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Osmium-catalyzed asymmetric dihydroxylation by carbon dioxide-activated hydrogen peroxide and *N*-methylmorpholine

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Abstract

An improved process has been developed for the osmium-catalyzed dihydroxylation of olefins via in situ formation of NMO from NMM using CO_2 catalysis and H_2O_2. All olefins examined were selectively cis-dihydroxylated to their corresponding diols in good to excellent yields, and by the use of chiral ligands, high enantiomeric excesses were obtained.

Keywords: Dihydroxylation; Asymmetric dihydroxylation; Peroxide; Peroxymonocarbonate; Carbon dioxide; Catalysis; Amine oxides

1. Introduction

Aqueous hydrogen peroxide is an ideal oxidant in view of its high effective oxygen content, water by-product, safety in storage and operation, and low cost of production and transportation. We recently investigated the N-oxidation of tertiary amines by bicarbonate-activated hydrogen peroxide (BAP) and CO_2/H_2O_2 catalytic systems.[1] Our earlier kinetic studies of bicarbonate-catalyzed organic sulfide oxidations strongly support the identification of peroxymonocarbonate HCO_4^- as the direct oxidant,[2] and it has been proposed that the peroxymonocarbonate ion (a covalent peroxide of structure $HOOCO_2^-$ abbreviated below as HCO_4^-) is the active species in the amine oxidation reaction catalyzed by bicarbonate or CO_2. Since amines are oxidized readily to their corresponding *N*-oxides by HCO_4^-, it was of interest to investigate if *N*-methylmorpholine-*N*-oxide (NMO) can be replaced by *N*-methylmorpholine (NMM) in osmium-catalyzed dihydroxylation reactions with in situ oxidation to NMO by HCO_4^-.

Osmium tetroxide (OsO_4) is an excellent catalyst for the cis-dihydroxylation of olefins.[3–5] Milas and Sussman[6,7] first reported the osmium tetroxide catalyzed oxidation of alkenes by hydrogen peroxide. The stoichiometric reaction was studied by Criegee who showed that pyridine accelerates the reaction considerably.[8,9] In the presence of metal chlorates or hydrogen peroxide, over-oxidation is a major problem resulting in diminished yields. Much better results are obtained with alkaline *tert*-butyl hydroperoxide, introduced by Sharpless and Akashi.[10] Tertiary amine oxides, such as NMO were introduced by Van Rheenen and coworkers in the Upjohn process.[11] Sharpless and co-workers used NMO as the reoxidant in the development of the catalytic asymmetric dihydroxylation of olefins,[12] which under slow addition conditions gave high yields of diol products in high enantiomeric excess.

Only a few procedures for re-oxidation of osmium(VI) by environmentally benign and selective oxidants such as H_2O_2 or O_2[13,14] are known. Recently Bäckvall and coworkers reported a tri-catalytic method for cis-dihydroxylation of olefins. In this procedure osmium(VI) is re-oxidized by NMO, generated from NMM and H_2O_2 with the aid of another co-catalyst. The three different co-catalysts they used for three different methods in these tricatalytic systems are flavin, *m*-CPBA, and methyl trioxorhenium.[15–17] In this Letter we report a simple and economical process for the osmium-catalyzed dihydroxylation of olefins by in situ

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formation of NMO from NMM via a clean, economical catalyst/oxidant combination (CO_2/H_2O_2).

Our studies on amine oxidation reactions have shown that the tertiary amines are efficiently oxidized to their corresponding *N*-oxides by H_2O_2 with CO_2 catalysis (under 1 atm pressure) at room temperature. The proposed mechanism is shown as Eqs. 1–5, with the net reaction as the CO_2-catalyzed peroxide oxidation of the substrate.

The HCO_4^- ion is formed via the reversible addition of OOH^- to CO_2 under the mildly basic conditions set by the amine substrate. Furthermore, the relatively high rate constant for oxidation of NMM to NMO by the catalytic intermediate HCO_4^- (Eq. 3, 0.016 $M^{-1}\,s^{-1}$) compared to slow oxidation by H_2O_2 alone reduces the oxidation time to <1 h under our conditions.

$$H_2O_2 \rightleftharpoons HOO^- + H^+ \quad (1)$$

$$HOO^- + CO_2 \rightleftharpoons HCO_4^- \quad (2)$$

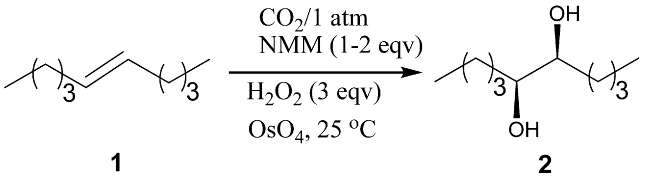
$$R_3N + HCO_4^- \longrightarrow R_3NO + HCO_3^- \quad (3)$$

$$H^+ + HCO_3^- \rightleftharpoons H_2O + CO_2 \quad (4)$$

$$H_2O_2 + R_3N \longrightarrow R_3NO + H_2O \text{ net} \quad (5)$$

In the Upjohn procedure,[11] NMO is employed as the terminal oxidant in the dihydroxylation of olefins. The re-oxidation of Os(VI) to Os(VIII) by NMO leads to formation of NMM. In our present one-pot, two-step method, instead of NMO we use NMM directly in stoichiometric amounts. In the initial step the NMM is oxidized to NMO by the CO_2/H_2O_2 catalytic system. The resulting NMO then re-oxidizes Os(VI) to Os(VIII) in the usual dihydroxylation cycle. This process is economical given the replacement of isolated and purified NMO by NMM, CO_2 gas, and H_2O_2.

Oxidation of *trans*-5-decene (**1**) was studied under different reaction conditions employing H_2O_2 as the terminal oxidant (Scheme 1, Table 1). The control reaction using NMO in stoichiometric amounts gave a 95% yield of diol **2**. Direct re-oxidation of osmium(VI) by H_2O_2[4] without using NMM results in a nonselective reaction, with 23% yield of diol **2** (Table 1, entry 1). In the presence of NMM the reaction with unactivated H_2O_2 gave 40% yield of diol **2** (Table 1, entry 2). In the absence of NMM, the reaction using CO_2 and H_2O_2 gave a similar 36% yield of **2** (Table 1, entry 3). The re-oxidation of Os(VI) using CO_2 and H_2O_2 (3 equiv based on substrate) in the presence of NMM gave the highest yield of diol (Table 1, entry 4, yield 95%). At higher and lower concentrations of H_2O_2 the yields of diol are reduced, and at higher peroxide (Table 1, entries 6 and 7) significantly lowers the yields due to overoxidation by excess peroxide. When the amount of NMM was decreased from 2 equiv (based on substrate) to 1.5, 1.3, 1.1, or 1 equiv, lower yields of diol **2** were observed (Table 1, entries 8–11).



Scheme 1. Osmium-catalyzed cis-dihydroxylation of *trans*-5-decene by in situ formation of NMO employing CO_2 and H_2O_2.

Table 1
Cis-dihydroxylation of *trans*-5-decene employing CO_2 and H_2O_2 as terminal oxidant[a]

Entry	Amine[b] (equiv)	CO_2/pressure (atm)	H_2O_2[b] (equiv)	TEAA[b] (equiv)	% Yield[c]
1[d]			3.0		23
2[d]	2.0		3.0		40
3[d]		1	3.0		36
4[d]	2.0	1	3.0		95
5[d]	2.0	1	2.0		55
6[d]	2.0	1	4.0		90
7[d]	2.0	1	5.0		20
8[e]	1.5	1	3.0		85
9[e]	1.3	1	3.0		75
10[e]	1.1	1	3.0		60
11[e]	1.0	1	3.0		35
12[f]	1.5	1	3.0	2.0	94
13[f]	1.3	1	3.0	2.0	93
14[f]	1.1	1	3.0	2.0	93
15[f]	1.0	1	3.0	2.0	85

[a] Solvent: acetone and water 3:1, $T = 25$ °C.

[b] Equivalents relative to alkene.

[c] Isolated yield.

[d] Experimental conditions: (Method A) *trans*-5-decene (1 mmol), NMM (2 mmol), H_2O_2 (2–5 mmol), OsO_4 (0.014 mmol) in water (1 mL) and acetone (3 mL).

[e] (Method B) *trans*-5-decene (1 mmol), NMM (1–1.5 mmol), H_2O_2 (3 mmol), OsO_4 (0.014 mmol) in water (1 mL) and acetone (3 mL).

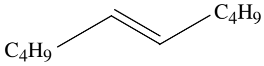
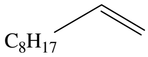
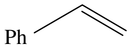
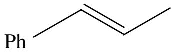
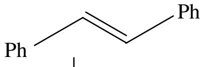
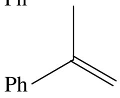
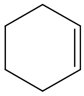
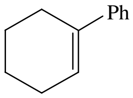
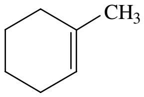
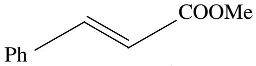
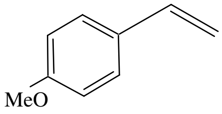
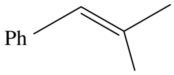
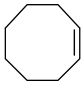
[f] (Method C) *trans*-5-decene (1 mmol), NMM (1–1.5 mmol), H_2O_2 (3 mmol), OsO_4 (0.014 mmol), TEAA (2 mmol) in water (1 mL) and acetone (3 mL).

The slow step in the osmium cycle is the most likely hydrolysis of the intermediate osmate ester.[10,18,19] The hydrolysis step is facilitated by addition of salts such as tetraethylammonium acetate (TEAA).[10,15,22,20] We therefore studied the influence of this salt on the NMM-catalyzed dihydroxylation of *trans*-5-decene based on CO_2 and H_2O_2 as the terminal oxidant. Addition of TEAA to the reaction mixture did indeed result in a major improvement of the yield of diol **2** (Table 1, entries 12–15) with yields in excess of 90% using as little as 10% excess of NMM (entry 14).

Several other olefins were oxidized to their corresponding cis-diols in good to excellent isolated yields by our present method (Table 2). Control reactions using NMO in place of NMM, CO_2 gas, and H_2O_2 gave comparable yields of cis-diols (Table 2, entries 1, 7, and 13).

We have also investigated the enantioselectivity of various oxidations (1 atm CO_2 and 3 equiv H_2O_2) using the Sharpless chiral ligand hydroquinidine 1,4-phthalazinediyldiether ($(DHQD)_2PHAL$), 0.03 equiv, with 0.014 equiv OsO_4 in 3:1 acetone/water (Table 3). With slow addition of olefin, ee values of 80–90% were obtained. Enantiomeric excesses and absolute configurations of diols were

Table 2
Comparison of osmium-catalyzed cis-dihydroxylation of olefins by NMO versus CO_2 and H_2O_2 as terminal oxidant[a]

Entry	Olefins	Yield[b] (%)	
		$NMM/CO_2/H_2O_2$	NMO[e]
1		93[c]	95
2		95[d]	
3		95[d]	
4		95[d]	
5		93[d]	
6		95[d]	
7		87[c]	90
8		97[d]	
9		84[d]	
10		83[d]	
11		93[d]	
12		83[d]	
13		82[c]	82

[a] Solvent system: acetone and water 3:1, $T = 25$ °C.

[b] Isolated yield.

[c] Experimental conditions: olefin (1 mmol), NMM (1.1 mmol), H_2O_2 (3 mmol), OsO_4 (0.014 mmol), TEAA (2 mmol) in water (1 mL) and acetone (3 mL) under CO_2 (1 atm).

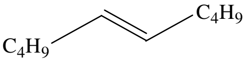
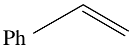
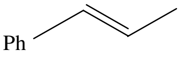
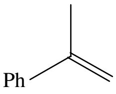
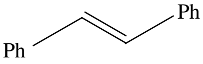
[d] Experimental conditions: Olefin (1 mmol), NMM (2 mmol), H_2O_2 (3 mmol), OsO_4 (0.014 mmol) in water (1 mL) and acetone (3 mL) under CO_2 (1 atm).

[e] Experimental conditions: olefin (1 mmol), NMO (1.1 mmol), OsO_4 (0.014 mmol), TEAA (2 mmol) in water (1 mL) and acetone (3 mL) under N_2 (1 atm).

determined by comparison of their optical rotations with the literature values.[21–24]

The overall catalytic mechanism for the dihydroxylation reaction using our modified Upjohn procedure is shown in Scheme 2.

Table 3
Osmium-catalyzed asymmetric dihydroxylation of olefins by in situ formation of NMO using H_2O_2 and CO_2[a]

Entry	Olefin	Yields[b] (%)	ee[c] (%)	Confign[d]
1		89	90	*RR* (+)[e]
2		95	83	*R* (−)[f]
3		90	89	*RR* (−)[g]
4		95	80	*R* (−)[h]
5		93	85	*RR* (+)[i]

[a] Conditions: Olefin (1 mmol), NMM (2 mmol), H_2O_2 (3 mmol), OsO_4 (0.014 mmol), Hydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2PHAL$ (0.03 mmol), solvent: acetone and water 3:1, $T = 25$ °C.

[b] Isolated yields of diol.

[c] Enantiomeric excess determined by polarimeter.

[d] Enantiomeric excess and absolute configurations of diols were determined by comparison of their optical rotations with the literature values.

[e] $[\alpha]_D$ +26.3.

[f] $[\alpha]_D$ −29.6.

[g] $[\alpha]_D$ −27.7.

[h] $[\alpha]_D$ −4.72.

[i] $[\alpha]_D$ +81.6.

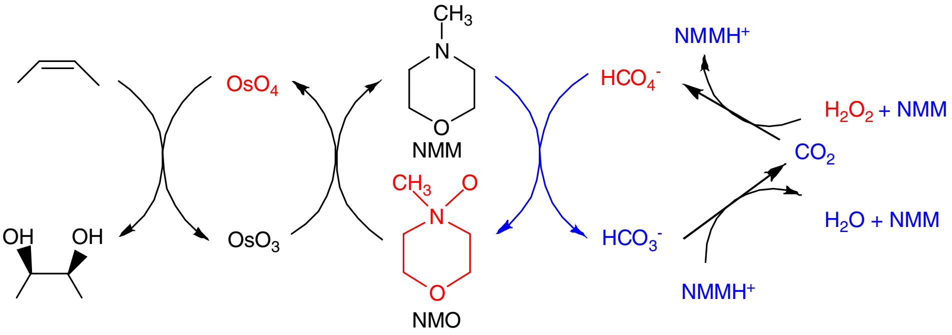
Carbon dioxide can be replaced in this chemistry by bicarbonate salts and buffers to obtain the optimal pH value. In the present work, the weakly basic NMM provides sufficient alkalinity to promote formation of peroxymonocarbonate and rapid oxidation of NMM. The use of carbon dioxide is a significant convenience as no extraneous salts are present upon completion of the conversion of NMM to NMO, thereby simplifying isolation and purification of the dihydroxyl product.

In summary, we have developed a simple and economical procedure for in situ formation of NMO from NMM by using the green oxidant system CO_2 and H_2O_2 in osmium-catalyzed dihydroxylation reaction. The key feature of this method is that NMO is formed cleanly and quantitatively in situ and need not be isolated. This method involves simple extraction methods, and 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 were obtained.

2. Experimental

2.1. General procedures

All ^1H and ^{13}C NMR spectra were recorded on a Mercury-300 spectrometer at 299.95 and 75.4 MHz for the proton and carbon channels, respectively. All olefins and reagents were purchased from commercial suppliers and used without further purification. 4-Methylmorpholine



Scheme 2. Mechanism of CO_2-assisted dihydroxylation of alkenes by hydrogen peroxide and NMM.

N-oxide (NMO, 97%) was purchased from Aldrich and *N*-methylmorpholine (NMM, 99%) and OsO_4 (as a 4 wt % solution in H_2O) were purchased from Fisher. The products were purified by chromatography on silica gel (100–200 mesh).

2.2. *Typical procedure for cis-dihydroxylation of alkenes by in situ formation of NMO from NMM, CO_2, and H_2O_2: 5,6-Decenediol* (**2**)

2.2.1. *Method A*

A 10 mL of round-bottomed flask was charged with 0.245 mL of 35% H_2O_2 (to yield 3 mmol) in 1 mL of water. The solution was stirred under CO_2 (1 atm) for 10 min. To this solution 0.202 g of NMM (2 mmol) was added, and stirring was continued for 2 h followed by addition of 3 mL of acetone, 0.0036 g of OsO_4 (0.014 mmol) and 0.189 mL of *trans*-5-decene (1 mmol) in one portion. The resulting reaction mixture was allowed to stir for 12 h. The reaction mixture was concentrated on a rotary evaporator to remove acetone, and the resulting residue was extracted with ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and concentrated to afford the crude diol product. Purification was by column chromatography (silica gel, 100–200 mesh; hexane/EtOAc (80:20) to give 165 mg (95%) of diol as a white solid. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.9 (t, 6H), 1.2–1.5 (m, 12H), 3.3 (m, 2H), 3.44 (br, 2H). ^{13}C NMR: δ 68.1, 74.5, 126.0, 128.5, 140.2.

2.3. *Typical procedure for cis-dihydroxylation of alkenes by in situ formation of NMO from NMM, CO_2, and H_2O_2: 5,6-Decenediol* (**2**)

2.3.1. *Method B*

0.245 mL of 35% H_2O_2 (3 mmol) was added to 1 mL of water in a 10 mL round-bottomed flask. The solution was stirred under CO_2 (1 atm) for 10 min. To this solution 0.121 mL of NMM (1.1 mmol) was added, and stirring was continued for 2 h followed by addition of 3 mL of acetone, 0.0865 mL of OsO_4 (4 wt % in H_2O, 0.014 mmol) and 0.189 mL of *trans*-5-decene (1 mmol) in one portion. The resulting reaction mixture was allowed to stir for an additional 12 h, and then quenched by addition of $Na_2S_2O_4$ (0.1 g) and magnesium silicate (0.5 g) in H_2O (3 mL) and aq NaCl (satd) (1.5 mL). After 2 h of stirring at room temperature, the mixture was filtered over Celite and subsequently rinsed with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (4 × 15 mL), and the combined organic phases were washed with aq NaCl (satd) (5 × 50 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuum to give the crude diol. The crude product was purified by column chromatography using a mixture of pentane/EtOAc (80:20) to afford **2** (0.105 g, 60%).

2.4. *Typical procedure for cis-dihydroxylation of alkenes by in situ formation of NMO from NMM, CO_2, and H_2O_2: 5,6-Decenediol* (**2**)

2.4.1. *Method C*

The same procedure as above (method B), except for the use of solid tetraethyl ammonium acetate (0.523 g, 2 mmol), afforded 2 as a white solid (0.162 g, 93%).

2.5. *Typical procedure for asymmetric dihydroxylation of alkenes by in situ formation of NMO from NMM, CO_2, and H_2O_2: oxidation of trans-5-decene to 5,6-decenediol*

A 10 mL round-bottomed flask was charged with 0.245 mL of 35% H_2O_2 (3 mmol) in 1 mL of water. The solution was stirred under CO_2 (1 atm) for 10 min. To this solution 0.202 g of NMM (2 mmol) was added, and stirring was continued for 2 h followed by addition of 0.0036 g of OsO_4 (0.014 mmol) and 0.023 g of hydroquinidine-1,4-phthalazinediyldiether ($(DHQD)_2PHA$) (0.03 mmol). A solution of *trans*-5-decene (1 mmol) in acetone (3 mL) was added slowly over 9 h. The resulting reaction mixture was allowed to stir for another 9 h. This mixture was concentrated on a rotary evaporator to remove acetone, and the resulting residue was extracted with ethyl acetate. The organic extract was washed with saturated brine, dried ($NaSO_4$), and concentrated to afford the crude diol product. Purification was by column chromatography (silica gel, 100–200 mesh; solvent system, hexane/EtOAc (80:20) to give 156 mg (90%) of diol as a white solid. ^1H

NMR ($CDCl_3$, 300 MHz): δ (ppm) 0.9 (t, 6H), 1.2–1.5 (m, 12H), 3.3 (m, 2H), 3.44 (br, 2H). ^{13}C NMR: δ 68.1, 74.5, 126.0, 128.5, 140.2. $[\alpha]_D$ +26.3 (*c* 1, $CHCl_3$).

Acknowledgements

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Supplementary data

Supporting NMR data are available for compounds synthesized. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.186.

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