MTO and OsO_4: An Efficient Catalytic Couple for Mild H_2O_2-Based Asymmetric Dihydroxylation of Olefins

Sandra Y. Jonsson, Hans Adolfsson,* and Jan-E. Bäckvall*[a]

Abstract: A novel and robust system for osmium-catalyzed asymmetric dihydroxylation of olefins by aqueous H_2O_2 with methyltrioxorhenium (MTO) as electron transfer mediator (ETM) has been developed. The MTO is catalyzing the H_2O_2 oxidation of the chiral ligand to its mono-*N*-oxide, which in turn reoxidizes Os^{VI} to Os^{VIII}. Thus the $(DHQD)_2PHAL$ plays a dual role serving as the chiral inductor as well as the tertiary amine generating the *N*-oxide required for the recycling of osmium. The present catalytic system gives vicinal diols in good isolated yields and high enantiomeric excess (up to 99% *ee*).

Keywords: asymmetric catalysis · dihydroxylation · hydrogen peroxide · osmium · rhenium

Introduction

The *cis*-dihydroxylation of olefins mediated by osmium tetroxide represents an important method for olefin functionalization.[1, 2] With respect to its general applicability, this protocol is probably the most powerful route toward 1,2-diols. The active reagent, OsO_4, being highly chemoselective although at the same time toxic and expensive, emphasizes the importance of developing good reoxidation systems for osmium(VI), rendering the dihydroxylation catalytic in osmium. Several efficient processes for reoxidation of Os^{VI} have been developed in the past. Tertiary amine oxides, such as *N*-methylmorpholine *N*-oxide (NMO), are commonly used oxidants introduced by VanRheenen and co-workers at the Upjohn company in 1976.[2] Sharpless and co-workers used NMO as the reoxidant in the development of the catalytic asymmetric dihydroxylation of olefins,[3] which under certain reaction conditions gave high yields of the diol products in high enantiomeric excess. Another addition to this list of co-oxidants is potassium hexacyanoferrate(III) ($K_3[Fe(CN)_6]$), which was introduced by Tsuji in the early 1990s as a reoxidant for the osmium(VI) species.[4] This iron salt was found to be superior to NMO in the asymmetric version of the reaction, giving diols with higher *ee* values.[5] Unfortunately, substantial quantities of salts are produced from the latter oxidant, which makes the method unpractical for large-scale applications.[6] Hence, there is a need for the development of methods employing alternative cheap environmentally benign and selective oxidants, such as molecular oxygen or hydrogen peroxide, for the osmium-catalyzed dihydroxylation of olefins. These oxidants are highly attractive since, in contrast to many commonly employed inorganic oxidants, they do not produce any toxic waste products.

The use of hydrogen peroxide as reoxidant for osmium(VI) was already reported by Milas and co-workers in the 1930s.[7] Catalytic *cis*-dihydroxylation using hydrogen peroxide resulted in good yields with certain olefins, but over-oxidation and non-selective reactions constitute serious limitations of this method. Apart from the Milas method,[7] only a few procedures for reoxidation of osmium(VI) by H_2O_2 or O_2 are known. Krief et al. have shown that O_2 can reoxidize osmium(VI) in the presence of a selenium oxide under irradiation by visible light.[8] Beller and co-workers have reported on a procedure for aerobic osmium-catalyzed dihydroxylation of olefins under strictly buffered conditions,[9] and our own group has developed a mild H_2O_2-based osmium-catalyzed dihydroxylation employing a flavin and *N*-methyl morpholine (NMM) as co-catalysts (Scheme 1).[10] In the latter procedure Os^{VI} is reoxidized by NMO, generated from NMM and H_2O_2 with the aid of a flavin.[11] Direct reoxidation of Os^{VI} by H_2O_2 does not work very well. In general, direct reoxidation of the reduced form of a substrate-selective metal catalyst by O_2 or H_2O_2 is usually not trivial, since the energy barrier for electron transfer can be high. In many biological oxidation systems, nature has solved this problem by the introduction of efficient electron transfer mediators (ETMs) between the substrate-selective redox catalyst and the terminal oxidant (O_2 or H_2O_2).[12] The same principle is also used in several synthetically important non-biological biomimetic oxidation reac-

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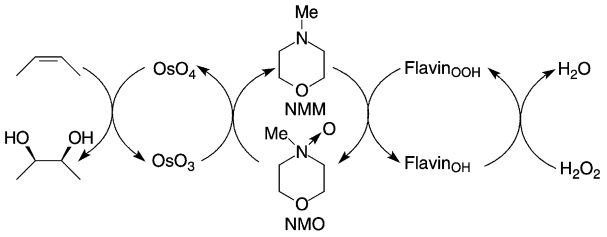
tions,[13] (e.g. the Wacker process[13a]), where the reduced form of the substrate-selective redox catalyst is reoxidized by the oxidized form of a suitable ETM (ETM_{ox}). The reduced form of the ETM (ETM_{red}) is recycled by molecular oxygen or hydrogen peroxide as the terminal oxidant. In the above mentioned H_2O_2-based dihydroxylation system the formal ETMs are NMM and a flavin (Scheme 1).[10]



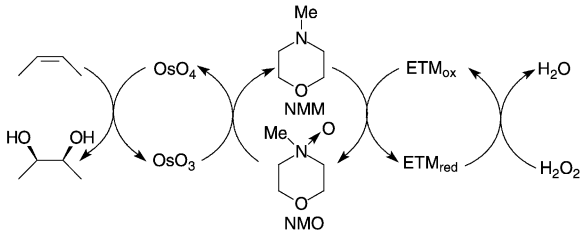
Scheme 1. Triple catalytic system for osmium-catalyzed dihydroxylation of olefins using H_2O_2 as the terminal oxidant.

With the objective to simplify the catalytic system according to Scheme 1 and enhance the utility of the H_2O_2-based dihydroxylation, attempts were made to replace the flavin by a more robust and stable hydrogen peroxide activator. Some success was achieved with $VO(acac)_2$[14] but this system gave lower activity and enantioselectivity compared to the catalytic system employing flavin. In the flavin-based system shown in Scheme 1 we recently discovered that the chiral ligand $(DHQD)_2PHAL$[15] can also serve as the tertiary amine in the electron transfer system. This dual role simplifies the oxidation system since no NMM is required.[16]

We have now found conditions that allow the use of methyltrioxorhenium (MTO) as the hydrogen peroxide activator in osmium-catalyzed asymmetric dihydroxylation. MTO has previously been successfully used as a redox catalyst in hydrogen peroxide oxidations.[17] In our new system we take advantage of the dual role of the cinchona alkaloid $(DHQD)_2PHAL$, which leads to an efficient osmium-catalyzed asymmetric dihydroxylation where the oxidant is aqueous hydrogen peroxide and the only added co-catalyst is MTO.

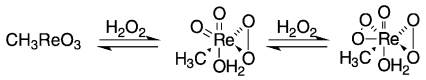
Results and Discussion

Asymmetric dihydroxylation by H_2O_2 with $MeReO_3$ as ETM: Several transition metal complexes are known to activate hydrogen peroxide and have been employed in oxidation reactions.[17–19] Vanadium complexes represent one such class of transition metal complexes that often has been used as catalysts in hydrogen peroxide oxidations.[19] For example, vanadyl acetylacetonate, $VO(acac)_2$, was found to catalyze the hydrogen peroxide oxidation of NMM to NMO.[20] We have previously shown that $VO(acac)_2$ and NMM can be used as efficient co-catalysts in the osmium-catalyzed dihydroxylation of olefins with high chemo-selectivity by means of hydrogen peroxide as the terminal oxidant (Scheme 2, $ETM_{red} = VO(acac)_2$).[14] However, employing the vanadium-based system in the presence of $(DHQD)_2PHAL$ in the dihydroxylation of styrene, produced (1*R*)-1-phenyl-1,2-ethanediol in 65% yield and a modest 80% enantiomeric excess.[14]



Scheme 2. Triple catalytic biomimetic dihydroxylation system.

Over the past years methyltrioxorhenium (MTO) has been shown to act as a powerful and versatile oxidation catalyst with interesting selectivity behavior.[17, 21, 22–24] MTO readily reacts with aqueous hydrogen peroxide forming mono- and bis-peroxo complexes (Scheme 3). The peroxo-complexes efficiently catalyze a number of oxidation reactions, for example epoxidation of olefins[17, 22] and *N*-oxidation of amines[23] and pyridines.[24]



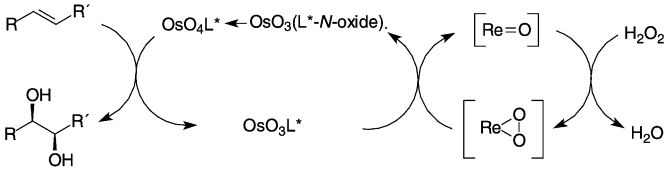
Scheme 3. Reaction of MTO with H_2O_2.

In initial experiments we found that MTO catalyzes the oxidation of NMM to NMO by hydrogen peroxide.[14] Attempts to replace the flavin by MTO as ETM in the H_2O_2-based dihydroxylation of *trans*-5-decene led to moderate success and the corresponding diol was obtained in only 50% yield.[14] The MTO catalyst is known to be stable under acidic reaction conditions; however, in basic reaction media, under oxidative conditions, it decomposes into methanol and catalytically inert perrhenate (ReO_4^-).[25] A likely explanation for the poor results obtained in the dihydroxylation reaction using MTO as ETM is therefore that decomposition of the rhenium catalyst occurs due to the rather high pH of the reaction medium. A lowering of the NMM concentration, which would decrease the pH, was therefore desirable.

We have recently observed that NMM can be omitted in the triple-catalytic asymmetric dihydroxylation by H_2O_2 (Scheme 1) when a flavin is employed as H_2O_2 activator.[16] In this reaction the cinchona alkaloid serves as the tertiary amine, participating (via the *N*-oxide) in the oxygen transfer from the flavin hydroperoxide to osmium(VI). This process will give a lower pH since there is no added tertiary amine (NMM). It was therefore of great interest to try these NMM-free conditions with the use of MTO as ETM in the asymmetric dihydroxylation.

Osmium-catalyzed asymmetric dihydroxylation by H_2O_2 with $(DHQD)_2PHAL$ as the ligand and employing MTO as the ETM under NMM-free conditions, led to a highly effective catalytic process (Table 1). Reaction of styrene with aqueous H_2O_2 in *t*BuOH/H_2O in the presence of 2 mol% of OsO_4 and 6 mol% of $(DHQD)_2PHAL$ using 2 mol% of MTO as ETM gave styrene diol in 90% yield and 95% *ee* (Table 1, entry 1). The olefin was added over a period of 9 h, since a low

olefin concentration efficiently prevents the reaction from entering the enantio-detrimental second catalytic cycle.[26] Thus, for the first time an enantioselective cascade dihydroxylation of alkenes by means of two homogeneously dissolved transition metal catalysts was realized.[27] This kinetically controlled protocol efficiently employs the chiral ligand $(DHQD)_2PHAL$ as electron transfer mediator and source of chirality, and H_2O_2 as the terminal oxidant (Scheme 4).



Scheme 4. Catalytic system with two transition metals using a chiral ligand as a dual-function catalyst and H_2O_2 as the terminal oxidant.

Various aromatic olefins were efficiently dihydroxylated employing this novel catalytic system. The results are summarized in Table 1. Previous optimization studies have revealed that a 3:1 ratio of *tert*-butyl alcohol and water was the optimum solvent mixture.[6, 10] With the use of the above conditions, excellent enantioselectivities were obtained in the oxidation of *trans*-stilbene (entry 2) and in that of methyl *trans*-cinnamate (entry 3). Initial experiments with *trans*-β-methylstyrene, using a ligand concentration Os/L 1:3, were rather disappointing giving an enantioselectivity of 73%. However, by increasing the ligand concentration to Os/L 1:7.5 an enantioselectivity of 90% (entry 4) was realized. The trisubstituted olefin 1-phenyl-1-cyclohexene (entry 6) gave a substantially lower *ee*, even though the addition times of both olefin and hydrogen peroxide were increased from 9 to 20 h (Os/L 1:7.5). Interestingly, α-methylstyrene gave only an *ee* of 64%, even if the ligand concentration was increased to Os/L 1:7.5 (entry 5). The substantially lower enantioselectivity (64% *ee*) observed in the dihydroxylation of α-methylstyrene using the MTO system compared with that of the flavin-based system (90% *ee*), could be explained by a competing epoxidation by MTO and subsequent ring-opening reaction. This was not a serious problem with the reaction of styrene, but the enhanced reactivity of α-methylstyrene could lead some MTO-catalyzed epoxidation.

Dihydroxylation by H_2O_2 with a flavin as ETM: The analogous asymmetric dihydroxylation in which the cinchona alkaloid serves as redox catalyst (via its *N*-oxide) as well as chiral ligand can also be carried out using a flavin as the hydrogen peroxide activator. The results from these asymmetric dihydroxylations are given in Table 2. Performing the asymmetric dihydroxylation on styrene using 2 mol% of osmium tetroxide, 5 mol% of flavin **1** and 6 mol% of $(DHQD)_2PHAL$, the latter as chiral ligand as well as ETM, gave the styrene diol in 75% yield and 95% *ee* (Table 2, entry 1). Dihydroxylation of *trans*-stilbene (entry 2) and α-methylstyrene (entry 3) gave the corresponding diols in 92 and 90% *ee*, respectively. Interestingly, with *trans*-β-methylstyrene (entry 4) an *ee* of 99% was obtained, a higher value than that obtained with MTO (see above) and also than that obtained previously with the method based on NMM.[10a] The results with the NMM-free conditions using either MTO (Table 1) or flavin (Table 2) as hydrogen peroxide activator complements one another.

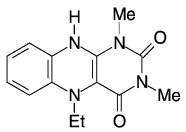


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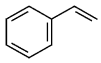
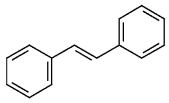
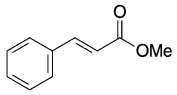
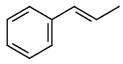
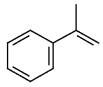
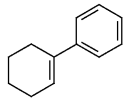
Table 1. MTO and OsO_4 as an efficient couple for asymmetric dihydroxylation of olefins using H_2O_2 as the terminal oxidant.[a]

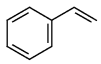
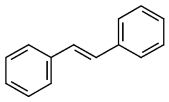
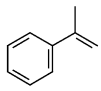
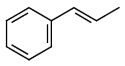
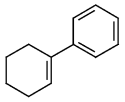
Entry	Olefin	Ligand and reoxidant[a]	Os:L	Yield [%][b]	*ee* [%][c]
1		$(DHQD)_2PHAL$	1:3	90	95
2[d]		$(DHQD)_2PHAL$	1:3	85	97
3		$(DHQD)_2PHAL$	1:3	87	98
4		$(DHQD)_2PHAL$	1:7.5	87	90
5		$(DHQD)_2PHAL$	1:7.5	85	64
6[e]		$(DHQD)_2PHAL$	1:7.5	68	77

[a] TEAA (2 equiv), $(DHQD)_2PHAL$ (0.06 equiv or 0.15 equiv), and MTO (0.02 equiv) were dissolved in *t*BuOH (1.88 mL) and H_2O (0.62 mL). After cooling to 0 °C, OsO_4 (0.02 equiv) was added, followed by ⅓ of the H_2O_2 (0.3 equiv, 30% aq). After stirring for 20 minutes, the olefin (0.5 mmol, 1 equiv) 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 excess was determined by HPLC (Daicel Chiracel OJ or ODH column, *i*PrOH/Hexane). [d] Acetone/H_2O 4.4:1 was employed. [e] The olefin and H_2O_2 were added over 20 h.

Mechanistic considerations: The proposed catalytic cycle of the reaction is depicted in Scheme 5. We envisage an ETM-catalyzed formation of the mono-*N*-oxide of the ligand, which via its non-oxidized tertiary amine coordinates to osmium tetroxide (**3**).

In the next step, the olefin enters the binding pocket of the ligand, which results in the enantioselective formation of an osmium glycolate **4**. Reoxidation of osmium(VI) can now take place, having the active oxidant within the complex **5**. Hydrolysis of the osmium-glycolate liberates the diol and osmium tetroxide coordinated to the ligand **2**, which can reenter the catalytic cycle. Thus, the ligand has a dual role in the reaction, and participates in both enantiodifferentation and oxygen transfer. The high activity and selectivity obtained employing this protocol suggests that the system is operating under strict kinetic control. Thus, MTO (or the flavin) efficiently reacts with H_2O_2 forming the peroxo-complexes, which are responsible for the mono-*N*-oxidation of the alkaloid ligand. OsO_4 selectively reacts with the olefin substrate (via its alkaloid complex) and the reduced form of

Table 2. Asymmetric dihydroxylation of olefins using a flavin as ETM and H_2O_2 as the terminal oxidant.[a]

Entry	Olefin	Ligand and reoxidant[a]	Yield [%][b]	*ee* [%][c]
1		$(DHQD)_2PHAL$	75	95
2[d]		$(DHQD)_2PHAL$	89	92
3		$(DHQD)_2PHAL$	81	90
4		$(DHQD)_2PHAL$	61	99
5[e]		$(DHQD)_2PHAL$	58	70

[a] TEAA (2 equiv), $(DHQD)_2PHAL$ (0.06 equiv), and flavin **1** (0.05 equiv) were dissolved in *t*BuOH (1.88 mL) and H_2O (0.62 mL). Cooled down to 0 °C and OsO_4 (0.02 equiv) was added followed by ⅕ of the H_2O_2 (0.3 equiv, 30 % aqueous). Stirred for 20 minutes, and then the olefin (0.5 mmol, 1 equiv) 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 excess was determined by HPLC (Daicel Chiracel OJ or ODH column, *i*PrOH/hexane). [d] Acetone/H_2O 4.4:1 was employed. [e] The olefin and H_2O_2 were added over 20 h.

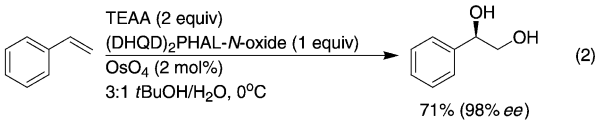
the osmium catalyst is reoxidized by the ligand *N*-oxide. Hence, the system brings about a mild kinetically controlled electron transfer from the olefin to hydrogen peroxide. Although reoxidation of osmium(VI) by either of the MTO peroxo-complexes, or directly from hydrogen peroxide can not be excluded, these background processes are unlikely as the major pathway. In fact, performing the dihydroxylation of styrene under the above optimized conditions, omitting the alkaloid ligand, resulted in the formation of the styrene glycol in only 31 % yield. Excluding OsO_4 from the protocol resulted in the formation of a complex mixture of products, where only a small amount of the diol (< 10 %) could be detected. The latter diol is most likely the result of a nucleophilic ring-opening reaction of the parent epoxide, formed by the MTO-catalyst and hydrogen peroxide.

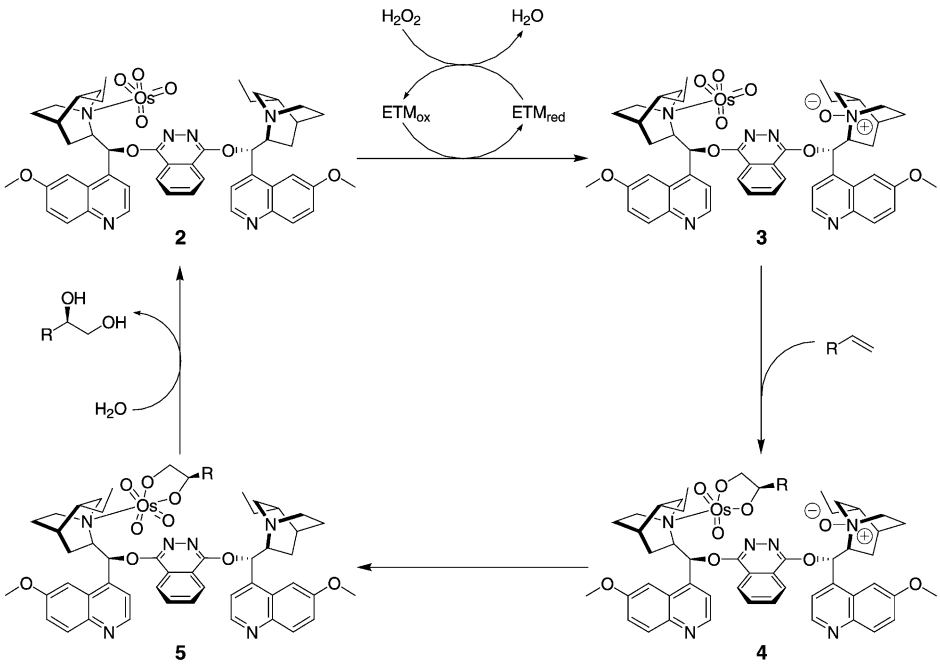
In a control experiment we demonstrated that $(DHQD)_2PHAL$ is selectively oxidized to the mono-*N*-oxide by H_2O_2 in the presence of catalytic amounts of MTO [Eq. (1)] The mono-*N*-oxide was isolated in 89 % yield and

$$(DHQD)_2PHAL + H_2O_2 \xrightarrow[\text{acetone-}H_2O\ (89\%)]{\text{2 mol\% of MTO}} (DHQD)_2PHAL\text{-}N\text{-oxide} + H_2O \quad (1)$$

fully characterized. The corresponding reaction using the flavin/H_2O_2 system also gave the same *N*-oxide.[28] Furthermore, when the isolated $(DHQD)_2PHAL$-mono-*N*-oxide was used as the stoichiometric reoxidant and chirality transfer agent in the dihydroxylation of styrene, the corresponding diol was formed in 71 % isolated yield and 98 % *ee* [Eq. (2)]. This supports that the major catalytic pathway in the NMM-free H_2O_2-based procedure involves the mono-*N*-oxide.

The high enantioselectivities obtained in this protocol suggests that the catalytic reaction predominantly proceeds via the proposed primary cycle.[26] Hence, for mono-substituted and 1,2-disubstituted olefins there is most likely only a





Scheme 5. The proposed catalytic cycle for the enantioselective dihydroxylation of olefins using $(DHQD)_2PHAL$ for oxygen transfer to Os^{VI} and as source of chirality.

minor involvement of the secondary catalytic cycle, where the intermediate Os^{VIII} glycolate is reacting with a second equivalent of olefin prior to hydrolysis.[29] Such a secondary cycle would lead to significantly lower enantioselectivities, as the formation of the Os^{VI} bis-glycolate occurs in the absence of chiral ligand. As outlined above, the observed enantioselectivities with the NMM-free H_2O_2-based system are comparable to the data previously published by Sharpless and coworkers. On the contrary, the more reactive 1,1-disubstituted and trisubstituted olefins substrates, that is α-methylstyrene and 1-phenyl-1-cyclohexene, were obtained in somewhat lower enantioselectivites. The slow osmate hydrolysis observed with highly functionalized olefins suggests that, in these specific cases, there is an involvement of the secondary catalytic cycle. Furthermore, the structural change of the binding pocket in the alkaloid ligand,[1b] enforced by the formation of the mono-*N*-oxide, could efficiently change the mode of olefin selectivity and thus lower the enantioselectivity for certain olefins.

The two hydrogen peroxide-based catalytic systems discussed in this paper, in which the cinchona alkaloid plays a dual role, utilize either MTO or a flavin as the hydrogen peroxide activating catalyst. Both systems provide an efficient and highly selective route for the production of enantiomerically enriched vicinal diols. The selectivities obtained using the flavin system, were in some cases slightly higher than those with the MTO-based protocol. However, the generally higher chemical yields obtained employing the latter system combined with the simplicity and stability of all components are factors favoring the MTO protocol.

Conclusion

To the best of our knowledge, this is the first example of a H_2O_2-based catalytic asymmetric dihydroxylation process, relying on two homogeneously dissolved transition metal catalysts, where the chiral ligand plays two such different and important roles. The catalytic system is simple with a robust electron transfer mediator (MTO) as the only added cocatalyst. The realization of an efficient asymmetric dihydroxylation process of alkenes, with a chiral amine-containing ligand as the source of chirality and ETM, is conceptually new. The reaction protocol based on MTO employs accessible reagents, in combination with a simple operational setup, for the selective dihydroxylation under mild and green conditions.

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 and coupling constants (J) are given in hertz. 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 OJ column. Mass-spectra were recorded on a Bruker BIFLEX MALDI-TOF. 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 were obtained from commercial suppliers and used without further purification. Tetraethylammonium acetate tetrahydrate (TEAA, 99%), $(DHQD)_2PHAL$ (99%), H_2O_2 (30% aqueous), OsO_4 (as a 2.5 wt% solution in *t*BuOH) and methyltrioxorhenium(VII) were purchased from Aldrich. The flavin was synthesized according to a previously published procedure.[11]

(1*R*)-1-Phenyl-1,2-ethanediol—General procedure for asymmetric dihydroxylation of styrene using OsO_4-$(DHQD)_2PHAL$-MTO: Tetraethylammonium acetate (261 mg, 1 mmol), $(DHQD)_2PHAL$ (23 mg, 0.03 mmol) and MTO (2.5 mg, 0.01 mmol) were added to a flask charged with *t*BuOH (1.88 mL) and H_2O (0.62 mL). The mixture was stirred and cooled to 0 °C and OsO_4 (125 μL, 0.01 mmol) was added, followed by ⅓ of the H_2O_2 (⅓ × 77 μL, 30% aqueous, ⅓ × 0.75 mmol). The yellow reaction mixture was stirred for 20 minutes and then the neat alkene (57 μL, 0.5 mmol) and the rest of the H_2O_2 was 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 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 pad 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 afford (1*R*)-1-phenyl-1,2-ethanediol (0.062 g, 90%). Analysis by HPLC showed that the product was of 95% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34-7.29$ (m, 5H), 4.83 (dd, $J = 3.6$, 8.0 Hz, 1H), 3.77 (d, $J = 10.8$ Hz, 1H), 3.67 (dd, $J = 8.4$, 11.6 Hz, 1H), 2.56 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 140.5$, 128.6, 128.0, 126.0, 74.7, 68.1; HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 95:5, flow rate 0.5 mL min^{-1}): t_R(major) = 30.2 min, t_R(minor) = 33.0 min.

(1*R*)-1-Phenyl-1,2-ethanediol—General procedure for asymmetric dihydroxylation of styrene using OsO_4-$(DHQD)_2PHAL$-flavin: The reaction was carried out according to the procedure described above but MTO was replaced by flavin **1** (6.7 mg, 0.025 mmol). Workup as described above furnished (1*R*)-1-phenyl-1,2-ethanediol (0.051 g, 75%). HPLC analysis of the pure diol showed an enantiomeric excess of 95%.

Oxidation of $(DHQD)_2PHAL$ with H_2O_2-MTO: MTO (2.5 mg, 0.01 mmol) was added to a stirred solution of $(DHQD)_2PHAL$ (389 mg, 0.5 mmol) in acetone (3.76 mL) and H_2O (1.24 mL) at room temperature. This stirred mixture was cooled to 0 °C and H_2O_2 (52 μL, 30% aqueous, 0.25 mmol) was added dropwise. Stirring continued for 19 h, during which the mixture was allowed to warm up to room temperature. The mixture was filtered through Celite and concentrated in vacuo to give the mono-*N*-oxide (0.35 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.63$ (d, $J = 4.4$ Hz, 2H), 8.32 (dd, $J = 3.6$, 6.4 Hz, 2H), 7.97 (d, $J = 9.2$ Hz, 2H), 7.93 (dd, $J = 3.2$, 5.6 Hz, 2H), 7.57 (d, $J = 2$ Hz, 2H), 7.43 (d, $J = 4.4$ Hz, 2H), 7.34 (dd, $J = 2.8$, 9.2 Hz, 2H), 7.05 (d, $J = 5.6$ Hz, 2H), 3.90 (s, 6H), 3.41 (q, $J = 6.4$ Hz, 2H), 2.85–2.64 (m, 9H), 2.02 (t, $J = 11.6$ Hz, 2H), 1.71 (s, 2H), 1.55–1–40 (m, 11H), 0.79 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 158.4$, 157.7, 156.6, 156.3, 155.3, 147.2, 146.9, 144.6, 142.8, 132.2, 131.5, 127.2, 127.0, 126.0, 123.1, 122.7, 122.5, 122.4, 122.2, 121.9, 121.8, 118.4, 116.9, 102.2, 102.0, 75.9, 72.1, 68.5, 65.9, 65.6, 60.0, 59.9, 56.2, 55.7, 50.7, 49.8, 38.4, 37.2, 26.9, 26.6, 26.2, 25.6, 25.3, 25.2, 23.0, 21.1, 11.8, 11.2; mass-spectral analysis showed that the mono-*N*-oxide had been generated: MS (MALDI-TOF): *m*/*z*: calcd for $C_{48}H_{55}N_6O_5$: 795.4234; found: 795.4261 $[M+H]^+$.

(1*R*)-1-Phenyl-1,2-ethanediol—Asymmetric dihydroxylation of styrene using OsO_4-$(DHQD)_2PHAL$-mono-*N*-oxide: Tetraethylammonium acetate (157 mg, 0.6 mmol) and $(DHQD)_2PHAL$-mono-*N*-oxide (239 mg, 0.3 mmol) were added to a flask charged with *t*BuOH (1.13 mL) and H_2O (0.37 mL). This stirred mixture was cooled down to 0 °C and OsO_4 (75 μL, 0.006 mmol) was added, and then the neat alkene (34 μL, 0.3 mmol) was added over a period of 9 h. After the addition was complete the resulting clear yellow solution was stirred at 0 °C for an additional 9 h. Quenched by addition of $Na_2S_2O_4$ (36 mg) and magnesium silicate (72 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 pentane/EtOAc (80:20) to afford (1*R*)-1-phenyl-1,2-ethanediol (0.030 g, 71%). Analysis by HPLC showed that the product was of 98% *ee*.

(*R*,*R*)-1,2-Diphenyl-1,2-ethanediol: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.24 – 7.12 (m, 10H), 4.72 (s, 2H), 2.83 (br s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 139.8$, 128.1, 127.9, 126.9, 79.1; HPLC (Daicel Chiralcel OJ column, hexane/2-propanol 90:10, flow rate 1.0 mL min^{-1}): t_R(minor) = 11.3 min, t_R(major) = 12.2 min.

(2*R*)-2-Phenylpropane-1,2-diol: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$ – 7.28 (m, 5H), 3.80 (d, $J = 11.2$ Hz, 1H), 3.63 (d, $J = 7.6$ Hz, 1H), 2.63 (s, 1H), 1.90 (s, 1H), 1.53 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 144.9$, 128.4, 127.2, 125.1, 74.8, 71.1, 26.0; HPLC (Daicel Chiralcel OJ column, hexane/2-propanol 90:10, flow rate 1.0 mL min^{-1}): t_R(minor) = 10.0 min, t_R(major) = 12.6 min.

(1*R*,2*R*)-1-Phenylpropane-1,2-diol: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ – 7.30 (m, 5H), 4.37 (d, $J = 7.6$ Hz, 1H), 3.87 – 3.84 (m, 1H), 2.60 (br s, 2H), 1.06 (d, $J = 6.4$, Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 141.0$, 128.5, 128.1, 126.8, 79.5, 72.2, 18.7; HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 95:5, flow rate 0.5 mL min^{-1}): t_R(major) = 24.2 min, t_R(minor) = 26.2 min.

(1*R*,2*R*)-1-Phenyl-1,2-cyclohexanediol: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.52 – 7.24 (m, 5H), 3.99 (dd, $J = 4.8$, 11.2 Hz, 1H), 2.59 (s, 2H), 1.91 – 1.38 (m, 8H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 146.3$, 128.5, 127.0, 125.1, 75.5, 74.5, 38.5, 29.2, 24.3, 21.1; HPLC (Daicel Chiralcel OJ column, hexane/2-propanol 90:10, flow rate 1 mL min^{-1}): t_R(minor) = 8.0 min, t_R(major) = 9.8 min.

(2*S*,3*R*)-Methyl 2,3-dihydroxy-3-phenylpropionate: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ – 7.31 (m, 5H), 5.02 (dd, $J = 2.7$, 7.2 Hz, 1H), 4.38 (dd, $J =$ 3.0, 5.7 Hz, 1H), 3.83 (s, 3H), 3.05 (d, $J = 5.7$ Hz, 1H), 2.66 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 173.1$, 139.9, 128.4, 128.0, 126.2, 74.7, 74.4, 52.8; HPLC (Daicel Chiralcel OJ column, hexane/2-propanol 90:10, flow rate 1 mL min^{-1}): t_R(minor) = 20.7 min, t_R(major) = 25.8 min.

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