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Comparing Two Models for the Selectivity in the Asymmetric Dihydroxylation Reaction (AD)

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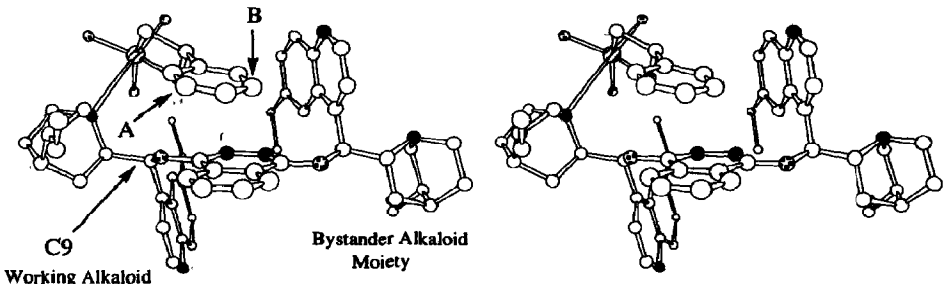
Abstract: Two models of the transition state arrangement for the asymmetric dihydroxylation reaction (AD) with bis-cinchona alkaloid ligands are discussed.

In order to rationalize the high enantioselectivity observed in the asymmetric dihydroxylation reaction (AD) using the bis-cinchona alkaloid class (PHAL and PDZ) of ligands, we[1] and others[2] have proposed and tested working models of the chiral architecture provided by the ligand. Because of its similarity to our model, the most recent Corey-Noe model[3] holds special interest for us. In our model (**1**), the ligand operates from one of its most stable conformers to form a chiral L-shaped binding cleft. The stereo structure below illustrates how the aryl group of styrenes can nestle snugly into the wedge of the binding platform. This

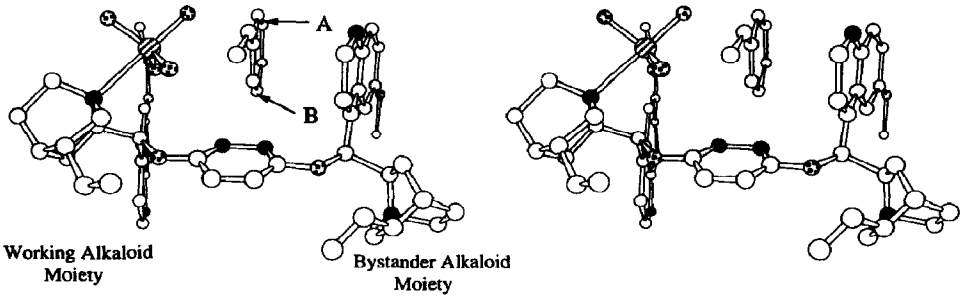


(DHQD)$_2$PHAL-Styrene Osmaoxetane Model (1)

arrangement allows simultaneous, attractive, face-to-face interactions with the highly polarized phthalazine floor, and edge-to-face interactions with the bystander aromatic group.[1a,b] In the styrene system, both the *R* and *S* diastereomeric oxetanes can be stabilized by favorable π–π interactions; however, the pro-*S* diastereomer is destabilized by repulsive interactions between the hydrogen on C9 of the working alkaloid unit and a hydrogen of the metallaoxetane (see ref. 1b for a detailed analysis). This model thus provides a clear basis for the enantioselectivities and rates observed with the bis-cinchona PHAL and PDZ ligand systems.[1]

In its latest iteration, the Corey-Noe model (**2**) features a ligand-osmium environment similar to that found in our proposal, but with two important differences: the location of the styrene in the two models is very different, and Corey and Noe postulate that the aromatic spacer must twist at the transition state to better

accommodate the incoming olefin.[3] The stereo structure below (**2**) shows their model without the invoked rotation of the pyridazine ring. The X-ray coordinates for their bis-methiodide complex[3] were used to produce this representation with one methyl group replaced by an OsO_4 and the iodides omitted for clarity.



Corey-Noe Model (2) (the pyridazine ring has not been rotated)

While their proposed "enzyme-like" transition-state arrangement has aesthetic appeal, fundamental problems exist. First, the proposed twist of the N=C–O–CH torsion angle (estimated at 70° to 90° from their diagrams)[2c,3] required for the pyridazine ring to form the floor of their "U-shaped binding pocket" gives a conformer of such high energy as to be virtually inaccessible. This is intuitive since alkoxy groups connected to such an electron-poor aromatic nucleus clearly prefer a planar, sp^2 configuration to allow conjugation, a preference quantified in note 5 showing relative energy as a function of the N=C–O–CH_3 torsion angle in 1,4-dimethoxypyridazine.[5] Moreover, all single-crystal X-ray data of similar ligand systems display dihedral angles under 12° (most are below 5°) and overall geometries similar to **1** and **2**.[3,4] For these reasons, a twist exceeding 20° at the transition state is unlikely. With such a small twist angle the face of the pyridazine ring cannot provide an effective floor for their pocket. In order to respond to this Corey-Noe model, we adjusted its pyridazine ring to a more reasonable orientation. A striking similarity emerges when comparing this revised model **2** with our proposed structure for osmaoxetane **1**[1d] (derived from high level *ab initio*[1c] and molecular mechanics calculations[1b]), since their molecular architecture is essentially identical (the minor differences are attributable to the substitution on the second quinuclidine nitrogen and the presence of the two iodide ions in the X-ray structure). However, the models differ dramatically in the position of the olefin (compare **1** and **2**). An important discovery made as we examined structure **2** using the "MacroModel" program is that both pro-(*R*) and pro-(*S*) approaches present very similar interactions with only a small rotation about the Os-nitrogen bond axis. In fact, while (*R*)-styrene diol is the observed product, the pro-(*S*) configuration appears to achieve better surface overlap with the arenes of the pocket in **2**, so the prediction of facial selectivity is not readily apparent from this model.

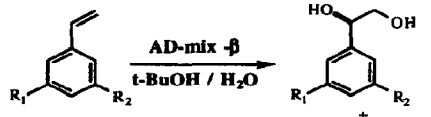
Their "sandwich binding" pocket is a misnomer: the working quinoline ring, in **2** is too far away to provide a significant wall, and the majority of transition state stabilization would be provided by only one face-to-face interaction with the bystander methoxyquinoline, and this interaction declines as the olefin unit of the substrate approaches the osmium for the [3+2] cycloaddition. Moreover, for non-charge transfer π–π interactions, the edge-to-face orientation can be more stabilizing than the face-to-face counterpart.[6] In summary, the stabilizing interactions appear to be superior for a transition state resembling **1** rather than **2**.

Corey and Noe's single crystal X-ray analysis of their adipate-bridged PDZ analog indicates that it also adopts a structure very similar to **1** and **2**.[3] Our model provides reasonable structures corresponding to both [3 + 2][7a] and [2+2][7b] cycloadditions in this ligand environment, so, contrary to their claim,[2c] the data presented for this bridged-ligand does not exclude a [2+2] mechanism involving an osmaoxetane.

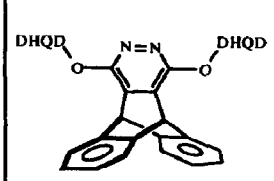
To further test our model, we synthesized a series of substituted styrenes, two of which are shown below (**Table 1**).[8] Since **1** shows there is room for a bulky group at position **A**, our model predicts enantioselectivity comparable to that of styrene for such a substrate (e.g. **ii**). With bulky groups at positions **A** and **B** (e.g. **iii**), the bystander methoxyquinoline would be forced aside, terminating the edge-to-face interactions and lowering the ee below that for styrene. In a transition-state structure similar to **2**, a large group at position **A** faces unfavorable interactions with the methoxy substituent on the working quinoline unit as the olefin approaches the OsO_4•L moiety, which should lead to a lower ee than that for the parent styrene (also see **Figure 2** in ref. 2c). The results for 3-*tert*-butyl styrene (**ii**) are consistent only with our model (**Table 1**). More convincing still is the datum for 3,5-di-*tert*-butyl styrene (**iii**), since a bulky group is now forced to reside at position **B** which should completely disrupt the binding pocket they propose. A moderate ee results nonetheless, a finding consistent with our model, but not model **2**.

Ligand modification provides another probe for distinguishing between the two models. Ligand **3** was synthesized and molecular mechanics calculations suggest that it adopts a conformation very similar to that shown for the PHAL and PDZ ligands in models **1** and **2**. The non-planar portion of the heterocyclic spacer in **3** encroaches on the binding cleft in model **1** but should have no effect on the binding pocket in model **2**. When ligand **3** was used in the AD of styrene, a significant drop in selectivity was seen (last entry in **Table 1**), consistent once again with our model, but not that of Corey and Noe.

Table 1 Asymmetric Dihydroxylation of Some Substituted Styrenes



	R_1	R_2	ee % at 0°C	$\Delta\Delta G^{\ddagger}$/Kcal mol^{-1}
(i)	H	H	97	2.3
(ii)	H	^{t}Bu	95	2.0
(iii)	^{t}Bu	^{t}Bu	49	0.6
			With Ligand **3**	
	H	H	87	1.4



3

Unlike the "U-shaped pocket" of the Corey-Noe model, the L-shaped cleft of ligand-architecture **1** is affirmed by the large volume of experimental data[1] and provides excellent predictive ability in PHAL-type systems for new olefinic substrates. Further, our model accounts for the enantiofacial selectivities observed in our first-generation ligands (CLB, PHN, MEQ, etc). Since these ligands contain only "floor" units and lack bystander aromatic groups, the Corey-Noe model cannot explain the selectivities observed in these systems.[9,10]

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Industrie (postdoctoral fellowship for HB), and the Deutsche Forschungsgemeinschaft (postdoctoral fellowship for HCK).

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1 (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278; (b) Norrby, P.-O.; Kolb, H. C., Sharpless, K. B. *J. Am. Chem. Soc.* in press; (c) Norrby, P.-O.; Kolb, H. C., Sharpless, K. B. *Organometallics* **1994**, *13*, 344; (d) The oxetane presented here could equally well be represented as a glycolate ([3+2] addition) for the structural environment and stabilizing interactions will be very similar in both cases. (e) Loren, S.; Sharpless, K.B. manuscript in preparation.

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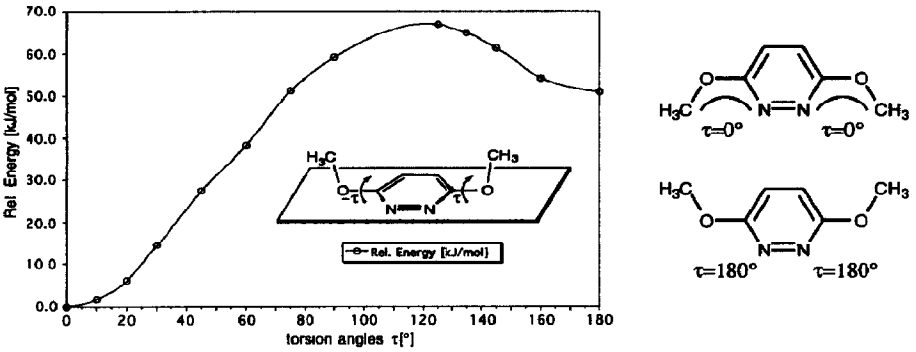
5 Conformers of 1,4-dimethoxypyridazine were calculated using direct *Hartree-Fock* calculation ([6-31G*] basis set, *SPARTAN 3.1* on an *IRIS INDIGO*). Both methoxy units were synchronously turned to the desired N=C–O–CH_3 torsion angle. The geometry was then optimized in C_S-symmetry at each point with only the aforementioned torsion angle fixed. The relative energies of the single point MP2 (6-31G*) calculations of the optimized structures shown in *Figure 1* are given relative to the 0° energy.



A similar calculation with 1,4-dimethoxyphthalazine (HF 3-21G(*))shows matching behavior for torsion angles between 0° and ~60° and *much* higher energies for all torsion angles higher than ~60°. Similar calculations have been done for anisole and phenol: Spellmeyer, D.C.; Grooenhuis, P.D.J; Miller, M.D.; Kuyper, L.F.; Kollman, P.A. *J. Phys. Chem.* **1990**, *94*, 4483; Kim, K.S.; Jordan, K.D. *Chem. Phys. Lett.* **1994**, *218*, 261.

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8 The reactions were carried out as described in 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*, 2768-2771.

9 In order to help the reader appreciate the three dimensional aspects of both models, we will be glad to supply coordinates for all structures presented herein. Please e-mail requests to sharpless@riscsm.scripps.edu.

10 All new compounds gave satisfactory analytical and spectroscopic data.

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