Supplementary Information (SI) for Dalton Transactions.

Supplementary Information for
Mechanism of Catalyst Activation in Iron(Porphyrin)-Catalysed Aerobic Oxidative Cleavage of 2,3-Dimethylindole

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1 General Considerations

5,10,15,20-Tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin iron(III) chloride (Fe(PFPP)Cl) (Frontier Specialty Chemicals), 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine iron(III) chloride (Fe(TPP)Cl) (Frontier Specialty Chemicals), tetrabutylammonium hexafluorophosphate ([*n*-Bu_4N][PF_6]) (Sigma Aldrich), ferrocene (Oakwood), decamethylferrocene (Sigma Aldrich), acetonitrile (Oakwood Chemical), chloroform-d (Sigma Aldrich), 1,4-bis(trimethylsilyl)benzene (Chem Scene), 2,6-dimethyl pyridine (Oakwood Chemical), 1,1,3,3-tetramethylguanidine (Oakwood Chemical), pyridine (Oakwood Chemical), and *N*,*N*-Di*iso*propylethylamine (Oakwood Chemical) were used as received without further purification. 2,3-dimethyl-1*H*-indole (Oakwood Chemical) was primarily used without further purification, except for one control experiment (*vide infra*).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using a BBFO probe and were referenced to residual proteo solvent. Optical UV-vis spectra were recorded on an Agilent 8452 diode-array spectrometer, Shimadzu IV-2600, or a Shimadzu UV-1900 spectrophotometer all using a 1 cm pathlength cuvette. Cyclic voltammetry was collected using a Pine Research WaveNow potentiostat.

2 Reactions of 2,3-dimethylindole

2.1 Standard reaction

A vial was charged with $1.5x10^{-4}$ mmol Fe(PFPP)Cl (0.16 mg, 0.05 mM), 0.06 mmol 2,3-dimethyl-1H-indole (8.7 mg, 20 mM) and 3 mL of acetonitrile. The solution was stirred at room temperature. After five hours, 1,4-(bistrimethylsilyl)benzene was added as an external standard, and the solution was analyzed using ^{1}H NMR spectroscopy in proteo-acetonitrile (35% yield). ^{1}H NMR (400 MHz, CH_3CN): δ 11.53 (s, 1H), 8.60 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 2.61 (s, 3H), 2.12 (s, 3H).

2.2 Reaction catalyzed by Fe(TPP)Cl instead of Fe(PFPP)Cl

A vial was charged with $1.5x10^{-4}$ mmol Fe(TPP)Cl (0.11 mg, 0.05 mM), 0.06 mmol 2,3-dimethyl-1*H*-indole (8.7 mg, 20 mM) and 3 mL of dichloromethane. The solution was stirred at room temperature. After five hours, the solvent was removed by rotary evaporation. The reaction was analyzed by ^{1}H NMR in $CDCl_3$.

2.3 Large scale reaction for isolation of products

A 100-mL round bottom flask was charged with 0.015 mmol Fe(PFPP)Cl (15.5 mg, 0.50 mM) and 1.24 mmol 2,3-dimethyl-1*H*-indole (180 mg, 41 mM) , and 30 mL of acetonitrile. After stirring for 5 hours, the solvent was removed under vacuum. The crude product was purified by flash column chromatography (80:20 hexanes:acetone), which afforded two major products. First, the desired oxidative cleavage product, *N*-(2-acetylphenyl)acetamide, was isolated in 7% yield (0.092 mmol, 16.3 mg). Second, 84.4 mg of an inseparable mixture of *N*-(2-acetylphenyl)acetamide (**2**) and dimer (**4**) was insolated in a 2.5:1 ratio (compound **2**: compound **4**): 23% yield **2** (0.28 mmol, 50.4 mg) and 17 % yield dimer **1** (0.11 mmol, 34 mg).

^{1}H NMR of *N*-(2-acetylphenyl)acetamide (**2**) matches literature.[1] ^{1}H NMR (400 MHz, CDCl$_3$): δ 11.69 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 2.66 (s, 3H), 2.22 (s, 3H).

Dimer (**4**): δ 7.25 – 7.15 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.80 – 6.68 (m, 3H), 6.39 (d, *J* = 7.3 Hz, 1H), 5.01 (s, 1H), 3.88 (s, 1H), 3.21 (s, 1H), 2.41 (s, 2H), 1.52 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H).

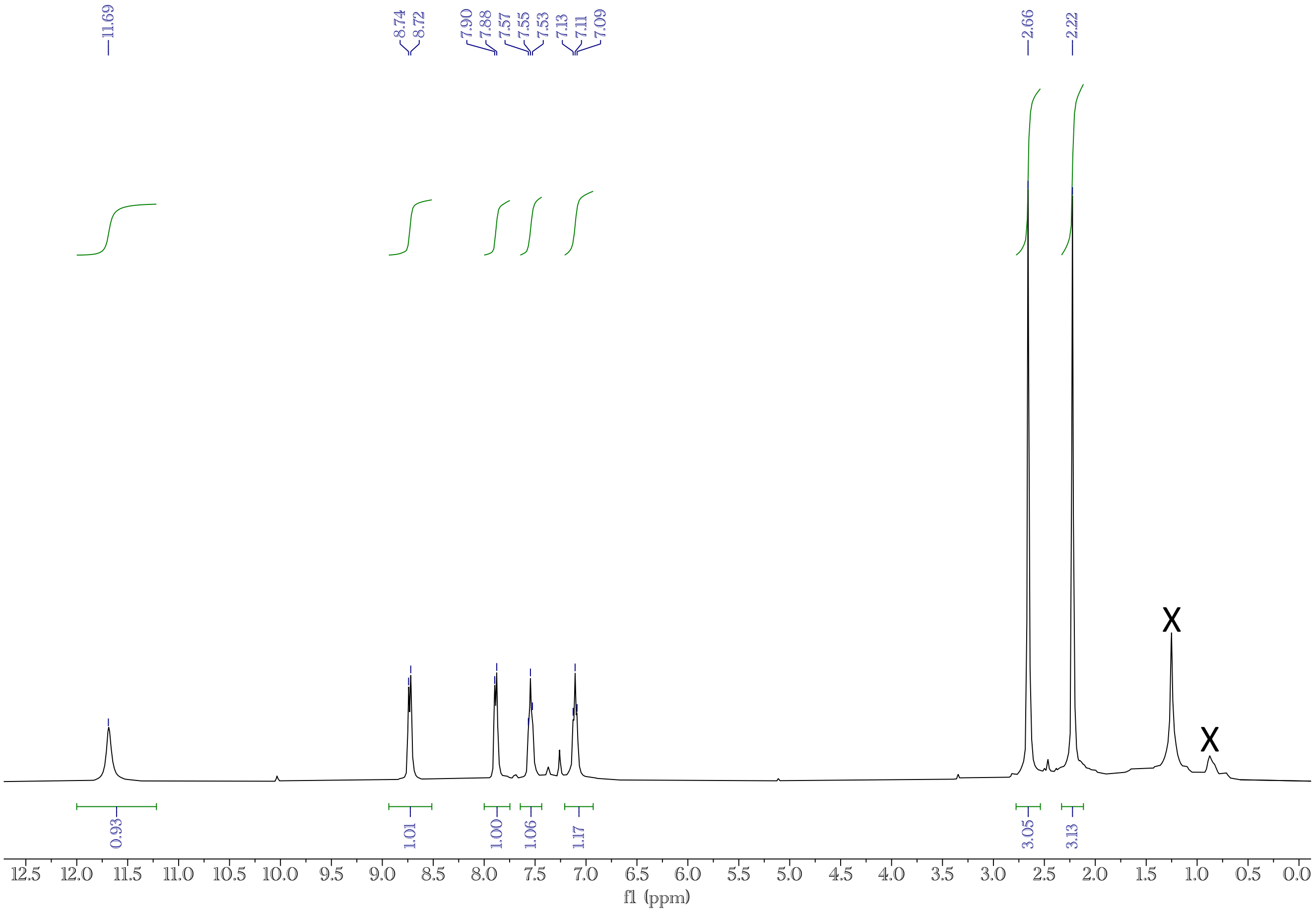


Figure S1. ^{1}H NMR in CDCl$_3$ of *N*-(2-acetylphenyl)acetamide (**2**) isolated after column chromatography. Residual hexanes solvent labelled with 'X.'

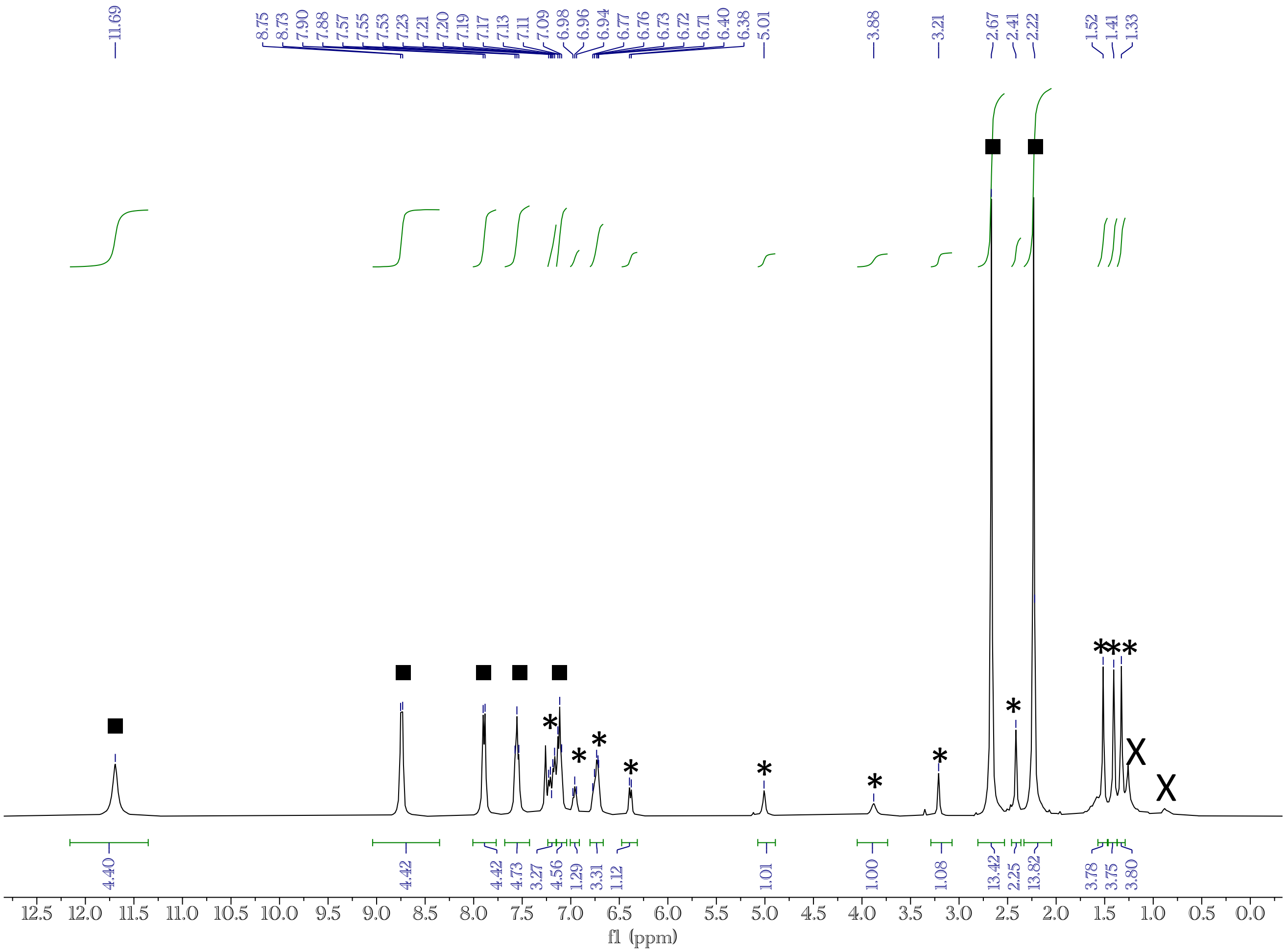


Figure S2. ^{1}H NMR in $CDCl_3$ of *N*-(2-acetylphenyl)acetamide (■) and dimer (**4**) (*) isolated after column chromatography. Residual hexanes solvent labelled with 'X.'

3 Control Experiments

3.1 Light

Control experiments were performed to rule out a photochemical process. The standard reaction (Section 2.1) was performed in ambient lab lighting, directly in front of a white LED (15 W) or a blue LED (15 W), or wrapped in foil to keep in the dark. The NMR yields of these reactions are identical within error.

Table S1. Control experiments under standard reaction conditions with different light sources.

Entry	Light Source	% Yield	% Conversion
1	Ambient light	32	94
2	White LED	36	94
3	Blue LED	35	95
4	Dark	37	98

3.2 Reaction of recrystallized 2,3-dimethylindole

2,3-Dimethyl-1*H*-indole was recrystallized twice from hot petroleum ether. 2,3-DMI was isolated as pale yellow needles. The recrystallized 2,3-DMI was reacted under standard reaction conditions (Section 2.1).

4 UV-Visible Experiments

4.1 UV-Vis of Catalytic Reaction

A vial was charged with 1.95×10^{-4} mmol Fe(PFPP)Cl (0.21 mg, 0.065 mM), 0.06 mmol 2,3-dimethyl-1*H*-indole (8.7 mg, 20 mM) and 3 mL of acetonitrile. The brown solution was stirred at 0 °C. After 3.5 hours, the solution appeared red and was transferred to a 1 cm pathlength cuvette. A UV-Vis spectrum focusing on the Q-bands was acquired (see text).

4.2 Generation of Genuine Fe^{II}PFPP(L) and $Fe^{III}(O_2^{\bullet-})$PFPP(L)

In order to compare UV-Vis spectra, genuine samples of Fe^{II}PFPP(L) and $Fe^{III}(O_2^{\bullet-})$PFPP(L) were prepared following the procedure from Mayer and coworkers.[2] A 0.10 mM solution of Fe(PFPP)Cl (0.0010 mmol, 1.1 mg in 10 mL) was prepared in acetonitrile. The solution was passed through a pipette filter of zinc amalgam in an N_2 filled glovebox to generate the ferrous porphyrin. The resulting red solution was transferred to a kontes valve cuvette, sealed, and removed from the box. A UV-Vis spectrum was acquired. Oxygen was then sparged through the solution to generate the $Fe^{III}(O_2^{\bullet-})$PFPP(L) complex and a UV-vis spectrum was acquired. These spectra align with other metal porphyrins (see text).[2–5]

The experiments were repeated at a lower concentration to obtain UV-Vis spectra of the Soret features for Fe^{III}(PFPP)Cl and Fe^{II}(PFPP)(L). A 7 μM solution of Fe(PFPP)Cl was prepared in acetonitrile. A UV-Vis spectrum was acquired (Figure S3, green). The solution was sparged with N_2 and 2.0 mL of the solution was transferred via gastight syringe to an N_2-filled cuvette containing solid Fc* (0.0123 mmol, 4.0 mg) and a UV-Vis spectrum was acquired (Figure S3, blue). The cuvette was sparged with O2 and a UV-Vis spectrum of the resulting $Fe^{III}(O_2^{\bullet-})$PFPP(L) complex was acquired (Figure S3, red).

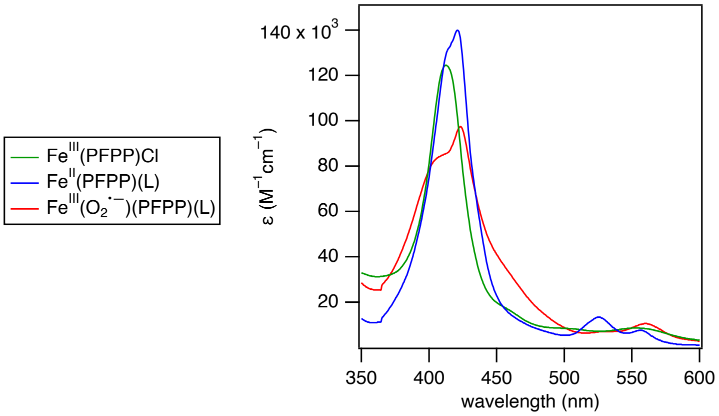


Figure S3. Soret features of Fe^{III}(PFPP)(Cl) (green), Fe^{II}(PFPP)(L) (blue), and $Fe^{III}(O_2^{\bullet-})$(PFPP)(L) (red).

In order to provide more evidence for the assignment of Fe^{II}PFPP(L), the complex was generated from the Fe^{III}PFPP(Cl) using two other methods. The first alternative method used decamethylferrocene (Fc*) as a soluble reductant. A 0.105 mM solution of Fe(PFPP)Cl was prepared in acetonitrile and sparged with N_2. 1.5 mL of the solution was transferred via gastight syringe to an N_2-filled cuvette containing solid Fc* (0.0129 mmol, 4.2 mg). Not all Fc* dissolved, but the solution turned red. A UV-Vis spectrum was acquired (Figure S4, green).

In the second alternative reduction method, the Fe^{III}PFPP(Cl) was reduced to Fe^{II}PFPP(L) by bulk electrolysis. A 15 mL solution of 0.05 mM Fe^{III}PFPP(Cl) (0.80 mg, 0.75 mmol), 100 mM [TBA][PF6] (581 mg, 1.5 mmol) in MeCN was prepared. The solution was sparged with N_2 and connected to a potentiostat with a reticulated vitreous carbon working electrode, Pt counter electrode separated by a frit, and a Ag pseudoreference. The working electrode was held at –0.8 V vs. Fc for 30 minutes. The solution visibly turned red, and a UV-Vis spectrum was acquired (Figure S4, black). A small amount of Fe^{III}(PFPP)Cl was still present. The same experiment was repeated in the presence of O_2, and the same Fe^{III}($O_2^{\bullet-}$)PFPP(L) spectrum was obtained as reported in the text.

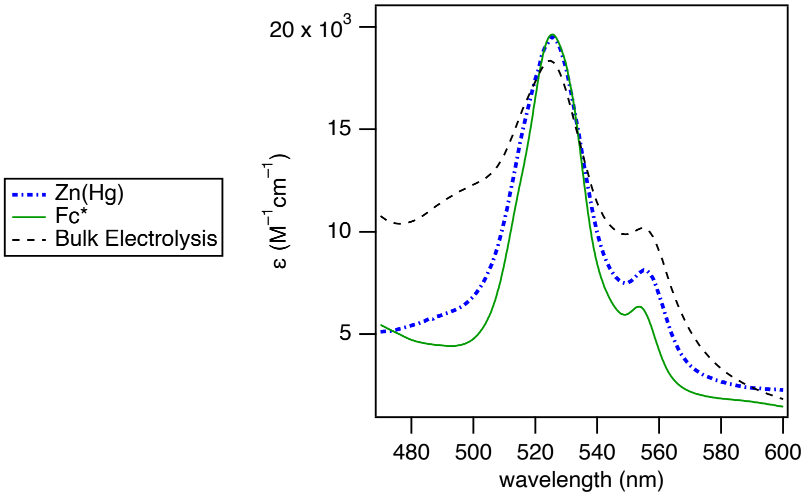


Figure S4. Fe^{II}(PFPP)(L) generated using three different reducing methods: Zn(Hg) (blue dots), decamethylferrocene (green), bulk electrolysis (black dashed).

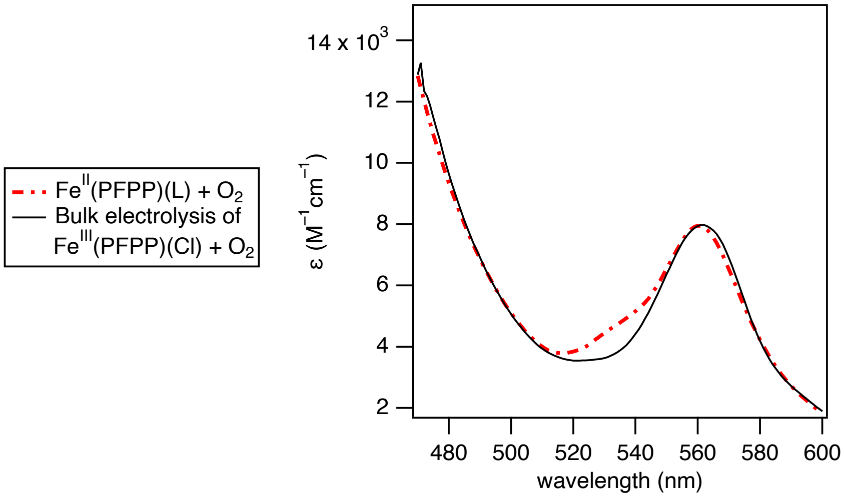


Figure 5. Fe^{III}($O_2^{\bullet-}$)(PFPP)(L) generated by two different methods: Fe^{II}(PFPP)(L) reaction with O2 (red dashed), bulk electrolysis of Fe^{III}(PFPP)(Cl) in the presence of O_2.

4.3 UV-Vis of 2,3-DMI + Fe^{III}PFPP(Cl) under N_2

2,3-dimethyl-1*H*-indole (8.7 mg, 0.06 mmol, 20 mM) was dissolved in 3 mL of acetonitrile, stirred at 0°C, and sparged with N_2. After 10 minutes, the solution was transferred via gastight syringe to an N_2-filled cuvette containing solid Fe(PFPP)Cl (1.4×10^{-4} mmol, 0.15 mg) and the reaction solution turned red. A UV-Vis spectrum was acquired showing the formation of Fe^{II}PFPP(L) (see text).

5 *N*-D-2,3-dimethylindole

5.1 Synthesis of *N*-D-2,3-dimethylindole

N-D-2,3-dimethylindole was synthesized according to a literature procedure.[1] A vial was charged with 0.75 mmol 2,3-dimethyl-1*H*-indole (109.4 mg) and 1 mL of methanol-d_4. The solution was stirred overnight at room temperature. After 21 hours, the solvent was removed under vacuum. The resulting solid was redissolved in 1 mL of methanol-d_4 and allowed to stir for 24 hours. Removal of the solvent under reduced pressure yielded the deuterated indole (109.0 mg, 99% yield). The ^{1}H NMR and ^{2}H NMR spectra match the literature reports.[1]

^{1}H NMR (400 MHz, CH_3CN): δ 7.37 (d, $J = 7.5$ Hz, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 7.2$ Hz, 1H), 6.96 (t, $J = 7.3$ Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H).

^{2}H NMR (61.4 MHz, CH_3CN): δ 8.85 (s, N-D)

5.2 Catalytic reaction of *N*-D-2,3-dimethylindole

A vial was charged with $3.8 \mathrm{x} 10^{-4}$ mmol Fe(PFPP)Cl (0.4 mg, 0.13 mM), 0.164 mmol *N*-D-2,3-dimethyl-1H-indole (24.0 mg, 55 mM) and 3 mL of acetonitrile. After stirring for 24 hours, the solution was analyzed by ^{2}H NMR spectroscopy. In order to compare the resulting spectrum to known products, the acetonitrile was removed by rotary evaporation. The solid was redissolved in $CHCl_3$ and a second ^{2}H NMR spectrum was acquired.

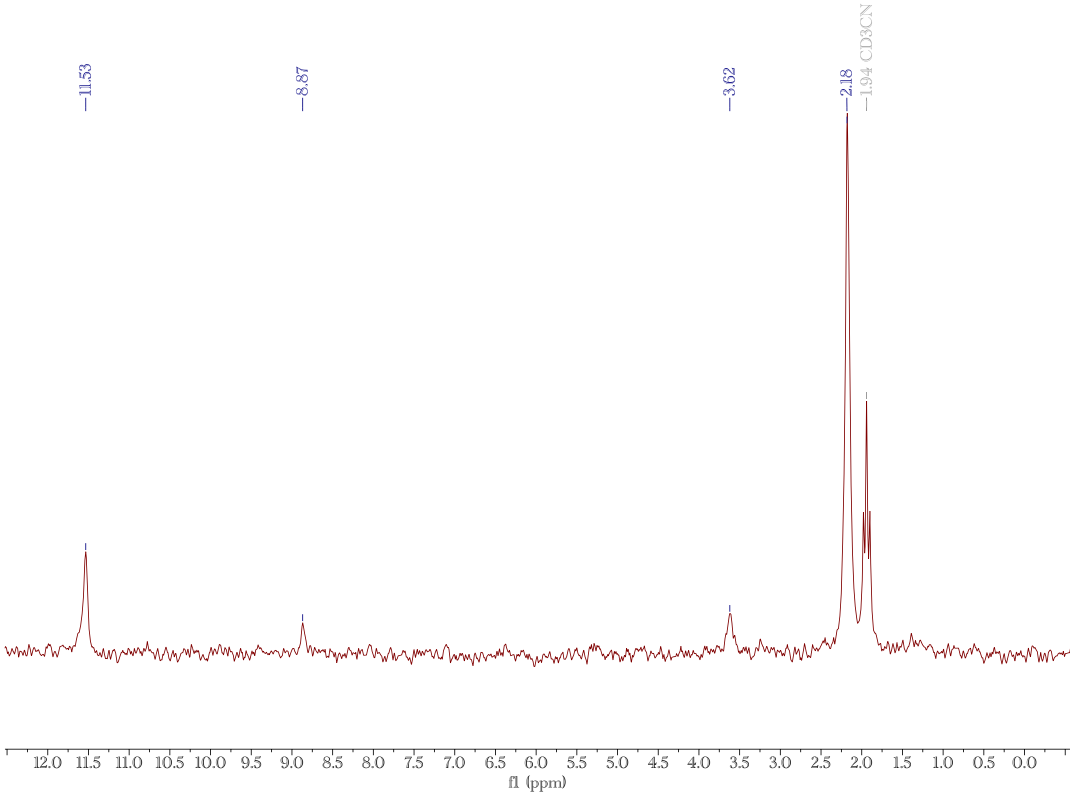


Figure S6. ^{2}H NMR in acetonitrile of product generated from the oxidative cleavage of *N*-D-2,3-dimethylindole by Fe(PFPP)Cl in acetonitrile.

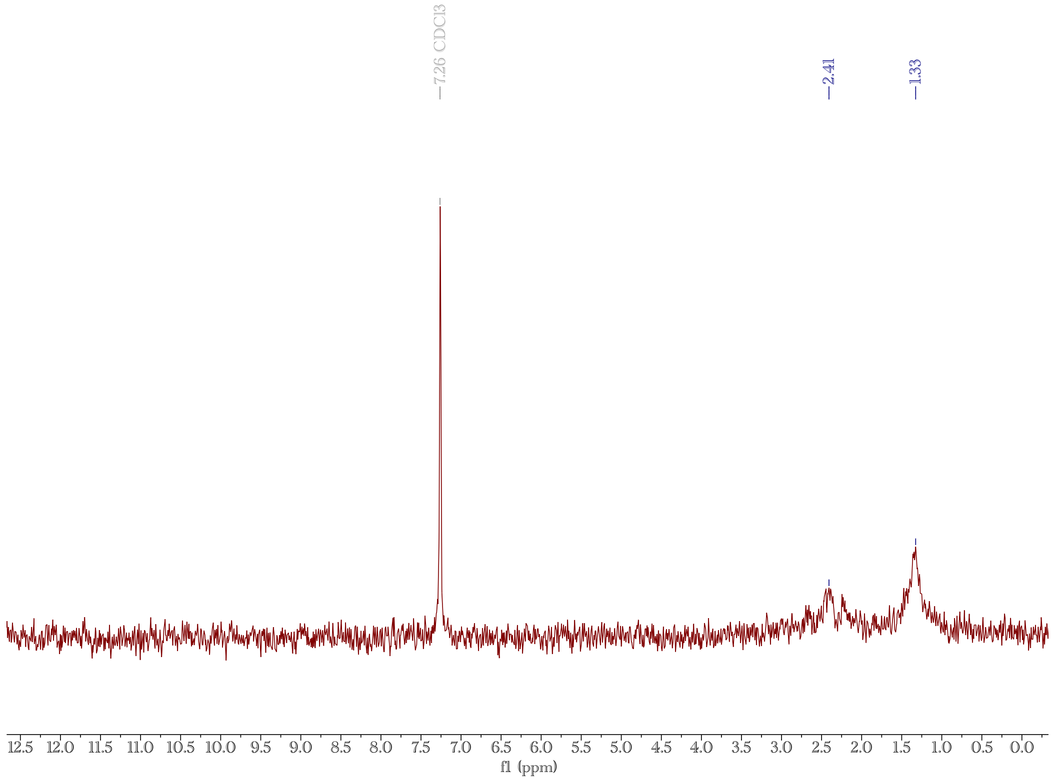


Figure S7. ^{2}H NMR in $CHCl_3$ of product generated from the oxidative cleavage of *N*-D-2,3-dimethylindole by Fe(PFPP)Cl in acetonitrile. The N-D peak at 11.5 ppm likely disappeared due to exchange with solvent.

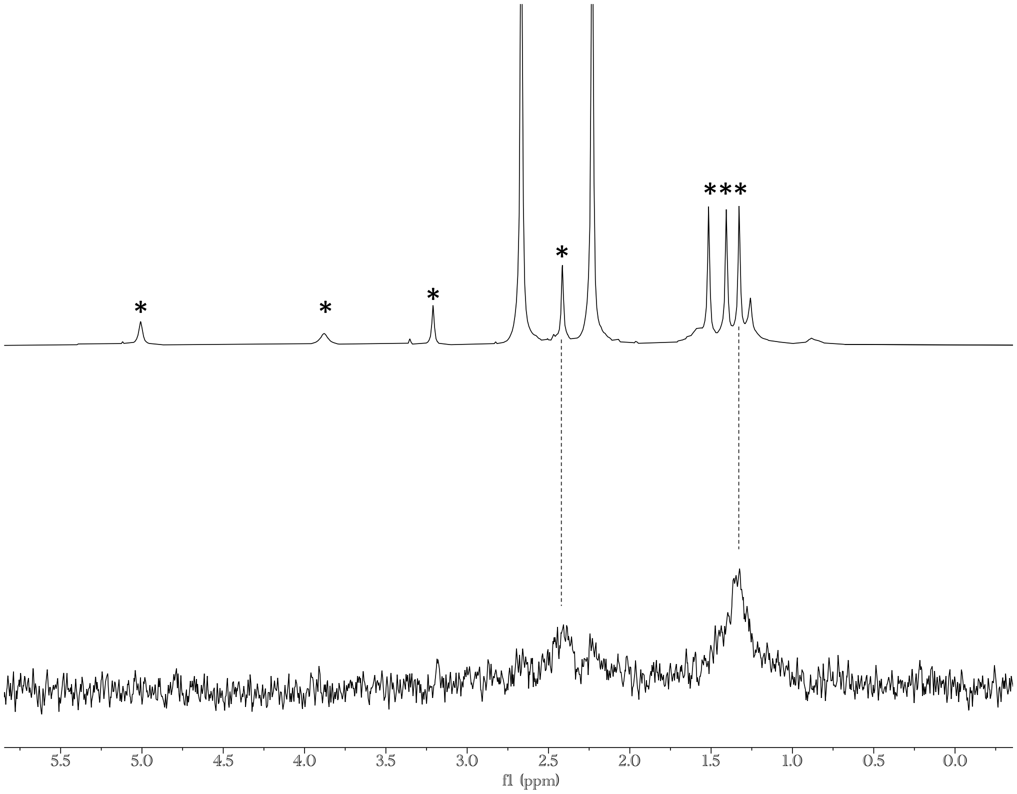
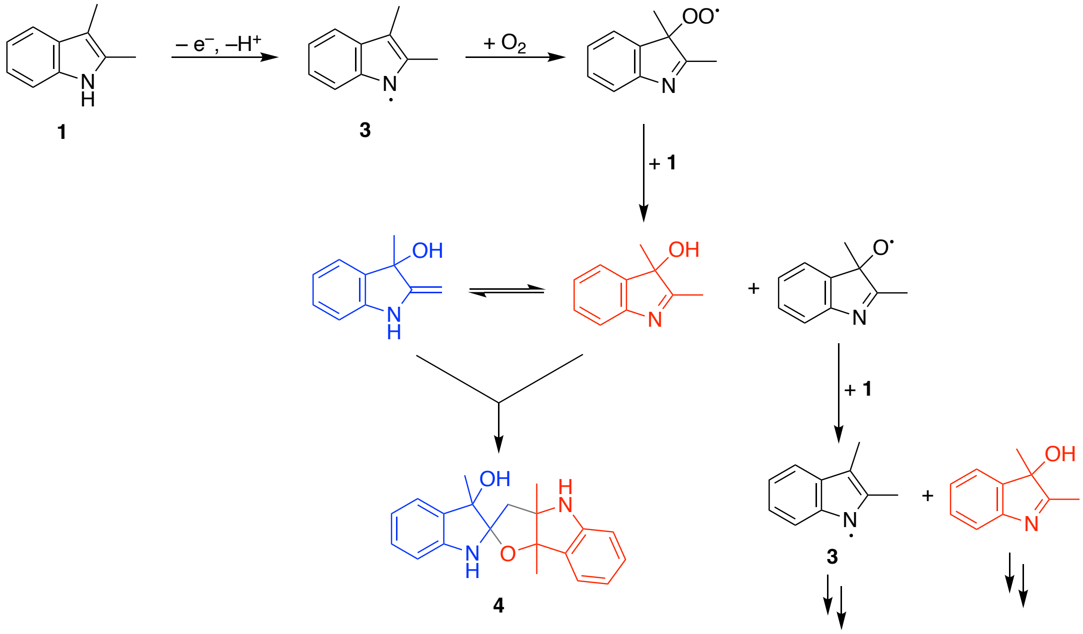


Figure S8. Top: ^{1}H NMR in $CDCl_3$ of cleavage product **2** and dimer **4** (*). Bottom: ^{2}H NMR in $CHCl_3$ of product generated from the oxidative cleavage of N-D-2,3-dimethylindole by Fe(PFPP)Cl in acetonitrile.

5.3 Proposed mechanism for deuterium scrambling



Scheme S1. Proposed mechanism for the formation of dimer (**4**) from a PCET oxidation of **1** based on literature reports.*[6–9]*

6 *N*-Methyl-2,3-dimethylindole

6.1 Synthesis of *N*-methyl-2,3-dimethylindole

The synthesis of *N*-methyl-2,3-dimethylindole followed a literature report.[10] 2,3-Dimethyl-1*H*-indole (2.0 mmol, 290.4 mg) and NaH (60% in mineral oil, 98 mg, 2.4 mmol) were added to 5 mL of dry dimethylformamide at 0 ºC. The reaction mixture was stirred for 5 minutes at 0 ºC and then allowed to warm to room temperature over 30 minutes with continued stirring. The reaction mixture was cooled to 0 ºC again, and iodomethane (150 µL, 2.4 mmol) was added dropwise. The solution was stirred at 0 ºC for 10 minutes before being warmed and stirred at room temperature overnight. The reaction was quenched with a slow addition of 7.5 mL of DI water and extracted with ethyl acetate (3x20 mL). The combined organic fraction was washed with DI water (3x10 mL) and brine (1x10 mL) and dried with anhydrous magnesium sulfate. The crude product was purified by flash chromatography (3% ethyl acetate in hexanes), giving *N*-methyl-2,3-dimethylindole as a pink solid (133.0 mg, 41% isolated yield). Product ^{1}H NMR matched literature values.[10,11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.7, 1H), 7.24 (d, *J* = 8.1, 1H), 7.15 (t, *J* = 7.5, 1H), 7.07 (t, *J* = 7.3, 1H), 3.68 (s, 3H), 2.40 (s, 3H), 2.33 (s, 3H).

6.2 Catalytic reaction of *N*-methyl-2,3-dimethylindole

A vial was charged with 1.5×10^{-4} mmol Fe(PFPP)Cl (0.16 mg, 0.05 mM), 0.06 mmol *N*-methyl-2,3-dimethylindole (9.5 mg, 20 mM) and 3 mL of MeCN. The solution was stirred at room temperature. After five hours, the solvent was removed by rotary evaporation. The reaction was analyzed by ^{1}H NMR in $CDCl_3$. Only starting material was recovered (100% NMR yield).

6.3 UV-Vis of *N*-methyl-2,3-DMI + Fe^{III}PFPP(Cl)

N-methyl-2,3-dimethyl-1*H*-indole (9.5 mg, 0.06 mmol, 20 mM) was dissolved in 3 mL of acetonitrile, stirred at 0°C, and sparged with N_2. After 10 minutes, the solution was transferred via gastight syringe to an N_2-filled cuvette containing solid Fe(PFPP)Cl (1.4×10^{-4} mmol, 0.15 mg) and the solution was stirred for 5 hours. A UV-Vis spectrum was acquired regularly throughout this period, and no change was observed.

7 Cyclic Voltammetry

Cyclic voltammetry was conducted using a Pine WaveNow potentiostat with a 3 mm glassy carbon working electrode, a platinum auxiliary electrode, and a Ag pseudoreference electrode made using a CHI non-aqueous reference electrode kit. The silver wire was immersed in a jacketed compartment (separated from solution with a glass frit) containing 0.1 M [*n*Bu$_4$N][PF$_6$] in acetonitrile. The glassy carbon working electrode was polished with 0.05 µm alumina on a Buehler felt pad between scans.

Fe(PFPP)Cl displayed a chemically reversible Fe$^{III/II}$ couple with $E_{1/2} = -0.37$ V vs Fc$^{+/0}$ (Figure S9). The solution was spiked with ferrocene (Fc) at the end of experiment to serve as an internal reference.

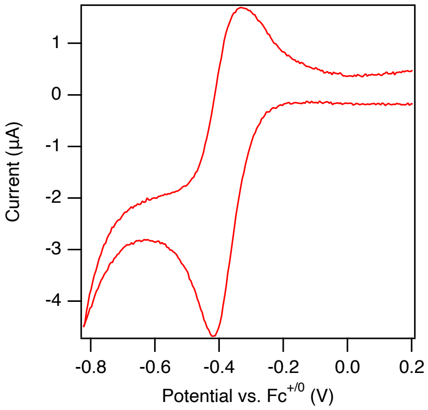


Figure S9. Cyclic voltammogram of Fe(PFPP)Cl in acetonitrile (0.1 M [nBu$_4$N][PF$_6$], 100 mV/s scan rate).

8 3-Methylindole

8.1 Standard Conditions

A vial was charged with 3.8x10^{-4} mmol Fe(PFPP)Cl (0.4 mg, 0.13 mM), 0.072 mmol 3-methylindole (9.4 mg, 24 mM) and 3 mL of acetonitrile. The solution was stirred open to air for 24 hours. The next day, 1,4-(bistrimethylsilyl)benzene was added as an external standard, and the solution was analyzed using ^{1}H NMR spectroscopy in proteo-acetonitrile. No evidence of reaction was observed—only starting material was recovered (100% NMR yield).

8.2 Oxidation of 3-methylindole with exogenous reductant

A vial was charged with of 3.8x10^{-4} mmol Fe(PFPP)Cl (0.4 mg, 0.13 mM), 0.070 mmol 3-methylindole (9.2 mg, 23 mM), 0.078 mmol decamethylferrocene (25.6 mg, 26 mM) and 3 mL of acetonitrile. The solution was stirred for 24 hours. The next day, 1,4-(bistrimethylsilyl)benzene (BTMSB, 0.045 mmol, 10.0 mg) was added as an external standard. The acetonitrile solvent was removed under vacuum and the solid was redissolved in CDCl$_3$. The ^{1}H NMR spectrum matches literature reports[12] for the oxidative cleavage product, *N*-(2-acetylphenyl)formamide, and shows a 49% NMR yield (Figure S10).

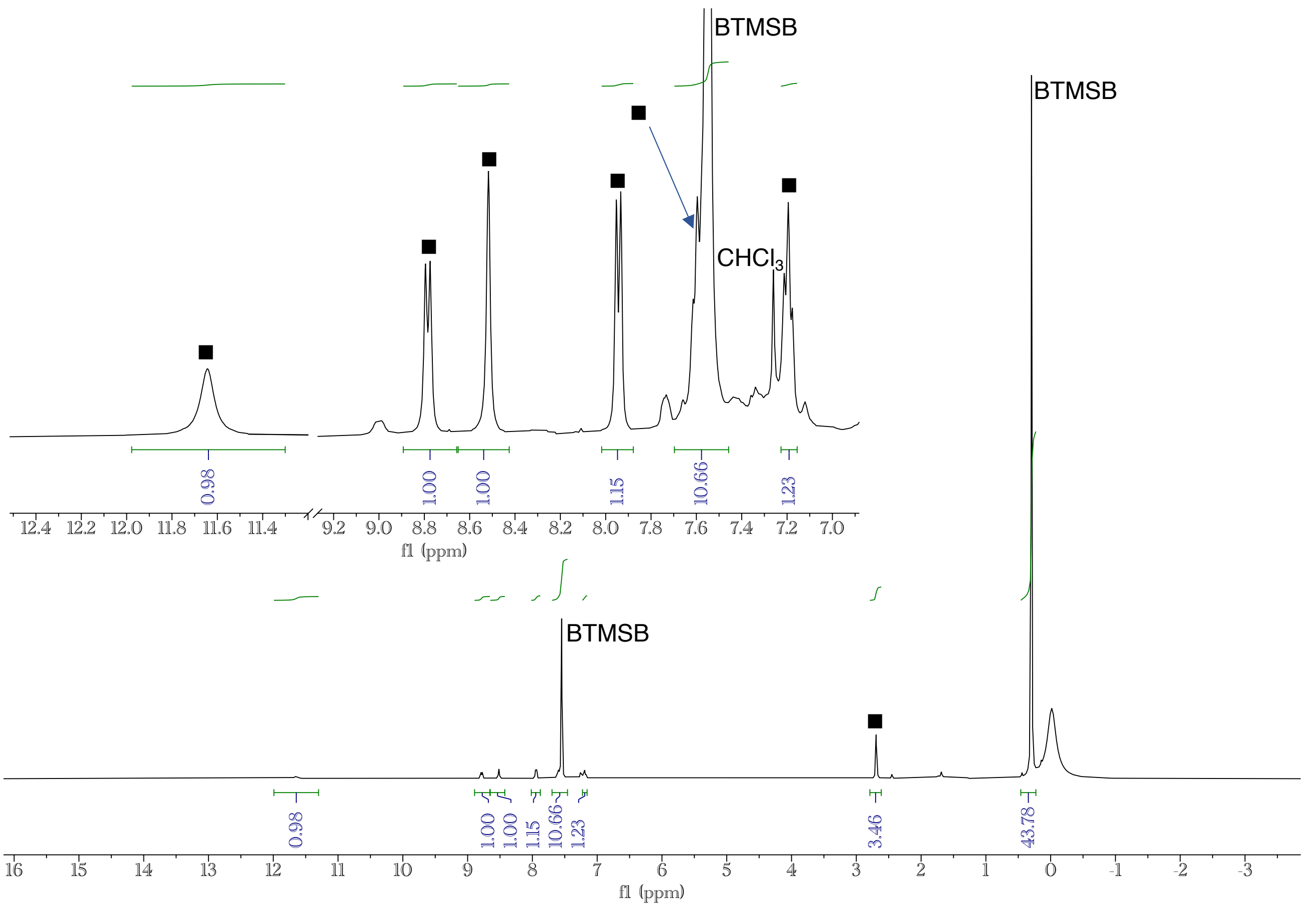


Figure S10. ^{1}H NMR spectrum of crude reaction of oxidative cleavage of 3-methylindole catalyzed by Fe(PFPP)Cl with decamethylferrocene reductant. *N*-(2-Acetylphenyl)formamide product (■) obtained in 49% yield.

9 References

1. Z. Zhang, L. Wu, J. Liao, W. Wu, H. Jiang, J. Li and J. Li, *J. Org. Chem.*, 2015, **80**, 7594–7603.
2. M. L. Pegis, D. J. Martin, C. F. Wise, A. C. Brezny, S. I. Johnson, L. E. Johnson, N. Kumar, S. Raugei and J. M. Mayer, *J. Am. Chem. Soc.*, 2019, **141**, 8315–8326.
3. D. J. Martin, S. I. Johnson, B. Q. Mercado, S. Raugei and J. M. Mayer, *Inorg. Chem.*, 2020, **59**, 17402–17414.
4. J. J. D. Sacramento and D. P. Goldberg, *Chem. Commun.*, 2020, **56**, 3089–3092.
5. P. Mondal and G. B. Wijeratne, *J. Am. Chem. Soc.*, 2020, **142**, 1846–1856.
6. E. Leete, *J. Am. Chem. Soc.*, 1961, **83**, 3645–3647.
7. V. Dave and E. Warnhoff, *Can. J. Chem.*, 1971, **49**, 1911–1920.
8. S. McLean and G. I. Dmitrienko, *Can. J. Chem.*, 1971, **49**, 3642–3647.
9. X. Shen, J. Lind, T. E. Eriksen and G. Merényi, *J. Chem. Soc. Perkin Trans. 2*, 1990, 597–603.
10. T. R. Pradhan, H. W. Kim and J. K. Park, *Org. Lett.*, 2018, **20**, 5286–5290.
11. Y. Liu, B. Yao, C.-L. Deng, R.-Y. Tang, X.-G. Zhang and J.-H. Li, *Org. Lett.*, 2011, **13**, 1126–1129.
12. K.-Q. Ling and L. M. Sayre, *Bioorg. Med. Chem.*, 2005, **13**, 3543–3551.