

Racemic or enantioselective osmium-catalyzed dihydroxylation of olefins under near-neutral conditions

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This paper is dedicated to my long-time friend Peter Jacobi in recognition of his many outstanding contributions to education and organic chemistry

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Abstract		

 $K_3Fe(CN)_6$ and NalO₄ serve as catalytic co-oxidants for osmium-catalyzed dihydroxylations that are performed under near-neutral conditions with $K_2S_2O_8$ as the stoichiometric oxidant and Na₂HPO₄ as the base. By using either quinuclidine or hydroquinidine 1,4-phthalazinediyl ether [(DHQD)₂Phal], good yields of racemic or enantioenriched diols are obtained. This simple, biphasic procedure offers advantages over other neutral dihydroxylation protocols that use *N*-methylmorpholine oxide as the stoichiometric oxidant, by suppressing the secondary catalytic cycle that leads to reduced enantioselectivities. The utility of the procedure, which is nicely suited for base-labile starting materials or products, is demonstrated by performing the dihydroxylation in the presence of an aliphatic aldehyde moiety.



Keywords: dihydroxylation of alkenes, enantioselectivity, mild conditions, base-sensitive substrates

Introduction

During the course of our unpublished investigations directed toward the synthesis of cortistatin A (**3**) from **2** (common atoms in **2** and **3** highlighted in blue), we were confronted by what seemed to be a routine osmiumcatalyzed dihydroxylation of the allyl furan **1** to give the dihydroxylated product **2**. To our surprise, when **1** was subjected to standard Sharpless asymmetric dihydroxylation conditions (AD) using AD-mix- β ,¹⁻³ the reaction required four to five days and provided the diol **2** in only 20–40% yield (Scheme 1, *Condition A*) together with a mixture of unidentified side products. We suspected that prolonged reaction times under the basic reaction conditions might be leading to deleterious aldol reactions involving the cyclopentanone moiety, but efforts to increase the rate of reaction using known hydrolysis aides such as MeSO₂NH₂^{4,5} and PhB(OH)₂^{6,7} failed to provide any improvement. After some experimentation, we found that supplementing the standard AD-mix with K₂S₂O₈ significantly increased the rate of the reaction and improved the yield to 55% (*Condition B*).⁸ Further increasing the quantity of K₂S₂O₈ and using K₃Fe(CN)₆ as the catalytic co-oxidant dramatically accelerated the reaction and enabled the isolation of **2** in 76% yield in less than 16 h without employing ligands or hydrolysis aides (Scheme 1, *Condition C*).



Condition A: AD-mix-b, *tert*-BuOH/H₂O (1:1), rt. **Condition B:** AD-mix-b, K₂S₂O₈, *tert*-BuOH/H₂O (1:1), rt. **Condition C:** K₂S₂O₈, K₂CO₃, cat. K₃Fe(CN)₆, cat. K₂OsO₂(OH)₄, *tert*-BuOH/H₂O (1:1), rt.



Scheme 1

Osmium-catalyzed dihydroxylations can generally be accelerated by either increasing the rate of olefin oxidation through the addition of ligands or by enhancing the rate of hydrolysis of the intermediate osmate ester, thereby returning osmium to the catalytic cycle. The latter can be facilitated by the addition of hydrolysis aides, such as MeSO₂NH₂, to the mixture or by maintaining the pH around 12 because an AD reaction typically starts at a pH of about 12.2 but drops to 9.9 over the course of the reaction.⁹ Some oxidants, such as NaClO₂¹⁰ and NaOCl,¹¹ appear to accelerate the hydrolysis of the osmate ester by releasing hydroxide ions, but hydroxide ions are not produced when K₂S₂O₈ is used as the terminal oxidant. Indeed, when K₂S₂O₈ is used, we observed that the pH of the reaction was about 11.3, a full pH unit *less* than the standard AD

conditions. The capability of K₂S₂O₈ to serve as an oxidant under less basic conditions led us to wonder if the pH could be further lowered, so that the asymmetric osmium-catalyzed dihydroxylations could be applied to base-sensitive substrates. Such a modification would offer several advantages over other currently available protocols that use NaHCO₃ to buffer the reaction to pH 10.3,¹² but AD reactions do not turn over if NaHCO₃ is replaced with K₂CO₃.¹ Use of *N*-methylmorpholine oxide (NMO) as the terminal oxidant can allow for the dihydroxylation of olefins under neutral,^{13–15} or even acidic conditions,¹⁶ but these reactions often suffer from slower rates and inferior enantioselectivities when compared to the normal biphasic Sharpless AD conditions. The reduced enantioselectivities have been attributed to a secondary catalytic cycle, which occurs when the oxidant is in the same phase as the osmium catalyst.¹ We thus explored the possibility of developing a Sharpless-style AD that could be performed at near-neutral pH, so it could be applied to base-sensitive substrates without sacrificing enantioselectivity.

Results and Discussion

The first step toward modifying *Condition C* to convert **1** into **2** involved screening different bases, and in initial studies we found that replacing K_2CO_3 with either NaHCO₃ or Na₂HPO₄ gave ~20% of the desired diol **2**, while buffering the reaction medium to pH 9.8 and 8.6, respectively. Having established that hydroxylation did occur at lower pH, we set to the task of optimizing the more challenging enantioselective dihydroxylation of methyl cinnamate (**4**) as the model substrate using Na₂HPO₄ as the base. We hypothesized that the reaction was not proceeding to completion because of slow catalytic turnover resulting from the absence of ligands or hydrolysis aides coupled with the lower pH.⁹ To remedy this problem, we investigated a variety of additives, and we discovered that adding quinuclidine¹⁷ as a ligand and MeSO₂NH₂^{4,5} to facilitate hydrolysis led to a complete reaction and provided the diol **5** in 66% yield (Table 1, entry 1). When K₃Fe(CN)₆ was omitted as the

Table 1. Dihydroxylation of methyl cinnamate



entry	co-oxidant	equiv	base	equiv	isolated yield (%)
1	K₃Fe(CN) ₆	0.1	Na ₂ HPO ₄	3	66
2	K₃Fe(CN) ₆	0	Na ₂ HPO ₄	3	no reaction
3	K₃Fe(CN) ₆	0.2	Na ₂ HPO ₄	3	70
4	K₃Fe(CN) ₆	0.2	Na ₂ HPO ₄	4	91
5	NalO ₄	0.1	Na ₂ HPO ₄	3	63
6	NalO ₄	0.2	Na ₂ HPO ₄	3	87
7	NalO ₄	0.1	K ₂ CO ₃	3	2

co-oxidant from the reaction, no **5** was isolated (Table 1, entry 2), while increasing the stoichiometry of $K_3Fe(CN)_6$ led to only a marginal increase in yield (Table 1, entry 3). On the other hand, increasing the stoichiometry of the base Na_2HPO_4 from three to four equivalents (equiv), furnished the **5** in 91% yield (Table

1, entry 4). Inasmuch as $K_3Fe(CN)_6$ functions only as a co-oxidant, we were curious whether any other co-oxidant might be used in lieu of $K_3Fe(CN)_6$.

Several co-oxidants were examined as possible replacements for $K_3Fe(CN)_6$, and although use of NaIO₄, KBrO₃, and NaClO₂ afforded **5**, NaIO₄ emerged as the best co-oxidant giving **5** in 63% yield (Table 1, entry 5). Increasing the stoichiometry of the co-oxidant provided the diol **5** in 87% yield (Table 1, entry 6). Interestingly, whereas the $K_3Fe(CN)_6$ may be used as the co-oxidant under more basic conditions, the rate of dihydroxylation of **4** using NaIO₄ decreases at higher pH. In fact, use of K_2CO_3 as the base with NaIO₄ as co-oxidant gave only small quantities of **5** (Table 1, entry 7).

That NalO₄ may be employed as the catalytic co-oxidant for olefin dihydroxylations under near neutral conditions is perhaps at first surprising and thus warrants brief comment. Although there are reports of a RuO₄-catalyzed dihydroxylation that uses NalO₄ as the stoichiometric oxidant,^{18,19} use of NalO₄ with OsO₄ usually results in oxidative cleavage of the olefin, a reaction widely-known as the Johnson-Lemieux oxidation. Indeed, when methyl cinnamate (**4**) was treated with a stoichiometric quantity of NalO₄ in the presence of a catalytic amount of OsO₄, the olefin suffered the expected oxidative cleavage to form benzaldehyde; no **5** was isolated. Notably, the pH of that reaction was 5.7, much lower than the pH of 8.6 that was used for the dihydroxylation of **4** using NalO₄. Indeed, it has been reported that the Johnson-Lemieux reaction occurs only slowly at neutral pH or in the presence of K₂CO₃,²⁰ and we found in an exploratory experiment that reducing the pH of the NalO₄ co-catalyzed dihydroxylation using phosphoric acid resulted in the formation of some benzaldehyde.

Having established optimized conditions for the racemic dihydroxylation of methyl cinnamate (**4**) using either NalO₄ or K₃Fe(CN)₆ as the catalytic co-oxidant, we explored the substrate scope with several substituted styrenes as standard substrates (Table 2, entries 1-4). The yields using either NalO₄ or K₃Fe(CN)₆ were comparable, and di- and trisubstituted alkenes are suitable substrates, although yields for the latter are somewhat lower. To demonstrate the potential utility of these conditions for the dihydroxylation of base sensitive substrates, 9-decenal (**12**) was chosen as a test compound. Dihydroxylation of **12** using AD-mix- β , with and without added NaHCO₃ as a buffer, provided diol **13** in 33% and 51% yields, respectively; the absolute stereochemistry of **13** is tentatively assigned based upon literature precedent for 1-decene.²¹ On the other hand, dihydroxylation of **12** under near-neutral conditions with K₃Fe(CN)₆ as the co-catalyst provided the diol **13** in 82% yield, whereas use of NalO₄ as the co-oxidant gave **13** in only 45% yield (Table 2, entry 5). Because reactions with K₃Fe(CN)₆ in the presence of Na₂HPO₄ are generally faster that those using NalO₄, we attribute this discrepancy to the instability of **13** to prolonged exposure under the reaction conditions.

We then applied our modified procedure for olefin dihydroxylation to the enantioselective variant. Because reactions using dihydroquinidine 1,4-phthalazinediyl diether $[(DHQD)_2Pha]$ are significantly faster than those using quinuclidine as a ligand, reduced quantities of $(DHQD)_2Pha]$ are required. Generally, the enantioselective dihydroxylations with $(DHQD)_2Pha]$ in the presence of NalO₄ are higher yielding than those using K₃Fe(CN)₆ as the co-oxidant, but the yields in the enantioselective processes are lower than those with quinuclidine as the ligand (Table 2, entries 1–5). The enantioselectivities were comparable to the those reported in the literature,⁴ and they did not depend on whether NalO₄ or K₃Fe(CN)₆ served as the co-oxidant. Although the yield of racemic **13** was better when K₃Fe(CN)₆ was used as the co-oxidant, NalO₄ gives superior yields under the conditions for enantioselective dihydroxylation of **12** (Table 2, entry 5).

Table 2.



		ligand	quinuclidine ^a		(DHQD)₂Phal ^b		
		co-oxidant	K₃Fe(CN) ₆	NalO ₄	K₃Fe(CN)6	NalO ₄	Ee % ^c
entry	substrate	product	isolated yield (%)				(lit ⁴)
1	O OMe 4	OH O OH OH OH 5	91 ^d	87	68	83	96 (97)
2	6	ОН ОН	99 ^e	99	80	78	97 (97)
3	8	9 OH OH OH	89 ^e	87	72	54	90 (94)
4	10		67	67	61	64 ^e	94 (99)
5 ^g	12	ОН ОН 13	82 ^{d,f}	45 ^f	49 ^d	71 ^{<i>f</i>}	ND ^h

^{*a*} Experimental details given under the general procedure for racemic dihydroxylation of olefins, using 3 equiv of Na₂HPO₄unless otherwise indicated. ^{*b*}) Experimental details given under the general procedure for enantioselective dihydroxylation of olefins, using 3 equiv of Na₂HPO₄ unless otherwise indicated. ^{*c*}) Enantiomeric excess (ee) was determined according to procedures reported by Sharpless.²¹ ^{*d*}) 4 equiv of Na₂HPO₄ were used. ^{*e*}) 0.1 equiv of co-oxidant was used. ^{*f*}) MeSO₂NH₂ was not used. *g*) The ¹H-NMR spectrum of **13** suggested it existed as a mixture of aldehyde hemiacetals, so it was characterized as 1,2,10-decanetriol (see Experimental Section for details). h) ND (not determined).

Conclusions

Experiments to identify mild conditions that effect the dihydroxylation of the base-sensitive allyl furan **1** to give the diol **2** revealed that using $K_2S_2O_8$ as the stoichiometric oxidant and $K_3Fe(CN)_6$ as a catalytic co-oxidant leads to faster reactions at a pH that is lower than other traditional osmium-catalyzed methods. Further optimization of these conditions led to a protocol for performing racemic and enantioselective dihydroxylations of alkenes that proceed under near-neutral conditions. In this modified procedure, Na₂HPO₄ serves as the base, MeSO₂NH₂ facilitates hydrolysis of the intermediate osmate ester, and either quinuclidine or (DHQD)₂Phal are used as the ligand. NalO₄ was found to function as a catalytic co-oxidant, and in some cases

of the enantioselective variant it outperformed $K_3Fe(CN)_6$. The utility of this procedure was demonstrated by obtaining good yields of diol even in the presence of a base-sensitive aliphatic aldehyde. We believe these conditions will expand the scope of the osmium-catalyzed dihydroxylation reaction to include a wider range of substrates, especially those that are sensitive to basic conditions.

Experimental Section

General procedure for racemic dihydroxylation of olefins

Water (5 mL/mmol substrate) was added to a solid mixture of $K_2S_2O_8$ (1.5 equiv), Na_2HPO_4 (3 or 4 equiv), $K_3Fe(CN)_6$ (0.2 equiv) or $NalO_4$ (0.2 equiv), $MeSO_2NH_2$ (1 equiv) and $K_2OsO_2(OH)_4$ (0.05 equiv) at room temperature, and the mixture was stirred for 5 min. Quinuclidine (0.3 equiv), *tert*-BuOH (5 mL/mmol substrate), and the olefin (1 equiv) were then added sequentially, and the reaction was stirred at room temperature until the olefin was consumed as judged by TLC. A solution of saturated aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol substrate). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the pure diol.

General procedure for the enantioselective dihydroxylation of olefins using (DHQD)₂Phal

Water (5 mL/mmol substrate) was added to a solid mixture of $K_2S_2O_8$ (1.5 equiv), Na_2HPO_4 (3 or 4 equiv), $NalO_4$ (0.2 equiv) or $K_3Fe(CN)_6$ (0.2 equiv), $MeSO_2NH_2$ (1 equiv) and $K_2OsO_2(OH)_4$ (0.05 equiv) at room temperature, and the mixture was stirred for 5 min. (DHQD)₂Phal (0.075 equiv), *tert*-BuOH (5 mL/mmol substrate), and the olefin (1 equiv) were then added sequentially, and the reaction was stirred at room temperature until olefin was consumed as judged by TLC. A solution of saturated aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 x 5 mL/mmol substrate). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the crude product was purified by flash chromatography to provide the pure diol.

Synthesis of 9-decenal (12)

Pyridinium chlorochromate (PCC) (830 mg, 3.85 mmol) was added to a slurry of basic alumina (3.84 g) in CH_2CI_2 (6 mL) and stirred at room temperature for 2 h. Dec-9-en-1-ol (300 mg, 355 μ L, 1.92 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a silica plug and eluted with a mixture of EtOAc/hexanes (1:3, 50 mL). The combined filtrate and washings were removed under reduced pressure to provide 288 mg (97%) of **12** that was used in the dihydroxylation reaction without further purification.

Characterization of diol 13 as its reduction product 1,2,10-decanetriol

NaBH₄ (78 mg, 2.06 mmol) was added to a solution of **13** (78 mg, 0.414 mmol) in MeOH (5 mL) at room temperature. The reaction was stirred for 4 h, whereupon AcOH (~0.1 mL) was added, and the mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with a gradient of acetone/hexanes (1:2 \rightarrow 3:4) to provide 54 mg (69%) of the triol as a white solid: mp 53–55 °C; ¹H NMR (CD₃OD, 500 MHz) δ 3.58–3.54 (m, 1 H), 3.54 (t, *J* 6.5 Hz, 2 H), 3.54 (dd, *J* 4.5, 11.0 Hz, 1 H), 4.41 (dd, *J* 6.5, 11.0 Hz, 1 H), 1.56–1.46 (comp, 4 H), 1.39–1.30 (comp, 10 H); ¹³C NMR (CD₃OD, 125 MHz) δ 73.3, 67.4, 63.0, 34.4, 33.7, 30.8, 30.7, 30.5, 26.9, 26.7; IR (film) 3373, 2924, 2851, 1644, 1466, 1073 cm⁻¹; HRMS (ESI) *m/z* calc for NaC₁₀H₂₂O₃ (M+Na)⁺, 213.1467; found, 213.1471.

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