dimethyl-1,6-octadiene, 10281-55-7; (3R)-3,7-dimethyl-1,6-octadiene, 10281-56-8; (R)-3-hydroxy-3,7-dimethyl-1,6-octadiene, 126-91-0; (3R,4S)-4-hydroxy-3,7-dimethyl-1,6-octadiene, 138332-65-7; (E)-8-methyl-2,7-nonadienoic acid methyl ester, 68654-11-5; (Z)-8-methyl-2,7-nonadienoic acid methyl ester, 68654-13-7; (E)-5,5,8-trimethyl-2,7-nonadienoic acid methyl ester, 104315-11-9; (Z)-5,5,8-trimethyl-2,7-nonadienoic acid methyl ester, 104315-12-0; *trans*-1,7-nonadiene, 13150-98-6; *cis*-1,7-nonadiene, 92230-16-5; 8-methyl-1,7-nonadiene, 90975-99-8; (3R)-3,8-dimethyl-1,7-nonadiene, 138260-68-1; (S)-3-hydroxy-3,8-dimethyl-1,7-nonadiene, 138260-69-2; (3S,4R)-4-hydroxy-3,8-dimethyl-1,7-nonadiene, 138260-70-5; (3R,6R)-3,6,8-trimethyl-1,7-nonadiene, 138260-71-6.

Supplementary Material Available: Archive entries of the ab initio calculations (6 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.

A New Model for the Stereoselectivities of Dihydroxylations of Alkenes by Chiral Diamine Complexes of Osmium Tetraoxide

Yun-Dong Wu, Ying Wang, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024

Received June 27, 1991 (Revised Manuscript Received December 2, 1991)

A symmetrical five-membered transition structure model for the dihydroxylations of alkenes by chiral diamine complexes of osmium tetraoxide has been developed based on X-ray crystal structures of OsO_4–amine complexes and osmate esters and ab initio transition structures of analogous reactions. The MM2 calculations based upon this model reproduce the stereoselectivities observed with a variety of chiral diamine ligands. Some predictions are also made using this force field.

Introduction

Highly enantioselective hydroxylations of alkenes by osmium tetraoxide, in the presence of chiral amines, have been discovered by several research groups. Examples of the chiral amine ligands are shown in Figure 1.[1-5] The presence of amine ligands accelerates the reaction rate in each case, but only Sharpless' ligand 1 leads to true catalysis. These reactions are important practically and serve as prototypes of a highly sought reaction type: enantioselective catalytic oxidations of hydrocarbons without functional groups.[6] Several different qualitative models have been proposed to explain the degree and sense of stereoselectivities obtained with various amines.[2,3] Sharpless and Gutierrez have recently used force-field calculations to support a two-step mechanism in which the rearrangement of a reversibly formed metallocyclic intermediate determines the stereoselectivity.[7] We have developed a new working model based upon considerations of crystal structures of reactants and products, as well as knowledge of calculated transition structures of related compounds. The model is qualitative, but we have nevertheless shown that a simple molecular mechanics force field provides semiquantitative predictions in accordance with available experimental results. While these results do not prove the mechanism of the reaction or of stereocontrol, they do give a transition state consistent with all of the available data and predictions to test the model. As a more varied set of alkenes is studied, more demanding challenges of the model will be offered, and the model can be further refined.

Background

Two mechanisms have been proposed for the reaction of OsO_4 with alkenes (Figure 2).[8] One is direct addition of both oxygens to the termini of an alkene double bond via a concerted five-membered cyclic transition state **5**. Jorgensen and Hoffmann's molecular orbital analysis indicated that such a reaction is an allowed process.[9] The other mechanism, proposed by Sharpless and co-workers,[10] involves a fast reversible [2 + 2] cycloaddition of the alkene C=C to a Os=O bond to form a four-membered metallocyclic intermediate **7**; this subsequently undergoes rate-determining rearrangement to form the osmate product **6**.

Either mechanism can rationalize the rate acceleration caused by amines; amine coordination causes distortion

(1) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, 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. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (c) Svendsen, J. S.; Marko, I.; Jacobsen, E. N.; Pulla Rao, C.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2264. (d) Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 639. (e) Sharpless, K. B.; Ambery, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.

(2) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.

(3) (a) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (b) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573. (c) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741.

(4) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. Hirama, M.; Oishi, T. *J. Chem. Soc., Chem. Commun.* **1989**, 665.

(5) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefenelli, S. *Ibid.* **1987**, *28*, 3139.

(6) For epoxidation: (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116. (c) Naruta, T.; Tani, F.; Maruyama, K. *Chem. Lett.* **1989**, 1269. (d) Sinigalia, R.; Michelin, R. A.; Pinna, F.; Strukul, G. *Organometallics* **1987**, *6*, 728. (e) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (f) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (g) Tani, K.; Hanafusa, M.; Otsuka, S. *Tetrahedron Lett.* **1979**, 3017. For hydroborations: (h) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. For hydrogenation: (i) Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E.; Bläser, D.; Boese, R. *J. Am. Chem. Soc.* **1987**, *109*, 8105.

(7) K. B. Sharpless and A. Gutierrez reported at 200th National Meeting of the American Chemical Society, Washington DC, Aug 29, 1990.

(8) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.

(9) Jorgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867.

(10) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. Sharpless, K. B.; Teranishi, A. Y. *Ibid.* **1977**, *99*, 3120.

0022-3263/92/1957-1362$03.00/0

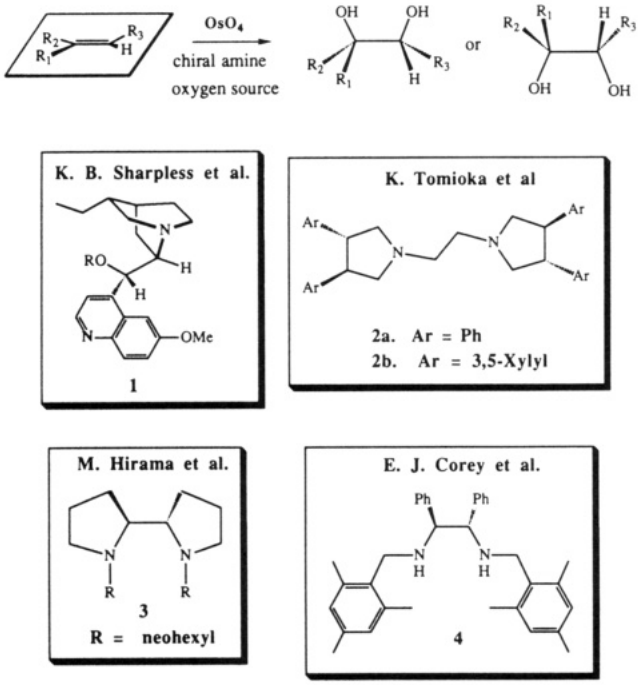

Figure 1. Examples of chiral amines for enantioselective dihydroxylation of alkenes by osmium tetraoxide.

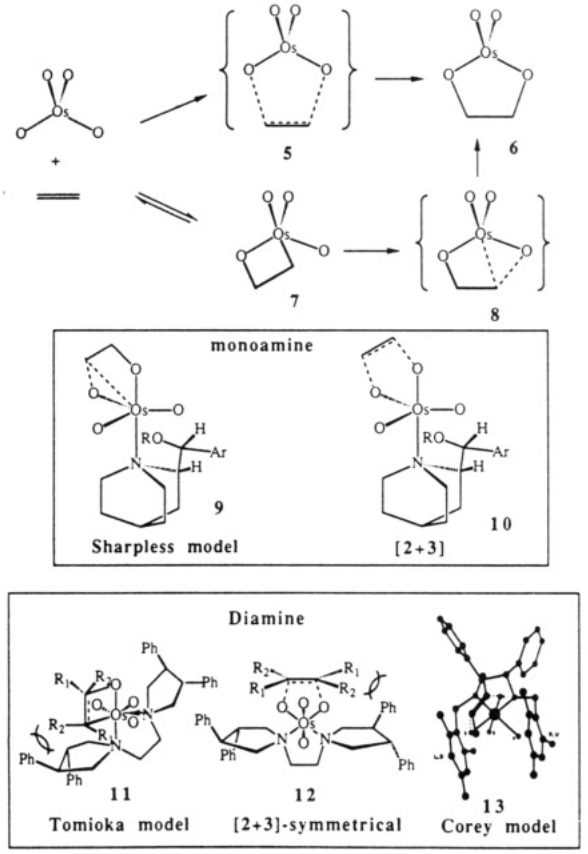

Figure 2. Proposed mechanisms and transition states for the dihydroxylation of alkenes by OsO_4–amine complexes.

of the OsO_4 geometry to a more reactive form according to Jorgensen and Hoffmann's calculations;[9] this distorted geometry resembles the transition-state geometry. That is, the transition state is stabilized more than the reactants by amine coordination. However, the stereochemical outcome via the two mechanisms has been suggested to be distinguishable. In the case of chiral amine **1**, Sharpless et al. suggested the transition structure model shown by

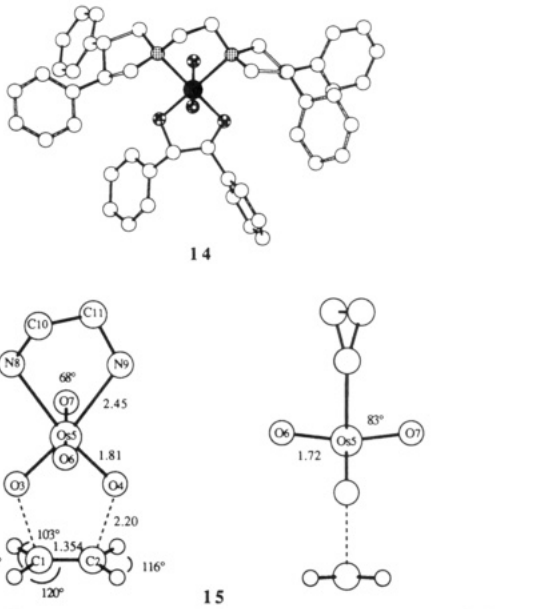

Figure 3. X-ray structure of the major osmate of **2a**·OsO_4–stilbene reaction, **14**,[15] and MM2 transition structure model, **15**, for the reaction of alkene with the OsO_4–diamine complex.

9. The osmium center is approximately trigonal-bipyramidal. The migrating C atom is partially bonded to O and Os. There are three possible orientations for the alkene moiety, depending on which equatorial O of OsO_4 is involved, and the preferred orientation is determined by the steric interactions with the chiral amine. Force-field calculations indicated that this model predicts the correct stereoselectivity.[7] Sharpless et al. also found that a transition-structure model resembling the four-membered intermediate **7** does not give the correct stereoselectivity. The alternative [2 + 3] concerted transition structure is represented by **10**.

When a diamine is involved in the reaction, both nitrogens are likely to be coordinated in the transition structure, since a diamine accelerates the oxidation reaction much more than a monoamine.[3] The X-ray crystal structure of the osmate products of the **2a**·OsO_4–stilbene and **3**·OsO_4–stilbene reactions are nearly symmetrical;[3,4] that is, the two forming O–C bonds involve equatorial oxygens as in **14**, the major osmate of **2a**·OsO_4–stilbene reaction. Tomioka et al. suggested that a symmetrical transition-structure model resembling this osmate coordination would predict the wrong stereoselectivity, since the major product observed experimentally seems to be sterically more crowded with regard to the phenyl group interactions as represented in **12**.[3] This led them to the conclusion that the reaction occurs by the stepwise mechanism. They proposed a transition-state model **11** similar to the four-membered intermediate to account for the observed stereoselectivity.[3] In this structure, one amine is anti to the Os–O bond in the four-membered ring, while the other amine is coordinated to Os from the least crowded direction. The minor product (R_1 = H, R_2 = Ph) is destabilized by the interaction indicated in the drawing.

Corey et al. favor the five-membered transition-state model.[2] They suggested that a four-centered transition structure would be disfavored by severe steric crowding, and a symmetrical transition structure model, **12**, would predict the wrong stereoselectivity for the Corey ligand. Because of this, they proposed that the alkene is attacked by one equatorial oxygen and one axial oxygen as shown by **13**. They suggested that such a transition state is electronically favorable as well.[2] The stereoselectivity with

this model is suggested to be well defined, since there is only one sterically feasible approach of the alkene.[2]

MM2 transition structure modeling has been successfully applied to the understanding of stereoselectivities in a variety of organic reactions.[11] In this paper we present the application of such modeling to the stereoselective reactions of dihydroxylations of alkenes by osmium tetraoxide mediated by chiral amines **2–4**.[12] We have chosen to test a symmetrical five-membered transition structure, **12**, based upon the following considerations. (1) Since osmate products have the symmetrical five-membered ring geometries, this must represent a favorable steric and electronic arrangement. (2) Hoffmann and Jorgensen's calculations suggested that the five-membered transition-structure model is a possible reaction pathway and the coordination of two pyridines in the manner of **12** facilitates the reaction.[9] (3) Arguments against the transition-structure model **12** are based on the assumption that the steric interactions in the transition structure are similar to those in the osmate product. Our calculations suggest that the steric interactions in the transition structure are quite different from those in the osmate product. As will be shown, the force-field model reproduces the observed stereoselectivities reasonably well, at least for the relatively limited set of data currently available.

MM2 Transition Structure Model

We have generally used ab initio transition structure geometries to build MM2 transition structure models in our previous modeling studies.[11] However, such ab initio calculations are beyond our present computational abilities for the current enormous reaction. In the present case, we constructed the MM2 transition-structure model based on geometrical information from analogous transition structure, as well as X-ray and ab initio structures of osmates (e.g., **14**) and amine–OsO_4 complexes.

As shown in **15**, the parameters for the alkene moiety were adapted from the transition structure of the ethylene–fulminic acid reaction.[13] The two forming C---O bonds were set to 2.2 Å, resembling the partially-formed C---O bonds in many pericyclic reaction transition structures.[14] The C=C bond was set to 1.354 Å. The two C centers are somewhat pyramidalized. The geometry around the Os atom came from the X-ray structure of an osmate ester.[15] The two in-plane Os–O_3 and Os–O_4 bonds were set to 1.81 Å, somewhat longer than normal Os–O double bonds (1.72 Å). The two Os–N bonds are 2.45 Å, which is somewhat shorter than the Os–N bond in a complex.[16] The N–Os–N angle is taken as 68°, so that the N---N distance is about 2.7 Å, which is close to nonbonded N---N distances in gauche conformations of diamines. We used a fixed transition structure model, that is, the atoms 1–5 and 8–9 were restricted in a plane, and the positions were not optimized. This choice is based on the following reasons. Since the MM2 program used in the present study only handles coordination number up to four,[17] we have to treat the Os center in a special way: the atoms O_3, O_4, Os_5, N_8, and N_9 were fixed in a plane, which is in accordance with the situation in the X-ray structure **14**; the two axial O atoms (O_6 and O_7) were fixed at the positions shown. We expect that the attack of the two oxygens on the alkene C=C bond is nearly coplanar, in order to maximize orbital overlap. Our experience on the modeling of stereoselectivities of intermolecular hydroborations,[18a] nitrile oxide cycloadditions,[18b] indicate that the fixed planar transition-structure model works reasonably well.

Since atoms 1–9 were fixed, the choice of force constants for these atoms becomes unimportant. No lone pairs were included on oxygens. The dipoles for Os–N and Os–O bonds were set to zero, since the interactions involving these bonds with alkene substituents do not affect calculated stereoselectivity due to the symmetrical feature of the transition structure. The VDW parameter for Os was arbitrary set to that of C_{sp^3}, for the same reason given above. Allinger's bond dipoles for the phenyl group were used.[19] Since the alkene double bond is only partially broken in the transition structure, partial conjugation between the double bond and phenyl substituent is expected. The rotation barrier for styrene was recently calculated to be about 2.5 kcal/mol.[20] This barrier to rotation can be reproduced by MM2 calculations by setting the V_2 torsional parameter for the C_1–C_2–C_3–C_4 dihedral angle to 3.5. We assumed that the overlap stabilization in the transition structure is somewhat smaller and incorporated this feature into the model by adjusting the V_2 torsional parameters for dihedral angles C_{sp^2}–C_{sp^2}–C_{Ph}–C_{Ph} and O–C_{sp^2}–C_{Ph}–C_{Ph} to be 2.0 and −0.5, respectively.

In calculating the osmate products (**26**, **27**, **32**, and **33**), the equilibrium bond lengths and bond angles were adapted from the X-ray structure **14**. All atoms were fully optimized except for atoms 3–5 and 8–9 which were restricted in a plane and O_6 and O_7 which were fixed. The Os_5 was treated as a C_{sp^3} in determining bending force constants and torsional parameters.

Results and Discussion

1. The Tomioka Chiral Diamine 2. We first applied the model to the **2**·OsO_4 systems. Structure **16** is the front view of the **2a**·OsO_4–ethylene MM2 transition structure. The Os–N–C–C–N five-membered ring is in a twist conformation, which is shown more clearly in the side view **17**. Since the transition structure has C_2 symmetry, only the front pyrrolidine ring is displayed for clarity. The pyrrolidine ring adopts an envelope conformation. The

(11) (a) Houk, K. N.; Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (c) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. (d) Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 906. (e) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (f) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (g) Dorigo, A. E.; Houk, K. N. *Adv. Molecular Modeling* **1988**, *1*, 135. (h) Dorigo, A. E.; Houk, K. N. *J. Org. Chem.* **1988**, *53*, 1650. (i) Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698. (j) Broecker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651.

(12) Corey et al. have proposed a dimeric transition structure model to rationalize the stereoselectivity using Sharpless' chiral amines **1**: Corey, E. J.; Lotto, G. *Tetrahedron Lett.* **1990**, *31*, 2665. A working model by Sharpless et al. is also found in ref 1e.

(13) Brown, F. K.; Ramondi, R.; Wu, Y.-D.; Houk, K. N. Submitted for publication.

(14) (a) Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6947. (b) Vance, R. L.; Rondan, R. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314. (c) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.*, in press.

(15) We thank Professor Tomioka for sending us X-ray data of the crystal structure, **14**, of the major osmate of **2a**·OsO_4-*trans*-stilbene reaction.

(16) The Os–N distance in **1**·OsO_4 is 2.48 Å; see ref 1c; the Os–N distance in the OsO_4–quinuclidine complex is 2.39 Å; see: Griffith, W. P.; Skapski, A.-C.; Woode, K. A.; Wright, M. *J. Inorg. Chim. Acta* **1978**, *31*, L413. The calculated Os–N distance in OsO_4–NH_3 using the LANL1DZ basis set is 2.55 Å.

(17) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Quantum Chemistry Program Exchange No. 406. Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1980.

(18) (a) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257. (b) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754.

(19) Allinger, N. L.; Lii, J.-H. *J. Comput. Chem.* **1987**, *8*, 1146.

(20) Tsuzuki, S.; Tanabe, K. *J. Phys. Chem.* **1990**, *94*, 6175.

Table I. Calculated and Experimental Stereoselectivities of Dihydroxylation of Alkenes by OsO_4 Complexed to Ligands 2a and 2b. The *S* or *R* in Parentheses Indicates the Configuration of the Major Product

		ligand **2a**		ligand **2b**	
entry	substrate	exp[a] ΔG (kcal/mol)	calcd ΔE (kcal/mol)	exp[a] ΔG (kcal/mol)	calcd ΔE (kcal/mol)
1	allylbenzene	0.4 (*S*)	0.4 (*S*)	0.4 (*S*)	0.7 (*S*)
2	(*E*)-methylstyrene	1.0 (*SS*)	0.9 (*SS*)	0.1 (*SS*)	0.0
3	styrene	0.6 (*S*)	0.7 (*S*)	0.5 (*R*)	0.5 (*R*)
4	(*E*)-stilbene	1.3 (*SS*)	1.5 (*SS*)	0.5 (*RR*)	1.1 (*RR*)
5	(*E*)-3-hexene	1.0 (*SS*)	0.9 (*SS*)		1.3 (*SS*)
6	3,3-dimethyl-1-butene		0.8 (*S*)		0.1 (*S*)
7	4-methylstyrene		1.0 (*S*)		0.1 (*S*)
8	2,4,6-trimethylstyrene		0.3 (*R*)		0.8 (*R*)

[a] The experimental ΔG's are calculated according to reported ee% values in toluene at −100 °C[3] except for entry 5, which was the value in THF at −100 °C.

phenyl groups occupy pseudoequatorial positions and are eclipsed with the benzylic C–H bonds. The two pyrrolidine rings are not symmetrical about the transition structure plane. The N–C bonds are pseudoaxial and pseudoequatorial about the Os–N–C–C–N ring, respectively. As a result, the upward phenyl group, which is on the right-hand side in **17**, is closer to the reaction plane, while the downward phenyl is extended away from the plane. Therefore, the downward phenyl causes less steric crowding than the upward phenyl. In general, alkyl substituents on an alkene should prefer the two positions as indicated in **16**. This qualitative prediction is opposite to the qualitative analysis of Tomioka et al., as mentioned earlier.[3]

Table I summarizes the predictions by the transition-structure model along with experimental results for several alkene reactions.[21] Overall, the predictions agree with the experimental observations reasonably well. With the (*R*,*R*)-diamine, allylbenzene and styrene reactions are calculated to give 0.4 and 0.7 kcal/mol preferences for the formation of *S* products, respectively, compared to 47% ee and 71% ee observed experimentally.[3] The calculated stereoselectivities are additive; namely, the stereoselectivities for trans-disubstituted alkenes double those of monosubstituted alkenes. Figure 4 gives transition structures of reaction of **2a**·OsO_4 with styrene. Structure **18** is more stable than **19** by 0.7 kcal/mol. The energy difference between the two structures is solely from VDW interactions, presumably due to the interactions in **19**.[22]

The observation of Tomioka et al. that stereoselectivity can be changed dramatically by a small change in the diamine ligand is most intriguing.[3] Ligand **2b** is different from **2a** by the addition of methyl groups at the 3 and 5 positions of each phenyl group. While the stereoselectivity is essentially not affected for the reaction of allylbenzene, the stereoselectivities of reactions of styrene and stilbene are opposite in the presence of **2a** and **2b** (Table I). The MM2 model calculations qualitatively reproduce these results, as given in Table I. Structures **20** and **21** are the MM2 transition structures for the reaction of **2b**·OsO_4–propene. The methyl groups of the diamine do not sterically interact with the alkene methyl in either structure, and the stereoselectivity is affected only slightly. Structures **22** and **23** are the MM2 transition structures for the reaction of **2b**·OsO_4–styrene. While the alkene phenyl

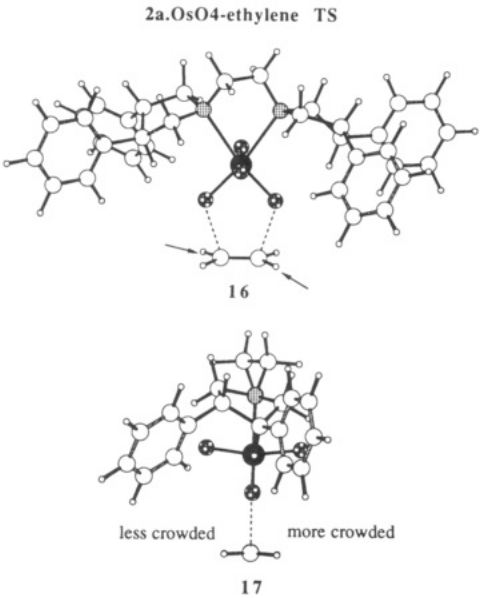

Figure 4. Front and side views of MM2 transition structure for the reaction of ethylene with **2a**·OsO_4 complex. In **17** only the front pyrrolidine is displayed. The arrows in **16** indicate favorable positions for substituents.

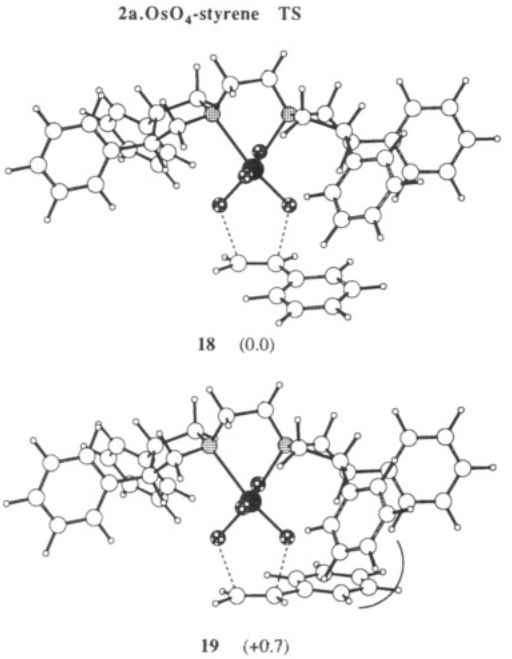

Figure 5. Transition structures for the reaction of styrene with **2a**·OsO_4 complex.

(21) In responding to a reviewer's suggestion, we also carried out calculations for the reactions of propene and styrene with a twist transition structure model by rotating the alkene moiety around the C_2 axis of **15** by 10°, so that the O_3–C_1–C_2–C_4 dihedral angle is 20°. The calculated stereoselectivities are 0.1 and 0.8 kcal/mol for propene and styrene, respectively, which compares favorably with 0.3 and 0.7 kcal/mol calculated with the planar transition structure model.

(22) The two transition structures for the reaction of allybenzene do not seem to be crowded; and the energy difference may be due to the difference in attractive VDW interactions between the methyl and phenyl groups.

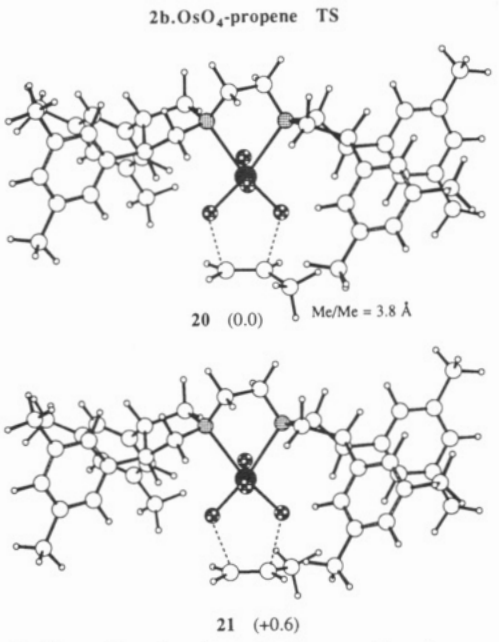

Figure 6. Transition structures for the reaction of propene with **2b**·OsO_4 complex.

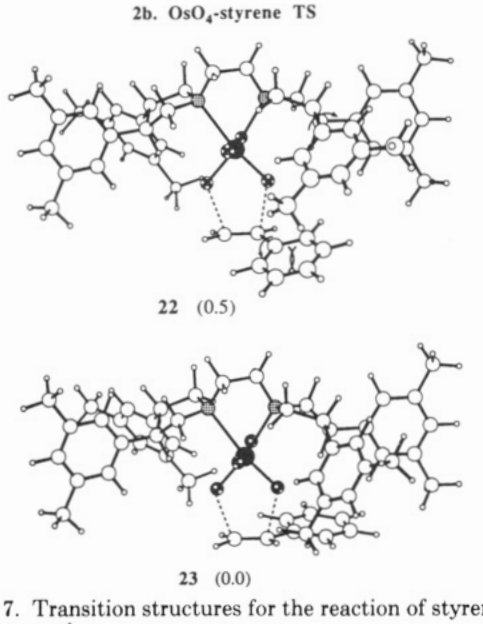

Figure 7. Transition structures for the reaction of styrene with **2b**·OsO_4 complex.

group in **23** does not suffer significantly from steric interactions with the diamine methyl groups, structure **22** is destabilized considerably by the Ph/Me interactions, resulting in reversed stereoselectivity. This is indicated by the rotations of the two interactive phenyl groups in order to minimize the interactions.

Table I also includes some predictions. The most interesting prediction is for the reaction of 2,4,6-trimethylstyrene. The trimethyl phenyl group is sterically much more demanding than a phenyl group. With **2a**·OsO_4, this compound is predicted to give a small preference for the formation of the minor enantiomer of the styrene reaction. Unlike styrene, the same sense of stereoselectivity is predicted for the compound if diamine **2b** is applied. This anomaly can be readily explained by steric interactions of the present model. As shown in Figure 8, when the diamine is **2a**, the introduction of the three methyl groups in **25** does not cause much additional steric crowding with the diamine unit. However, steric crowding

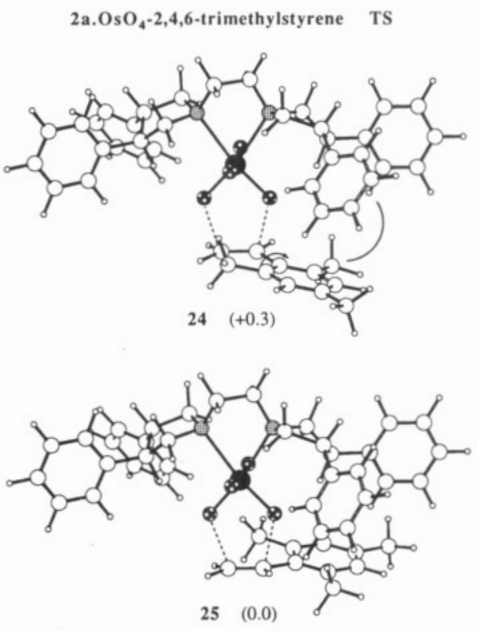

Figure 8. Transition structures for the reaction of 2,4,6-trimethylstyrene with **2a**·OsO_4 complex.

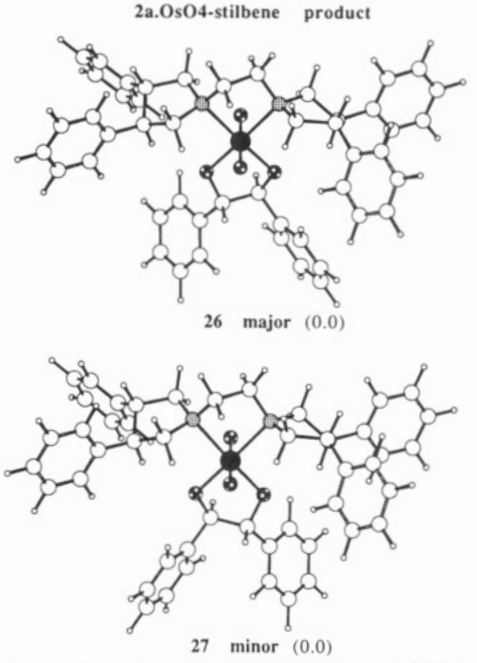

Figure 9. MM2-optimized adducts of the **2a**·OsO4–stilbene reaction.

in **24** is increased considerably by the backward methyl, which interacts sterically with the upward phenyl, as indicated. This is clearly indicated by the rotation of the trimethyl phenyl group in **24** as compared to structure **18**. This steric crowding becomes even more severe in structure **24** if the diamine is replaced by **2b**.

Structures **26** and **27** are MM2-optimized structures of osmates of the **2a**·OsO_4–stilbene reaction. Structure **26**, which corresponds to the major product, is very similar to the X-ray crystal structure **14** reported by Tomioka et al.[3] The only differences in the X-ray crystal structure are the rotations of the two left-hand side diamine phenyl groups, which could be due to crystal packing forces. Besides the shortening of the two forming C–O bond lengths, two major geometrical changes occur when the transition structure is converted to the osmate. One is the twisting of the forming Os–O–C–C–O ring from planar to

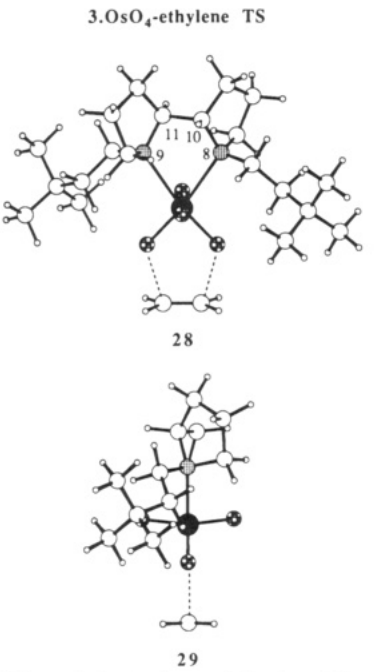

Figure 10. Side and front views of the transition structure of reaction of ethylene with $3\cdot OsO_4$ complex. In **29** only the front amine substituents are displayed.

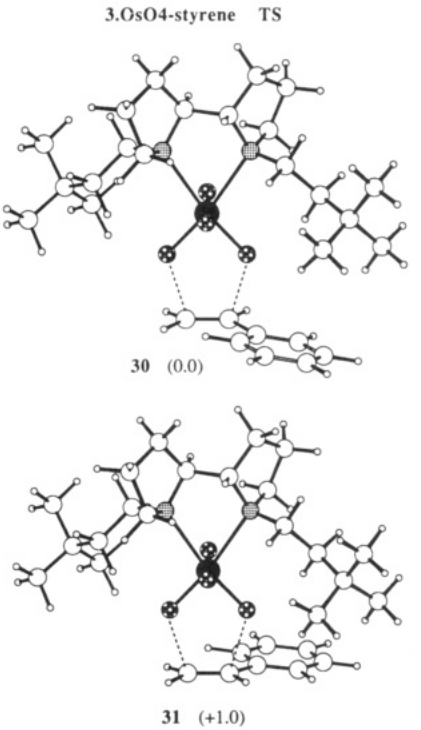

Figure 11. Transition structures for the reaction of styrene with $3\cdot OsO_4$ complex.

a twist-boat conformation. The other is the rotation of the phenyl groups of stilbene; in the transition structure, the phenyls are nearly coplanar with the C–C bond; in the osmate, the phenyls become nearly perpendicular to the C–C bond. As a result, the steric interactions with the upward phenyls are partially avoided in structure **27**. On the other hand, the two same-side phenyl groups in structure **26** are brought closer, and steric interactions are introduced. The calculations gave identical stability to the two structures, in accord with Tomioka and Koga's observation that the two diastereomeric osmate products are in a 1:1 equilibrium.[3] Thus, the steric interactions in the osmate products are quite different from those in the transition structure models.

2. The Hirama Chiral Diamine 3. Structure **28** is the front view of the transition structure of the $3\cdot OsO_4$–ethylene reaction. The structure possesses C_2 symmetry. The two neopentyl groups are anti to the N_8–C_{10} and N_9–C_{11} bonds, respectively. This structure is much more stable than the other rotamers of the two neohexyl groups. Structure **29** is a side-view of **28**, with only the front neohexyl group displayed. Overall, the neohexyl group is on the left side of the transition-structure plane. At first glance, one would expect that the left-hand side is blocked, leading to stereoselectivity opposite to what is actually observed.[5] MM2 calculations, however, indicate that substituents such as methyl, phenyl, and carboxylate groups prefer the left-hand side, reproducing qualitatively the stereoselectivity observed. Structures **30** and **31** are the two transition structures for the reaction of styrene. Structure **30**, which has the phenyl and neohexyl groups on the same side, is calculated to be about 1 kcal/mol more stable than structure **31**. The same sense of stereoselectivity was predicted for propene and methyl acrylate, but with smaller magnitudes (0.2 and 0.5 kcal/mol, respectively, Table II). Once again, the stereoselectivity is twice as large for trans-disubstituted alkenes.

The calculated preference for the structure **30** is from VDW interactions, indicating that the neohexyl group causes more steric crowding for the substituent in **31**. It is not completely clear why this should be so. The calculations with *N*-ethyl groups instead of *N*-neohexyl groups give the same sense of stereoselectivity; once again, this agrees with experiment.[4] It is interesting that the *tert*-butyl substituent on the alkene is predicted to give low, but reversed stereoselectivity. In this case, the neohexyl and *tert*-butyl groups have effective contact when they are on the same side of the transition-state plane.

Table II. Calculated and Experimental Stereoselectivities of Dihydroxylation of Alkenes by $3\bullet OsO_4$

entry	substrate	expt[a] ΔG (kcal/mol)	calcd ΔE (kcal/mol)
1	1-heptene	1.2 (*S*)	0.3 (*S*)
2	(*E*)-3-hexene	1.5 (*SS*)	0.6 (*SS*)
3	styrene	1.1 (*S*)	1.0 (*S*)
4	stilbene	>2.0 (*SS*)	2.1 (*SS*)
5	dimethyl fumarate	1.9 (*RR*)	1.0 (*RR*)
6	3,3-dimethyl-1-butene		0.1 (*R*)

[a] The ΔG's are calculated according to reported ee%[4] in toluene (entries 3 and 4) or CH_2Cl_2 (entries 1, 2 and 5) at −78 °C.

The osmate products of the reaction of stilbene have also been optimized with the MM2 force field. Structure **32**, which corresponds to the major product, is quite similar to the X-ray crystal structure reported by Hirama et al.[4] By contrast to the **2a**·OsO4–stilbene case, where the two products have identical stability, the structure **32** is calculated to be about 1 kcal/mol more stable than structure **33**, which corresponds to the minor product. Thus, the relative stabilities of the two products are of the same sense as in the two transition structures, but with a reduced magnitude.

3. The Corey Chiral Diamine 4. Drawings **34** and **35** are two MM2-calculated transition structures for the reaction of $4\cdot OsO_4$ with ethylene. Structure **35**, which has two pairs of parallel 1,3-diaxial phenyl–phenyl interactions as indicated, is calculated to be less stable than **34** by about 1 kcal/mol. This is mainly caused by a destabilizing π-stacking effect in **35**.[16] This effect is calculated by assigning 0.9 and 0.3 Debye dipoles to C(Ph)–C and C(Ph)–H bonds.[16] Without the dipole interactions, **35** is calculated

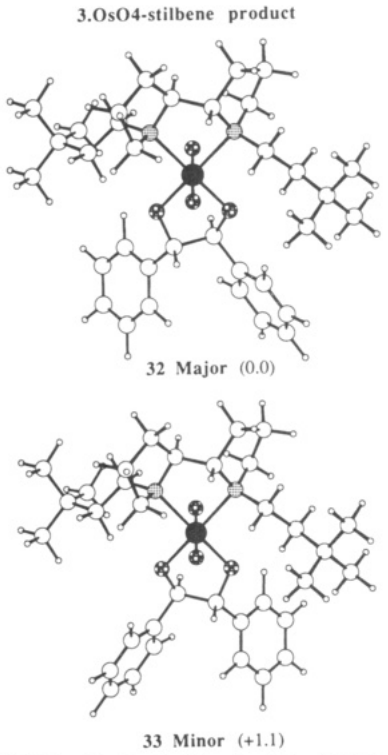

Figure 12. MM2-optimized adducts of the 3·OsO_4–stilbene reaction.

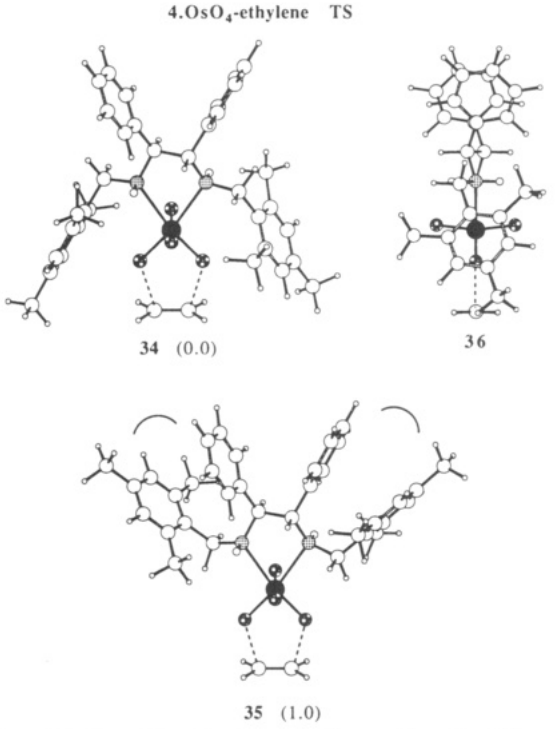

Figure 13. Transition structures for the reaction of ethylene with 4·OsO_4 complex. Structure **36** is a side view of structure **34**, with only the front mesityl group displayed.

to be more stable than **34** by 2 kcal/mol. The preference of **34** is in accord with Corey's deductions about the nature of the 3·OsO_4 complex.[2] In addition, the amine ligand in **35** is far away from alkene moiety. As expected, calculations with this model give no stereoselectivity. Therefore, the following discussions are only based on the calculations with **34**.

Interestingly, the conformations of the two mesityl groups in **34** are quite different from that in **13**, the model

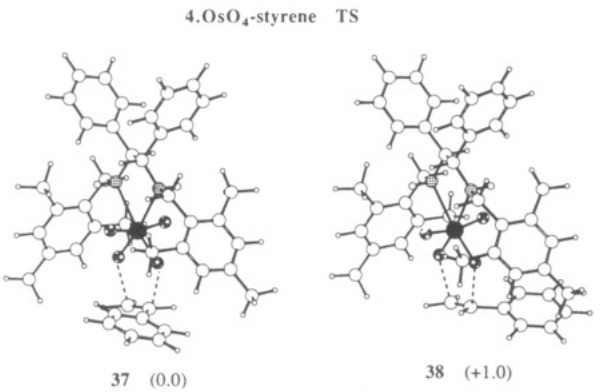

Figure 14. Transition structures for the reaction of styrene with 4·OsO_4 complex.

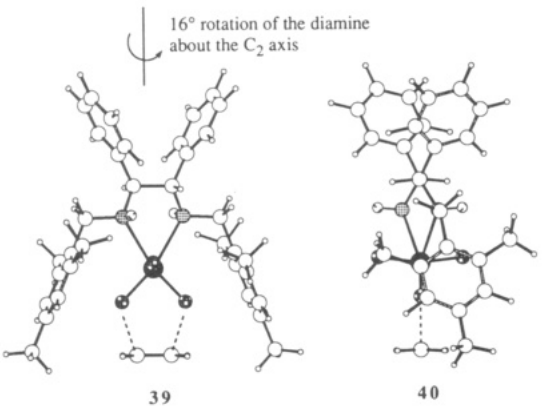

Figure 15. The structure derived from 16° rotation of the diamine about the C_2 axis of structure **34**.

proposed by Corey et al. The two mesityl groups are spread apart so that the attack of the ethylene on O_3 and O_4 is not blocked. Structure **36** is a side view of structure **34**, in which only the front mesityl group is displayed. It is interesting that the front mesityl group, which would be expected to be on the left-hand side, mostly covers the right-hand side and the back mesityl mostly covers the left-hand side, which is not shown. This conformational feature has a significant consequence on stereoselectivity. For the reaction of styrene, the MM2 calculations give about 1 kcal/mol preference for transition structure **37**, in which the mesityl–phenyl steric interaction is absent. On the other hand, structure **38** apparently suffers from mesityl–phenyl steric interactions. The same sense of stereoselectivity is also predicted for the reaction of methyl acrylate; calculations give a 0.3 kcal/mol preference for the transition structure analogous to **37**. These predicted stereoselectivities are in agreement with the observations by Corey et al.[2] However, essentially no stereoselectivity is predicted by the model calculations for the reaction of propene.

We note that the present system is somewhat different from the previous cases where the nitrogens are both disubstituted. In structure **34**, the two N–H bonds are parallel to the two axial Os–O bonds. Electrostatic interaction of the NH group with a nearby O (essentially hydrogen-bonding) may influence geometries in the present situation. The effect of H(N)–O attraction would be to twist the diamine moiety so that the two N atoms move away from the transition structure plane; one moves forward, and one moves backward. While this speculation needs to be checked by experiment, calculations have been carried out to model such a situation. The diamine moiety was rotated about the C_2 axis of the transition structure

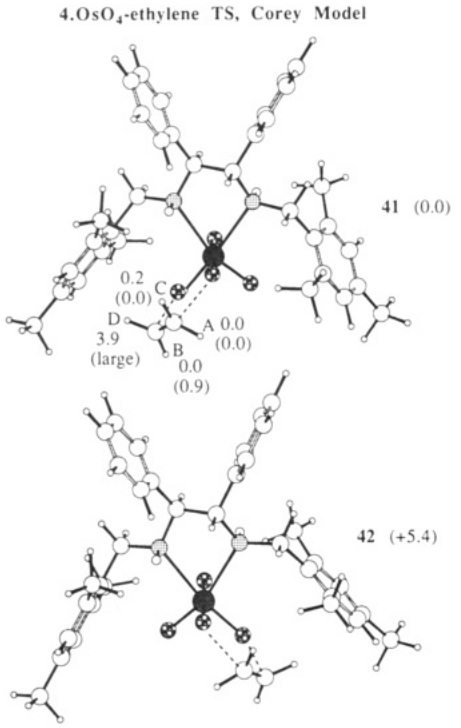

Figure 16. Transition structures for the reaction of ethylene with 4·OsO_4 complex calculated with the Corey model. The values shown in **41** are the relative energies calculated for methyl and phenyl (in parentheses) at different positions of ethylene.

34 by 16°. This rotation gives structure **39**, in which the (N)H---O(Os) distance is about 2.1 Å, near the value for normal hydrogen-bonding. Structure **40** is a side view of this transition structure, in which the front mesityl group totally covers the left-hand side of the transition structure plane. As a result, the calculated stereoselectivity increases. Even for the reaction of propene, a 0.6 kcal/mol preference for the structure corresponding to **37** is predicted.

Corey et al. reported that the *N,N'*-bis(benzyl) analogue of **4** was not an effective controller for the stereoselectivity.[2] They attributed this to great flexibility of the benzyl groups. Our MM2 model calculations suggest that the flexibility of a benzyl group in the transition structure is about the same as a mesityl group. Essentially no stereoselectivity is predicted by the calculations. This is mainly caused by the removal of the steric effect of the *p*-methyl groups in the analogous structure of **38**.

We also tested the Corey model **13** in the present case. Structures **41** and **42** are two possible transition structures for the reaction of ethylene with the 4·OsO_4 complex. Structure **42** is calculated to be less stable by 5.4 kcal/mol. This results from steric interactions with the mesityl R in **42**, as indicated by significant rotation of this group. The relative energies of methyl and phenyl substituents (in parentheses) at the four alkene sites in structure **41** are given in Figure 16. The positions A, B, and C have equal preferences for a methyl group, while a phenyl group can equally well occupy the A and C positions. Therefore, this model predicts essentially no stereoselectivity for monosubstituted alkenes. For trans-disubstituted alkenes, this model appears to give the right stereoselectivity.

In summary, we have developed a symmetrical five-membered transition structure model for the dihydroxylations of alkenes by chiral diamine complexes of osmium tetroxide based on X-ray crystal structures of OsO_4–amine complexes and osmate esters, and ab initio transition structures of analogous reactions. The MM2 calculations based upon this model qualitatively reproduce the stereoselectivities observed with several chiral diamine ligands. Some predictions are made using this force field, which will stimulate further experiments. It is found that the steric interactions in transition structures can be quite different from those in osmate products.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research, and to Professors Sharpless, Tomioka and Corey for helpful discussions.