

Iron-Catalyzed Oxidation Reactions

Fe

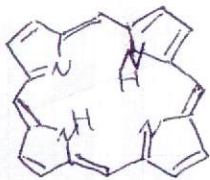
Iron is one of the most abundant metals in the universe. It is inexpensive, environmentally benign, and relatively nontoxic in comparison to other metals.

Biology

Iron is essential to all organisms, except for a few bacteria.

- metalloprotein
- metalloenzyme

① Heme = Iron complex of porphyrin, which is a substituted derivative of the porphyrin ring system.



porphyrin ring

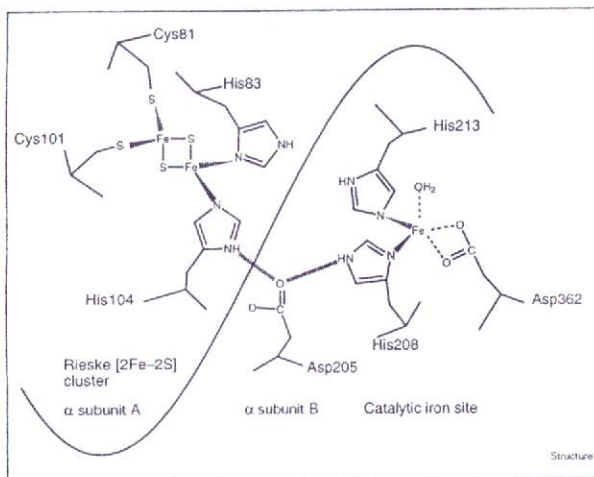
ex. cytochrome P-450

② Non-heme iron enzyme

Rieske oxygenase

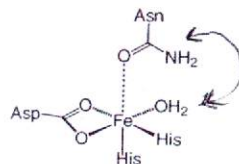
- naphthalene 1,2-dioxygenase

Figure 8



Structure 1998, 6, 572-

Proposed route of electron transfer between adjacent α subunits. The Rieske center in α subunit A is connected to the catalytic center of the adjacent α subunit B. The connection is through Asp205, which is hydrogen bonded to His104 of the Rieske center and His208 at the active site.



two cis sites available for exogenous ligands.

It is proposed that the Fe^{II} center binds O_2 and accepts an electron from the Rieske cluster to give an Fe^{III} peroxo species.

Olefin Cis-Dihydroxylation versus Epoxidation by Non-Heme Iron Catalysts: Two Faces of an Fe^{III}-OOH Coin

Kui Chen, Miquel Costas, Jinheung Kim, Adrienne K. Tipton, and Lawrence Que, Jr.*

JACS, 2002, 124, 3026-3035

Olefin oxidation reaction.

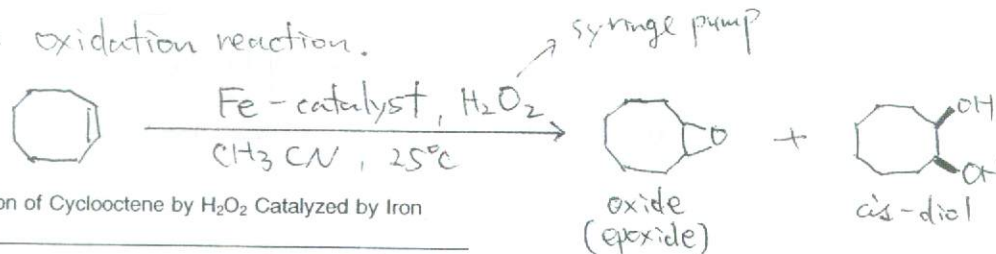


Table 2. Oxidation of Cyclooctene by H₂O₂ Catalyzed by Iron Complexes^a

	catalyst	cis-diol ^b	oxide ^b	cis-diol:oxide	conv ^c (%)
1	[Fe(BPMEN)(CH ₃ CN) ₂] ²⁺	0.9(2)	7.5(6)	1:8	84
2	[Fe(5-Me ₂ -BPMEN)(OTf) ₂]	1.3(4)	7.8(3)	1:6	91
3	[Fe(6-Me ₂ -BPMEN)(OTf) ₂]	6.2(1) ^d	1.5(1)	4:1	79
4	[Fe(TPA)(CH ₃ CN) ₂] ²⁺	4.0(2)	3.4(1)	1.2:1	74
4a	[Fe ₂ O(TPA) ₂ (H ₂ O) ₂] ⁴⁺	4.1(1)	4.0(1)	1:1	81
5	[Fe(5-Me ₃ -TPA)(CH ₃ CN) ₂] ²⁺	3.9(4)	2.8(1)	1.4:1	67
6	[Fe(6-Me-TPA)(CH ₃ CN) ₂] ²⁺	2.8(1)	2.1(2)	1.3:1	49
7	[Fe(6-Me ₂ -TPA)(CH ₃ CN) ₂] ²⁺	5.5(1)	1.1(2)	5:1	66
8a	[Fe(6-Me ₃ -TPA)(CH ₃ CN) ₂] ²⁺	4.9(6)	0.7(2)	7:1	56
8b	[Fe(6-Me ₃ -TPA)(O ₂ CC ₆ H ₄ -4-Me)] ⁺	5.0(6)	0.5(1)	10:1	55
8c	[Fe(6-Me ₃ -TPA)(O ₂ CC ₆ H ₅)] ⁺	6.1(4)	0.5(1)	12:1	66
8d	[Fe(6-Me ₃ -TPA)(O ₂ CC ₆ H ₄ -3-NO ₂)] ⁺	6.7(3)	0.4(1)	17:1	71
9	[Fe(N4Py)(CH ₃ CN) ₂] ²⁺	0	0.6		6
10	[Fe(cyclam)(OTf) ₂] ^c	0	4		40
11	[Fe(TMP)Cl] ^c	0	0.2		2
12	[Fe(F ₂₀ TPP)Cl] ^c	0	8.6		86

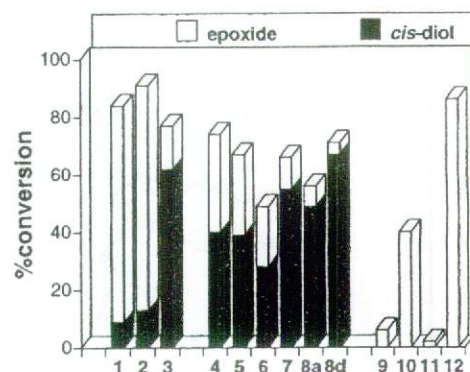
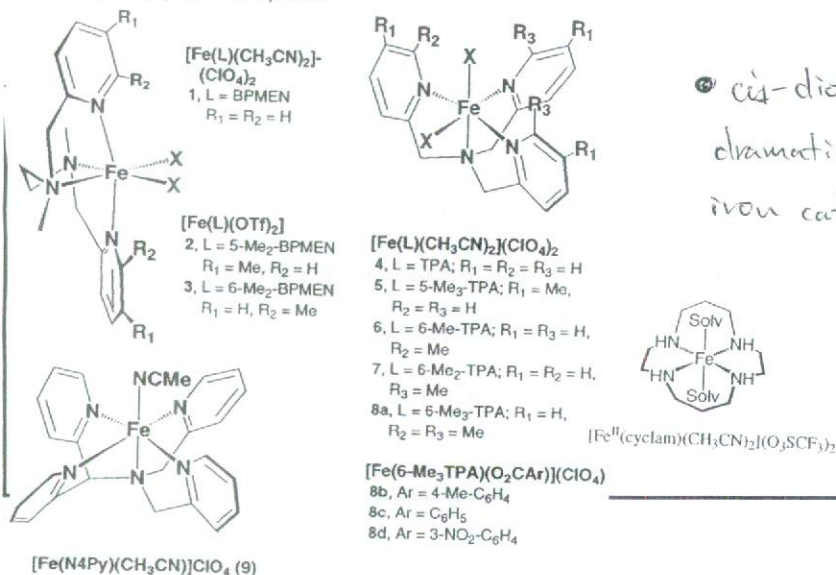


Figure 2. Percent conversion of H₂O₂ into epoxide and cis-diol products derived from cyclooctene oxidation catalyzed by complexes 1–12 based on data listed in Table 2. See Chart 1 for structures of complexes 1–9; 10 = [Fe(cyclam)(OTf)₂]; 11 = [Fe(TPP)Cl]; 12 = [Fe(F₂₀TPP)Cl].

^a See Experimental Section for reaction conditions. ^b Yields expressed in moles of product per mole of iron. ^c Percent conversion of H₂O₂ into epoxide and cis-diol products. ^d 0.2(1) TN of trans-diol also observed. ^e Values scaled to 10 equiv of H₂O₂ for comparison; cyclam = 1,4,8,11-tetraazacyclotetradecane; TMP = tetramesitylporphinato dianion; F₂₀TPP = tetrakis(pentafluorophenyl)porphinato dianion.

Reaction Conditions for Catalytic Oxidations. In a typical reaction, 0.3 mL of a 70 mM H₂O₂ solution (diluted from a 35 or 50% H₂O₂ solution) in CH₃CN was delivered by syringe pump over 30 min at 25 °C in air to a vigorously stirred CH₃CN solution (2.7 mL) containing iron catalyst and olefin substrate. The final concentrations were 0.7 mM mononuclear iron catalyst (or 0.35 mM dinuclear iron catalyst 4a), 7.0 mM H₂O₂, and 0.70 M olefin. + 5 min.

Chart 1. Ligands Used in This Study and the Numbering Scheme for Corresponding Iron Complexes



- The diol did not come from the epoxide.
- Complexes 1-8 all have two cis labile coordination sites.

↳ required for cis-dihydroxylation

- cis-diol/epoxide ratio depends dramatically on the nature of the iron catalyst employed.

BPMEN = N,N'-dimethyl-N,N'-bis(2-pyridylmethyl)-1,2-diaminoethane
TPA = tris(2-pyridylmethyl)amine

Physical Properties of the Catalysts. 1, 4, 8a

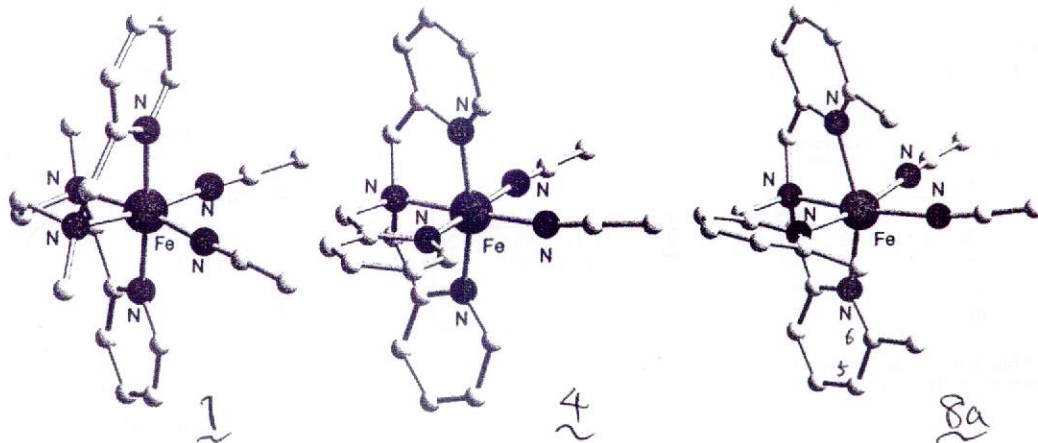
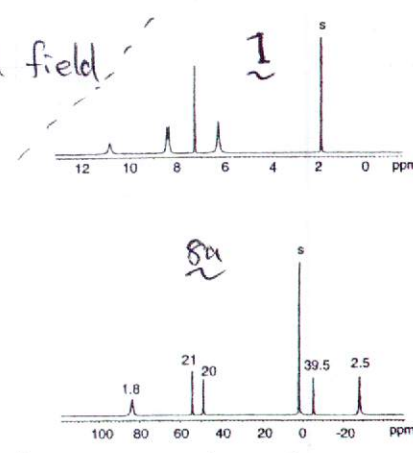
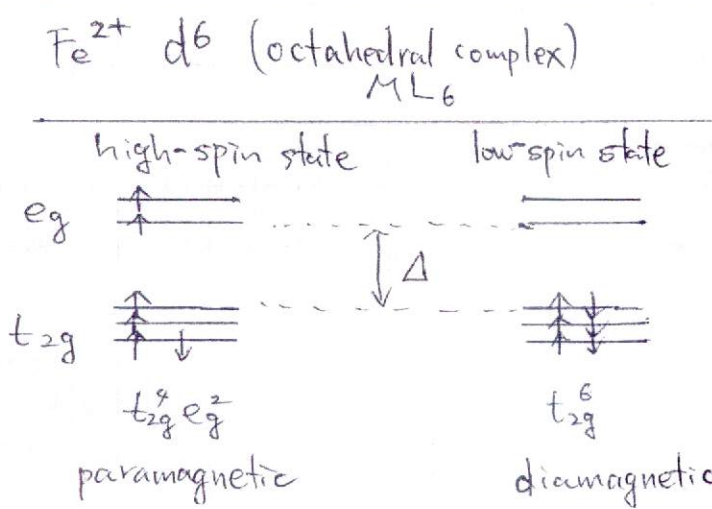


Figure 38. Crystal structures of $[\text{Fe}^{\text{II}}(\text{BPMEN})(\text{CH}_3\text{CN})_2]^{2+}$, $[\text{Fe}^{\text{II}}(\text{TPA})(\text{CH}_3\text{CN})_2]^{2+}$, and $[\text{Fe}^{\text{II}}(6\text{-Me}_3\text{-TPA})(\text{CH}_3\text{CN})_2]^{2+}$.

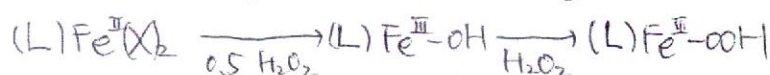
	<u>1</u>	<u>4</u>	<u>8a</u>
Fe-N bond length	1.94-2.05 Å	1.92-1.99 Å	2.17-2.24 Å
	low-spin Fe^{II} center [category A]		high-spin Fe^{II} center [category B]

Steric repulsion between the methyl group and the metal center prevents the formation of the shorter Fe-N bonds required for the low-spin state.



^1H NMR spectra of 1 and 8a in CD_3CN at rt.

Formation of an $\text{Fe}^{\text{III}}\text{-OOH}$ intermediate



^{18}O -Labeling Experiment GC/CI-MS analysis

Table 6. Isotope Labeling Results from the Oxidation of Cyclooctene by H_2O_2 Catalyzed by Iron Complexes^a

ligand	cyclooctene oxide- $^{18}\text{O}\%$			cis-cyclooctane-1,2-diol			
	H_2^{18}O	$\text{H}_2^{18}\text{O}_2$	$^{18}\text{O}_2^b$	H_2^{18}O		$\text{H}_2^{18}\text{O}_2$	
				$^{16}\text{O}^{18}\text{O}$	$^{18}\text{O}^{18}\text{O}$	$^{16}\text{O}^{18}\text{O}$	$^{18}\text{O}^{18}\text{O}$
4 TPA	9(1)	90(8)	1	86(5)	1(1)	97(3)	3(1)
5 5-Me ₃ -TPA	2(1)	93(6)	5	83(9)	1(1)	97(3)	2(2)
6 6-Me-TPA	7(1)	71(9)	22	80(1)	2(1)	94(4)	6(1)
7 6-Me ₂ -TPA	3(1)	61(8)	36	3(1)	1(1)	7(1)	93(3)
8a 6-Me ₃ -TPA	3(1)	54(2)	43	1(1)	0	4(1)	96(1)

^a See Experimental Section for reaction conditions. ^b Calculated considering mass balance of the oxygen atom.

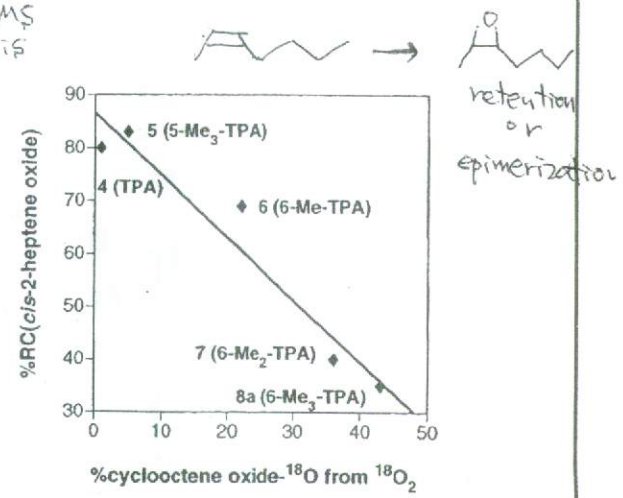


Figure 5. Linear correlation between the RC value for cis-2-heptene epoxidation and the amount of O_2 incorporation into cyclooctene oxide for the TPA series of catalysts ($r^2 = 0.94$). Data obtained from Tables 5 and 6.

category A (4, 5, 6)

Epoxide and cis-diol products incorporate ^{18}O from H_2^{18}O .
No incorporation of O_2 from air.

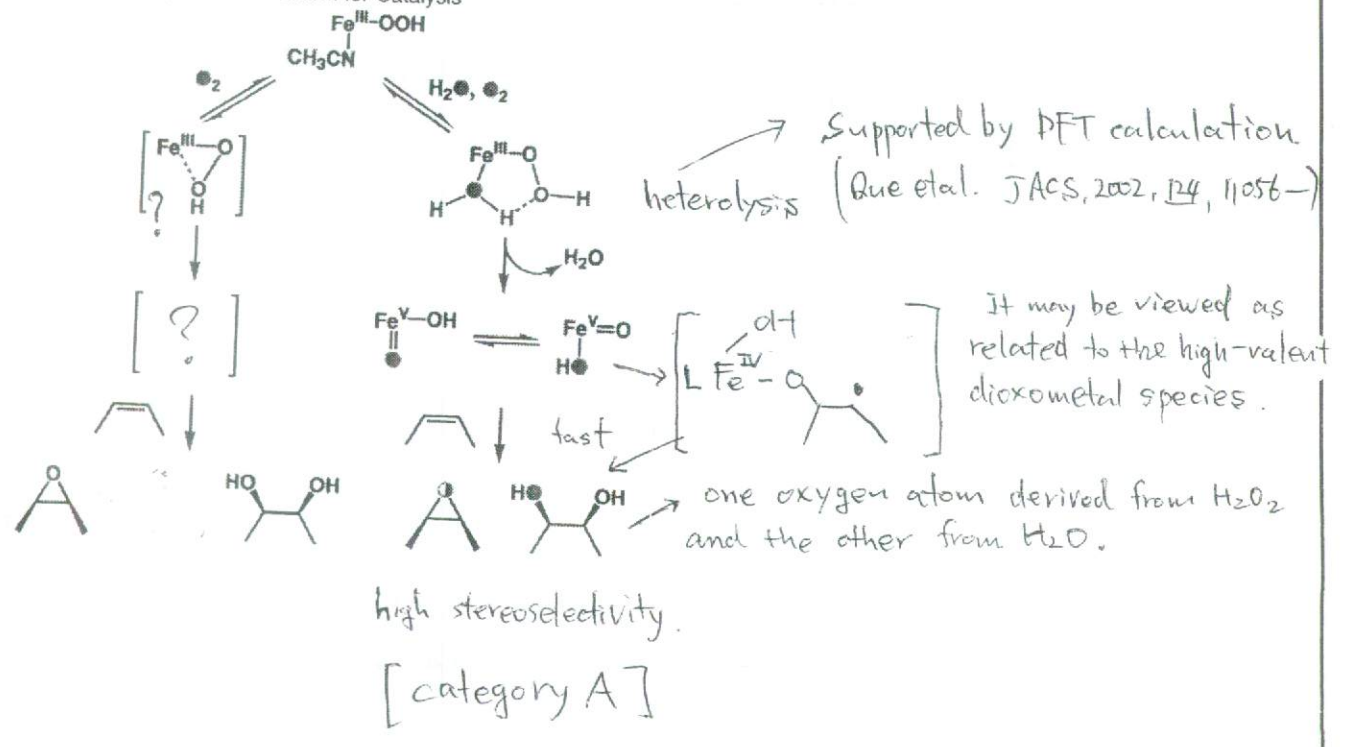
category B (7, 8a)

cis-diol products incorporate both oxygen atoms from $\text{H}_2^{18}\text{O}_2$.
Epoxide product derives its oxygen atom from O_2 in air?

$$\text{RC} = \frac{\text{cis} - \text{trans}}{\text{cis} + \text{trans}} \times 100$$

Increased involvement of a radical cation intermediate leading to epimerization and autoxidation.

Scheme 2. Proposed Mechanism for Catalysis



Iron-Catalyzed Olefin *cis*-Dihydroxylation by H₂O₂: Electrophilic versus Nucleophilic Mechanisms

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Table 1. Olefin Oxidation Products^a

entry	olefin	1	2
		diol/epoxide ^b [%RC] ^c	diol/epoxide ^b [%RC] ^c
1	acrylonitrile	8.5(4)/-	7.3(7)/-
2	methacrylonitrile	7.0(12)/-	6.9(12)/-
3	<i>tert</i> -butyl acrylate	5.8(8)/-	6.2(6)/-
4	ethyl <i>trans</i> -crotonate	6.9(5)/- [>99]	4.5(1)/- [>99]
5	dimethyl fumarate	9.5(3)/- [>99]	5.2(4)/- [>99]
6	dimethyl maleate	7.8(4)/- [79]	4.2(3)/- [10]
7	<i>cis</i> -2-heptene ^{1b}	3.0(3)/1.9(1) [96]	4.1(4)/0.4(1) [93]
8	<i>cis</i> -cyclooctene ^{1b}	4.2(2)/3.4(1)	4.9(6)/0.7(2)
9	1-octene	6.1(3)/1.1(2)	4.7(9)/0.1(1)

^a Reaction conditions: An H₂O₂ solution (21 μ mol or 0.30 mL of a 70 mM solution in CH₃CN with ≥ 245 mM H₂O) was added via syringe pump over 22 min to a solution of olefin (1050 μ mol) and the catalyst (2.1 μ mol) in CH₃CN (2.7 mL) at 22–25 °C under air. ^b Yield expressed as turnover numbers (μ mol product/ μ mol catalyst) determined by GC analysis; average of 2–3 runs. ^c %RC: $100 \times (A - B)/(A + B)$ where A = yield of *cis*-diol with retention of configuration and B = yield of epimer.

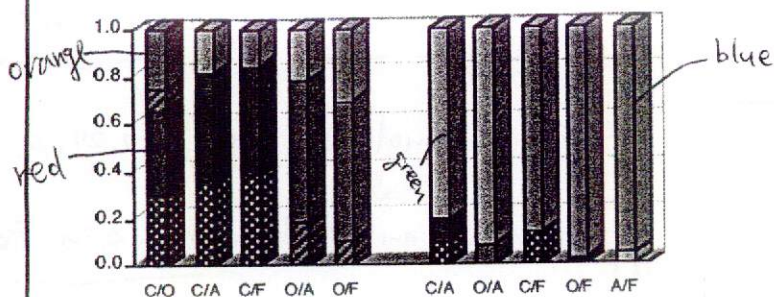
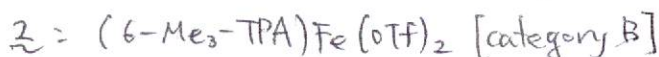
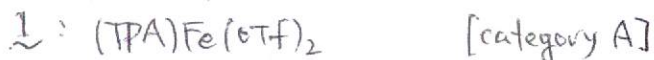
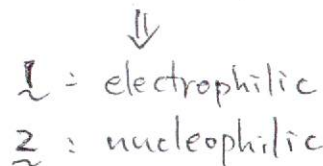
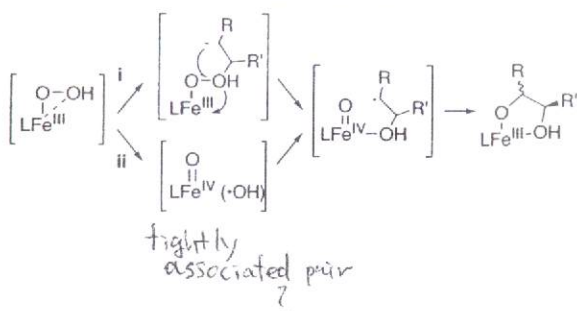


Figure 1. Competition experiments for the oxidation of olefin pairs by catalysts 1 (left) and 2 (right): C = cyclooctene (red), O = 1-octene (orange), A = *tert*-butyl acrylate (green), F = dimethyl fumarate (blue). Conditions as described under Table 1 except that 1050 μ mol each of two olefins was used. Solid blocks represent the fraction of diol formed, while patterned blocks represent the fraction of epoxide formed.

Competition experiment between electron-rich and electron-deficient olefins show that 1 prefers to oxidize electron-rich olefins, while 2 prefers to oxidize electron-deficient olefins.



Scheme 2. Proposed Mechanisms of *cis*-Dihydroxylation by a Nucleophilic Oxidant Generated from 2/H₂O₂



The rate of oxygen rebound on the stability of the transient alkyl radical.
 \Rightarrow high RC value for *cis*-2-heptene
 lower for dimethyl maleate

J. Am. Chem. Soc. 2001, 123, 6722–6723

Modeling Rieseke Dioxygenases: The First Example of Iron-Catalyzed Asymmetric *cis*-Dihydroxylation of Olefins

Miquel Costas, Adrienne K. Tipton, Kui Chen, Du-Hwan Jo, and Lawrence Que, Jr.*

Table 1. Oxidation of Olefins with H₂O₂ Catalyzed by 1–4^a

cat	substrate/eq H ₂ O ₂	epox(de) ^b	diol(de) ^b	ee ^c
1	cyclooctene/10	7.5(100)	0.9(100)	
2	cyclooctene/10	1.5(100)	6.4(94)	
1 <i>R</i> ,2 <i>R</i> -3	cyclooctene/10	5.8(100)	0.7(100)	
	<i>trans</i> -2-heptene/10	5.4(100)	0.3(100)	29(2)
1 <i>S</i> ,2 <i>S</i> -4	cyclooctene/10	3.5(100)	5.8(79)	
	cyclooctene/20	5.4(100)	11.2(89)	
	<i>cis</i> -2-heptene/20	4.5(56)	7.8(82)	9(2)
	<i>cis</i> -3-heptene/20	4.8(26)	5.5(85)	3(2)
	1-octene/20	1.3	8.1	60(2)
	vinylcyclohexane/20	2.5	9.0	48(2)
	<i>tert</i> -butyl acrylate/20	0.5	10.1	23(2)
	<i>trans</i> -2-heptene/20	2.4(100)	7.5(100)	79(2)
	<i>trans</i> -2-octene/20	2.3(100)	7.5(100)	82(5)
1 <i>R</i> ,2 <i>R</i> -4	<i>trans</i> -2-heptene/20	2.1(100)	8.2(100)	76(2)

^a Reaction conditions: 0.7 mM catalyst and 700 mM olefin in 3 mL of CH₃CN at 30 °C under air to which 10–20 equiv of H₂O₂ (from 50% aqueous H₂O₂) in MeCN is added via syringe pump over 30 min. Results are given as mmol product/mmol of catalyst and are the average of 2–3 runs. ^b de = diastereomeric excess. ^c ee of the predominant diol isomer. Determined by GC with a Hewlett-Packard Chiral-Permethy-lated β-Cyclodextrin column.

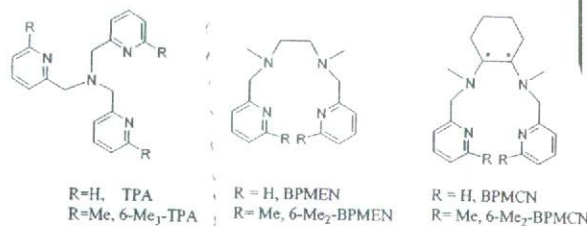
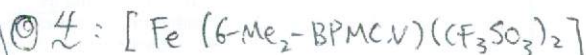
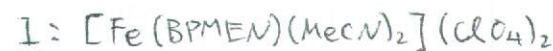


Figure 1. Tetradentate ligands used in this study.



88% ee at 50°C

values which approach those reported for the Os-catalyzed reactions.

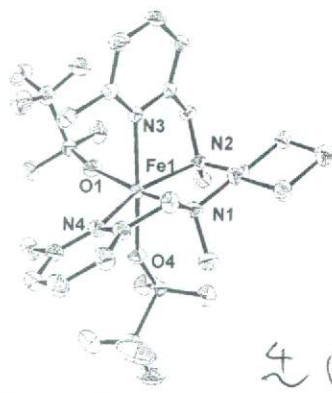
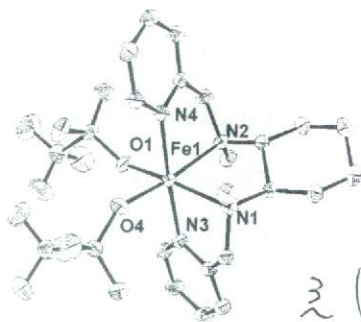


Figure 2. ORTEP plots for 3 (top) and 4 (bottom) showing 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) for 3: Fe–N1 = 2.237(2), Fe–N2 = 2.220(2), Fe–N3 = 2.151(2), Fe–N4 = 2.162(2), Fe–O1 = 2.131(2), Fe–O4 = 2.159(2). For 4: Fe–N1 = 2.203(4), Fe–N2 = 2.239(3), Fe–N3 = 2.274(3), Fe–N4 = 2.191(4), Fe–O1 = 2.084(3), Fe–O4 = 2.190(3).

Fe–N bond ... 2.151 ~ 2.274 Å

both 3 and 4 have high spin Fe^{II}

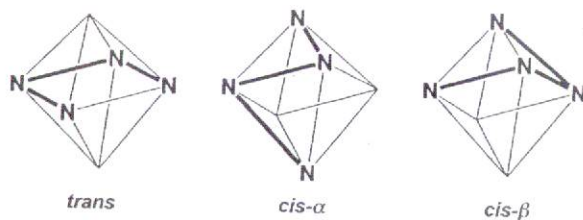
Contrary to the Os-catalysis. (lower temp. → higher ee)

There may be more than one active species present in solution. Increasing the temp. would favor population of the more enantioselective isomer.

Ligand Topology Tuning of Iron-Catalyzed Hydrocarbon Oxidations**

Miquel Costas and Lawrence Que, Jr.*

Angew. Chem. Int. Ed. 2002, 41, 2179



Scheme 1. Three different topologies that can be adopted by tetradentate ligands such as *N,N'*-bis(2-pyridylmethyl)-*N,N'*-dimethyl-*trans*-1,2-diaminocyclohexane (bpmcn).

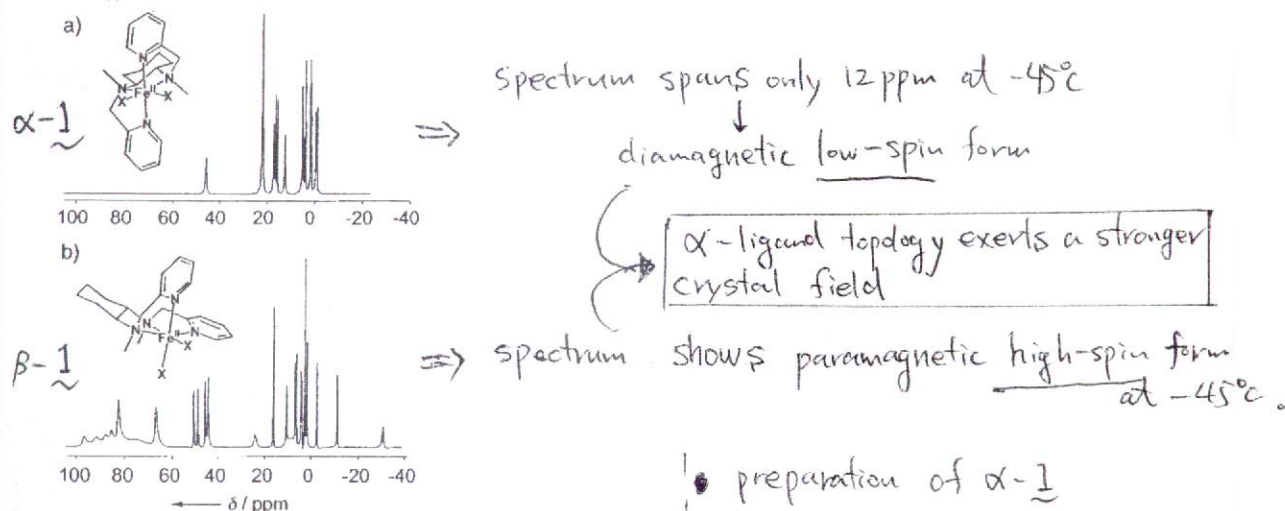


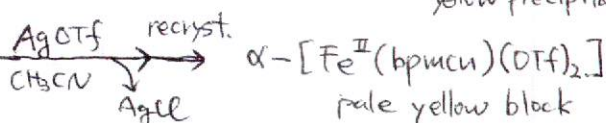
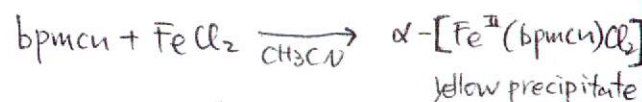
Figure 1. ^1H NMR spectra of α -[Fe^{II}(bpmcn)(CD₃CN)₂]²⁺ (a) and β -[Fe^{II}(bpmcn)(CD₃CN)₂]²⁺ (b) in CD₃CN solution at ambient temperature.

These isomers do not interconvert at 50°C.

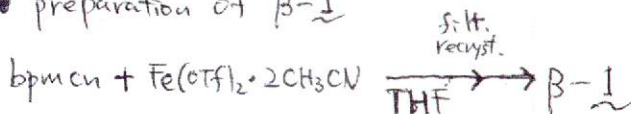
Table 2. Olefin oxidation reactivities of nonheme iron catalysts.^[a]

	Fe(tpa) ^[b]	α -1	β -1	Fe(6-Me ₃ -tpa) ^[b]
cyclooctene				
diol + epoxide (TN) ^[c]	7.4	6.5	7.7	5.6
[diol]/[epoxide]	1.2:1	0.1:1	1.8:1	7.0:1
epoxide % ¹⁸ O	90/9	90/11	66/15	54/3
[H ₂ ¹⁸ O ₂ /H ₂ ¹⁸ O](%) ^[d]				
diol % ¹⁸ O from				
H ₂ ¹⁸ O ₂ [noO/1O/2O](%) ^[e]	0/97/3	3/89/7	2/4/93	4/96
H ₂ ¹⁸ O [noO/1O/2O](%) ^[f]	13/86/1	11/88/1	97/3/0	99/1/0
<i>cis</i> -2-heptene				
diol + epoxide (TN) ^[c]	4.9	7.0	6.8	4.5
[diol]/[epoxide]	1.6:1	0.1:1	0.8:1	10:1
% RC ^[g] epoxide	80	>99	67	35
% RC ^[g] diol	96	>99	85	93
<i>trans</i> -2-heptene				
diol + epoxide (TN) ^[c]	4.8	5.7	5.6	4.1
[diol]/[epoxide]	2.2:1	0.05:1	0.6:1	13:1
% RC ^[g] epoxide	>99	>99	86	>99
% RC ^[g] diol	96	>99	81	96
1-octene				
diol + epoxide (TN) ^[c]	7.5	6.4	4.7	5.8
[diol]/[epoxide]	2.0:1	0.2:1	2.1:1	18:1

• preparation of α -1



• preparation of β -1



[a] Reaction conditions: 0.7 mM catalyst, 7 mM H₂O₂, and 0.7 M substrate in CH₃CN at room temperature in air. H₂O₂ solution added by syringe pump over a 30-min period. [b] Data from references [5] and [6]. [c] TN = Turn-over number [d] ¹⁸O incorporated into cyclooctene epoxide when H₂¹⁸O₂ was used as an oxidant/when reaction was carried out in presence of 1000 equiv of H₂¹⁸O. Other conditions as stated in [a]. [e] Percentage of *cis*-cyclooctane-1,2-diol that contains no ¹⁸O/1 ¹⁸O atom/2 ¹⁸O atom when H₂¹⁸O₂ was used as an oxidant. Other conditions as stated in [a]. [f] Percentage of *cis*-cyclooctane-1,2-diol that contains no ¹⁸O/1 ¹⁸O atom/2 ¹⁸O atom when reaction was carried out in presence of 1000 equiv of H₂¹⁸O. Other conditions as stated in [a]. [g] % RC = 100 × (*cis*-*trans*)/(*cis* + *trans*).

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A Synthetically Useful, Self-Assembling MMO Mimic System for Catalytic Alkene Epoxidation with Aqueous H₂O₂

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Scheme 1. Epoxidation of 1-Decene by the 1/Acetic Acid System

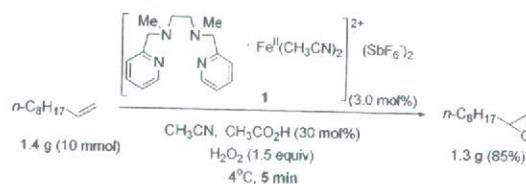


Table 1. Epoxidations Catalyzed by the 1/Acetic Acid System (2)^a

Entry	Substrate	Isolated Yields ^b (GC yield) ^c
1	<i>n</i> -C ₈ H ₁₇	85%
2	<i>n</i> -C ₁₀ H ₂₁	90% ^d
3	cyclo-C ₈ H ₁₇	76% ^e
4	EtO ₂ C	63% ^f
5	TBSO	61% ^g
6		77%
7	cyclooctene	86%
8		87%
9		80% (90%)
10		85% (90%)

^a Reaction conditions (see ref 12 and Supporting Information): olefin (2.0 mmol, 0.16 M in CH₃CN), **1** (3.0 mol %), CH₃CO₂H (10 equiv relative to **1**), H₂O₂ (aqueous 50 wt %, 3.0 mmol, 1.5 M in CH₃CN, added dropwise over 2 min), 4 °C, 5 min. ^b Isolated yields based on an average of 3 runs. ^c GC yields were determined using nitrobenzene as an internal standard for especially volatile substrates. ^d Reaction carried out at [olefin]₀ = 0.13 M due to poor solubility in CH₃CN. ^e 5 mol % **1**. ^f 1.5 mol % **1**/1.5 mol % CH₃CO₂H. ^g 6 mol % CH₃CO₂H.

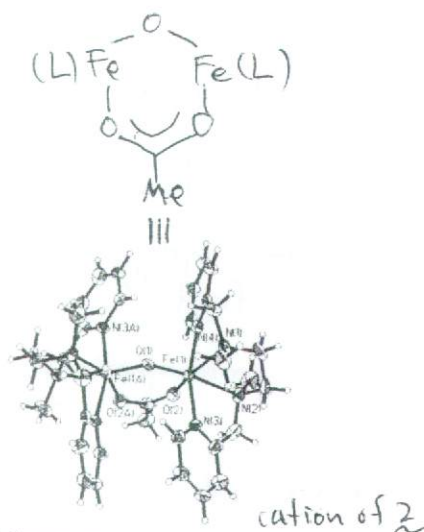


Figure 1. ORTEP diagram of [Fe₂(μ-O)(μ-CH₃CO₂)(mep)₂]⁺

Binuclear structure is maintained in solution.
(UV-vis spectrum)

2 exhibited the same selectivity in the epoxidation of 1-decene.

5 mol % **1**, no additive
71% of 1,2-epoxydecane
↓ screening

- The addition of 1 eq of AcOH (to cat.)
reductions in catalyst loading
H₂O₂ addition rates (rapid addition)

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High conversion of olefins to *cis*-diols by non-heme iron catalysts and H₂O₂

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Table 2 Oxidation of oct-1-ene with different iron catalysts^a

Catalyst	Diol yield (%)	Epoxide yield (%)
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[Fe ₂ (μ-O)(TPA) ₂ (H ₂ O) ₂] ⁴⁺	59	21
[Fe ₂ (μ-O)(L) ₂ (OAc)] ³⁺		
L = 5-Me ₃ -TPA	0	1
L = TPA	0	2
L = BPMEN ^b	0	2

^a Unless otherwise indicated, reaction conditions are the same as listed in footnote a of Table 1. ^b H₂O₂ (0.18 mmol) diluted in CH₃CN (0.3 mL) was added via syringe pump over 10 min to a CH₃CN solution (0.45 mL) containing the iron catalyst (3.5 μmol) and the olefin (0.12 mmol) at 4 °C. Final catalyst: substrate:H₂O₂ ratio = 1:34:51.

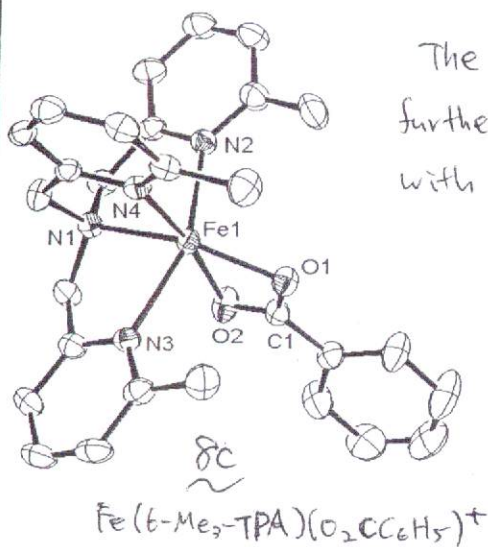
The only effective dinuclear complex.
 • readily displaceable aqua ligand

essentially ineffective at olefin epoxidation.



requirement for two *cis* labile sites

Que et al.
 JACS, 2002, 124, 3026-3035.
 J. Biol. Inorg. Chem. 2001, 6, 276-284.



The high selectivity for δ_a for the *cis* diol product is further improved when two CH₃CN ligands are replaced with bidentate benzoate (δ_b - δ_d)

	<i>cis</i> -diol : epoxide	conv(x)
δ_a	7 : 1	56
δ_c	12 : 1	66

speculation:

At the end of the catalytic cycle, PhCOOH protonates the bound diolate product to enhance its displacement.

