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Communication

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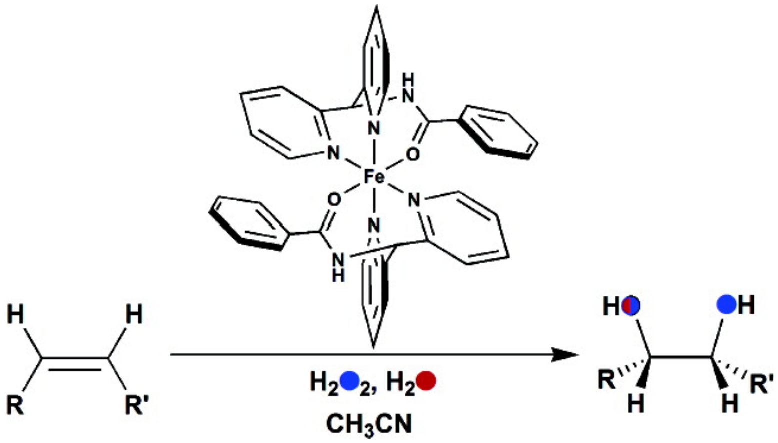

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Iron-Catalyzed Olefin *cis*-Dihydroxylation Using a Bio-Inspired *N*,*N*,*O*-Ligand

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Nature has evolved enzymes that carry out the *cis*-dihydroxylation of C=C bonds in the biodegradation of arenes in the environment.[1] These enzymes, called Rieske dioxygenases,[2] have mononuclear iron centers coordinated to a 2-His-1-carboxylate facial triad motif that has emerged as a common structural element among many nonheme iron enzymes.[3] In contrast, olefin *cis*-dihydroxylation is conveniently carried out by OsO_4 and related species in synthetic procedures. The toxicity and cost of these heavy metal reagents have prompted us to explore more environmentally benign and less expensive strategies for carrying out these transformations and led us to design bio-inspired nonheme iron catalysts for olefin *cis*-dihydroxylation. Indeed, the first examples of such iron complexes have been reported,[4] along with manganese complexes,[5] that use H_2O_2 as oxidant. The best iron catalysts thus far utilize tetradentate N4 ligands, and much has been learned about how the metal center activates the H_2O_2 to effect *cis*-dihydroxylation. In an effort to obtain a ligand environment that more closely mimics the facial *N*,*N*,*O* site of the mononuclear iron center in the Rieske dioxygenases, we have designed the potentially tridentate ligand Ph-DPAH [(di-(2-pyridyl)methyl)benzamide, Figure 1]. Reported herein are its synthesis, the characterization of its iron(II) complex, and the reactivity of the most effective iron catalyst for olefin *cis*-dihydroxylation to date.

Ph-DPAH, readily obtained from the benzoylation of di-(2-pyridyl)methylamine (for details, see Supporting Information), can provide a facial array of two pyridine ligands and a carbonyl oxygen analogous to the 2-His-1-carboxylate facial triad. The suitability of this design is evidenced by the crystal structure of $[Fe^{II}(Ph\text{-}DPAH)_2](OTf)_2$ (**1**), shown in Figure 1. At the iron(II) center lies a center of inversion with the coordination of two face capping ligands in a nearly octahedral geometry. This structure is similar to those of iron(II) complexes of a heteroscorpionate ligand consisting of two pyrazoles and one carboxylate developed by Burzlaff and co-workers.[6] The Fe−N distances of **1** are 2.171 and 2.181 Å, typical of high-spin iron(II) complexes.[7] The Fe−O distance of 2.043 Å in **1** is appreciably shorter than those of Burzlaff's complexes (Fe−O, 2.076 and 2.080 Å) with sterically less bulky pyrazoles, suggesting that the amide carbonyl oxygen of Ph-DPAH can bind to the metal center more strongly than these carboxylate ligands.

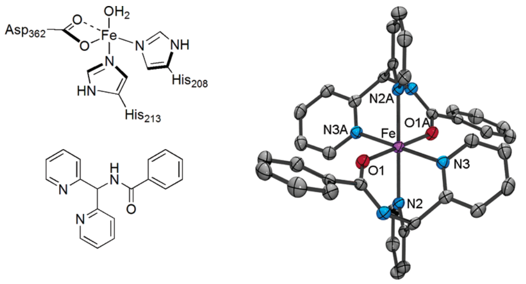

Figure 1. Structures of the monoiron(II) active site of naphthalene 1,2-dioxygenase (top left, pdb code 1O7W), the ligand Ph-DPAH (bottom left), and the ORTEP plot for $[Fe^{II}(Ph\text{-}DPAH)_2](CF_3SO_3)_2$ (**1**) showing 50% probability ellipsoids (right). Hydrogen atoms and counterions have been omitted for clarity. Selected bond lengths (Å): Fe−O1, 2.0431(17); Fe−N2, 2.171(2); Fe−N3, 2.181(2).

Table 1. Olefin Oxidation Products of **1**[a]

substrate	diol[b] [%RC][c]	epoxide[b] [%RC][c]	diol:epoxide
styrene[d,e]	8.0(5)	0.1(1)	80:1
cyclooctene	7.0(6)	0.5(1)	14:1
1-octene			
5 equiv of H_2O_2	3.6(3)	0.04(1)	90:1
10 equiv of H_2O_2	7.6(3)	0.1(1)	76:1
20 equiv of H_2O_2	10.3(7)	0.2(1)	52:1
cyclohexene[d,f]	6.2(2)	0.7(1)	9:1
cis-2-heptene	4.9(4) [99]	0.7(1) [57]	7:1
trans-2-heptene	4.9(3) [>99]	0.5(1) [>99]	10:1
ethyl *trans*-crotonate	7.4(4)		>100:1
tert-butyl acrylate	5.5(2)		>100:1
dimethyl fumarate	5.3(4)		>100:1

[a] Reaction conditions: H_2O_2 (10 equiv except where indicated) was added by syringe pump over a 5 min period (to minimize H_2O_2 disproportionation) to a solution of catalyst (0.35 mM) and substrate (0.35 M) in CH_3CN. See Supporting Information for further details. [b] Yields expressed as turnover numbers, TON, (μmol product/μmol catalyst). [c] $\%RC = 100 \times (A - B)/(A + B)$, where A = yield of *cis*-diol with retention of configuration and B = yield of epimer. [d] Results were obtained under an Ar atmosphere with degassed solutions prior to oxidant introduction. [e] A minor amount of benzaldehyde product was observed, TON = 0.4(1). [f] Allylic oxidation products, alcohol (A) and ketone (K), were detected with TON(A) = 1.1(2) and TON(K) = 0.3(1). In a similar experiment under air, epoxide, diol, and allylic alcohol yields remained constant, while the allylic ketone yield increased, TON(K) = 2.5(2).

Table 1 shows that **1** is an excellent catalyst for olefin *cis*-dihydroxylation with H_2O_2 as the oxidant. With various olefins ranging from electron donating to electron withdrawing, the *cis*-diol was the dominant product, representing the conversion of 50−80% of the H_2O_2 introduced. For both *cis*- and *trans*-2-heptene, 99% of the diol products were observed with retention of configuration, characterizing this oxidation as a true *cis*-dihydroxylation. When compared with the best Fe(N4) catalysts reported thus far, such as $[Fe(TPA)(NCMe)_2]^{2+}$ (**2**, TPA = tris(2-pyridylmethyl)amine) and $[Fe(6\text{-}Me_3\text{-}TPA)(O_2CC_6H_4\text{-}3\text{-}NO_2)]^+$ (**3**), **1** is superior in its high selectivity for producing *cis*-diol for a variety of olefins, three of which are compared in Figure 2.

In addition to *cis*-diol, other oxygenated species were produced, but only to a limited extent. For the more electron-rich olefins, some epoxide was formed, corresponding to the conversion of at most 7% of the oxidant or less than 13% of the total product yield. For styrene, 0.4 TON benzaldehyde (<5% of total yield) was formed under Ar, which is a 4- to 5-fold lower yield than that found for either **2** or **3**. Even for easily autoxidizable cyclohexene, allylic oxidation products represented <17% of the total yield.

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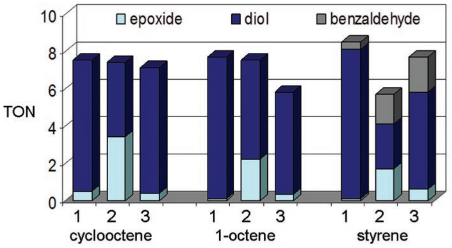

Figure 2. Comparison of **1** with the *cis*-dihydroxylation catalysts **2** and **3** in the oxidation of selected substrates. Note the higher selectivities (and conversion efficiencies) of **1** for *cis*-diol: 93% (75%) for cyclooctene, 99% (77%) for 1-octene, and 94% (85%) for styrene.

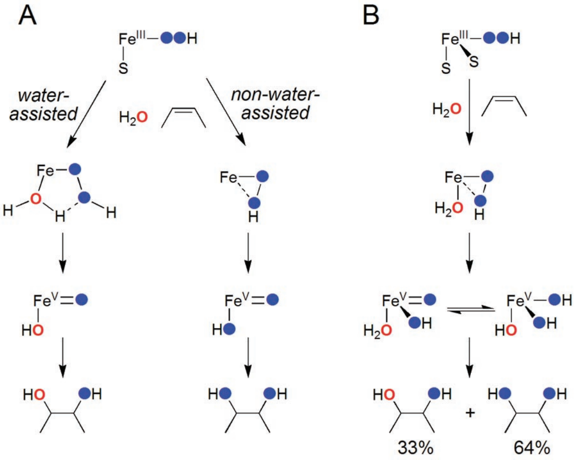

Figure 3. Proposed dihydroxylation mechanisms for **2** and **3** (A) and for **1** (B) (S = CH_3CN). See Supporting Information for details of the isotope labeling experiments for 1-octene.

The longevity of catalyst **1** was investigated by varying the amount of oxidant introduced. As shown in Table 1 for the oxidation of 1-octene, significant deterioration of catalyst efficacy was observed with the addition of more than 10 equiv of H_2O_2. The ESI-MS spectrum of the catalyst solution at the end of an oxidation experiment showed the formation of a large amount of free ligand, together with a small amount of an oxo-bridged diiron(III) byproduct, suggesting catalyst decomposition (see Figure S2 in Supporting Information).

Previous studies of **2** and **3** have led to the postulation of *cis*-dihydroxylation mechanisms that require metal catalysts with at least two *cis*-labile sites for the activation of H_2O_2 to form an Fe^{V}-(O)(OH) oxidant.[4b,8] Such an oxidant can be formed by a water-assisted pathway on the $S = {}^{1}/_{2}$ H$_2$O−Fe^{III}−OOH reaction surface or by a non-water-assisted pathway on the $S = {}^{5}/_{2}$ Fe^{III}−(η^2-OOH) reaction surface (Figure 3A). Extending this mechanistic framework to coordinatively saturated **1** requires some extent of ligand dissociation. Although it can be imagined that each Ph-DPAH ligand becomes bidentate during catalysis, we favor the complete dissociation of one Ph-DPAH ligand to make three sites available for exogenous ligand binding (Figure 3B). This notion is supported by ESI-MS data showing the presence of free ligand and the 1:1 [Fe^{II}(Ph-DPAH)]$^{2+}$ complex ion in solution prior to the start of catalysis, indicative of a ligand dissociation equilibrium (see Figure S1 in Supporting Information).

Because of its high selectivity for diol formation, **1** resembles **3** more closely in its catalytic behavior,[4a−d] both of which would be expected to exert a weaker ligand field than TPA and thus favor the non-water-assisted pathway.[4b,c] Indeed ^{18}O labeling studies for the oxidation of 1-octene show that the predominant diol product (64%) is doubly labeled by H_2O_2, as found for **3**[4a,b] (see Table S2 in Supporting Information). Interestingly, unlike for **3**, there is also a significant fraction of diol with an oxygen atom from H_2O (33%), suggesting possible involvement of the water-assisted pathway. Alternatively, water incorporation via the non-water-assisted pathway can be rationalized if the active catalyst were considered to be the 1:1 Fe(Ph-DPAH) complex. Since this complex would have three labile sites, it would then be possible to accommodate both a side-on hydroperoxo and a water ligand (Figure 3B). Prior cleavage of the peroxo O−O bond would form a transient Fe^{V}-(O)(OH)(OH$_2$) oxidant in equilibrium with an Fe^{V}(OH)$_3$ isomer that then transfers two of the three oxygen atoms to the olefin.

In summary, **1** is the first iron catalyst for olefin *cis*-dihydroxylation with a facial *N*,*N*,*O*-ligand arrangement mimicking that found for the Rieske dioxygenases. It can oxidize a wide range of olefins efficiently and has proven to be the most selective thus far for dihydroxylation. ^{18}O labeling experiments suggest the participation of an Fe^{V} oxidant for this bio-inspired catalyst, which carries implications for the action of the Rieske dioxygenases.[1c,d,9]

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Supporting Information Available: Procedures for the synthesis of Ph-DPAH and **1** and for the catalytic reactions, as well as crystallographic and ESI-MS data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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