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

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Rieske dioxygenases are bacterial enzymes that catalyze the O_2-dependent enantioselective *cis*-dihydroxylation of arene and olefin double bonds.[1] These enzymes utilize a mononuclear non-heme iron center coordinated to a 2-histidine-1-carboxylate facial triad motif that leaves at least two labile sites available for catalysis.[2,3] To date, the role of the metal center in the enzyme mechanism is not well established, but the recent report of a synthetic iron complex that can catalyze *cis*-dihydroxylation of olefins with H_2O_2 demonstrates a key role for the mononuclear iron active site.[4] We have thus embarked on an effort to develop synthetic catalysts that model this chemistry as a potential "green" alternative to traditional heavy metal reagents such as OsO_4 and RuO_4^-, which are effective but less desirable due to their toxicity. We have extended this chemistry by replacing the tripodal tetradentate ligand with a linear tetradentate ligand based on a chiral diamine backbone (Figure 1).[5] In this report, we demonstrate the first enantioselective olefin *cis*-dihydroxylations catalyzed by an iron complex.

The use of ligands based on an ethylenediamine backbone is an established strategy for chiral induction in metal-catalyzed oxidations.[6] We thus first explored the ability of the BPMEN ligand framework to form iron complexes capable of catalyzing olefin *cis*-dihydroxylation. To this end, the complexes [Fe(BPMEN)(MeCN)$_2$](ClO$_4$)$_2$ (**1**)[7] and the 6-methyl substituted [Fe(6-Me$_2$-BPMEN)(CF$_3$SO$_3$)$_2$] (**2**) were tested as catalysts. In the reaction catalyzed by **1**, addition via syringe pump of 10 equivalents of H_2O_2 to a 0.7 mM solution of the complex in acetonitrile with 0.7 M in cyclooctene afforded cyclooctene oxide and the *cis*-diol in respective yields of 75 and 9% relative to H_2O_2 (Table 1). Thus, **1** is an excellent catalyst for olefin epoxidation. In sharp contrast, **2** under the same conditions afforded epoxide and *cis*-diol in respective yields of 15 and 64%. Thus, as observed earlier in the Fe(TPA) catalysts,[4] the introduction of the 6-methyl substituents dramatically alters the course of olefin oxidation and strongly favors the *cis*-dihydroxylation pathway. These data indicate that the catalytic activity associated with TPA iron complexes can be also extended to a new class of complexes.

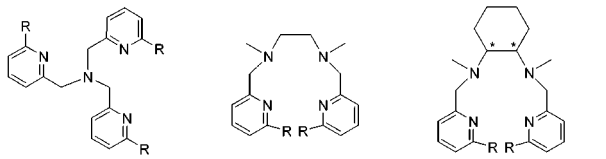

Figure 1. Tetradentate ligands used in this study.

Encouraged by these findings we synthesized [Fe(BPMCN)(CF$_3$SO$_3$)$_2$] (**3**) and [Fe(6-Me$_2$-BPMCN)(CF$_3$SO$_3$)$_2$] (**4**), the analogous complexes with the chiral *trans*-cyclohexane-1,2-diamine backbone. The oxidation of *trans*-2-heptene demonstrates that 1*R*,2*R*-**3** can carry out enantioselective olefin oxidation (Table 1); however the ee's are modest, 29% for *cis*-diol and 12% for epoxide. More promising are the results for the same reaction catalyzed by 1*S*,2*S*-**4**, which affords the *cis*-diol with an ee of 79% and racemic epoxide. The use of the 1*R*,2*R* enantiomer affords the same ee values but with the opposite configuration for the major diol product. Therefore, catalytic reactions performed by **4** emphasize the important role the 6-methyl substituents play. Not only does the fraction of *cis*-diol increase significantly, ee's for the *cis*-dihydroxylation of *trans*-olefins as high as 82% at 30 °C (Table 1) and 88% at 50 °C are obtained, values which approach those reported for the osmium-catalyzed reactions.[8] Not surprisingly, the major *cis*-diol products obtained in the oxidation of *trans*-2-heptene by 1*R*,2*R*-**3** and 1*R*,2*R*-**4** have the same chirality**.** Therefore, the configuration of the 1,2-cyclohexanediamine moiety determines the chirality of the product.

Table 1. Oxidation of Olefins with H_2O_2 Catalyzed by **1**−**4**[a]

cat	substrate/eq H_2O_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*R*,2R-**3**	cyclooctene/10	5.8(100)	0.7(100)	
	trans-2-heptene/10	5.4(100)	0.3(100)	29(2)
1*S*,2*S*-**4**	cyclooctene/10	3.5(100)	5.8(79)	
	cyclooctene/20	5.4(100)	11.2(89)	
	cis-2-heptene/20	4.5(56)	7.8(82)	9(2)
	cis-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)
	tert-butyl acrylate/20	0.5	10.1	23(2)
	trans-2-heptene/20	2.4(100)	7.5(100)	79(2)
	trans-2-octene/20	2.3(100)	7.5(100)	82(5)
1*R*,2*R*-**4**	*trans*-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 CH_3CN at 30 °C under air to which 10−20 equiv of H_2O_2 (from 50% aqueous H_2O_2) 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-Permethylated β-Cyclodextrin column.

The crystal structures of **3** and **4** may help us understand the differences in the degree of asymmetric induction. Both **3** and **4** have high-spin iron(II) centers, as indicated by Fe−N bond

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(5) Abbreviations used. TPA; tris(2-pyridylmethyl)amine, 6-Me$_3$-TPA; tris(6-methyl-2-pyridylmethyl)amine, 6-Me$_2$−BPMCN; *N*,*N*′-bis-(6-methyl-2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine, BPMCN; *N*,*N*′-bis-(2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-cyclohexanediamine, BPMEN; *N*,*N*′-bis-(2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-ethylenediamine, 6-Me$_2$-BPMEN; *N*,*N*′-bis-(6-methyl-2-pyridylmethyl)-*N*,*N*′-dimethyl-1,2-ethylenediamine.

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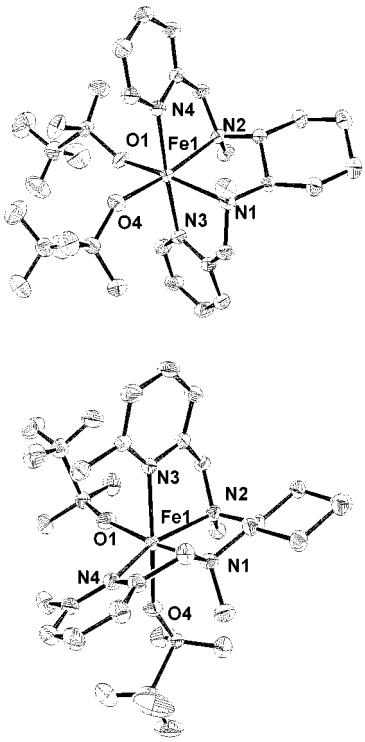

Figure 2. ORTEP plots for **3** (top) and **4** (bottom) showing 50% thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) for **3**: Fe−N1 = 2.237(2), Fe−N2 = 2.220(2), Fe−N3 = 2.151(2), Fe−N4 = 2.162(2), Fe−O1 = 2.131(2), Fe−O4 = 2.159(2). For **4**: Fe−N1 = 2.203(4),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

distances that range from 2.151 to 2.274 Å. The structure of 1*S*,2*S*-**4** reveals that the ligand adopts a *cis*-β topology around the iron center with the two pyridine rings *cis* to each other (Figure 2) and the two N-Me groups in a *syn* conformation. In contrast, the parent bpmcn ligand in 1*R*,2*R*-**3** adopts the *cis*-α topology, where the two pyridine groups coordinate *trans* to each other and the two N-Me groups are oriented *anti* to each other. Thus, the difference in topologies may rationalize the different degrees of asymmetric induction. It should be noted that the *cis*-α topology found in **3** is structurally closely related to other C_2-symmetric complexes which make effective asymmetric catalysts.[9] However it appears that the *cis*-β structure may be superior in inducing chirality, at least with respect to *cis*-dihydroxylation. A caveat to be made at this point is that we cannot ascertain whether these different conformations are maintained in the structures of the reactive peroxo species that undoubtedly must be formed to carry out this novel transformation;[10] therefore, efforts to characterize such reactive intermediates are underway.

Other studies provide further mechanistic insight. In osmium-catalyzed asymmetric *cis*-dihydroxylation, lowering the reaction temperature results in an increase in enantioselectivity.[11] Contrary to this expectation, ee values for the **4**-catalyzed oxidation of *trans*-2-heptene decrease upon lowering the temperature (e.g., 40% at 0 °C); however, raising the temperature has the opposite effect, and ee values reach a maximum of 88% at 50 °C. This behavior suggests that there may be more than one active species present in solution capable of effecting asymmetric *cis*-dihydroxylation, perhaps corresponding to intermediates with different BPMCN conformations. Increasing the temperature would thus favor in this case population of the more enantioselective isomer.

The relative order in asymmetric induction with respect to the olefin parallels that observed in the osmium-catalyzed reaction.[8a] Accordingly *trans* di-substituted olefins yield the best results, followed by terminal olefins with ee values of 23−60% and then *cis* di-substituted olefins with ee values around 3−9%. Thus, similar steric considerations may apply to both reactions,[12] suggesting that the active species responsible for the *cis*-dihydroxylation in Os and Fe are structurally related. The analogue to the (*cis*-dioxo)osmium(VIII) moiety in this iron chemistry has been proposed to be either an η^2-hydroperoxo iron(III) species or its valence tautomer, a *cis*-iron(V)−oxo(hydroxo) species.[4]

In conclusion, we have found the first iron catalyst capable of performing enantioselective *cis*-dihydroxylation of olefins. Although the requirement for a large excess of substrate severely limits its current utility as a synthetic method, it does establish a precedent for using iron catalysts for such reactions and will hopefully stimulate the future development of biomimetic iron catalysts that could replace the more toxic and expensive traditional oxidants used for *cis*-dihydroxylation.

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Supporting Information Available: X-ray crystallographic files for **3** and **4** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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