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

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Abstract
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.

Disciplines
Chemistry

Comments
C–H Insertion Catalyzed by Tetratolylporphyrinato Methyliridium via a Metal–Carbene Intermediate

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ABSTRACT: C–H insertion reactions between different substrates and diazo reagents were catalyzed by tetratolylporphyrinato methyliridium (Ir(TTP)(CH3)). The highest yields were achieved for reactions between the bulky diazo reagent methyl 2-phenyldiazoacetate (MPDA) and substrates containing electron-rich C–H bonds. An intermediate metalloloporphyrin complex was identified as a metal–carbene complex, Ir(TTP)((=C[Ph]CO2CH3)(CH3)) (4), using 1H NMR and UV/vis absorption spectroscopy. The presence of 4 was further supported by computationally modeling the absorption spectra with time-dependent DFT (6-31G(d,p)/SBKJC basis set, PBE0 functional). Kinetic studies for C–H insertion reactions using different substrates showed substantial differences in the rate of MPDA consumption, suggesting that carbene transfer is rate-limiting. Furthermore, primary kinetic isotope effects of 3.7 ± 0.3 and 2.7 ± 0.4 were measured using toluene and cyclohexane, respectively. These data are consistent with a mechanism that involves direct C–H insertion rather than a radical rebound pathway.

INTRODUCTION

Selective functionalization of unactivated carbon–hydrogen bonds is still a great challenge in synthetic chemistry. Insertion of carbene fragments, generated from diazo reagents, into C–H bonds using transition metal catalysts provides a promising, atom-economical method to accomplish this goal. High selectivities were found using Cu, Ni, and Rh catalyst complexes for intramolecular C–H insertions.1,2 However, general and selective catalysts for intermolecular insertions are rare. Among the promising candidates, rhodium(III) porphyrin catalysts are particularly appealing because they have demonstrated unique selectivity for intermolecular carbene insertion into the primary C–H bonds of simple aliphatic compounds.3 The most selective catalyst utilized the bulky tetra(2,4,6-triphenylphenyl)porphyrin (TTPPP).4 In the presence of Rh(TTPPP)I, the reaction between octane and methyl 2-phenyldiazoacetate (MPDA) generated insertion products in 55% yield, with primary insertion favored over secondary insertion in a ratio of 10:5:1. Recently, intermolecular C–H insertion was also accomplished in high yield and enantioselectivity using iridium(III) complexes with chiral N,N′-bis(salicylidene)ethylenediaminato (salen) and D2-symmetric Halterman porphyrin ligands.5,6 At low temperatures, the Ir(III) complexes catalyzed the insertion of alkyl- and aryl diazoacetates into the C–H bonds of THF and cyclohexadiene in good yields and with 81–99% ee values. These promising results prompted us to explore further the scope and mechanism for C–H insertion catalyzed by the iridium(III) porphyrin complex (5,10,15,20-tetratolylporphyrinato)methyliridium (Ir(TTP)(CH3)).

RESULTS AND DISCUSSION

Optimization studies were carried out in neat cyclohexane with 1.0 mol % Ir(TTP)(CH3). Initial reactions with ethyl diazoacetate (EDA) failed to generate the desired insertion product, 1. Instead, the only observed products resulted from dimerization of the diazo reagent to afford diethyl fumarate and diethyl maleate, 2 (Table 1). Attempts to decrease dimerization by lowering the reaction temperature failed, which was due in part to the low solubility of Ir(TTP)(CH3) in cyclohexane. Changing the diazo reagent to MPDA, which is more resistant to dimerization, afforded C–H insertion products in low yields at room temperature. The major product of this reaction, azine 3, resulted from MPDA dimerization. The structure of the Z,Z-isomer of 3 was verified by an analysis of single-crystal X-ray diffraction data with metrical parameters that matched published molecular structures.7,8 High yields of 1 were achieved using elevated temperatures and dropwise addition of MPDA. Increasing the catalyst loading to 5.0 mol % also significantly increased the yield of product 1, but such a high catalyst loading is not practical given the cost of Ir(TTP)(CH3).

Attempts to catalyze C–H insertion with Ir(TTP)(Cl(CO)) under these conditions yielded trace amounts of 1 and incomplete MPDA conversion.

The optimized method was extended to several other substrates (Table 2). Treating Ir(TTP)(CH3) with MPDA in refluxing pentane afforded azine 3 in nearly quantitative yields. With the higher boiling octane, C–H insertion products were

 supporting information

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isolated in 37% yield. Insertion occurred preferentially into secondary (C₂ and C₃, 18%) carbons, but a considerable amount of primary insertion (7%) was also observed. Although the selectivity was modest, Ir(TTP)CH₃ was more selective for primary insertion than that for the previously reported Rh(TTP)I.⁹ Extending this method to toluene and cyclohexadiene gave good yields of the products corresponding to benzyl and allylic C–H insertion, respectively. Products corresponding to vinyl or aryl C–H insertion were not detected. Furthermore, unlike reactions with Fe(TPP)Cl, there were no signs of competitive cyclopropanation or Büchner additions.¹⁰ THF was also a suitable substrate for C–H insertion. In this case, the products corresponding to α-C–H insertion were isolated in 75% yield with a moderate selectivity for the anti-isomer. No β-insertion products or ring-opened ethers were identified. In all cases, as the reaction temperature was decreased, yields of the insertion products decreased, the formation of azine increased, and catalyst decomposition was more evident. This effect was more pronounced with octane and toluene than with THF and cyclohexadiene. Additionally, trace water contamination, specifically with THF, generated considerable amounts of the competitive O–H insertion product, methyl 2-hydroxy-2-phenylacetate.

Addition of MPDA in the above reactions, specifically those with cyclohexane, octane, and toluene, resulted in a temporary color change from orange to greenish-brown, indicating the presence of an observable intermediate. This intermediate was investigated by UV/vis absorption spectroscopy for the reaction between a cyclohexane solution of Ir(TTP)CH₃ and MPDA over three consecutive additions of the diazo reagent. The Soret band of Ir(TTP)CH₃ was observed at 404 nm. After the first addition of MPDA (5.7 equivalents), the peak at 404 nm was immediately consumed and three new bands were formed at 375, 417, and 443 nm (Figure 1). The intermediate bands endured for approximately 5 minutes before reverting back to the single Soret peak of Ir(TTP)CH₃. The conversion between Ir(TTP)CH₃ and intermediate bands occurred too rapidly to observe isosbestic behavior. Furthermore, catalyst solubility seemed to increase throughout the reaction. Addition of a second portion of MPDA resulted in similar behavior, except that the band at 417 nm was larger throughout the reaction relative to other peaks (Figure S7). The resulting equilibrated solution displayed a significant shoulder at 417 nm, which seemed to form at the expense of Ir(TTP)CH₃. Finally, with

<table>
<thead>
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<th>diazo reagent</th>
<th>temperature (°C)</th>
<th>yield 1 (%)</th>
<th>yield dimers (%)</th>
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<tbody>
<tr>
<td>EDA</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>MPDAᵇ</td>
<td>0</td>
<td>trace</td>
<td>31</td>
</tr>
<tr>
<td>MPDA</td>
<td>80</td>
<td>28</td>
<td>68</td>
</tr>
<tr>
<td>MPDAᵃ</td>
<td>80</td>
<td>74</td>
<td>14</td>
</tr>
<tr>
<td>MPDAᵇ,ᵈ</td>
<td>80</td>
<td>94</td>
<td>3</td>
</tr>
</tbody>
</table>

ᵃConditions: Ir(TTP)CH₃ (1.0 mol %) and diazo reagent (0.30 mmol) in cyclohexane (4.5 mL). ᵃUnreacted MPDA remained (24% determined by NMR). ᵃDropwise addition of MPDA. ᵃUsing 5.0 mol % catalyst. ᵃIsolated yields. ᵃDetermined by NMR.

<table>
<thead>
<tr>
<th>Sub–H</th>
<th>Major Product</th>
<th>Yield (%)</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>37</td>
<td>1 : 2.5 : 1.6ᵇ</td>
</tr>
<tr>
<td></td>
<td>C₂</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C₃</td>
<td>56 (76)b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C₄</td>
<td>75</td>
<td>3.8 : 1ᵈ</td>
</tr>
</tbody>
</table>

ᵇIsolated yields. ᵇYield determined by NMR. ᵇC₂=C₃=C₄ normalized by the number of hydrogen atoms. ᵇanti:syn. ᵇConditions: A solution of MPDA (0.12 mmol) and substrate (1.0 mL) was added dropwise to a refluxing solution of Ir(TTP)CH₃ (1.0 mol %) and substrate (4.5 mL) over the course of 2 h.
the third addition of MPDA, the band at 417 nm was dominant and persisted indefinitely (Figure S8). This resulting metalloporphyrin was unreactive with further additions of MPDA and prolonged heating, indicating it is a product of catalyst decomposition. The catalyst TON was between 11.4 and 17.1 under these conditions.

In analogy with the mechanism proposed for iridium porphyrin-catalyzed cyclopropanation, the observed intermediate was believed to be the metal–carbene complex \( \text{Ir(TTP)} \) (Scheme 1), analogous to related C–H insertion and cyclopropanation systems. Coordination of MPDA to \( \text{Ir(TTP)} \) initially generates a diazonium complex, which forms a metal–carbene intermediate. The intermediate carbene complex was also investigated by \( ^1\text{H} \) NMR. Addition of MPDA (ca. 5 equivalents) to a solution of \( \text{Ir(TTP)}\text{CH}_3 \) in benzene-\( d_6 \) resulted in the complete formation of a new metalloporphyrin complex, as indicated by the clean singlets for the porphyrin \( \beta \)-pyrrole and \( \text{Ir–CH}_3 \) protons at 8.83 and \(-4.80 \) ppm, respectively (Figure S10). The \( \text{Ir–CH}_3 \) protons were shifted significantly downfield from those of \( \text{Ir(TTP)}\text{CH}_3 \) (\(-5.92 ppm \)). Furthermore, the appearance of new phenyl proton signals [6.55 (t, \( J = 7.6 \) Hz, 1H), 5.92 (d, \( J = 7.6 \) Hz, 2H)] and a new methyl singlet at 2.19 ppm (3H) suggested that the carbene fragment derived from MPDA was coordinated to iridium; the carbene signals were strongly shifted upfield due to the porphyrin ring current effect. After 20 h, the major remaining porphyrin species was \( \text{Ir(TTP)}\text{CH}_3 \). MPDA had been completely consumed, forming azine 3 as the predominant product. Despite numerous efforts, including attempts with chromium(III) acetylacetonate, a signal corresponding to the putative carbene carbon of the intermediate was not located by \( ^{13}\text{C} \) NMR.

The calculated geometrical parameters for \( \text{Ir(TTP)}\text{CH}_3 \) are consistent with the reported crystallographic structure of \( \text{Ir(TPP)}\text{CH}_3 \). Specifically, the calculated Ir–CH\(_3\) bond length, 2.037 Å, agrees with the reported distance of 2.059(11) Å. Upon coordination of the carbene ligand, the Ir–CH\(_3\) bond in 4 lengthened to 2.123 Å due to the trans influence exerted by the carbene ligand. The calculated Ir–C carbene bond length was 2.045 Å, which is slightly long compared to the metal–carbene complexes of group 8 metalloporphyrins. Previous studies of similar systems report M–C bond lengths ranging from 1.767(3) to 2.035(2) Å. Considering the high carbene transfer reactivity of iridium porphyrin complexes compared to that of group 8 metal complexes, a slightly elongated Ir–C carbene bond is reasonable. Coordination of the carbene ligand also caused noticeable distortion to the porphyrin core. The out-of-plane displacement (\( D_{oop} \)) and in-plane displacement (\( D_{ip} \)) were calculated by normal-coordinate structure decomposition (NSD) analysis (Table S2).

Results for complex 4 showed \( D_{oop} = 0.5154 \) and \( D_{ip} = 0.1430 \). The most prominent distortions were ruffling (\( B_{fl} \)) and doming (\( A_{dom} \)) out-of-plane displacements. Deformations were considerably less significant for \( \text{Ir(TTP)}\text{CH}_3 \), which had \( D_{oop} = 0.1071 \) and \( D_{ip} = 0.2598 \). In general, the distortions exhibited by \( \text{Ir(TTP)}\text{CH}_3 \) and 4 are relatively small compared to other metalloporphyrin systems.

The calculated electronic spectra of \( \text{Ir(TTP)}\text{CH}_3 \) and 4 are shown in Figure 2. The main absorption band of \( \text{Ir(TTP)}\text{CH}_3 \) arising from a \( \pi \) to \( \pi^* \) transition, occurred as one large peak centered at 371 nm, which was consistent with the experimentally observed transition at 404 nm. The calculated spectrum of 4 showed \( \pi \) to \( \pi^* \) transitions at 357, 366, and 427 nm. Similar spectral changes were reported for other six-coordinate alkyl Ir porphyrin complexes with neutral donor ligands trans to the alkyl group. The resolution of the experimental spectrum likely coalesces the bands at 357 and 366 nm into one peak. Thus, the calculated spectrum is in good agreement with the observed peaks of the intermediate complex at 375 and 445 nm. Overall, TD-DFT modeling of \( \text{Ir(TTP)}\text{CH}_3 \) and 4 adequately reproduced the observed absorption spectra, providing additional evidence in support of a metal–carbene intermediate.

Figure 2. TD-DFT absorption spectra for \( \text{Ir(TTP)}\text{CH}_3 \) (bold) and 4 (dotted).
Scheme 1. Proposed Catalytic Cycle for C–H Insertion of Hydrocarbons Using MPDA and Ir(TTP)CH₃

![Scheme 1](image)

be the diazonium complex,³³ UV/vis absorption spectroscopy, TD-DFT, and kinetic studies all support carbene complex 4 as the observed intermediate. Furthermore, an N≡N stretch corresponding to a diazonium intermediate was not observed by IR spectroscopy. After carbene formation, subsequent nucelophic attack at the carbene carbon with a C–H bond results in product formation. Insight into the mechanism of carbene transfer was gained from kinetic isotope studies. Separate competition reactions between toluene/toluene-d₈ and cyclohexane/cyclohexane-d₁₂ revealed kinetic isotope effects (KIE) of 3.7 ± 0.3 and 2.7 ± 0.4, respectively. These values support a mechanism involving direct C–H insertion rather than a radical rebound pathway, which exhibits a larger KIE typically between 7 and 12.⁹ Direct C–H insertion may be most accurately described as a concerted, nonsynchronous hydride transfer and C–C bond formation.³⁴,³⁵

### CONCLUSIONS

In summary, C–H insertion catalyzed by Ir(TTP)CH₃ was examined using different substrates and diazo reagents. The highest yields were found using MPDA and substrates with electron-rich C–H bonds, such as THF and cyclohexadiene. Mechanistic studies and spectroscopic examination of the reaction intermediate suggest that C–H insertion proceeds through a metal–carbene intermediate and that carbene transfer is the rate-limiting step.

### EXPERIMENTAL SECTION

**General Considerations.** All manipulations were performed under a dry nitrogen atmosphere. Most substrates were dried over 4 Å molecular sieves, freeze−pump−thawed, and run through a plug of activated alumina under a glovebox atmosphere. THF was deoxygenated and dried by passage through columns of reduced copper and alumina. Ir(TTP)CH₃ and MPDA were prepared according to previously reported methods.³⁶−³⁸ Absorption spectra were collected using a Hewlett-Packard/Agilent Technologies 8453 UV−vis spectrophotometer. General NMR spectra were collected using Varian VXR 300 MHz and Varian VXR 400 MHz spectrometers, and kinetic measurements were done using a Bruker DRX 400 MHz spectrometer. ¹H NMR peak positions were referenced against residual proton resonances of deuterated solvents (δ, ppm: CDCl₃ 7.26; C₆D₆ 7.16). Ratios for kinetic isotope data were determined using a Finnegan Magnum GC-MS fitted with a HP-S column (30 m × 0.25 μm) and a time-of-flight mass analyzer. Column chromatography was performed using silica gel (40−63 μm) purchased from Sorbent Technologies. Characterization data for the C−H insertion products were previously reported.³⁹,⁴⁰,⁴¹

**Computational Details.** The ground-state geometries of Ir(TTP)CH₃, MPDA, and 4 were determined without any symmetry constraints using the program GAMESS.¹²−¹⁵ Exchange and correlation were treated by the hybrid density functional PBE0 and included a mixed basis set. All main group elements were calculated with the 6-31G(d,p) basis set, while an effective core potential (SBKJC) was utilized for Ir. The electronic absorption spectra were calculated by the TD-DFT method implemented within the GAMESS code. The effects of hexane as a solvent were handled using the polarizable continuum model.⁴²−⁴⁵

**General C−H Insertion Procedure.** A CH₃Cl₂ stock solution of Ir(TTP)CH₃ (216 μL from a 3.54 × 10⁻³ M stock solution, 1.15 μmol) was transferred to a side arm, round-bottom flask and taken to dryness under a nitrogen stream. Substrate (4.5 mL) was added and the solution was taken to reflux. Meanwhile, a solution of MPDA (0.115 mmol) and substrate (1.0 mL) was prepared in a dry round-bottom flask. The MPDA solution was added dropwise to the Ir(TTP)CH₃ solution over the course of 2 h using a syringe pump. After MPDA addition and after the color reverted back to orange, volatiles were removed in vacuo. Products were isolated by column chromatography using silica gel using hexanes and ethyl acetate (40:1) as the eluent system.

**Observation of Complex 4 by ¹H NMR Spectroscopy.** Solid Ir(TTP)CH₃ (5.7 mg, 6.5 μmol) was transferred into a medium-walled NMR tube and dissolved in ca. 0.5 mL of C₆D₆. The solution was treated with MPDA (3.5 μL, 22.3 μmol); spectra were acquired immediately and after 20 h. ¹H NMR (C₆D₆, 400 MHz): δ 8.83 (s, 8H), 8.14 (d, J = 7.6 Hz, 4H), 7.93 (m, 4H, overlapping with a signal from azine solvent signal), 6.55 (d, J = 7.6 Hz, 4H), 7.18 (d, J = 7.6 Hz, 4H), 6.18 (d, J = 7.6 Hz, 2H), 2.38 (s, 12H), 2.19 (s, 3H), and −4.80 (s, 3H).

**Kinetic Measurement Experiments.** A CH₃Cl₂ stock solution of Ir(TTP)CH₃ (400 μL, 4.26 × 10⁻³ M, 1.70 μmol) was transferred to a medium-walled NMR tube and taken to dryness at 45 °C. In a glovebox, the tube was loaded with triphenylmethane as an internal standard (9.96 μmol) and substrate (-ranging from 0 to 94 μmol) and diluted to a total volume of 420 μL with C₆D₆. The tube was fitted with a septum and taken to the NMR spectrometer, where the temperature was equilibrated to 300.0 K prior to dazio additon. Then, MPDA (8.40 μmol) from a 0.240 M, room-temperature C₆D₆ stock solution was added, and reaction progress was monitored at 60 s intervals.

**Procedure for Kinetic Isotope Studies.** A CH₃Cl₂ stock solution of Ir(TTP)CH₃ (100 μL from a 3.83 × 10⁻³ M stock solution, 0.383 μmol) was transferred to a round-bottom flask fitted with a side arm and taken to dryness under a nitrogen stream. Ir(TTP)CH₃ was dissolved in 1.8 mL of a premixed solution of substrate (1.0 mL) and deuterated substrate (1.0 mL), where the substrates are either toluene or cyclohexane. In a separate round-bottom flask, MPDA was dissolved in the remaining 0.2 mL of the mixed substrate solution. Then, to a refluxing solution of Ir(TTP)CH₃ the MPDA solution was added manually dropwise. After each drop, the color of the solution was allowed to revert back to orange before the next drop of MPDA
solution was added. Once MPDA addition was complete and the color returned to orange, the product mixture was analyzed by GC-MS.

- ASSOCIATED CONTENT
  - Supporting Information
    Optimized structures of MPDA, Ir(TTP)CH₃, and complex 4, normal-coordinate structure decomposition analysis, experimental and calculated absorption spectra, ¹H NMR spectrum of complex 4, and kinetics data. This material is available free of charge via the Internet at http://pubs.acs.org.

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