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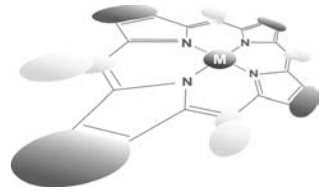

O-H insertion and tandem N-H insertion/cyclization reactions using an iron porphyrin as catalyst with diazo compounds as carbene sources

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ABSTRACT: Iron(III) tetraphenylporphyrin chloride, Fe(TPP)Cl, efficiently catalyzed the insertion of carbenes derived from methyl 2-phenyldiazoacetates into O-H bonds of aliphatic and aromatic alcohols, with yields generally above 80%. Although the analogous N-H insertions are rapid at room temperature, the O-H insertion reactions are slower and required heating in refluxing methylene chloride for about 8 hours using 1.0 mol.% catalyst. Fe(TPP)Cl was also found to be effective for tandem N-H insertion/cyclization reactions when 1,2-diamines and 1,2-alcoholamines were treated with diazo reagents to give piperazinones and morpholinones and related analogs such as quinoxalinones and benzoxazin-2-ones. This approach provides a new one-pot route for synthesizing these classes of heterocyclic compounds.

KEYWORDS: iron porphyrin, catalysis, insertion, carbene, cyclization.

INTRODUCTION

The synthesis of α-hydroxy and α-alkoxy carboxylic acid derivatives is of considerable importance since these compounds are useful synthetic intermediates for the construction of natural products and biologically active molecules. Diazocarbonyl compounds are useful reagents for the synthesis of these types of derivatives due to their ready availability, relative kinetic stability, and facile decomposition under thermal, photochemical, and metal-catalyzed conditions. Transition-metal-catalyzed procedures are often the method of choice, taking place under relatively mild conditions. The original catalytic reactions with diazo reagents were based on copper metal or simple copper(II) salts [1]. Rhodium(II) carboxylates were introduced later by Teyssie and co-workers in the early 1970s [2]. In recent years, new transition-metal catalysts have been developed that are now widely used since they mediate a broad range of carbenoid transformations such as cyclopropanation, C-H insertion, addition to aromatic rings, and ylide formation [3]. Consequently, synthetic uses of diazocarbonyl compounds have increased dramatically.

Our recent interest in iron porphyrin reactions with diazo reagents centers on C-H and N-H insertion reactions [4], which despite their potential in synthesis, have not been widely utilized [5]. Earlier work done by our group established that iron tetraphenylporphyrin chloride, Fe(TPP)Cl, is one of the most effective catalysts for the insertion of carbenes from diazo esters into N-H [6] and C-H bonds [7]. The present study sought to extend the use of iron porphyrins to O-H insertion reactions and also determine if the highly efficient N-H insertion process could be coupled with subsequent cyclization reactions to give products that contain piperazinone or morpholinone moieties. A typical multi-step synthesis of piperazinone is shown in Scheme 1 [8]. Improved synthetic methods for 2-piperazinone intermediates could lead to important applications, such as the production and use of peptide nucleic acids (PNAs) [9]. This has the potential for rapid identification of PNA oligomers for use in therapeutics, diagnostics and gene characterization tools. Derivatives of 2-piperazinones are known to have therapeutic properties and generally act by controlling or inhibiting cell-adhesion [10].

◊SPP full member in good standing

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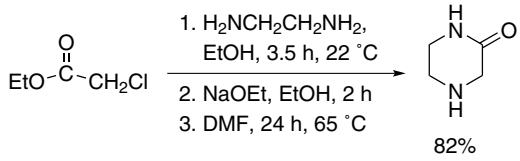


Scheme 1.

RESULTS AND DISCUSSION

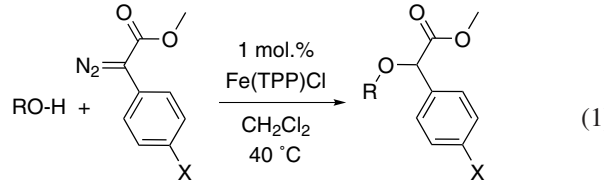
O-H insertion reactions

Substituted methyl 2-phenyldiazoacetates (MPDAs) were found to be useful carbene sources for O-H insertion reactions with alcohols when Fe(TPP)Cl was used as the catalyst (Equation 1). However, when ethyl diazoacetate (EDA) was tried as the carbene source for O-H insertion reactions using Fe(TPP)Cl as a catalyst, only maleates and fumarates were formed. This is in contrast to analogous N-H insertions reactions where EDA was shown to be an excellent carbene source [6]. Treating an alcohol with 1–2 equiv. of substituted methyl 2-phenyldiazoacetate in refluxing methylene chloride using 1.0 mol.% catalyst efficiently produced O-H insertion products. The yields obtained were as high as 88% (Table 1). No aromatic C-H insertion products [7] were detected by GC when phenol was used as the substrate. These products were readily characterized by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. For example, methyl 2-phenoxy-2-(*p*-tolyl)acetate, **1a**, produced from phenol and methyl 2-(*p*-tolyl)-diazoacetate, gave a characteristic methine singlet ^{1}H NMR signal at 5.63 ppm while the methine carbon exhibited a ^{13}C NMR signal at 78.5 ppm. Both the ^{1}H and ^{13}C NMR spectra were found to match literature values [11]. This reaction was extended to aliphatic alcohols. Treatment of ethanol with *p*-MeO-MPDA in refluxing methylene chloride and 1.0 mol.% Fe(TPP)Cl produced methyl 2-ethoxy-2-(*p*-methoxy-phenyl)acetate, **3b**. This product was purified by elution through a silica gel column using 20:1 hexanes/ethyl acetate, resulting in an isolated yield of 74%. The product exhibited a ^{1}H NMR singlet for the new methine proton at 4.84 ppm while the two α-methylene hydrogens gave diastereotropic multiplets at 3.53 ppm.

Table 1. Summary of catalytic reactions of *para*-substituted methyl 2-phenyldiazoacetate compounds with various alcohols[a]

Alcohol	MPDA *p*-X	Product	% yield[b]
phenol	CH_3-	**1a**	80
phenol	CH_3O-	**1b**	83
cyclohexanol	CH_3-	**2a**	86
cyclohexanol	CH_3O-	**2b**	88
ethanol	CH_3O-	**3b**	74
n-propanol	CH_3-	**4a**	71
2-propanol	CH_3O-	**5b**	56[c]

[a] Conditions: CH_2Cl_2 used as solvent, 40 °C for 8 hours, alcohol:diazo reagent ratio of 2:1, 1.0 mol.% Fe(TPP)Cl catalyst. [b]Isolated yield. [c]Methyl C-H insertion product also detected by NMR.

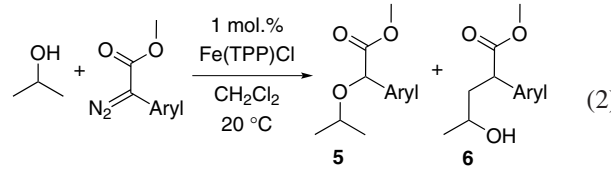


(1)

R = Ph (**1**), cyclohexyl (**2**), Et (**3**), *n*-Pr (**4**), *i*-Pr (**5**)

X = Me (**a**), OMe (**b**)

Isopropanol was found to react with *p*-MeO-MPDA to give a mixture of O-H insertion product **5b** and C-H insertion product **6b** in a ratio of 6:1, respectively (Equation 2).



(2)

5 **6**

Aryl = -C_6H_4-*p*-X; X = H, Cl, Me, OMe

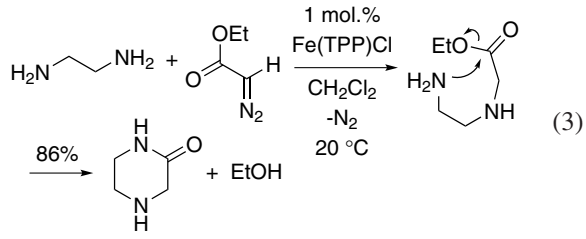
The O-H insertion product **5b** exhibited characteristic NMR signals for the two types of methine protons. The isopropyl methine hydrogen appeared at 3.67 (1H, m) and a singlet at 4.95 ppm was assigned to the methine hydrogen alpha to the ester group. The diastereotropic nature of the isopropyl methyl groups is manifested by distinct doublets at 1.24 and 1.19 ppm, each integrating as three protons. Although it was not possible to isolate a pure sample of the C-H insertion product, the presence of doublets for the terminal CH_3 proton signal at 0.96 ppm (3H) and multiplets at 3.65 (2H) and 4.03 ppm (1H) for the methylene and methine protons, respectively, suggested that an insertion into the terminal C-H group occurred to give **6b**. These results illustrate that Fe(TPP)Cl is an effective catalyst for O-H insertion reactions and is more efficient than typical rhodium catalysts that produce lower O-H insertion yields under similar conditions [12].

The mechanism for catalytic O-H insertion is likely to be similar to that proposed for the analogous N-H process [6]. This involves reaction of the iron porphyrin with the diazo reagent to form a transient carbene complex. Subsequent attack of the alcohol oxygen at the electrophilic carbene-carbene ligand produces the insertion product. The need to heat the O-H insertion reactions is consistent with the lower nucleophilicity of alcohols relative to amines. In contrast, N-H insertion reactions catalyzed by Fe(TPP)Cl typically occurred within minutes at ambient temperature.

Tandem insertion/cyclization reactions

Ethylenediamine reacted rapidly with ethyl diazoacetate in the presence of 1.0 mol.% catalyst at ambient temperature to give 2-piperazinone in yields above 80%

(Equation 3, Table 2). This was confirmed by the absence of the ^{1}H NMR methine signal for EDA that appears at 4.72 ppm.



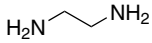
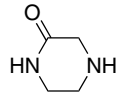
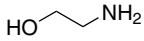
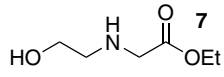
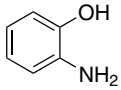
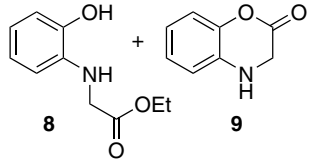
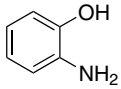
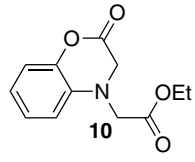
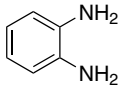
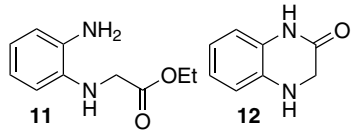
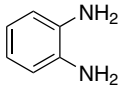
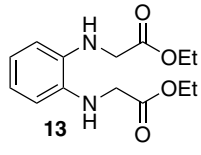
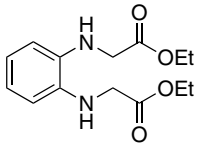
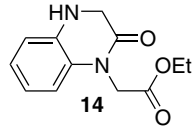
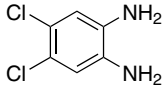
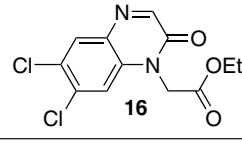
(3)

The absence of ^{1}H NMR signals around 4.2 (q) and 1.2 (t) indicated that the ethyl group of the ester had been lost. The highly polar 2-piperazinone was found to be soluble in water and insoluble in organic solvents and could not therefore be purified by silica gel chromatography. However, it was extracted from methylene chloride with a 1:1 mixture of methanol and water to give a 90% pure product. This product exhibited a proton NMR singlet at 3.53 ppm for the two hydrogens at C3, a triplet of doublets at 3.38 ppm for the two protons at C6, and a triplet at 3.04 for the two hydrogens at C5. The amide N-H proton was detected as a broad peak at 6.47 ppm while the amine proton was not observed. These NMR data compare well with spectra of other 2-piperazinone nucleoside analogs substituted at the amine nitrogen [13].

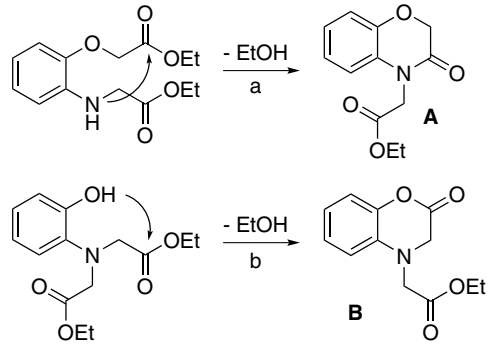
In contrast, ethanolamine reacted with one equiv. of EDA to give a single product, **7**, that resulted from an insertion at the amino group. Unlike the reaction of ethylenediamine with EDA, this product did not undergo an ensuing cyclization, even after reaction times greater than one day and elevated temperature or with added acid. This linear product was purified by flash column chromatography using 10:1 methylene chloride/methanol as the eluent. No product derived from O-H insertion was observed. This is consistent with earlier observations that have clearly shown that N-H insertion reactions are more facile than O-H insertions [6]. Slow addition of 2 equiv. of EDA to ethanolamine resulted only in maleates and fumarates as determined by GC-MS analysis.

Geometrically constrained 1,2-aminoalcohols and phenylene diamines were found to undergo partial cyclization after N-H insertion with 1 equiv. EDA (Table 2). For example, the reaction of 2-aminophenol with one equiv. of EDA afforded a mixture of products. The major species was a N-H insertion product **8** which exhibited a characteristic glycyl methylene proton singlet at 3.91 ppm [6a]. GC-MS analysis revealed the formation of about 10% of another minor product. Although the minor product could not be isolated, its molecular ion peak of 150 *m/z* reflected loss of an ethoxy group and was consistent with the cyclization product **9**. When 2 equiv. of EDA were added slowly to 2-aminophenol, three different insertion products were detected by GC-MS along with maleates and fumarates. However, when the mixture was separated by SiO_2 chromatography, cyclized product **10** was obtained in 42% yield. Two isomers are possible

Table 2. Summary of products from 1,2-disubsituted substrates

Substrate	Eq. EDA	Product	% yield[a]
	1		86
	1	 **7**	62
	1	 **8** **9**	71 (**8**)
	2	 **10**	42
	1	 **11** **12**	40 (**12**)
	2	 **13**	68
	0	 **14**	88[b]
	2	 **16**	44[c]

[a] Typical conditions: 0.500 mmol substrate, 1.0 mol.% Fe(TPP)Cl, 5.0 mL CH_2Cl_2, 22 °C, stirring for 10–30 min. [b] Heating substrate neat for 12 h at 60 °C under N_2. [c] See experimental section for details.



Scheme 2.

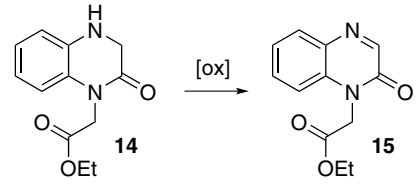
for the benzomorpholinone product as shown in Scheme 2. Pathway (a) involves a double OH/NH insertion intermediate and produces 3-keto product **A** *via* amine attack at the O-bound ester. Given the lower propensity for carbene insertion at the OH position, this is the less likely pathway. Alternatively, 2-keto isomer **B** arises from phenol attack (pathway b) at one of the N-bound diesters.

The structure of compound **10** was initially assigned by a comparison of its ^{13}C NMR spectrum with those of two similar compounds, 2*H*-1,4-benzoxazin-3(4H)-one (benzomorpholin-3-one) [14], and 3,4-dihydro-1,4-benzoxazin-2-one (benzomorpholin-2-one) [15]. The methylene carbon (C2) on the aliphatic ring appears at 67 ppm for the 3-keto isomer, while the methylene carbon (C3) on the aliphatic ring appears at 45 ppm for the 2-keto analog. In compound **10**, the methylene carbon on the aliphatic ring appears at 51 ppm. This value is more consistent with a 2-keto product, **B**. The structure of **10** was confirmed spectroscopically through 2D ^{13}C-^{1}H HSQC, ^{13}C-^{1}H HMBC, and ^{15}N-^{1}H HMBC experiments. The ^{13}C-^{1}H HSQC showed no direct C-H couplings to the two carbonyl peaks (169.2 and 164.3 ppm) nor to the two aromatic carbons (141.7 and 133.4 ppm). The ^{13}C-^{1}H HMBC spectrum exhibited cross peaks between the carbonyl signal at 169.2 ppm and the methylene resonances at 4.01 (s, 2H) and 4.24 (q, 2H) ppm. These 2- and 3-bond couplings definitively allow the assignment of these signals to the carbonyl and methylene units of the ester side chain. In addition, an HMBC cross peak between the ring carbonyl (164.3 ppm) and the CH_2 signal at 4.13 ppm (s, 2H) definitively assigned this proton resonance to the methylene unit in the morpholinone ring. Both methylene singlets (4.01 and 4.13 ppm) also showed cross peaks with the quarternary aromatic carbon at 133.4 ppm. These 3-bond correlations can only occur with the ring junction carbon at C5 in the 2-keto structure. It is not possible for both methylene singlets to correlate to the same quarternary aromatic carbon in the 3-keto isomer. Further support for the 2-keto isomer was derived from the ^{15}N-^{1}H HMBC data in which the ^{15}N resonance (243 ppm) showed 2-bond correlations to both methylene singlets at 4.13 and 4.01 ppm. This correlation is only possible if both these units are adjacent to the nitrogen. The observed product **10** is most likely formed through a double insertion at the amine nitrogen, followed by an ensuing cyclization (Scheme 2).

Treatment of 1,2-phenylenediamine with one equiv. of EDA in methylene chloride and 1.0 mol.% catalyst afforded three products as detected by GC-MS. The two major products had molecular ion peaks of 191 *m/z*, **11**, and 148 *m/z*, **12**, in about a 3:1 ratio. The third product was a bisinsertion product, **13**, observed in small amounts. The main product exhibited a molecular ion peak at 191 *m/z,* suggesting that it was a product in which one of its amino groups has undergone a single insertion of EDA. However, separation by silica gel chromatography using hexane/ethyl acetate (1:1) as the eluent resulted in the isolation of only product **12**. The ^{1}H NMR spectrum of the product showed no ^{1}H NMR peaks around 4.2 (q) or 1.2 (t), indicating that the ethyl unit of the ester group had been lost, most likely following a cyclization pathway similar to that involved in the reaction of ethylenediamine and EDA (Equation 3). This suggested that subsequent cyclization occurred on the column.

Treatment of 1,2-phenylenediamine with 2 equiv. of EDA resulted in clean formation of product **13** in which both the amine groups had undergone N-H insertions. This double insertion product gave a four-proton ^{1}H NMR doublet at 3.90 ppm for the new methylene hydrogens of the two *N*-acetate groups. Heating solid **13** under nitrogen at 60 °C for 12 h produced bicyclic compound **14** in an 88% isolated yield in analytically pure form. The increased complexity in the ^{1}H NMR spectrum relative to that of the diester **13** indicated a reduction of symmetry in the product. Moreover, the loss of an ethoxy group indicated that the molecule had undergone a cyclization.

Over time, compound **14** converted to a new product **15** in solution (Equation 4). The new aromatic protons of **15** shifted strongly downfield relative to **14** by an average of 0.7 ppm to 7.93 (1H, dd), 7.58 (1H, td), 7.39 (1H, td), and 7.12 (1H, d). Proton signals at 4.26 (2H, q) and 1.28 (3H, t) indicated that the ethyl ester group was retained. New downfield signals at 8.36 (1H, s) and 5.03 (2H, s) were observed. These NMR data are consistent with quinoxalin-3-one structure **15**, in which the imine proton is assigned to the downfield resonance at 8.36 ppm and the methylene protons are assigned to the 5.03 ppm singlet. The quinoxalinone product was prepared independently by treatment of **14** with DDQ. Heating this mixture in benzene for 30 minutes at 60 °C resulted in clean oxidation to produce **15** in a 79% isolated yield.



(4)

In general, the addition of one equiv. of EDA to a 1,2-diamine or aminoalcohol substrate led to mixtures

that typically contained an N-H insertion product and a subsequent partial cyclization to a piperazinone or morpholinone structure. Under various conditions, it was not possible to cleanly cyclize all of the initial N-H insertion product. However, using 2 equiv. of EDA allowed the isolation of a clean product as illustrated by the preparation of compounds **10** and **14**. As further demonstration of the utility of this approach, 1,2-diamino-4,5-dichlorobenzene was treated with 2 equiv. of EDA and 1 mol.% Fe(TPP)Cl. The intermediate N,N′ bisinsertion product was subsequently heated under N_2 at 60 °C for 12 h to produce cyclized, dehyrogenated imine compound **16** in 44% yield.

EXPERIMENTAL

Fe(TPP)Cl was obtained from Aldrich and used without further purification. Substituted methyl 2-phenyldiazoacetates were prepared as outlined in the literature [11]. All reactions were performed under an atmosphere of nitrogen. Proton NMR and ^{13}C NMR spectra were run in $CDCl_3$ and recorded on a Varian VXR 300 or a Bruker DRX400 spectrometer. Two dimensional NMR experiments were run on a Bruker 700 MHz Avance II 700 spectrometer with a Bruker Z-gradient inverse TXI $^1H/^{13}C/^{15}N$ 5 mm cryoprobe at 25 °C. ^1H NMR peak positions were referenced against residual proton resonances of $CDCl_3$ (δ, 7.27). Gas chromatographic analyses were performed on a HP 5890 series II or a Finnigan GC-MS instrument. IR data was collected on a Bruker IFS-66V FT-IR using samples that were prepared as a thin film on NaCl plates. Elemental analyses were performed on a PerkinElmer Model 2400 CHN/S elemental analyzer by Iowa State University Chemical Instrument Services.

General procedure

O-H insertion reactions. The alcohol (0.32–0.64 mmol) was accurately weighed, placed in a 50 mL round bottom flask containing a stir bar and dissolved in 5.0 mL of methylene chloride. A condenser, fitted with a rubber septum, was attached to the flask and the contents thoroughly flushed with nitrogen. The catalyst (1.0 mol.%) and 1.0 equiv. diazo reagent were added and the contents bubbled with dry nitrogen for 5 min. The mixture was then heated for 8 h at reflux while being stirred. The products were purified by eluting on a flash silica gel column (4 cm diameter, 30 cm height, hexane/ethyl acetate; 20:1).

N-H insertion reactions. About 0.500 mmol of the amine were accurately weighed, placed in a 50 mL round bottom flask containing a stir bar and dissolved in 5.0 mL of methylene chloride. A condenser, fitted with a rubber septum, was attached to the round bottom flask and the contents thoroughly flushed with nitrogen. The catalyst (1.0 mol.%) and the desired amount of the diazo reagent was then added over a period of 40 minutes by syringe pump. The mixture was then stirred until the diazo reagent was consumed, as monitored by TLC or GC. The products were purified using a flash column as above.

Synthesis

Methyl 2-(*p*-tolyl)diazoacetate insertion with phenol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol.%), phenol (30.0 mg, 0.320 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-phenoxy-2-(4-methylphenyl)acetate, **1a**, (66.2 mg, 0.257 mmol, 80% yield) was obtained. The proton NMR and ^{13}C NMR spectra matched literature values [11]. ^1H NMR (400 MHz, $CDCl_3$): δ, ppm 7.47 (d, 2H, J_H = 7.9, aryl-H), 7.29 (d, 2H, J_H = 7.9, aryl-H), 7.22 (d, 2H, J_H = 7.9, aryl-H), 6.97 (m, 3H, aryl-H), 5.63 (s, 1H, methine C-H), 3.75 (s, 3H, OCH_3), 2.37 (s, 3H, Ar-CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 170.6, 157.4, 139.0, 132.5, 129.6, 129.5, 127.1, 121.8, 115.5, 78.5, 52.6, 21.3. MS (EI): *m/z* 258 $[M]^+$.

Methyl 2-(*p*-methoxyphenyl)diazoacetate insertion with phenol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol.%), phenol (30.0 mg, 0.320 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-phenoxy-2-(4-methoxyphenyl)acetate, **1b**, (72.2 mg, 0.265 mmol, 83% yield) was obtained. The proton NMR and ^{13}C NMR spectra matched literature values [11]. ^1H NMR (400 MHz, $CDCl_3$): δ, ppm 7.50 (d, 2H, J_H = 8.4, aryl-H), 7.36 (d, 2H, J_H = 8.4, aryl-H), 6.95 (m, 5H, aryl-H), 5.61 (s, 1H, methine C-H), 3.82 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 170.7, 160.2, 157.3, 129.6, 128.6, 127.5, 121.8, 115.5, 114.3, 78.2, 55.4, 52.6. MS (EI): *m/z* 272 $[M]^+$.

Methyl 2-(*p*-tolyl)diazoacetate insertion with cyclohexanol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP) FeCl (2.20 mg, 1.0 mol.%), cyclohexanol (48.0 mg, 0.480 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-cyclohexanoxy-2-(4-methylphenyl)acetate, **2a**, (72.2 mg, 0.276 mmol, 86% yield) was obtained. ^1H NMR (400 MHz, $CDCl_3$): δ, ppm 7.36 (d, 2H, J_H = 8.0, aryl-H), 7.17 (d, 2H, J_H = 8.0, aryl-H), 5.03 (s, 1H, methine C-H), 3.71 (s, 3H, OCH_3), 3.34 (m, 1H, cyclo-methine C-H), 2.35 (s, 3H, $ArCH_3$), 1.99

(m, 1H), 1.88 (m, 1H), 1.74 (m, 2H), 1.53 (m, 1H) 1.41 (m, 2H), 1.23 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 172.3, 138.3, 134.4, 129.3, 127.1, 78.0, 52.2, 32.3, 32.2, 25.7, 24.2, 21.2. MS (EI): *m/z* 262 $[M]^+$.

Methyl 2-(*p*-methoxyphenyl)diazoacetate insertion with cyclohexanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol.%), cyclohexanol (48.0 mg, 0.480 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-cyclohexanoxy-2-(4-methoxyphenyl)acetate, **2b**, (78.3 mg, 0.282 mmol, 88% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.38 (d, 2H, J_H = 8.4, aryl-H), 6.89 (d, 2H, J_H = 8.4, aryl-H), 5.00 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, OCH_3), 3.32 (m, 1H, cyclo-methine C-H), 1.99 (m, 1H), 1.87 (m, 1H), 1.73 (m, 2H), 1.53 (m, 1H) 1.39 (m, 2H), 1.22 (m, 3H). ^{13}C NMR (100.5, $CDCl_3$): δ, ppm 172.3, 159.7, 129.5, 128.5, 114.0, 77.6, 55.3, 52.2, 32.3, 32.2, 25.7, 24.2. MS (EI): *m/z* 278 $[M]^+$. Anal. calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.70; H, 7.40.

Methyl 2-(*p*-methoxyphenyl)diazoacetate insertion with ethanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl) diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol.%), ethanol (29.4 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-ethoxy-2-(4-methoxyphenyl)acetate, **3b**, (53.0 mg, 0.237 mmol, 74% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.38 (d, 2H, J_H = 8.8, aryl-H), 6.90 (d, 2H, J_H = 8.8, aryl-H), 4.84 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.72 (s, 3H, OCH_3), 3.53 (m, 2H, OCH_2), 1.27 (t, 3H, J_H = 8.8, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 170.3, 159.2, 128.8, 128.6, 114.1, 80.5, 65.1, 55.3, 52.3, 15.2. MS (EI): *m/z* 224 $[M]^+$.

Methyl 2-(*p*-tolyl)diazoacetate insertion with *n*-propanol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP) FeCl (2.20 mg, 1.0 mol.%), *n*-propanol (39.7 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-propanoxy-2-(4-methoxyphenyl)acetate, **4a**, (50.4 mg, 0.227 mmol, 71% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.35 (d, 2H, J_H = 8.0, aryl-H), 7.18 (d, 2H, J_H = 8.0, aryl-H), 4.85 (s, 1H, methine C-H), 3.71 (s, 3H, OCH_3), 3.48 (m, 1H, OCH_2), 3.40 (m, 1H, OCH_2), 2.35 (s, 3H, $ArCH_3$), 1.67 (m, 2H, CH_2), 0.94 (t, 3H, J_H = 7.6, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 171.7, 138.5, 133.8, 129.3, 127.2, 80.9, 71.5, 52.2, 22.8, 21.2, 10.5. MS (EI): *m/z* 222 $[M]^+$.

Methyl 2-(*p*-methoxyphenyl)diazoacetate insertion with isopropanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.2 mg, 1.0 mol.%), isopropanol (39.4 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-isopropanoxy-2-(4-methoxyphenyl)acetate, **5b**, (42.6 mg, 0.179 mmol, 56% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 7.39 (d, 2H, J_H = 8.6, aryl-H), 6.89 (d, 2H, J_H = 8.6, aryl-H), 4.95 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, OCH_3), 3.65 (m, 1H, OCH), 1.24 (d, 3H, J_H = 6.2, RCH_3), 1.19 (d, 3H, J_H = 6.2, RCH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 171.3, 159.4, 128.7, 115.6, 114.4, 78.2, 70.8, 55.5, 52.4, 22.4, 22.1. MS (EI): *m/z* 238 $[M]^+$.

EDA insertion with ethylenediamine. Ethylenediamine (30.0 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen and ethyl diazoacetate (57.0 mg, 0.500 mmol), dissolved in 3.0 mL of methylene chloride, added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 10 min. The product was extracted using distilled water and dried under reduced pressure to obtain 2-piperazinone (43.1 mg, 0.431 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 6.47 (bs, 1H, NH), 3.53 (s, 2H, CH_2), 3.38 (td, 2H, J_H = 5.4, J_H = 2.4, CH_2), 3.01 (t, 2H, J_H = 5.4, CH_2). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 170.1, 49.9, 43.0, 42.3. MS (EI): *m/z* 100 $[M]^+$. Spectral results match reported values [16].

EDA insertion with ethanolamine. Ethanolamine (30.0 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen, after which ethyl diazoacetate (57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was done within 15 min. The product was purified by eluting through a silica gel column using a 10:1 methylene chloride/methanol mixture. The product N-(2-hydroxyethyl) glycine ethyl ester, **7**, (45.6 mg, 0.310 mmol, 62% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 4.21 (q, 2H, J_H = 7.2, CH_2), 3.63 (t, J_H = 5.1, 2H, CH_2), 3.44 (s, 2H, CH_2), 2.82 (t, J_H = 5.1, 2H, CH_2), 2.14 (bs, 2H, OH, NH), 1.29 (t, J_H = 7.2, 3H, CH_2). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 172.5, 60.8, 60.7, 51.0, 50.3, 14.1. MS (EI): *m/z* 148 $[M + 1]^+$. Spectral data matched literature values [17].

EDA reaction with 2-aminophenol (1:1). 2-aminophenol (54.2 mg, 0.500 mmol) and (TPP)FeCl (3.5 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen, after which ethyl diazoacetate

(57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 20 min. The products were purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product N-(2-hydroxyphenyl) glycine ethyl ester, **8**, (69.3 mg, 0.355 mmol, 71% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 6.57–6.86 (m, 4H, aryl-H), 4.27 (q, J_H = 7.2, 2H, CH_2), 3.95 (s, 2H, CH_2), 1.31 (t, J_H = 7.2, 3H, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 172.4, 153.6, 127.9, 126.4, 120.4, 116.0, 61.7, 56.4, 14.5. MS (EI): *m/z* 195 $[M]^+$. Anal. calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.02; H, 6.60; N, 6.96.

EDA reaction with 2-aminophenol (2:1). 2-aminophenol (54.2 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen, after which ethyl diazoacetate (114 mg, 1.00 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was finished within 30 min. The product was purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product, **10**, ethyl (2-oxo-2-,3-dihydro-4*H*-1,4-benzoxazin-4-yl) acetate (49.4 mg, 0.210 mmol, 42% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 7.07 (m, 2H, aryl-H), 6.89 (td, 1H, J_H = 7.8, J_H = 1.5, aryl-H), 6.63 (dd, 1H, J_H = 7.8, J_H = 1.5, aryl-H), 4.24 (q, 2H, J_H = 7.2, CH_2), 4.13 (s, 2H, CH_2), 4.01 (s, 2H, CH_2), 1.59 (bs, 0.4H, H_2O), 1.29 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 169.2, 164.3, 141.7, 133.4, 125.2, 120.5, 117.2, 112.5, 61.4, 51.1, 50.8, 14.2. MS (EI): *m/z* 236 $[M + 1]^+$. Anal. calcd. for $C_{12}H_{13}NO_4 \cdot 0.2\ H_2O$: C, 60.35; H, 5.66; N, 5.86. Found: C, 60.56; H, 5.40; N, 6.02.

EDA insertion on 1,2-phenylenediamine (1:1). 1,2-phenylenediamine (54.4 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen, after which ethyl diazoacetate (57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 20 min. The products were purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product, 3,4-dihydroquinoxalin-2(1H)-one, **12**, (29.5 mg, 0.199 mmol, 40% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 8.84 (bs, 1H, NH), 6.90 (m, 1H, aryl-H), 6.77 (m, 2H, aryl-H), 6.68 (d, 1H, J_H = 7.8, aryl-H), 4.01 (s, 2H, CH_2), 3.88 (bs, 1H, NH). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 167.1, 133.6, 125.4, 123.9, 119.5, 115.7, 114.0, 47.1. MS (EI): *m/z* 148 $[M]^+$. IR (NaCl): $\nu_{C=O}$, cm^{-1} 1680. Spectral results match reported values [18].

EDA insertion on 1,2-phenylenediamine (2:1). 1,2-phenylenediamine (54.3 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol.%) were placed in a 50 mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen, after which ethyl diazoacetate (114 mg, 1.00 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was finished within 20 min. The product was purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product N,N-bis(2-aminophenyl)glycine ethyl ester, **13**, (95.2 mg, 0.340 mmol, 68% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ, ppm 6.82 (m, 2H, aryl-H), 6.60 (m, 2H, aryl-H), 4.26 (q, J_H = 7.2, 4H, CH_2), 4.09 (bt, 2H, J_H = 6.0, NH), 3.90 (d, 4H, J_H = 6.0, CH_2), 1.31 (t, 6H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 171.3, 136.5, 120.0, 112.6, 61.2, 46.5, 14.2. MS (EI): *m/z* 280 $[M]^+$. IR (NaCl): $\nu_{C=O}$, cm^{-1} 1741. Anal. calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.04; H, 6.91; N, 9.98.

Cyclization of diester compound 13. Upon heating at 60 °C, under nitrogen for 12 hours, solid compound **13** (70.1 mg, 0.250 mmol) cyclized to product **14**, ethyl (2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetate and was obtained in 88% yield (51.4 mg, 0.220 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 6.94 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 6.83 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H) 6.73 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 6.70 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 4.66 (s, 2H, CH_2), 4.25 (q, 2H, J_H = 7.2, CH_2), 4.01 (s, 2H, CH_2), 3.96 (bs, 1H, N-H), 1.29 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 168.2, 166.1, 135.5, 128.1, 123.9, 119.9, 114.5, 114.4, 61.6, 47.5, 43.7, 14.1. MS (EI): *m/z* 234 $[M]^+$. IR (NaCl): $\nu_{C=O}$, cm^{-1} 1742, 1675. Anal. calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.50; H, 5.95; N, 11.63.

Oxidation of 14 with DDQ. Ethyl (2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetate (50.2 mg, 0.215 mmol) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (50.0 mg, 0.218 mmol) were placed in a 50 mL round bottom flask and dissolved in 10.0 mL of benzene. The flask was then stirred and heated at 60 °C. Complete conversion of the starting material was seen after 30 min. The grayish precipitate that formed ($DDQH_2$) was removed by vacuum filtration. The desired product **15**, ethyl (2-oxoquinoxalin-1(2H)-yl) acetate (39.3 mg, 0.169 mmol) was obtained in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.36 (s, 1H, CH), 7.93 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.58 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.39 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.12 (d, 1H, J_H = 8.0, aryl-H), 5.03 (s, 2H, CH_2), 4.26 (q, 2H, J_H = 7.2, CH_2), 1.28 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ, ppm 166.8, 154.5, 149.9, 133.4, 132.3, 131.2, 130.8, 124.1, 113.2, 62.2, 43.1, 14.1. MS (EI): *m/z* 232 $[M]^+$. IR (NaCl): $\nu_{C=O}$, cm^{-1} 1737, 1664. Anal. calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.68; H, 5.08; N, 11.72.

EDA insertion on 4,5-dichloro-1,2-phenylenediamine (2:1) and cyclization. Using Schlenk techniques under N_2, Fe(TPP)Cl (1 mol.%) and 4,5-dichloro-1,2-phenylenediamine (305 mg, 1.78 mmol) were transferred

to a 50 mL flask and 15 mL of dry, deoxygenated CH_2Cl_2 was added *via* syringe. A 2.09 M solution of EDA (1.79 mL, 427 mg, 3.74 mmol) in dry, air-free CH_2Cl_2 was added to the flask dropwise over an hour. Immediate N_2 evolution was noticed as EDA was added. The reaction was stirred for 16 h, producing three products as detected by GC. The solution was subsequently concentrated under vacuum and purified on a silica gel column. Unreacted EDA was removed with 10:1 hexane/EtOAc, and the products eluted with 1:1. The solid double-insertion product was dried *in vacuo* overnight and and converted to the pyrazinone form by heating N_2 at 60 °C for approximately 12 h. The resulting brown solid was suspended in CH_2Cl_2, filtered, and washed with CH_2Cl_2. Recrystallization from ethyl acetate resulting in a white hydrate, **16**, containing one equiv. of water (228 mg, 44.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ, ppm 8.33 (s, 1H, aryl-H), 8.00 (s, 1H, aryl-H), 7.20 (s, 1H, N=C-H), 4.95 (s, 2H, N-CH_2), 4.29 (q, 2H, J_H = 8.0, OCH_2CH_3), 1.32 (t, 3H, J_H = 8.0, OCH_2CH_3), 1.58 (s, 2H, H_2O). MS (EI): *m/z* 301 $[M]^+$. Anal. calcd. for $C_{12}H_{10}N_2O_3Cl_2{\cdot}H_2O$: C, 45.16; H, 3.79; N, 8.78. Found: C, 44.98; H, 2.91; N, 8.59.

CONCLUSION

Fe(TPP)Cl is an effective catalyst for the O-H insertion reactions of alcohols when substituted MPDAs are used as carbene sources. Aromatic and normal aliphatic alcohols gave O-H insertion as the only product. Treatment of isopropanol with *p*-MeO-MPDA and Fe(TPP)Cl yielded O-H insertion as the major product and a minor C-H insertion at the terminal position. This catalyst was also found to be very efficient in the syntheses of 2-piperazinone and 2-morpholinone through a tandem N-H insertion/cyclization process using EDA as the carbene source. The tandem N-H insertion/cyclization process provides an easy one-pot procedure for the syntheses of novel piperazinones and their substituted analogs.

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Supporting information

Supplementary NMR data (Figs S1–S15) are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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