures that increase safety hazards when diazo compounds are used,[5a, 5b] b) high catalyst loading (>5mol%),[5a-5c] c) stereoselectivities[5c] that often depend strongly on the choice of the aldehydes and d) low yields.[5a, 5c] In 1998, Fujimura reported a one-pot olefination method using a ruthenium(II) complex as the catalyst.[6] In this methodology, the amount of catalyst was reduced to 2.5 mol% and a temperature of 50 °C was employed. For some aldehyde substrates, the isolated yields were not particularly high.

We recently reported a similar system using iron(II) tetratolylporphyrin as the catalyst.[7] Compared to the methods above, high stereoselectivities and high yields of olefins are generally produced from a variety of aldehydes using this method. Also our reaction conditions are the mildest among all the catalytic olefination methods reported. Since iron tetraphenylporphyrin chloride is commercially available and the catalytic properties of iron(II) tetraphenylporphyrin are similar to those of iron(II) tetratolylporphyrin, we changed our catalyst and report our results here.

Results and discussion

Olefination of Aldehydes. A one-pot approach for the catalytic synthesis of α,β-unsaturated esters was examined using 1 equivalent of aldehyde, 2 equivalents of ethyl diazoacetate, N_2CHCO_2Et (EDA), and 1.1 equivalents of triphenylphosphine, Ph_3P, in the presence of catalytic amounts of iron(II) *meso*-tetraphenylporphyrin (0.1-2 mole %), in toluene (Equation 1). Initially 1.1 equivalents of ethyl diazoacetate was used. However, EDA tended to undergo catalytic dimerization and decreased the reaction yield. A useful stoichiometry was 2 equivalents of EDA. Excess EDA also helped to keep Fe(TPP) in its reduced state.[1c] The ratio of triphenylphosphine was also examined. Qualitatively, the rate of reaction with two equivalents of triphenylphosphine was faster than when 1 equivalent was used, with no noticeable change in yields. Above 2 equivalents of Ph_3P, the rate appeared to saturate. Because excess Ph_3P made the product separation harder, a 1.1 equivalent of Ph_3P was used in our optimized reaction conditions.

A variety of aromatic and aliphatic aldehydes were examined and the results are listed in Table 1, entries 1-8.

$$\underset{\mathbf{1}}{RCHO} + N_2CHCO_2Et + Ph_3P \xrightarrow[-N_2]{Fe^{II}TPP} \underset{\mathbf{2}}{RCH{=}CHCO_2Et} + Ph_3P{=}O \qquad (1)$$

R = Ph-, *p*-$CH_3C_6H_4$-, *p*-ClC_6H_4-, *p*-$O_2NC_6H_4$-, *p*-NCC_6H_4-, $PhCH_2$-, $(Ph)_2CH$-, PhCH=CH-

In a typical reaction with benzaldehyde (Table 1, entry 1), 100% conversion was achieved within 3 hours and purification of reaction mixture gave a 94% isolated yield of the olefins with *trans/cis* ratio of 24. Ethyl maleate and ethyl fumarate were also produced in a combined yield of 15% (GC), but were readily removed by chromatography. The reaction is

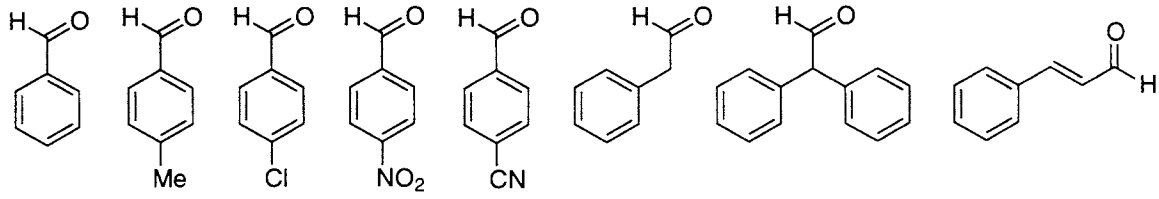
catalytic as no olefination products were produced without Fe^{II}(TPP). To test whether isomerization of the olefin products occurred, a control reaction was set up with ethyl cinnamate (*trans/cis* = 6) and Fe(TPP) in toluene. No change in the *trans/cis* ratio was observed over 4 days in either the presence or absence of ethyl diazoacetate. Thus, olefin isomerization does not occur under catalytic conditions. In the absence of the catalyst, the azine, $PhCH{=}N{-}N{=}CHCO_2Et$ was produced in 40% yield when the reaction mixture was allowed to stir for a period of four days. The reaction in the absence of triphenylphosphine also produced no olefination product. We found that this reaction required a stoichiometric amount of triphenylphosphine relative to that of the aldehydes to give a high conversion to olefination products. The aldehyde oxygen is transferred to triphenylphosphine, producing 1 equivalent of triphenylphosphine oxide. GC and GC-MS analysis confirmed the formation of $Ph_3P{=}O$ (m/z 278).

With an electron-donating group on the phenyl ring, the 4-tolualdehyde reaction required a longer reaction time of 6 hours to achieve a 95% conversion. The reaction is slower due to the fact that the electron-donating methyl group makes the nucleophilic attack at the carbonyl group more difficult.

On the other hand, aromatic aldehydes with electron-withdrawing groups, such as 4-chlorobenzaldehyde, 4-nitrobenzaldehyde and 4-cyanobenzaldehyde, reacted much faster than benzaldehyde. It only took 4-chlorobenzaldehyde 2 hours to completely convert to the corresponding olefin. The reaction time for 4-nitrobenzaldehyde is 10 min, and 30 min for 4-cyanobenzaldehyde.

We also examined two aliphatic aldehyde substrates, phenylacetaldehyde and diphenylacetaldehyde. Olefination of phenylacetaldehyde was slow and required 24 hours of

reaction time for a 91% conversion. However, the reaction of diphenylacetaldehyde was substantially faster and after 2 hours, a 95% conversion was achieved with a *trans/cis* selectivity of 40:1.



1a **1b** **1c** **1d** **1e** **1f** **1g** **1h**

Table 1. Olefination of Aldehydes with EDA/Ph_3P/Fe^{II}(TPP)

aldehyde	reaction time (h)	turnover number	product	isolated yield (%)	*trans/cis* selectivity
1a	3	128	**2a**	94	24:1
1b	6	119	**2b**	99	28:1
1c	2	98	**2c**	95	18:1
1d	0.2	80	**2d**	90	15:1
1e	0.5	103	**2e**	95	18:1
1f	24	95	**2f**	85	10:1
1g	2	64	**2g**	93	40:1
1h	2	103	**2h**	95	10:1

Olefination of *trans*-cinnamaldehyde was also a facile reaction. A 100% conversion was achieved after 2 hours of stirring. Purification of the reaction mixture by column chromatography afforded a 95% isolated yield with a *trans/cis* selectivity of 10:1.

Olefination of Ketones. Reactions of ketones were substantially slower than the aldehyde reactions. For 4-methylcyclohexanone, initially a similar reaction ratio as aldehyde reactions was followed, but no olefin was observed after two days of stirring, a 30% (GC yield) EDA dimerized products were observed. Then a higher temperature condition was also examined with the same reagent ratios. At 50°C, still no olefin product was observed after two days of stirring, a 60% (GC yield) EDA dimerized products were observed.

Our optimized reagent ratio is 10 equivalents of ketone, 1.1 equivalents of triphenylphosphine and 1 equivalent of ethyl diazoacetate, with 5 mg (1 mol% versus ethyl diazoacetate) $Fe^{II}TPP$ catalyst (equation 2). Isomer assignments were determined by 2D-NOSY. For *Z*-isomers, a through-space interaction was observed between the vinyl hydrogen and methyl hydrogens on the double bond. Results for ketone reactions are sumarized in Table 2.

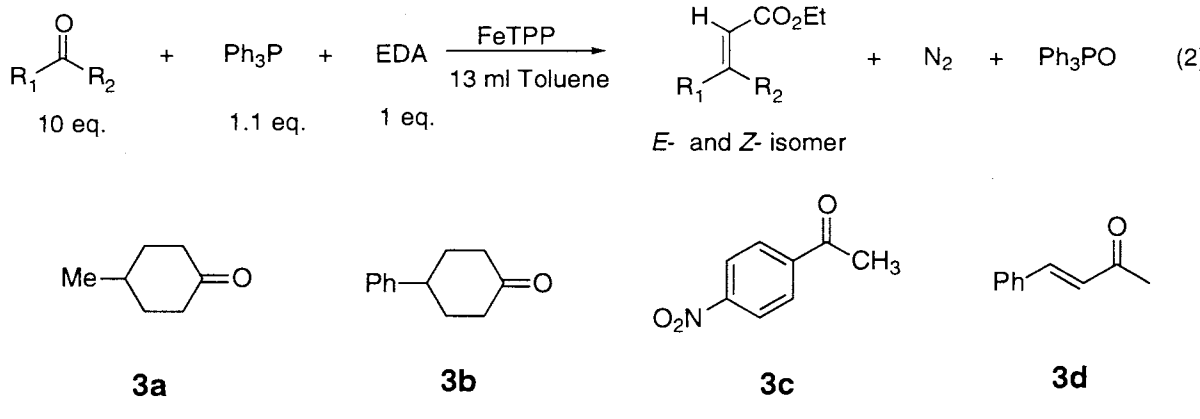


Table 2. Olefination of Ketones with EDA/Ph_3P/Fe^{II}(TPP)

ketone	reaction time (days)	product	isolated yield (%)	*Z/E* selectivity
3a	3	**4a**	64	none
3b	3	**4b**	75	none
3c	4	**4c**	80	2:1
3d	2	**4d**	66	2.8:1

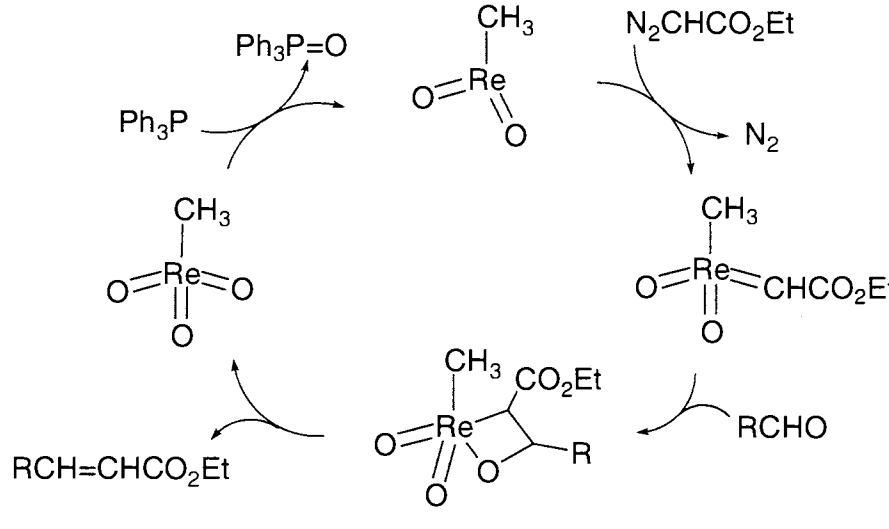
Effect of Catalyst Loading. A lower catalytic loading (0.1 mol% catalyst) was examined for three aldehydes and one ketone. For benzaldehyde (**1a**), the reaction was slightly slower than when 1.0 mol% catalyst was used. A two hour reaction time was required for reaction to achieve 95% conversion. For 4-nitrobenzaldehyde (**1d**), qualitative estimates were insufficient to detect rate differences as a function of catalyst amounts. Within 3 minutes, an 85% conversion was achieved for 0.1 mol% catalyst, compared to an 81% conversion with 1 mol% catalyst. Interestingly, the *trans/cis* selectivity of this reaction increased substantially from 15:1 to 24:1 with the lower catalyst loading. The same trend was observed for 4-cyanobenzaldehyde (**1e**). Within half an hour, 100% conversions were achieved for both 1 mol% and 0.1 mol% catalyst loadings. The *trans/cis* selectivity was 17:1 with 1 mol% catalyst, compared to a 26:1 with 0.1 mol% catalyst. Higher catalyst loadings (10 mol%) were applied to the 4-nitrobenzaldehyde and 4-cyanobenzaldehyde reactions. The

trans/cis selectivities in these cases were 4:1 (4-nitrobenzaldhyde) and 6:1 (4-cyanobenzaldehyde).

With 4-methylcyclohexanone (**3a**), lowering the catalyst had a different effect. When 0.1 mol% catalyst was used, the azine, $CH_3C_6H_9$=N-N=$CHCO_2Et$, became the major product.

Fe^{III}(TPP)Cl as the catalyst. For practical applications, the possibility of using Fe^{III}(TPP)Cl as a catalyst was examined. The olefination of benzaldehyde reaction was slower than with Fe^{II}(TPP). When 1 mol% Fe^{III}(TPP)Cl was used under N_2, a 4-hour reaction time was required to get to 95% conversion. The *trans/cis* selectivity remained the same as with Fe^{II}(TPP).

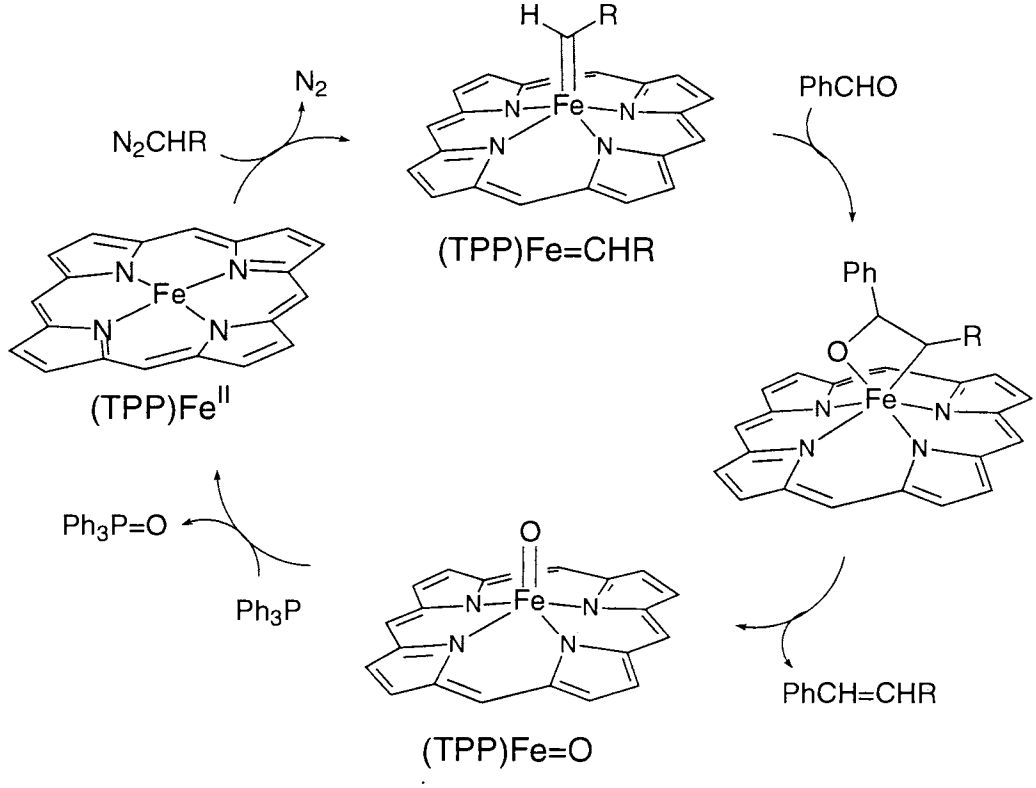
Mechanistic Studies. Herrmann *et al.* reported a methyltrioxorhenium (MTO) catalyzed olefination method in 1991.[5c] To account for the mechanism of this reaction, a catalytic cycle (Scheme 1) was proposed.



Scheme 1

In the first step, an oxygen atom was abstracted from MTO by triphenylphosphine. The resultant Re(V) dioxo complex then reacted with a diazo reagent to produce a carbene complex that subsequently formed a metallaoxetane species in the presence of aldehydes. Fragmentation of the metallaoxetane produced the new olefin and regenerates MTO.

In analogy to the MTO system, a similar catalytic cycle for the iron(II) porphyrin is shown in Scheme 2.



(Phenyl substituents on porphyrin rings were omitted for clarity)

Scheme 2

A likely active species in the iron porphyrin catalyzed reactions is an iron-carbene complex formed by reaction of the iron(II) porphyrin with EDA. Even though

(TPP)Fe=$CHCO_2Et$ is very reactive and has never been isolated or detected spectroscopically, related complexes prepared from mesityl diazomethane and trimethylsilyl diazomethane are readily observed by ^1H NMR spectroscopy.[1c, 1d] The more electron rich analogue, (TTP)Os=$CHCO_2Et$, has been isolated and well characterized.[1a, 1b] The iron-carbene complex may serve as a nucleophile[8] that attacks the carbonyl functional group of the aldehydes and ketones to produce a metallaoxetane intermediate. This is consistent with the higher reactivity of electron poor aldehydes. Subsequent ring cleavage of the metallaoxetane would produce an olefin and an oxoiron porphyrin complex. Regeneration of the Fe(TPP) would occur by oxidation of triphenylphosphine to triphenylphosphine oxide.

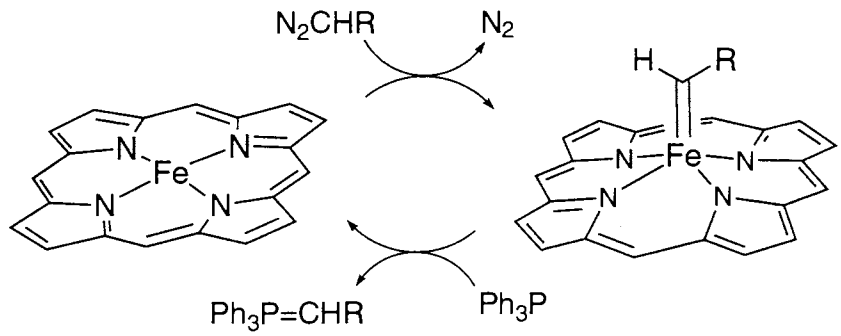
For this mechanism to be viable, the inner sphere reaction between unencumbered oxoiron(IV) and iron(II) porphyrins, producing a μ-oxo Fe(III) dimer,[9] must be minimal. Formation of the Fe(III) dimer would serve to quickly inactivate the catalyst. In a control experiment, catalyst Fe(TPP) was tested for three generations of substrate addition (benzaldehyde, triphenylphosphine and EDA) over a 15-hours period. The catalyst showed no significant deactivation.

Attempts were then made to test for the presence of the oxoiron(IV) with other oxygen atom acceptors. Olefins were chosen since oxoiron(IV) porphyrin complexes effectively epoxidize the double bond.[10] To examine this possibility, an experiment was run with benzaldehyde, ethyl dizaoacetate, 1.0 mol% Fe(TPP), and styrene as the reductant in place of triphenylphosphine. After the reaction, no ethyl cinnamate was observed. The only product was ethyl 2-phenylcyclopropylcarboxylate (100%), indicating that styrene was much more efficient in reacting with the carbene complex than was the aldehyde. An alternative oxygen acceptor, cyclohexene, was subsequently employed. 1,2-Disubstituted olefins are poor

cyclopropanation substrates,[1c] but readily undergo epoxidation.[10] However, using cyclohexene in place of triphenylphosphine under catalytic conditions resulted in neither olefination of the aldehyde nor epoxidation of the alkene. The organic products were ethyl maleate and fumarate produced by carbene dimerization. These studies indicated that an iron-carbene complex was involved but that the oxoiron(IV) species was an unlikely intermediate.

The reactivity profile of the Fe(TPP)-catalyzed olefination reaction differs significantly from the $MoO(S_2CNEt_2)_2$-mediated process. The catalytic cycle for the Mo system purportedly involves metalloazines,[5a] $(Et_2NCS_2)_2OMo{=}N{-}N{=}CHCO_2Et$, and phosphazines, $Ph_3P{=}N{-}N{=}CHCO_2Et$.[11] The phosphazine is presumably responsible for the formation of large amounts of azines with electron-poor aldehydes in this system.

An alternative mechanism for the Fe(TPP) olefination reaction is shown in Scheme 3. In this process, Fe(TPP) serves to catalytically convert the diazo reagent and phosphine to phosphorane. The phosphorane in turn produces a new olefin and phosphine oxide on reaction with the aldehyde. An experiment set up with Ph_3P, EDA and Fe(TPP) (1 mol%) was consistent with this. After 30 minutes of stirring, phosphorane, $Ph_3P{=}CHCO_2Et$, was detected by ^1H and ^{31}P NMR spectroscopy as the major product along with a combined 5% yield of Ph_3P and Ph_3PO. Purification of the reaction mixture afforded pure phosphorane in 60% yield. Key ^1H NMR signals indentifying the phosphorane are the methine signals at 2.94 ppm (cisoid isomer) and 2.76 ppm (transoid isomer). In addition, the ^{31}P NMR spectrum contained resonances for the cisoid isomer at δ 18.8 ppm and the transoid isomer at δ 17.3 ppm. These spectral data were experimentally identical to reported values.[12] Particularly diagnostic is the coupling constant J = 21 Hz between the phosphorus and the methine proton.[12a]



$Ph_3P{=}CHR + PhCH{=}O \longrightarrow PhCH{=}CHR + Ph_3P{=}O$

Scheme 3

The proposed catalytic cycle in Scheme 3 suggests that an increased phosphine concentration should enhance the rate of reaction. However, phosphine can bind to Fe(TPP)[13] and may inhibit the formation of the carbene complex. These competition factors were observed. Qualitatively, the rate of reaction with two equivalent of Ph_3P was faster than when 1 equivalent was used, with no noticeable change in yields. Above 2 equivalents of Ph_3P, the rate appeared to saturate.

A set of experiments were then set up to test the olefination selectivities under three different conditions as shown in reactions 3-5. The results are listed in Table 3. For ketones and electron-rich aldehydes, little or no differences in reaction rates or yields were observed as a function of conditions. These data give strong support for the mechanism shown in Scheme 3 for benzaldehyde and less reactive aldehydes and ketones.

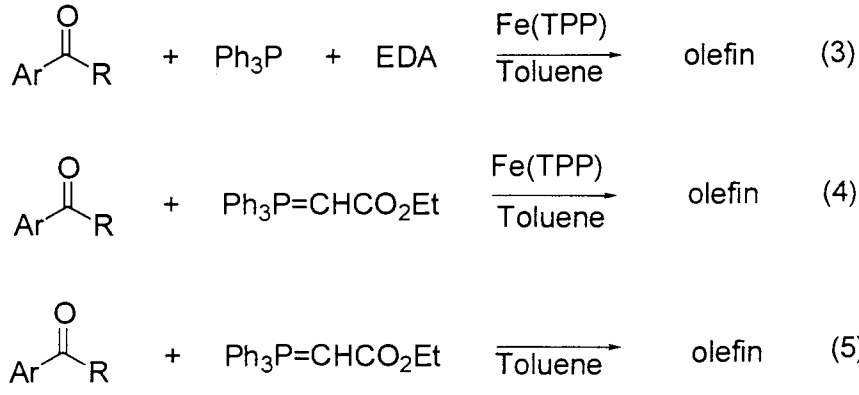


Table 3. Control Experiment Results

Substrate	*E*/*Z* ratio		
	reaction 3	reaction 4	reaction 5
Benzaldehyde	24:1	23:1	23:1
4-tolualdehyde	28:1	28:1	28:1
4-nitroacetophenone	1:2.8	1:2.7	1:2.8
4-nitrobenzaldehyde	15:1	17:1	31:1
4-cyanobenzaldehyde	18:1	19:1	33:1

For more reactive aldehydes such as 4-nitrobenzaldehyde and 4-cyanobenzaldehyde, the mechanism seems to be more complicated than that shown in Scheme 3. The results with

4-nitrobenzaldehyde are listed in Table 4. The trend is consistent for either the catalytic olefination reaction or the stoichiometric reaction. The key finding is that the larger the catalyst loading, the higher the amount of *cis* olefin produced from electron-poor aldehydes. Since $Ph_3P{=}CHCO_2Et$ is involved in both processes, Fe(II)(TPP) must perturb the oxetane formation with electron-poor aldehydes.

Table 4. 4-Nitrobenzaldehyde Olefination Results

reactants	*trans/cis* selectivity under different catalyst loading			
	10 mol%	1 mol%	0.1 mol%	0 mol%
4-nitrobenzaldehyde + Ph_3P + EDA	4.1:1	15:1	24:1	none
4-nitrobenzaldehyde + $Ph_3P{=}CHCO_2Et$	6.0:1	17:1	24:1	31:1

Transition metal complexes have recently been reported to have π-interactions with electron-poor aromatic aldehydes.[14] An UV-vis study indicates similar behavior for iron(II) porphyrin (Figure 1).The Soret region for Fe(II)(TPP) exhibits distinct peaks at 422 nm and 440 nm in toluene.[15] Addition of benzaldehyde (0.0632 M) resulted in no change to the spectrum. However, addition of 4-nitrobenzaldehyde (0.0629 M) to the iron(II) porphyrin solution resulted in the disappearance of the peak at 440 nm.

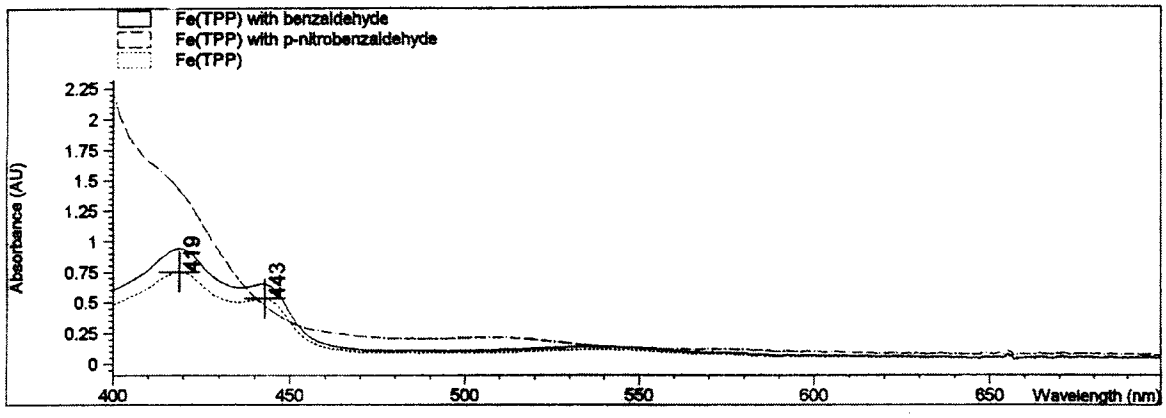
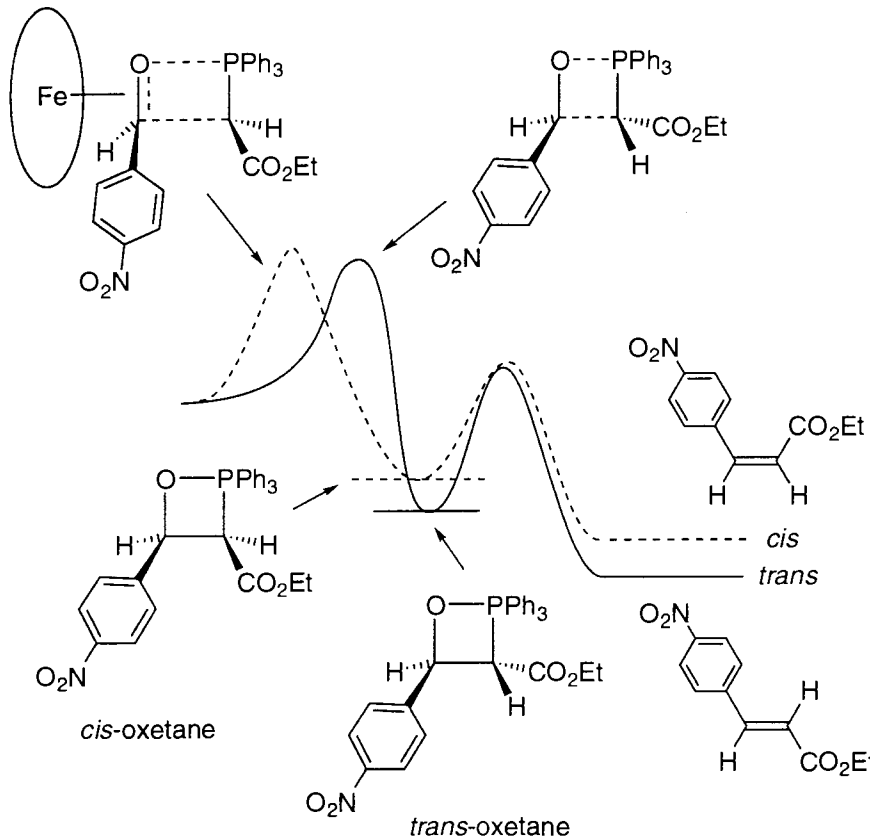


Figure 1. UV studies of benzaldehyde and 4-nitrobenzaldehyde in the presence of Fe(TPP)

This study suggests that a π-interaction occurs between iron(II) porphyrin and electron-poor aromatic aldehydes. Complexation of unsaturated organic molecules to transition metals is well-known to activate multiple bonds towards attacks by nucleophiles.[16]

Formation of the π-complex between Fe(TPP) and 4-nitrobenzaldehyde is consistent with the change in *trans/cis* selectivity on increasing the amount of Fe(TPP) in both catalytic and stoichiometric reaction as shown in Scheme 4. Without iron(II) porphyrin, steric effects play an important role in the formation of the *trans*-oxetane with stabilized ylides.[17] In this case, the transition state for the formation of the oxetane is likely to be late in the reaction coordinate and is presumably product-like, favoring the formation of the *trans*-product. When Fe(II)(TPP) is present, the π-interaction between the aldehyde carbonyl and the Lewis acidic iron(II) porphyrin will activate the carbonyl group towards nucleophilic attack by the phosphorane. Consequently, the transition state for oxetane formation occurs earlier than without the metal complex. In the earlier transition state, steric factors are not as important as in the late transition state and a larger fraction of *cis*-oxetane will be produced.



Scheme 4

The proposed mechanism in Scheme 4 suggests that changing the electronic nature of the iron(II) porphyrin will modify the stability of the π-complex and alter the *trans/cis* selectivities. This effect was observed with the electron-deficient iron(II) tetra(pentafluorophenyl)porphyrin and the more electron-rich iron(II) tetra(4-methoxyphenyl)porphyrin. When 1.0 mol% iron(II) tetra(pentafluorophenyl)porphyrin was used in the 4-nitrobenzaldehyde olefination reaction, a *trans/cis* ratio of 23:1 was observed, compared to the *trans/cis* ratio of 15:1 when 1.0 mol% Fe(TPP) was used. This is due to the reduced π-backbonding from iron(II) tetra(pentafluorophenyl)porphyrin to

4-nitrobenzaldehyde, which makes the π-complex less accessible. The opposite effect was observed when a more electron-rich complex was used in the 4-nitrobenzaldehyde olefination reaction. With 1.0 mol% iron(II) tetra(4-methoxyphenyl)porphyrin as catalyst, a *trans/cis* ratio of 13:1 was observed.

Conclusion

We have reported the first application of an Fe(II) porphyrin catalyst for the olefination of carbonyl compounds with EDA and Ph_3P. Both aromatic and aliphatic aldehydes were efficiently converted to olefin products in excellent yield (>85%) with high selectivity for *trans*-olefin isomer (>90%). Ketones react slowly but are also converted to olefins using this method.

Experimental section

General method. All reactions involving Fe(TPP) were carried out under dry nitrogen in a Vacuum Atmosphere glove box equipped with a MO40H DriTrain gas purification system. THF was distilled from blue solutions of sodium benzophenone ketyl. Toluene was passed through a column of catalytic copper and alumina as described by Grubbs *et al.*[18] All aldehydes and ethyl diazoacetate were purchased from Aldrich and degassed by three freeze-pump-thaw cycles prior to use. Iron(III) tetraphenylporphyrin chloride, iron(III) tetra(pentafluorophenyl)porphyrin chloride, iron(III) tetra(4-methoxyphenyl)porphyrin chloride and 200-425Mesh Silica were purchased from Aldrich and used as received. Iron(II) tetraphenylporphyrin was synthesized using the procedure of Reed by reducing iron(III)

tetraphenylporphyrin chloride with Zn/Hg amalgam in toluene for 6 hours.[19] The UV/vis spectrum for iron(II) tetraphenylporphyrin was analogous to that reported in the literature.[15] iron(II) tetra(pentafluorophenyl)porphyrin and iron(II) tetra(4-methoxyphenyl)porphyrin were synthesized by similar methods as that of iron(II) tetraphenylporphyrin.

^{1}H NMR and ^{13}C spectra were recorded on Varian VXR300 or Bruker CRX400 spectrometers. ^{1}H NMR peak positions were referenced against residual proton resonances of deuterated solvent (δ (ppm): $CHCl_3$, 7.26). ^{13}C NMR peak positions were referenced against the center line of the deuterated solvent resonance (δ (ppm): $CDCl_3$, 77). ^{31}P NMR spectra were recorded on Varian VXR400 spectrometer, peak positions were referenced against the internal standard of Ph_3P (δ (ppm): -4.71).[20] Gas chromatography was performed using a HP 5890 Series II instrument[21] and GC/MS data was obtained from a Finnegan Magnum GC-MS.[22] High-resolution mass spectrometry for exact mass determination was performed on a Kratos MS50 spectrometer using electron impact (EI) ionization.

The stereochemistry of the aldehyde olefination products was assigned by ^{1}H NMR spectroscopy using coupling constants of the vinyl protons. The stereochemistry of the ketone olefination products was assigned by ^{1}H NMR and 2D-NOSY. Once the major isomer was assigned, product ratios were determined by GC.

Aldehyde olefination reactions using Fe(TPP) (Procedure A). In a typical experiment, 0.100 g (0.943 mmol, 1 equiv.) aldehyde, 272 mg (1.04 mmol, 1.1 equiv.) of triphenylphosphine and 5 mg (1-2 mol% versus aldehyde) of Fe^{II}(TPP) were placed into a roundbottom flask and dissolved in 10 mL of toluene at ambient temperature. A solution of 215 mg (1.88 mmol, 2 equiv.) ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 minutes to the reaction mixture with vigorous stirring. After the

addition was finished, the progress of the reaction was monitored by GC. When the reaction reached maximum conversion, the reaction flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5cm × 25 cm) using 20:1 hexane/EtOAc to isolate the olefin. *Trans/cis* selectivity was determined by GC and ^{1}H NMR. ^{1}H NMR analysis showed a $^3J_{HH}$ of 15.9 Hz for *trans*-hydrogens and a $^3J_{HH}$ of 12.6 Hz for *cis*-hydrogens. In GC analyses, the *cis* isomer appeared at a shorter retention time relative to that of the *trans* isomer.

Ketone olefination reactions using Fe(TPP) (Procedure B). In a typical experiment, 0.980 g (8.74 mmol, 10.0 equiv.) aldehyde, 253 mg (0.961 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus ethyl diazoacetate) Fe^{II}(TPP) were placed in a round bottom flask and dissolved in 10 mL of toluene at ambient temperature. A solution of 99.7 mg (0.874 mmol, 1.00 equiv.) of ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 minutes to the reaction mixture with vigorous stirring. After the addition was finished, the progress of the reaction was monitored by GC as described above. On termination of the reaction, the flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5cm × 25 cm) using 20:1 hexane/EtOAc to isolate the olefin.

Control reaction without catalyst. As in procedure A except with no catalyst, a control reaction was set up with 0.100 g (0.943 mmol, 1.00 equiv.) benzaldehyde, 272 mg (1.04 mmol, 1.10 equiv.) of triphenylphosphine and 215 mg (1.88 mmol, 2.00 equiv.) of ethyl diazoacetate. After the addition of the diazo reagent was finished, the reaction was monitored by GC over a period of four days. The reaction mixture was taken subsequently out of the box and the solvent was removed in vacuo. The residue was purified by flash

column chromatography (SiO_2, 1.5cm × 25 cm) using 20:1 hexane/EtOAc to afford a yellowish oil which proved to be the azine, PhCH=N-N=CHCO$_2$Et (77 mg, 40%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.38 (t, 3H, -C*H*$_3$), 4.39 (q, 2H, -C*H*$_2$), 7.41-7.53 (m, 3H, 3,4-phenyl), 7.79-7.84 (m, 2H, 2,-phenyl), 7.90 (s, 1H, =C*H*CO$_2$Et), 8.59 (s, 1H, =C*H*Ph). MS (EI): m/z 204 [M]$^+$, 131 [M - CO$_2$Et]$^+$, 104, 77. Spectral data were practically identical to the reported value.[5a]

Control reaction without triphenylphosphine. Using procedure A except with no triphenylphosphine, a control reaction was set up with 0.100 g (0.943 mmol, 1.00 equiv.) benzaldehyde, 5 mg (1 mol% versus aldehyde) Fe^{II}(TPP) and 215 mg (1.88 mmol, 2.00 equiv.) ethyl diazoacetate. After the addition of the diazo reagent was finished, the reaction was monitored by GC over a period of 4 days. No consumption of benzaldehyde was observed.

C$_6$H$_5$CH=CHCO$_2$Et (2a). Procedure A was used with 0.100 g (0.943 mmol, 1.00 equiv.) benzaldehyde , 272 mg (1.04 mmol, 1.10 equiv.) triphenylphosphine, 5 mg (1 mol% versus benzaldehyde) Fe^{II}(TPP) and 215 mg (1.88 mmol, 2.00 equiv.) of ethyl diazoacetate. In 1 hour, a 95% conversion was achieved. The reaction was left stirring for another 2 hours to get to 100% conversion. A colorless oil was obtained after column chromatogrophy (SiO_2, 1.5cm × 25 cm) using hexane/EtOAC (20/1 v/v). Yield: 156 mg, 94%. The *cis* isomer was produced in small amount and could not be cleanly separated from *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.34 (t, 3H, -C*H*$_3$), 4.27 (q, 2H, -C*H*$_2$), 6.44 (d, 1H, J = 15.9Hz, =C*H*CO$_2$Et), 7.37-7.40 (m, 3H, 3, 4- phenyl), 7.51-7.53 (m, 2H, 2- phenyl), 7.69 (d, 1H, J = 15.9Hz, =C*H*C$_6$H$_5$). Spectral data were practically

identical to reported values.[23] GC chromatograms indicated the product had a *trans/cis* ratio of 24.

4-MeC$_6$H$_4$CH=CHCO$_2$Et (2b). Procedure A was used with 0.100 g (0.833 mmol, 1.00 equiv.) 4-tolylaldehyde, 241 mg (0.920 mmol, 1.10 equiv.) triphenylphosphine, 5 mg (1 mol% versus 4-tolylaldehyde) Fe^{II}(TPP) and 190 mg (1.67 mmol, 1.99 equiv.) ethyl diazoacetate. In 6 hours, a 95% conversion was achieved. A colorless oil was ontained after column chromatography (SiO$_2$, 1.5cm × 25 cm) using hexane/EtOAC (20/1 v/v). Yield: 157 mg, 99%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR (CDCl$_3$, 300 MHz): δ1.33 (t, 3H, -CH$_2$C*H*$_3$), 2.37 (s, 3H, -C$_6$H$_4$C*H*$_3$), 4.26 (q, 2H, -C*H*$_2$-), 6.39 (d, 1H, J = 15.9 Hz, =C*H*CO$_2$Et), 7.19 (d, 2H, J = 7.8 Hz, 3-phenyl), 7.42 (d, 2H, J = 8.1 Hz, 2-phenyl), 7.66 (d, 1H, J = 15.9 Hz, =C*H*C$_6$H$_4$CH$_3$). Spectral data were practically identical to reported values.[24] GC chromatograms indicated the product had a *trans/cis* ratio of 28.

4-ClC$_6$H$_4$CH=CHCO$_2$Et (2c). Procedure A was used with 0.100 g (0.712mmol, 1.00 equiv.) 4-chlorobenzaldehyde, 205 mg (0.782 mmol, 1.10 equiv.) triphenylphosphine, 5 mg (1 mol% versus 4-chlorobenzaldehyde) Fe^{II}(TPP) and 162 mg (1.42 mmol, 2.00 equiv.) ethyl diazoacetate. In 2 hours, a 97% conversion was achieved. A light yellow solid was obtained after column chromatography (SiO$_2$, 1.5cm × 25 cm) using hexane/EtOAC (20/1 v/v). Yield: 142 mg, 95%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR (CDCl$_3$, 300 MHz): δ1.34 (t, 3H, -C*H*$_3$), 4.26(q, 2H, C*H*$_2$), 6.40 (d, 1H, J = 15.9 Hz, =C*H*CO$_2$Et), 7.34 (d, 2H, J = 8.4 Hz, 3-phenyl), 7.45 (d, 2H, J = 8.4 Hz, 2-phenyl), 7.63 (d, 1H, J = 15.9 Hz, =C*H*C$_6$H$_4$Cl). For *cis* isomer, δ5.96 (d, 1H, J = 12.6 Hz, =C*H*CO$_2$Et), 6.88

(d, 1H, J = 12.6 Hz, =C*H*C_6H_4Cl). Spectral data were practically identical to reported values.[24] GC chromatogram indicated the product had a *trans/cis* ratio of 18.

4-O_2N-C_6H_4CH=CHCO_2Et (2d). Procedure A was used with 0.100 g (0.662 mmol, 1.00 equiv.) 4-nitrobenzaldehyde, 191 mg (0.729 mmol, 1.10 equiv.) triphenylphosphine, 5 mg (1 mol% versus 4-nitrobenzaldehyde) Fe^{II}(TPP) and 151 mg (1.32 mmol, 1.99 equiv.) ethyl diazoacetate. In 30 minutes, a 100% conversion was achieved. A light yellow solid was obtained after column chromatography (SiO_2, 1.5cm × 25 cm) using 200 mL pure hexane then hexane/EtOAC (2/1 v/v). Yield: 132 mg, 90%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.35 (t, 3H, -CH_3). 4.29 (q, 2H, -CH_2), 6.56 (d, 1H, J = 16.2 Hz, =C*H*CO_2Et), 7.67 (d, 2H, J = 8.7 Hz, 2-phenyl), 7.70 (d, 1H, J = 15.0 Hz, =C*H*$C_6H_4NO_2$), 8.25 (d, 2H, J = 9.0Hz, 3-phenyl). For *cis* isomer, δ6.13 (d, 1H, J = 12.6 Hz, =C*H*CO_2Et), 7.01 (d, 1H, J = 12.6 Hz, =C*H*$C_6H_4NO_2$). Spectral data were practically identical to reported values.[25] GC chromatograms indicated the product had a *trans/cis* ratio of 15.

4-NC-C_6H_4CH=CHCO_2Et (2e). Procedure A was used with 0.100 g (0.763 mmol, 1.00 equiv.) 4-cyanobenzaldehyde, 0.220 g (0.840 mmol, 1.10 equiv.) triphenylphosphine, 5 mg (1 mol% versus 4-nitrobenzaldehyde) Fe^{II}(TPP) and 174 mg (1.53 mmol, 2.00 equiv.) ethyl diazoacetate. In half and hour, a 100% conversion was achieved. A colorless solid was obtained after column chromatography (SiO_2, 1.5cm × 25 cm) using 200 mL pure hexane then hexane/EtOAC (2/1 v/v). Yield: 146 mg, 95%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.33 (t, 3H, -CH_3). 4.27 (q, 2H, -CH_2), 6.50

(d, 1H, J = 16.2 Hz, =C*H*CO_2Et), 7.59 (d, 2H, J = 8.1 Hz, 2-phenyl), 7.64 (d, 1H, J = 16.2 Hz, =C*H*C_6H_4CN), 7.67 (d, 2H, J = 8.4 Hz, 3-phenyl). ^{13}C NMR ($CDCl_3$, 300MHz): δ14.4, 61.1, 113.5, 118.5, 122.0, 128.5, 132.8, 138.9, 142.3, 166.3. MS (EI): m/z 201 $[M]^+$, 173, 156, 128, 110. GC chromatogram indicated the product had a *trans/cis* ratio of 18.

$C_6H_5CH_2CH{=}CHCO_2Et$ (2f). Procedure A was used with 0.100 g (0.833 mmol, 1.00 equiv.) phenylacetaldehyde, 241 mg (0.920 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus phenylacetaldehyde) Fe^{II}(TPP) and 151 mg (1.67 mmol, 1.99 equiv.) ethyl diazoacetate. In 24 hours, a 91% conversion was achieved. A colorless oil was afford after column chromatography (SiO_2, 1.5cm × 25 cm) using hexane/EtOAC (8/1 v/v). Yield: 135 mg, 85%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.27 (t, 3H, -C*H*$_3$), 3.52 (dd, 2H, J = 6.9, 1.5Hz, -C*H*$_2C_6H_5$), 4.18 (q, 2H, -C*H*$_2CH_3$), 5.81 (dt, 1H, J = 15.6, 1.5Hz, =C*H*CO_2Et), 7.10 (dt, 1H, J = 15.6, 6.9Hz, =C*H*CH_2), 7.15-7.25 (m, 3H, 3,4-phenyl), 7.28-7.35 (m, 2H, 2-phenyl). Spectral data were practically identical to reported values[26] GC chromatograms indicated the product had a *trans/cis* ratio of 10.

$(C_6H_5)_2CHCH{=}CHCO_2Et$ (2g). Procedure A was used with 0.100 g (0.510 mmol, 1.00 equiv.) phenylacetaldehyde, 147 mg (0.561 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1.4 mol% versus phenylacetaldehyde) Fe^{II}(TPP) and 116 mg (1.02 mmol, 2.00 equiv.) ethyl diazoacetate. In two hours, a 96% conversion was achieved. A colorless oil was obtained after column chromatography (SiO_2, 1.5cm × 25 cm) using hexane/EtOAC (20/1 v/v). Yield: 127 mg, 93%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR

($CDCl_3$, 300 MHz): δ1.28 (t, 3H, -C*H*$_3$), 4.19 (q, 2H, -C*H*$_2$), 4.87 (d, 1H, J = 7.2 Hz, -C*H*Ph$_2$), 5.73 (dd, 1H, J = 15.6, 1.5 Hz, =C*H*CO$_2$Et), 7.15-7.20 (m, 4H, 3-phenyl), 7.23-7.27 (m, 2H, 4-phenyl), 7.29-7.35 (m, 4H, 2-phenyl), 7.41 (dd, 1H, J = 15.6, 7.2 Hz, =C*H*CHPh$_2$). Spectral data were practically identical to reported value.[27] GC chromatogram indicated the product had a *trans/cis* ratio of 40.

$C_6H_5CH=CH-CH=CHCO_2Et$ (2h). Procedure A was used with 0.100 g (0.757 mmol, 1.00 equiv.) *trans*-cinnamaldehyde, 219 mg (0.83 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus cinnamaldehyde) Fe^{II}(TPP) and 173 mg (1.52 mmol, 2.00 equiv.) ethyl diazoacetate. In two hours, a 100% conversion was achieved. A colorless oil was afford after column chromatography (SiO_2, 1.5cm × 25 cm) using hexane/EtOAC (20/1 v/v). Yield: 145 mg, 95%. The *cis* isomer was produced in a small amount and could not be cleanly separated from the *trans* isomer. Only the *trans* isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.32 (t, 3H, -C*H*$_3$), 4.23 (q, 2H, -C*H*$_2$), 6.00(d, 1H, 15.3 Hz), 6.86-6.90 (m, 2H), 7.30-7.50 (m, 6H), ^{13}C NMR (CDCl, 300MHz) δ167.3, 144.7, 140.6, 136.3, 129.2, 129.0, 127.4, 126.5, 121.6, 60.6, 14.5. Spectral data were practically identical to reported value.[28] GC chromatograms indicated the product had a *trans/cis* ratio of 10.

Ethyl 1-(4-methylcyclohexylidene)-acetate (4a): Procedure B was used with 0.980 g (8.76 mmol, 10.0 equiv.) 4-methylcyclohexanone, 253 mg (0.966 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus ethyl diazoacetate) Fe^{II}(TPP) were placed in a round bottom flask and dissoved in 10 mL of toluene at ambient temperature. A solution of 0.100 g (0.876 mmol, 1.00 equiv.) of ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 min to the reaction mixture with vigorous stirring. After the addition was finished, the progress of the reaction was monitored by GC as described above.

After 3 days, the flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5 cm × 25 cm) using hexane/EtOAC (20/1 v/v) to afford a colorless oil. Yield: 102 mg, 64%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ0.91 (d, 3H, $CH_3C_6H_9$-), 1.29 (t, 3H, -CH_2CH_3), 4.13 (q, 2H, -CH_2CH_3), 9 Hs on the ring: 1.10-1.20 (m, 2H), 1.55-1.70 (m, 1H), 1.80-2.00 (m, 3H), 2.10-2.30 (m, 2H), 3.70-3.78 (m, 1H), 5.60 (s, 1H, =C*H*). Spectral data were practically identical to reported value.[29]

Ethyl 1-(4-phenylcyclohexylidene)-acetate (4b): Procedure B was used with 1.53 g (8.79 mmol, 10.0 equiv.) 4-phenylcyclohexanone, 253 mg (0.967 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus ethyl diazoacetate) Fe^{II}(TPP) were placed in a round bottom flask and dissoved in 10 mL of toluene at ambient temperature. A solution of 0.100 g (0.878 mmol, 1.00 equiv.) of ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 min to the reaction mixture with vigorous stirring. After the addition was finished, the progress of the reaction was monitored by GC as described above. After 3 days, the flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5 cm × 25 cm) using hexane/EtOAC (20/1 v/v) to afford a colorless solid. Yield: 161 mg, 75%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ1.30 (t, 3H, -CH_2CH_3), 4.18 (q, 2H, -CH_2CH_3), 2.75-2.85 (m, 1H, -*CH*Ph), 8 Hs on the ring: 1.57-1.72 (m, 2H), 2.00-2.13 (m, 3H), 2.31-2.45 (m, 2H), 3.97-4.04 (m, 1H), 5.70 (s, 1H, =C*H*), 7.18-7.23 (m, 3H, 3,4-phenyl), 7.28-7.33 (m, 2H, 2-phenyl). Spectral data were practically identical to reported value.[30]

Ethyl 3-(4-nitro-phenyl)-crotonate (4c): Procedure B was used with 1.45 g (8.80 mmol, 10.0 equiv.) 4-nitroacetophenone, 253 mg (0.967 mmol, 1.10 equiv.)

triphenylphosphine and 5 mg (1 mol% versus ethyl diazoacetate) Fe^{II}(TPP) were placed in a round bottom flask and dissoved in 10 mL of toluene at ambient temperature. A solution of 0.100 g (0.879 mmol, 1.00 equiv.) of ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 min to the reaction mixture with vigorous stirring. After the addition was finished, the progress of the reaction was monitored by GC as described above. After 4 days, the flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5 cm × 25 cm) using hexane/EtOAC (20/1 v/v) to afford a colorless solid. Yield: 165 mg, 80%. The Z and E isomers were identified by 2D-NOSY. Only the Z isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz) for Z isomer: δ1.11 (t, 3H, $-CH_2CH_3$), 2.19 (d, 3H, J = 1.5 Hz, $=CPhCH_3$), 4.01 (q, $-CH_2CH_3$), 6.00 (q, J = 1.5 Hz, 1H, =C*H*), 7.35 (d, 2H, J = 8.7 Hz, 2-phenyl), 8.22 (d, 2H, J = 8.7 Hz, 3-phenyl). GC chromatograms indicated the product had a Z/E ratio of 2:1.

Ethyl 3-methyl-5-phenyl-2,4--pentadieneoate (4d): Procedure B was used with 1.27 g (8.70 mmol, 10.0 equiv.) *trans*-4-phenyl-3-butene-2-one, 251 mg (0.957 mmol, 1.10 equiv.) triphenylphosphine and 5 mg (1 mol% versus ethyl diazoacetate) Fe^{II}(TPP) were placed in a round bottom flask and dissoved in 10 mL of toluene at ambient temperature. A solution of 99.3 mg (0.870 mmol, 1.00 equiv.) of ethyl diazoacetate in 3 mL of toluene was added dropwise over approximately 2 min to the reaction mixture with vigorous stirring. After the addition was finished, the progress of the reaction was monitored by GC as described above. After 2 days, the flask was removed from the glove box and the solvent was removed in vacuo. The residue was then purified by flash column chromatography (SiO_2, 1.5 cm × 25 cm) using hexane/EtOAC (20/1 v/v) to afford a yellowish solid. Yield: 124 mg,

66%. The Z and E isomers were identified by 2D-NOSY. Only the Z isomer was cleanly isolated. ^{1}H NMR ($CDCl_3$, 300 MHz) for Z isomer: δ1.32 (t, 3H, -CH_2CH_3), 2.13 (d, 3H, J = 1.2 Hz, =CCH_3), 4.20 (q, -CH_2CH_3), 5.75 (s, 1H, =C*H*), 6.92 (d, 1H, J = 16.2Hz, -*CH*CHPh), 7.25-7.38 (m, 3H, 3,4-phenyl), 7.52-7.58 (m, 2H, 2-phenyl), 8.42 (d, 1H, =C*H*Ph). Spectral data were practically identical to reported value.[31] GC chromatograms indicated the product had a Z/E ratio of 2.8:1.

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CHAPTER 4.

GENERAL CONCLUSION

This dissertation focuses on the use of iron(II) porphyrin as a catalyst for olefination of carbonyl compounds

Iron(II) porphyrin is an excellent catalyst for the olefination of carbonyl compounds. At room temperature, (TPP)Fe catalyzed the production of α,β-unsaturated esters from a variety of aldehydes in high yield with excellent stereoselectivities. *Trans/cis* ratios up to 40:1 were obtained at ambient temperature using 1 mol% Fe(TPP). With lower catalyst loading (0.1 mol% catalyst), reactions proceeded more slowly for benzaldehyde. The electronic nature of the aldehyde is important for this reaction. Electron-poor aldehydes reacted faster than than more electron-sufficient ones. Ketones, because of their rich-electron nature, reacted even slower than electron-rich aldehydes. Additionally, Fe(TPP)Cl was also examined as olefination catalyst, but proved to be less potent as Fe(TPP).

The mechanism of this reaction was investigated, and phosphorane ($Ph_3P{=}CHCO_2Et$) was identified as an intermediate. Stoichiometric reactions with electron-rich aldehydes and ketones also gave comparable results with those under catalytic conditions. However, electron-poor aldehydes such as 4-nitrobenzaldehyde and 4-cyanobenzaldehyde gave different *trans/cis* ratios in these two reactions. Further studies shows that a weak π-interaction most likely exists between Fe(TPP) and the electron-rich aldehyde. Thus an early transition state will account for the different ratios from different catalyst loadings.

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