The Origin of High Enantioselectivity in the Dihydroxylation of Olefins Using Osmium Tetraoxide and Cinchona Alkaloid Catalysts

E. J. Corey,* Mark C. Noe, and Sepehr Sarshar

Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

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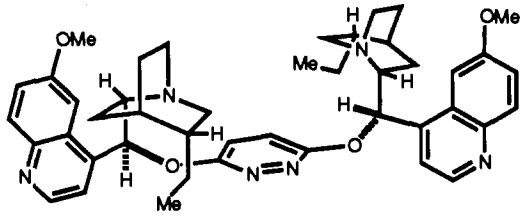
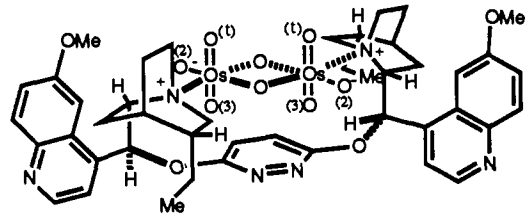
Remarkable progress has been made recently in the development of the enantioselective dihydroxylation of achiral olefins by means of osmium tetraoxide and a variety of chiral ligands.[1,2] Especially practical are the catalytic systems based on cinchona alkaloids which have been reported by the Sharpless group.[2,3] In this report we outline the results of a study of the mechanistic basis of enantioselectivity in the Sharpless catalytic system with dihydroquinine or quinidine (Q) ethers as ligands which supports an earlier proposal[4] that these dihydroxylations proceed by way of the μ-oxo-bridged bisOs(VIII) species, $QO_3Os[O_2]OsO_3Q$, in which Q is bonded to hexacoordinate Os at the basic bridgehead nitrogen. The catalysts used in this work, which were selected to favor reaction via the μ-oxo-bridged bisOs pathway, involve the ligands **1a** (3,6-pyridazine bridge) and **1b** (2,5-pyrazine bridge).[5]



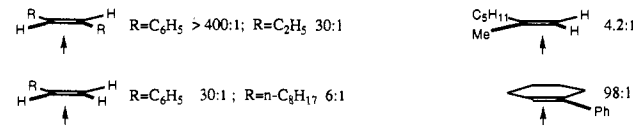
1a
1b, pyrazine analog



2
3, pyrazine analog

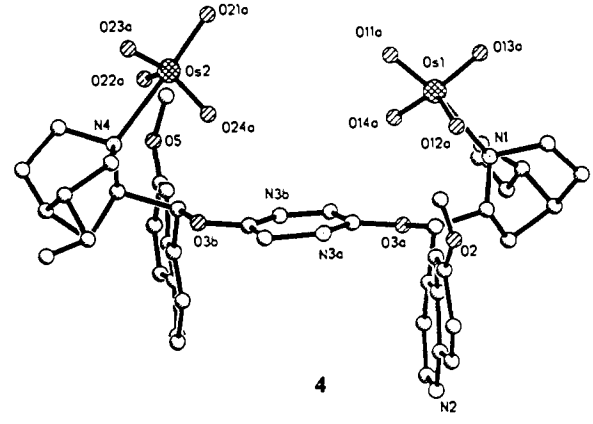
Ligand **1a** is a superb catalyst for enantioselective dihydroxylation since it provides enantioselectivities comparable to the best previously reported[3] across the range of olefin types and since it is available in one step from cheap 3,6-dichloropyridazine (Aldrich).[6] Ligand **1b** showed similar catalytic behavior, although enantioselectivities were somewhat lower with certain olefins.[7]

Using 1 mol % of dihydroquinidine-derived ligand **1a** and 0.01 mol % of potassium osmate under Sharpless' conditions, the following olefins underwent clean dihydroxylation with the face selectivities indicated.[8]



These face selectivities place severe constraints on possible mechanisms. The simplest conceptually, (3 + 2) cycloaddition of the olefin to pentacoordinate (approximately trigonal bipyramidal as in **4**) OsO_4·Q seems unlikely, since it provides no basis whatsoever for explaining such high enantioselectivities.[4] The same is true for (2 + 2) cycloaddition to Q·OsO_4 at Os=O. On the other hand, (3 + 2) cycloaddition to the bridged species **2** at O(1) and O(2) provides a firm basis for the facial preferences (at least for cases with >10:1 enantioselectivity; note that O(3) is blocked by the pyridazine linker in **2**). This can easily be verified by bringing the olefinic substrate to the O(1)–O(2) binding site in **2**, using either space-filling or Dreiding-type models, which leads to the correct prediction of absolute stereochemistry for (*E*)-disubstituted and -trisubstituted olefins. In the case of terminal olefins the correct absolute stereochemistry follows with the additional assumption that the more electrophilic O(1) attacks the terminal methylene of the olefin.[1e,4] Dihydroxylation via a bridged intermediate analogous to **2** also explains the face selectivities observed for the phthalazine-linked cinchona ligand,[3] for cinchona bis-terephthalate ester as ligand,[9] and for the pyrazine-linked ligand **1b**. A third hypothetical mechanistic possibility, (3 + 2) cycloaddition of the olefin to a C_2-symmetric hexacoordinate species (*trans*-Q_2OsO_4), seems very improbable because of internal steric repulsions within Q_2OsO_4, especially if Q is the Sharpless phthalazine ligand (*cis*-Q_2OsO_4 is even more implausible).

A crystalline complex was obtained from ligand **1b** and 6 equiv of OsO_4 from a CH_2Cl_2–isooctane bilayer at 4 °C. X-ray diffraction analysis of this compound revealed structure **4** rather than the bridged structure **3**.[10] It is interesting, however, that



4

the two OsO_4 subunits in **4**, although not bonded, are in a position to bridge with only a modest change of molecular geometry. Despite the X-ray results, the kinetic data described below suggest

(1) (a) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. (b) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. (c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (d) Hirama, H.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665. (e) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P. W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (f) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6421.

(2) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *Ibid.* **1989**, *111*, 1123. (c) Lohray, B. B.; Kalantar, T. H.; Kim, B. M.; Park, C. Y.; Shibata, T.; Wai, J. S. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (d) Kwong, H. L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Ibid.* **1990**, *31*, 2999. (e) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Ibid.* **1990**, *31*, 3817. (f) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Utika, T. *J. Org. Chem.* **1991**, *56*, 4585. (g) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761.

(3) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(4) Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, *31*, 2665.

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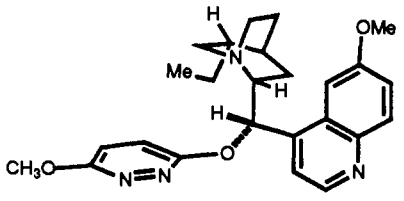
that the enantioselective reaction occurs not via **4** but via bridged structure **3** which is in equilibrium with it and is much more reactive.

The key issue of whether dihydroxylation occurs by reaction of the olefin with one Q–OsO_4 unit or two bridged Q–OsO_4 units is susceptible to analysis by means of reaction rates and stereochemistry. Ligand **5**, an ether prepared by stepwise reaction of 3,6-dichloropyridazine with dihydroquinidine–KH followed by methanol–potassium methoxide, served as a model ligand for the unbridged complex **4**. It was found that the dihydroquinidine



5

ligand **5** led to poor enantioselectivity in the dihydroxylation of olefins as compared to the bis-cinchonidine ligand **1a**. Thus, *o*-(trifluoromethyl)styrene (Aldrich)[11] was dihydroxylated to *R*-diol with only 2.3:1 enantioselectivity with **5** as ligand, as compared to 65:1 enantioselectivity using **1a** as ligand. *The rate of this dihydroxylation was also much faster with the bis-ether ligand* **1a** *than with the mono ether ligand* **5**, as demonstrated by the following experiment. Reaction of 0.3 equiv of *o*-(trifluoromethyl)styrene with 3 equiv of OsO_4 in the presence of a mixture of 1 equiv each of **1a** and **5** in *tert*-butyl alcohol at 23 °C afforded the *R*-diol in 95% yield with 50:1 enantioselectivity, indicating that the oxidation rate with ligand **1a** is approximately 100-fold greater than with ligand **5**. This result cannot be reconciled with a reaction involving the unbridged pentacoordinate species **4** and argues strongly for reaction via the hexacoordinate bridged intermediate **2**. As pointed out earlier,[1e] 1,2-diamines greatly accelerate the dihydroxylation of olefins by OsO_4 through bidentate coordination which allows the dihydroxylation process to occur via the more reactive hexacoordinate species.[12] The faster rate with the bidentate ligand **1a**, via complex **2**, as compared with ligand **5** is in line with these results.

Further evidence that the dihydroxylation reaction proceeds via the bridged complex **2** was obtained by more detailed kinetic studies using *o*-(trifluoromethyl)styrene as substrate in $CDCl_3$ at −50 °C using ^{19}F NMR spectroscopy to monitor the reaction. Thus, to a −50 °C solution of **1a** and 2 equiv of OsO_4 in $CDCl_3$ was added 1 equiv of *o*-(trifluoromethyl)styrene, and the rate of reaction was followed by ^{19}F NMR spectroscopy. Under these conditions, all of the OsO_4 is complexed with **1a** (as revealed by ^1H NMR analysis)[13] and the reaction is approximately proportional to the product of complex and olefin concentrations. Upon complete reaction, an additional equivalent of olefin was added and the rate of reaction was measured. The apparent second-order rate constant for reaction with the first equivalent of olefin was found to be 20 times greater than that for the second equivalent. This result is difficult to rationalize for reaction via a flexible complex **4** with each OsO_4 unit reacting independently but can be easily reconciled with the pathway involving **2**.

Kinetic studies of the OsO_4 dihydroxylation reaction of *o*-(trifluoromethyl)styrene in the presence of monodentate ligand **5** or the analogous 2-pyrazine ether **6** confirmed slower rates for these ligands as compared with **1a** and **1b**. The rates of the reactions of **5** and **6** were approximately proportional to the product of the concentrations of complex Q·OsO_4 and olefin to about 85% consumption of reactants. However, the corresponding "second-order" rate constants were found to increase with concentration of the complex as shown in supplementary material. This complicated kinetic behavior is inconsistent with a reaction pathway involving one molecule each of **5** (or **6**), OsO_4, and olefin. However, it can be reconciled with the more complex process involving reaction of the olefin with the OsO_4-ligand dimer in competition with a less enantioselective reaction (with a smaller rate constant) involving the OsO_4-ligand monomer.[13,14] This conclusion was further tested by studying the enantioselectivity of the stoichiometric reaction of *trans*-stilbene, methoxy pyridazine ether **5**, and OsO_4 at different concentrations in *tert*-butyl alcohol at 29 °C. The enantioselectivity dropped from 74:1 (97.4% ee) when the initial concentration of reactants was 0.028 M to 11.8:1 (84.4% ee) when the initial concentration of reactants was 0.000 56 M. That this large drop in enantioselectivity with 50-fold decrease in initial concentration is not due to a competing nonenantioselective process involving free OsO_4 was shown by control experiments with OsO_4 and stilbene alone in *tert*-butyl alcohol.[15]

Supplementary Material Available: Experimental procedures for the preparation of ligand **1a** and a procedure for its use in the catalytic oxidation of (*E*)-stilbene on a 10-g scale; X-ray diffraction data on complex **5**; and graphical kinetic data (27 pages). Ordering information is given on any current masthead page.

(5) These new catalysts are clearly related to the improved Sharpless system recently reported.[3]

(6) Preparation of **1a**: A suspension of 1 g of hydroquinidine, 0.226 g of 3,6-dichloropyridazine and 0.252 g of KOH in 20 mL of toluene was stirred at reflux with azeotropic removal of water for 6 h. Dilution of the mixture with water, followed by extraction of the product into ethyl acetate, drying and removal of solvent gave the crude product as a light yellow syrup. Filtration through silica gel with 5% MeOH–$CHCl_3$ (saturated with ammonia) gave 0.73 g (65%) of pure **1a** as a colorless solid.

(7) Preparation of **1b** was carried out using a similar procedure to that for **1a**, substituting 2,5-dichloropyrazine for 3,6-dichloropyridazine. 2,5-Dichloropyrazine was prepared from 2-amino-5-chloropyrazine according to Palamadessi, G.; Bernardi, L. *J. Org. Chem.* **1964**, *29*, 2491. 2-Amino-5-chloropyrazine was prepared from commercially available aminopyrazine according to the method of Sato, N. *J. Heterocycl. Chem.* **1982**, *19*, 673.

(8) The general procedure is similar to that of Sharpless.[3]

(9) Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1992**, *33*, 5113. Contrary to the statement in this paper, the terephthalate-bridged structure analogous to **2** is readily constructed using molecular models. On the other hand, the proposal by these authors that a π-complex of the terephthalate ring and the olefin is attacked internally by complexed OsO_4 lacks credibility on geometrical grounds and suffers from a lack of analogy.

(10) The deep-red triclinic crystals of **4** were found to contain 2 molecules of **4**, 1 molecule of CH_2Cl_2, and 2 other molecules of OsO_4 in the unit cell. The other two molecules of OsO_4 interact with quinoline N_5 of each of the two molecules of **4** in the unit cell (N_5–Os distance 2.61 Å): empirical formula $C_{89}H_{106}Cl_2N_{12}O_{32}Os_6$ (3068.0); crystal size 0.6 × 0.5 × 0.4 mm^3; space group $P\bar{1}$; a = 9.951(2) Å; b = 15.539(8) Å, c = 19.477(4) Å, α = 78.99(3)°, β = 75.30(2)°, γ = 71.56(3)°; V = 2743.4(16) Å^3; Z = 1; d = 1.857 g/cm^3; (Mo Kα radiation 20 °C); 5516 reflections collected, of which 3807 with $F_o > 4.0\ \sigma(F_o)$ were used in the solution of structure; R index = 0.0711; GOF 1.97. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. For the X-ray crystal structure of the related quinuclidine–OsO_4 complex see: Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413.

(11) (Trifluoromethyl)styrene is a useful substrate for kinetic study of the dihydroxylation reaction by ^{19}F NMR as described herein.

(12) An X-ray crystal structure determination has been carried out by us on the 1:1 complex of OsO_4 and *trans*-1,2-(1-pyrrolidino)cyclohexane, which has a 5-membered chelated octahedral arrangement about osmium (manuscript in preparation). It is also relevant that a careful study of the pyridine-catalyzed reaction of OsO_4 with olefins demonstrated that (1) concentrated solutions of OsO_4 and pyridine show only bonds attributable to OsO_4, pyridine, and a 1:1 complex but that (2) the catalyzed rate was second order in pyridine, indicating a transition state of composition olefin·OsO_4·2 pyridine. See: Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425.

(13) The catalysts **1**, **5**, and **6** and OsO_4 are fully associated with OsO_4 under conditions of the kinetic measurements described herein (concentrations 0.02–0.15 M, $CDCl_3$ at −50 °C), as shown by ^1H NMR studies which can be summarized as follows. The ^1H NMR spectra of the free ligands **1**, **5**, and **6** are changed by the addition of OsO_4, indicating complexation with fast on–off rates. Full complexation can be determined by the lack of further change with increasing concentration or decreasing temperature.

(14) A previous kinetic study of the cinchonine alkaloid-catalyzed oxidation of olefins by OsO_4, reported by Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737, does not appear to be sufficiently discriminating to detect a complex reaction involving competing pathways via OsO_4·Q monomer and dimer.

(15) This research was supported by the National Science Foundation.