Rigid and Highly Enantioselective Catalyst for the Dihydroxylation of Olefins Using Osmium Tetraoxide Clarifies the Origin of Enantiospecificity

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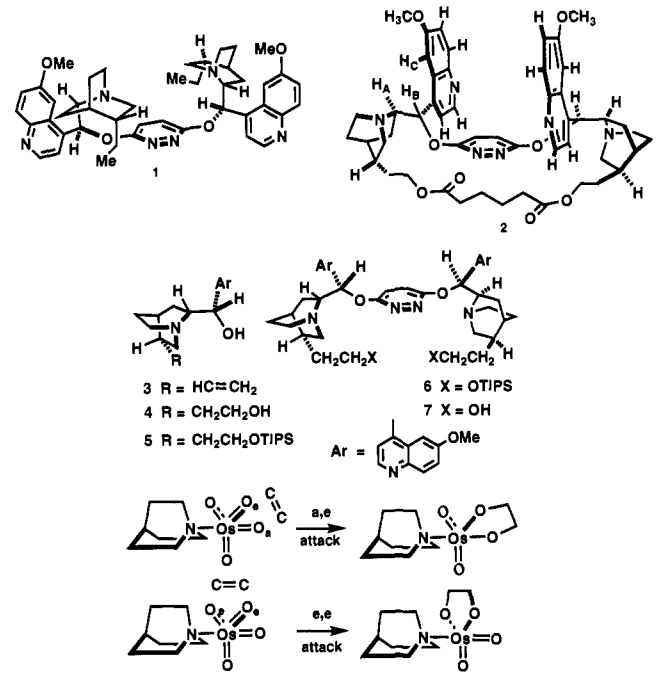
The origin of enantioselectivity in the dihydroxylation of olefins by osmium tetraoxide complexes with chiral 1,2-diamines[1] and cinchona alkaloids[2] is of special interest because of the magnitude and practical implications of the observed enantioselectivity. On the basis of the reasonable assumption that the transition states for these very enantioselective oxidations are highly organized, the investigation of such organization and related mechanistic questions assumes unusual importance. We have previously discussed the ordering in transition states for olefin dihydroxylation catalyzed by chiral 1,2-diamines[1e] and by cinchona alkaloids (Q).[3] In the latter case it has been pointed out that a process involving μ-oxo-bridged bis-Os(VIII) species, $QO_3Os[O_2]OsO_3Q$, provides a simple explanation of the observed olefinic facial selectivities and also the high effectiveness of bis-cinchona catalysts such as **1** (Chart I) in which two molecules of alkaloid are linked by a suitable spacer.[3] In this paper we report new data which not only allow the μ-oxo-bridged pathway to be excluded from consideration but also define a unique geometry for the catalyst–olefin–OsO_4 interaction which clarifies the origin of enantioselectivity.

The macrocyclic bis-quinidine derivative **2**, a crucial element in the present study, was synthesized from quinidine (**3**, Aldrich Co.) by the following sequence: (1) hydroboration (4 equiv of BH_3–THF in THF at 0 °C for 3 h followed by oxidation with aqueous LiOH–H_2O_2 at 0–23 °C for 2 h and 65 °C for 2 h) to form the *N*-borane adduct of **4** (at the quinuclidine N), which was converted to **4** by heating with hydrochloric acid in methanol–acetone at 65 °C for 30 min, basification, and extractive isolation; (2) selective silylation of **4** (2.0 equiv of triisopropylsilyl (TIPS) chloride, 2.5 equiv of imidazole in DMF at 23 °C for 6 h) to form **5** (58% from **3**), mp 135 °C; (3) reaction of **5** with 0.5 equiv of 3,6-dichloropyridazine and powdered KOH in toluene at 120 °C for 2 h[3] to give the bis-quinidine derivative **6**; (4) desilylation using 10% hydrofluoric acid in acetonitrile at 23 °C for 2 h to the diol **7** (56% from **5**), mp 152 °C; and (5) slow simultaneous addition (double syringe drive) of diol **7** and 1 equiv of adipyl chloride to 2.5 equiv of pyridine in CH_2Cl_2 to afford the macrocyclic adipate ester **2** as a syrup in 30% yield after chromatography. The byproduct in the last step was polyester, which was cleanly saponified by methanolic KOH to allow recovery of diol **7**.

The structure of the macrocyclic ester **2** was confirmed by the ^1H NMR, ^{13}C NMR, infrared, and high-resolution mass spectra; (HRMS (FAB) calcd for $C_{50}H_{58}N_6O_8$ + H 871.4394; found 871.4428). The adipate bridge in **2** lies over one face of the pyridazine ring, leaving the two quinoline units in approximately parallel planes which extend away from the opposite pyridazine ring face and at approximately a right angle to it. This geometry is depicted by the space-filling (CPK) model shown in Figure 1 for the complex of **2** with one OsO_4 molecule attached to a quinuclidine nitrogen.[4] Attached to the pentacoordinate osmium (yellow) in Figure 1 are three equatorial oxygens (red) and one axial oxygen (white with red stripes) with an N–Os–O (axial) angle of 180°. The ^1H NMR spectrum of **2** is completely consistent with the three-dimensional structure shown in Figure 1, with the following being of special significance: (1) J_{AB} in **2** of ca. 1.5 Hz indicating a dihedral angle of ca. 80° and (2) positive NOE values between H_B and H_C in **2** (14.5%) and H_A and H_C in **2** (4.3%). The ^1H NMR spectrum of **2**·OsO_4 indicates very similar geometry, and in addition, H_A, H_B, and H_C are shifted downfield by the proximate oxygens of OsO_4.

The adipate-bridged ligand **2** is an excellent catalyst for the enantioselective dihydroxylation of many olefins and compares very well with the unbridged PYDZ ligand **1** as shown in Table I.[5] It is clear from the data in Table I that catalysts **1** and **2** behave so similarly that they probably operate through corresponding transition-state geometries. This conclusion is strengthened by the nearly identical variation of observed ee values with solvent under standard conditions.[5] For example, for *o*-fluorostyrene as substrate, ee values with CH_2Cl_2 as solvent were 73% for **1** and 74% for **2**, and with ether as solvent they were 91% for **1** and 91% for **2**, with the same diol predominating in each instance. The catalytic rates for **1** and **2** were also found to be essentially the same under the standard catalytic conditions[5] by a competition experiment. Using a mixture of 1 mol % each of the dihydroquinine PYDZ analog of **1** (which converts styrene to the (*S*)-diol) and ligand **2**, styrene was oxidized[5] to *racemic* styrene glycol.

Chart I



(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*, 1741.

(2) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3817. (c) 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. (d) 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. (e) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047. (f) Morikawa, K.; Park, J.; Andersson, P.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463 and references cited therein.

(3) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828.

(4) The pentacoordinate osmium complex shown has geometry corresponding to the crystalline OsO_4–quinuclidine complex (O(axial)–Os–N angle of 180°; staggering of OsO (equatorial) and quinuclidine N–C bonds); see: Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413.

(5) The following procedure was used for the catalytic dihydroxylations summarized in Table I. To 1 mol % of ligand **1** or **2** in 1:1 *tert*-butyl alcohol–water was added 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, and 0.1 mol % of K_2OsO_4, and 1 equiv of $CH_3SO_2NH_2$ (omitted for terminal olefins), and the mixture was stirred at 0 °C for 20 min. The olefin was added, and the mixture was stirred at 0 °C for 3–12 h. The product was isolated by addition of Na_2SO_3, extraction with CH_2Cl_2, and filtration through a small plug of silica gel.

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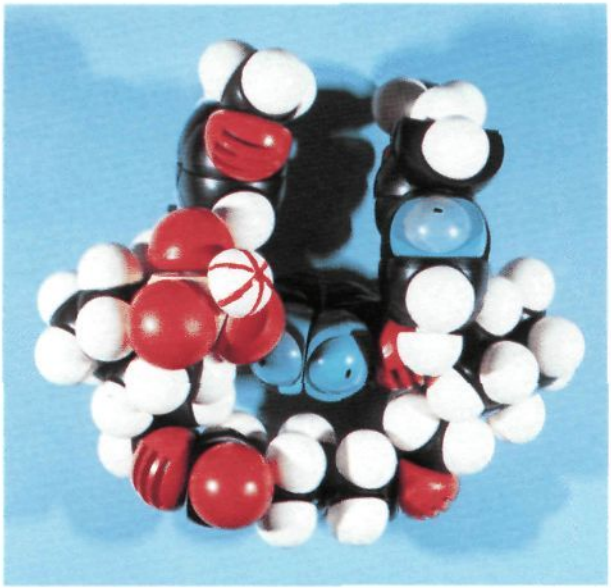

Figure 1. CPK model of catalyst **2**-OsO_4 complex.[4]

Table I. Enantioselective Dihydroxylation of Olefins Catalyzed by **1** and **2**[a]

olefin	ee (% yield) catalyst **1**	catalyst **2**	diol confign
(*E*)-stilbene	>99 (99)	>99 (99)	*R*,*R*
(*E*)-3-hexene	93 (58)[b]	88 (71)[b]	*R*,*R*
styrene	96 (95)	97 (91)	*R*
o-fluorostyrene	98 (98)	99 (82)	*R*
tert-butylethylene	44 (90)	56 (52)[b]	*R*
1-decene	79 (95)	88 (92)	*R*
1-phenylcyclohexene	98 (88)	95 (88)	*R*,*R*
2-methyl-1-heptene	62 (74)	68 (67)[b]	*R*

[a] Reactions were conducted according to footnote 5. [b] Yields not optimum because of less efficient extractive isolation.

Having established nearly identical catalytic behavior of ligands **1** and **2**, we turn to the mode of action of the highly constrained macrocyclic catalyst **2**. Clearly, in the almost C_2 symmetric **2**[6] the two quinuclidine nitrogens are held so far apart as to exclude any mechanism that requires both to participate in bonding to osmium, ruling out *inter alia* the μ-oxo-bridged bis-Os(VIII) pathway.[3] On the other hand the highly organized structure of the 1:1 complex of **2** with OsO_4 (Figure 1) immediately suggests a basis for enantioselectivity. The space between the quinoline rings in **2** represents a binding site which can readily accommodate an aromatic ring or *n*-aliphatic chain. Such sandwich binding, for example with styrene, would provide a complex in which the olefinic bond is positioned perfectly with regard to [3 + 2] cycloaddition to the axial and one of the equatorial oxygens of complexed OsO_4. Figure 2 depicts the 1:1:1 complex of **2**, OsO_4, and styrene with the proper geometry to induce dihydroxylation. This geometry ensures formation of the observed (*R*)-diol. The diastereomeric structures for the production of (*S*)-diol from styrene are disfavored because they do not allow simultaneous [3 + 2] cycloaddition to the complexed OsO_4 and binding in the cleft formed by the pyridazine and quinoline rings. The substrates listed in Table I which undergo highly enantioselective dihydroxylation (>10:1) are readily accommodated by the type of binding shown for styrene in Figure 2. Poorer selectivity is expected for the others. The *tert*-butyl group of *tert*-butylethylene is too large to fit well in the binding cleft. In the case of 2-methyl-1-heptene, the similar thickness of methyl and *n*-amyl substituents on the ethylenic carbon leads to almost equally good binding in the cleft for the two diastereomeric assemblies leading to enantiomeric diols. Similarly, two diastereomeric complexes of nearly the same stability are expected for *Z*-disubstituted *n*-alkenes, in accord with the observed low enantioselectivities for such substrates.[2]

(6) If the dissymmetry of the pyridazine ring about the C(3)–C(6) axis is removed from consideration, the remainder of **2** would be C_2 symmetric.

Figure 2. CPK model of catalyst **2**-OsO_4 complex and styrene in a position to attach to an axial (red striped) and an equatorial (red) oxygen of OsO_4.

Two further mechanistic points require consideration. First, implicit in the above arguments for the origin of enantioselectivity for dihydroxylation with catalysts such as **1** or **2** is the expectation of slower rates of reaction for pathways not involving snug binding between the olefin and the aromatic cleft, for example those involving the osmium oxygens distal to the quinoline moieties. This expectation is consistent with the known acceleration in the rate of dihydroxylation of olefins with cinchona catalysts as compared to quinuclidine itself.[2c] Second, it seems likely that the preferred mode of [3 + 2] cycloaddition of C=C to Q·OsO_4 is to one axial and one equatorial oxygen rather than to two equatorial oxygens, since the former leads most directly to the experimentally observed geometry for O–OsO_4–olefin adducts (least motion pathway).[7] Thus there is a consistency between the preferred addition of C=C to axial and equatorial Q·OsO_4 oxygens, the geometry of ligand **2** (Figure 1), and the observed facial preference for enantioselective dihydroxylation by **2**·OsO_4 (Figure 2).

It is noteworthy that the methoxy substituent of the Q unit which is coordinated to OsO_4 is part of the binding site of catalysts **1** or **2**. We have prepared a number of analogs of **1** in which the methoxy groups have been replaced by a substituent X and have measured ee values for the catalytic dihydroxylation of styrene by OsO_4.[5] The results are as follows: X = H, 82% ee; X = OMe, 96% ee; X = C_2H_5, 93% ee; X = O-*n*-Bu, 97% ee; X = OTIPS, 50% ee. As expected, enantioselectivity is sensitive to the steric size of the substituent X, with the effectively large (triisopropylsilyl)oxy group having a large adverse effect.[8]

Supplementary Material Available: Experimental and characterization data for new compounds (7 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 for ordering information.

(7) (a) Cartwright, B. A.; Griffith, W. P.; Schröder, M.; Skapsky, A. C. *J. Chem. Soc., Chem. Commun.* **1978**, 853. (b) Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 639. (c) Pathways involving [2 + 2] cycloaddition of olefin to an Os=O linkage (Sharpless mechanism) can be excluded for ligand **2**, most obviously for olefins such as *trans*-stilbene and 1-phenylcyclohexene, because of prohibitive steric repulsion.

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