Iron porphyrin catalyzed N-H insertion reactions

by

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has met the thesis requirements of Iowa State University

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LIST OF ABBREVIATIONS

cat	catalyst
cm	centimeter
DMM	dimethyl diazomalonate
EDA	ethyl diazoacetate
ee	enantiomeric excess
eq	equation
Et	ethyl
fig	figure
GC	gas chromatography
hr	hour
m	meter
mg	milligram
MHz	megahertz
μm	micrometer
min	minutes
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MPDA	methyl phenyl diazoacetate

MS	mass spectrometry
MTO	methylrhenium trioxide
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
R	generic alkyl group
saldach	dianion of *trans*-1,2-bis(salicylidene)cyclohexanediamine
t-Bu	*tert*-butyl
TMeO-PP	dianion of *meso*-tetra(*p*-methoxyphenyl)porphyrin
TMP	dianion of *meso*-tetramesitylporphyrin
Tp*	tris(3,5-dimethylpyrazol)borate
TPFPP	dianion of *meso*-tetra(pentafluorophenyl)porphyrin
TPP	dianion of *meso*-tetraphenylporphyrin
Ts	*para*- toluenesulfonyl
TTP	dianion of *meso*-tetratolylporphyrin

CHAPTER 1

GENERAL INTRODUCTION

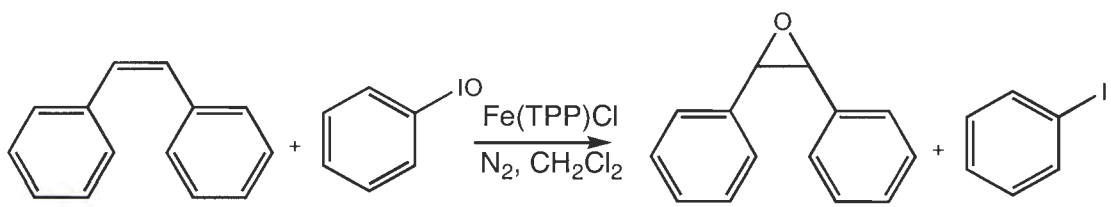
Thesis Organization

This thesis is organized in three chapters. The first chapter includes a survey of iron porphyrin catalysis and a summary of reported N-H insertion reactions. The second chapter is a paper to be submitted to *Organometallics* on iron porphyrin catalyzed N-H insertion reactions. In this paper, the initial survey of metalloporphyrin complexes and the study of catalyst loadings with piperidine was done by Goudong Du. The third chapter highlights the conclusions of the work presented in chapter two.

Iron Porphyrin Catalysis

Iron porphyrin complexes are effective catalysts for several organic reactions. Among the reported reactions are epoxidation, aziridination, and cyclopropanation of olefins. More recently, iron porphyrin complexes have been shown to catalyze the olefination of aldehydes and ketones. Each reaction will be briefly discussed below.

Epoxidation of alkenes by metalloporphyrins has been studied for some time. In 1979 Groves reported the use of Fe(TPP)Cl to catalyze epoxidation reactions of olefins with iodosylbenzene as the oxygen atom source(eq. 1).[1]



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Four years later the same group reported an enantioselective epoxidation by chiral metallophorphyrins.[2] Using 5α,10β,15α,20β-tetrakis(*o*-(R)-hydratropamidophenyl) iron(III) porphine chloride, FeT(α,β,α,β-Hyd)PPCl (Fig. 1), with styrene and iodosylbenzene, the reaction provided an epoxidation product in 65% yield and 31% enantiomeric excess. Collman showed improved yields (95%) and selectivity (83% ee) using an ααββ-binaphthyl strapped porphyrin which provided access to the active site, but also some steric hindrance at the metal center.[3]

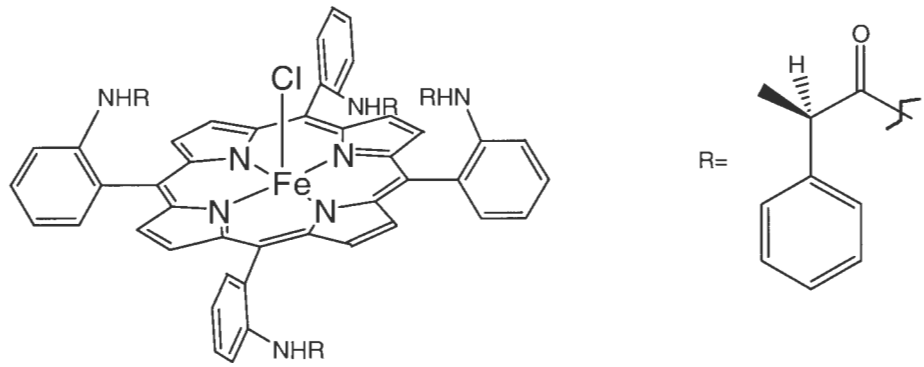


Fig. 1. FeT(α,β,α,β-Hyd)PPCl.

Similar to the epoxidations, iron porphyrins can also catalyze aziridination reactions of alkenes by transfer of a nitrene from PhI=NTs or bromamine-T (Fig. 2). Mansuy showed

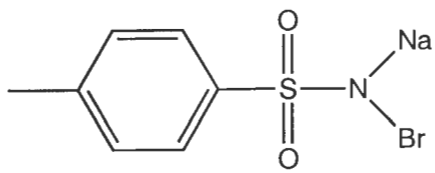
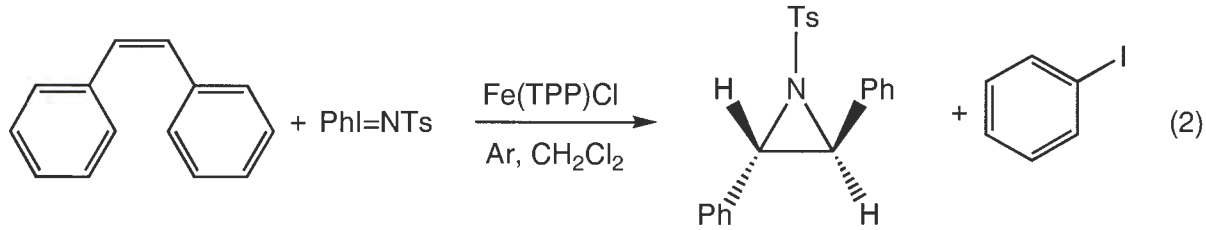


Fig. 2. Bromamine-T

that Fe(TPP)Cl catalyzed the formation of aziridines from styrene, *cis*- and *trans*-stilbenes, and 1,1-diphenylethylene using PhI=NTs as the nitrene source and the limiting reagent

(eq.2).[4,5] Aziridination of both *cis*- and *trans*-stilbene resulted in the formation of the thermodynamically preferred *trans*-*N*-tosyl-2,3-diphenylaziridine in 37% yield from the *cis*-



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isomer and 32% yield from the *trans*- isomer. A side reaction from hydrolysis of PhI=NTs formed toluene-*p*-sulfonamide. The combined yields of the *N*-tosylaziridine and sulfonamide were near 100%. A proposed mechanism for aziridination involves the formation of an iron-nitrene complex, formally a radical species. The radical species then adds to the alkene double bond (Fig. 3).[5] When stilbene is the substrate, the benzylic radical formed would have a sufficient lifetime to allow rotation around the C-C bond and form the thermodynamically favored *trans* product.

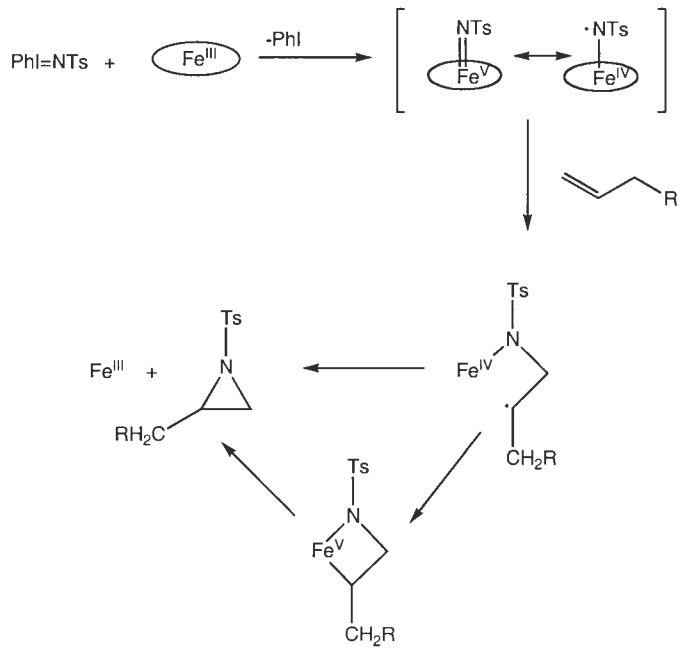
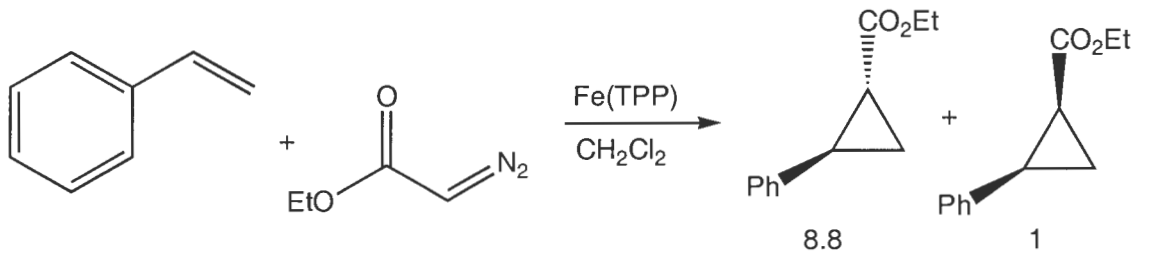


Fig. 3. Proposed aziridination mechanism for an olefin.

Zhang showed bromamine-T to be a better nitrene source than PhI=NTs for aziridination of alkenes.[6] Using iron(III) porphyrin complexes, the reactions could be performed at room temperature with alkene as the limiting reagent. Fe(TPP)Cl was shown to effectively catalyze the reaction with various alkenes ranging from *para*-substituted styrenes to cyclic and straight chain olefins giving moderate to good yields (36% - 72%). Zhang proposed that the aziridination mechanism with bromamine-T is similar to that of aziridination with PhI=NTs.

Another transformation catalyzed by iron porphyrins is the cyclopropanation of olefins. In 1995 our group showed that iron(II) porphyrins were effective cyclopropanation catalysts for olefins using ethyl diazoacetate, EDA (eq. 3).[7] In the presence of styrene and EDA, Fe(TPP) catalyzed the cyclopropanation reaction to give the *trans*- and *cis*-



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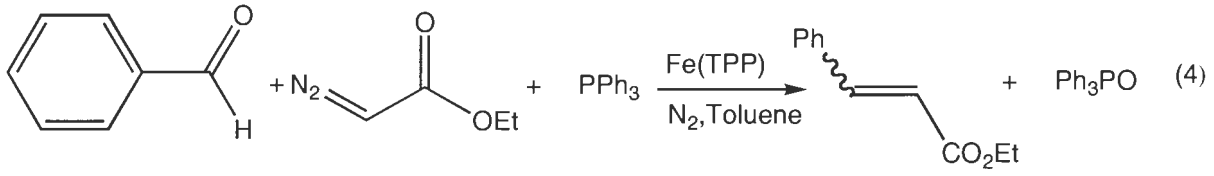
cyclopropyl esters in a ratio of 8.8:1 respectively within one hour with only a trace of diethyl maleate detected. Iron(III) porphyrins could be used as pre-catalysts in the presence of a reducing agent such as EDA at reflux, or with cobaltocene at room temperature. The electron deficient Fe(TPFPP)Cl was also an effective catalyst and it could be reduced by EDA at room temperature. However, Fe(TPFPP)Cl gave a lower *trans* selectivity and up to 25% diethyl maleate. Using styrene as the substrate, the *trans*:*cis* product ratio was 6:1 and the reaction was much slower, taking six hours to reach completion. Slow addition of EDA over one hour was necessary in the cyclopropanation reactions to reduce the formation of

dimers. Iron(II) porphyrin complexes dimerize EDA in seconds, so dimer formation from the attack of EDA on the carbene complex competes with the desired cyclopropanation reaction.

Iron(II) porphyrins were also found to be effective catalysts for cyclopropanation reactions using various diazo compounds as carbene sources. For example, the cyclopropanation of styrene with slow addition of *p*-tolyldiazomethane gave a *trans*:*cis* ratio of up to 17:1.[8] The use of mesityldiazomethane with styrene produced the *cis*- isomer as the major product.

Recently, iron porphyrins have also been shown by our group[9] and others[10] to catalyze the olefination of aldehydes and ketones in the presence of triphenylphosphine and diazo compounds. Our group achieved excellent yields (85-99%) of olefination products from aromatic and aliphatic aldehydes using Fe(TTP) as the catalyst. Using a 1:2:1.1 ratio of benzaldehyde: EDA: triphenyl phosphine, a 94% yield of olefin with a *trans*- to *cis*-selectivity of 24:1 was achieved (eq. 4).[9a] The proposed mechanism involves the formation



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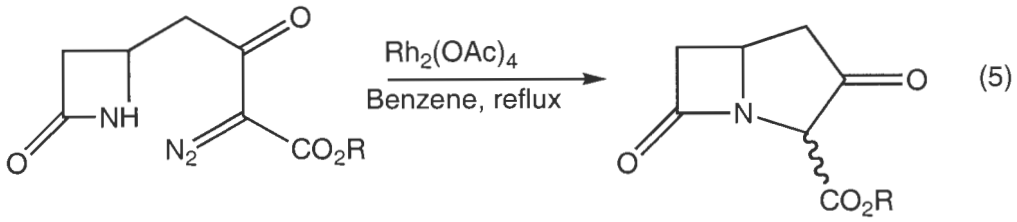
of an iron carbene complex and conversion of PPh_3 to a phosphorane. Reaction between the phosphorane and aldehyde produces phosphine oxide and the desired olefin. Olefination of ketones using Fe(TPP) was much slower than aldehyde olefination. No olefination product was observed with 4-methylcyclohexanone, while 4-nitroacetophenone gives an 80% yield and a Z/E selectivity of 2:1 in 4 days.[9b]

N-H Insertion Reactions

Iron porphyrins are efficient catalysts for several organic reactions as discussed above. To our knowledge, they have not been reported as N-H insertion catalysts. Insertion of diazo compounds into N-H bonds has been studied for several decades. The products of EDA insertion into amine N-H bonds could be used as precursors for amino acids. Intramolecular insertions have been developed and are important in the Merck synthesis of carbapenams (eq 5).[11]



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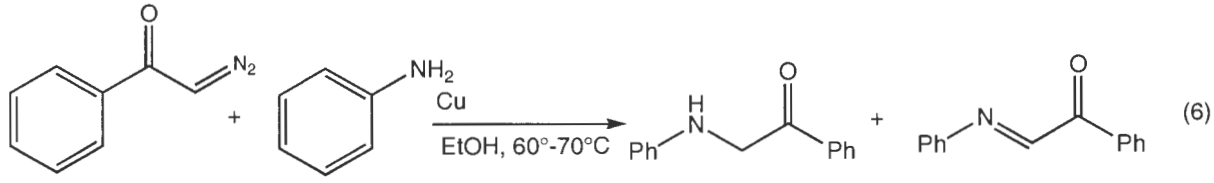
One of the first reported metal catalyzed N-H insertions by a diazo compound was in 1952 by Yates.[12] Copper bronze catalyzed the N-H insertion of α-diazoacetophenone into aniline (eq. 6) and piperidine. The reaction was carried out in ethanol at 60 -70°C using excess amine. A 33% yield of α-anilinoacetophenone was obtained along with the side



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product 1-phenyl-2phenylimino ethanone which was formed from the oxidation of the N-H insertion product. Under similar conditions piperidine was also found to give both dibenzoylethane and the N-H insertion product α-(1-piperidyl)-acetophenone (80% yield). The mechanism of this reaction involved the loss of N_2 gas and formation of a copper complex with the phenylacetylidene fragment. The electron-deficient carbene carbon from

the diazo can be attacked by the lone pair of electrons on the amine nitrogen followed by a prototropic shift.

Copper complexes with homoscorpionate ligands, Tp* (Fig. 4) were shown to significantly improve yields of copper catalysts.[13] At ambient temperature, Tp*Cu

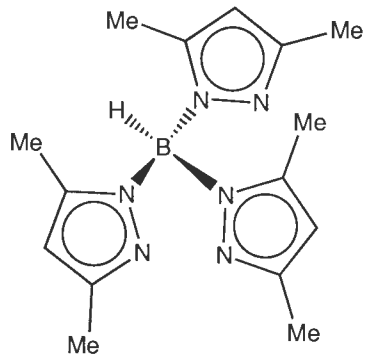


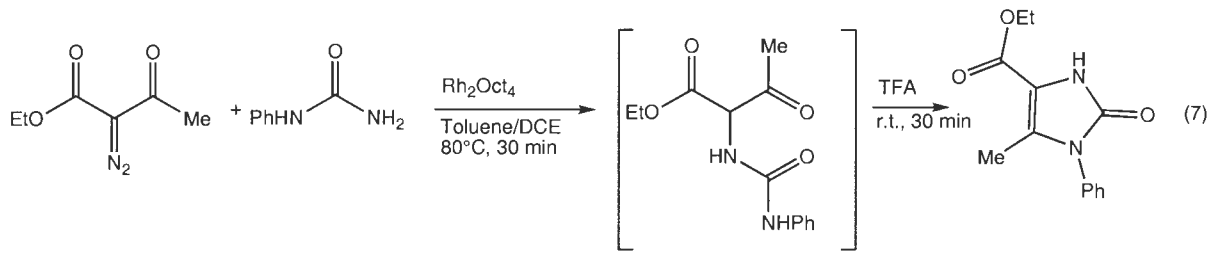
Fig. 4 Homoscorpionate ligand, Tp*

catalyzed EDA insertion into aniline giving yields of greater than 95% along with less than 5% of diethyl maleate and fumarate side products. This copper complex also catalyzed the insertion of EDA into trimethylacetamide giving a yield of 85% at a slower reaction rate than insertion into aniline.

Dirhodium(II) tetraacetate has been extensively studied as a catalyst for the decomposition of diazo compounds and their insertion into N-H bonds of amines, amides, carbamates, and lactams.[14] Moody found rhodium acetate catalyzed insertion reactions with methyl 2-diazo-2-phenylacetate into anilines, amines, and carbamates in 67-83% yield at ambient temperature.[14b] A color change was observed, indicating the nucleophilic amines were coordinated to the catalyst. The same group used diazophosphonates to form aminophosphonate derivatives. The diazophosphonates required higher reaction

temperatures and the reactions were carried out in refluxing toluene. Reactions with simple amides resulted in low yields (<33%) while anilines gave yields varying from 16% for toluidine to 76% for *p*-chloroaniline.

Livant used dirhodium tetraacetate catalyzed reactions to successfully form tertiary amines from secondary amines and dimethyl diazomalonate in refluxing benzene.[14c] Amines with bulky substituents were used. For example, dicyclohexyl amine gave an 85% yield of insertion product and diphenyl amine gave an 84% yield. Janda used dirhodium tetraoctanoate to catalyze an N-H insertion into primary ureas followed by acid catalyzed dehydration to form imidazolones (eq. 7) in good yields (72-85%).[14e]



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Methylrhenium trioxide (MTO) was reported by Espenson to catalyze N-H insertions of EDA into amines.[15] At 0.4 mole percent of MTO, a variety of aromatic and aliphatic amines were tested and glycine ester products were formed within one hour, affording isolated yields of >85%. Only trace amounts of diethyl maleate and diethyl fumarate were detected. The proposed mechanism involves the formation of a metallacycle intermediate (Fig. 5), followed by nucleophilic attack by the amine.

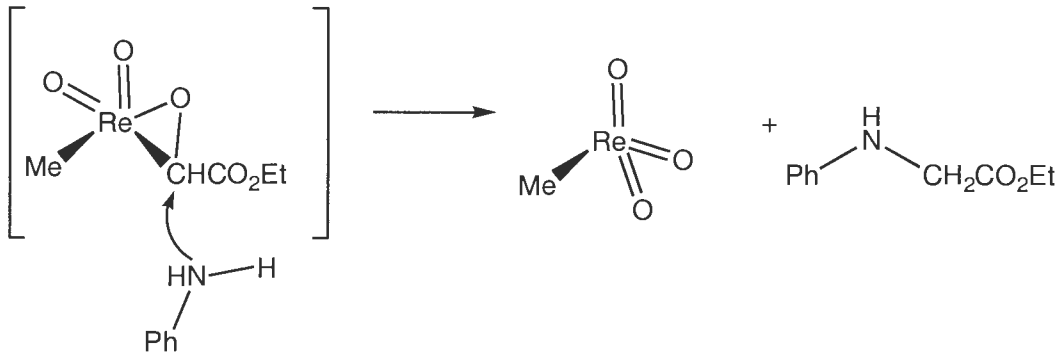

Fig. 5. Proposed mechanistic step for MTO catalyzed reactions.

Simonneaux found ruthenium(II) porphyrins to be effective at catalyzing N-H insertion reactions at room temperature under an inert atmosphere.[16] Using EDA and various primary and secondary amines, Ru(TMP)CO produced glycine esters in 63 to 81% yield along with the fumarate and maleate. The amine and EDA needed to be added simultaneously to minimize poisoning of the catalyst due to coordination of excess amine. Nucleophilic amines were known to coordinate to the ruthenium and partially poison the catalyst. Compared to secondary amines, primary amines led to lower yields because they were better ligands for the porphyrin complex. A ruthenium carbene complex was assumed to be the active intermediate.

Given the success of iron porphyrin catalysis for various organic transformations, our group examined its ability to catalyze N-H insertion reactions. The following chapter covers our recent work on catalytic N-H insertions of EDA into primary and secondary aliphatic amines and aromatic amines using Fe(TPP)Cl as the catalyst. This is an effective catalyst for N-H insertion of EDA into amines. Furthermore, it does not require the slow addition of

EDA or an inert atmosphere. The catalyst is not poisoned by amine, is commercially available, and relatively inexpensive.

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CHAPTER 2

IRON PORPHYRIN CATALYZED N-H INSERTION REACTIONS WITH ETHYL DIAZOACETATE

A paper to be submitted to *Organometallics*

Lynnette K. Baumann, Goudong Du and L. Keith Woo*

Abstract

A series of metalloporphyrin complexes was surveyed as catalysts for ethyl diazoacetate insertion into N-H bonds of amines. Iron(III) tetraphenylporphyrin chloride, Fe(TPP)Cl, was found to be an efficient catalyst for N-H insertion reactions with a variety of aliphatic and aromatic amines, with yields ranging from 68-97%. Primary amines were able to undergo a second insertion of EDA when done in a step-wise process. N-Heterocyclic compounds were poor substrates giving low yields of insertion products or no N-H insertion products. To gain insight into the mechanism of the insertion reaction, several experiments were conducted including the decomposition of EDA and competition reactions. These experiments suggested that iron(III) porphyrin is involved in the catalysis. Competition reactions were conducted with a series of *para*- substituted aniline derivatives and the relative rates correlated with σ^+ on a Hammett plot. Electron donating groups enhanced the reaction as indicated by the negative value of ρ (ρ=-0.66 ± 0.05, R^2=0.93).

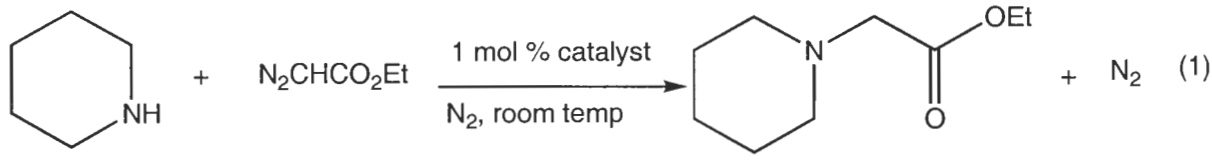
Introduction

Iron porphyrins are useful catalysts for a variety of organic reactions. These include cyclopropanation,[1] epoxidation,[2] and aziridination[3] of olefins. Recently, iron porphyrins were shown to catalyze the olefination of aldehydes and ketones in the presence of triphenylphosphine by our group[4] and others.[5] This suggested to us that iron porphyrins may have the potential to mediate a variety of other processes.

Using diazo compounds as carbene sources, transition metal complexes that have been shown to catalyze N-H insertion reactions include methyl trioxorhenium,[6] rhodium[7] and copper[8] complexes, and ruthenium porphyrins.[9] Reactions that use diazoacetate reagents for insertion into N-H bonds may provide useful precursors for amino acids. In addition, intramolecular insertions resulting in N-heterocyclic compounds, such as indoles[10] and imidazolones are also of great synthetic interest. We now report insertion reactions into aliphatic and aromatic N-H bonds using ethyl diazoacetate (EDA) as the carbene source and iron tetraphenylporphyrin chloride, Fe(TPP)Cl,[11] as the catalyst.

Results and Discussion

The activity of a series of metalloporphyrin complexes as catalysts for N-H insertion reactions was surveyed, using piperidine and EDA (eq. 1). Among the catalysts examined, iron porphyrins proved to be the most active giving high yields in relatively short periods of



time (Table 1). Fe(TPP)Cl, was found to be one of the most efficient in catalyzing the insertion of EDA into the piperidine N-H bond, resulting in a quantitative yield in under 10 minutes. The reactions were run under mild conditions at ambient temperature in a one-pot

Table 1. N-H insertion of EDA into piperidine catalyzed by metalloporphyrins[a]

Entry	Catalyst	Time	N-H insertion yield (%)
1	Fe(TPP)Cl	<10 min	>97
2	Mn(TPP)Cl	24 hr	nd
3	Zn(TPP)	24 hr	nd
4	Co(TTP)	24 hr	nd
5	Os(TTP)(CO)	28 hr	4
6	Os(TTP)(CO)[b]	20 min	90
7	no cat	24 hr	nd
8	Fe(TMeO-PP)Cl	<5 min	>97
9	Fe(TPFPP)Cl	40 min	>97
10	Fe(TMP)	1 hr	80
11	Fe(Saldach)Cl	22 hr	nd

[a] A molar ratio of 1:100:120 for catalyst:EDA:piperidine was employed. [b] The reaction was carried out under refluxing conditions.

fashion, without the need for slow addition of EDA. The insertion reaction proceeded in seconds, as the reaction mixture warmed up upon addition of EDA, accompanied by

observable gaseous N_2 release. Evidence of the desired insertion product was observed in the ^1H NMR spectrum with the appearance of a new two-proton methylene singlet at 3.17 ppm and the disappearance of the one-proton singlet at 4.72 ppm for the methine proton of EDA. No formation of diethyl fumarate or maleate was observed by GC analysis. These results validate that Fe(TPP)Cl is among the best porphyrin catalysts for amine N-H insertion reactions. For example, a ruthenium porphyrin catalyzed N-H insertion required longer reaction times (2-18 h) and afforded lower yields (63-81%).[9a] The only results comparable with Fe(TPP)Cl were obtained with copper complexes bearing homoscorpinate (Tp) type ligands.[8] An osmium porphyrin complex, Os(TTP)(CO), was also able to catalyze the insertion of EDA into an N-H bond. While the reaction yield was low at ambient temperature, it afforded 90% yield of insertion product after heating at reflux for 20 minutes.

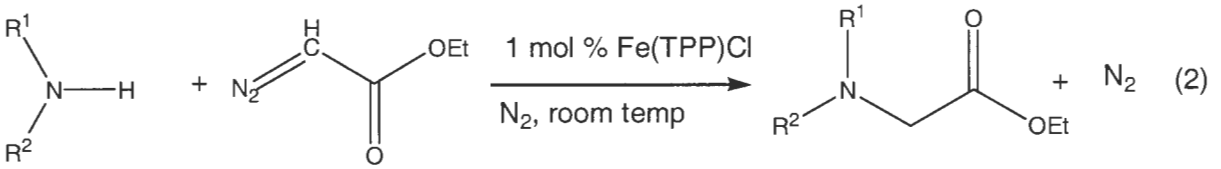
A number of iron porphyrins with different steric and electronic properties were examined in catalytic N-H insertions (Table 1 entries 8-11). The varying completion times and yields indicated that the catalytic activity of these complexes depended on their steric and electronic properties. Electron-donating groups in the porphyrin periphery enhanced the activity. Fe(TMeO-PP)Cl appeared to be the best catalyst among those investigated with the reaction reaching completion in under 5 minutes. In contrast, the electron deficient complex, Fe(TPFPP)Cl, required 40 minutes to complete the N-H insertion into piperidine with EDA. Fe(TMP) catalyzed the same reaction affording an 80% yield after 1 hr, suggesting that steric hindrance may also play a role.

The subsequent studies focused on Fe(TPP)Cl because it is commercially available and relatively inexpensive. The catalyst loadings can be lowered, for example, to 0.1 mol%, albeit requiring a longer reaction time at ambient temperature (Table 2).

Table 2. N-H insertion of EDA into amines with various loadings of Fe(TPP)Cl.

Entry	amine	% catalyst	time	yield (%)
1	aniline	1.0	5 min	91
2	aniline	0.50	5 min	87
3	aniline	0.25	10 min	90
4	aniline	0.14	25 min	88
5	aniline	0.10	1 hour	89
6	piperidine	1.0	10 min	>95
7	piperidine	0.5	10 min	>95
8	piperidine	0.1	5 hour	82

A variety of amine substrates were used to study the scope of Fe(TPP)Cl as a catalyst for insertion into N-H bonds with EDA. N-H insertions were successfully achieved using primary and secondary alkyl amines (eq. 2) in good to high yields of 68 to 97% (Table 3 entries 1-4). Evidence of the desired insertion product with diethyl amine was observed in



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the ^{1}H NMR spectrum with the appearance of a new two-proton methylene singlet at 3.27 ppm and the disappearance of the one-proton singlet at 4.72 ppm for the methine proton of EDA. Aryl amine substrates also gave successful insertion reactions (eq. 3) giving yields of 74 to 95 % (Table 3, entries 8 - 14), comparable to reported yields for reactions catalyzed by

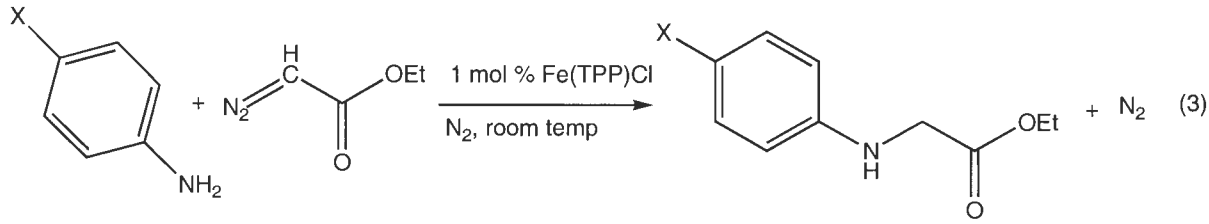
copper, ruthenium, and rhenium complexes.[6,7,8,9] The ^{1}H NMR spectrum of the product of EDA insertion into aniline showed a new two-proton methylene singlet at 3.91 ppm. Almost

Table 3. Results for single EDA insertion into amines.

Entry	Amine	Amine:EDA	Time	%yield[a]
1	Et_2NH	1:1.1	10 min	86
2	t-Bu-NH_2	1:1	10 min	68
3	$C_5H_{10}NH$	1:1.2	10 min	85
4	$PhCH_2NH_2$	1:1	10 min	76
5	Ph_2NH	1:1.1	1 hr, 60°C	<5
6	Tetramethylpiperidine	1:1.1	48 hr	NR
7	Benzamide	1:1.1	48 hr	NR
8	p-CH_3O-C_6H_4-NH_2	1:1.2	10 min	82
9	p-CH_3-C_6H_4-NH_2	1:1.2	10 min	95
10	C_6H_5-NH_2	1:1.2	10 min	91
11	p-Cl-C_6H_4-NH_2	1:1.0	20 min	58, 13 double insert
12	p-Br-C_6H_4-NH_2	1:1.1	10 min	92
13	p-CN-C_6H_4-NH_2	1:1.2	20 min	87
14	p-NO_2-C_6H_4-NH_2	1:1.1	1 hr	91
15	Imidazole	1:1.4	48 hr	51
16	Pyrrole	1:1.3	48 hr	37 C-H insertion
17	Indole	1:2.4	48 hr	NR

a) NMR yield

all of the single N-H insertion reactions reached completion in 20 minutes or less. The exception was the *p*-nitroaniline reaction that took 1 hour for complete consumption of the reagents.



(3)

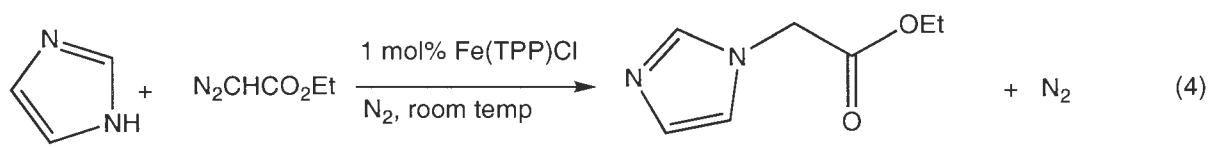
Primary amines were able to undergo a double N-H insertion reaction (Table 4) with excess EDA. This process could be done step-wise, first forming the single insertion product then adding an additional equivalent of EDA. Addition of two equivalents of EDA to the substrate in one aliquot, resulted in single insertion product, low yields of double insertion product, and more dimer formation. The second insertion is a slower reaction, allowing more dimer to form in these reactions compared to the single insertion reaction. Increasing the electron-withdrawing ability of the substituents on the aniline made the second insertion more difficult, requiring longer reaction times. When aminobenzonitrile was the substrate, a low yield of double insertion product was observed by GC and GC-MS, but could not be isolated from the single insertion product. No double insertion product was formed when *p*-nitroaniline was the substrate (Table 4, entry 8) possibly due to the electron-withdrawing abilities of the nitro substituent and the N-acetate fragment inserted previously. The excess EDA available formed the dimer product. The double insertion product of aniline gives a ^{1}H NMR signal of a four-proton methylene singlet at 4.14 ppm for the two N-acetate groups, a smaller upfield shift than for that of the single insertion product.

Table 4. Results for double insertion of EDA into amines.

Entry	Amine	Amine:EDA	Time	%yield[a]
1	$PhCH_2NH_2$	1:3	15 min	97
2	p-CH_3O-C_6H_4-NH_2	1:2.4	1 hr	64
3	p-CH_3-C_6H_4-NH_2	1:2.4	1 hr	76
4	C_6H_5-NH_2	1:2.9	2hr	92
5	p-Cl-C_6H_4-NH_2	1:2.4	1.5 hr	72, 16 single insertion
6	p-Br-C_6H_4-NH_2	1:4.1	2 hr	78, 14 single insertion
7	p-CN-C_6H_4-NH_2	1:4	4 hr	81% single, <20% double
8	p-NO_2-C_6H_4-NH_2	1:4	48 hr	91% single insertion

[a]NMR yield

Reactions with N-heterocyclic compounds gave significantly different results from the aniline derivatives. Using imidazole as the substrate, the N-H insertion product was formed in a 51% yield (eq.4), while under the same conditions EDA inserted into the α-C-H bond of pyrrole in low yields and did not react with indole. EDA insertion into the C-H bond of pyrrole has been previously reported.[12] Imidazole is more basic than pyrrole and indole making it more nucleophilic and able to attack the carbene.



(4)

Diethyl maleate and diethyl fumarate from dimerization of EDA were generally observed in only trace amounts. Therefore, it was not necessary to add EDA and amine simultaneously or slowly to the catalyst solution. This also indicated that Fe(TPP)Cl is not poisoned by coordination of amine. This poisoning effect has been reported for a ruthenium porphyrin[10a] and a rhodium catalyst.[13]

Several *ortho*- substituted anilines were also evaluated (Table 5). A single insertion of EDA into 2-chloroaniline gave a yield of 70% and insertion into 2-aminoacetophenone resulted in a 57% yield. Additional equivalents of EDA did not result in any double insertion product of either substrate, indicating the reaction site may be too sterically hindered. Single insertion into 2,6-lutidine was unsuccessful also indicating steric hindrance affects the reaction. This hindrance was also seen with 2,2,6,6-tetramethylpiperidine (Table 3 entry 6). Insertion into 2-aminophenol was also unsuccessful. This substrate may poison the catalyst as there was no dimerization product of EDA observed.

Table 5. *Ortho*- substituted anilines with EDA.

Entry	Amine	Amine:EDA	Time	%yield[a]
1a	2-chloroaniline	1:1.2	10 min	70 single insertion
1b	2-chloroaniline	1:2.5	48 hr	70 single insertion
2	2-aminoacetophenone	1:1.2	20 min	57 single insertion
3	2-aminophenol	1:1.1	48 hr	NR
4	2,6-lutidine	1:1.5	24 hr	NR

[a] NMR yield

Fe(TPP)Cl was also tried as a catalyst for insertion of EDA into N-H bonds of amides and O-H bonds of alcohols. Insertion of EDA into the N-H bond of benzamide was not successful (Table 3 entry 7). O-H insertions were attempted using phenol, ethanol, and cyclohexanol as substrates. All were unsuccessful producing only the EDA dimer product, possibly due to the lower nucleophilicity of these substrates compared to amines.

Dimethyl diazomalonate (DMM) and methyl phenyldiazoacetate (MPDA) (Fig. 1) were also investigated as carbene sources for insertion into aniline. Insertion of MPDA into aniline gave 92% yield of the N-H insertion product. This reaction required refluxing

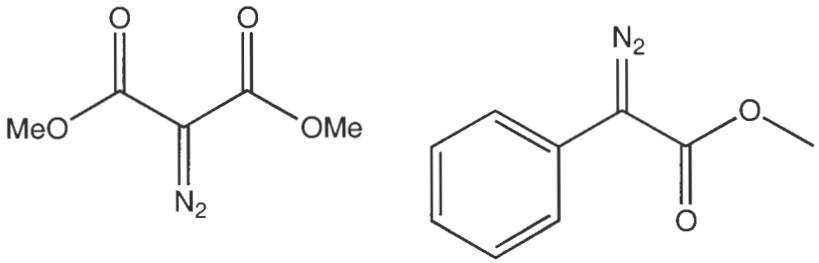


Figure 1. Dimethyl diazomalonate and methyl phenyldiazoacetate.

conditions in methylene chloride for 40 hours. These are harsher reaction conditions compared to the ambient temperature used for EDA insertions. The ^{1}H NMR of the product showed a new one-proton methine singlet at 5.09 ppm for the inserted fragment. Insertion of DMM into aniline in refluxing benzene for 72 hours yielded only a trace of the single insertion product by GC-MS analysis 224(M+1), 104 (base peak).

Our group previously used Fe(TPP)Cl as a pre-catalyst for the cyclopropanation of olefins using EDA as a reductant.[1c] In this study, a competition experiment between cyclopropanation of styrene and N-H insertion of aniline was conducted. Equimolar amounts

of aniline, styrene and EDA were used with 1.0 mole % Fe(TPP)Cl in methylene chloride. The reaction was run at both room temperature and in refluxing methylene chloride. In both reactions only N-H insertion product was observed by GC-MS and ^{1}H NMR. The preference for insertion over cyclopropanation has been previously reported for ruthenium catalyzed N-H and S-H insertions[9b] and a rhodium catalyzed O-H insertion.[14]

Mechanistic Considerations

Competition reactions were undertaken to gain insight into the mechanism of the insertion reaction. *Para*-substituted anilines were paired with aniline in equimolar amounts and treated with EDA in the presence of Fe(TPP)Cl. Relative rate results are summarized in a Hammett plot (Fig. 2). A better correlation was found with σ^+ (R^2=0.93) than with σ (R^2=0.88) or σ^- (R^2=0.70) indicating that a partial positive charge exists on the intermediate, presumably involving an iron carbene species. Electron-donating groups on the aniline derivatives increased the reaction rate as indicated by a negative value of ρ (ρ=-0.66 $\pm$ 0.05). This is consistent with a nucleophilic attack of the amine on the electron deficient carbon of the carbene intermediate.

Initially the catalytic cycle for N-H insertion was thought to parallel a proposed mechanism for the cyclopropanation of olefins by Fe(TPP)Cl involving the reduction of Fe(III) to Fe(II) as shown in Fig. 3.[1c] Fe(TPP)Cl was shown not to catalyze cyclopropanation reactions as they needed to be done under an inert atmosphere to allow for the reduction of iron. EDA is known to be a mild reducing agent[15] and we have shown previously that EDA reduces Fe^{III} porphyrins to Fe^{II} porphyrins in refluxing methylene chloride.[1c] After the reduction of Fe(TPP)Cl to Fe(TPP) and formation of an iron carbene, the carbene inserts into

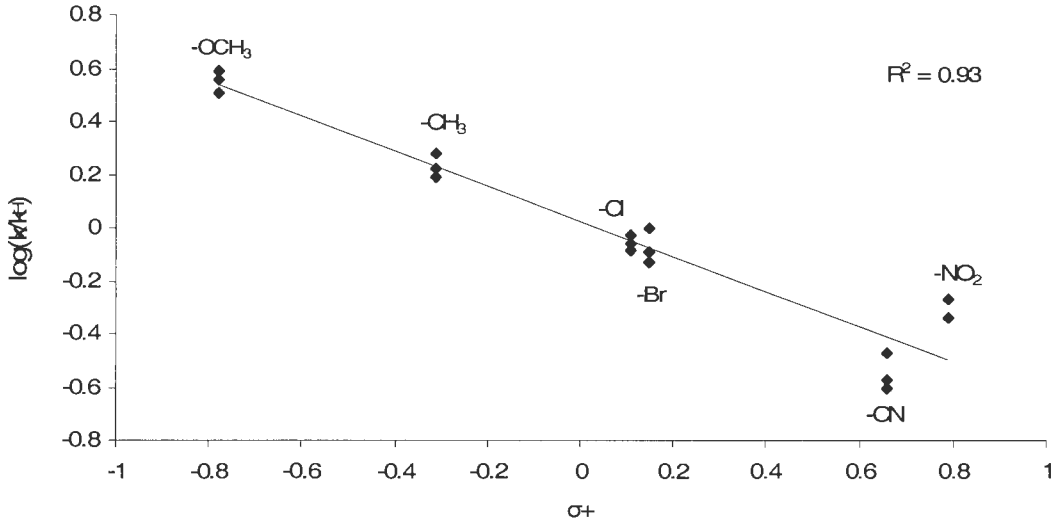


Figure 2. Hammett plot from competition reactions.

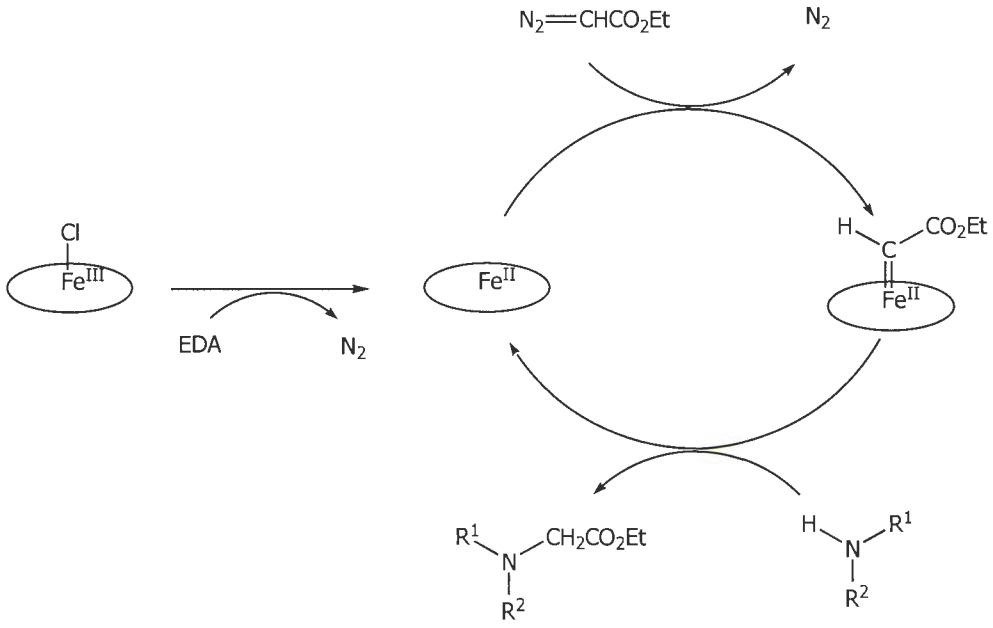


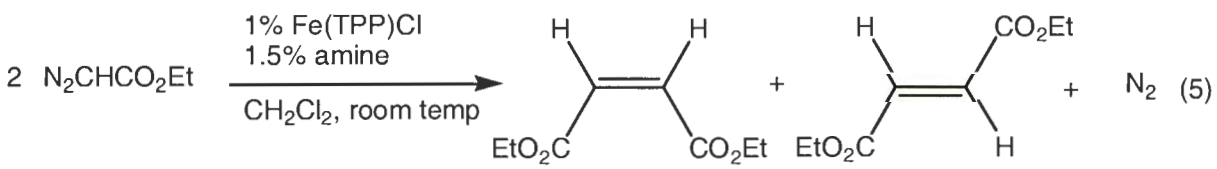
Figure 3. Initial proposed catalytic cycle for N-H insertion.

the N-H bond to form a glycine ester. While (TPP)Fe=$CHCO_2Et$ is very reactive and has not been detected, iron(II) carbenes prepared from mesityl diazomethane and trimethylsilyl diazomethane have been spectroscopically detected.[1b,c] The osmium analogue prepared with EDA has also been characterized.[16]

However, additional experiments indicate that reduction of the Fe(III) is not necessary in the N-H insertion reaction. The insertion reactions could be done without a nitrogen atmosphere with only a slight decrease in yield. In assessing a possible prereduction step, we looked at the decomposition of EDA in the presence of Fe(TPP)Cl and in the presence and absence of tertiary amines that could coordinate to the porphyrin complex, but not undergo N-H insertion (Table 5). The decomposition of EDA formed the dimers diethyl fumarate and diethyl maleate (eq. 5). When no amine was added, EDA dimerized slowly in 5.5 hours.

Table 5. Decompostion of EDA with Fe(TPP)Cl and 1.5% tertiary amine.

Entry	**amine**	**time**
1	no amine	5.5 hrs
2	Et_3N	< 30 min
3	pyridine	< 10 min



When small amounts of tertiary amines such as triethyl amine and pyridine were present, the reaction times were significantly reduced. This indicated that the amine is important to the active catalytic species. The proposed mechanism for N-H insertion into aniline is shown in Fig. 4. The amine coordinates to Fe(TPP)Cl donating electron density so a carbene can be formed with the Fe(III) porphyrin. The carbene carbon then undergoes nucleophilic attack by an additional amine molecule to form the insertion product. The nitrogen on the amine molecule is more nucleophilic than the available EDA, so the single insertion occurs faster than dimerization. The N-glycine ester formed from the first insertion is less nucleophilic than the original amine and therefore the second insertion occurs slower (Table 4). This makes the double insertion process less competitive with the dimerization process, thus the need for step-wise formation of the double insertion product.

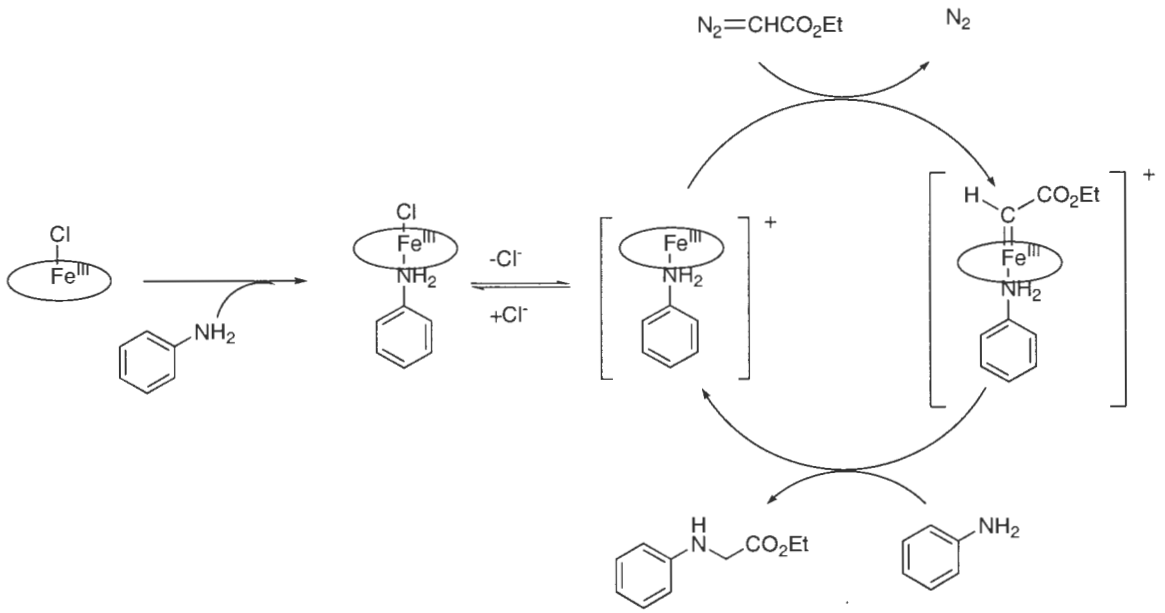


Figure 4. Proposed mechanism for N-H insertion.

Conclusions

Insertion of EDA into amine N-H bonds using Fe(TPP)Cl is a very efficient process. Fe(TPP)Cl appears to be among the best catalysts for insertion of EDA into amine N-H bonds. Successful single and double insertion was obtained in both aliphatic and aromatic amines in high yields. These reactions could be performed at ambient temperatures and atmospheric conditions while not requiring slow addition of EDA or long reaction times. As an insertion catalyst, Fe^{III}(TPP)Cl has the advantages of not being poisoned by the amine and producing little of the dimerization side products from EDA. Fe(TPP)Cl is also commercially available and relatively inexpensive.

Experimental Procedures

General Methods. EDA, solvents and amines were used as received, except as noted. Fe(TPP)Cl, Mn(TPP)Cl, Fe(TMeO-PP)Cl, and Fe(TPFPP)Cl were all used as received. Os(TTP)(CO),[17] Fe(saldach)Cl[18] and Zn(TPP)[19] were prepared according to literature prodcedures. Co(TTP) was prepared using a modified literature procedure.[20] DMM[21] and MPDA[22] were synthesized following literature procedures. Aniline was distilled from CaH_2 under reduced pressure. Diethyl amine was distilled from KOH pellets. The reaction progress and competition reactions were monitored by gas chromatography on a HP5890 Series II Plus gas chromatograph using a HP-5 cross-linked 5% PH ME silicone column, 30m x 0.32 mm x 0.25 μm film thickness. ^{1}H and ^{13}C spectra were obtained on a Varian VXR-300 spectrometer. MS analysis was done on a Finnigan Magnum GC-MS. Elemental analyses were performed on a Perkin-Elmer Model 2400 Series II CHN/S elemental analyzer.

Synthesis of Fe(TMP). Fe(TMP) was prepared according to a literature procedure[23] then reduced with Zn/Hg in toluene.

General procedure for single insertion reactions (A). In a typical experiment, an amine (0.250 – 1.0 mmol) was dissolved in 5 mL methylene chloride in a 25 mL round bottom flask. Fe(TPP)Cl (0.0025 – 0.010 mmol) was added and nitrogen was bubbled through the solution for 20 minutes. Ethyl diazoacetate (EDA) (1.20 equiv., 0.275 – 1.20 mmol) in 2 mL CH_2Cl_2 was added by syringe over 1 minute and the reaction mixture was stirred 10 minutes. Almost immediate release of N_2 was evident in most reactions. Upon completion of the reaction as indicated by GC analysis, the solvent was removed in vacuo and the reaction yield was determined by ^1H NMR with triphenylmethane as an internal standard. The product was isolated by column chromatography on silica gel (2.5 cm x 11 cm) eluted with hexane:ethyl acetate (10:1). All products were analyzed by ^1H and ^{13}C NMR, and MS. Previously uncharacterized compounds were also analyzed by elemental analysis.

General procedure for double insertion reactions (B). The single insertion product was formed using the reaction conditions described above. An additional 1.20 equiv. EDA in 2 mL CH_2Cl_2 was added by syringe over one minute and the reaction was stirred for an additional hour and monitored by GC. Upon completion of the reaction, the solvent was removed in vacuo and the reaction mixture was analyzed by ^1H NMR with triphenylmethane as an internal standard. The product was isolated by column chromatography (2.5 cm x 11 cm) on silica gel eluted with hexane:ethyl acetate (10:1). All products were analyzed by ^1H and ^{13}C NMR, and MS. Previously uncharacterized compounds were also analyzed by elemental analysis.

General Procedure for competition reactions. Equimolar quantities (0.300 mmol) of aniline and an aniline derivative and Fe(TPP)Cl (0.0030 mmol) in 4 mL methylene chloride were stirred under nitrogen. EDA (0.300 mmol) in 2 mL methylene chloride was added by syringe in one aliquot. After five minutes, a sample was removed and the ratio of product yields was determined by gas chromatography using dodecane as an internal standard.

Synthesis of $Et_2NCH_2CO_2CH_2CH_3$. The general method **A** was followed, amine (43.7 mg, 0.597 mmol), EDA (83.5 mg, 0.732mmol), Fe(TPP)Cl (4.2 mg, 0.0060 mmol). A yellow oil was isolated (74.0 mg). ^{1}H-NMR δ ppm 1.02 (t, 6H, NCH_2CH_3), 1.27 (t, 3H, OCH_2CH_3), 2.61(q, 4H, CH_2CH_3), 3.27(s, 2H, NCH_2CO), 4.14(q, 2H, OCH_2CH_3), NH not observed. ^{13}C-NMR δ ppm 12.4(NCH_2CH_3), 14.5(OCH_2CH3), 48.0(NCH_2CH_3), 54.5(NCH_2CO), 60.6(OCH_2CH_3), 171.8(CO). MS 160 (M+1). Anal. Calcd.: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.26; H, 10.83; N, 8.42.

Synthesis of *t*-BuNH($CH_2CO_2CH_2CH_3$). A yellow oil (87.9 mg) was obtained from general method **A** amine (75.8 mg, 1.04 mmol), EDA (126.6 mg, 1.11 mmol), Fe(TPP)Cl (7.4 mg, 0.011mmol). ^{1}H-NMR δ ppm 1.11(s, 9H, CCH_3), 1.28(t, 3H, OCH_2CH_3), 1.7(broad, NH), 3.40(s, 2H, NCH_2CO), 4.19(q, 2H, OCH_2CH_3). ^{13}C-NMR δ ppm 14.3(CCH_3), 28.9, 45.0, 50.3, 60.9, 173.1(CO). MS 160 (M+1). Spectral results match reported values.[6]

Synthesis of $C_5H_{10}NCH_2CO_2CH_2CH_3$. A yellow oil (83.0mg) was obtained from general method **A** amine (48.7 mg, 0.572 mmol), EDA (78.3 mg, 0.687 mmol), Fe(TPP)Cl (3.5 mg, 0.0050mmol). ^{1}H-NMR δ ppm 1.27(t, 3H, OCH_2CH_3), 1.43(m, 2H, C_5H_{10}), 1.62(m, 4H, C_5H_{10}), 2.50(m, 4H, C_5H_{10}), 3.17(s, 2H, NCH_2CO), 4.18(q, 2H, OCH_2CH_3). ^{13}C-NMR

δ ppm 14.3, 23.9, 25.8, 54.4, 60.4, 60.5, 170.7. MS 172(M+1), 98 base peak. Spectral results match reported values.[6]

Synthesis of $PhCH_2NH(CH_2CO_2CH_2CH_3)$. A yellow oil (201.0 mg) was obtained from general method **A** amine (198.4 mg, 1.85 mmol), EDA (140.7 mg, 1.23mmol), Fe(TPP)Cl (7.5 mg, 0.011 mmol). ^{1}H-NMR δ ppm 1.27(t, 3H, OCH_2CH_3), 1.85(s, 1H, N*H*), 3.41(s, 2H, NCH_2CO), 3.81(s, 2H, $PhCH_2N$), 4.19(q, 2H, OCH_2CH_3), 7.27 to 7.34(m, 5H, C_6H_5). ^{13}C-NMR δ ppm 14.5, 50.3, 53.5, 60.9, 127.4, 128.5, 128.7, 139.7, 172.6. MS 194(M+1), 91 base peak. Spectral results match reported values.[6]

Synthesis of $PhCH_2N(CH_2CO_2CH_2CH_3)_2$. Procedure **B** was followed using an overall amine:EDA ratio of 1:3 and total reaction time of 15 minutes, amine (60.9 mg, 0.568 mmol), EDA (218.4 mg, 1.92 mmol), Fe(TPP)Cl (3.8 mg, 0.0054 mmol). A yellow-green oil was obtained (153.5 mg). ^{1}H-NMR δ ppm 1.29(t, 6H, OCH_2CH_3), 3.59(s, 4H, NCH_2CO), 3.96(s, 2H, $PhCH_2N$), 4.20(q, 4H, OCH_2CH_3), 7.21 to 7.37(m, 5H, C_6H_5). ^{13}C-NMR δ ppm 14.2, 54.2, 57.8, 60.4, 127.3, 128.3, 129.0, 138.1, 171.1. MS 280(M+1), 206 base peak. Spectral results match that of the commercially available compound from Aldrich.

Synthesis of *p*-CH_3O-C_6H_4-$NH(CH_2CO_2CH_2CH_3)$. Anisidine (123.3 mg, 1.001 mmol) was reacted with EDA (128.7 mg, 1.128 mmol) and Fe(TPP)Cl (6.5 mg, 0.0092 mmol) by general method **A**. A white solid (125.0 mg) was isolated. ^{1}H-NMR δ ppm 1.29(t, 3H, OCH_2CH_3), 3.74(s, 3H, CH_3O), 3.86(s, 2H, NCH_2CO), 4.23(q, 2H, OCH_2CH_3), 6.59(d, 2H, C_6H_4), 6.79(d, 2H, C_6H_4), NH not observed. ^{13}C-NMR δ ppm 14.2, 46.8, 55.7, 61.2, 114.4, 114.9, 141.2, 152.6, 171.4. MS 209(M). Anal. Calcd.: C, 63.14; H, 7.23; N, 6.70. Found: C, 63.16; H, 7.25; N, 6.99.

Synthesis of *p*-CH_3O-C_6H_4-$N(CH_2CO_2CH_2CH_3)_2$. A yellow-orange oil (245.7mg) was obtained from general method **B**; amine (126.7 mg, 1.029 mmol), EDA (235.7 mg, 2.854 mmol), Fe(TPP)Cl (7.5 mg, 0.011 mmol). ^{1}H-NMR δ ppm 1.26(t, 6H, OCH_2CH_3), 3.73(s, 3H, OCH_3), 4.10(s, 4H, NCH_2CO), 4.20(q, 4H, OCH_2CH_3), 6.61(m, 2H, C_6H_4), 6.80(m, 2H, C_6H_4). ^{13}C-NMR δ ppm 14.2, 54.0, 55.6, 60.9, 114.4, 114.7, 142.3, 152.6, 171.1. MS 295(M). Anal. Calcd.: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.32; H, 7.70; N, 5.27.

Synthesis of *p*-CH_3-C_6H_4-$NH(CH_2CO_2CH_2CH_3)$. A white solid (86.8 mg) was obtained from general method **A**; amine (53.5 mg, 0.499 mmol), EDA (65.6 mg, 0.5749 mmol), Fe(TPP)Cl (3.7 mg, 0.0053 mmol). ^{1}H-NMR δ ppm 1.29(t, 3H, OCH_2CH_3), 2.24(s, 3H, $CH_3C_6H_4$), 3.88(s, 2H, NCH_2CO), 4.24(q, 2H, OCH_2CH_3), 6.53(m, 2H, C_6H_4), 7.00(d, 2H, C_6H_4) NH not observed. ^{13}C-NMR δ ppm 14.2, 20.4, 46.2, 61.2, 113.1, 127.4, 129.8, 144.8, 171.3. MS 193 (M+1). Spectral results match reported values.[6]

Synthesis of *p*-CH_3-C_6H_4-$N(CH_2CO_2CH_2CH_3)_2$. A yellow oil (405.3 mg) was isolated from general method **B**; amine (206.7 mg, 1.929 mmol), EDA (500.1 mg, 4.383 mmol), Fe(TPP)Cl (12.8 mg, 0.0182 mmol). ^{1}H-NMR δ ppm 1.30(t, 6H, OCH_2CH_3), 2.27(s, 3H, $CH_3C_6H_5$), 4.15(s, 4H, NCH_2CH_3), 4.24(q, 4H, OCH_2CH_3), 6.59(d, 2H, C_6H_4), 7.07(d, 2H, C_6H_4). ^{13}C-NMR δ ppm 14.2, 54.0, 55.6, 60.9, 114.4, 114.7, 142.3, 152.6, 171.1. MS 279(M), 206 base peak. Anal. Calcd.: C, 64.49; H, 7.58; N, 5.02. Found: C, 63.93; H, 7.70; N, 5.41.

Synthesis of C_6H_5-$NH(CH_2CO_2CH_2CH_3)$. A yellow oil (115.0 mg) was obtained from general method **A** amine (68.7 mg, 0.738 mmol), EDA (99.7 mg, 0.874 mmol), Fe(TPP)Cl (4.0 mg, 0.0057 mmol). ^{1}H-NMR δ ppm 1.30(t,3H), 3.91(s,2H), 4.25(q,2H),

6.65(d,2H), 6.77(t,1H), 7.21(t,2H) NH not observed. ^{13}C-NMR 14.1, 45.8, 61.2, 112.9, 118.1, 129.2, 146.9, 171.0. MS 180(M+1) base peak. Spectral results match reported values.[6]

Synthesis of C_6H_5-N($CH_2CO_2CH_2CH_3$)$_2$. A yellow oil (106.4 mg) was isolated from general method **B** using an overall amine: EDA ratio of 1:2.9 and a reaction time of 2 hours after the second addition of EDA; amine (47.1 mg, 0.506 mmol), EDA (169.5 mg, 1,485 mmol), Fe(TPP)Cl (3.5 mg, 0.0050 mmol). ^{1}H-NMR 1.28(t, 6H, OCH_2CH_3), 4.14(s, 4H, NCH_2CO), 4.22(q, 4H, OCH_2CH_3), 6.60-6.65(m, 2H, C_6H_5), 6.75-6.80(m, 1H, C_6H_5), 7.19-7.25(m, 2H, C_6H_5). ^{13}C-NMR 14.0, 53.3, 60.9, 112.3, 118.0, 129.1, 147.7, 170.7. MS 265(M). Anal. Calcd.: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.17; H, 7.68; N, 5.57.

Synthesis of *p*-Cl-C_6H_4-NH($CH_2CO_2CH_2CH_3$). A pale yellow solid (42.4 mg) was isolated from general method **A**; amine (63.3 mg, 0.496 mmol), EDA (57.3 mg, 0.502 mmol), Fe(TPP)Cl (3.7 mg, 0.0053 mmol). ^{1}H-NMR 1.30(t, 3H, OCH_2CH_3), 3.88(s, 2H, NCH_2CO), 4.25(q, 2H, OCH_2CH_3), 6.52-6.56(m, 2H, C_6H_4), 7.12-7.16(m, 2H, C_6H_4), NH not observed. ^{13}C-NMR 14.2, 45.9, 61.5, 114.1, 122.9, 129.1, 145.5, 170.8. MS 213(M), 140 base peak. Spectral results match reported values.[6]

Synthesis of *p*-Cl-C_6H_4-N($CH_2CO_2CH_2CH_3$)$_2$. A yellow oil (91.8mg) was isolated from general method **B**; amine (64.4 mg, 0.505 mmol), EDA (140.0 mg, 1.227 mmol), Fe(TPP)Cl (3.5 mg, 0.0050 mmol). ^{1}H-NMR 1.28(t, 6H, OCH_2CH_3), 4.10(s, 4H, NCH_2CO), 4.21(q, 4H, OCH_2CH_3), 6.54(d, 2H, C_6H_4), 7.16(d, 2H, C_6H_4). ^{13}C-NMR 14.4, 53.8, 61.4, 114.0, 123.4, 129.3, 146.8, 170.7. MS 299(M), 154 base peak. Anal. Calcd.: C, 56.09; H, 6.05; N, 4.67. Found: C, 55.69; H, 6.49; N, 4.92.

Synthesis of *p*-Br-C_6H_4-NH($CH_2CO_2CH_2CH_3$). A pale yellow solid (183.6 mg) was obtained from general method **A** amine (153.9 mg, 0.8947 mmol), EDA (108.1 mg, 0.9473 mmol), Fe(TPP)Cl (6.5 mg, 0.0092 mmol). ^{1}H-NMR 1.30(t, 3H, OCH_2CH_3), 3.86(s, 2H, NCH_2CO), 4.25(q, 2H, OCH_2CH_3), 6.49(d, 2H, C_6H_4), 7.27(d, 2H, C_6H_4), NH not observed. ^{13}C-NMR 14.2, 45.7, 61.5, 109.9, 114.5, 132.0, 146.0, 170.6. MS 258(M+1). Anal. Calcd.: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.65; H, 4.79; N, 5.57.

Synthesis of *p*-Br-C_6H_4-N($CH_2CO_2CH_2CH_3$)$_2$. A yellow oil (208.8 mg) was isolated from general method **B** using an overall amine:EDA ratio of 1:4.1 and a reaction time of 24 hours after the second addition of EDA; amine (143.3 mg, 0.8330 mmol), EDA (389.3 mg, 3.412 mmol), Fe(TPP)Cl (5.4 mg, 0.0077 mmol). ^{1}H-NMR 1.27(t, 6H, OCH_2CH_3), 4.09(s, 4H, NCH_2CO), 4.21(q, 4H, OCH_2CH_3), 6.49(d, 2H, C_6H_4), 7.29(d, 2H, C_6H_4). ^{13}C-NMR 14.2, 53.6, 61.2, 110.4, 114.2, 131.9, 146.9, 170.5. MS 343(M-1), 59 base peak. Anal. Calcd.: C, 48.85; H, 5.27; N, 4.07. Found: C, 48.38; H, 5.84; N, 3.90.

Synthesis of *p*-CN-C_6H_4-NH($CH_2CO_2CH_2CH_3$). A pale yellow solid (166.2 mg) was obtained from general method **A** in 20 minutes; amine (110.5 mg, 0.9353 mmol), EDA (123.4 mg, 1.081 mmol), Fe(TPP)Cl (7.0 mg, 0.0099 mmol). Eluent hexane:ethyl acetate 5:1. ^{1}H-NMR 1.29(t, 3H, OCH_2CH_3), 3.90(s, 2H, NCH_2CO), 4.25(q, 2H, OCH_2CH_3), 6.55(d, 2H, C_6H_4), 7.42(d, 2H, C_6H_4) NH not observed. ^{13}C-NMR 14.1, 44.7, 61.7, 99.6, 112.4, 120.1, 133.6, 150.0, 169.9. MS 204(M), 131 base peak. Anal. Calcd.: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.64; H, 6.12; N, 13.89.

Synthesis of *p*-CN-C_6H_4-N($CH_2CO_2CH_2CH_3$)$_2$. Procedure **B** was followed using an overall amine:EDA ratio of 1:4. and a reaction time of 4 hours after the second addition of

EDA. This reaction had a low double insertion yield (<20%) and the desired product could not be isolated from the single insertion product. MS 290(M^+), 217 base peak

Synthesis of *p*-NO_2-C_6H_4-NH($CH_2CO_2CH_2CH_3$). A yellow solid (200.6 mg) was obtained from general method **A** with a slow reaction being complete in 18 hours; amine (141.0 mg, 1.02 mmol), EDA (128 mg, 1.12 mmol), Fe(TPP)Cl (7.2 mg, 0.010 mmol). Eluent hexane:ethyl acetate 5:1. ^{1}H-NMR δ ppm 1.33(t, 3H, OCH_2CH_3), 3.98(s, 2H, NCH_2CO), 4.29(q, 2H, OCH_2CH_3), 6.56(d, 2H, C_6H_4), 8.12(d, 2H, C_6H_4) NH not observed. ^{13}C-NMR δ ppm 14.4, 45.1, 62.2, 111.7, 126.6, 139.1, 152.1, 169.9. MS 224(M), 151 base peak. Anal. Calcd.: C, 53.56; H, 5.39; N, 12.50. Found: C, 53.20; H, 5.58; N, 12.35.

Insertion into Imidazole. A yellow oil (157.4 mg) was obtained from general method **A** with the reaction being complete in 48 hours; amine (135.4 mg, 1.989 mmol), EDA (321.7 mg, 2.819 mmol), Fe(TPP)Cl (13.3 mg, 0.019 mmol). Eluent ethyl acetate: methanol 10:1. ^{1}H-NMR δ ppm 1.26(t, 3H, OCH_2CH_3), 4.21(q, 2H, OCH_2CH_3), 4.66(s, 2H, NCH_2CO) 6.93(s, 1H, C=C*H*), 7.06(s, 1H, C=C*H*) 7.47(s, 1H, NC*H*N). ^{13}C-NMR δ ppm 14.3, 48.3, 62.3, 120.2, 129.9, 138.1, 167.6. MS 154(M), 81 base peak. Anal. Calcd.: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.12; H, 6.58; N, 18.17.

Insertion of MPDA into aniline. A whitish-yellow solid (69.6 mg, 92% yield) was prepared by the general method **A** except the reaction solution was refluxed, aniline (29.2mg, 0.314 mmol), MPDA (63.9 mg, 0.363mmol) with the reaction being complete in 40 hours. Eluent hexane: ethyl acetate 10:1. ^{1}H-NMR δ ppm 3.74(s, 3H, CH_3), 4.97(s, 1H, N*H*), 5.09(s, 1H, NC*H*CO), 6.57(d, 2H, C_6H_5), 6.71(t,1H, C_6H_5), 7.13(t,2H, C_6H_5), 7.35(m, 3H,

C_6H_5), 7.51(dd, 2H, C_6H_5). ^{13}C-NMR δ ppm 52.8, 60.7, 113.4, 118.1, 127.2, 128.3, 128.8, 129.2, 137.6, 145.9, 172.3. MS 242(M+1), 121 base peak.

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[11] Abbreviations: TPP – *meso*-tetraphenylporphyrin, TMeO-PP – *meso*-tetra(*p*-methoxyphenyl)porphyrin, TPFPP – *meso*-tetrakis(pentafluorophenyl)porphyrin, TMP – *meso*-tetramesitylporphyrin

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CHAPTER 3

GENERAL CONCLUSIONS

Fe(TPP)Cl is commercially available and relatively inexpensive. It was found to be a very efficient catalyst for insertion of ethyl diazoacetate (EDA) into the N-H bond of amines with little formation of the side products diethyl maleate or diethyl fumarate from the dimerization of EDA. Insertion was achieved into both primary and secondary amines forming glycine esters in good to excellent yields (64-97%). The reactions were also relatively fast with many reaching completion in less than 20 minutes when 1 mole% catalyst was used. Using a series of *para*- substituted aniline derivatives, it was shown that electron-donating groups enhanced the insertion of EDA into the N-H bond. Less nucleophilic reaction centers such as the N-H in benzamide or the O-H bonds in various alcohols did not undergo insertion reactions. Strong electron-withdrawing groups prevented the insertion reaction as was observed with the attempted second insertion into *p*-nitroaniline. Steric hindrance also played a role. This was observed in the case of 2,6-lutidine which did not undergo insertion while 2-chloroaniline only formed the single insertion product.

Experiments designed to gain insight into the mechanism of the insertion transformation indicate that the catalytic cycle involves iron(III) porphyrin rather than iron(II) porphyrin. Slow addition of EDA was not needed to reduce dimerization. In examining the decomposition of EDA to form the dimer, apparent coordination of an amine to the porphyrin complex significantly aided the reaction, indicating that this coordination is part of the catalytic cycle. The dimerization of EDA occurred slowly in the absence of amine

and presence of iron(III) porphyrin. Competition experiments of substituted anilines were conducted. Electron-donating groups on the aryl ring enhanced the insertion reaction, giving a ratio of substituted aniline:aniline insertion product of greater than one for electron-donating groups and less than one for electron-withdrawing groups. A Hammett plot correlation with σ^+ (ρ=-0.66±0.05, R^2=0.93) was consistent with a nucleophilic attack of the amine substrate at the carbene carbon.

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