On "The Origin of High Enantioselectivity in the Dihydroxylation of Olefins Using Osmium Tetraoxide and Cinchona Alkaloid Catalysts" [1]

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The mechanism of the osmium-catalyzed asymmetric dihydroxylation remains subject to debate.[2] Recently a mechanistic scheme presented by Corey *et al.*[1] claimed that this system's high stereoselectivity originates from the reaction being funneled through a very reactive μ-oxo-bridged bis-OsO_4 species **1** (Chart I). Their publication prompts us to present some selected results collected over the last few years. These are in disagreement with this proposal and support the mechanistic pathways shown in Scheme I.

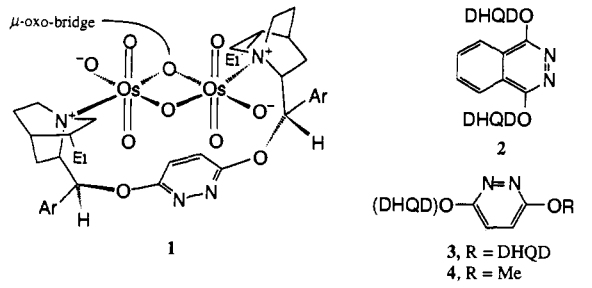
Our kinetic studies[4] lead to a rate law which is consistent with the [2 + 2] or [3 + 2] mechanistic pathways proposed earlier[2,5] (Scheme I). The results are in conflict with a mechanism involving a μ-oxo-bridged bis-OsO_4 species like **1** as the most reactive component and, for that matter, with any mechanism involving two osmium centers in the rate-determining step.

The rate law was confirmed by kinetic studies carried out in ^{t}BuOH as solvent, since this solvent is the one used in the asymmetric dihydroxylation (AD) reaction.[6] All rate measurements were performed at 25 °C in the presence of a greater than 10-fold excess of ligand[7] and olefin as compared to OsO_4, by monitoring the absorbance of the forming glycolate–ligand complexes at 680 nm (for quinuclidine derivatives), or glycolate–bis-ligand complexes at 520 nm (for pyridines), using stopped-flow techniques.

(a) Order in Osmium and Olefin. Under limiting OsO_4 conditions the reaction clearly proceeds with *first-order* kinetics in OsO_4 with a number of ligands {4- and 2-substituted quinuclidines, substituted pyridines, and DHQD derivatives [including $(DHQD)_2PHAL$]}. Figure 1 demonstrates that much better fits of the absorbance data are obtained with a rate law which is first order in OsO_4 compared with a rate law which is second order in OsO_4.[8] This first-order behavior in OsO_4 is supported by the fact that the rate constant is invariant over a range of osmium concentrations.[8]

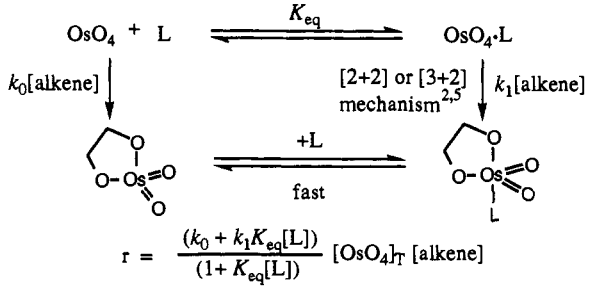
The first-order behavior in olefin was established in another set of kinetic experiments,[9] and the rate law can, therefore, be written as $r = k[\text{alkene}][OsO_4]$. The rate constant k is a function of *only* the ligand concentration and is *independent* of the OsO_4 concentration for all ligands tested[8] (including the phthalazine ligand **2**). This contradicts the idea of **2** reacting mainly *via* a μ-oxo-bridged bis-OsO_4 species, since such a path would require the rate law to have a second-order component in OsO_4. Theoretically, a reaction *via* a bis-OsO_4 complex could be first

Chart I[a]



[a] Reference 3.

Scheme I. Kinetic Scheme for the Reaction of OsO_4 with Olefins[a]



[a] References 2 and 5.

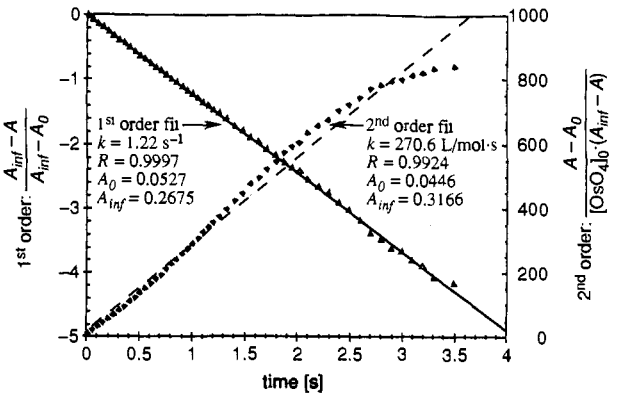


Figure 1. The data were obtained under limiting OsO_4 conditions in ^{t}BuOH at 25 °C using a stopped-flow system. $[(DHQD)_2PHAL]$ = 0.086 mol/L, $[\text{cyclohexene}]_0$ = 0.057 mol/L, $[OsO_4]_0$ = 0.005 mol/L. Values for A_0 and A_{inf} were estimated for either rate law by fitting of the absorption data to the corresponding rate laws.[8] The observed values (A_0 = 0.055, A_{inf} = 0.267) agree very well with the ones obtained from the first order fit.

(1) (a) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (b) Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, *31*, 2665.

(2) For a discussion of the mechanisms considered to date, see: (a) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329 and references cited therein. For a review, see: (b) Jørgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483.

(3) The pyridazine ligand **3** was first prepared in our group as a predecessor of our phthalazine ligand **2** (both ligands are included in MIT's U.S. Pat. Appl. No. 07/775, 683, Oct 10, 1991). However, we prefer to use **2**, since it is superior to **3**, especially in the dihydroquinine series: Crispino, G. A.; Makita, A.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.*, in press.

(4) For our previous kinetic studies, see: (a) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737. (b) Kwong, H.-L. Ph.D. Thesis, Massachusetts Institute of Technology, 1993.

(5) The [2 + 2] and [3 + 2] pathways are kinetically indistinguishable, despite the different mechanistic schemes (see ref 4b). $[OsO_4]_T$ is the total concentration of OsO_4 in the reaction mixture, defined as $[OsO_4]_T = [OsO_4] + [OsO_4 \cdot L]$, and independent of the ligand concentration.

(6) (a) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 2999. See also: (b) 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. (c) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

(7) This produces relevant data, since we also use an excess of ligand in the AD reaction. In contrast, Corey *et al.* employed equimolar amounts of OsO_4 and ligand.[1a]

(8) See the supplementary material for further plots regarding first-order *versus* second-order behavior, as well as the complete rate laws for reaction via (a) Scheme I or (b) a bis-OsO_4 species.

(9) The rates in this particular set of experiments were determined by monitoring changes in olefin concentration by GC using relatively "slow" ligands, i.e., quinuclidine and pyridine. Clean first-order behavior in both olefin and OsO_4 was observed (supplementary material).

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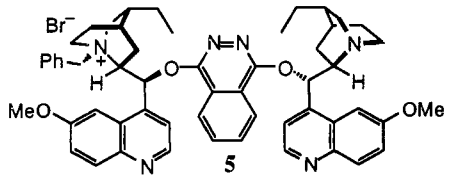
Table I. Enantioselectivities (% ee) Obtained with Ligands 2 and 5



olefin	ligand 2	ligand 5
1-decene	84	85
styrene	97	98

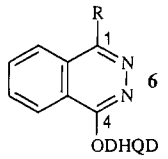
order in OsO_4 if such a complex were the ground state, i.e., if its formation constant were extremely high, in analogy to our Ti-based AE system.[10] However, this is certainly not the case in the AD system. All our X-ray data of ligand–osmium complexes, including Corey's X-ray,[1a] show no evidence for stabilizing interactions between the ligated OsO_4 units.[11] IR spectroscopy clearly shows the presence of free OsO_4 even if excess ligand is present and establishes that $[(OsO_4)_2L]$ is negligible compared to $[OsO_4]$ and $[(OsO_4)L]$ (supplementary material). Thus, the rate expression would have to be second order in OsO_4 if the reaction proceeded exclusively *via* a bridged bis-OsO_4 complex.[8]

(b) Order in Ligand. To reexamine the kinetic behavior with respect to ligand[4] (pyridine and DHQD 9-*O*-*p*-chlorobenzoate), pseudo-first-order rate constants ([cyclohexene]:[OsO_4] = 10:1) were measured in ^{t}BuOH at various ligand concentrations using stopped-flow techniques. Saturation behavior was observed for *both* ligands[12] (supplementary material). The rate law in Scheme I was obeyed, as the $(k_{obs}/c_{olefin})(1 + K_{eq}c_L)$ *versus* c_L plots were *linear*, thereby confirming earlier studies in aqueous acetone[4a] establishing the involvement of only a single ligand molecule in the rate-determining step.[12] Additionally, the fact that the enantioselectivity of the reaction is almost invariant from very high down to very low ligand concentrations[4b] would indicate that the mechanism does not change with the ligand concentration, since such a change should also affect the enantioselectivity.

In summary, we have shown the reaction to obey rate laws derived for the [2 + 2] and [3 + 2] mechanisms (Scheme I). These results rule out the pathway proposed by Corey *et al.*,[1] which is based on a [3 + 2] addition of a μ-oxo-bridged bis-OsO_4 complex as the reactive species.[13]

Kinetic and Enantioselectivity Studies with the Monoquaternary Salt 5. The quaternary salt **5** was prepared earlier[14] to test the possibility that the two quinuclidine units in $(DHQD)_2PHAL$ were somehow acting in concert in the AD reaction. Compound **5** gives enantioselectivities which are virtually identical to those obtained with the phthalazine ligand **2** (Table I).

Table II



ligand, R	% ee[a]
Cl	40
$OCEt_3$	66
1-naphthylmethoxy	57
1,1′-bis(naphthylmethoxy)	78
9,9′-bis(phenanthrylmethoxy)	84
O(DHQD)	84

[a] All ADs were performed under the standard conditions (1 mol % ligand; 0.2 mol % OsO_4; *t*-BuOH:H_2O 1:1; 0 °C, 12 h) on 1-decene. Enantiomeric excesses (ee) of diols were determined by HPLC on the corresponding bis-MTPA esters (0.5% *i*-PrOH–hexane on a Pirkle I-A column).

Kinetic measurements were performed with styrene to also address the rate question. Ligand **5** turned out to have a *higher* ceiling rate constant k_c than the phthalazine ligand **2** [**5**, k_c = 34.6 L/(mol·s); **2**, k_c = 29.3 L/(mol·s)]. Thus, our data strongly suggest that the two quinuclidine units in **2** act independently during the reaction and, therefore, that a μ-oxo-bridged bis-OsO_4 complex such as **1** cannot play an important role.

Enantioselectivities Observed for Phthalazine Ligand Modifications. A series of unsymmetrically substituted phthalazine ligands **6** were prepared to further test the structure/function relationship, if any, between the 1,4-substituents. Their enantioselectivities with 1-decene are shown in Table II.

The results show that a second alkaloid unit is not a requirement for high enantioselectivities, and that the most likely function of the second alkaloid group in **2** (and therefore also in **3**) is merely to position its flat methoxyquinoline unit in the correct relative orientation to the phthalazine ring system.[15]

In conclusion, both the studies with the quaternary salt **5** and those with the modified phthalazine ligands **6** reveal that the high enantioselectivites and rates observed for **2** are *not* due to the two quinuclidine units acting in concert. Rather, the two pendant alkaloid moieties appear to be acting independently, and the excellent results obtained with **2** are probably due to a favorable arrangement which can be achieved between the quinuclidine and aromatic units, to allow optimum stabilization of the transition state.

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Supplementary Material Available: Rate laws for both the [2 + 2]/[3 + 2] mechanism and Corey's mechanistic pathway, kinetic plots regarding the order in ligand, OsO_4, and olefin, and experimental details for the preparation of ligands **5** and **6** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page of ordering information.

(10) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

(11) Svendsen, J. S.; Markó, I.; Jacobsen, E. N.; Rao, C. P.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2263. X-ray crystal structures of OsO_4 complexes of pyridines and quinuclidines: Kolb, H. C.; McGrath, D. V.; Sharpless, K. B. Unpublished results.

(12) Behrman *et al.* found that the dihydroxylation of thymidine in water showed second-order dependence on pyridine. However, analysis of our data according to Behrman's methods leads to physically unreasonable results (negative rate constants). Consequently, our system does not obey the rate law proposed by Behrman, probably due to the very different reaction conditions; see (a) Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425. (b) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972**, *11*, 2621. (c) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Bioinorg. Chem.* **1971**, *1*, 35.

(13) Corey's observation that a second equivalent of olefin reacts more slowly and with lower enantioselectivity with the bis-OsO_4 complex of $(DHQD)_2$-pyridazine than the first equivalent[1] was taken as evidence for a reaction *via* the bridged species **1**. However, it is likely that the second equivalent of OsO_4 bound to the ligand is less reactive than the first one, due to steric interactions, so that complex kinetics in OsO_4 would indeed be expected.

(14) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K.-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844.

(15) The most interesting feature of ligand **2**, our best to date, is that it appears to present a chiral "binding pocket" for one of the olefin substituents, with the phthalazine spacer as the floor and the bystander methoxyquinoline moiety as an abutting, perpendicular watt. Evidence supporting this hypothesis is presented in two full papers: (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.*, in press. (b) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.*, submitted. In line with this theory DHQD-phthalazine-Cl **6** gives lower enantioselectivities since it lacks the bystander methoxyquinoline ring. Hence, the DHQD-pyridazine-OMe ligand **4** does not appear to be a good model for $(DHQD)_2$-pyridazine **3**, contrary to Corey's arguments.[1]