

A New Coupled Catalytic System for Dihydroxylation of Olefins by H₂O₂

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A number of oxidation reactions rely on the use of a substrate-selective redox system (often Mⁿ⁺/M^m) involving a two-electron oxidation. For a catalytic reaction it is necessary to reoxidize the reduced form of the redox system to its oxidized state. Attractive oxidants for this reoxidation are O₂ and H₂O₂, since they are inexpensive and environmentally friendly.¹ Unfortunately, direct reoxidation of the reduced form of the substrate-selective catalyst by these oxidants is usually not viable due to a high-energy barrier for electron transfer. This energy barrier may be lowered by a relaying redox couple (electron-transfer mediator) between the substrate-selective redox catalyst and the oxidant, a feature common in biochemical processes.² In industrial catalysis a successful example of this principle is given by the palladium-(II)-catalyzed oxidation of ethylene to acetaldehyde (Wacker Process),³ where copper chloride catalyzes reoxidation of Pd(0) to Pd(II) by O₂. We have recently designed and developed several electron-transfer systems for selective aerobic oxidations employing Pd and Ru complexes as substrate-selective catalysts.^{4–6}

The osmium-catalyzed dihydroxylation of olefins involves an Os(VIII)/Os(VI) substrate-selective redox system.⁷ Viable catalytic procedures for this reaction were reported in 1976,^{8,9} and in particular the Upjohn procedure,⁹ in which *N*-methylmorpholine *N*-oxide (NMO) is employed for the reoxidation of Os(VI) to Os(VIII), was a major breakthrough (Scheme 1). The synthetic utility of the reaction was dramatically enhanced when Sharpless et al. developed an enantioselective version.^{10,11}

In this communication we have designed an electron-transfer system for H₂O₂ oxidation of olefins to diols, in which NMM in Scheme 1 is recycled to NMO by catalytic flavin/H₂O₂.

Scheme 1. Upjohn Procedure for the Osmium-Catalyzed Dihydroxylation⁹

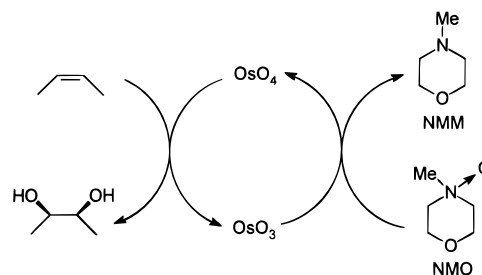
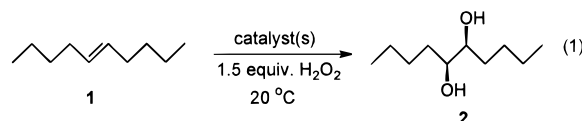


Table 1. Cis-Selective Dihydroxylation of *trans*-5-Decene Employing H₂O₂ as the Terminal Oxidant^a

entry	NMM equiv ^b	flavin (3) equiv ^b	additive	% yield of 2 ^c
1 ^d				10
2				16
3	0.27	0.05		72
4	0.27	0.05	2 equiv of TEAA ^e	95

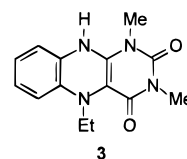
^a The olefin (0.5 mmol), OsO₄ (0.01 mmol, 0.02 equiv), and additional catalysts/additives (according to the table) were dissolved in acetone (1.88 mL) and H₂O (0.62 mL). To this mixture H₂O₂ (1.5 equiv, 30% aqueous) was added over 9 h, unless otherwise noted. After complete addition of the oxidant, the mixture was stirred for an additional 7–15 h. ^b Equivalent to olefin. ^c Isolated yields. ^d In this case the H₂O₂ was added in one portion. ^e Tetraethylammonium acetate.

Oxidation of *trans*-5-decane (1) was studied under different reaction conditions employing H₂O₂ as the terminal oxidant (eq 1), (Table 1). Stoichiometric amounts of NMO were employed



in a control experiment, which gave a 95% yield of diol 2. Direct reoxidation of osmium(VI) by H₂O₂¹² led to a nonselective reaction where 2 was a minor product obtained in 10% yield (Table 1, entry 1). Slow addition of the oxidant did not change the outcome of the reaction much (entry 2).

We have recently shown that biomimetic flavin analogue 3 efficiently catalyzes H₂O₂ oxidation of tertiary amines to amine



oxides via a flavin hydroperoxide.¹³ It would be highly attractive to apply this biomimetic *N*-oxidation to the recycling of NMM

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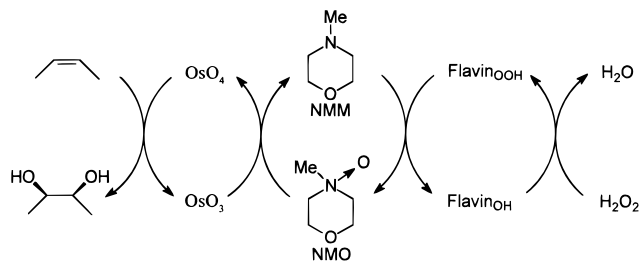
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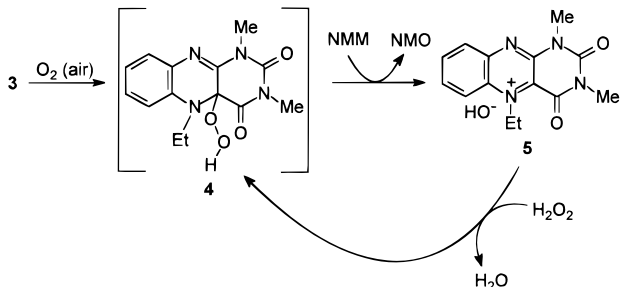
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Scheme 2. Triple Catalytic System for the Osmium-Catalyzed Dihydroxylation of Olefins Using H_2O_2 as the Terminal Oxidant



Scheme 3. The Flavin Cycle in the Osmium-Catalyzed Dihydroxylation Employing H_2O_2 as the Terminal Oxidant



to NMO in the osmium-catalyzed dihydroxylation, which would provide a favorable reoxidation of Os(VI). Thus, in situ generation of NMO from a catalytic amount of NMM by the use of catalytic amounts of **3** (5 mol %) in the dihydroxylation of **1** (eq 1) afforded diol **2** in a good isolated yield (72%, entry 3). It has previously been observed that addition of tetraethylammonium acetate (TEAA) improves the outcome of osmium-catalyzed dihydroxylation,^{8b,14} probably due to the increased rate of hydrolysis of the intermediate osmate ester. Addition of TEAA to the reaction mixture did indeed result in a significant improvement and **2** was obtained in an excellent yield (95%, >99% cis-addition, entry 4).

The mechanism of the triple catalytic H_2O_2 oxidation is depicted in Scheme 2. The flavin hydroperoxide generated from flavin and H_2O_2 is rapidly recycling the NMM to NMO, which in turn reoxidizes the OsO_3 to OsO_4 . The system leads to a mild kinetically controlled^{14a,15} electron transfer from the substrate (olefin) to hydrogen peroxide at room temperature. The stepwise electron transfer with falling redox potential is reminiscent of electron-transfer processes occurring in biological systems.

The role of flavin **3** is most likely to act as a precursor of the active catalyst. In the presence of molecular oxygen (air), an intermediate flavin hydroperoxide **4** is easily generated (Scheme 3).^{13,16} The latter is thought to be the actual oxidizing species, which can transfer one of its oxygen atoms to NMM giving NMO in a mild and fast reaction. During the reaction the cationic flavin **5** is formed, which will react with hydrogen peroxide to regenerate the flavin hydroperoxide **4**.

Several other olefins were oxidized to diols in good to excellent yields employing the mild triple catalytic system developed (Table 2, B). The use of hydrogen peroxide as oxidant without the electron-transfer mediators (NMM, flavin) in osmium-catalyzed dihydroxylation is inefficient and nonselective.¹² In all cases control experiments were carried out in the absence of NMM

Table 2. Cis-Dihydroxylation of Different Olefins Employing H_2O_2 as the Terminal Oxidant^a

entry	substrate	% yield of diol ^b	
		A. cat. OsO_4	B. cat. OsO_4 / cat. NMM/cat. 3
1	<i>trans</i> -5-decene	10	95
2	<i>trans</i> -stilbene	10 ^c	74 ^c
3	<i>trans</i> -2-octene	18	95
4	<i>trans</i> -4-octene	34	92
5	cyclohexene	50	91
6	1-methyl-1-cyclohexene	25	77
7	<i>cis</i> -stilbene	62 ^c	72 ^{c,d}
8	α -methylstyrene	79	93

^a Experimental conditions unless otherwise noted: (A) H_2O_2 (1.5 equiv, 30% aqueous) was added all at once to a mixture of the olefin (1.0 mmol) and OsO_4 (2 mol %) in acetone (3.8 mL) and H_2O (1.2 mL). The reaction mixture was stirred 20–26 h. (B) The olefin (0.5 mmol), *N*-methylmorpholine (27 mol %), TEAA (2 equiv), flavin **3** (5 mol %), and OsO_4 (2 mol %) were dissolved in acetone (1.88 mL) and H_2O (0.62 mL). H_2O_2 (1.5 equiv, 30% aqueous) was added to this mixture over 9 h using a syringe pump. After complete addition of the oxidant, the mixture was stirred for an additional 7–15 h. ^b Isolated yields of cis-addition product. ^c 4.4:1 acetone/ H_2O was employed. ^d Addition time 14 h.

and flavin **3** (Table 2, A),¹⁷ and these experiments gave the corresponding diols in low yields in nonselective reactions. For example, the diols from *trans*-5-decene and *trans*-stilbene were formed in only 10% yield in each case in the H_2O_2 oxidation without NMM and flavin, whereas 95 and 74% yield, respectively, were obtained in the corresponding triple catalytic H_2O_2 oxidations (entries 1 and 2). A substrate like α -methylstyrene (entry 8) works well with the traditional OsO_4 – H_2O_2 system,¹² but also in this case a significant improvement was observed with the triple catalytic system. The turnover rate of this system is comparable to standard osmium-catalyzed dihydroxylation.^{9,18}

An interesting question is if the system is compatible with the use of Sharpless' chiral ligands,^{10,11b} since one may suspect that the tertiary amino groups of the ligands could be oxidized by the flavin hydroperoxide. In a preliminary experiment H_2O_2 oxidation of *trans*-stilbene employing the catalytic system OsO_4 –NMM–flavin **3** and chiral ligand (DHQD)₂PHAL^{10,11b,19} afforded the corresponding diol in 87% yield and 88% ee. The triple catalytic H_2O_2 oxidation of styrene (in *t*-BuOH/ H_2O) employing the same ligand gave the corresponding diol in 84% yield and 88% ee.²⁰

In the present work it was found that hydrogen peroxide can be used as a selective oxidant in the osmium-catalyzed dihydroxylation of olefins by the use of *N*-methylmorpholine (NMM) and flavin **3** as cocatalysts. The process does not require access to an amine oxide but rather a tertiary amine in catalytic amounts. This also allows a useful variation of the tertiary amine employed if needed. The system is compatible with the use of Sharpless' chiral ligands.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) These H_2O_2 oxidations were carried out according to the procedure by Milas (see ref 12).

(18) A shorter addition time of H_2O_2 (2.5 h) in the oxidation of **1** did not result in any considerable change in the reaction outcome, and the diol **2** was isolated in 83% yield.

(19) (a) Only the ligand (DHQD)₂PHAL^{11b,19b} has been tested so far. (b) (DHQD)₂PHAL = hydroquinidine 1,4-phthalazinediyl diether.

(20) In this case it was necessary to change solvent to *t*-BuOH since the oxidation in acetone gave a lower ee. Also, the olefin had to be added slowly (over 9 h), since addition of all olefin at once gave only 74% ee. Optimization of the enantioselectivity for different olefins with the present system will require further studies (variation of solvent, addition time, temperature, etc).

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(15) This system contains four oxidants with falling redox potentials, and four species that can be oxidized. Therefore, there are ten redox reactions that can occur but only four of these are involved due to the high kinetic control.^{14a}

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