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COMMUNICATION

A new efficient iron catalyst for olefin epoxidation with hydrogen peroxide[†]

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A new aminopyridine ligand derived from bipiperidine (the product of full reduction of bipyridine, bipy) coordinates to $iron(\pi)$ in a *cis*- α fashion, yielding a new selective catalyst for olefin epoxidation with H₂O₂ under limiting substrate conditions.

Alkene oxides (epoxides) are often used as starting materials or intermediates in important technological processes in chemical or pharmaceutical industry. Therefore, discovery of efficient, selective and practical epoxidation methods is an important goal in synthetic chemistry. While a number of catalysts of epoxidation are known,¹ some problems remain, including the development of catalytic systems with high conversion and selectivity that utilize non-toxic, environmentally benign metals and oxidants. Biomimetic systems that model non-heme iron oxidative enzymes are particularly attractive, since these enzymes are proficient at oxygen and peroxide activation using a cheap, readily available, non-toxic metal (Fe). Examples of non-native, biomolecule-catalyzed epoxidations include epoxidation of small terminal olefins with methane monooxygenase (a well-known diiron enzyme responsible for hydroxylating methane into methanol in bacteria),^{2a,b} and olefin epoxidation with iron bleomycin (a mononuclear metal-dependent antibiotic that oxidatively cleaves nucleic acids in the presence of O_2 or H_2O_2).^{2c,d} Active sites of non-heme iron enzymes usually contain coordinatively unsaturated iron centers bound to nitrogen donors from aromatic heterocycles (e.g. imidazole of histidine sidechain) and carboxylate oxygen donors, and generate metalbased intermediates that carry out selective oxidations.

Increasing interest in catalytic applications of iron complexes motivated our search for new, simple, efficient and



Scheme 1 Selected aminopyridine ligands that form redox-active iron catalysts.⁴⁻⁷

selective iron catalysts for biomimetic oxidations. Fenton chemistry often dominates the reactivity of iron salts or complexes with peroxides, generating non-discriminatory hydroxyl radicals that hamper selectivity.³ In contrast, tetradentate aminopyridine ligands (Scheme 1) show promise in H₂O₂ activation for selective oxidations;^{4–6} *cis* geometry of two labile sites is important for catalytic activity of their iron(II) complexes,^{4c,d,6b} and increased rigidity of the ligand framework (BPBP *vs.* BPMEN, Scheme 1) prevented leakage of iron and increased the activity of the catalysts, enabling regioselective aliphatic and aromatic C–H oxidation.⁷

In this communication we introduce a new rigid ligand, rac-PYBP (Fig. 1), and describe a new non-heme iron complex, $[Fe(PYBP)(CH_3CN)_2](ClO_4)_2$ (1), which proved to be a highly active and selective catalyst for olefin epoxidation with H₂O₂. The new ligand, PYBP (Fig. 1), is structurally related to BPMEN and BPBP (Scheme 1): the flexibility of the former molecule is reduced by incorporating methyl-amine moiety into rigid 6-membered piperidine rings. Olefin oxidations with hydrogen peroxide in the presence of known iron(II) complexes with BPMEN or BPBP usually yield cis-diols and/or epoxides, often in mixtures.⁵ The new ligand, PYBP, affords an iron(II) complex of superior reactivity and selectivity. This ligand is readily synthesized from a commercially available starting material (2,2'-bipyridine, bipy), and it allows for a variety of structural modifications, because a large range of bipy derivatives are available. Fully reduced bipyridines serve as a highly promising diamine platform for expanding the toolbox of biomimetic redox catalysts.

Attaching two picolyl fragments to the previously reported diamine BP⁸ afforded *rac*-PYBP (Fig. 1); the identity and purity of the compound was confirmed by elemental analysis, NMR, and ESI-MS. The iron(II) complex 1 was synthesized by the reaction of PYBP and Fe(ClO₄)₂·6H₂O in acetonitrile (Fig. 1),

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[†] Electronic supplementary information (ESI) available: Full experimental details for the preparation of the complex **1**, experimental procedures for catalytic epoxidation reactions, and crystallographic details. CCDC 839714. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15935f



Fig. 1 Synthesis and molecular structure of **1** (drawn with thermal ellipsoids at the 50% probability level). A perchlorate anion and hydrogen atoms have been omitted for clarity. Symmetry transformation used to generate equivalent atoms: -x + 1, y, -z + 1/2. Fe–N(1) 1.947(4) Å; Fe–N(2) 2.046(3) Å; Fe–N(3) 1.936(4) Å.

and crystallized by slow ether diffusion under argon (see ESI[†] for details).

The X-ray structure of the complex **1** (Fig. 1) revealed distorted octahedral geometry of iron(II). All four nitrogen atoms of the ligand PYBP are coordinated, in a *cis*- α -topology, to the iron(II) center: two pyridine rings are located in opposite vertices. Two acetonitrile molecules are in *cis*-positions to each other (and *trans*- to tertiary amines); *cis* orientation of labile sites is believed to be critically important for catalysis.^{4c,d} Average Fe–N bond length is 2.0 Å, the value that is typical of low-spin aminopyridine iron(II) complexes. The overall structure of complex **1** is very similar to the structures of known oxidation catalysts, such as $[Fe(BPMEN)(CH_3CN)_2]^{2+1a}$ and $[Fe(BPBP)(CH_3CN)_2]^{2+}$.^{7a,b} The redox properties of the three complexes are also similar: the Fe^{III}/Fe^{II} redox potentials are 0.656 V, 0.660 V, and 0.728 V *vs*. Fc⁺/Fc for **1**, $[Fe(BPBP)(CH_3CN)_2]^{2+}$, and $[Fe(BPMEN)(CH_3CN)_2]^{2+}$, respectively.

Complex 1 was investigated as a catalyst in alkene epoxidation with H₂O₂, and demonstrated excellent activity at low catalyst loadings (Table 1). At 0.5 mol% catalyst with respect to substrate in the presence of 500 mol% of acetic acid (HOAc), nearly quantitative conversion of olefins occurred in 5 to 10 minutes at room temperature, affording *ca.* 1000 mol of respective epoxides per 1 mol of 1 (under similar conditions, 5 mol% of the catalyst was used in [Fe(BPMEN)(CH₃CN)₂]²⁺-catalyzed epoxidations).^{1a} High activity of the new catalyst, especially in the presence of HOAc, allowed us to drastically lower catalyst loadings and observe reasonable to high olefin conversions in 10 minutes with only 0.1 mol% of 1 (Table 1). Although the conversion of alkenes under these conditions was not quantitative, increasing the reaction time to 1 hour did not improve the product yields, but increasing the amount of catalyst to 0.5 mol% did.

Epoxidation results presented in Table 1 demonstrate variable reactivity of alkene substrates: cyclooctene and cyclohexene afford higher epoxide yields, while aliphatic terminal alkenes (1-decene and 1-octene) are less reactive. The susceptibility of tested olefins with respect to catalytic epoxidation with $1/H_2O_2$ increases as the electron density of the double bond increases due to substituent inductive effects (CH₃ > CH₂ > H), a trend

Table 1 Catalytic epoxidation of alkenes with $1/H_2O_2/HOAc$

Alkene	Catalyst loading, mol%	Conversion, % (time, min)	Selectivity ^{<i>c</i>} , %	TON
<i>cis</i> -Cyclooctene ^a	0.5	100 (5)	100	$> 200^{d}$
cis-Cyclooctene ^a	0.1	72 (10)	100	715
Cyclohexene ^{<i>a</i>}	0.1	50 (10)	94	490
Octene-1 ^a	0.5	88 (5)	99	200
Octene-1 ^a	0.1	19 (10)	100	190
Decene-1 ^a	0.5	97.7 (5)	100	195 ^d
Decene-1 ^a	0.1	17 (10)	100	165
Cyclohexadiene-1,4 ^{b,e}	0.5	100 (10)	N/D	$> 200^{d}$
Cyclohexadiene-1,4 ^{<i>b,e</i>}	0.1	29 (10)	83	240
Cyclooctadiene-1,3 ^{b,e}	0.1	8.5 (10)	83	70
Cyclooctadiene-1.3 ^{b,e}	0.5	100 (5)	69	$> 200^{d}$

Reaction conditions: Olefin (200 µmol), H_2O_2 (^{*a*} 300 µmol and ^{*b*} 600 µmol, 30% aqueous solution), HOAc (1 mmol) in 2 mL of CH₃CN, room temperature. ^{*c*} Determined from GCMS. ^{*d*} Accurate determination of TON is impossible. ^{*e*} Only mono-epoxide. Conversion = [products]/(olefin + products); selectivity = [epoxide]/ (all products); turnover number (TON) = amount of epoxide (moles) per 1 mole of 1 over the entire reaction time (5 or 10 minutes).

consistent with redox potentials of alkenes, which becomes less positive upon alkyl substitution.⁹ Nucleophilic reactivity of olefins suggests an electrophilic character of the oxidant. Similarly to other epoxidations catalyzed by non-heme iron complexes, the most reactive are cyclooctene and cyclohexene and less reactive are terminal olefins. For several olefins screened in this work, the new complex 1 reported herein shows very high epoxide yields and turnover numbers at low catalyst loadings compared with other known complexes.^{1a,6a,b} Another beneficial feature of 1 is its high selectivity with respect to epoxide products. In some known catalytic systems, epoxide becomes predominant in the presence of acid, but diol is the main product without it.^{6b} In our case, the major (or sole) product is always epoxide, not diol. Remarkably, cyclic dienes (cyclooctadiene-1,3 and cyclohexadiene-1,4) yielded primarily (if not exclusively) mono-epoxides; this selectivity is potentially useful for synthetic applications. Some relatively reactive alkenes, such as cyclohexene, are known to often favor allylic oxidation; this was not the case in olefin epoxidations catalyzed by 1, where epoxides were the major products and only traces (1-3%) of allylic alcohol and ketone formed. Aromatic olefins were not tested in this work, since aromatic hydroxylation^{7c,d} (ESI^{\dagger}, Fig. S1) may interfere with epoxidation.

In view of known effects of carboxylic acids on the outcomes of catalytic olefin oxidations with H_2O_2 ,^{1*a*,6} we varied the amounts of HOAc in *cis*-cyclooctene and 1-decene epoxidations with $1/H_2O_2$ (Fig. 2). While TON with respect to epoxide uniformly increased in the presence of HOAc, the shapes of the plots of TON *vs.* the amount of HOAc depend on the nature of olefin, and on relative amounts of reactants. Under synthetically relevant conditions (slight excess of the oxidant with respect to substrate), the turnover number goes through the maximum at *ca.* 5000 equivalents of HOAc for *cis*-cyclooctene, while TON for oxidation of 1-decene continues to increase (albeit slowly) at high concentrations of acid. For the system with limiting H_2O_2 , TON for 1-decene epoxidation goes through the maximum at *ca.* 400 equivalents of acid (Fig. S2, ESI†). Decrease of TON at high concentrations of



Fig. 2 Epoxide TON (Table 1) depends on the amount of HOAc added (with respect to 1; logarithmic scale). Olefin (200 μ mol), 1 (0.2 μ mol), H₂O₂ (300 μ mol, 30% aqueous solution), 25 °C, 10 min.

HOAc is explained by the decomposition of complex 1 and the formation of less active binuclear carboxylato-bridged iron(III) compounds, and by a possible competing catalase reaction. Control experiments with iron(II) salts in place of complex 1 did not yield epoxide products.

Stopped-flow studies of the direct reaction between 1 and H₂O₂ identified a short-lived intermediate with $\lambda_{\text{max}} = 560 \text{ nm}$ (Fig. 3). The optical spectrum of this intermediate is similar to the spectra of known mononuclear Fe^{III}(OOH) complexes that typically have an intense band at \sim 500–550 nm. The EPR spectrum of the frozen sample prepared by manual rapid mixing of 1 and a 10-fold excess H_2O_2 (g = 2.185, 1.98, and 1.955) is also very similar to the spectra of known LS iron(III) hydroperoxides¹⁰ and confirms that Fe^{III}(OOH) is present in the reaction mixture. By analogy with reaction mechanisms proposed for related systems,^{6b,7c} HOAc-assisted O-O bond heterolysis would generate a reactive electrophilic intermediate, Fe(V) = O(OAc), that transfers a single oxygen atom to olefins, generating epoxide (Scheme 2). Isotope labeling experiments showed the lack of incorporation of ¹⁸O from water in epoxidations of 1-decene and cyclooctene with $1/H_2O_2/HOAc$, and incorporation of oxygen from $H_2^{18}O_2$ into epoxide products (see ESI⁺ for details). Slow exchange of metal-based oxidant with water implies low accumulation of



Fig. 3 Time-resolved UV-vis spectra of the Fe^{III}(OOH) formation at 27 °C in acetonitrile ([1] = 1 mM, [H₂O₂] = 30 mM). Maximum accumulation of Fe^{III}(OOH) was seen in 2 s after mixing reagents (red-spectrum of 1, purple-spectrum of Fe^{III}(OOH)). Inset: EPR spectrum (120 K) of the Fe^{III}OOH, generated by mixing 1 and H₂O₂ in acetonitrile at 0 °C and freezing in ~7 s after reagents were mixed ([1] = 5 mM, [H₂O₂] = 50 mM after mixing). Spectrum simulated with SimFonia with g values 2.185, 1.98, and 1.955. Another low-spin species (g = 2.40, 2.17, 1.90) most likely results from Fe^{II} \rightarrow Fe^{III} oxidation without OOH coordination.



Scheme 2 Proposed epoxidation pathway.^{6b,7c}

 $Fe(v)(OH)_2$ in excess HOAc, and agrees with exclusive formation of epoxides rather than diols, ^{5b,c,6b-d} which was now observed in catalytic oxidations with $1/H_2O_2/HOAc$.

In conclusion, we have discovered a new iron catalyst of very high selectivity and efficiency in epoxidation of aliphatic olefins with hydrogen peroxide; no diol formation was observed. The epoxide yield strongly depends on the amount of HOAc in the reaction mixture. Acid-promoted O–O bond cleavage in the observed Fe(III)–OOH intermediate generates an electrophilic metal-based oxidant.

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