Efficient Osmium/Rhenium-Catalyzed Dihydroxylation of Olefins with Hydrogen Peroxide under Acidic Conditions

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Abstract: Simple addition of citric acid confers great stability to the catalytically active osmium and rhenium species involved in a triple catalytic system utilizing aqueous hydrogen peroxide as the terminal oxidant. The resulting system is capable of dihydroxylating traditionally resistant olefins in high yields.

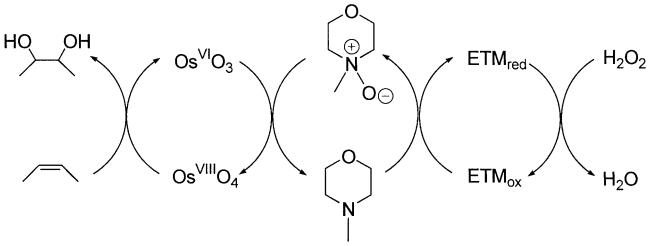
Keywords: alkenes; dihydroxylation; homogeneous catalysis; osmium; oxidation

Introduction

The osmium-catalyzed dihydroxylation of olefins is one of the most useful oxidation reactions in organic synthesis.[1] The reaction is highly specific, and easy to carry out. In this redox process, osmium(VIII) is reduced to osmium(VI) through reaction with an olefin to yield an osmium(VI) glycolate. The latter is then hydrolyzed to yield a diol. A catalytic amount of osmium may be used if an appropriate reoxidant is present, that can oxidize osmium(VI) back to the active osmium(VIII). Typical reoxidants for osmium used in catalytic reactions are *N*-methylmorpholine *N*-oxide (Upjohn reaction)[2] and potassium ferricyanide, commonly used in the asymmetric dihydroxylation reaction.[3] Work in our group has focused on allowing the use of H_2O_2 as the terminal reoxidant in the dihydroxylation reaction. Hydrogen peroxide is attractive as a terminal oxidant because it is inexpensive and environmentally friendly.[4] Hydrogen peroxide may be used as a direct reoxidant for Os(VI)[5] in dihydroxylation reactions, but in most cases this results in overoxidation and non-selective reactions. Our solutions to this problem have revolved around the use of organic or inorganic compounds as electron transfer mediators (ETMs).[6] This biomimetic approach couples the oxidation of the ETM by hydrogen peroxide with the following oxidation of a tertiary amine (for example, *N*-methylmorpholine) to its *N*-oxide. The *N*-oxide can then reoxidize Os(VI) to Os(VIII) (Scheme 1).

Specific ETMs that we have used for the *N*-oxidation of NMM in this triple catalytic system include flavin analogues[6a, b] of type **1**, vanadyl acetylacetonate[6c] [$VO(acac)_2$, **2**], and methyltrioxorhenium (MTO, **3**) (Figure 1).[6c, d] Each of these ETMs has its own advantages and drawbacks. For example, MTO rapidly and efficiently catalyzes the reaction between H_2O_2 and NMM[6c], but it is unstable in basic reaction media under oxidizing conditions, decomposing into methanol and catalytically inert perrhenic acid.[7] Unfortunately, this MTO deactivation may occur in the H_2O_2-based dihydroxylation reaction, as the necessary presence of tertiary amine makes the reaction mixture basic. Careful control of the amount of tertiary amine used has been vital to successfully utilize MTO as an ETM in this process.[6d]

Major classes of substrates still pose problems in the catalytic dihydroxylation reaction. Among these are α,β-unsaturated esters and amides, as well as sterically encumbered or tetrasubstituted olefins.[8] In a recent reexamination of the Os-catalyzed dihydroxylation reaction, Sharpless and co-workers reported that citric acid, when added to the reaction mixture, greatly improved yields of diol from these normally recalcitrant com-



Scheme 1. Triple catalytic system applied to dihydroxylation.

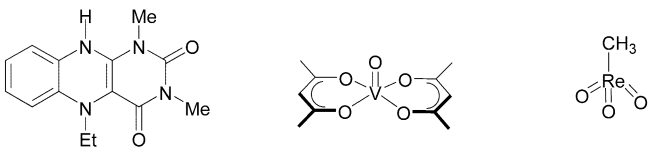


Figure 1. Electron transfer mediators (ETMs).

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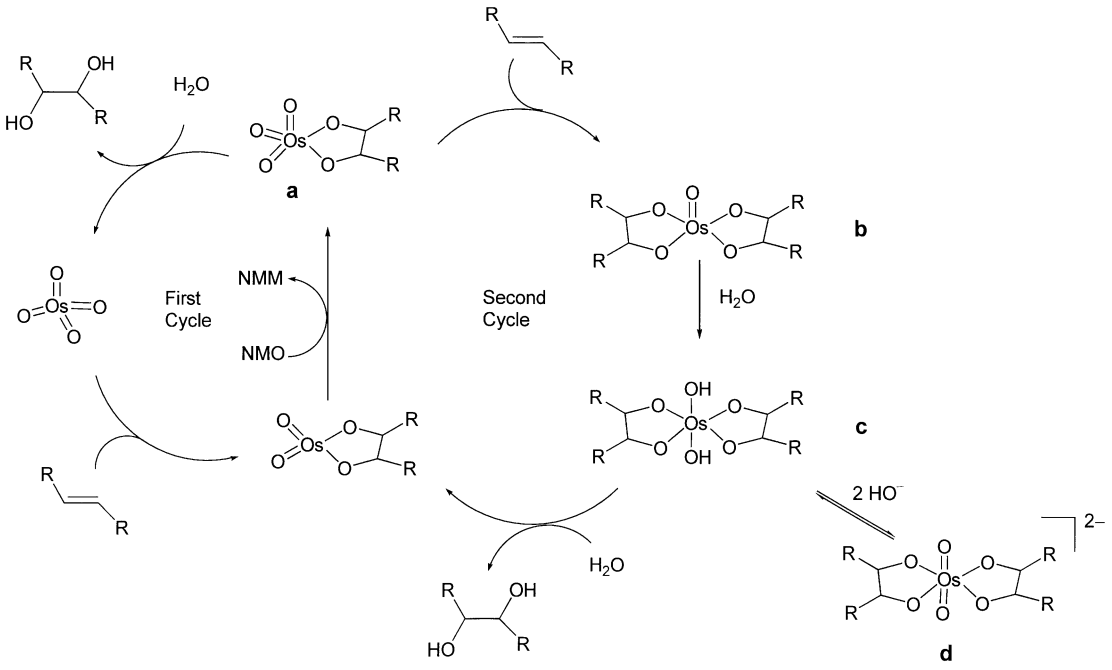
pounds.[9] The authors attribute this effect to low pH blocking the major OsO_4 decomposition pathway. Under conditions where reoxidant has access to all the catalytic intermediates, turnover is achieved only through the second cycle (Scheme 2).[10] They propose that a major loss of catalytic osmium is through the deprotonation of bis-glycolate intermediate **c**, found in the second cycle, which results in the formation of the inert osmium dianion **d**. This therefore explains the poor reactivity of electron-deficient olefins, for example, as intermediate **c** would be easier to deprotonate than usual. The low pH conferred by the presence of citric acid would keep osmium from being trapped *via* intermediate **d**, and lead to increased yield by preserving the catalyst. We noted that these reaction conditions would be beneficial not only for the conservation of OsO_4, but also for MTO, which becomes more stable at a low pH.[7] We therefore decided to apply this modification to the H_2O_2/MTO/NMM triple catalytic system. Not only would the MTO be more resistant towards hydrolysis under these reaction conditions, but it would greatly enhance the usefulness of the H_2O_2-based dihydroxylation reaction if a similar improvement in the reactivity towards these important substrate classes could be obtained.

Results

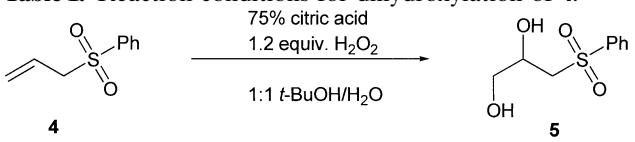
We chose first to examine the dihydroxylation of allyl phenyl sulfone **4** with the H_2O_2/MTO/NMM triple catalytic system (Table 1). This olefin is reported in the literature to yield under 40% of diol using standard Upjohn conditions. Sharpless and co-workers reported an improvement to 78% in the modified Upjohn procedure (25 mol % citric acid).[9] In our initial studies a reaction mixture consisting of olefin, 75 mol % citric acid, 1 mol % $K_2OsO_4 \cdot 2\,H_2O$, 1 mol % MTO, and 20 mol % NMM was dissolved in a 1:1 mixture of water/*t*-BuOH. Hydrogen peroxide (1.2 equivalents) was then added over a period of four hours *via* a syringe pump. The yield of diol obtained by this method was 95% (Table 1, entry 1). Increasing the concentration of the reaction mixture from 1 M to 2 M allowed the reduction of osmium present to 0.5 mol %, without a substantial difference in yield (Table 1, entry 5). Control reactions run without NMM or MTO (entries 2 and 3) resulted in lower yields, indicating that although the direct reoxidation of osmium by H_2O_2 is possible under these conditions, it is beneficial to utilize the triple catalytic system. The conditions used for entry 5 were then applied to a number of other substrates which are known to be problematic, for example, those bearing common electron-withdrawing functional groups such as ester and amide moieties. We also included styrene as a "standard" substrate. Table 2 shows the results. Yields of diols obtained from the esters and styrene are high (82 – 93%), while the yield of diol from amide **6** was a bit lower (67% conversion).

Presented with these results, we realized that the 75 mol % of citric acid is optimal for the stoichiometric NMO reoxidation of osmium because NMM, which neutralizes citric acid, slowly accumulates during the reaction, eventually reaching high concentrations. However, in our system, only small amounts of NMM are present. We therefore decided to limit the amount of



Scheme 2. The two possible pathways of dihydroxylation.

Table 1. Reaction conditions for dihydroxylation of **4**.[a]



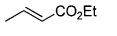
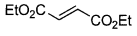
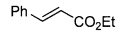
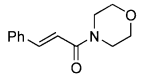
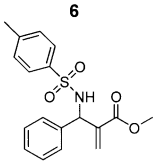
Entry	$K_2OsO_4 \cdot 2H_2O$ [mol %]	MTO [mol %]	NMM [mol %]	Conc. of **4**	H_2O_2 addition time + stirring [h]	Yield [%][b]
1	1	1	20	1 M	4 + 1	95
2	1	1	0	1 M	4 + 1	62
3	1	0	0	1 M	4 + 1	65
4	0	1	0	1 M	4 + 1	0
5	0.5	1	20	2 M	4 + 1	91
6	0.5	1	20	2 M	Addition at once	87[c]
7	0.5	1	20	2 M	Addition at once[d]	88[c]

[a] Reaction conditions: olefin (1 mmol) was dissolved in 1:1 *t*-BuOH:H_2O, other reaction components added as indicated. H_2O_2 solution (1.2 equiv.) added *via* syringe pump over 4 h when indicated.
[b] Isolated yield.
[c] Percent conversion.
[d] 1.5 equivalents of H_2O_2.

citric acid to the lowest possible levels. Dihydroxylations were carried out again with amide **6** and 5 mol % of citric acid (Table 2). Reaction time was lengthened and one equivalent of tetraethylammonium acetate (TEAA) was added to facilitate hydrolysis.[11] Under these conditions the diol could be obtained in 84% yield. The rest of the substrates were then resubmitted to dihydroxylation with 5 mol % of citric acid, and the results were comparable to those obtained with 75 mol % (Table 2). Control reactions run without citric acid with allyl phenyl sulfone and ethyl crotonate as substrates resulted in yields of 60% and 47% of the diol, respectively.

As a final test of functional group tolerance of the optimal conditions, sulfonamide **7** was subjected to dihydroxylation using 5 mol % citric acid and the longer reaction time.[12] The yield is shown in Table 2. A possible explanation for the difference in yields for amides is that with 75% citric acid present, the small amount of NMM used in our system may become almost completely protonated. This would result in slower turnover as the system depends on NMM being oxidized to NMO *in situ*, as well as the possibility of direct oxidation of the substrate by free H_2O_2.

Table 2. Yields of diols under various conditions.[a]

Entry	Substrate	Yield%[b] 75% citric acid	Yield%[b] 5% citric acid
1		91	93
2		90	90
3		87	85
4		85	84
5		88	82
6	 **6**	67[c]	84[d]
7	 **7**	–	88[e]

[a] Reaction conditions: olefin (1 mmol) in 0.5 mL 1:1 *t*-BuOH:H_2O, 0.5 mol % $K_2OsO_4 \cdot 2H_2O$, 1 mol % MTO, 20 mol % NMM, H_2O_2 added over 1 h, followed by 1 h stirring before quenching with 60 mg $Na_2S_2O_4$ and 120 mg magnesium silicate.
[b] Isolated yields.
[c] Percent conversion; 1 equiv. TEAA, H_2O_2 added over 4 h, followed by 1 h stirring before quenching.
[d] 1 equiv. TEAA, H_2O_2 added over 4 h, followed by 1 h stirring before quenching.
[e] Reaction carried out at 0.66 M in 2:1 acetone:H_2O, H_2O_2 added over 4 h, followed by 8 h stirring.

Conclusion

The simple addition of citric acid to dihydroxylation reaction mixtures has several advantages. Under these conditions MTO is stabilized, which allows its use as an ETM in conjunction with hydrogen peroxide. Furthermore, the resulting low pH preserves osmium catalyst, and thus improves the yield of diols from traditionally difficult substrate classes. The result of the application of

citric acid to our triple catalytic system is a robust and effective hydrogen-peroxide based system for dihydroxylation of olefins.

Experimental Section

General Methods

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 (400 MHz ^{1}H, 100 MHz ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm, using residual solvent as internal standard. Millipore Matrex silica gel (60 Å pore size, 35 – 70 μm) was used for flash chromatography. Potassium osmate and tetraethylammonium acetate (TEAA) were purchased from Aldrich. Olefins 6 and 8 were prepared according to published procedures.[12,13] All other reagents and olefins were obtained from commercial suppliers and used without further purification.

Representative Procedure for Dihydroxylation of Ester-Substituted Olefins (Procedure A), as Exemplified for Ethyl Crotonate

Water (0.25 mL) and *t*-BuOH (0.25 mL) were combined in a small round-bottom flask with a small stir bar. Citric acid (5 mol %, 9.6 mg) was then added, followed by ethyl crotonate (114 mg, 1 mmol), and potassium osmate (1.8 mg, 0.5 mol %). Methyltrioxorhenium (2.4 mg, 1.0 mol %) and *N*-methylmorpholine (20.2 mg, 20 mol %) were then added to the solution. Hydrogen peroxide solution (1.2 mmol, 0.124 mL 30.3% solution) was injected into the solution over a period of 1 h *via* a syringe pump. The solution was allowed to stir for a further 1 h after addition was completed. The reaction was then quenched *via* the addition of sodium dithionite (60 mg) and magnesium silicate (120 mg). The resulting slurry was stirred for 2 h in order to ensure the reduction of all the Os species, diluted with ethyl acetate, and loaded directly onto a silica gel column. The product diol was eluted using ethyl acetate, affording a white solid; yield: 133 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (q, 2H, J = 7 Hz), 4.07 (qd, 1H J = 6, 3 Hz), 4.00 (d, 1H, J = 3 Hz), 2.96 – 2.61 (br s, 2H), 1.31 (d, 3H, J = 6 Hz), 1.31 (t, 3H, J = 7 Hz).[14]

Dihydroxylation of Amide 6

Water (0.25 mL) and *t*-BuOH (0.25 mL) were combined in a small round-bottom flask with a small stir bar. Citric acid (5 mol %, 9.6 mg) and tetraethylammonium acetate (1 mmol, 261 mg) were then dissolved in the solvent mixture. Amide **6** (217 mg, 1 mmol) was then added to the solution, followed by potassium osmate (1.8 mg, 0.5 mol %) and methyltrioxorhenium (2.4 mg, 1.0 mol %). *N*-Methylmorpholine (20.2 mg, 20 mol %) was then dissolved in the reaction flask. Hydrogen peroxide (1.2 mmol, 0.124 mL 30.3% solution) was injected into the solution over a period of 4 h *via* a syringe pump. The reaction mixture was allowed to stir a further 1 h after the addition of peroxide was completed. After this time, sodium dithionite (60 mg) and magnesium silicate (120 mg) was added to quench the reaction. The resulting slurry was stirred for 2 h to ensure the reduction of all Os species, diluted with ethyl acetate, and loaded directly onto a silica gel column. The product diol was eluted using ethyl acetate, affording a white solid; yield: 210 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.30 (m, 5H), 4.76 – 4.72 (br s, 2H), 4.67 (d, 1H, J = 6.5 Hz), 4.37 (d, 1H, J = 6.5 Hz), 3.65 – 3.55 (m, 2H), 3.55 – 3.44 (m, 2H), 3.40 – 3.32 (m, 1H), 3.15 – 3.05 (m, 1H), 2.98 – 2.90 (m, 1H), 2.70 – 2.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.64, 138.97, 128.85, 128.80, 127.06, 76.70, 72.57, 66.55, 66.04, 45.67, 42.75.

Dihydroxylation of Sulfonamide 7

The substrate **7** (101 mg, 0.29 mmol, 0.66 M) was dissolved in 0.43 mL of 1 : 2 H_2O:acetone. Citric acid (3 mg, 5 mol %) was dissolved in the reaction mixture. Potassium osmate (0.5 mg, 0.5 mol %) was then added to the solution. This was followed by 0.7 mg MTO (1 mol %) and *N*-methylmorpholine (5.5 mg, 20 mol %). To this mixture a H_2O_2 solution (0.34 mmol, 0.036 mL 30.3% solution) was injected over a 4 h period *via* a syringe pump. After stirring for an additional 8 h, the insoluble product could be isolated as a white solid by a simple filtration; yield: 98 mg (88%) as a 2:1 mixture of diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$): **major diastereoisomer**, δ = 7.39 (d, J = 8.1 Hz, 2H), 7.14 – 6.92 (m, 7H), 5.82 (d, J = 10.6 Hz, 1H), 4.69 (d, J = 10.6 Hz, 1H), 3.85 (s, 3H), 3.68 (d, J = 11.6 Hz, 1H), 3.21 (d, J = 11.6 Hz, 1H), 2.27 (s, 3H); **minor diastereoisomer**, δ = 7.38 (d, J = 9.6 Hz, 2H), 7.14 – 6.92 (m, 7H), 5.92 (d, J = 10.4 Hz, 1H), 4.68 (d, J = 10.4 Hz, 1H), 4.097 (d, J = 12 Hz (H_A of AB system), 1H), 4.030 (d, J = 12 Hz (H_B of AB system), 1H), 3.61 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.65, 142.99, 137.22, 135.39, 129.10, 128.20, 127.99, 127.85, 126.92, 81.18, 65.78, 59.92, 53.78, 21.33. Minor diastereomer distinguishible at 172.7, 137.13, 128.15, 128.03, 127.4, 126.83, 81.4, 65.84, 59.27, 53.09.

Dihydroxylation of Allyl Phenyl Sulfone

See procedure A. Yield: 202 mg (93%) of white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 – 7.92 (m, 2H), 7.71 – 7.66 (m, 1H), 7.62 – 7.52 (m, 2H), 4.28 – 4.22 (m, 1H), 3.70 (dd, 1H, J = 11.8, 4 Hz), 3.55 (dd, 1H, J = 11.4, 4.9 Hz), 3.39 (dd, 1H, J = 14.1, 9 Hz), 3.25 (dd, 1H, J = 14.3, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.37, 134.37, 129.73, 128.14, 66.83, 65.60, 59.22.[9]

Dihydroxylation of Ethyl Cinnamate

See procedure A. Yield: 176 mg (84%) of white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.4 – 7.3 (m, 5H), 4.97 (d, 1H, J = 3 Hz), 4.33 (d, 1H, J = 3.2 Hz), 4.23 (q, 2H, J = 7.3 Hz), 3.30 – 3.04 (br s, 2H), 1.25 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.97, 140.19, 128.65, 128.26, 126.53, 74.99, 74.82, 62.36, 14.28.[14]

Dihydroxylation of Diethyl Fumarate

See procedure A. Yield: 175 mg (85%) of white solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (s, 2H), 4.31 (q, 4H, J = 7.1 Hz),

3.7 – 3.1 (br s, 2H), 1.32 (t, 6H, $J = 7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.77$, 72.21, 62.71, 14.35.[15]

Dihydroxylation of Styrene

See procedure A. Yield: 113 mg (82%) of white solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.3 – 7.2$ (m, 5H), 4.8 (dd, 1H, $J = 8.4$, 3.6 Hz), 3.7 – 3.6 (m, 2 h), 3.4 – 3.0 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.46$, 128.47, 127.91, 126.04, 74.67, 68.04.[16]

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