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Paper

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

Shawn Blumberg[†] and Stephen F. Martin*

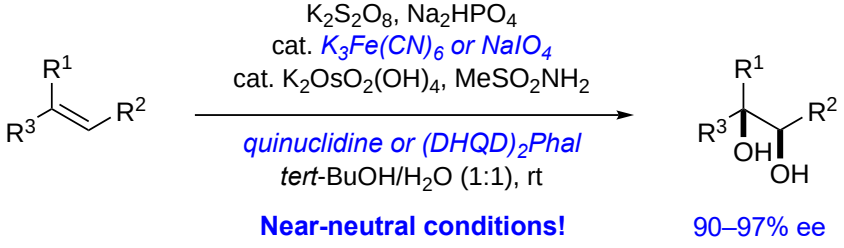
Department of Chemistry, The University of Texas at Austin, Austin, TX 78712, USA
Email: sfmartin@mail.utexas.edu

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

Received 06-05-2020 **Accepted** 07-20-2020 **Published on line** 07-25-2020

Abstract

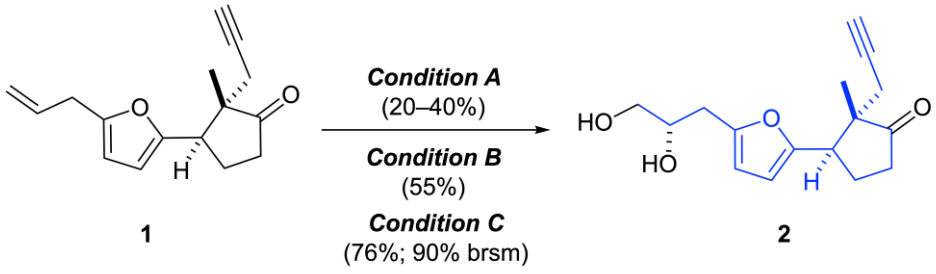
$K_3Fe(CN)_6$ and $NaIO_4$ serve as catalytic co-oxidants for osmium-catalyzed dihydroxylations that are performed under near-neutral conditions with $K_2S_2O_8$ as the stoichiometric oxidant and Na_2HPO_4 as the base. By using either quinuclidine or hydroquinidine 1,4-phthalazinediyl ether [$(DHQD)_2Phal$], 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.



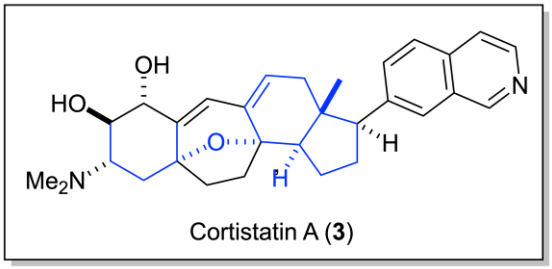
Keywords: dihydroxylation of alkenes, enantioselectivity, mild conditions, base-sensitive substrates

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During the course of our unpublished investigations directed toward the synthesis of cortistatin A (**3**) from **2** (common atoms in **2** and **3** highlighted in blue), we were confronted by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 osmium-catalyzed 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 $MeSO_2NH_2$[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 $K_2S_2O_8$ significantly increased the rate of the reaction and improved the yield to 55% (*Condition B*).[8] Further increasing the quantity of $K_2S_2O_8$ and using $K_3Fe(CN)_6$ 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-β, *tert*-BuOH/H_2O (1:1), rt.
Condition B: AD-mix-β, $K_2S_2O_8$, *tert*-BuOH/H_2O (1:1), rt.
Condition C: $K_2S_2O_8$, K_2CO_3, cat. $K_3Fe(CN)_6$, cat. $K_2OsO_2(OH)_4$, *tert*-BuOH/H_2O (1:1), rt.



Cortistatin A (**3**)

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 $MeSO_2NH_2$, 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 $NaClO_2$[10] and NaOCl,[11] appear to accelerate the hydrolysis of the osmate ester by releasing hydroxide ions, but hydroxide ions are not produced when $K_2S_2O_8$ is used as the terminal oxidant. Indeed, when $K_2S_2O_8$ is used, we observed that the pH of the reaction was about 11.3, a full pH unit *less* than the standard AD

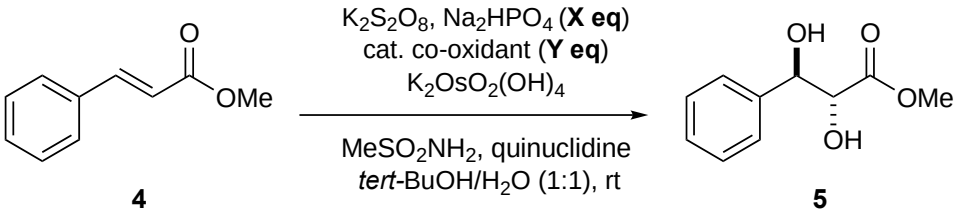
conditions. The capability of $K_2S_2O_8$ to serve as an oxidant under less basic conditions led us to wonder if the pH could be further lowered, so that the asymmetric osmium-catalyzed dihydroxylations could be applied to base-sensitive substrates. Such a modification would offer several advantages over other currently available protocols that use $NaHCO_3$ to buffer the reaction to pH 10.3,[12] but AD reactions do not turn over if $NaHCO_3$ is replaced with K_2CO_3.[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 $NaHCO_3$ or Na_2HPO_4 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 dihydroxylation of methyl cinnamate (**4**) as the model substrate using Na_2HPO_4 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 quinuclidine[17] as a ligand and $MeSO_2NH_2$[4,5] to facilitate hydrolysis led to a complete reaction and provided the diol **5** in 66% yield (Table 1, entry 1). When $K_3Fe(CN)_6$ was omitted as the 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 $NaIO_4$, $KBrO_3$, and $NaClO_2$ afforded **5**, $NaIO_4$ 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 $NaIO_4$ decreases at higher pH. In fact, use of K_2CO_3 as the base with $NaIO_4$ as co-oxidant gave only small quantities of **5** (Table 1, entry 7).

Table 1. Dihydroxylation of methyl cinnamate



entry	co-oxidant	equiv	base	equiv	isolated yield (%)
1	$K_3Fe(CN)_6$	0.1	Na_2HPO_4	3	66
2	$K_3Fe(CN)_6$	0	Na_2HPO_4	3	no reaction
3	$K_3Fe(CN)_6$	0.2	Na_2HPO_4	3	70
4	$K_3Fe(CN)_6$	0.2	Na_2HPO_4	4	91
5	$NaIO_4$	0.1	Na_2HPO_4	3	63
6	$NaIO_4$	0.2	Na_2HPO_4	3	87
7	$NaIO_4$	0.1	K_2CO_3	3	2

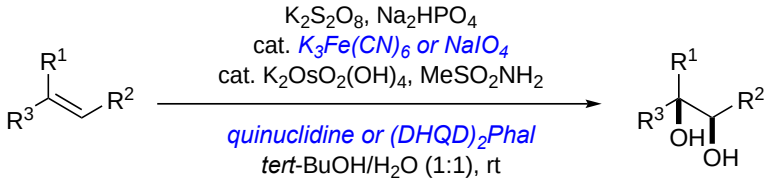
That $NaIO_4$ may be employed as the catalytic co-oxidant for olefin dihydroxylations under near neutral conditions is perhaps at first surprising and thus warrants brief comment. Although there are reports of a RuO_4-catalyzed dihydroxylation that uses $NaIO_4$ as the stoichiometric oxidant,[18,19] use of $NaIO_4$ with OsO_4 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 $NaIO_4$ in the presence of a catalytic amount of OsO_4, 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 $NaIO_4$. Indeed, it has been reported that the Johnson-Lemieux reaction occurs only slowly at neutral pH or in the presence of K_2CO_3,[20] and we found in an exploratory experiment that reducing the pH of the $NaIO_4$ co-catalyzed dihydroxylation using phosphoric acid resulted in the formation of some benzaldehyde.

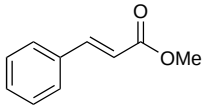
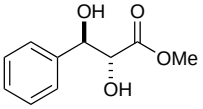
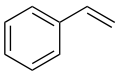
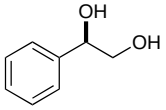
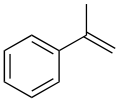
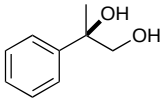
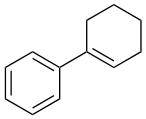
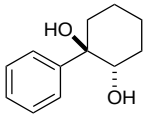
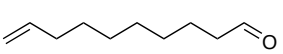
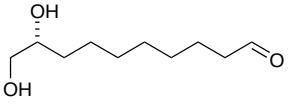
Having established optimized conditions for the racemic dihydroxylation of methyl cinnamate (**4**) using either $NaIO_4$ or $K_3Fe(CN)_6$ as the catalytic co-oxidant, we explored the substrate scope with several substituted styrenes as standard substrates (Table 2, entries 1-4). The yields using either $NaIO_4$ or $K_3Fe(CN)_6$ 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 $NaHCO_3$ 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 $K_3Fe(CN)_6$ as the co-catalyst provided the diol **13** in 82% yield, whereas use of $NaIO_4$ as the co-oxidant gave **13** in only 45% yield (Table 2, entry 5). Because reactions with $K_3Fe(CN)_6$ in the presence of Na_2HPO_4 are generally faster that those using $NaIO_4$, 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 [$(DHQD)_2Phal$] are significantly faster than those using quinuclidine as a ligand, reduced quantities of $(DHQD)_2Phal$ are required. Generally, the

enantioselective dihydroxylations with $(DHQD)_2Phal$ in the presence of $NaIO_4$ are higher yielding than those using $K_3Fe(CN)_6$ 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 $NaIO_4$ or $K_3Fe(CN)_6$ served as the co-oxidant. Although the yield of racemic **13** was better when $K_3Fe(CN)_6$ was used as the co-oxidant, $NaIO_4$ gives superior yields under the conditions for enantioselective dihydroxylation of **12** (Table 2, entry 5).

Table 2



entry	substrate	ligand co-oxidant product	quinuclidine[a] $K_3Fe(CN)_6$	quinuclidine[a] $NaIO_4$	$(DHQD)_2Phal$[b] $K_3Fe(CN)_6$	$(DHQD)_2Phal$[b] $NaIO_4$	Ee %[c] (lit[4])
			isolated yield (%)				
1	 **4**	 **5**	91[d]	87	68	83	96 (97)
2	 **6**	 **7**	99[e]	99	80	78	97 (97)
3	 **8**	 **9**	89[e]	87	72	54	90 (94)
4	 **10**	 **11**	67	67	61	64[e]	94 (99)
5[g]	 **12**	 **13**	82[d,f]	45[f]	49[d]	71[f]	ND[h]

[a] Experimental details given under the general procedure for racemic dihydroxylation of olefins, using 3 equiv of Na_2HPO_4unless otherwise indicated. [b]) Experimental details given under the general procedure for enantioselective dihydroxylation of olefins, using 3 equiv of Na_2HPO_4 unless otherwise indicated. [c]) Enantiomeric excess (ee) was determined according to procedures reported by Sharpless.[21] [d]) 4 equiv of Na_2HPO_4 were used. [e]) 0.1 equiv of co-oxidant was used. [f]) $MeSO_2NH_2$ was not used. *g*) The ^{1}H-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, Na_2HPO_4 serves as the base, $MeSO_2NH_2$ facilitates hydrolysis of the intermediate osmate ester, and either quinuclidine or $(DHQD)_2Phal$ are used as the ligand. $NaIO_4$ 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 $NaIO_4$ (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), $NaIO_4$ (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_2Cl_2 (6 mL) and stirred at room temperature for 2 h. Dec-9-en-1-ol (300 mg, 355 µL, 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

$NaBH_4$ (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 → 3:4) to provide 54 mg (69%) of the triol as a white solid: mp 53–55 °C; ^{1}H NMR (CD_3OD, 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); ^{13}C NMR (CD_3OD, 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 $NaC_{10}H_{22}O_3$ $(M+Na)^+$, 213.1467; found, 213.1471.

Acknowledgments

We wish to thank the Robert A. Welch Foundation (F-0652) for generous support of this research.

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[†]Current address: Pharmaceuticals and Bioengineering Department, Southwest Research Institute, San Antonio, TX 78228, USA

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