Catalytic C−H Insertions Using Iron(III) Porphyrin Complexes

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Fe(III), Cu(II), and Ag(II) porphyrin complexes are active catalysts for benzylic and ring C−H insertions by carbene fragments transferred from methyl diazomalonate, **2**. Temperatures above 100 °C are required, and yields greater than 70% have been achieved. C−H insertions with cyclohexane and tetrahydrofuran are catalyzed at a lower temperature of 60 °C with 60% yields when *para*-substituted methyl 2-phenyldiazoacetates, **15a**−**d**, are used as carbene sources. The rate for Fe(TPP)Cl-catalyzed insertion into the C−H bond of cyclohexane was found to be first-order in the concentration of methyl 2-(*p*-chlorophenyl)diazoacetate, *p*-Cl-MPDA, indicating that formation of a carbene complex is the rate-determining step. Competition reactions for cyclohexane insertion with *para*-substituted methyl 2-phenyldiazoacetates correlated linearly with σ^+ Hammett parameters with a ρ value of -1.11 ± 0.05 when Fe(TPP)Cl was used as a catalyst, demonstrating that electron-donating *para*-substituents on the phenyl group of the methyl 2-aryldiazoacetates enhanced reactivity. These data are consistent with the involvement of an electrophilic iron−carbene complex in the catalytic cycle. A mechanistic model for the iron-mediated C−H insertion reactions is proposed.

Introduction

Transition metal catalyzed decomposition of diazo compounds and subsequent transformations constitute a variety of useful synthetic reactions.[1] For example, cyclopropanation of olefins with diazo compounds has been extensively studied. Iron(II) porphyrins[2] and dirhodium tetracarboxylate complexes[3] are among the most efficient catalysts reported for this reaction. High yields of cyclopropanation products have been achieved with styrene using iron(II) porphyrin complexes.[2] Currently, dirhodium tetracarboxylate complexes are also among the best catalysts for C−H insertion reactions using diazo reagents.[4] Although both iron(II) porphyrin and dirhodium complexes are also efficient and selective catalysts for other reactions such as the epoxidation of olefins,[5] iron porphyrins have not been studied as catalysts for C−H insertion using diazo compounds.

The development of practical methods for catalytic C−H activation has been a long-term goal of the organometallic chemical community.[6] One method for C−H activation involves the use of metal carbene complexes. Impressive advances have been made in asymmetric intramolecular C−H insertions involving diazo compounds.[4] In contrast to numerous studies on intramolecular C−H insertions; the intermolecular analogue has not enjoyed widespread application. Indeed until very recently, these intermolecular C−H insertions were not considered to be of great synthetic utility.[7] A major difficulty with intermolecular reactions is that the most widely studied alkyl diazoacetates are very prone to carbene dimerization.[8] Furthermore, this carbene source exhibits poor chemoselectivity in intermolecular C−H insertions.[9] Consequently, in order for intermolecular C−H insertion to become a convenient method, it is necessary to develop systems with improved chemoselectivity.

In this paper, we report the application of iron(III) porphyrin complexes in catalytic intermolecular C−H insertion using different classes of diazo compounds. The ability of silver(I) scorpionate complexes $(Tp^{Br3}Ag)_2 \cdot CH_3COCH_3$ and $Tp^{Br3}Ag$ (THF) to catalyze the insertion of the carbene fragment from ethyl diazoacetate (EDA) into the saturated C−H bonds of several C_5, C_6, and C_8 linear and branched alkanes, including secondary and tertiary sites,[10] led us to also briefly examine Ag and Cu porphyrins.

Results and Discussion

Diazomalonate Reactions. Dimethyl diazomalonate, **2**, undergoes benzylic C−H insertion with toluene to give dimethyl 2-benzylmalonate (**3a**, eq 1) as the major product when Ag(TPP), Cu(TPP), and Fe(TPP)Cl (TPP ≡ 5,10,15,20-tetraphenylporphyrinato) are used as catalysts.

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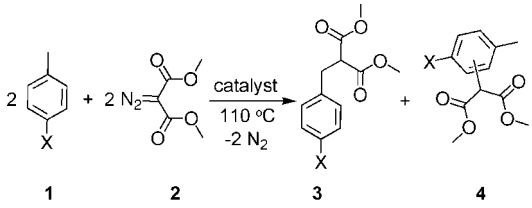


(1)

a, X = H
b, X = Cl
c, X = CH_3

No products were formed when Mn(TPP)Cl, Co(TPP), and Zn(TPP) were tried as catalysts. This reaction was found to require temperatures above 100 °C and 32 to 48 h when 2 mol % catalyst was used. Furthermore, anaerobic conditions were necessary to avoid side reactions that produced uncharacterizable products. The insertion products were identified by ^{1}H NMR spectroscopy and mass spectrometry. For example, formation of dimethyl 2-benzylmalonate, **3a**, was established by ^{1}H NMR with the appearance of a diagnostic two-proton resonance for the benzylic hydrogens at 3.23 (d) ppm. The composition of the product was also verified by its mass of 222 *m*/*z*. The ^{1}H and ^{13}C NMR data for **3a** were found to match literature values.[11] Minor species with masses identical to **3a** were observed by GC/MS. These products were identified by ^{1}H NMR as ring C−H insertion products. Partial separation of the product mixture was achieved by silica gel chromatography using hexane/ethyl acetate (20:1) as the eluent. Compound **3a** could be isolated cleanly, but the toluene ring C−H insertion products *o*-, *p*-**4a** were not separable from each other. The ^{1}H NMR spectrum of the *o*,*p*-mixture gave a broad singlet at 2.35 revealing benzylic CH_3 groups. Furthermore, the ^{1}H NMR signals at 4.63 and 4.92 ppm, in an integrated ratio of 1:1, agree with the methine protons of dimethyl *p*-tolylmalonate[12] and dimethyl *o*-tolylmalonate,[13] respectively, that would result from ring C−H insertions. Reactions with *p*-chlorotoluene **1b** were found to result in lower yields and a higher ratio of benzylic C−H insertion, **3b**, to ring C−H insertion products (10:1) as indicated in Table 1. In this case, the ring C−H insertion products *o*-, *p*-**4b** were minor and detectable by GC, but could not be isolated.

GC yields of the products varied slightly as a function of the catalyst as shown in Table 1. When *p*-xylene was used as the substrate, a benzylic C−H insertion product, dimethyl (*p*-methylbenzyl)malonate (**3c**), was obtained along with a ring C−H insertion product, dimethyl 2,5-xylylmalonate (**4c**), in a ratio of about 5:1, respectively. Benzylic product **3c** could be obtained in relatively pure form, and its ^{1}H NMR spectrum showed signals that matched with literature values.[14] A small amount of dimethyl 2-(2,5-xylyl)malonate, **4c**, was produced but could not be isolated in pure form.

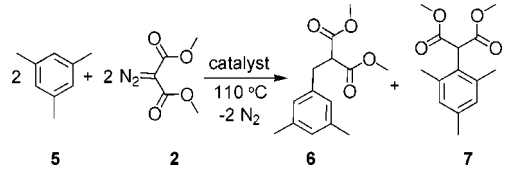
When mesitylene was heated to 110 °C in the presence of 2 mol % catalyst and dimethyl diazomalonate, dimethyl 2-(3,5-dimethylbenzyl)malonate (**6**, eq 2) could be isolated pure in 74% yield. A minor ring C−H insertion product, 2-(mesityl)malonate

Table 1. Summary of Catalytic Reactions with Dimethyl Diazomalonate[a]

entry	substrate	catalyst	products	time (h)	yield[b]	ratio
1	toluene	Fe(TPP)Cl	**3a**:**4a**	54	68	2:1
2	toluene	Ag(TPP)	**3a**:**4a**	54	74	2:1
3	toluene	Cu(TPP)	**3a**:**4a**	54	72	2:1
4	toluene	Fe(TPPF$_{20}$)Cl[c]	**3a**:**4a**	72	51	2:1
5	toluene	ZnTPP	NR[d]	72	NA	NA
6	toluene	CoTPP	NR	72	NA	NA
7	toluene	MnTPPCl	Mixture[e]	72	NA	NA
8	*p*-Cl-toluene	Fe(TPP)Cl	**3b**:**4b**	48	51	10:1
9	*p*-xylene	Fe(TPP)Cl	**3c**:**4c**	32	76	5:1
10	mesitylene	Fe(TPP)Cl	**6**:**7**	32	74	9:1
11	mesitylene	Ag(TPP)	**6**:**7**	32	79	9:1
12	mesitylene	Cu(TPP)	**6**:**7**	32	78	9:1
13	mesitylene	Fe(TPPF$_{20}$)Cl[c]	**6**:**7**	48	56	9:1
14	C_6H_5Cl	Fe(TPP)Cl	**9**:**10**	54	61	2:1
15	C_6H_5Cl	Ag(TPP)	**9**:**10**	54	62	2:1
16	C_6H_5Cl	Cu(TPP)	**9**:**10**	54	58	2:1
17	anisole	Fe(TPP)Cl	**12a**:**13a**	16	74	5:1
18	anisole	Ag(TPP)	**12a**:**13a**	16	78	5:1
19	anisole	Cu(TPP)	**12a**:**13a**	16	75	5:1
20	*p*-Me-anisole[f]	Fe(TPP)Cl	**12b**:**13b**	16	76	8:1

[a] Substrate used as solvent (5 mL), dimethyl diazomalonate (30.0 mg, 0.19 mmol), (TPP)FeCl (2.7 mg, 2 mol %), the mixture thoroughly purged with dry nitrogen, heated at 110 °C with continuous stirring. [b] Combined yields of all products determined by GC. [c] TPPF$_{20}$ = tetrakis(pentafluorophenyl)porphyrinato. [d] No reaction. [e] Several unidentified minor products. [f] *p*-Me-anisole = *p*-methylanisole.

(**7**) was detected by GC and identified by ^{1}H NMR in the product mixture, but could not be isolated in pure form. The 9:1 ratio of **6** to **7** suggested that the ring C−H insertion products could be minimized by steric factors. Reactions run in the absence of catalysts did not yield product **6** or **7**, but other minor, unidentified compounds were detected by GC.



(2)

To explore further ring C−H insertions, other aromatic substrates were examined. Benzene did not undergo reaction, presumably due to its low boiling point. However, chlorobenzene was found to give the *ortho*- (**9**) and *para*-products (**10**) resulting from ring C−H insertions as shown in eq 3. With all catalysts (Table 1), the *ortho/para* product ratios were approximately 2. A third product was detected in trace amounts by GC/MS but could not be isolated. This minor product had a mass identical to those of compounds **9** and **10** (242 *m*/*z*) and is presumably the *meta*-isomer. Surprisingly, when anisole was treated under identical conditions, dimethyl phenoxymalonate, **12a**, was isolated as the major product in a yield of 60% (eq 4). This product had a mass of 224 *m*/*z* and exhibited a new ^{1}H resonance at 5.25 (s) ppm due to the new methine proton. The new carbon α to the oxygen of **12a** produced a ^{13}C NMR signal at 82.29 ppm. A mixture of two minor ring C−H insertion isomers was also obtained from the anisole reaction and

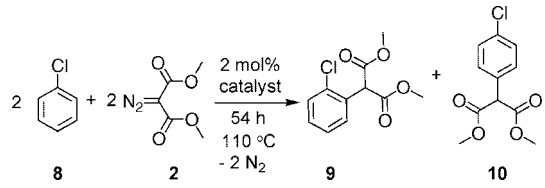


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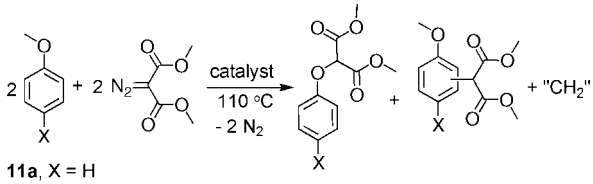
Table 2. Summary of Catalytic Reactions of Substituted Methyl 2-Phenyldiazoacetate Compounds[a]

entry	substrate	catalyst	diazo	products	time (h)	% yield[b]	ratio
1	cyclohexane	Fe(TPP)Cl	**15a**	**16a**	24	66	n/a
2	cyclohexane	Fe(TPP)Cl	**15b**	**16b**	32	58	n/a
3	cyclohexane	Fe(TPP)Cl	**15c**	**16c**	24	72	n/a
4	cyclohexane	Fe(TPP)Cl	**15d**	**16d**	16	78	n/a
5	THF	Fe(TPP)Cl	**15a**	**18a**:**19a**	48	62	3.4:1
6	THF	Fe(TPP)Cl	**15b**	**18b**:**19b**	54	67	3.5:1
7	THF	Fe(TPP)Cl	**15c**	**18c**:**19c**	48	75	3.7:1
8	THF	Fe(TPP)Cl	**15d**	**18d**:**19d**	32	82	3.6:1
9	mesitylene	Fe(TPP)Cl	**15a**	**21a**:**22a**	16	82[c]	1:1.5
10	mesitylene	Fe(TPP)Cl	**15b**	**21b**:**22b**	24	78[c]	1:2.3
11	mesitylene	Fe(TPP)Cl	**15c**	**21c**:**22c**	16	84[c]	1:0.9
12	mesitylene	Fe(TPP)Cl	**15d**	**21d**:**22d**	12	86[c]	1:0.7
13	mesitylene	$Fe(TPPF_{20})Cl$[d]	**15a**	**21a**:**22a**	16	79[c]	1:0.7
14	mesitylene	$Fe(TPPF_{20})Cl$[d]	**15b**	**21b**:**22b**	16	72[c]	1:1.3
15	mesitylene	$Fe(TPPF_{20})Cl$[d]	**15c**	**21c**:**22c**	16	79[c]	1:0.4
16	mesitylene	$Fe(TPPF_{20})Cl$[d]	**15d**	**21d**:**22d**	16	72[c]	1:0.3
17	2,2,4-TMP[e]	Fe(TPP)Cl	**15b**	**24b**:others	54	36[c]	2:1[f]
18	2,2,4-TMP[e]	Fe(TPP)Cl	**15c**	**24c**:others	54	41[c]	3:1[f]
19	2,2,4-TMP[e]	Fe(TPP)Cl	**15d**	**24d**:others	54	46[c]	4:1[f]

[a] Substrate used as solvent (5 mL), substituted methyl phenyldiazoacetates (0.19 mmol), (TPP)FeCl (2.5 mg, 2 mol %), mixture thoroughly flushed with dry nitrogen, heated at 80 °C with continuous stirring. [b] Isolated yields. [c] Combined isolated yields of all products. [d] $TPPF_{20}$ = tetrakis(pentafluorophenyl)-porphyrinato. [e] 2,2,4-TMP = 2,2,4-trimethylpentane. [f] Ratio of major product to all other isomers combined.

constituted a combined yield of about 10%. These two compounds had molecular ion masses of 238 *m*/*z*. The proton NMR spectrum of the minor isomer mixture gave resonances at 4.6 (s) and 5.1 (s) ppm that corresponded to the methine hydrogen of dimethyl *p*-methoxyphenylmalonate[15] and dimethyl *o*-methoxyphenylmalonate,[16] with an integrated ratio of 1:1. *p*-Methylanisole was found to give similar reaction results to anisole (eq 4) in addition to 4% benzylic C−H insertion. Attempts to use *meta*-directing substituents with substrates such as benzonitrile and nitrobenzene resulted in no reactions after 3 days at 110 °C. Nonetheless, given the general success with Fe(TPP)Cl in catalysis, iron porphyrins were utilized in the remainder of this study.



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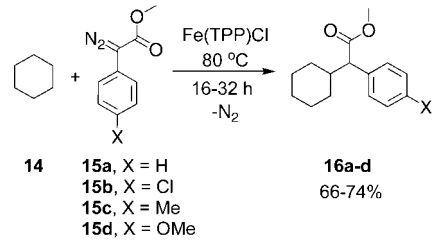
Substituted Methyl 2-Phenyldiazoacetates. Catalytic C−H activation using Fe(TPP)Cl was extended to the chemistry of another class of diazo compounds, substituted methyl 2-phenyldiazoacetates. These diazo reagents contain an electron-withdrawing ester and an electron-donating aryl group on the incipient carbene carbon. The substituents on these compounds result in higher chemoselectivity and lower tendency toward carbene dimerization compared to alkyl diazoacetates.[17] These properties should lead to more proficient intermolecular C−H insertion. The feasibility of the intermolecular C−H insertion reaction was demonstrated by treatment of a series of *p*-substituted methyl 2-phenyldiazoacetates in neat cyclohexane with catalytic amounts of iron porphyrins (eq 5). Yields of the C−H insertion products were found to be about 20% higher,



(5)

and fewer unidentified side products were detected when the reactions were conducted under anaerobic conditions at 60 °C as compared to reactions run under air. C−H insertion products were obtained in yields ranging from 58% to 78%. These yields are comparable to those obtained when dirhodium carboxylate catalysts were used, and ^{1}H NMR data for the products matched literature values.[18] The efficiency of the *p*-substituted methyl 2-phenyldiazoacetates for C−H insertion is in sharp contrast to the results that were obtained when alkyl diazoacetates and dimethyl diazomalonate were used as the carbene sources. The reactions with ethyl diazoacetate or dimethyl diazomalonate did not generate any C−H insertion products with cyclohexane, but a significant amount of butenedioate product is formed in the case of ethyl diazoacetate. Only trace amounts of dimeric carbene products were detected in the reactions with *p*-substituted methyl 2-phenyldiazoacetates.

Extension of the reaction to tetrahydrofuran using Fe(TPP)Cl as a catalyst (eq 6) illustrated that the C−H insertion of *p*-substituted methyl 2-phenyldiazoacetates was highly regioselective (Table 2). No insertion into the β-position of THF was observed. The catalyzed decomposition of *p*-substituted methyl 2-phenyldiazoacetates in the presence of tetrahydrofuran, heated under reflux, resulted in the formation of products **18a**−**d** in yields ranging from 62% to 82%. These products are formed by C−H insertion into the methylene group adjacent to the oxygen atom. A minor ring-opened product, **19a**−**d** (∼20% yield), was also isolated in pure form. These products were

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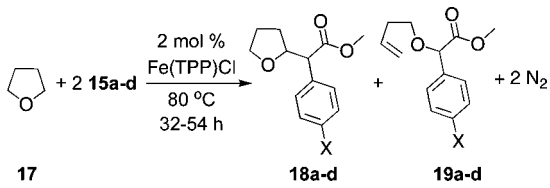
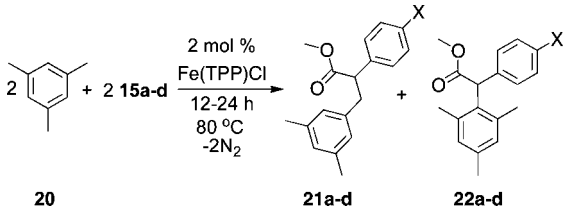


(6)

identified by ^{1}H and ^{13}C NMR spectroscopy. For example, in **19c**, the 3-butenyl fragment exhibited proton signals at 5.84 (m, 1H, vinyl CH), 5.09 (dm, 1H, vinyl CH_2) 5.04 (dm, 1H, vinyl CH_2), 3.57 (m, 1H, methylene CH_2), 3.48 (m, 1H, methylene CH_2), and 2.45 (m, 2H, methylene CH_2). Formation of these ring-opened products likely arises from nucleophilic attack by the THF oxygen on an electron-deficient carbene ligand (*vide infra*) followed by C−O bond cleavage and hydrogen transfer.

Mesitylene was found to undergo reaction at both benzylic C−H and ring C−H positions (eq 7), and the two products were not separable from each other except in the reaction with *p*-MeO-MPDA, **15d**. ^{1}H NMR data from the isolated methoxy-substituted compounds **21d** and **22d** aided in the proton peak



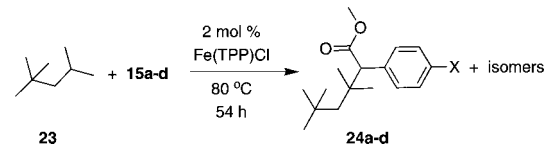
(7)

assignments for the inseparable mixtures. The electronic nature of the *para*-substituent in the substituted methyl 2-phenyldiazoacetates slightly influenced the product ratio. The less electron-donating Cl in methyl 2-(*p*-chlorophenyl)diazoacetate resulted in a ring C−H insertion as the major product, **22**. As the electron donor ability of the aryl substituent was increased, this product decreased. The methoxy substituent produced benzylic C−H insertion as the major product (Table 2, entries 9–12). This suggests that a more electrophilic carbene complex favors ring C−H insertion over benzylic C−H insertion. However, a fluorinated porphyrin iron(III) complex that would result in a more electrophilic carbene intermediate produced anomalous results. Surprisingly, in all cases the ratio of the ring C−H insertion product was significantly lowered, as indicated in Table 2, entries 13–16.

Competition experiments with *p*-MeO-MPDA, **15d**, using cyclohexane and THF in equimolar amounts and 1 mol % Fe(TPP)Cl catalyst loading resulted in the formation of products **16d** (cyclohexane C−H insertion), **18d** (THF C−H insertion), and **19d** (THF ring-opening) in a ratio of 11:4:1, respectively. A similar competition experiment with cyclohexane and mesitylene gave products **16d** (cyclohexane C−H insertion), **21d** (benzylic C−H insertion), and **22d** (aromatic C−H insertion) in a ratio of 2.7:1.2:1, respectively. This indicates that the substrate reactivity using methyl 2-(*p*-methoxyphenyl)diazoacetate follows the trend cyclohexane > mesitylene > THF. This is in contrast to the dirhodium tetraacetate catalyst, which catalyzes the insertion of carbenes from MPDAs, **15a**−**d**, 1700 times faster with THF than for cyclohexane.[18] However, the study also found that, similar to our observations, secondary C−H insertion was more favored than benzylic C−H insertion.

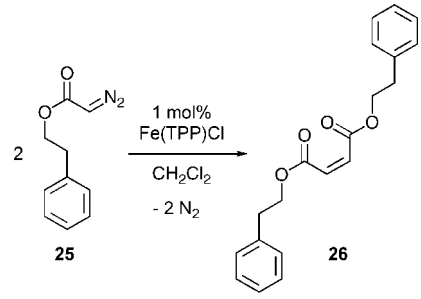
To explore the reactivity profile between primary, secondary, and tertiary sites, the reaction of substituted methyl 2-phenyldiazoacetates with 2,2,4-trimethylpentane was examined. In these reactions a mixture of isomeric C−H insertion products

Scheme 1



was obtained as determined by GC-MS. In each reaction, three GC-MS peaks were observed for compounds with the same molecular masses. In all cases these three isomeric products were not cleanly separable. However, a major isomer was produced and identified in the reaction mixture by ^{1}H NMR spectroscopy. For example, treatment of *p*-MeO-MPDA with 2,2,4-trimethylpentane at 60 °C in the presence of 2 mol % Fe(TPP)Cl resulted in formation of methine C−H insertion species **24d** as the major product (Scheme 1). The newly formed methine proton of the major isomer appeared as a singlet at 3.45 ppm. The lack of coupling of this methine hydrogen to other protons indicated that insertion for the major product occurred at the tertiary site of the substrate. Isomers formed by insertion at primary and secondary sites would result in splitting of the new methine resonance due to three-bond proton–proton coupling. It was not possible to clearly identify the minor isomers by either GC or NMR methods. The ratio of tertiary C−H insertion to all other insertion products combined was 4:1. The selectivity for tertiary insertion decreased as the electron-withdrawing nature at the *para*-position of the diazo reagent increased (Table 2). These trends are consistent with C−H insertions occurring via an electrophilic transition state.

An attempt to effect an intramolecular benzylic C−H insertion with 2-phenylethyldiazoacetate, **25**, resulted in formation of a carbene dimer product, **26** (eq 8), at both ambient temperature



(8)

and 40 °C. The reaction progress was monitored by ^{1}H NMR spectroscopy. Loss of the singlet at 3.96 ppm for the proton attached to the diazo carbon was accompanied by the appearance of a new vinyl proton NMR signal at 6.23 ppm. This dimer formed even when a very dilute solution of substrate was used, and in all cases only one geometric isomer was observed. The vinyl signal at 6.23 ppm identifies the product as the *Z*-isomer, in agreement with the olefin signal of diethyl maleate at 6.2 ppm. In comparison, the diethyl fumarate (*E*-isomer) vinyl signal is observed at 6.8 ppm. The absence of cyclized product is in contrast to the use of Rh(II) acetates as catalysts, where a similar substrate resulted in intramolecular C−H insertion at the benzylic carbon to give a substituted lactone.[19]

In another effort toward catalyzing an intramolecular reaction, 1-(2-methylphenyl)-2-diazo-1,3-butanedione, **27**, was examined and found to be unreactive at ambient temperature in the presence of Fe(TPP)Cl. However, refluxing conditions in toluene produced 46% of 2-methylbenzaldehyde **28** along with other

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Scheme 2

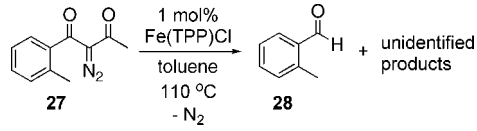
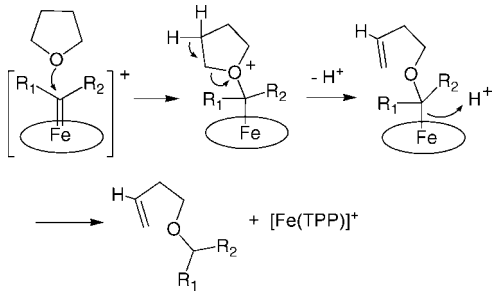


Table 3. Competition Reactions of Cyclohexane with *p*-Substituted Methyl 2-Phenyldiazoacetates Using Fe(TPP)Cl and Fe(TPPF$_{20}$)Cl as a Catalyst[a]

p-substituent	σ^+	Fe(TPP)Cl k_x/k_H	Fe(TPPF$_{20}$)Cl k_x/k_H
OMe	−0.78	8.7	5.53
Me	−0.31	2.2	1.89
Cl	0.11	0.9	1.03

[a] Substrate used as solvent (10 mL), methyl 2-phenyldiazoacetate (30.6 mg, 0.17 mmol), equivalent amount of substituted methyl 2-phenyldiazoacetate, *p*-X-MPDA (0.17 mmol), (TPP)FeCl (2.40 mg, 2.0 mol %), or (TPPF$_{20}$)FeCl (3.60 mg, 2.0 mol %), reaction stirred at 70 °C for 8 h.

Scheme 3



unidentified products (Scheme 2). The presence of a signal of a ^{1}H NMR signal at 10.27 ppm from a sample of the reaction mixture indicated the presence of the aldehyde. Co-injection of the reaction mixture with authentic aldehyde **28** confirmed the results. The NMR spectrum of product was also found to be identical with that of the authentic aldehyde.

Mechanistic Studies. Initial rates for C−H insertion with cyclohexane catalyzed by Fe(TPP)Cl were determined under pseudo-first-order conditions at 70 °C with different concentrations of *p*-Cl-MPDA. The rates were found to be first-order with respect to the concentration of the diazo compound (0.095 mM, 3.70 ± 0.4 μM/h; 0.19 mM, 7.2 ± 0.4 μM/h; 0.29 mM, 10.3 ± 0.6 μM/h). This confirmed that the loss of N_2 and concomitant formation of a metal carbene complex is the rate-determining step. This concurs well with homogeneous metal catalyzed C−H activation via diazocarbonyl reagents, which are generally assumed to involve an intermediate metal carbene complex, produced by metal-mediated extrusion of nitrogen from the diazo compound, followed by concerted C−H activation and C−C bond formation.[18] DFT and saturation kinetics studies using dirhodium tetracarboxylate catalysts suggested that the rate-determining step is either nitrogen extrusion when highly reactive substrates are involved or insertion into the C−H bond when less reactive substrates are used.[20,21]

Competition experiments with substituted methyl 2-phenyldiazoacetates were used to investigate the electronic effects on cyclohexane C−H activation using Fe(TPP)Cl and its fluorinated analogue, Fe(TPPF$_{20}$)Cl, as catalysts (Table 3). Methyl 2-phenyldiazoacetates with electron-donating *p*-substituents were

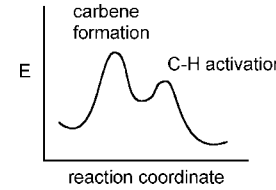


Figure 1. Energy profile of the Fe(TPP)Cl-catalyzed reaction of methyl (*p*-chlorophenyl)diazoacetate with cyclohexane.

more effective reagents for C−H insertion with either of the catalysts. A Hammett analysis showed a stronger correlation to σ^+ (R = 0.99) than to σ (R = 0.59) for Fe(TPP)Cl. Similar correlations were obtained for Fe(TPPF$_{20}$)Cl (σ^+, R = 0.98; σ, R = 0.59). The ρ value of –1.11 ± 0.05 for Fe(TPP)Cl and –0.82 for Fe(TPPF$_{20}$)Cl suggests that the C−H insertion involves a positive charge buildup in the transition state. In both complexes, this charge buildup is stabilized by resonance with the *para*-substituents. The electrophilic nature of the carbene intermediate is also supported by its selectivity toward tertiary C−H groups and the 2-position of tetrahydrofuran. These sites are best suited to stabilizing a positive charge buildup. Additional support for the intermediate electrophilic carbene complex is provided by the formation of minor ring-opened products in the Fe(TPP)Cl-catalyzed reaction of THF with *p*-substituted methyl 2-phenyldiazoacetates (eq 6). It is likely that these side reactions occur by nucleophilic attack of the THF oxygen on an electron-deficient carbene ligand coordinated to Fe(TPP). Subsequent C−O bond cleavage and hydrogen transfer produces the butenyl fragment (Scheme 3). Moreover, the intermediate electrophilic carbene complex is unreactive toward aryl substrates with electron-withdrawing groups such as benzonitrile and nitrobenzene.

The C−H insertion process was found to exhibit a kinetic isotope effect (KIE) of 1.97 ± 0.03 when a 1:1 mixture of cyclohexane and d_{12}-cyclohexane was heated at 70 °C with methyl 2-(*p*-methoxyphenyl)diazoacetate and catalytic amounts of Fe(TPP)Cl. The KIEs were also measured for methyl 2-(*p*-tolyl)diazoacetate (1.96 ± 0.03) and methyl 2-(*p*-methoxyphenyl)diazoacetate (1.97 ± 0.03). This indicates that after the rate-determining step to form a carbene complex, a subsequent C−H activation process occurs in which the C−H bond is partially broken (Figure 1).

Several theories exist for the reaction mechanism of transition metal catalyzed carbine insertion, including Taber's four-centered hypothesis,[22,23] Doyle's three-centered concerted bond formation process,[24] Davies's concerted yet nonsynchronous process,[25] and Pirrung's stepwise pathway.[26] The generally accepted mechanism for intermolecular C−H insertions involves the direct three-centered interaction between the carbene complex and the C−H bond.[18,27,28] The kinetic isotope effect of 1.97 ± 0.03 that was observed for the Fe(TPP)Cl-catalyzed process is most consistent with a C−H insertion that occurs in a concerted but nonsynchronous manner with buildup of positive

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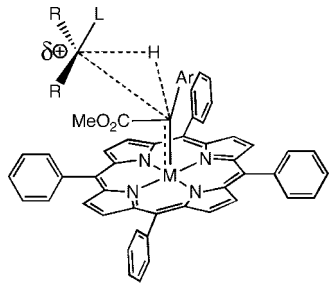
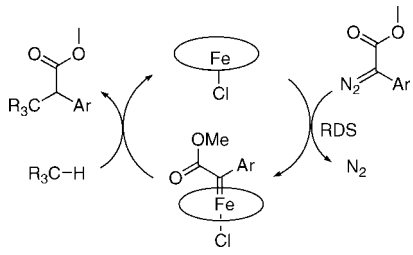
Scheme 4



Scheme 5



charge at the reacting carbon of the substrate (Scheme 4).[18,29] The overall mechanism involves metalloporphyrin-mediated extrusion of N_2 in the slow step to form a metal carbene complex followed by insertion of the carbene fragment between a C−H bond in a concerted step to regenerate the active catalyst (Scheme 5).

Conclusions

Ag(II), Cu(II), and Fe(III) porphyrins serve as effective catalysts for C−H activation and provide a general method for insertion of carbene fragments from diazo reagents into aromatic and aliphatic C−H bonds with high yields. Reactions can be run conveniently in one pot without the need for slow addition of the diazo compound and with a low catalyst loading of 1–2%. The Fe(TPP)Cl complex, easily prepared and also commercially available, can be used to achieve this useful and simple catalytic process. Initial rates for reactions with cyclohexane catalyzed by Fe(TPP)Cl were found to be first-order with respect to *p*-Cl-MPDA. This indicates that the slow step is formation of a reactive carbene intermediate coordinated to the iron porphyrin. The reaction of MPDAs with cyclohexane was found to exhibit a kinetic isotope effect of 1.97 ± 0.03. This indicates that after the rate-determining step a product-forming step subsequently occurs in which the substrate C−H bond is partially broken. Hammett studies on the reaction of substituted MPDAs with cyclohexane support the involvement of an electrophilic carbene complex. On the basis of these mechanistic studies and reactivity trends, the C−H activation step in these Fe(TPP)Cl-catalyzed insertion reactions appears to involve a concerted, nonsynchronous process.[30]

Experimental Section

Fe(TPP)Cl was obtained from Aldrich. Ag(TPP) and Cu(TPP) were synthesized using literature methods.[31] Toluene was deoxygenated and dried by passage through columns of reduced copper and alumina as described by Grubb's et al.[32] Dimethyl diazomalonate was prepared by transferring a diazo group from tosylazide to dimethylmalonate under basic conditions.[33] Substituted methyl 2-phenyldiazoacetates were prepared as outlined in the literature.[34] Synthesis of 2-phenyleth-1-yl diazoacetate (**25**) was done using a literature method.[35] Proton NMR and ^{13}C NMR spectra were run in $CDCl_3$ and recorded on a Varian VXR 300 or a Bruker DRX400 spectrometer. ^1H NMR peak positions were referenced against residual proton resonances of $CDCl_3$ (δ, 7.27). Gas chromatographic analysis was performed on a HP 5890 series II or a Finnigan GC-MS instrument. Dodecane was used as an internal standard. All reactions were performed under an atmosphere of nitrogen.

General Procedure for C−H Insertion Reactions. About 30.0 mg of the diazo reagent were accurately weighed and placed in a 50 mL round-bottom flask containing a stir bar. A condenser, fitted with a rubber septum, was then attached to the round-bottom flask, and the contents were thoroughly flushed with nitrogen. A catalyst (1–2 mol %) was placed in a separate flask, dissolved in 5 mL of substrate, and the contents were bubbled with dry nitrogen for 15 min. This solution was transferred to the diazo reagent by a cannula. The mixture was then heated to an appropriate temperature while stirring until the diazo reagent was consumed. The products were separated or purified by eluting on a silica gel column (4 cm diameter, 30 cm, hexane/ethyl acetate, 20:1).

Dimethyl Diazomalonate Insertion with Toluene. The general procedure was used with dimethyl diazomalonate (30.5 mg, 0.193 mmol), (TPP)FeCl (2.70 mg, 1.99 mol %), and 5.0 mL of toluene. The mixture was stirred at 110 °C for 54 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. Pure benzylic C−H insertion product dimethyl-2-benzylmalonate, **3a** (23.0 mg, 0.104 mmol, 53.7% yield based on dimethyl diazomalonate), was obtained as a yellow oil. The proton NMR and ^{13}C NMR spectra matched literature values.[11] A mixture of dimethyl *p*-tolylmalonate[12] and dimethyl *o*-tolylmalonate[13] (6.10 mg, 0.0275 mmol, 14.2% yield based on dimethyl diazomalonate) was obtained but not separable.

Dimethyl Diazomalonate Insertion with *p*-Chlorotoluene. The general procedure was used with dimethyl diazomalonate (30.2 mg, 0.191 mmol), (TPP)FeCl (2.60 mg, 1.93 mol %), and 5.0 mL of *p*-chlorotoluene. The mixture was stirred at 110 °C for 48 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. Pure benzylic C−H insertion product dimethyl (*p*-chlorobenzyl)malonate, **3b** (24.8 mg, 0.0969 mmol, 50.7% yield based on dimethyl diazomalonate), was obtained as a yellow oil. The proton NMR and ^{13}C NMR spectra matched literature values.[36] Small amounts of ring C−H insertion products were detected on GC but not isolatable.

Dimethyl Diazomalonate Insertion with *p*-Xylene. The general procedure was used with dimethyl diazomalonate (30.5 mg, 0.193 mmol), (TPP)FeCl (2.70 mg, 1.99 mol %), and 5.0 mL of *p*-xylene. The mixture was stirred at 110 °C for 32 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. A mixture of the benzylic C−H insertion product dimethyl (*p*-methylbenzyl)malonate, **3c**, and ring C−H insertion product dimethyl 2,5-xylylmalonate, **4c** (34.4 mg, 0.146 mmol, 75.5% yield based on dimethyl diazomalonate), was obtained as a yellow oil. Although it was possible to get a pure portion of the major product dimethyl (*p*-methylbenzyl)malonate,

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3c, the minor ring C−H product **4c** was not obtained in pure form. The proton NMR and ^{13}C NMR spectra of the benzylic C−H product matched literature values.[36] Ring insertion product **4c**: ^{1}H NMR (400 MHz): δ 7.19 (b, 1H, aryl-H), 7.10–7.04 (m, 2H, aryl-H), 4.89 (s, 1H, methine C-H), 3.77 (s, 3H, OCH_3), 2.33 (s, 3H, Ar-CH_3), 2.30 (s, 3H, Ar-CH_3). MS{EI}: 236 $[M]^+$, 205 [M − (OMe)], 175 [M − HCO_2Me].

Dimethyl Diazomalonate Insertion with Mesitylene. The general procedure was used with dimethyl diazomalonate (30.4 mg, 0.192 mmol), (TPP)FeCl (2.70 mg, 2.00 mol %), and 5.0 mL of mesitylene. The mixture was stirred at 110 °C for 32 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. Pure benzylic C−H insertion product 3,5-dimethyl 2-(3,5-dimethylbenzyl)malonate, **6**, was obtained as a yellow oil (35.4 mg, 0.142 mmol, 73.8% yield based on dimethyl diazomalonate). The proton NMR and ^{13}C NMR spectra matched literature values.[37] Small amounts of ring C−H insertion products were detected by GC but were not isolated.

Dimethyl Diazomalonate Insertion with Chlorobenzene. The general procedure was used with dimethyl diazomalonate (30.6 mg, 0.194 mmol), (TPP)FeCl (2.70 mg, 1.98 mol %), and 5.0 mL of chlorobenzene. The mixture was stirred at 110 °C for 54 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. Pure dimethyl-*o*-chlorophenylmalonate, **9** (18.2 mg, 0.0752 mmol, 38.8% yield based on dimethyl diazomalonate), and dimethyl-*p*-chlorophenylmalonate, **10** (10.2 mg, 0.0421 mmol, 21.7% yield based on dimethyl diazomalonate), were obtained. The ^{1}H NMR and ^{13}C NMR spectra matched literature values.[15,16]

Dimethyl Diazomalonate Insertion with Anisole. The general procedure was used with dimethyl diazomalonate (30.7 mg, 0.194 mmol), (TPP)FeCl (2.70 mg, 1.98 mol %), and 5.0 mL of anisole. The mixture was stirred at 110 °C for 16 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The major product dimethyl phenoxymalonate, **12a** (27.7 mg, 0.124 mmol, 63.7% yield based on dimethyl diazomalonate), was obtained in pure form as a white solid. Small amounts of ring C−H insertion products were detected on GC but not isolatable. ^{1}H NMR (400 MHz) δ: 7.30 (m, 2H, aryl-H), 7.03 (m, 1H, aryl-H), 6.95 (m, 2H, aryl-H), 5.25 (s, 1H methine-CH), 3.84 (s, 6H, OCH_3). ^{13}C NMR (100.5 MHz) δ: 166.2, 157.0, 130.0, 123.0, 115.6, 82.3, 53.5. MS{EI}: 224 $[M]^+$. Anal. Found (calcd): C 58.62 (58.93), H 4.92 (5.39).

Dimethyl Diazomalonate Insertion with *p*-Methylanisole. The general procedure was used with dimethyl diazomalonate (30.5 mg, 0.193 mmol), (TPP)FeCl (2.60 mg, 1.91 mol %), and 5.0 mL of *p*-methylanisole. The mixture was stirred at 110 °C for 32 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The major product dimethyl *p*-methylphenoxymalonate, **12b** (31.2 mg, 0.131 mmol, 67.9% yield based on dimethyl diazomalonate), was obtained along with 4% benzylic C−H insertion product. Small amounts of ring C−H insertion products were also detected on GC but not isolatable. ^{1}H NMR (400 MHz) δ: 7.10 (m, 2H, aryl-H), 6.84 (m, 2H, aryl-H), 5.21 (s, 1H methine-*H*), 3.84 (s, 6H, OCH_3), 2.28 (s, 3H, aryl-CH_3). ^{13}C NMR (100.5 MHz) δ: 166.3, 155.0, 132.4, 130.4, 115.6, 76.8, 53.5, 20.7. MS{EI}: 238 $[M]^+$. HRMS: 242.2249, calcd 242.2256.

Methyl 2-Phenyldiazoacetate Insertion with Cyclohexane. The general procedure was used with methyl 2-phenyldiazoacetate (30.1 mg, 0.171 mmol), (TPP)FeCl (2.50 mg, 2.08 mol %), and 5.0 mL of cyclohexane. The mixture was stirred at 80 °C for 24 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl cyclohexylphenylacetate, **16a** (26.2 mg, 0.113 mmol, 66.0% yield based on methyl 2-phenyldiazoacetate), was obtained. The proton NMR and ^{13}C NMR spectra matched literature values.[18]

Methyl 2-(*p*-Chlorophenyl)diazoacetate Insertion with Cyclohexane. The general procedure was used with methyl 2-(*p*-chlorophenyl)diazoacetate (30.6 mg, 0.145 mmol), (TPP)FeCl (2.20 mg, 2.16 mol %), and 5.0 mL of cyclohexane. The mixture was stirred at 80 °C for 32 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl cyclohexyl-4-chloro-phenylacetate, **16b** (26.2 mg, 0.0985 mmol, 67.9% yield based on methyl 2-(*p*-chlorophenyl)diazoacetate), was obtained. (80% purity) The proton NMR and ^{13}C NMR matched literature values.[18]

Methyl 2-(*p*-Tolyl)diazoacetate Insertion with Cyclohexane. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (30.3 mg, 0.159 mmol), (TPP)FeCl (2.20 mg, 1.97 mol %), and 5.0 mL of cyclohexane. The mixture was stirred at 80 °C for 24 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl cyclohexyl-4-methyl-phenylacetate, **16c** (28.2 mg, 0.114 mmol, 71.5% yield based on methyl 2-(*p*-tolyl)diazoacetate), was obtained. The proton NMR and ^{13}C NMR spectra matched literature values.[18]

Methyl 2-(*p*-Methoxyphenyl)diazoacetate Insertion with Cyclohexane. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (30.4 mg, 0.148 mmol), (TPP)FeCl (2.20 mg, 2.11 mol %), and 5.0 mL of cyclohexane. The mixture was stirred at 80 °C for 16 h. The products were isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl cyclohexyl-4-methoxyphenylacetate, **16d** (30.2 mg, 0.115 mmol, 77.9% yield based on methyl 2-(*p*-methoxyphenyl)diazoacetate), was obtained. The proton NMR and ^{13}C NMR spectra matched literature values.[18]

Methyl 2-Phenyldiazoacetate Insertion with THF. The general procedure was used with methyl 2-(phenyl)diazoacetate (30.2 mg, 0.172 mmol), (TPP)FeCl (2.20 mg, 1.82 mol %), and 10.0 mL of tetrahydrofuran. The mixture was stirred at 80 °C for 48 h. The products were separated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-phenyl-2-(tetrahydrofuran-2-yl)acetate, **18a** (21.9 mg, 0.100 mmol, 58.4% yield based on methyl 2-phenyldiazoacetate), and **19a** (6.40 mg, 0.0293 mmol, 17.1% yield based on methyl 2-phenyldiazoacetate) were obtained. The proton NMR and ^{13}C NMR spectra for **18a** matched literature values.[18] Minor product **19a**: ^{1}H NMR (400 MHz) δ: 7.46 (m, 2H, aryl-H), 7.27–7.37 (m, 3H, aryl-H), 5.83 (m, 1H, vinyl-CH), 5.10 (m, 1H, geminal-CH_2), 5.04 (m, 1H, geminal-CH_2), 4.90 (s, 1H, benzylic C-H), 3.72 (s, 3H, OCH_3), 3.60 (m, 1H, CH_2), 3.49 (m, 1H, CH_2), 2.43 (m, 2H, CH_2). HRMS: 218.13071, calcd 218.13068.

Methyl 2-(*p*-Chlorophenyl)diazoacetate Insertion with THF. The general procedure was used with methyl 2-(*p*-chlorophenyl) diazoacetate (30.4 mg, 0.144 mmol), (TPP)FeCl (2.20 mg, 2.17 mol %), and 10.0 mL of tetrahydrofuran. The mixture was stirred at 80 °C for 54 h. The products were separated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 4-chlorophenyl(tetrahydrofuran-2-yl)acetate, **18b** (19.1 mg, 0.0752 mmol, 52.2% yield based on methyl 2-(*p*-chloro)diazoacetate), and **19b** (5.50 mg, 0.0216 mmol, 15.0% yield based on methyl 2-phenyldiazoacetate) were obtained. The proton NMR and ^{13}C NMR spectra of **18b** matched literature values.[18] Minor product **19b**: ^{1}H NMR (400 MHz) 7.40 (d, 2H, J_H = 8.8), 7.34 (d, 2H, J_H = 8.8), 5.82 (m, 1H, vinyl-CH), 5.15 (m, 1H, geminal-CH_2), 5.05 (m, 1H, geminal-CH_2), 4.87 (s, 1H, benzyl C-H), 3.72 (s, 3H, OCH_3), 3.60 (m, 1H, CH_2), 3.48 (m, 1H, CH_2), 2.42 (dd, 2H, J_H = 6.8, CH_2). ^{13}C NMR (100.5 MHz) δ: 171.0, 135.0, 134.6, 131.6, 128.9, 128.5, 116.8, 80.4, 69.4, 52.4, 34.0. HRMS: 252.09187, calcd 252.09171.

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Methyl 2-(*p*-Tolyl)diazoacetate Insertion with THF. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (30.3 mg, 0.159 mmol), (TPP)FeCl (2.20 mg, 1.97 mol %), and 10.0 mL of tetrahydrofuran. The mixture was stirred at 80 °C for 48 h. The product was isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl-4-methylphenyl(tetrahydrofuran-2-yl)acetate, **18c** (22.2 mg, 0.949 mmol, 59.7% yield based on methyl 2-(*p*-tolyl)diazoacetate), and **19c** (6.00 mg, 0.0256 mmol, 16.1% yield based on methyl 2-(*p*-tolyl)diazoacetate) were obtained. The proton NMR and ^{13}C NMR spectra for **18c** matched literature values.[18] Minor product **19c**: ^1H NMR (400 MHz) δ: 7.35 (d, 2H, $J_H = 8.0$, aryl-H), 7.18 (d, 2H, $J_H = 8.0$, aryl-H), 5.83 (m, 1H, vinyl-CH), 5.09 (m, 1H, geminal-CH_2), 5.04 (m, 1H, geminal-CH_2), 4.87 (s, 1H, benzylic-CH), 3.72 (s, 3H, OCH_3), 3.58 (m, 1H, CH_2), 3.48 (m, 1H, CH_2), 2.42 (m, 2H, CH_2), 2.36 (s, 3H, Ar-CH_3). ^{13}C NMR (100.5 MHz) δ: 171.7, 138.8, 134.9, 133.7, 129.5, 127.4, 116.9, 81.1, 69.3, 52.5, 34.3, 21.5. Anal. Found (calcd): C 71.44 (71.77), H 7.46 (7.74).

Methyl 2-(*p*-Methoxyphenyl)diazoacetate Insertion with THF. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (30.4 mg, 0.148 mmol), (TPP)FeCl (2.20 mg, 2.11 mol %), and 10.0 mL of tetrahydrofuran. The mixture was stirred at 80 °C for 32 h. The products were separated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The products methyl-4-methoxyphenyl(tetrahydrofuran-2-yl)acetate, **18d** (23.6 mg, 0.0944 mmol, 63.8% yield based on methyl 2-(*p*-methoxyphenyl)diazoacetate), and **19d** (6.60 mg, 0.0264 mmol, 17.8% yield based on methyl 2-(*p*-methoxyphenyl) diazoacetate) were obtained. The proton NMR and ^{13}C NMR spectra for **18d** matched literature values.[18] Minor product **19d**: ^1H NMR (400 MHz): 7.37 (d, 2H, $J_H = 8.7$, aryl-H), 6.90 (dd, 2H, $J_H = 8.7$, aryl-H), 5.82 (m, 1H, vinyl-CH), 5.08 (m, 1H, geminal-CH_2), 5.03 (m, 1H, geminal-CH_2), 4.85 (s, 1H, benzylic C-H), 3.80 (s, 3H, $ArOCH_3$), 3.72 (s, 3H, OCH_3), 3.52 (m, 2H, CH_2), 2.41 (m, 2H, CH_2). ^{13}C NMR (100.5 MHz) δ: 171.8, 160.1, 134.9, 128.9, 128.8, 116.8, 114.2, 80.8, 69.2, 55.5, 52.4, 34.2. HRMS: 250.12087; Calcd. 250.12051.

Methyl 2-Phenyldiazoacetate Insertion with Mesitylene. The general procedure was used with methyl 2-phenyldiazoacetate (30.6 mg, 0.174 mmol), (TPP)FeCl (2.40 mg, 1.96 mol %), and 5.0 mL of mesitylene. The mixture was stirred at 80 °C for 16 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. A mixture of the benzylic C−H insertion product, **21a**, and the ring C−H insertion product, **22a** (38.2 mg, 0.143 mmol, 81.9% yield based on methyl methyl 2-phenyldiazoacetate), was obtained. Benzylic C−H insertion product **21a**: ^1H NMR (400 MHz) δ: 7.24–7.38 (m, 5H, aryl-H), 6.83 (s, 1H, aryl-H), 6.75 (s, 2H, aryl-H), 3.85 (dd, 1H, $J_H = 9.2$, $J_H = 6.0$, methine C-H), 3.61 (s, 3H, O-CH_3), 3.45 (dd, 1H, $J_H = 13.6$, $J_H = 9.2$, Ar-CH_2), 2.95 (dd, 1H, $J_H = 13.6$, $J_H = 6.0$, Ar-CH_2), 2.26 (s, 6H, Ar-CH_3). Ring C−H insertion product **22a**: ^1H NMR (400 MHz) δ: 7.22–7.32 (m, 3H, aryl-H), 7.11 (m, 2H, aryl-H), 6.93 (s, 2H, aryl-H), 5.39 (s, 1H, methine C-H), 3.74 (s, 3H, OCH_3), 2.32 (s, 3H, Ar-CH_3), 2.26 (s, 6H, Ar-CH_3).

Methyl 2-(*p*-Chlorophenyl)diazoacetate Insertion with Mesitylene. The general procedure was used with methyl 2-(*p*-chlorophenyl)diazoacetate (30.3 mg, 0.144 mmol), (TPP)FeCl (2.10 mg, 2.07 mol %), and 5.0 mL of mesitylene. The mixture was stirred at 80 °C for 24 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. A mixture of the benzylic C−H insertion product, **21b**, and the ring C−H insertion product, **22b** (33.9 mg, 0.112 mmol, 78.0% yield based on methyl 2-(*p*-chlorophenyl)diazoacetate), was obtained. Benzylic C−H insertion product **21b**: ^1H NMR (300 MHz) δ: 7.44 (d, 2H, $J_H = 8.7$ aryl-H), 7.37 (d, 2H, $J_H = 8.7$ aryl-H), 6.83 (s, 1H, aryl-H), 6.72 (s, 2H, aryl-H), 3.82 (dd, 1H, $J_H = 8.8$, $J_H = 5.6$, methine C−H), 3.62 (s, 3H, O-CH_3), 3.33 (dd, 1H, $J_H = 13.5$, $J_H = 8.7$, Ar-CH_2), 2.91 (dd, 1H, $J_H = 13.5$, $J_H = 6.6$, Ar-CH_2), 2.26 (s, 6H, Ar-CH_3). Ring C−H insertion product **22b**: ^1H NMR (300 MHz) δ: 7.25 (d, 2H, $J_H = 8.7$, aryl-H), 7.06 (d, 2H, $J_H = 8.7$, aryl-H), 6.92 (s, 2H, aryl-H), 5.32 (s, 1H, methine C-H), 3.74 (s, 3H, OCH_3), 2.31 (s, 3H, Ar-CH_3), 2.16 (s, 6H, Ar-CH_3).

Methyl 2-(*p*-Tolyl)diazoacetate Insertion with Mesitylene. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (30.7 mg, 0.162 mmol), (TPP)FeCl (2.30 mg, 2.02 mol %), and 5.0 mL of mesitylene. The mixture was stirred at 80 °C for 16 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. A mixture of the benzylic C−H insertion product, **21c**, and the ring C−H insertion product, **22c** (38.9 mg, 0.138 mmol, 85.1% yield based on methyl methyl 2-(*p*-tolyl)diazoacetate), was obtained. Benzylic C−H insertion product **21c**: ^1H NMR (400 MHz) δ: 7.24 (d, 2H, $J_H = 8.4$, aryl-H), 7.15 (d, 2H, $J_H = 8.4$, aryl-H), 6.84 (s, 1H, aryl-H), 6.78 (s, 2H, aryl-H), 3.84 (dd, 1H, $J_H = 9.2$, $J_H = 6.0$, methine C−H), 3.61 (s, 3H, OCH_3), 3.36 (dd, 1H, $J_H = 13.6$, $J_H = 9.2$, Ar-CH_2), 2.93 (dd, 1H, $J_H = 13.6$, $J_H = 6.0$, Ar-CH_2), 2.35 (s, 3H, Ar-CH_3), 2.28 (s, 6H, Ar-CH_3). Ring C−H insertion product **22c**: ^1H NMR ($CDCl_3$) δ: 7.11 (d, 2H, $J_H = 8.4$, aryl-H), 7.01 (d, 2H, $J_H = 8.4$, aryl-H), 6.93 (s, 2H, aryl-H), 5.35 (s, 1H, methine C−H), 3.74 (s, 3H, O-CH_3), 2.34 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.19 (s, 6H, Ar-CH_3).

Methyl 2-(*p*-Methoxyphenyl)diazoacetate Insertion with Mesitylene. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (30.5 mg, 0.148 mmol), (TPP)FeCl (2.30 mg, 2.21 mol %), and 5.0 mL of mesitylene. The mixture was stirred at 80 °C for 12 h. The products were partially isolated by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. A mixture of the benzylic C−H insertion product, **21d**, and the ring C−H insertion product, **22d** (37.9 mg, 0.127 mmol, 85.9% yield based on methyl 2-(*p*-methoxyphenyl)diazoacetate), was obtained. Benzylic C−H insertion product **21d**: ^1H NMR (400 MHz) δ: 7.25 (d, 2H, $J_H = 8.8$, aryl-H), 6.86 (d, 2H, $J_H = 8.8$, aryl-H), 6.82 (b, 1H, aryl-H), 6.75 (b, 2H, aryl-H), 3.81 (dd, 1H, $J_H = 9.1$, $J_H = 6.3$, methine C−H,), 3.80 (s, 3H, $ArOCH_3$), 3.61 (s, 3H, CO_2CH_3), 3.33 (dd, 1H, $J_H = 13.8$, $J_H = 9.1$, Ar-CH_2), 2.92 (dd, 1H, $J_H = 13.8$, $J_H = 6.3$, Ar-CH_2), 2.26 (s, 6H, Ar-CH_3). ^{13}C NMR (100.5 MHz) δ: 174.3, 158.9, 139.1, 137.8, 131.1, 129.0, 128.0, 126.8, 55.3, 52.8, 51.9, 39.8, 30.6, 21.3. Anal. Found (calcd): C 76.20 (76.48), H 7.41 (7.43). Ring C−H insertion product **22d**: ^1H NMR (400 MHz) δ: 7.05 (d, 2H, $J_H = 8.8$, aryl-H), 6.93 (b, 2H, aryl-H), 6.84 (d, 2H, $J_H = 8.8$ aryl-H), 5.32 (s, 1H, methine C-H), 3.80 (s, 3H, $ArOCH_3$), 3.74 (s, 3H, CO_2CH_3), 2.32 (s, 3H, Ar-CH_3), 2.19 (s, 6H, Ar-CH_3). ^{13}C NMR (100.5 MHz) δ: 174.2, 158.4, 137.3, 136.8, 132.6, 129.9, 129.8, 128.6, 113.6, 55.3, 52.3, 50.0, 21.0, 20.8. Anal. Found (calcd): C 76.56 (76.48), H 7.36 (7.43).

Methyl 2-(*p*-Methoxyphenyl)diazoacetate Insertion with 2,2,4-Trimethylpentane. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (30.4 mg, 0.148 mmol), (TPP)FeCl (2.20 mg, 2.11 mol %), and 10.0 mL of 2,2,4-trimethylpentane. The mixture was stirred at 80 °C for 54 h. The major product, methine C−H insertion, **24d**, with 20% of the other C−H insertion products was obtained by eluting through a silica gel column using a 30:1 hexane/ethyl acetate mixture (20.5 mg, 0.0702 mmol 47.4% yield based on methyl 2-(*p*-methoxyphenyl) diazoacetate). ^1H NMR (400 MHz) δ: 7.31 (d, 2H, $J_H = 8.8$, aryl-H), 6.84 (d, 2H, $J_H = 8.8$, aryl-H), 3.80 (s, 3H, $ArOCH_3$), 3.63 (s, 3H, CO_2CH_3), 3.45 (s, 1H, methine C-H), 1.53 (d, 1H, $J_H = 14.4$, $-CH_2-$), 1.29 (d, 2H, $J_H = 14.4$, $-CH_2-$), 1.12 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.98 (s, 9H, CH_3). ^{13}C NMR (100.5 MHz) δ: 174.0, 158.7, 131.4, 129.0, 113.1, 62.3, 55.2, 51.9, 51.3, 38.8, 32.2,

26.0. MS{EI}: 292 $[M]^+$, 233 [M − OCOMe], 180 [M − $C(CH_3)_3CH_2C(CH_3)_2$]. HRMS: 292.20347, calcd 292.20304.

Methyl 2-(*p*-Chloro)diazoacetate Insertion with 2,2,4-Trimethylpentane. The general procedure was used with methyl 2-(*p*-chlorophenyl)diazoacetate (30.6 mg, 0.145 mmol), (TPP)FeCl (2.10 mg, 2.06 mol %), and 10.0 mL of 2,2,4-trimethylpentane. The mixture was stirred at 80 °C for 54 h. The major product, methine C−H insertion, **24b**, with 30% of the other C−H insertion products was obtained by eluting through a silica gel column using a 30:1 hexane/ethyl acetate mixture (16.5 mg, 0.0557 mmol 38.4% yield based on methyl methyl 2-(*p*-chlorophenyl)diazoacetate). ^{1}H NMR (300 MHz) δ: 7.27–7.39 (m, 4H, aryl-H), 3.76 (s, 1H, methine C-H), 3.65 (s, 3H, OCH_3), 1.51 (d, 1H, $J_H = 14.6$, -CH_2-), 1.27 (d, 2H, $J_H = 14.6$, −CH_2−), 1.12 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.99 (s, 9H, CH_3). MS{EI}: 297 $[M]^+$, 239 [M − OCOMe], 184 [M − C_8H_{17}]. HRMS: 296.15371, calcd 296.15431.

Methyl 2-(*p*-Tolyl)diazoacetate Insertion with 2,2,4-Trimethylpentane. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (30.7 mg, 0.162 mmol), (TPP)FeCl (2.10 mg, 1.84 mol %), and 10.0 mL of 2,2,4-trimethylpentane. The mixture was stirred at 80 °C for 54 h. The major product, methine C−H insertion, **24c**, with 25% of the other C−H insertion products was obtained by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture (18.7 mg, 0.0678 mmol, 41.8% yield based on methyl 2-(*p*-tolyl)diazoacetate). ^{1}H NMR (300 MHz) δ: 7.27 (d, 2H, $J_H = 8.1$, aryl-H), 7.11 (d, 2H, $J_H = 8.1$ aryl-H), 3.63 (s, 3H, OCH_3), 3.48 (s, 1H, methine C-H), 2.34 (s, 3H, $ArCH_3$), 1.55 (d, 1H, $J_H = 14.3$, −CH_2−), 1.30 (d, 2H, $J_H = 14.3$, −CH_2−), 1.13 (s, 3H, CH_3), 1.04 (s, 3H,CH_3), 1.00 (s, 9H, CH_3), MS{EI}: 276 $[M]^+$, 217 [M − OCOMe]. HRMS: 276.20804, calcd 276.20893.

Dimerization of 2-Phenyleth-1-yl Diazoacetate (25). In an oven-dried 25 mL round-bottom flask, 2-phenyleth-1-yl diazoacetate, **25** (32.0 mg, 0.168 mmol), was dissolved in 10 mL of dry dichloromethane. The solution was flushed with nitrogen before Fe(TPP)Cl (2.40 mg, 2.02 mol %) was added and the reaction was monitored by GC or TLC. The reaction reached completion in 12 h, after which the solvent was removed under reduced pressure. A quantitative (27.2 mg, 0.0840 mmol, 100%) amount of dimer was obtained. ^{1}H NMR (400 MHz) δ: 7.31 (m, 2H aryl-H), 7.24 (m, 3H aryl-H), 6.24 (s, 1H, vinyl-H), 4.38 (t, $J = 7.2$ Hz, 2H, CH_2) 2.98 (t, $J = 7.2$ Hz, 2H, CH_2). ^{13}C NMR (100.5 MHz) δ: 165.1, 137.5, 129.9, 128.9, 128.6, 126.7, 65.7, 34.9. anal. Found (calcd): C 74.21 (74.06), H 6.21 (6.28).

Synthesis of 1-(2-Methylphenyl)-2-diazo-1,3-butanedione (27). The diketone 1-(2-methylphenyl)-1,3-butanedione was prepared using literature methods.[38]

Determination of k_H/k_D for Cyclohexane Insertion. Determination of the kinetic isotope effect for C−H insertion in cyclohexane was done following a literature procedure.[18] Equimolar amounts of cyclohexane (3.00 mL, 2.32 g, 27.6 mmol) and cyclohexane-d_{12} (99.6 atom % D, 2.97 mL, 2.65 g, 27.6 mmol) were placed in a 25 mL round-bottom flask. Methyl 2-(*p*-methoxyphenyl)diazoacetate (30.4 mg, 0.147 mmol) and (TPP)FeCl (2.20 mg, 2.12 mol %) were added, and the contents were flushed with nitrogen for about 5 min. The mixture was then refluxed for 8 h, after which the mixture was analyzed by GC-MS (Finnigan 4500 ITD) (detecting masses 262 and 274). Baseline-resolved GC peak areas for the d_{12} and d_0 products were integrated and corrected for the k_H/k_D of ionization. The observed kinetic isotope effect was 1.97 ± 0.03 and represents an average of three runs each of two reactions. Similar procedures were used for the determination of the KIE for methyl 2-(*p*-tolyl)diazoacetate and methyl 2-(*p*-methoxyphenyl)diazoacetate.

Kinetic Experiments for Cyclohexane Insertion with *p*-Cl-MPDA. Three 10 mL two-necked round-bottom flasks were charged with the same amounts of Fe(TPP)Cl (2.50 mg, 3.55 μmol) and dodecane (14.4 mg, 0.09 mmol) dissolved in 2.00 mL of cyclohexane. To each flask was added a different amount of *p*-Cl-MPDA [flask 1: (40.0 mg, 0.190 mmol), flask 2: (81.0 mg, 0.385 mmol), flask 3: (121.0 mg, 0.575 mmol)]. A condenser was inserted in one neck, all openings were sealed with septa, and the assembly was purged with nitrogen and then stirred under nitrogen at 70 °C. The formation of product was monitored hourly with GC by extracting samples via syringe through the septum. The amount of product was determined using dodecane as an internal standard. The initial rate was found to be first-order with respect to the diazo reagent (40.0 mg, 3.7 ± 0.4 μM/h; 81.0 mg, 7.2 ± 0.4 μM/h; 121.0 mg, 10.3 ± 0.6 μM/h).

Competition Experiments with *para*-Substituted MPDAs and Cyclohexane. In a round-bottom flask, methyl 2-phenyldiazoacetate (30.6 mg, 0.174 mmol), an equivalent amount of a *para*-substituted methyl 2-phenyldiazoacetate, *p*-X-MPDA (0.174 mmol), and (TPP)FeCl (2.40 mg, 1.96 mol %) were dissolved in 10.0 mL of cyclohexane. The mixture was purged with nitrogen and heated at 70 °C for 8 h while stirring. The contents were then cooled to room temperature, and volatiles were removed under reduced pressure. The ratio of the products was determined using ^{1}H NMR by integrating the signal of the benzylic methine protons that appear at doublets at 3.23 ppm for the unsubstituted product, methyl cyclohexylphenylacetate, **16a**, and at slightly higher field for the substituted products.

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