

Supplementary Information:

Mechanistic Investigation of Sustainable Heme-inspired Biocatalytic Synthesis of Cyclopropanes for Challenging Substrates

*Dongrun Ju, Vrinda Modi, Rahul L. Khade, Yong Zhang**

Department of Chemistry and Chemical Biology, Stevens Institute of Technology, 1 Castle Point
Terrace, Hoboken, NJ 07030

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Supplementary Note 1. Spin state effect

Experimental studies on iron porphyrin carbenes have demonstrated that the most favorable spin state is closed-shell singlet (CSS)^{1,2} with Fe^{II}-based features, providing accurate predictions of experimental features including Mössbauer, X-ray, and NMR properties, as opposed to Fe^{III}-based open-shell singlet (OSS) structures.^{1,3} Such a CSS feature is supported by additional experimental XANES studies and high-level multi-reference quantum chemical calculations.^{2,4} Therefore, the spin states of the iron-containing reactants (heme carbenes) in all of the studied reactions are CSS. The spin state of the iron-containing His-ligated product was previously determined to be quintet.⁵⁻⁷ As such, to determine the best spin state for **TS**, both singlet and quintet **TSs** were investigated here for the representative transition states in each studied pathway category as described below, including that of reactions **3**, **6**, **7**, **8**, **10**, and **13**. **TS(3)** was selected to explore the effect of spin under the substrate substituent effect (as opposed to **TS(1, 2)**, which share similar features with each other). Compared to **TS(3)**, **TS(6)** exhibited the largest difference in free energy and geometric and electronic parameters under the axial ligand effect, so this was also investigated. Under the experimentally studied macrocycle effect, **TS(7)** and **TS(8)** were selected as candidates due to their unique geometric interactions in this category. For the computationally studied macrocycles, **TS(10)** and **TS(13)** were selected due to their low free energy barriers and thus, high potential for future experimental applications, with both being ~ 0.2 kcal mol⁻¹ within each other. Because the previous experimental results show that iron carbene heme catalyst catalyzed cyclopropanation reaction has CSS feature^{5,8-10} and the high-level multi-reference quantum chemical calculations showed that the lowest OSS state has a significantly higher ΔE of 22.14 kcal mol⁻¹ than the CSS ground state of a similar heme carbene,⁴ only CSS was studied for the singlet. For quintet, we investigated different spin features including A) Fe^{II} (S=2) and carbene (S=0), B) ferromagnetically coupled Fe^{III} (S=3/2) and carbene (S=1/2), and C) anti-ferromagnetically coupled Fe^{III} (S=5/2), carbene (S=-1/2).

As seen from Supplementary Table 1, for **TS(3)**, only two spin features, A and B, were successfully located after geometry optimizations, while the initial spin feature C was optimized to A with Fe^{II} (S=2) feature (spin density $\rho^{\text{Fe}}_{\alpha\beta} = 3.996$ e). Quintet calculations for **TS(6)** are similar with only two spin features, A and B, found after geometry optimizations. For **TS(7)**, although two stable states were finally optimized, one resembles the Fe^{II} (S=2) feature A with $\rho^{\text{Fe}}_{\alpha\beta}$ of 3.956 e, while the other is close to Fe^{III} (S=3/2) coupled with radical carbene and substrate of opposite spins based on spin densities of 3.595 e on Fe ($\rho^{\text{Fe}}_{\alpha\beta}$), -0.479 e on carbene's carbon C1, and 0.748 e on substrate (see Supplementary Table 1). For **TS(8)**, all tries ended up with spin feature A after optimizations. **TS(13)** shows the same trend as **TS(8)**. However, for **TS(10)**, all initial setups were optimized with spin feature B: spin densities concentrated on Fe ($\rho^{\text{Fe}}_{\alpha\beta}$ of 3.264 e) and carbene carbon ($\rho^{\text{C1}}_{\alpha\beta}$ of 0.446 e). As shown in Supplementary Table 1, although different quintet **TS** results could be obtained with different reactions, all of them are of significantly higher energy than the CSS **TS**, which is consistent with the CSS concerted mechanism found in several experimental heme catalyzed cyclopropanation studies.^{5,8-10}

The above-mentioned most favorable spin states were used in the main text discussion.

Supplementary Table 1. TS Spin States and their Relative Energies* (unit: $kcal\ mol^{-1}$) and Spin Densities (unit: e)

TS	S	ρ_{Fe}	ρ_{C1}	ρ_{C2}	ρ_{C3}	$\rho_{R'}$	ρ_{Por}	ρ_L	ΔE	ΔE_{ZPE}	ΔH	ΔG
3	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.996	-0.345	0.111	-0.167	-0.024	0.351	0.041	11.38	9.67	10.28	19.68
	2	3.269	0.455	-0.144	0.216	0.034	0.151	0.015	15.39	12.43	13.47	7.65
6	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.987	-0.322	0.113	-0.174	-0.024	0.355	0.031	12.46	8.98	10.14	4.68
	2	3.319	0.423	-0.135	0.199	0.031	0.145	0.013	14.21	12.27	13.12	8.76
7	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.956	-0.296	0.067	-0.107	-0.015	0.342	0.016	15.53	12.00	13.22	8.55
	2	3.595	-0.479	-0.084	0.674	0.158	0.132	0.030	15.47	12.53	13.52	9.83
8	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.980	-0.342	0.074	-0.110	-0.016	0.338	0.038	15.01	11.76	12.63	9.42
10	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.264	0.446	-0.154	0.234	0.039	0.144	0.016	14.02	12.25	12.77	10.59
13	0	/	/	/	/	/	/	/	0.00	0.00	0.00	0.00
	2	3.928	-0.284	0.043	-0.059	-0.007	0.294	0.045	17.85	14.76	15.69	11.44

* Energies are relative to CSS species.

Supplementary Note 2. Substrate substituent effect

Supplementary Table 2. Absolute Energies of Species in Cyclopropanation Pathways of Different Olefins (unit: *Hartrees*)

Reaction	Species	E	E _{ZPE}	H	G
1^{a)}	R₁	-1683.67858	-1683.20091	-1683.16901	-1683.26230
	R₂	-309.59817	-309.46383	-309.45613	-309.49592
	TS	-1993.28963	-1992.67451	-1992.63575	-1992.74350
	P₁	-1377.27975	-1376.90283	-1376.87739	-1376.95905
	P₂	-616.08496	-615.84844	-615.83452	-615.88945
2	R₂	-314.43944	-314.21538	-314.20394	-314.25200
	TS	-1998.12778	-1997.42309	-1997.38038	-1997.49887
	P₂	-620.92923	-620.60232	-620.58479	-620.64811
3	R₂	-345.75738	-345.63270	-345.62389	-345.66536
	TS	-2029.44078	-2028.83575	-2028.79583	-2028.90676
	P₂	-652.24758	-652.02060	-652.00542	-652.06407

^{a)} All results for X=Ph are from previous work.⁵

Supplementary Table 3. Relative Energies of Species in Cyclopropanation Pathways of Different Olefins (unit: *kcal mol⁻¹*)

Reaction	System	ΔE	ΔE _{ZPE}	ΔH	ΔG
1	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-8.08	-6.13	-6.66	9.24
	P₁+P₂	-55.20	-54.30	-54.45	-56.65
2	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-6.13	-4.27	-4.66	9.68
	P₁+P₂	-57.08	-55.76	-55.99	-58.27
3	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-3.02	-1.34	-1.84	13.11
	P₁+P₂	-57.34	-56.36	-56.42	-59.90

Supplementary Table 4. Geometric Parameters of Species in Cyclopropanation Pathways of Different Olefins

Reaction	System	R _{FeC1} (Å)	R _{C1C2} (Å)	R _{C1C3} (Å)	R _{C2C3} (Å)	R _{FeL} (Å)	∠ _{HClY} ^{a)} (°)
1	R₁	1.755	/	/	/	2.122	113.3
	R₂	/	/	/	1.331	/	/
	TS	1.863	2.361	2.666	1.345	2.095	109.7
	P₁	/	/	/	/	2.173	/
	P₂	/	1.509	1.526	1.496	/	112.6
2	R₂	/	/	/	1.328	/	/
	TS	1.869	2.404	2.578	1.341	2.072	109.6
	P₂	/	1.519	1.518	1.490	/	112.5
3	R₂	/	/	/	1.327	/	/

TS	1.898	2.250	2.546	1.345	2.060	110.7
P₂	/	1.500	1.524	1.500	/	113.6

^{a)} H is the hydrogen atom connected to C1; Y is the carbonyl carbon connected to C1.

Supplementary Table 5. Atomic Charge of Species in Cyclopropanation Pathways of Different Olefins (unit: e)

Reaction System	Q _{Fe}	Q _{C1}	Q _H	Q _Y	Q _{C2}	Q _{C3}	Q _{R'} ^{a)}	Q _{Por} ^{b)}	Q _L	
1	R₁	0.089	0.087	0.193	-0.043	/	/	/	-0.583	0.246
	R₂	/	/	/	/	-0.349	-0.200	0.549	/	/
	TS	0.144	-0.055	0.199	-0.032	-0.337	-0.146	0.662	-0.680	0.265
	P₁	1.121	/	/	/	/	/	/	-1.278	0.157
	P₂	/	-0.316	0.234	-0.001	-0.354	-0.210	0.647	/	/
2	R₂	/	/	/	/	-0.386	-0.168	0.554	/	/
	TS	0.142	-0.057	0.195	-0.041	-0.344	-0.115	0.650	-0.696	0.265
	P₂	/	-0.326	0.230	-0.012	-0.370	-0.188	0.666	/	/
3	R₂	/	/	/	/	-0.267	-0.318	0.585	/	/
	TS	0.168	-0.100	0.201	-0.037	-0.264	-0.266	0.689	-0.670	0.278
	P₂	/	-0.302	0.244	0.010	-0.343	-0.308	0.699	/	/

^{a)} R' is substrate excluding C2 and C3; ^{b)} Por is the whole porphyrin with substituent(s).

Supplementary Note 3. Axial ligand effect

Supplementary Table 6. Absolute Energies of Species in Cyclopropanation Pathways of Different Axial Ligands (unit: *Hartrees*)

Reaction	System	E	E _{ZPE}	H	G
3	R₁	-1683.67858	-1683.20091	-1683.16901	-1683.26230
	TS	-2029.44078	-2028.83575	-2028.79583	-2028.90676
	P₁	-1377.27975	-1376.90283	-1376.87739	-1376.95905
4	R₁	-1782.91254	-1782.44281	-1782.41008	-1782.50498
	TS	-2128.67426	-2128.07757	-2128.03667	-2128.14996
	P₁	-1476.51585	-1476.1477	-1476.12200	-1476.20458
5	R₁	-2026.51069	-2026.04851	-2026.01657	-2026.11137
	TS	-2372.27309	-2371.68381	-2371.64370	-2371.75522
	P₁	-1720.11225	-1719.75138	-1719.72563	-1719.80920
6	R₁	-1705.72980	-1705.23462	-1705.20218	-1705.29610
	TS	-2051.48901	-2050.86630	-2050.82570	-2050.93885
	P₁	-1399.33140	-1398.93704	-1398.91095	-1398.99377

Supplementary Table 7. Relative Energies of Species in Cyclopropanation Pathways of Different Axial Ligands (unit: *kcal mol⁻¹*)

Reaction	System	ΔE	ΔE_{ZPE}	ΔH	ΔG
3	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-3.02	-1.34	-1.84	13.11
	P₁+P₂	-57.34	-56.36	-56.42	-59.90
4	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-2.73	-1.29	-1.70	12.79
	P₁+P₂	-58.68	-58.25	-58.64	-61.69
5	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-3.15	-1.63	-2.04	13.50
	P₁+P₂	-57.58	-56.96	-56.84	-60.58
6	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-1.15	0.64	0.23	14.19
	P₁+P₂	-57.61	-56.68	-56.66	-60.48

Supplementary Table 8. Geometric Parameters of Species in Cyclopropanation Pathways of Different Axial Ligands

Reaction	System	R _{FeC1} (Å)	R _{C1C2} (Å)	R _{C1C3} (Å)	R _{C2C3} (Å)	R _{FeL} (Å)	\angle_{HC1Y} (°)
3	R₁	1.755	/	/	/	2.122	113.3
	TS	1.898	2.250	2.546	1.345	2.060	110.7
	P₁	/	/	/	/	2.173	/
4	R₁	1.745	/	/	/	2.196	113.5
	TS	1.894	2.235	2.529	1.346	2.119	110.5
	P₁	/	/	/	/	2.204	/

5	R₁	1.749	/	/	/	2.167	113.4
	TS	1.896	2.244	2.541	1.345	2.090	110.6
	P₁	/	/	/	/	2.213	/
6	R₁	1.749	/	/	/	2.191	113.4
	TS	1.902	2.232	2.536	1.346	2.143	110.1
	P₁	/	/	/	/	2.220	/

Supplementary Table 9. Atomic Charge of Species in Cyclopropanation Pathways of Different Axial Ligands (unit: *e*)

Reaction System	Q _{Fe}	Q _{C1}	Q _H	Q _Y	Q _{C2}	Q _{C3}	Q _{R'}	Q _{Cycle} ^{a)}	Q _L	
3	R₁	0.089	0.087	0.193	-0.032	/	/	/	-0.583	0.246
	TS	0.168	-0.100	0.201	-0.037	-0.264	-0.266	0.689	-0.670	0.278
	P₁	1.121	/	/	/	/	/	/	-1.278	0.157
4	R₁	0.089	0.093	0.194	-0.027	/	/	/	-0.572	0.222
	TS	0.168	-0.099	0.202	-0.822	-0.265	-0.260	0.693	-0.666	0.259
	P₁	1.116	/	/	/	/	/	/	-1.271	0.155
5	R₁	0.097	0.097	0.194	-0.026	/	/	/	-0.577	0.214
	TS	0.172	-0.096	0.203	-0.033	-0.266	-0.259	0.694	-0.664	0.248
	P₁	1.105	/	/	/	/	/	/	-1.250	0.145
6	R₁	0.097	0.093	0.194	-0.026	/	/	/	-0.570	0.212
	TS	0.198	-0.100	0.202	-0.034	-0.270	-0.252	0.698	-0.677	0.234
	P₁	1.068	/	/	/	/	/	/	-1.211	0.143

^{a)} Cycle is the macrocycle without substituent(s).

Supplementary Note 4. Effects of experimentally studied macrocycle (reactions 7-9)

Supplementary Table 10. Absolute Energies of Species in Pathways of Reactions 7-9 (unit: *Hartrees*)

Reaction	System	E	E _{ZPE}	H	G
7	R ₁	-2270.90693	-2270.04962	-2269.99618	-2270.13731
	TS	-2580.52202	-2579.52664	-2579.46691	-2579.61982
	P ₁	-1964.50736	-1963.75040	-1963.70362	-1963.83230
	P ₂	-616.08626	-615.84955	-615.83570	-615.89052
8	R ₁	-2273.34679	-2272.44158	-2272.38776	-2272.52691
	TS	-2582.96233	-2581.91970	-2581.85897	-2582.01367
	P ₁	-1966.94695	-1966.13920	-1966.09203	-1966.21919
	P ₂	-1966.94695	-1966.13920	-1966.09203	-1966.21919
9	R ₁	-2273.33680	-2272.43202	-2272.37764	-2272.52019
	TS	-2582.95731	-2581.91385	-2581.85338	-2582.00765
	P ₁	-1966.93561	-1966.12982	-1966.08253	-1966.21136

Supplementary Table 11. Relative Energies of Species in Pathways of of Reactions 7-9 (unit: *kcal mol⁻¹*)

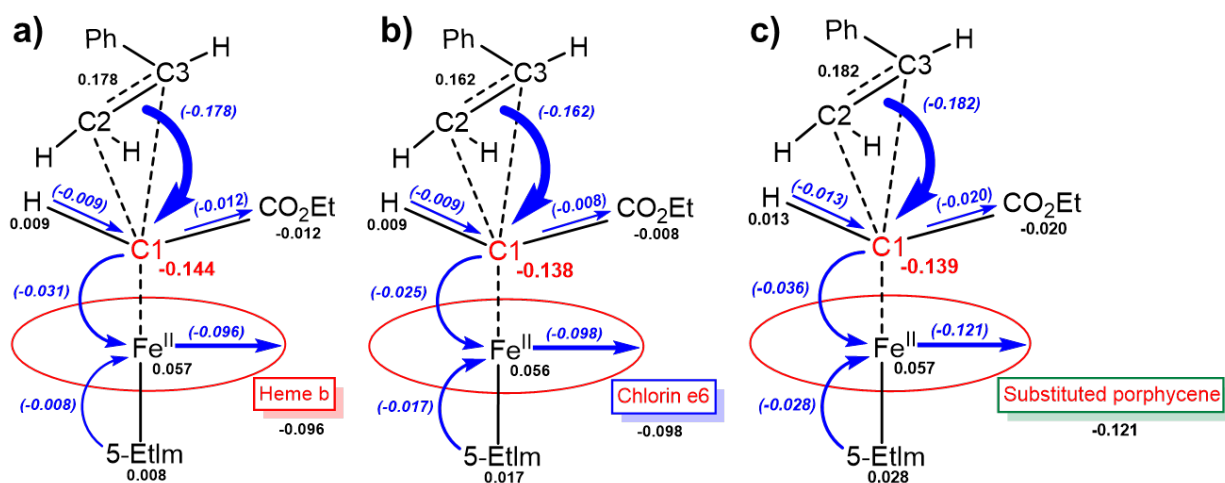
Reaction	System	ΔE	ΔE _{ZPE}	ΔH	ΔG
7	R ₁ +R ₂	0.00	0.00	0.00	0.00
	TS	-10.62	-8.28	-9.16	8.41
	P ₁ +P ₂	-55.55	-54.28	-54.60	-56.23
8	R ₁ +R ₂	0.00	0.00	0.00	0.00
	TS	-10.90	-8.97	-9.46	5.75
	P ₁ +P ₂	-55.38	-52.30	-52.60	-54.52
9	R ₁ +R ₂	0.00	0.00	0.00	0.00
	TS	-14.02	-11.30	-12.31	5.31
	P ₁ +P ₂	-53.71	-51.71	-52.26	-53.15

Supplementary Table 12. Geometric Parameters of Species in Pathways of Reactions 7-9

Reaction	System	R _{FeC1} (Å)	R _{C1C2} (Å)	R _{C1C3} (Å)	R _{C2C3} (Å)	R _{FeL} (Å)	∠ _{HC1Y} (°)
7	R ₁	1.759	/	/	/	2.111	113.0
	TS	1.862	2.358	2.636	1.345	2.092	110.3
	P ₁	/	/	/	/	2.182	/
	P ₂	/	1.509	1.523	1.495	/	115.5
8	R ₁	1.753	/	/	/	2.132	113.8
	TS	1.857	2.360	2.664	1.345	2.089	110.1
	P ₁	/	/	/	/	2.190	/
9	R ₁	1.750	/	/	/	2.139	113.5
	TS	1.866	2.330	2.639	1.346	2.075	112.1
	P ₁	/	/	/	/	2.199	/

Supplementary Table 13. Atomic Charge of Species in Pathways of Reactions 7-9 (unit: e)

Reaction System	Q_{Fe}	Q_{C1}	Q_H	Q_Y	Q_{C2}	Q_{C3}	$Q_{R'}$	Q_{Cycle}	Q_L	
7	R₁	0.095	0.083	0.192	-0.032	/	/	/	-0.588	0.251
	TS	0.152	-0.061	0.201	-0.044	-0.328	-0.153	0.659	-0.684	0.259
	P₁	1.120	/	/	/	/	/	/	-1.273	0.153
	P₂	/	-0.320	0.233	-0.003	-0.350	-0.208	0.647	/	/
8	R₁	0.107	0.077	0.192	-0.035	/	/	/	-0.583	0.242
	TS	0.163	-0.061	0.201	-0.043	-0.344	-0.154	0.660	-0.682	0.259
	P₁	1.138	/	/	/	/	/	/	-1.283	0.146
9	R₁	0.044	0.075	0.190	-0.039	/	/	/	-0.517	0.246
	TS	0.101	-0.064	0.203	-0.059	-0.332	-0.147	0.661	-0.636	0.274
	P₁	1.119	/	/	/	/	/	/	-1.268	0.149

**Supplementary Figure 1.** Atomic charge changes from reactants to transition state (in black) and charge transfers (in blue) in reactions 7-9. **a)** reaction 7, **b)** reaction 8, and **c)** reaction 9.

Supplementary Note 5. Effects of macrocycles not being experimentally studied yet (reactions 10-13)

Supplementary Table 14. Absolute Energies of Species in Pathways of Reactions **10-13** (unit: *Hartrees*)

Reaction	System	E	E _{ZPE}	H	G
10	R₁	-1684.89448	-1684.39316	-1684.36072	-1684.45464
	TS	-2030.65936	-2030.03149	-2029.99067	-2030.10492
	P₁	-1378.49910	-1378.09852	-1378.07226	-1378.15759
11	R₁	-1683.65514	-1683.17799	-1683.14602	-1683.23970
	TS	-2029.41472	-2028.81013	-2028.77010	-2028.88191
	P₁	-1377.24857	-1376.87204	-1376.84644	-1376.92913
12	R₁	-2362.38104	-2361.76068	-2361.71871	-2361.83434
	TS	-2708.14448	-2707.39671	-2707.34663	-2707.48005
	P₁	-2055.96607	-2055.44685	-2055.41140	-2055.51631
13	R₁	-2052.60782	-2052.13545	-2052.09615	-2052.20666
	TS	-2398.37381	-2397.77492	-2397.72706	-2397.85726
	P₁	-1746.20884	-1745.83714	-1745.80435	-1745.90246

Supplementary Table 15. Relative Energies of Species in Pathways of Reactions **10-13** (unit: *kcal mol⁻¹*)

Reaction	System	ΔE	ΔE_{ZPE}	ΔH	ΔG
10	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-4.71	-3.54	-3.80	9.46
	P₁+P₂	-59.50	-58.53	-58.40	-63.79
11	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-1.38	0.35	-0.11	14.53
	P₁+P₂	-52.48	-51.42	-51.43	-55.31
12	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-3.80	-2.09	-2.53	12.33
	P₁+P₂	-47.21	-46.48	-46.57	-50.63
13	R₁+R₂	0.00	0.00	0.00	0.00
	TS	-5.40	-4.24	-4.40	9.26
	P₁+P₂	-57.24	-56.22	-56.30	-59.30

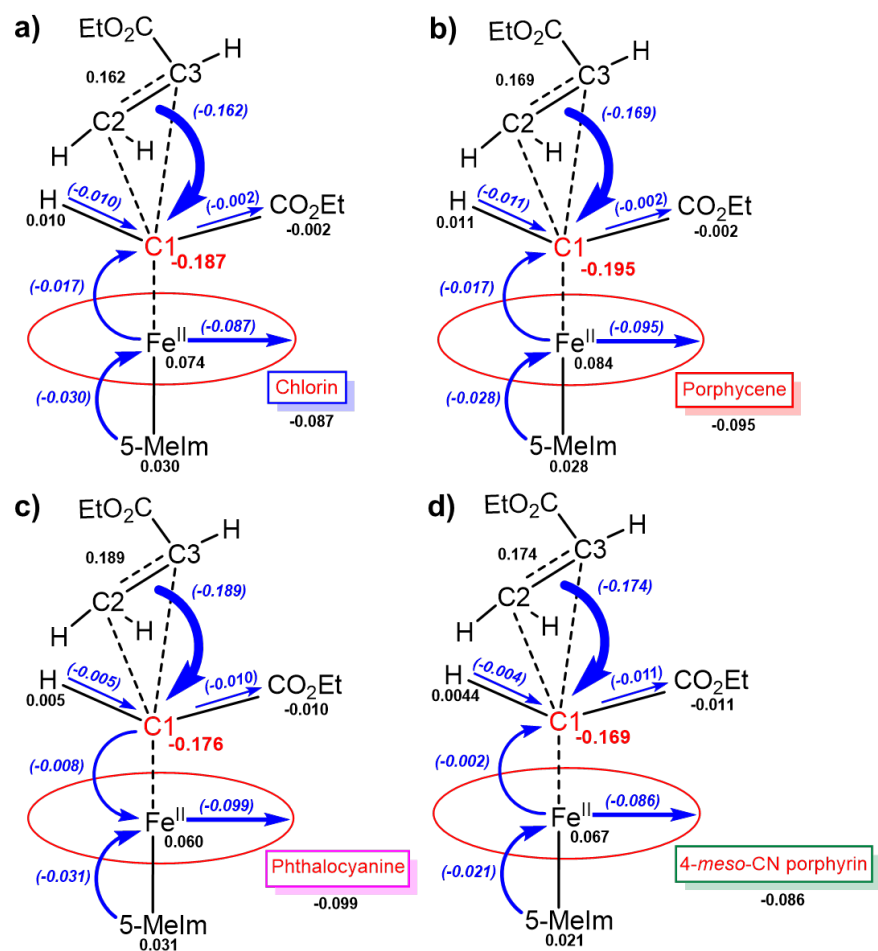
Supplementary Table 16. Geometric Parameters of Species in Pathways for Reactions **10-13**

Reaction	System	R _{FeC1} (Å)	R _{C1C2} (Å)	R _{C1C3} (Å)	R _{C2C3} (Å)	R _{FeL} (Å)	\angle_{HC1Y} (°)
10	R₁	1.757	/	/	/	2.116	113.4
	TS	1.895	2.256	2.510	1.346	2.056	110.3
	P₁	/	/	/	/	2.173	/
11	R₁	1.754	/	/	/	2.114	113.6
	TS	1.898	2.208	2.522	1.347	2.064	111.0
	P₁	/	/	/	/	2.151	/

12	R₁	1.764	/	/	/	2.136	113.1
	TS	1.901	2.305	2.524	1.343	2.075	110.7
	P₁	/	/	/	/	2.146	/
13	R₁	1.771	/	/	/	2.094	113.1
	TS	1.893	2.356	2.572	1.341	2.056	110.7
	P₁	/	/	/	/	2.149	/

Supplementary Table 17. Atomic Charge of Species in Pathways for Reactions **10-13** (unit: *e*)

Reaction System	Q _{Fe}	Q _{C1}	Q _H	Q _Y	Q _{C2}	Q _{C3}	Q _{R'}	Q _{Cycle}	Q _L	
10	R₁	0.100	0.085	0.190	-0.031	/	/	/	-0.592	0.248
	TS	0.174	-0.103	0.200	-0.033	-0.255	-0.272	0.690	-0.679	0.278
	P₁	1.124	/	/	/	/	/	/	-1.280	0.155
11	R₁	0.029	0.090	0.192	-0.036	/	/	/	-0.534	0.259
	TS	0.113	-0.105	0.203	-0.038	-0.269	-0.254	0.692	-0.629	0.287
	P₁	1.104	/	/	/	/	/	/	-1.270	0.166
12	R₁	-0.002	0.109	0.197	-0.013	/	/	/	-0.550	0.259
	TS	0.058	-0.067	0.202	-0.023	-0.262	-0.250	0.701	-0.649	0.290
	P₁	1.093	/	/	/	/	/	/	-1.269	0.176
13	R₁	0.083	0.106	0.199	-0.008	/	/	/	-0.647	0.268
	TS	0.150	-0.063	0.202	-0.019	-0.264	-0.256	0.694	-0.733	0.289
	P₁	1.141	/	/	/	/	/	/	-1.311	0.170



Supplementary Figure 2. Atomic charge changes from reactants to transition state (in black) and charge transfers (in blue) in reactions 10-13. **a)** reaction 10, **b)** reaction 11, **c)** reaction 12, and **d)** reaction 13.

Supplementary Note 6. Imaginary frequencies of transition states

Supplementary Table 18. Imaginary Frequencies of all TSs (unit: cm^{-1})

TS	Frequency	TS	Frequency
1	-218	8	-198
2	-191	9	-242
3	-296	10	-296
4	-310	11	-328
5	-299	12	-260
6	-310	13	-215
7	-211		

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