Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins by H_2O_2 Using a Biomimetic Flavin-Based Coupled Catalytic System

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Abstract: Selective *cis*-dihydroxylation of olefins with the aid of a triple catalytic system using H_2O_2 as the terminal oxidant has been developed. In this process Os(VI) is recycled to Os(VIII) by a coupled electron-transfer-mediator system based on *N*-methylmorpholine and a biomimetic flavin, leading to a mild and selective electron transfer. Aliphatic, aromatic, and functionalized olefins were successfully *cis*-dihydroxylated, employing the triple catalytic system. The present biomimetic catalytic system works well in asymmetric dihydroxylation and gave optically active diols in good isolated yields and high enantiomeric excesses (up to 99% ee).

Selective oxidation reactions are of current interest in synthetic organic chemistry both on the laboratory scale and on large-scale industrial production.[1,2] A good oxidation system should be highly selective for oxidation of one specific functionality without cross-oxidation of other functionalities. Furthermore, the oxidation system should work with high selectivity for as many variations as possible within the functionality class.

In a selective oxidation a substrate-selective redox reagent or oxidant interacts with the substrate, and this leads to a specific oxidative transformation. Many oxidations are two-electron oxidations where the redox couple (often M^{n+2}/M^n) will take up two electrons from the substrate. Often these types of oxidations are carried out with stoichiometric amounts of the redox couple, which produces stoichiometric amounts of the reduced form of the oxidant. In a catalytic reaction the reduced form of the redox reagent is reoxidized to its oxidized state. It is attractive if this reoxidation could be accomplished by the use of O_2 or H_2O_2, since these oxidants are inexpensive and environmentally friendly.[2] However, reoxidation of the reduced form of the substrate-selective catalyst by O_2 or H_2O_2 may not always be trivial, since the energy barrier for electron transfer can be high. In nature, where oxidations are common in various biological systems, this has been solved by the use of electron-transfer mediators (ETMs) between the substrate-selective redox system and O_2 or H_2O_2.[3]

The concept of an ETM has also been used in nonbiological biomimetic oxidation reactions.[4−8] For example, in the industrial process for aerobic oxidation of ethene to acetaldehyde, palladium chloride is used as the substrate-selective catalyst, and copper chloride is employed as the ETM for the reoxidation of Pd(0) by O_2.[4] We have recently designed and developed selective catalytic systems for aerobic 1,4-oxidation of 1,3-dienes,[5] aerobic allylic oxidation of olefins,[5a] and aerobic oxidation of alcohols[6] on the basis of the principle of selective electron transfer involving ETMs.

Osmium tetroxide is one of the most selective oxidants known: it dihydroxylates all olefins and it reacts *only* with olefins.[1c] Thus, being an ideal substrate-selective catalyst but at the same time toxic and expensive, it is highly desirable to develop good reoxidation systems for osmium, rendering the dihydroxylation catalytic on osmium. Several reoxidation systems have been developed,[8−12] of which the two most commonly used today are based on *N*-methylmorpholine *N*-

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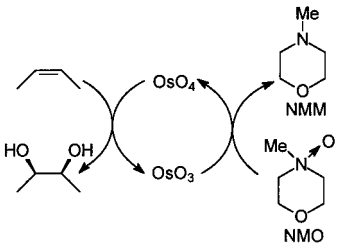
Scheme 1. Upjohn Procedure for the Osmium-Catalyzed Dihydroxylation



oxide (NMO)[11] and $K_3[Fe(CN)_6]$,[12] the latter being mainly used in asymmetric dihydroxylation. However, only very few procedures for reoxidation of osmium(VI) by H_2O_2 or O_2 are known.[9,13−16] Milas[9] found that H_2O_2 can be employed as a direct reoxidant for Os(VI), but in many cases this leads to nonselective reactions with low yields due to over-oxidations. Krief has shown that O_2 can reoxidize Os(VI) in the presence of a selenoxide under irradiation by visible light.[14] Recently, Beller reported a procedure for aerobic osmium-catalyzed dihydroxylation of olefins.[15] At the same time we published a preliminary communication on the biomimetic osmium-catalyzed dihydroxylation by H_2O_2.[16] In the latter process the Os(VI) is recycled to Os(VIII) by a coupled catalytic ETM system based on NMO/flavin, leading to a mild and selective electron transfer. We now give a full account on this work, report on the asymmetric dihydroxylation of the reaction, and discuss the versatility and mechanistic aspects of this new biomimetic process.

Results and Discussion

In the Upjohn procedure,[11] NMO is employed as the terminal oxidant in the dihydroxylation of olefins. The reoxidation of Os(VI) to Os(VIII) by NMO leads to formation of *N*-methylmorpholine (NMM) (Scheme 1).

One objective with the present project was to continuously recycle NMM back to NMO by either O_2 or H_2O_2 in a catalytic process. It was known from previous work in our group that tertiary amines undergo efficient flavin-catalyzed oxidations by H_2O_2 to the corresponding *N*-oxides.[17]

A. Osmium-Catalyzed Dihydroxylation by H_2O_2. The combined catalytic ETM system NMO-flavin for the reoxidation of Os(VI) to Os(VIII) by H_2O_2 has been studied under different reaction conditions.

1. Regeneration of NMO by H_2O_2. For our initial investigations we chose *trans*-5-decene **1** as a model substrate, and several reaction conditions employing H_2O_2 as the terminal oxidant and osmium tetroxide as catalyst (Table 1, eq 1) were

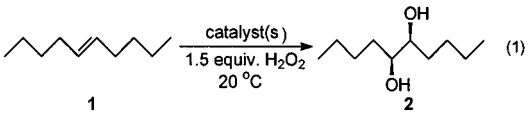


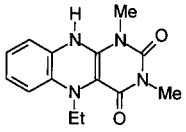
Table 1. *cis*-Selective Dihydroxylation of *trans*-5-Decene Employing H_2O_2 as the Terminal Oxidant[a]

entry	NMM equiv[b]	flavin (**3**) equiv[b]	additive	yield (%) of **2**[c]
1[d]				10
2				16
3	0.27			58
4	0.27		2 equiv of TEAA[e]	69
5	0.27	0.05		72
6		0.05	2 equiv of TEAA[e]	47
7[f]	0.27	0.05	2 equiv of TEAA[e]	83
8	0.27	0.05	2 equiv of TEAA[e]	95

[a] The olefin (0.5 mmol), OsO_4 (0.01 mmol, 0.02 equiv), and additional catalysts (according to the Table) were dissolved in acetone (1.88 mL) and H_2O (0.62 mL). Then H_2O_2 (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 7−17 h. [b] Equivalent to olefin. [c] Isolated yields of *cis*-addition product. [d] H_2O_2 was added in one portion. [e] Tetraethylammonium acetate. [f] H_2O_2 was added over 2.5 h.

examined. A mixture of acetone and water was used as the solvent system throughout the study. Stoichiometric amounts of NMO were employed in a control experiment, which gave 95% yield of diol **2**. Direct reoxidation of osmium(VI) by H_2O_2[9] led to a nonselective reaction where **2** was a minor product obtained in 10% yield (Table 1, entry 1). Slow addition of the H_2O_2 to the reaction mixture did not change the outcome of the reaction much (entry 2). The next precaution undertaken to avoid over-oxidation was to include NMM in the system, which can trap the peroxide via in situ generation of NMO. Including 0.27 mol % NMM in the system led to less over-oxidation, and the diol was isolated in 58% yield (entry 3). It has previously been observed that addition of tetraethylammonium acetate (TEAA) improves the outcome of osmium-catalyzed dihydroxylations,[10,18,19] probably due to the increased rate of hydrolysis of the intermediate osmate ester. Addition of 2 equiv of TEAA to the reaction mixture afforded an improved yield of 69% (entry 4).

We have recently shown that tertiary amines are efficiently oxidized to their corresponding *N*-oxides by a biomimetic flavin hydroperoxide **4** generated from the flavin analogue **3**.[17]



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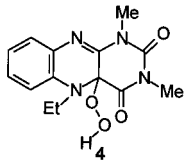

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Furthermore, the catalytic intermediate flavin hydroperoxide oxidizes NMM to NMO more than 6000 times faster than H_2O_2 does. It was therefore highly attractive to apply this biomimetic *N*-oxidation to the recycling of NMM to NMO in the osmium-catalyzed 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 flavin **3** (5 mol %) in the dihydroxylation afforded a good isolated yield (72%, entry 5). Excluding NMM, and thereby using only the flavin as ETM, led to a dramatic decrease in yield (47%, entry 6).

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

entry	olefin	yield (%) of diol[b] A. cat. OsO_4	B. cat. OsO_4/ cat. NMM/ 2 equiv. TEAA	C. cat. OsO_4/ cat. NMM/ 2 equiv. TEAA/ cat. **3**
1		10	69	95
2		10[c]	50[c]	95[c]
3		32	79	95
4		35	75	92
5		50	58	91
6		25	50	77
7		-[e]	63	93
8		62[c]	43[c]	72[c,d]
9		79	77	93
10		72	81	91
11		24	52	82
12		85	85	88
13		53	86	95

[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 at 20 °C. (B) The olefin (0.5 mmol), *N*-methylmorpholine (27 mol %), TEAA (2 equiv), 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. After complete addition of the oxidant, the mixture was stirred for an additional 7−15 h. (C) As in B, also the flavin **3** was added before addition of the H_2O_2 started. [b] Isolated yields. [c] 4.4:1 acetone−H_2O was employed. [d] Addition time 14 h. [e] No diol could be isolated.

Next, we examined the effect of TEAA on the dihydroxylation employing the triple catalytic system. Addition of TEAA to the reaction mixture did indeed result in a significant improvement, and **2** was obtained in an excellent yield (95%, entry 8). Interestingly, a shorter addition time of H_2O_2 (2.5 h) did not result in any considerable change in the reaction outcome, and the diol **2** was isolated in 83% yield (entry 7). The turnover rate of the triple catalytic system is comparable to standard osmium-catalyzed dihydroxylation.[11] When decreasing the amount of OsO_4 to 1 mol % in the triple catalytic alkaline system, the yield of the diol dropped to 64%.

Several different olefins, were dihydroxylated to their corresponding diols, employing the optimal conditions from entry 8, Table 1. As can be seen from Table 2 (method C), most olefins tested were efficiently *cis*-dihydroxylated to the corresponding diols in good to excellent yields. Control experiments were carried out in all cases in which H_2O_2 was applied as co-oxidant without the electron-transfer mediators NMM and flavin (method A), or with the electron-transfer mediator NMM in combination with TEAA (method B). The use of hydrogen peroxide as oxidant without the electron-transfer mediators NMM and flavin in the osmium-catalyzed dihydroxylation (method A) led to inefficient and nonselective reactions. For example, the diols from *trans*-5-decene (entry 1) and *trans*-stilbene (entry 2) were formed in only 10% yield in each case in the H_2O_2 oxidation without NMM and flavin (method A).

Table 3. Effect of Solvent on the *cis*-Dihydroxylation of *trans*-5-Decene Employing the Triple Catalytic System

entry	solvent	yield (%)
1	H_2O−acetone	95
2	H_2O−*t*-BuOH	81
3	H_2O−CH_3CN	60

[a] Experimental conditions: The olefin (0.5 mmol), *N*-methylmorpholine (27 mol %), TEAA (2 equiv), OsO_4 (2 mol %), and flavin **3** (5 mol %) were dissolved in acetone or CH_3CN or *t*-BuOH (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. After complete addition of the oxidant, the mixture was stirred for an additional 7 h. [b] Isolated yields.

With NMM and TEAA (method B) the yield was improved to 69 and 50%, respectively, whereas a 95% yield was obtained in both cases for the corresponding optimized triple catalytic H_2O_2 oxidation (method C). Also *trans*-2-octene (entry 3), *trans*-4-octene (entry 4), 1-methyl-cyclohexene (entry 6), and 2,2-dimethyl styrene (entry 11), which under Milas conditions (method A) gave 24−35% yield, afforded 82−95% yield with the triple catalytic system (method C). Substrates such as α-methylstyrene (entry 9), styrene (entry 10), and 2-methyl-1-heptene (entry 12) work well with the traditional Milas[9] system (A) and the system B, but also in these cases a significant improvement was obtained employing the triple catalytic system. The functionalized substrate, allyl phenyl ether (entry 13), proceeded excellently, giving the diol in 95% yield. Dihydroxylation of 1-phenyl-1-cyclohexene (entry 7) did also proceed nicely with our triple catalytic system, and the diol was isolated in 93% yield.

2. Solvent Effects. It was found that the solvent has a significant effect on the yield in the dihydroxylation with the triple catalytic system. A few solvent systems were studied in the dihydroxylation of *trans*-5-decene, and the results are given in Table 3 (eq 2). The highest yield was obtained with H_2O−

acetone as solvent, which is employed in typical OsO_4-catalyzed dihydroxylations when *N*-methylmorpholine is used as the oxidant.[20] When the solvent was changed to H_2O-*tert*-BuOH the yield decreased slightly (to 81%). A moderate yield (60%) was obtained when H_2O−acetonitrile was used as solvent.

3. Variation of Tertiary Amine. Various *N*-oxides have been employed in osmium-catalyzed dihydroxylation. For example trimethylamine *N*-oxide was used as an efficient oxidant in the hydroxylation of sterically hindered olefins[21] and in the oxidation of allylic alcohols.[22] *N*-methylmorpholine *N*-oxide has recently been successfully used in the dihydroxylation of olefins with a polymer-supported osmium catalyst,[23] and with homogeneous conditions on an industrial scale.[20] Since the flavin/H_2O_2 system works very well for oxidation of various tertiary amines to their corresponding *N*-oxides[17] it was of interest to investigate if NMM can be replaced by other tertiary amines in the triple catalytic system. Under the optimized conditions from above, dihydroxylation of *trans*-5-decene was carried out with five

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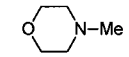
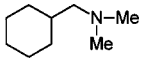
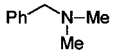
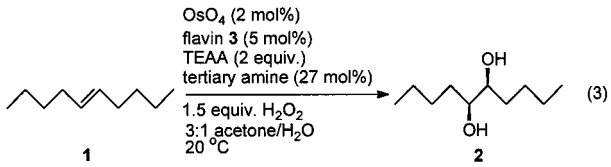
Table 4. *cis*-Selective Dihydroxylation of *trans*-5-Decene Using Different Tertiary Amines in the Triple Catalytic System[a]

entry	amine	yield (%) of **2**[b]
1		96
2	NEt_3	91
3		90
4		89
5	NMe_3	81

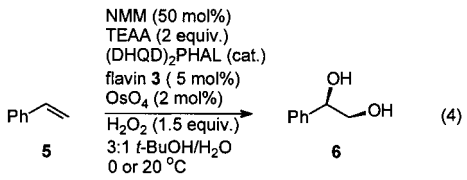
[a] The olefin (0.5 mmol), tertiary amine (27 mol %), TEAA (2 equiv), flavin **3** (5 mol %), and OsO_4 (2 mol %) were dissolved in acetone (1.88 mL) and H_2O (0.62 mL). H_2O_2 (1.5 equiv, 30% aqueous) was added to this mixture over 9 h. After complete addition of the oxidant, the mixture was stirred for an additional 5−10 h. [b] Isolated yields.

different tertiary amines (Table 4, eq 3).



Triethylamine, *N*,*N*-dimethyl(cyclohexylmethyl)amine, and *N*,*N*-dimethylbenzylamine gave around 90% of diol under these conditions, whereas trimethylamine afforded 81% yield of diol. Thus, it is possible to use different tertiary amines with essentially the same outcome. This is of importance since a particular amine oxide is known to have certain advantages in a given dihydroxylation. For example Donohoe et al.[22] demonstrated that the *anti*/*syn* selectivity observed for dihydroxylation of *E*-allylic alcohols under Upjohn conditions[11] (NMO) was improved significantly under the so-called Poli[24] conditions (Me_3NO),[22] in one case from 5:1 to 12:1. The advantage with the present procedure is that any tertiary amine can be used instead of the corresponding *N*-oxide.

4. Enantioselective Dihydroxylation. Encouraged by the promising results obtained with the triple catalytic system (Table 2), we investigated if the system was compatible with the use of Sharpless' chiral ligands.[1c,25] We chose styrene as a model substrate and hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2PHAL$)[25b] as the ligand, and several reaction conditions were examined to optimize the enantioselectivity (Table 5, eq 4). In the preliminary experiment we used 3 mol % chiral



ligand. In these asymmetric dihydroxylations the solvent was changed to *t*-BuOH since the oxidation in acetone gave lower ee.[20] The rate of addition of olefin has previously been shown to be important for the enantioselectivity in NMO-based reactions.[25a] Therefore also, the olefin was added slowly (over 9 h) according to the optimized version of the asymmetric Upjohn process reported by Sharpless,[25a] since excess olefin in solution considerably reduces the ee of the product. This led to an improvement from 74% ee when all olefin was added at once (entry 1, Table 5) to 79% ee when the olefin was added over 9 h (entry 2). When the olefin was introduced slowly, the reaction mixture remained yellow, but when it was added in one portion in the beginning of the reaction, the solution took on a brown-blackish tint.[25a]

Table 5. Asymmetric Dihydroxylation of Styrene under Different Conditions Employing the Chiral Ligand $(DHQD)_2PHAL$[a]

entry	mol % chiral ligand	temperature °C	method A[b] or method B[c]	yield (%)[d]	ee (%)[a]
1	3	0	A	91	74
2[e]	3	0	A	87	79
3	3	0	B	84	88
4	3	20	B	85	86
5	6	0	A	80	87
6	6	0	B	80	95

[a] Enantiomeric excesses were determined by HPLC. [b] (A) Styrene (0.5 mmol), *N*-methylmorpholine (27 mol %), TEAA (2 equiv), $(DHQD)_2PHAL$ as shown in the table, flavin **3** (5 mol %) and OsO_4 (2 mol %) were dissolved in *t*-BuOH (1.88 mL) and H_2O (0.62 mL). Then H_2O_2 (1.5 equiv, 30% aqueous) was added over 9 h. After complete addition of the oxidant, the mixture was stirred for an additional 3−6 h. [c] (B) *N*-methylmorpholine (0.50 equiv), TEAA (2 equiv), $(DHQD)_2PHAL$ as shown in the table, and flavin **3** (0.05 equiv) were dissolved in *t*-BuOH (1.88 mL) and H_2O (0.62 mL). OsO_4 (0.02 equiv) was added followed by $^1/_5$ of the H_2O_2 (0.3 equiv, 30% aqueous). The mixture was stirred for 20 min, and then styrene (0.5 mmol) and the remaining H_2O_2 (1.2 equiv) were added over 9 h. After complete addition of the oxidant and olefin, the mixture was stirred for an additional 2−7 h. [d] Isolated yields. [e] The olefin was introduced dropwise over 9 h.

It was also found that an improvement of the ee was obtained when $^1/_5$ of the hydrogen peroxide was added to the reaction mixture 20 min prior to the introduction of the olefin (Method B). Presumably, this builds up a low buffer concentration of NMO by transforming some of the NMM to NMO. After this initial preactivation, the remaining H_2O_2 as well as the olefin were added over 9 h via separate syringe pumps. With this procedure, a considerable improvement in the enantiomeric excess was observed (entry 3). An attempt to run the oxidation at room temperature (entry 4) gave a slight drop in ee.[25a] When increasing the amount of chiral ligand from 3 mol % (entry 1) to 6 mol % (entry 5) employing method A, an improvement of the ee was obtained. Finally, with method B, in the presence of 6 mol % of ligand at 0 °C, an optimized ee of 95% was obtained.

Under the above-optimized conditions, asymmetric dihydroxylation of *trans*-stilbene, α-methylstyrene, trans-β-methylstyrene, and 1-phenyl-1-cyclohexene was carried out in the presence of the $(DHQD)_2PHAL$ ligand (Table 6). It was found that for the asymmetric dihydroxylation, employing the triple catalytic system, the enantioselectivity is strongly influenced by the ligand concentration. To obtain enantioselectivities over 90%, an excess of chiral ligand compared to osmium (Os/L = 1:3) is required.

In the case of *trans*-stilbene the highest ee was observed when the solvent was replaced by acetone−H_2O using 6 mol % ligand. Table 6 shows the effect of solvent, for example 91% ee was obtained in acetone−H_2O (entry 5) versus 79% ee in *t*-BuOH−H_2O (entry 4). These results are in contrast to those previously reported by Sharpless et al.,[26] where the best yield for the

(24) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385.

(25) (a) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

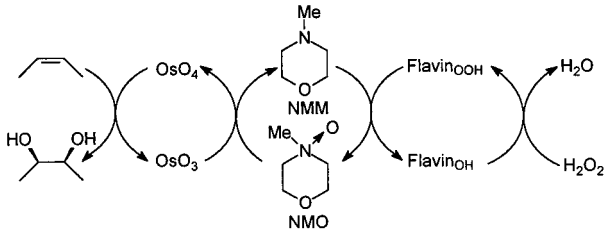
(26) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.

Table 6. Asymmetric Dihydroxylation of Different Alkenes Using OsO_4-NMM-Flavin-H_2O_2[a]

entry	olefin	mol% chiral ligand	yield (%)[b]	ee (%)[c]
1	Ph	3	84	88
2		6	80	95
3[d,e]	Ph	3	87	88
4[e]	Ph	6	37	79
5[d,e]		6	94	91
6	Ph	3	73	48
7		6	88	99
8	Ph	3	64	88
9		6	67	96
10	Ph	3	11	26
11		6	50	69
12[f]		6	50	92

[a] *N*-methylmorpholine (0.14 mmol, 0.50 equiv), TEAA (2 equiv), chiral ligand as shown in the table, and flavin **3** (0.05 equiv) were dissolved in *t*-BuOH (1.88 mL) and H_2O (0.62 mL). The mixture was cooled down to 0 °C, and OsO_4 (0.01 mmol, 0.02 equiv) was added followed by $^1/_5$ of the H_2O_2 (0.3 equiv, 30% aqueous). The mixture was stirred for 20 min, and then the olefin (0.5 mmol) and the remaining H_2O_2 (1.2 equiv) were added over 9 h. After complete addition of the oxidant and olefin, the mixture was stirred for an additional 2−7 h. [b] Isolated yields. [c] Enantiomeric excesses were determined by HPLC. [d] 4.4:1 acetone/H_2O was employed. [e] The absolute configurations of the diols were determined by comparison of optical rotations with literature values.[22] [f] The olefin and H_2O_2 were introduced over 20 h.

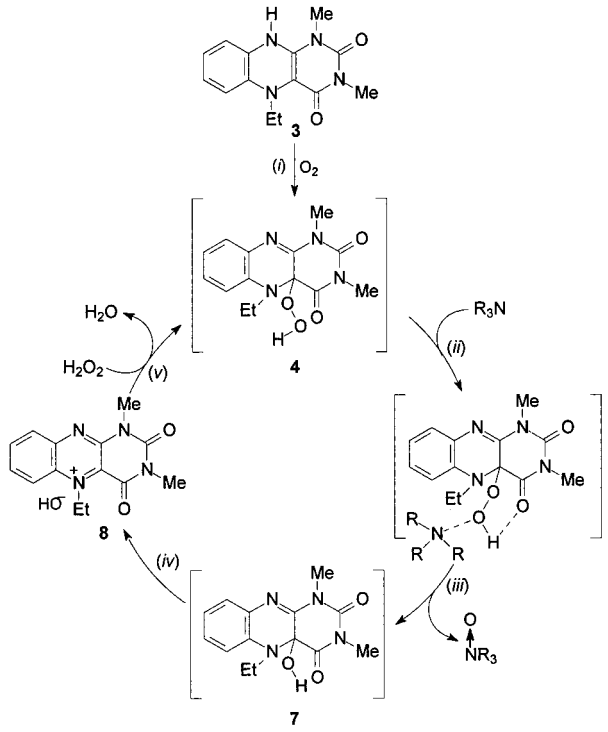
Scheme 2. Triple Catalytic System for Osmium-Catalyzed Dihydroxylation of Olefins Using H_2O_2 as the Terminal Oxidant



asymmetric dihydroxylation of *trans*-stilbene was obtained in *t*-BuOH/H_2O. The oxidation of α-methylstyrene proceeded excellently in our triple catalytic system, and we were able to obtain an enantiomeric excess of 99% (entry 7). The methyl substituent on *trans*-*β*-methylstyrene (entry 9) seems to have very little effect on the enantioselectivity, and the ee was the same as that of styrene (entries 1 and 2). The trisubstituted olefin 1-phenyl-1-cyclohexene required a longer addition time of both olefin and hydrogen peroxide.[25a] When increasing the addition time from 9 to 20 h, the enantioseletivity was improved from 69% (entry 11) to 92% (entry 12). Thus, by employing slow addition techniques, good enantiocontrol can be obtained for substrates that are problematic.[1d,25a] Aliphatic alkenes gave substantially lower enantioselectivities. For example *trans*-5-decene gave the corresponding diol in 57% ee using 3 mol % chiral ligand and 63% ee with 6 mol % ligand, respectively.

B. Mechanistic Aspects. The mechanism of the biomimetic triple catalytic H_2O_2 oxidation is depicted in Scheme 2. The oxidation involves a cascade of selective electron-transfer reactions, which transport two electrons from the substrate (olefin) to hydrogen peroxide. The substrate-selective catalyst

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



OsO_4 (Os(VIII)) dihydroxylates the olefin, and the Os(VI) produced is efficiently reoxidized to Os(VIII) by NMO. The flavin hydroperoxide is in turn rapidly recycling NMM to NMO, and the reduced flavin is reoxidized by H_2O_2. This coupled biomimetic system leads to a mild kinetically controlled[5a,27] electron transfer from the substrate (olefin) to H_2O_2 at room temperature and does not require the complex structure of naturally occurring enzymes to distinguish between the electron-transfer processes.[27] The high kinetic control requires close interaction (contact) between the redox couples involved in the cascade through coordination or weak bonding. For example, the olefin is coordinated to Os(VIII), and the *N*-oxide coordinates to Os(VI). Furthermore, it is known that flavoenzymes via their hydroperoxides are the active species in amine oxidases and hepatic flavoenzymes.[28] Presumably, intramolecular hydrogen bonding in the flavin hydroperoxide leads to an efficient interaction between the peroxy oxygen and the amine (Scheme 3), resulting in the high rate-enhancement (6000−8000 compared to H_2O_2).[17] Finally, it is known that H_2O_2 selectively reacts with the reduced form of the reactive flavin hydroperoxide.

The role of flavin **3** is most likely to act as a precursor for the active catalyst. In the presence of molecular oxygen (air), an intermediate flavin hydroperoxide **4** is easily generated from **3** (Scheme 3).[17,29] 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 (steps ii and iii). The flavin hydroperoxide **4** is highly active for amine oxidation, and similar hydroperoxides are known to be involved in hepatic flavoenzymes.[28] The reduced flavin **7** is recycled to the active hydroperoxide **4** by loss of OH^- to give the cationic alloxazine **8** (step iv), which subsequently reacts with H_2O_2.[17,30]

(27) This system contains four oxidants with falling redox potentials, and four species that can be oxidized. Therefore, there are 10 redox reactions that can occur but only four of these are involved due to the kinetic control.

(28) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443.

(29) For reaction of O_2 with related flavins to give flavin hydroperoxides, see: (a) Kemal, C.; Bruie, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 995. (b) Mager, H. I. X.; Berends, W. *Tetrahedron* **1976**, *32*, 2303.

Ever since the Upjohn procedure was published in 1976[11] the NMO-based procedure has become one of the standard methods for osmium-catalyzed dihydroxylation. However, in the asymmetric dihydroxylation (AD) NMO has not been fully appreciated since it was difficult to obtain high ee with this oxidant. The preferred oxidant for AD, introduced by Sharpless as the AD-mix,[1c] is $K_3Fe(CN)_6$, which gives high ee with various olefins when phthalazine ligands $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$) are employed.

More recently, however, it was demonstrated that NMO can be employed as oxidant in the AD reaction to give high ee (up to 98%) in aqueous *tert*-BuOH with slow addition of the olefin.[20] Also, recent work by Kobayashi[23] and our present study show that NMO is indeed a viable oxidant in AD under appropriate reaction conditions. In light of this renaissance of NMO as a useful oxidant in AD, the catalytic in situ generation of the *N*-oxide from tertiary amine is of particular importance.

In the osmium-catalyzed AD, two catalytic cycles have been inferred by Sharpless and co-workers,[25a] one cycle with a monoglycolate ester giving high ee and a second cycle with a bisglycolate ester giving poor ee. A problem with NMO is apparently that it is difficult to avoid involvement of the second cycle. By slow addition of the olefin, formation of the bisglycolate ester is depressed, and hence the involvement of the second cycle becomes less important. Also, slow addition of the oxidant may have a similar effect as well as addition of TEAA. A good example demonstrating the effect of slow addition is the dihydroxylation of 1-phenylcyclohexene (Table 6). An increase of the addition time for olefin and H_2O_2 from 9 to 20 h increased the enantioselectivity from 69 to 92% ee (entries 11 and 12). To the best of our knowledge this is the highest ee reported for this olefin when NMO is used to recycle Os(VI) to Os(VIII) (cf. Scheme 2).

Conclusions

We have developed a mild triple catalytic system consisting of osmium tetroxide, *N*-methylmorpholine, and the biomimetic flavin analogue **3**, where hydrogen peroxide is used as the terminal oxidant. With this multistep electron-transfer system the oxidation potential of H_2O_2 has been lowered stepwise, and thus it is possible to direct the selectivity toward the desired transformation. This stepwise electron transfer with falling redox potential is reminiscent of electron-transfer processes occurring in biological systems. A number of olefins were selectively *cis*-dihydroxylated to their corresponding diols in good to excellent yields, and by the use of chiral ligands high enantiomeric excesses (ee's) were obtained. The process does not require access to an amine oxide but rather a tertiary amine in catalytic amounts, which generates the amine oxide in situ. Since a variety of tertiary amines are readily available this allows a useful variation of the in situ generated amine oxide.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm, using residual solvent as internal standard. Merck silica gel 60 (240−400 mesh) was used for flash chromatography, and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Analytical high-pressure liquid chromatography (HPLC) was performed on a Waters liquid chromatograph using a Daicel Chiralcel OD-H column or a Daicel Chiracel OK-H column. Gas chromatography (GC) was performed on a Varian CP-3380 chromatograph using a DBWAX-5 column. Optical rotations were obtained on a Perkin-Elmer 241 Polarimeter and are reported as follows $[\alpha]^{temperature}_{wavelength}$, concentration ($c$ = g/100 mL), and solvent. Slow additions of olefins were carried out using a Sage model 355 syringe pump. Plastic syringes and a syringe pump Sage model 365 were used for slow addition of H_2O_2.

All olefins and reagents were obtained from commercial suppliers and used without further purification. *N*-methylmorpholine (NMO) was obtained from Fluka, and H_2O_2 (30% aqueous) and OsO_4 (as a 2.5 wt % solution in *t*-BuOH) were purchased from Aldrich. Tetraethylammonium acetate (TEAA, 99%) and $(DHQD)_2PHAL$ (99%) were acquired from Aldrich. The flavin **3** used was synthesized according to a previously published procedure.[17]

***threo*-5,6-Decanediol (2). General Procedure A for Dihydroxylation of *trans*-5-Decene with OsO_4 and H_2O_2.** *trans*-5-Decene (1 mmol) was dissolved in acetone (3.75 mL) and H_2O (1.25 mL) at room temperature. OsO_4 (251 μL, 2.5 wt% 0.02 mmol) was added followed by H_2O_2 (155 μL, 30% aqueous 1.5 mmol). The reaction mixture was stirred for 26 h at room temperature and then quenched by addition of $Na_2S_2O_4$ (120 mg) and magnesium silicate (240 mg). After 2 h of stirring the mixture was diluted with ethyl acetate and filtered through a pad of Celite, and the Celite bed was washed thoroughly with ethyl acetate. The solvent was removed to give a residue which was purified by flash chromatography using a mixture of pentane/EtOAc (80:20) to afford **2** (0.018 g, 10%).

***threo*-5,6-Decanediol (2). General Procedure B for Dihydroxylation of *trans*-5-Decene Using OsO_4-NMM with Slow Addition of H_2O_2 in the Presence of TEAA.** *trans*-5-Decene (0.5 mmol) was dissolved in acetone (1.88 mL) and H_2O (0.62 mL) at room temperature. To this mixture was added NMM (15 μL, 0.14 mmol), tetraethylammonium acetate (261 mg, 1 mmol), and OsO_4 (125 μL, 2.5 wt %, 0.01 mmol). H_2O_2 (77 μL, 30% aqueous, 0.75 mmol) was then introduced over 9 h using a syringe pump. The yellow mixture was stirred for an additional 14 h and then quenched by addition of $Na_2S_2O_4$ (60 mg) and magnesium silicate (120 mg). After 2 h of stirring the mixture was diluted with ethyl acetate and filtered through a pad of Celite, and the Celite bed was washed thoroughly with ethyl acetate. The solvent was removed, and the residue was purified by flash chromatography using a mixture of pentane/EtOAc (80:20) to give **2** (0.060 g, 69%)

***threo*-5,6-Decanediol (2). General Procedure C for Dihydroxylation of *trans*-5-Decene Using OsO_4-NMM-Flavin with Slow Addition of H_2O_2 in the Presence of TEAA.** *trans*-5-Decene (0.5 mmol) was dissolved in acetone (1.88 mL) and H_2O (0.62 mL) at room temperature. To this mixture was added NMM (15 μL, 0.14 mmol), tetraethylammonium acetate (261 mg, 1 mmol), flavin **3** (6.7 mg, 0.025 mmol), and OsO_4 (125 μL, 2.5 wt %, 0.01 mmol). H_2O_2 (77 μL, 30% aqueous, 0.75 mmol) was then introduced over 9 h using a syringe pump. The yellow mixture was stirred for an additional 7 h and then quenched by addition of $Na_2S_2O_4$ (60 mg) and magnesium silicate (120 mg). After 2 h of stirring the mixture was diluted with ethyl acetate and filtered through a pad of Celite, and the Celite bed was washed thoroughly with ethyl acetate. The solvent was removed to give the crude diol. The crude diol was purified by flash chromatography using a mixture of pentane/EtOAc (80:20) to afford **2** (0.084 g, 96%)

(*1R*)-1-Phenyl-1,2-ethandiol. General Procedure for Asymmetric Dihydroxylation of Styrene Using OsO_4-NMM-Flavin with Slow Addition of Olefin and H_2O_2 in the Presence of TEAA. To a flask charged with t-BuOH (1.88 mL) and H_2O (0.62 mL) was added NMM (27 μL, 0.25 mmol), tetraethylammonium acetate (261 mg, 1 mmol), $(DHQD)_2PHAL$ (23 mg, 0.03 mmol), and flavin **3** (6.7 mg, 0.025 mmol). This stirred mixture was cooled to 0 °C, and OsO_4 (125 μL, 2.5 wt% 0.01 mmol) was added, followed by $^1/_5$ of the H_2O_2 ($^1/_5 \times 77$ μL, 30% aqueous, $^1/_5 \times 0.75$ mmol). The yellow reaction mixture was stirred for 20 min, and then the neat alkene (0.5 mmol) and the rest of the H_2O_2 were added over a period of 9 h using separate syringe pumps. After the addition was complete, the resulting clear yellow solution was stirred at 0 °C for an additional 2 h and quenched by addition of $Na_2S_2O_4$ (60 mg) and magnesium silicate (120 mg). After 2 h of stirring the mixture was diluted with ethyl acetate and filtered through a pad of Celite, and the Celite bed was washed thoroughly with ethyl acetate. The solvent was removed, and the residue was purified by flash

(30) For the use of isomeric flavins in catalytic oxidations, see: (a) Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc*. **1989**, *111*, 5002. (b) Mazzini, C.; Lebreton, J.; Furstoss, R. *J. Org. Chem*. **1996**, *61*, 8.

chromatography using a mixture of pentane/EtOAc (80:20) to afford (1*R*)-1-phenyl-1,2-ethanediol (0.055 g, 80%). Analysis by HPLC showed that the product was of 95% ee.

Characterization of Products. The following compounds are known compounds, and their spectra were in accordance with those reported in the literature: *threo*-5,6-decanediol (**1b**),[31] (*R*,*R*)-5,6-decanediol ($[\alpha]^{25}_D$ +19.8 (*c* 1.00, $CHCl_3$)),[31] (*R*,*R*)-1,2-Diphenyl-1,2-ethanediol[32] ($[\alpha]^{25}_D$ +86.5 (*c* 1.00, EtOH)),[26] octane-2,3-diol,[33] octane-4,5-diol,[34] *cis*-1,2-cyclohexanediol,[35] *cis*-1-methyl-1,2-cyclohexanediol,[36] (1*R*,2*R*)-1-phenyl-1,2-cyclohexane-diol[37] (Daicel Chiralcel OD-H column, 90:10 hexane/2-propanol, flow rate 0.5 mL/min): t_R(major) = 31.4 min, t_R(minor) = 33.9 min[25b]), 1,2-diphenyl-1,2-ethanediol (*meso*),[38] (1*R*)-1-phenyl-1,2-propanediol[39] (HPLC (Daicel Chiralcel OD-H column, 95:5 hexane/2-propanol, flow rate 0.5 mL/min): t_R(major) = 34.7 min, t_R(minor) = 38.9 min[25b]), (1*R*)-1-phenyl-1,2-ethanediol[40] (HPLC (Daicel Chiralcel OK column, 98:2 hexane/2-propanol, flow rate 1.0 mL/min): t_R(major) = 53.2 min[25b]), 2-methyl-1-phenyl-1,2-propanediol,[41] 2-methyl-1,2-heptanediol,[42] 3-phenoxy-1,2-propanediol,[43] (1*R*,2*R*)-1-phenylpropane-1,2-diol[44] (HPLC (Daicel Chiralcel OD-H column, 95:5 hexane/2-propanol, flow rate 0.5 mL/min): t_R(major) = 28.1 min, t_R-(minor) = 30.5 min[44]).

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