Asymmetric Catalysis

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Iron-Catalyzed Asymmetric Olefin *cis*-Dihydroxylation with 97% Enantiomeric Excess**

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The rising number of pharmaceuticals with chiral centers[1] has heightened the necessity to discover catalysts that provide asymmetric induction into the products of their respective reactions.[2] In addition, stringent constraints on trace impurities allowed in the marketed pharmaceutical products make the use of catalysts composed of physiologically benign metal centers increasingly attractive. The *cis*-dihydroxylation of olefins has become an important chemical reaction in the design of pharmaceuticals[3] and natural product synthesis[4] because this reaction is both stereospecific and, through the use of the Sharpless asymmetric dihydroxylation (AD) mixes, enantiospecific.[5] A potential disadvantage of the Sharpless procedure is the extraordinary toxicity associated with the osmium metal in the AD mixes.

In contrast, nature has evolved an important class of nonheme iron enzymes, called the Rieske dioxygenases, that perform a novel, asymmetric *cis*-dihydroxylation of arene C=C bonds.[6] Such enzymes can be used as biocatalysts,[7] but they are effective for only a narrow range of substrates, limiting their applicability. The catalytically relevant mononuclear iron center in the Rieske dioxygenases is coordinated by the 2-His-1-carboxylate facial triad,[8] a common structural motif among nonheme iron enzymes,[9] which leaves *cis*-oriented available coordination sites on the iron octahedron for the activation of dioxygen. Inspired by these enzymes, researchers have developed the first examples of biomimetic complexes involving iron[10] or manganese[11] that catalyze olefin *cis*-dihydroxylation using H_2O_2 as oxidant. Two of these complexes (**4** and **5** in Figure 1) incorporate the optically active

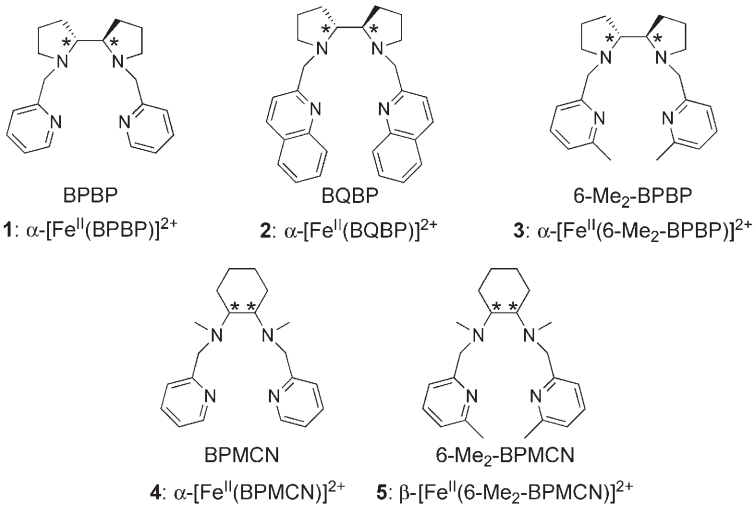

Figure 1. Optically active ligands (chiral centers indicated by *) and their corresponding iron complexes (in which the ligand coordinates in either a *cis*-α or *cis*-β topology) capable of promoting asymmetric olefin *cis*-dihydroxylation.

trans-1,2-diaminocyclohexane backbone into the ligand framework and exhibit asymmetric *cis*-dihydroxylation of *cis*-2-heptene with *ee* values of 29 and 79%.[10c] With the goal of achieving greater *ee* values, the *trans*-1,2-diaminocyclohexane unit was replaced by bipyrrolidine to give the tetradentate ligands (*R*,*R*)-BPBP, (*R*,*R*)-BQBP, and (*R*,*R*)-6-Me_2-BPBP (Figure 1). Herein, we compare the asymmetric *cis*-dihydroxylation abilities of three iron complexes and find the 6-Me_2-BPBP complex capable of achieving up to 97% enantiomeric excess of the *cis*-diol product from two *cis*-disubstituted olefins. These *ee* values are comparable to those obtained with the osmium-based AD mixes.

The ligands (*R*,*R*)-BPBP, (*R*,*R*)-BQBP, and (*R*,*R*)-6-Me_2-BPBP (Figure 1) were obtained by following literature procedures,[12] and corresponding iron(II) complexes were obtained by the reactions of equimolar amounts of ligand and $Fe^{II}(OTf)_2{\cdot}2NCMe$[13] in CH_2Cl_2 under a N_2 atmosphere (OTf = trifluoromethanesulfonate). Overnight stirring and subsequent solvent removal gave light brown powders, which were recrystallized from CH_2Cl_2/ether to afford pale yellow crystals, formulated as $[Fe^{II}(BPBP)(OTf)_2]$ (**1**), $[Fe^{II}(BQBP)(OTf)(EtOH)](OTf)$ (**2**), and $[Fe^{II}(6\text{-}Me_2\text{-}BPBP)(OTf)_2]$ (**3**). These crystals were suitable for X-ray crystallographic analysis,[14] and the structures of the three complexes are shown in Figure 2.[15]

In all three structures, the BPBP ligands coordinate the iron center in a *cis*-α topology, in which equivalent available coordination sites (occupied by triflate or ethanol in the solid

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

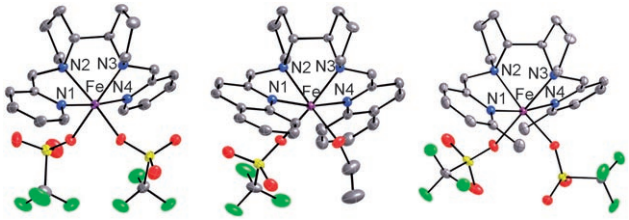

Figure 2. ORTEP plots for $[Fe^{II}(BPBP)(OTf)_2]$ (**1**), $[Fe^{II}(BQBP)(OTf)(EtOH)](OTf)$ (**2**), and $[Fe^{II}(6\text{-}Me_2\text{-}BPBP)(OTf)_2]$ (**3**) showing 50% probability ellipsoids. Hydrogen atoms and noncoordinating solvent molecules have been omitted for clarity. Average Fe–N bond lengths [Å]: for **1**, 2.197; for **2**, 2.230; and for **3**, 2.234. C gray, O red, S yellow, F green.

state) are *trans* to the amine donors derived from the bipyrrolidine backbone. The $Fe-N_{pyrrolidine}$ bond lengths for all three complexes are similar, but the average $Fe-N_{pyridine/quinoline}$ bond length increases from 2.192 Å for **1** to 2.272 and 2.264 Å for **2** and **3**, respectively, as a result of α-substitution. These distances are indicative of high-spin iron centers.

The structures of **1**–**3** can also be compared with those of two other iron complexes with chiral diamine ligands that promote asymmetric olefin *cis*-dihydroxylation with H_2O_2, namely α-$[Fe^{II}\{(1R,2R)\text{-BPMCN}\}(OTf)_2]$ (**4**) and $[Fe^{II}\{(1S,2S)\text{-6-Me}_2\text{-BPMCN}\}(OTf)_2]$ (**5**).[10c] Interestingly, all ligands in the BPBP series adopt a *cis*-α topology upon complex formation. In contrast, the BPMCN ligand forms both *cis*-α and *cis*-β iron(II) complexes,[10b] whereas 6-Me_2-BPMCN adopts a *cis*-β ligand topology in **5**.[10c] It is clear from an examination of the structures in Figure 2 that the *cis*-α topology in **1**–**3** is determined by the constraints of the bipyrrolidine moiety.

Table 1 compares the abilities of the five complexes as catalysts for the asymmetric *cis*-dihydroxylation of olefins with H_2O_2 as oxidant and reveals the outstanding performance of **3**. This catalyst is quite *cis*-diol-selective, affording a diol/epoxide ratio of about 6 for cyclooctene oxidation and as much as 60 or greater for the oxidation of 1-octene, styrene, and crotonate. As can be seen in the trend for the **1**–**3** series and illustrated previously for the BPMCN complexes,[10b,c] the high selectivity for *cis*-diol undoubtedly arises from the introduction of the α-methyl substituents on the two pyridine ligands. As the steric bulk at that position increases, the catalyst goes from being epoxide-selective, as in the case of **1**, to being *cis*-diol-selective in **2**, and even more *cis*-diol-selective in **3**.

The asymmetric induction results obtained in **3**-catalyzed reactions are to date the best for an iron catalyst (Table 1) and rival those obtained with the AD mixes.[5] The highest *ee* values were obtained for electron-rich, *trans*-disubstituted olefins, such as *trans*-2-heptene and *trans*-4-octene (97 and 96% *ee*, respectively). These values diminished with the replacement of alkyl groups on the *trans*-disubstituted olefins with electron-withdrawing groups, for example, ethyl *trans*-crotonate (78%) and dimethyl fumarate (23%). Terminal olefins, however, offered moderate to good *ee* values, for example, 1-octene (76%), allyl chloride (70%), and *tert*-butyl acrylate (68%).

Table 1: Oxidation of olefins with H_2O_2 catalyzed by iron complexes.[a]

Cat.	Substrate	Epoxide TON[b] [% *de*][c]	*cis*-Diol TON[b] [% *de*][c]	% *ee*[d]	Diol/ Epox.
1	*trans*-2-heptene	5.1(1) [98]	1.1(4) [90]	38(3)	1:4.6
1	1-octene	2.6(3)	1.7(1)	11(1)	1:1.5
1	*tert*-butyl acrylate	3.0(1)	0.1(1)		1:30
2	*trans*-2-heptene	0.9(2) [90]	3.6(2) [99]	78(3)	4:1
2	1-octene	0.5(1)	4.6(3)	29(4)	9:1
2	*tert*-butyl acrylate	<0.1	2.7(4)	23(1)	>27:1
3	*trans*-2-heptene	0.2(1) [67]	5.2(2) [99]	97(1)	26:1
3	*cis*-2-heptene	0.6(1) [95]	3.4(1) [95]	11(1)	5.7:1
3	*trans*-4-octene	0.3(1) [80]	3.9(2) [93]	96(1)	13:1
3	cyclooctene	0.7(1) [94]	4.0(5)		5.7:1
3	1-octene	0.1(1)	6.4(3)	76(1)	64:1
3	styrene	<0.1	6.5(2)	15(2)	>65:1
3	allyl chloride	<0.1	4.9(1)	70(1)	>49:1
3	*tert*-butyl acrylate	<0.1	4.0(1)	68(1)	>40:1
3	ethyl *trans*-crotonate	<0.1	7.5(5) [99]	78(4)	>75:1
3	dimethyl fumarate	<0.1	5.3(5) [99]	23(2)	>53:1
4	*trans*-2-heptene	5.4 [99]	0.3 [99]	29	1:18
5[e]	*trans*-2-heptene	1.2 [99]	3.8 [99]	79	3.2:1
5[e]	1-octene	0.7	4.1	60	5.9:1
5[e]	*tert*-butyl acrylate	0.3	5.1	23	17:1

[a] Reaction conditions: A 70 mM solution of H_2O_2 (10 equiv) in CH_3CN was delivered by syringe pump over a period of 20 min to a degassed and stirred solution of catalyst (0.7 mM) and substrate (0.35 M) at ambient temperature in air for **1** and **2** and under Ar atmosphere for **3**. See the Supporting Information for further details. [b] Catalyst turnover number, TON = μmol product/μmol catalyst with standard deviation values reported in parentheses. [c] Percent of diastereomeric excess (*de*). [d] Percent of enantiomeric excess (*ee*) of the predominant diol isomer. [e] Results are normalized to 10 equiv H_2O_2.

The asymmetric induction provided by **3** is significantly greater than for **5** (Table 1).[10c] The improvement most likely arises from two factors: the more rigid bipyrrolidine backbone of **3** relative to the 1,2-diaminocyclohexane backbone of **5** and the *cis*-α ligand topology of **3** in contrast to the *cis*-β topology of **5**. From a comparison of **1**–**3**, it is also clear that the size of the pyridine α-substituent is important, as a systematic increase in *ee* value is observed on going from H in **1** to an sp^2-hybridized C–H group in **2** to a CH_3 group in **3**.

Complex **3** is thus the most effective iron-based asymmetric olefin *cis*-dihydroxylation catalyst reported to date. These results demonstrate for the first time that a synthetic nonheme iron catalyst can approach the high enantioselectivity found in *cis*-dihydroxylating enzymatic systems. However, more work needs to be done in improving reaction conditions to overcome the requirement for limiting oxidant in these reactions.

Experimental Section

1, **2**, and **3**: Under a nitrogen atmosphere, a solution of (*R*,*R*)-BPBP, (*R*,*R*)-BQBP, or (*R*,*R*)-6-Me_2-BPBP (96.7 mg, 0.3 mmol) in dichloromethane (2 mL) was added to a suspension of $Fe(OTf)_2{\cdot}2NCMe$[13] (130.8 mg, 0.3 mmol) in dichloromethane (2 mL) at room temperature with stirring. The mixture was stirred overnight and the solvent

removed in vacuo to give a light brown powder, which was recrystallized from dichloromethane and ether to afford pale yellow crystals in 72% yield for **1**, 60% yield for **2**, and 75% yield for **3**, which were suitable for X-ray crystallographic analysis. Characterization data for **1**: Anal. calcd (found) [%] for $C_{22}H_{26}F_6FeN_4O_6S_2{\cdot}H_2O$: C 38.05 (38.10), H 4.06 (4.15), N 8.07 (8.04), S, 9.23 (9.26). Characterization data for **2**: Anal. calcd (found) [%] for $C_{30}H_{30}F_6FeN_4O_6S_2{\cdot}H_2O$: C 45.35 (45.41), H 4.06 (4.02), N 7.05 (6.95), S 8.07 (7.96). Characterization data for **3**: Anal. calcd (found) [%] for $C_{24}H_{30}F_6FeN_4O_6S_2{\cdot}0.5\,CH_2Cl_2$: C 39.40 (39.83), H 4.18 (4.38), N 7.50 (7.54), S 8.59 (8.64).

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[1] S. C. Stinson, *Chem. Eng. News* **2001**, *79*(40), 79.
[2] R. Schmid, M. Scalone in *Comprehensive Asymmetric Catalysis*, *Vol. III* (Eds: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 41.2, pp. 1439–1450.
[3] For recent examples, see: a) N. Costes, S. Michel, F. Tillequin, M. Koch, A. Pierré, G. Atassi, *J. Nat. Prod.* **1999**, *62*, 490; b) J.-K. Jung, B. R. Johnson, T. Duong, M. Decaire, J. Uy, T. Gharbaoui, P. D. Boatman, C. R. Sage, R. Chen, J. G. Richman, D. T. Connolly, G. Semple, *J. Med. Chem.* **2007**, *50*, 1445; c) B. W. Trotter, K. K. Nanda, N. R. Kett, C. P. Regan, J. J. Lynch, G. L. Stump, L. Kiss, J. Wang, R. H. Spencer, S. A. Kane, R. B. White, R. Zhang, K. D. Anderson, N. J. Liverton, C. J. McIntyre, D. C. Beshore, G. D. Hartman, C. J. Dinsmore, *J. Med. Chem.* **2006**, *49*, 6954.
[4] For recent examples, see: a) A. Padwa, H. Zhang, *J. Org. Chem.* **2007**, *72*, 2570; b) S. Ghosh, T. Bhaumik, N. Sarkar, A. Nayek, *J. Org. Chem.* **2006**, *71*, 9687.
[5] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[6] a) D. T. Gibson, V. Subramanian in *Microbial Degradation of Organic Compounds* (Ed.: D. T. Gibson), Marcel Dekker, New York, **1984**, pp. 181; b) L. P. Wackett, *Enzyme Microb. Technol.* **2002**, *31*, 577.
[7] a) S. M. Resnick, D. T. Gibson, *J. Ind. Microbiol.* **1996**, *17*, 438; b) D. R. Boyd, G. N. Sheldrake, *Nat. Prod. Rep.* **1998**, *15*, 309; c) D. T. Gibson, R. E. Parales, *Curr. Opin. Biotechnol.* **2000**, *11*, 236; d) D. R. Boyd, N. D. Sharma, C. C. R. Allen, *Curr. Opin. Biotechnol.* **2001**, *12*, 564.
[8] D. J. Ferraro, L. Gakhar, S. Ramaswamy, *Biochem. Biophys. Res. Commun.* **2005**, *338*, 175.
[9] K. D. Koehntop, J. P. Emerson, L. Que, Jr., *J. Biol. Inorg. Chem.* **2005**, *10*, 87.
[10] a) K. Chen, M. Costas, J. Kim, A. K. Tipton, L. Que, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 3026; b) M. Costas, L. Que, Jr., *Angew. Chem.* **2002**, *114*, 2283; *Angew. Chem. Int. Ed.* **2002**, *41*, 2179; c) M. Costas, A. K. Tipton, K. Chen, D.-H. Jo, L. Que, Jr., *J. Am. Chem. Soc.* **2001**, *123*, 6722; d) M. Klopstra, G. Roelfes, R. Hage, R. M. Kellogg, B. L. Feringa, *Eur. J. Inorg. Chem.* **2004**, 846; e) P. D. Oldenburg, A. A. Shteinman, L. Que, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 15672; f) P. D. Oldenburg, L. Que, Jr., *Catal. Today* **2006**, *117*, 15.
[11] a) D. E. De Vos, S. de Wildeman, B. F. Sels, P. J. Grobet, P. A. Jacobs, *Angew. Chem.* **1999**, *111*, 1033; *Angew. Chem. Int. Ed.* **1999**, *38*, 980; b) J. W. de Boer, J. Brinksma, W. R. Browne, A. Meetsma, P. L. Alsters, R. Hage, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 7990; c) J. W. de Boer, W. R. Browne, J. Brinksma, P. L. Alsters, R. Hage, B. L. Feringa, *Inorg. Chem.* **2007**, *46*, 6353–6372.
[12] a) O. Fuentes, W. W. Paudler, *J. Org. Chem.* **1975**, *40*, 1210; b) M. Renz, C. Hemmert, B. Meunier, *Eur. J. Org. Chem.* **1998**, 1271; c) G. Alvaro, F. Grepioni, D. Savoia, *J. Org. Chem.* **1997**, *62*, 4180; d) A. Alexakis, A. Tomassini, C. Chouillet, S. Roland, P. Mangeney, G. Bernardinelli, *Angew. Chem.* **2000**, *112*, 4259; *Angew. Chem. Int. Ed.* **2000**, *39*, 4093.
[13] K. S. Hagen, *Inorg. Chem.* **2000**, *39*, 5867.
[14] Single-crystal structure and refinement data for **1**: $C_{22}H_{26}F_6FeN_4O_6S_2$, $M_w = 676.44$, monoclinic, space group $P2_1$, $a = 9.184(1)$, $b = 28.648(3)$, $c = 10.614(1)$ Å, $\beta = 90.950(2)°$, $V = 2792.1(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.609$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, $\mu = 0.774$ mm^{-1}), $T = 173(2)$ K. A total of 12444 ($R_{int} = 0.0435$) independent reflections with $2\theta < 27.50°$ were collected. The resulting parameters were refined to converge at $R_1 = 0.0438$ ($I > 2\theta$) for 739 parameters on 12444 independent reflections ($wR_2 = 0.0971$). Max./min. residual electron density 0.626/−0.487 e Å^{-3}; GOF = 1.026. Single-crystal structure and refinement data for **2**: $C_{33}H_{38}Cl_2F_6FeN_4O_7S_2$, $M_w = 907.54$, monoclinic, space group $P2_1$, $a = 9.497(1)$, $b = 12.343(2)$, $c = 16.643(2)$ Å, $\beta = 92.008(2)°$, $V = 1949.7(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.546$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, $\mu = 0.711$ mm^{-1}), $T = 173(2)$ K. A total of 7722 ($R_{int} = 0.0346$) independent reflections with $2\theta < 27.51°$ were collected. The resulting parameters were refined to converge at $R_1 = 0.0457$ ($I > 2\theta$) for 510 parameters on 7722 independent reflections ($wR_2 = 0.1200$). Max./min. residual electron density 0.750/−0.599 e Å^{-3}; GOF = 1.034. Single-crystal structure and refinement data for **3**: $C_{25}H_{32}Cl_2F_6FeN_4O_6S_2$, $M_w = 789.42$, orthorhombic, space group $P2_12_12_1$, $a = 12.618(1)$, $b = 14.662(2)$, $c = 17.678(2)$ Å, $V = 3270.6(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.603$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, $\mu = 0.832$ mm^{-1}), $T = 173(2)$ K. A total of 7510 ($R_{int} = 0.0338$) independent reflections with $2\theta < 27.52°$ were collected. The resulting parameters were refined to converge at $R_1 = 0.0297$ ($I > 2\theta$) for 417 parameters on 7510 independent reflections ($wR_2 = 0.0597$). Max./min. residual electron density 0.426/−0.358 e Å^{-3}; GOF = 1.061. Further experimental details are provided in the Supporting Information. CCDC-657096 (**1**), CCDC-657097 (**2**), and CCDC-657098 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[15] While this paper was being reviewed, the crystal structure of $[Fe^{II}\{(S,S)\text{-BPBP}\}(NCCH_3)_2](SbF_6)_2$, a complex closely related to **1**, was reported (M. S. Chen, M. C. White, *Science* **2007**, *318*, 783). In this work, the authors reported that this complex reacted with H_2O_2 in the presence of acetic acid to generate an oxidant capable of hydroxylation of tertiary C–H bonds with predictable selectivity, which is quite a remarkable achievement.

