Iron Porphyrin Catalyzed N−H Insertion Reactions with Ethyl Diazoacetate

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Received December 1, 2006

A series of metalloporphyrin complexes were surveyed as catalysts for carbene insertion from ethyl diazoacetate into the 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 to 97%. Primary amines were able to undergo a second insertion when another equiv of EDA was added by slow addition. N-Heterocyclic compounds were poor substrates, giving low yields or no N−H insertion products. Competition reactions and linear free energy relationships provided mechanistic insights for the insertion reaction. The relative rates for N−H insertion into para-substituted aniline derivatives correlated with Hammett σ^+ parameters. Electron-donating groups enhanced the reaction, as indicated by the negative value of ρ ($\rho = -0.66 \pm 0.05$, $R^2 = 0.93$). These results are consistent with a rate-determining nucleophilic attack of the amine on an iron carbene complex. In addition, the decomposition of EDA catalyzed by Fe^{II}(TPP) or Fe^{III}(TPP)Cl was examined with various amounts of added pyridine. The Fe(II) catalyst is strongly inhibited by the presence of pyridine. In contrast, catalysis by the Fe(III) porphyrin is accelerated by amines. These experiments suggested that an iron(III) porphyrin carbene complex is the active catalyst.

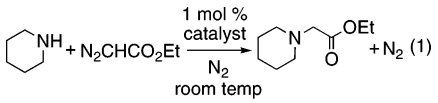
Introduction

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 catalyze N−H insertion reactions include methyltrioxorhenium,[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(III) tetraphenylporphyrin chloride, Fe(TPP)Cl,[11] as the catalyst.[12] Similar work appeared recently that also illustrated the utility of Fe(III/IV) corrole and Fe(III) porphyrin complexes for catalytic reactions between EDA and amines.[13]

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 min. The reactions were run in CH_2Cl_2 under mild conditions at ambient temperature in a one-pot fashion, without the need for slow addition of EDA. The insertion

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(11) Abbreviations: TPP, *meso*-tetraphenylporphyrin; TMeO-PP, *meso*-tetrakis(*p*-methoxyphenyl)porphyrin; TPFPP, *meso*-tetrakis(pentafluorophenyl)porphyrin; TMP, *meso*-tetramesitylporphyrin, Saldach, *N*,*N*′-bis(salicylidene)-1,2-cyclohexyldiamine.

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10.1021/om0610997 CCC: $37.00 © 2007 American Chemical Society
Publication on Web 07/04/2007

Table 1. Piperidine N−H Insertion with EDA Catalyzed by Metalloporphyrins[11] in CH_2Cl_2[a]

entry	cat.	time	yield (%)
1	Fe(TPP)Cl	<5 min	>97
2	Mn(TPP)Cl	24 h	nd[b]
3	Zn(TPP)	24 h	nd
4	Co(TTP)	24 h	nd
5	Os(TTP)(CO)	28 h	4
6	Os(TTP)(CO)[c]	20 min	90
7	no catalyst	24 h	nd
8	Fe(TMeO-PP)Cl	<5 min	>97
9	Fe(TPFPP)Cl	40 min	>97
10	Fe(TMP)Cl	1 h	80
11	Fe(Saldach)Cl	22 h	nd

[a] A molar ratio of 1:100:120 for catalyst−EDA−piperidine was employed at ambient temperature with 0.0025−0.01 mmol of catalyst. Yields were determined by GC. [b] nd = not detected. [c] This reaction was carried out under reflux conditions.

Table 2. N−H Insertion Using EDA with Various Loadings of Fe(TPP)Cl in CH_2Cl_2[a]

entry	amine	amt of cat. (%)	time	yield (%)[b]
1	aniline	1.0	1 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 h	89
6	piperidine	1.0	10 min	>95
7	piperidine	0.5	10 min	>95
8	piperidine	0.1	5 h	82

[a] Amounts used were 1.0 mmol of EDA and 1.2 mmol of amine at ambient temperature. [b] Yields determined by GC.

reactions proceeded rapidly, and the reaction mixtures warmed up upon addition of EDA, accompanied by observable gaseous N_2 release. Evidence of the desired piperidine insertion product was obtained by ^{1}H NMR spectroscopy with the appearance of a new two-proton singlet at 3.17 ppm for the N-acetate methylene hydrogens 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 illustrate 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 those of Fe(TPP)Cl were obtained with copper complexes bearing homoscorpionate (tris(pyrazolyl)borate) 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, the complex afforded a 90% yield of insertion product after heating at reflux for 20 min.

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 on 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 min. In contrast, the electron-deficient complex Fe(TPFPP)Cl required 40 min to complete the N−H insertion into piperidine with EDA. Fe(TMP)Cl catalyzed the same reaction, affording an 80% yield after 1 h, suggesting that steric hindrance also plays a role.

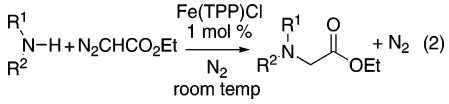
The subsequent studies focused on Fe(TPP)Cl because it is commercially available and relatively inexpensive. The catalyst

Table 3. Results for Single EDA Insertion into Amines with 1 mol % Fe(TPP)Cl[a]

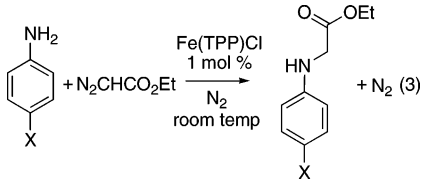
entry	amine	amine−EDA ratio	time	yield (%)[b]
1	Et_2NH	1:1.1	10 min	86
2	*t*-Bu-NH_2	1:1	10 min	68
3	$C_5H_{10}NH$	1:1.2	10 min	85
4	$PhCH_2NH_2$	1:1	10 min	76
5	Ph_2NH	1:1.1	1 h (60 °C)	<5
6	tetramethylpiperidine[c]	1:1.1	48 h	NR
7	benzamide	1:1.1	48 h	NR
8	*p*-CH_3O-C_6H_4-NH_2	1:1.2	10 min	82
9	*p*-CH_3-C_6H_4-NH_2	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	20 min	58 (13)[d]
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 h	91
15	imidazole	1:1.4	48 h	51
16	pyrrole	1:1.3	48 h	0 (37)[e]
17	indole	1:1.4	48 h	NR

[a] Reactions were run with 1.0 mmol of amine in 7.0 mL of CH_2Cl_2 at ambient temperature. [b] NMR yields using Ph_3CH as an internal standard. [c] 2,2,6,6-Tetramethylpiperidine. [d] Yield of double-insertion product given in parentheses. [e] α-C−H insertion product.

loadings can be lowered to 0.1 mol %, albeit requiring longer reaction times at ambient temperature (Table 2). 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. Originally, amines were used in slight excess to EDA on the basis of previous methods used to suppress maleate and fumarate formation.[9a] However, 1:1 ratios of EDA to amine could be used with Fe(TPP)Cl without significant formation of side products. N−H insertions were successfully achieved using primary and secondary alkyl amines (eq 2) in good to high yields



of 68−97% (Table 1, entry 1; Table 3, entries 1−4). Evidence of the desired insertion product with diethylamine was observed in the ^{1}H NMR spectrum, with the appearance of a new two-proton N-acetate methylene singlet at 3.27 ppm and the disappearance of the one-proton singlet at 4.72 ppm for the methine proton of EDA. Arylamine substrates also gave successful insertion reactions (eq 3) with yields of 58−95%



(Table 3, entries 8−14), comparable to reported yields for reactions catalyzed by copper, ruthenium, and rhenium complexes.[6−9] The ^{1}H NMR spectrum of the product from EDA and aniline showed a new two-proton methylene singlet at 3.91 ppm. Almost all of the single N−H insertion reactions reached completion in 20 min or less. The exception was the *p*-nitroaniline reaction, which took 1 h for complete consumption of the reagents. Also, insertion of EDA into the N−H bond of benzamide was not successful (Table 3, entry 7).

Side products from the dimerization of EDA, diethyl maleate and diethyl fumarate, were generally observed in only trace amounts, and reactions could be run in a practical one-pot

Table 4. Results for Double Insertion of EDA into Amines with 1 mol % Fe(TPP)Cl[a]

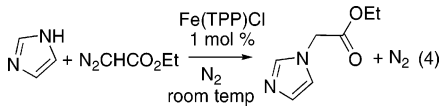
entry	amine	amine−EDA ratio	time	yield (%)[b]
1	$PhCH_2NH_2$	1:3	15 min	97
2	*p*-CH_3O-C_6H_4-NH_2	1:2.8	1 h	81
3	*p*-CH_3-C_6H_4-NH_2	1:2.4	1 h	76
4	C_6H_5-NH_2	1:2.9	2 h	92
5	*p*-Cl-C_6H_4-NH_2	1:2.4	1.5 h	72 (16)[c]
6	*p*-Br-C_6H_4-NH_2	1:4.1	2 h	78 (14)[c]
7	*p*-CN-C_6H_4-NH_2	1:4	4 h	<20 (81)[c]
8	*p*-NO_2-C_6H_4-NH_2	1:4	48 h	0 (91)[c]

[a] Reactions were run with 1.0 mmol of amine in 7.0 mL of CH_2Cl_2 at ambient temperature. [b] NMR yields using Ph_3CH as an internal standard. [c] Single-insertion product yield given in parentheses.

fashion. Therefore, it was not necessary to add EDA and/or amine slowly to the catalyst solution. This also indicated that Fe(TPP)Cl is not poisoned by coordination of amine. In contrast, an amine poisoning effect was reported for a ruthenium porphyrin[10a] and a rhodium catalyst.[14]

Primary amines were able to undergo a double N−H insertion reaction (Table 4) with excess EDA. The double-insertion product of aniline gives a four-proton NMR singlet at 4.14 ppm for the methylene hydrogens of the two *N*-acetate groups, exhibiting an upfield shift smaller than that observed for the methylene fragment of the single-insertion product. This dual reaction could be done stepwise: first forming the single insertion product and then introducing a second equivalent of EDA by slow addition. Addition of 2 equiv of EDA to the substrate in one aliquot resulted mainly in the single-insertion product, low yields of double-insertion product, and more dimeric side products. The second insertion is a slower reaction, allowing more dimer to form in these reactions in comparison to the single-insertion reaction. Increasing the electron-withdrawing ability of the substituents on the aniline made the second insertion more difficult and prolonged the reaction times. When aminobenzonitrile was the substrate, the double-insertion product was observed in low yield, as monitored 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), indicating that the strong electron-withdrawing effect of the nitro substituent was reinforced by the first *N*-acetate fragment.

Reactions with N-heterocyclic compounds gave results significantly different from those of the aniline derivatives. With imidazole as the substrate, the N−H insertion product was formed in 51% yield (eq 4). Under the same conditions, carbene



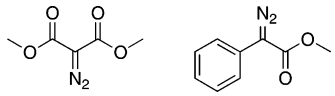
insertion from EDA occurred at the α-C−H bond of pyrrole in low yields, and no reaction was observed with indole. Carbene insertion from EDA into the C−H bond of pyrrole was previously reported.[15] Imidazole is more basic than pyrrole and indole and is a better nucleophile for attack at the carbene intermediate (vide infra). Several ortho-substituted anilines were also evaluated (Table 5). A single insertion of carbene from EDA into 2-chloroaniline gave a yield of 70%, and insertion into 2-aminoacetophenone resulted in a 57% yield. Additional

Table 5. Single Insertion of EDA into Ortho-Substituted Anilines with 1 mol % Fe(TPP)Cl[a]

entry	amine	amine−EDA ratio	time	yield (%)[b]
1a	2-chloroaniline	1:1.2	10 min	70
1b	2-chloroaniline	1:2.5	48 h	70
2	2-aminoacetophenone	1:1.2	20 min	57
3	2,6-dimethylaniline	1:1.5	24 h	NR

[a] Reactions were run with 1.0 mmol of amine in 7.0 mL of CH_2Cl_2 at ambient temperature. [b] NMR yield.

Scheme 1



equivalents of EDA did not result in any double-insertion product of either substrate, indicating the reaction site may be too sterically hindered after the initial insertion reaction. Single insertion into 2,6-dimethylaniline was unsuccessful, also indicating that steric hindrance affects the reaction. Steric hindrance was also observed with 2,2,6,6-tetramethylpiperidine (Table 3, entry 6).

Dimethyl diazomalonate (DMM) and methyl phenyldiazoacetate (MPDA) (Scheme 1) were also investigated as carbene sources for insertion into aniline. Catalytic reactions with MPDA and aniline gave a 92% yield of the N−H insertion product. This reaction required refluxing in methylene chloride for 40 h, harsher conditions in comparison to the ambient temperature used for insertions with EDA. The ^1H NMR spectrum of the product showed a new one-proton singlet at 5.09 ppm for the new malonyl methine hydrogen. Insertion reactions with DMM and aniline in refluxing benzene for 72 h yielded only a trace of the single-insertion product, as detected by GC-MS analysis: *m*/*z* 224 (M + 1), 104 (base peak).

Our group previously used Fe(TPP)Cl as a precatalyst for the cyclopropanation of olefins using EDA as both a reductant and a carbene source.[1c] In the present 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 mol % Fe(TPP)Cl in methylene chloride. The reaction was run both at room temperature and in refluxing methylene chloride. Under both conditions, only the N−H insertion product was observed by GC-MS and ^1H NMR. The preference for X−H insertion over cyclopropanation has been previously reported for ruthenium-catalyzed N−H and S−H insertions,[9b] a rhodium-catalyzed O−H insertion,[16] and iron porphyrin and iron corrole catalyzed N−H insertions.[13]

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 data are summarized in a Hammett plot (Figure 1). 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 develops in the transition state that is stabilized by resonance effects.[17] Electron-donating groups on the aniline derivatives increased the reaction rate, as indicated by a negative value of ρ ($\rho = -0.66 \pm 0.05$). This is consistent

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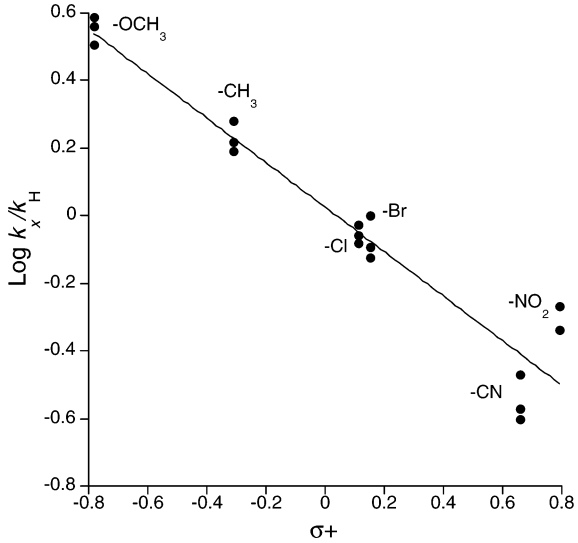
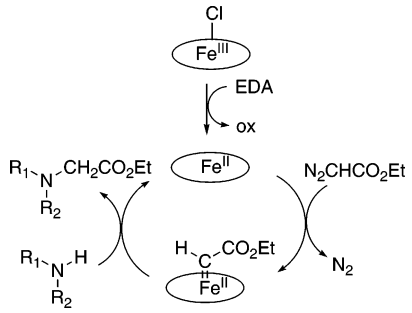


Figure 1. Hammett plot from competition reactions.

Scheme 2



with a nucleophilic attack of the amine on the electron-deficient carbon of a putative carbene intermediate as the rate-determining effect.

Competitive N−H/N−D experiments were undertaken to measure the kinetic isotope effects on the insertion reaction. The reaction of Et_2NH and Et_2ND (88.5% D) in a 1:1 molar ratio was treated with a limiting amount of EDA with 1 mol % Fe(TPP)Cl in C_6D_6 at ambient temperature. The resulting kinetic product ratio was determined on a 700 MHz Bruker NMR spectrometer by integrating the baseline-resolved methylene proton peaks of the products: $Et_2NCH_2CO_2Et$ (s) and $Et_2NCHDCO_2Et$ (t). After correction for the percent H content in Et_2ND, the measured k_H/k_D value was 1.41 ± 0.05. A similar competition experiment with aniline and aniline-d_7 (98% D) produced a comparable ratio: $k_H/k_D = 1.40 \pm 0.04$.

Initially, the catalytic cycle for N−H insertion was thought to parallel the proposed mechanism for the cyclopropanation of olefins by Fe(TPP)Cl, involving the reduction of Fe(III) to Fe(II), as shown in Scheme 2.[1c] These cyclopropanation reactions were done under an inert atmosphere to prevent oxidation of the iron(II) species. EDA is a mild reducing agent,[18] and we have proposed previously that EDA reduces Fe^{III} porphyrins to Fe^{II} porphyrins in refluxing methylene chloride.[1c] After the reduction, the resulting Fe^{II}(TPP) is sufficiently nucleophilic to displace N_2 from the α-carbon of EDA to produce a reactive iron(II) carbene complex. The carbene ligand is subsequently attacked by the amine, and proton migration from nitrogen to carbon produces the amino acid ester. While (TPP)Fe=$CHCO_2Et$ is very reactive and has not been detected, the reaction of Fe^{II}(TTP) and mesityldiazomethane or (trimethylsilyl)diazomethane produced carbene complexes that have been spectroscopically detected.[1b,c] An osmium analogue prepared from EDA, (TTP)Os=$CHCO_2Et$, has been isolated and fully characterized.[19]

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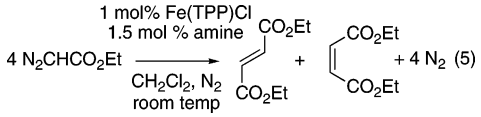
Table 6. Dimerization of EDA by 1 mol % Iron Porphyrin Complexes at 20 °C under N_2[a]

run	cat.	amine (amt (mol %))	yield (%)[b]	time to completion	DEM−DEF ratio
1	Fe^{III}(TPP)Cl		82	6 h	33:1
2	Fe^{III}(TPP)Cl	pyridine (1)	94	20 min	6:1
3	Fe^{III}(TPP)Cl	pyridine (2)	95	20 min	6:1
4	Fe^{III}(TPP)Cl	pyridine (3)	93	20 min	6:1
5	$[Fe^{III}(TPP)py_2]BF_4$		96	20 min	6:1
6	Fe^{II}(TPP)		94	50 min	32:1
7	Fe^{II}(TPP)	pyridine (1)	56	16 h	11:1
8	Fe^{II}(TPP)	pyridine (2)	<2	16 h	NA
9	Fe^{III}(TPP)Cl	2,6-lutidine (1)	86	8 h	31:1
10	Fe^{III}(TPP)Cl	2,6-lutidine (2)	86	8 h	30:1
11	Fe^{III}(TPP)Cl	2,6-lutidine (3)	88	8 h	32:1
12	Fe^{II}(TPP)	2,6-lutidine (1)	92	50 min	32:1
13	Fe^{II}(TPP)	2,6-lutidine (2)	93	50 min	36:1

[a] Reactions were run with 0.08 mmol of EDA in 5 mL of CH_2Cl_2. [b] NMR yields using $CHPh_3$ as an internal standard.

A series of experiments indicate that reduction of the Fe(III) does not appear to be necessary in the N−H insertion process with EDA. For example, the insertion reactions could be done in air with only a slight decrease in yield. In assessing a possible prereduction step at ambient temperature, the Fe(TPP)Cl-catalyzed decomposition of EDA was examined in the presence and absence of tertiary amines that could coordinate to the porphyrin complex but not undergo an N−H insertion. These reactions were followed by ^1H NMR with $CHPh_3$ as an internal standard. GC analysis was unreliable, as the temperature in the injection port was sufficient to convert EDA to butenediolates in the absence of a catalyst. When no amine was added, EDA dimerized slowly (eq 5) in 6 h to form diethyl fumarate (DEF)



and diethyl maleate (DEM). When small amounts (1−3%) of amine were present, the reaction times were significantly reduced to 20 min (Table 6). This indicated that the amine is important to the active Fe(III) catalytic species.

To probe further the nature of the catalytic species, a comparison of Fe^{III}(TPP)Cl and Fe^{II}(TPP) was undertaken for the dimerization of EDA. As shown in Table 6, Fe^{II}(TPP) is a more efficient catalyst (entry 6) than Fe^{III}(TPP)Cl (entry 1), promoting the formation of DEF and DEM in a shorter time in the absence of amine with slightly higher yields, albeit with similar product ratios. However, addition of 1% pyridine to Fe^{III}(TPP)Cl (py:Fe = 1:1, entry 2) substantially enhanced the catalytic rate of dimerization of EDA and improved the product yields. In contrast, the addition of 1% pyridine to Fe^{II}(TPP) had the opposite effect (entry 7), degrading the reaction time by more than 16-fold and decreasing the yield by approximately half. In both cases, the DEM:DEF ratio also dropped significantly with the addition of 1% pyridine. Increasing the amount of pyridine above 1% in the Fe(III) system did not produce any further changes (entries 3 and 4). Moreover, the previously

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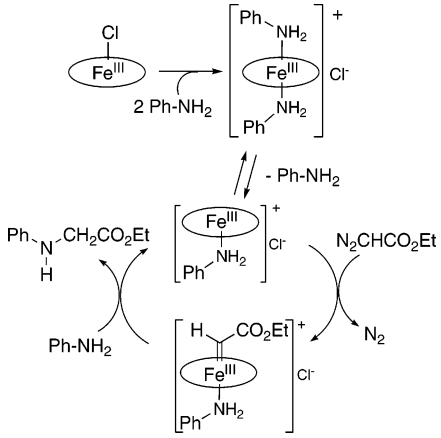
Scheme 3



characterized Fe(III) bis(pyridine) complex $[Fe(TPP)py_2]BF_4$[20] catalyzed the decomposition of EDA (entry 5) in a manner similar to that for the Fe^{III}(TPP)Cl−pyridine system. However, addition of 2% pyridine to Fe^{II}(TPP) (py:Fe = 2:1, entry 8) drastically inhibited the dimerization of EDA. These results indicate that if Fe(III) were reduced to Fe(II), the presence of pyridine would strongly inhibit its catalytic behavior. Thus, it is highly likely that prereduction of Fe(III) is not necessary for catalytic carbene insertion from EDA into N−H bonds of amines.

Additional support for ligand binding effects on the catalytic dimerization of EDA by Fe^{III}(TPP)Cl was illustrated with 2,6-lutidine (Table 6, entries 9−11). Since 2,6-lutidine is sterically hindered and is a poor ligand for metalloporphyrins,[21] no enhancement was expected as was observed when pyridine was added to a catalytic Fe^{III}(TPP)Cl system. Indeed, the rate of EDA dimerization by Fe^{III}(TPP)Cl with 1−3 equiv of 2,6-lutidine was qualitatively the same as that by Fe^{III}(TPP)Cl alone. In complementary experiments, addition of 1−2 equiv of 2,6-lutidine to Fe^{II}(TPP) also had no effect on the catalytic dimerization of EDA. Thus, the rate acceleration of EDA dimerization on addition of pyridine must involve binding of the amine to the metal center of Fe^{III}(TPP)Cl.

The proposed mechanism for N−H insertion into aniline is shown in Scheme 3. In the presence of unhindered bases, Fe(TPP)Cl typically forms bis(amine) complexes, $[(TPP)FeL_2]^+$.[22] Dissociation of a ligand produces a five-coordinate mono(amine) species that has sufficient electron density and an open coordination site at the metal center so that a six-coordinate Fe(III) porphyrin carbene complex can be produced readily. Formation of the carbene complex is extremely rapid, as is evident by the notable evolution of gas on addition of EDA to the reaction flask. In the absence of amine, formation of a carbene complex directly from Fe(TPP)Cl is unfavorable. The carbene carbon then undergoes nucleophilic attack by an additional amine to form the insertion product. The amine nitrogen is more nucleophilic than EDA, and single N−H insertion occurs faster than dimerization. Moreover, the qualitative variation of rates as a function of the amine indicated that the rate-determining step is the addition of amine to the carbene carbon. In addition, the hydrogen transfer step exhibits N−H/N−D isotope effects, $k_H/k_D = 1.41 \pm 0.05$ (diethyl amine) and 1.40 ± 0.04 (aniline).

The *N*-glycine ester formed from the first insertion is less nucleophilic than the original amine, resulting in a slower second N−H insertion step. Since the second insertion process is less competitive with carbene dimerization, stepwise addition of EDA is necessary to optimize the formation of the double-insertion product. Although it is possible that the N−H insertion reactions catalyzed by the related Fe(III) corrole complexes[13] may involve a similar mechanism, it is unclear what pathway the corresponding Fe(IV) corrole compounds employ. Although no induction period was reported for the Fe(IV) case, a possibility involves reduction of the iron center from IV to III.

Conclusions

Catalytic carbene insertion from EDA into N−H bonds mediated by 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, and insertion reactions could also be performed at ambient temperatures and under atmospheric conditions in relatively short reaction times. Aliphatic and aromatic amines were both shown to be good substrates, giving high yields (>85%). Single- and double-insertion products were successfully obtained when primary amines were used as the substrate. Unlike other reported N−H insertion catalysts, the insertion reaction was faster than EDA dimerization and slow addition of EDA is not necessary with Fe(TPP)Cl. Mechanistic studies and comparisons with Fe^{II}(TPP) suggest that an Fe(III) form of the porphyrin complex is the active catalyst. Moreover, Fe^{III}(TPP)Cl has the advantages of not being poisoned by the amine, producing little of the dimerization side products from EDA, and being commercially available and relatively inexpensive.

Experimental Section

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),[23] Fe(saldach)Cl,[24] and Zn(TPP)[25] were prepared according to literature procedures. Co(TTP) was prepared using a modified literature procedure.[26] DMM[27] and MPDA[28] were synthesized by following literature procedures. Aniline was distilled from CaH_2 under reduced pressure. Diethylamine 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, with 30 m × 0.32 mm × 0.25 μm film thickness. ^{1}H and ^{13}C spectra were obtained in $CDCl_3$ on a Varian VXR-300 spectrometer. MS analysis was done on a Finnigan Magnum GC-MS. Elemental analyses for new compounds were performed on a Perkin-Elmer Model 2400 Series II CHN/S elemental analyzer. Fe(TMP)Cl was prepared

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according to a literature procedure[29] and then reduced with Zn/Hg in toluene. $[Fe(TPP)py_2]BF_4$ was synthesized as reported previously.[20]

General Procedure for Single-Insertion Reactions (Method A). In a typical experiment, an amine (0.250−1.0 mmol) was dissolved in 5 mL of methylene chloride in a 25 mL round-bottom flask. Fe(TPP)Cl (0.0025−0.010 mmol, 1 mol %) was added, and nitrogen was bubbled through the solution for 20 min. Ethyl diazoacetate (EDA; 1.20 equiv, 0.275−1.20 mmol) in 2 mL of CH_2Cl_2 was added in one aliquot, and the reaction mixture was stirred for 10 min. 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 ^{1}H NMR with triphenylmethane as an internal standard. Products were purified by column chromatography on silica gel (2.5 cm × 11 cm) and eluted with hexane−ethyl acetate (10:1) unless specified otherwise.

General Procedure for Double-Insertion Reactions (Method B). The single-insertion product was formed using the reaction conditions described above. An additional 1.20 equiv of EDA in 2 mL of CH_2Cl_2 was added by syringe over 1 min, and the reaction mixture was stirred for an additional 1 h and monitored by GC. Upon completion of the reaction, the solvent was removed in vacuo and the reaction mixture was analyzed by ^{1}H NMR with triphenylmethane as an internal standard. Products were purified by column chromatography (2.5 cm × 11 cm) on silica gel and eluted with hexane−ethyl acetate (10:1) unless specified otherwise.

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 of methylene chloride were stirred under nitrogen. EDA (0.300 mmol) in 2 mL of methylene chloride was added by syringe in one aliquot. After 5 min, a sample was removed and the ratio of product yields was determined by gas chromatography using dodecane as an internal standard.

Synthesis of $Et_2NCH_2CO_2CH_2CH_3$. Method A was followed using diethylamine (43.7 mg, 0.597 mmol), EDA (83.5 mg, 0.732 mmol), and 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). ^{13}C NMR (δ, ppm): 12.4 (NCH_2CH_3), 14.5 (OCH_2CH_3), 48.0 (NCH_2CH_3), 54.5 (NCH_2CO), 60.6 (OCH_2CH_3), 171.8 (*C*O). MS (*m*/*z*): 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 using method A with *tert*-butylamine (75.8 mg, 1.04 mmol), EDA (126.6 mg, 1.11 mmol), and Fe(TPP)Cl (7.4 mg, 0.011 mmol). ^{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 (*C*O). MS (*m*/*z*): 160 (M + 1). Spectral results match reported values.[6]

Synthesis of $C_5H_{10}NCH_2CO_2CH_2CH_3$. A yellow oil (83.0 mg) was obtained using method A with piperidine (48.7 mg, 0.572 mmol), EDA (78.3 mg, 0.687 mmol), and Fe(TPP)Cl (3.5 mg, 0.0050 mmol). ^{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 (*m*/*z*): 172 (M + 1), 98 (base peak). Spectral results match reported values.[6]

Synthesis of $PhCH_2NH(CH_2CO_2CH_2CH_3)$. A yellow oil (164.2 mg) was obtained using method A with benzylamine (124.8 mg, 1.16 mmol), EDA (148.0 mg, 1.30 mmol), and 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, NH), 3.41 (s, 2H, NCH_2CO), 3.81 (s, 2H, $PhCH_2N$), 4.19 (q, 2H, OCH_2CH_3), 7.27−7.34 (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 (*m*/*z*): 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 to EDA ratio of 1:3 and a total reaction time of 15 min: benzylamine (60.9 mg, 0.568 mmol), EDA (218.4 mg, 1.92 mmol), and 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), 7.21−7.37 (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 (*m*/*z*): 280 (M + 1), 206 (base peak). Spectral results match those 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 treated with EDA (128.7 mg, 1.128 mmol) and Fe(TPP)Cl (6.5 mg, 0.0092 mmol) using 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 (*m*/*z*): 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 (245.7 mg) was obtained using method B: *p*-anisidine (126.7 mg, 1.029 mmol), EDA (235.7 mg, 2.854 mmol), and 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 (*m*/*z*): 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 using method A: toluidine (53.5 mg, 0.499 mmol), EDA (65.6 mg, 0.575 mmol), and 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 (*m*/*z*): 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 using method B; toluidine (206.7 mg, 1.929 mmol), EDA (500.1 mg, 4.383 mmol), and 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 (*m*/*z*): 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 using method A: aniline (68.7 mg, 0.738 mmol), EDA (99.7 mg, 0.874 mmol), and 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 (δ, ppm): 14.1, 45.8, 61.2, 112.9, 118.1, 129.2, 146.9, 171.0. MS (*m*/*z*): 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 using method B with an overall amine to EDA ratio of 1:2.9 and a reaction time of 2 h after the second addition of EDA: aniline (47.1 mg, 0.506 mmol), EDA (169.5 mg, 1.485 mmol), and Fe(TPP)Cl (3.5 mg, 0.0050 mmol). ^{1}H NMR (δ, ppm): 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 (δ, ppm): 14.0, 53.3,

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60.9, 112.3, 118.0, 129.1, 147.7, 170.7. MS (*m*/*z*): 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 using method A: *p*-chloroaniline (63.3 mg, 0.496 mmol), EDA (57.3 mg, 0.502 mmol), and Fe(TPP)Cl (3.7 mg, 0.0053 mmol). ^{1}H NMR (δ, ppm): 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 (δ, ppm): 14.2, 45.9, 61.5, 114.1, 122.9, 129.1, 145.5, 170.8. MS (*m*/*z*): 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 (91.8 mg) was isolated using method B: *p*-chloroaniline (64.4 mg, 0.505 mmol), EDA (140.0 mg, 1.227 mmol), and Fe(TPP)Cl (3.5 mg, 0.0050 mmol). ^{1}H NMR (δ, ppm): 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 (δ, ppm): 14.4, 53.8, 61.4, 114.0, 123.4, 129.3, 146.8, 170.7. MS (*m*/*z*): 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 using method A: *p*-bromoaniline (153.9 mg, 0.8947 mmol), EDA (108.1 mg, 0.9473 mmol), and Fe(TPP)Cl (6.5 mg, 0.0092 mmol). ^{1}H NMR (δ, ppm): 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 (δ, ppm): 14.2, 45.7, 61.5, 109.9, 114.5, 132.0, 146.0, 170.6. MS (*m*/*z*): 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 using method B with an overall amine to EDA ratio of 1:4.1 and a reaction time of 24 h after the second addition of EDA: *p*-bromoaniline (143.3 mg, 0.8330 mmol), EDA (389.3 mg, 3.412 mmol), and Fe(TPP)Cl (5.4 mg, 0.0077 mmol). ^{1}H NMR (δ, ppm): 1.27 (t, 6H, OCH_2CH_3), 4.09 (s, 4H, NCH_2-CO), 4.21 (q, 4H, OCH_2CH_3), 6.49 (d, 2H, C_6H_4), 7.29 (d, 2H, C_6H_4). ^{13}C NMR (δ, ppm): 14.2, 53.6, 61.2, 110.4, 114.2, 131.9, 146.9, 170.5. MS (*m*/*z*): 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 using method A and a reaction time of 20 min with *p*-cyanoaniline (110.5 mg, 0.9353 mmol), EDA (123.4 mg, 1.081 mmol), and Fe(TPP)Cl (7.0 mg, 0.0099 mmol). The chromatography eluent was 5:1 hexane−ethyl acetate. ^{1}H NMR (δ, ppm): 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), N*H* not observed. ^{13}C NMR (δ, ppm): 14.1, 44.7, 61.7, 99.6, 112.4, 120.1, 133.6, 150.0, 169.9. MS (*m*/*z*): 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 to EDA ratio of 1:4 and a reaction time of 4 h 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 (*m*/*z*): 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 using method A, requiring 18 h: *p*-nitroaniline (141.0 mg, 1.02 mmol), EDA (128 mg, 1.12 mmol), and Fe(TPP)Cl (7.2 mg, 0.010 mmol). The chromatography eluent was 5:1 hexane−ethyl acetate. ^{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 (*m*/*z*): 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 using method A, with the reaction being complete in 48 h: imidazole (135.4 mg, 1.989 mmol), EDA (321.7 mg, 2.819 mmol), and Fe(TPP)Cl (13.3 mg, 0.019 mmol). The chromatography eluent was 10:1 ethyl acetate−methanol. ^{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 (*m*/*z*): 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 yellow-white solid (69.6 mg, 92% yield) was prepared using method A, except that the reaction solution was refluxed: aniline (29.2 mg, 0.314 mmol), MPDA (63.9 mg, 0.363 mmol). The reaction was complete in 40 h. The chromatography eluent was 10:1 hexane−ethyl acetate. ^{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 (*m*/*z*): 242 (M + 1), 121 (base peak).

General Procedure for Dimerization of EDA using Fe(TPP)Cl. In a typical experiment, Fe(TPP)Cl (1.1 mg, 0.0015 mmol) was dissolved in 2 mL of deuterated methylene chloride and the mixture stirred under nitrogen. From a pyridine or a 2,6-lutidine stock solution (0.018 mmol/mL of CD_2Cl_2), an appropriate volume was added to the Fe(TPP)Cl mixture to produce the required catalyst to amine ratio. EDA (18 mg, 0.15 mmol) in 1 mL of deuterated methylene chloride was added by syringe in one aliquot. The progress of the reactions was monitored by ^{1}H NMR spectroscopy. Triphenylmethane (24 mg, 0.1 mmol) was used as an internal standard to determine the yields.

General Procedure for Dimerization of EDA using Fe^{II}(TPP). In a typical experiment, Fe(TPP)Cl (2.1 mg, 0.0030 mmol) was dissolved in 2 mL of THF and excess Zn/Hg amalgam (6−8 mg) added in a glovebox. This mixture was stirred overnight (about 16 h). The resulting solution was then filtered through a fine frit to remove the Zn/Hg amalgam. The solvent was removed under reduced pressure. The resulting Fe(TPP) was then redissolved in 2 mL of deuterated methylene chloride. From this solution, an appropriate volume of Fe(TPP) (0.0008 mmol) was measured and placed in a 5 mL round-bottom flask. From a pyridine or a 2,6-lutidine stock solution (0.018 mmol/mL of CD_2Cl_2), an appropriate volume was added to the Fe(TPP)Cl mixture to produce the required catalyst to amine ratio. EDA (9.0 mg, 0.08 mmol) in 1 mL of deuterated methylene chloride was added by syringe in one aliquot. The progress of the reactions was monitored by ^{1}H NMR spectroscopy. Triphenylmethane (12 mg, 0.05 mmol) was used as an internal standard to determine the yields.

Et_2N-D. N-deuterated diethylamine was prepared by three fractional distillations of a mixture of the amine and a 10-fold molar excess of D_2O using a 20 cm Vigreux column.[30] The product was dried and distilled from calcium hydride. The percent deuteration was determined by reaction with excess EDA to form monodeuterated $Et_2NCHDCO_2Et$ catalyzed by Fe(TPP)Cl in CD_2Cl_2. Residual H−N protons resulted in the production of $Et_2NCH_2CO_2Et$, and amounts of the d_0/d_1 products could be quantitatively measured by ^{1}H NMR at 700 MHz by integration of the baseline-separated *N*-methylene signals. A d_1/d_0 product ratio of 7.72:1 was obtained (88.5 atom % *d*). Aniline-d_7 was obtained from Aldrich and used as received.

Kinetic Isotope Effect. C_6D_6 was dried by stirring with phosphorus pentoxide for 18 h in a sealed Schlenk tube under reduced pressure. Using vacuum line techniques, ca. 0.6 mL of

(30) Garcia-Rio, L.; Leis, J. R.; Moreira, J. A.; Serantes, D. *Eur. J. Org. Chem.* **2004**, *3*, 614.

dry C_6D_6 was added by trap-to-trap distillation to a dry 20 mL round-bottom flask containing Fe(TPP)Cl (0.5 mg, 0.07 μmol) and a magnetic bar. The flask was warmed to ambient temperature, back-filled with dry nitrogen, and immediately capped using a rubber septum under a positive flow of N_2. Diethylamine (10.0 μL, 7.07 mg, 96.7 μmol) and diethylamine-*N*-*d* (10.0 μL, 7.07 mg, 96.6 μmol, 88.5 atom % D) were added to the stirred solution using a gastight syringe. To initiate the reaction, a limiting amount of ethyl diazoacetate (10.0 μL, 8.50 mg, 74.6 μmol) was added by syringe. The resulting contents were transferred to an NMR tube, and the kinetic ratio of products was determined on a 700 MHz Bruker NMR spectrometer by integrating the baseline-resolved methylene proton peaks of the products, $Et_2NCH_2CO_2Et$ (s) and $Et_2NCHDCO_2Et$ (t). A similar procedure was used for deuterated aniline. The kinetic isotope effect was determined from averaging the results of three separate reactions.

Acknowledgment. We gratefully acknowledge funding from the Petroleum Research Fund and the National Science Foundation.

OM0610997