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Communications

New Ligands Double the Scope of the Catalytic Asymmetric Dihydroxylation of Olefins

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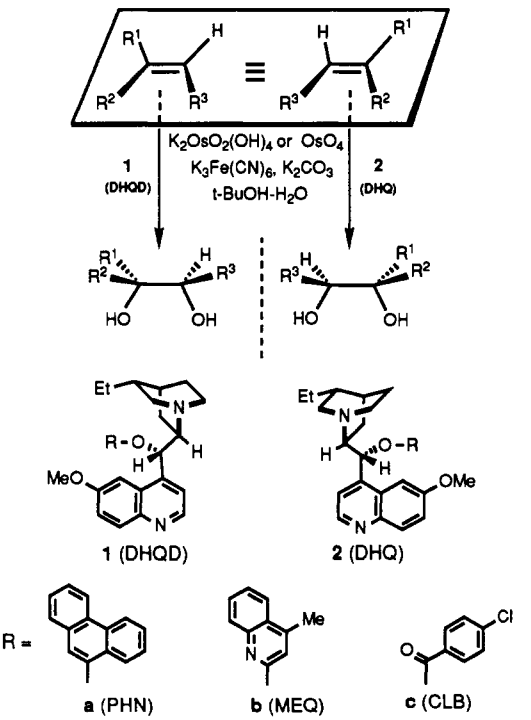
Summary: Improved ligands render terminal olefins good substrates for the osmium-catalyzed asymmetric dihydroxylation (ADH) process, and the amounts of chiral ligand and osmium catalyst required diminish dramatically.

Unlike the titanium-catalyzed asymmetric epoxidation (AE),[1] for which the inaugural ligand is still the best, the osmium-catalyzed asymmetric dihydroxylation (ADH) (Scheme I) is responsive to substantial enantioselectivity improvement through ligand variation.[2,3] In the cinchona alkaloid family alone, we have now evaluated over 75 derivatives and herein disclose what are at present the two top contenders for "best ligand": the 9-*O*-(9′-phenanthryl) ethers (PHN) and the 9-*O*-(4′-methyl-2′-quinolyl) ethers (MEQ) of dihydroquinidine (**1a** and **1b**) and dihydroquinine (**2a** and **2b**).

The improvements achieved with these new ligands[4-6] are best appreciated through the results shown in Table I. The outstanding change here is for the terminal olefins (entries 1–7), which have for the first time moved into the "useful" ee range. In Table I, the data for the new ligands **1a** and **1b** are compared to the results with the best previous ligand, the *p*-chlorobenzoate (CLB) **1c**. Note that, between them, the new ligands **1a** and **1b** offer across-the-board improvements in enantioselectivity (the best ee's are highlighted by brackets).

Of the six possible substitution patterns for olefins shown in Scheme II, four are represented in Table I. The present success with the monosubstituted and *gem*-disubstituted types essentially doubles the scope of the catalytic ADH, since ligand **1c** is mainly good for trans-di-

Scheme I. The Osmium-Catalyzed ADH and New Chiral Ligands



and certain trisubstituted olefins.[11] Happily, ligands **1a** and **1b** also deliver a significant ee enhancement over **1c** for trans-disubstituted olefins, especially those lacking aromatic substituents (entries 8 and 9). Thus, with the advent of the aromatic ether ligand family, four of the six olefin substitution patterns now fall into the "good substrate" classification, and only the cis-di- and tetra-

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Table I. Enantiomeric Excesses (ee, %)[a] of the Diols Resulting from Catalytic Asymmetric Dihydroxylation[b]

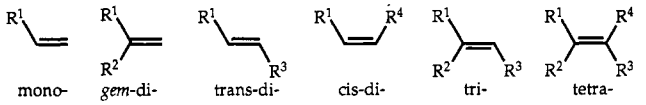
class of olefin	entry	olefin[c]	1a (PHN)	1b (MEQ)	1c (CLB)	config[d]
	1	n-C_6H_{17}	74	65	45[e]	R
	2	cyclo-C_6H_{15}	93	85	64[e]	(R)
R^1	3	t-Bu	79	79	44[e]	R
	4	Ph	78	87	74[e]	R
	5		83	93	88[e]	R
R^1 R^2	6	cyclo-C_6H_{11}	82	73	37[e]	R
	7	MeO	69	88	74[e]	(R)
	8	n-Bu n-Bu	95	90	79	R,R
R^1 R^3	9	n-C_5H_{11} CO_2Et	94	85	67	(2S,3R)
	10	Ph CO_2Me	98	98	91	2S,3R
	11	Ph Ph	99	98	99	R,R
R^1 R^3 R^2	12	Ph	84	81	74	R
	13	Ph	93	92	91	R,R

[a] Enantiomeric excesses were determined by HPLC, GLC, or ^1H NMR analysis of the bis-MTPA esters[7] (see supplementary material for details of analyses). [b] All reactions were performed essentially as described in ref 13 with some variations: (1) 1–1.25 mol % (0.4–1.7 mM) OsO_4 or $K_2OsO_2(OH)_4$; (2) 2–25 mol % (4–33 mM) ligand; (3) 0.1–0.2 M in olefin; (4) 18–24 h reaction time. Unless otherwise noted, entries 1–7 were carried out at 0 °C and entries 8–13 at room temperature (≤25 °C). In all cases the isolated yield of the diol was 75–95%. [c] All olefins are commercially available except entries 6 and 7.[8] [d] The absolute configurations of the diols were determined by comparison of their optical rotations with literature values[9] (entries 1, 3–5, 8, 10, 11, 13), or those of authentic diols (entries 6 and 12).[10] The remaining three (entries 2, 7, 9) were tentatively assigned by analogy from optical rotations of closely related diols and the retention times of their bis MTPA esters in HPLC (see supplementary material for details). [e] Reaction was carried out at room temperature.

substituted types (missing from Table I) are still outside the "useful" ee range.[12]

Space restrictions prevent detailed presentation of the results for the dihydroquinine ligand analogues (**2a**, **2b**, and **2c**),[6] but suffice it to say that the quinine analogues of these new ligands also give very good results with the same olefin classes shown in Table I. Like the original

Scheme II. Olefin Substitution Patterns



p-chlorobenzoate ligand comparison (**1c** vs **2c**),[2b] the new quinine ether analogues give somewhat lower ee's than their dihydroquinidine counterparts (**1a** vs **2a** and **1b** vs **2b**). For example, vinylcyclooctane (entry 2) gives the *S*-diol in 88% ee using **2a** as compared with the result in Table I where the *R*-diol is obtained in 93% ee using **1a**.

A detailed procedure for the catalytic ADH is given in ref 13, using ligand **1a** and vinylcyclooctane as the substrate. Note the experimental simplicity of the process. It is performed in the presence of air and water at either ambient or ice bath temperatures. The solid *and* nonvo-

(1) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(2) (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. (b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (c) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *Ibid.* **1989**, *111*, 1123. (d) 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. (e) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Ibid.* **1990**, *31*, 2999. (f) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Ibid.* **1990**, *31*, 3817. (g) McKee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.*, In press.

(3) Since our original success with the cinchona alkaloid ligands[2a] a variety of bidentate chiral amines for the ADH transformation have been reported: (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. Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741. (d) Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665. Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. (e) Corey, E. J.; Jardin, P. D.; Virgil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. However, all these bidentate ligands require stoichiometric use of the osmium and the ligand—they do not turnover.

(4) **Ligand Preparations and Properties.** (For more details on the synthesis and physical data for these ligands, see the supplementary material.) **1a.** To a room temperature solution of dihydroquinidine (48.9 g, 0.15 mol) in dry DMSO (600 mL) is added NaH (4.0 g, 0.17 mol) followed by pyridine (12.1 mL, 0.15 mol), CuI (28.6 g, 0.15 mol), and then 9-phenanthryl iodide (45.6 g, 0.15 mol) under argon. After 70 h of reaction at 120 °C, **1a** is obtained in 73% yield (55.0 g). (In the final purification of the ligand, the alkaloid is converted to the hydrochloride salt which is then recrystallized. The hydrochloride[14] can be converted quantitatively to the free alkaloid using ammonium hydroxide.) See also: Lindley, J. *Tetrahedron* **1984**, *40*, 1433 and references therein. Properties: mp 98–100 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, 3 H, J = 7.0 Hz), 1.6 (m, 6 H), 1.81 (s, 1 H), 2.39 (m, 1 H), 2.55 (s br, 1 H), 2.78 (m, 1 H), 2.97 (m, 2 H), 3.16 (m, 1 H), 3.38 (m, 1 H), 4.03 (s, 3 H), 6.33 (d, 1 H, J = 3.8 Hz), 6.63 (s, 1 H), 7.4 (m, 6 H), 7.57 (d, 1 H, J = 2.6 Hz), 7.75 (m, 2 H), 8.07 (d, 1 H, J = 9.2 Hz), 8.38 (dd, 1 H, J = 3.1 Hz, J = 9.3 Hz), 8.7 (m, 2 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 21.7, 25.2, 26.6, 27.1, 37.4, 50.1, 51.0, 55.8, 60.3, 78.8, 100.9, 104.8, 118.1, 121.9, 122.2, 122.8, 124.5, 126.4, 126.6, 126.7, 127.2, 127.4, 131.5, 132.0, 132.3, 143.7, 144.6, 147.5, 150.4, 158.2; IR (KBr) 1622, 1508, 1452, 1227 cm^{-1}; $[\alpha]^{23}_D$ −281.3° (*c* 1.12, $CHCl_3$). **1b.** To a room temperature suspension of dihydroquinidine (65.2 g, 0.20 mol) in DMF (300 mL) is added NaH (6.06 g, 0.24 mol), followed by 2-chloro-4-methylquinoline (42.6 g, 0.24 mol). After stirring for 24 h at room temperature, **2a** is obtained in 82% yield (76.3 g): mp 151–153 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz), 1.4–1.7 (m, 6 H), 1.76 (s, 1 H), 2.12 (t, 1 H, J = 10.0 Hz), 2.61 (s, 3 H), 2.7–3.0 (m, 4 H), 3.43 (dd, 1 H, J = 6.4, 8.8 Hz), 3.94 (s, 3 H), 6.82 (s, 1 H), 7.2–7.6 (m, 6 H), 7.73 (d, 1 H, J = 2.5 Hz), 7.81 (d, 1 H, J = 8.0 Hz), 7.98 (d, 1 H, J = 9.2 Hz), 8.67 (d, 1 H, J = 4.6 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.8, 18.4, 22.9, 25.2, 25.8, 27.1, 37.2, 49.8, 50.6, 55.4, 59.2, 73.1, 101.7, 112.5, 118.5, 121.4, 123.3, 123.7, 125.2, 127.5, 129.0, 131.3, 144.5, 145.8, 147.3, 157.4, 160.4; IR (KBr) 1608, 1573, 1508, 1466, 1228, 1182, 1039, 848, 758 cm^{-1}; $[\alpha]^{21}_D$ −194.7° (*c* 1.0, EtOH). **2a** and **2b** were synthesized using identical procedures (vide supra). *Like the p-chlorobenzoate derivatives, these new ligands are also available from Aldrich.*

(5) These new ligands are the fruits of an extensive (>50) "SAR-study" on aromatic ether substituents,[6] which was triggered by a promising lead with a simple aryl ether case (**1**, R = phenyl).[2f] In this earlier study,[2f] no monosubstituted olefins were tried!

(6) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. Manuscript in preparation.

(7) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(8) The olefins in entries 6 and 7 were synthesized from the corresponding ketones by a Wittig reaction ($Ph_3P{=}CH_2$).

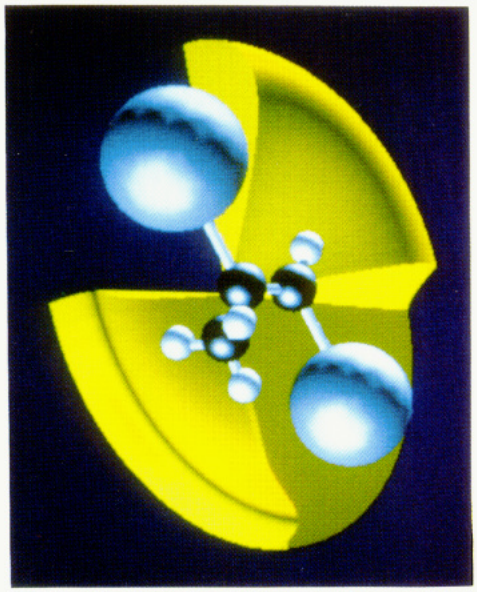
(9) (a) 1-Decene: Masaoka, Y.; Sakakibara, M.; Mori, K. *Agric. Biol. Chem.* **1982**, *46*, 2319. (b) 3,3-Dimethyl-1-butene: Guettê, J.-P.; Spasky, N. *Bull. Soc. Chim. Fr.* **1972**, 4217. (c) Styrene: Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1970**, *35*, 4002. (d) 2-Vinylnaphthalene: Howe, R.; Moore, R. H.; Rao, B. S. *J. Med. Chem.* **1973**, *16*, 1020. (e) Methyl cinnamate: Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957. (f) (*E*)-Stilbene and 1-phenylcyclohexane-1,2-diol: Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. C* **1971**, 3371. (g) (*E*)-5-Decene: Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

(10) **Entry 6**: Authentic (*R*)-(+)-2-cyclohexylpropane-1,2-diol was prepared by hydrogenation (Rh/Al_2O_3) of (*R*)-(−)-2-phenylpropane-1,2-diol. **Entry 12**: Authentic (*R*)-(−)-phenyl-2,2-dimethyl-1,2-dihydroxypropane was prepared by the Grignard reaction of (*R*)-(−)-methyl mandelate with methylmagnesium iodide. (See the supplementary material for detailed procedures and physical data.)

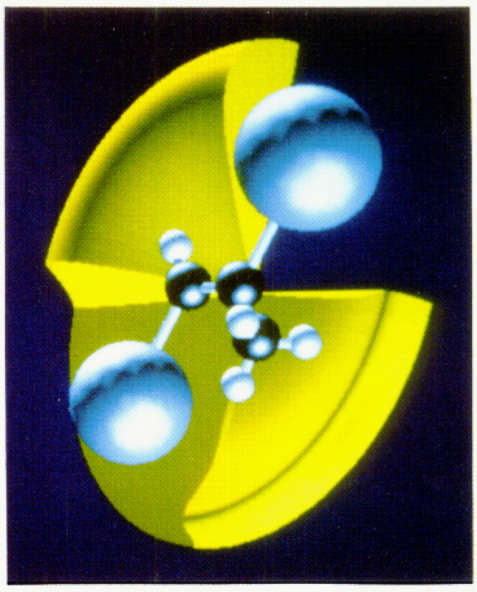
(11) However, note that **1c** gives good to very good results with certain aromatic terminal olefins (e.g., entries 4, 5, and 7, Table I), especially if one allows for the temperature differential.

(12) For several reasons (e.g. see Scheme III) the tetrasubstituted class of olefins is unlikely to work well in this type of ADH system. The cis-disubstituted olefin class is just beginning to show promise in further ligand-variation studies (Wang, L.; Sharpless, K. B. Unpublished results).

Scheme III. Imaginary Asymmetric Catalyst Surface: A Mnemonic Device for Predicting Enantiofacial Selection[a]



Quinidine-Based Catalyst



Quinine-Based Catalyst

[a] The olefin is drawn as in Scheme I (i.e. large ball = R^1, methyl = R^2, medium ball = R^3, hydrogen = R^4).

latile osmium(VI) salt, $K_2OsO_2(OH)_4$, is used here in place of osmium tetraoxide,[15] an innovation which should be useful in all catalytic oxidations involving OsO_4 for it avoids almost all risk of exposure to volatile osmium species. In the case of terminal olefins (e.g. entries 1–7), catalytic turnover is rapid even at 0 °C, and as little as 0.05 mol % (1/2000) $K_2OsO_2(OH)_4$ can lead to complete reaction in less than 24 h.[16] Recent work has revealed that much lower ligand concentrations are necessary than were previously recommended.[17a] Originally it was suggested that the concentration of ligand be in the 0.1–0.2 M range.[2b] We have now found that it can usually be dropped to ca. 0.02 M at room temperature and to 0.004 M at 0 °C without noticeable detriment to the ee.[13,17b] With these advances, the required loadings of the chiral ligand and osmium catalyst diminish almost to the point of vanishing, and in any case, the chiral ligand is easily recovered and reused.

This extension of the catalytic ADH to terminal olefins signals a vast expansion in the substrate scope. Mono- and disubstituted terminal olefins dominate the olefin family sextet since they are by far the most available olefins. They are also the only two olefin classes free of geometrical isomerism and the synthetic challenges it begets.

The mnemonic device in Scheme III is presented as an aid for deciding if a given olefin will be a good substrate. We have evolved this empirical model based on the cumulative experience gained in testing the ADH on ap-

(13) **Procedures and General Guidelines for Catalytic ADH** [An olefin concentration of between 0.1 and 0.2 M (based on *t*-BuOH volume)[17a] is recommended]. **A. Vinylcyclooctane** (and other terminal olefins, e.g. entries 1–7). To a well-stirred mixture (especially important on a larger scale due to the need for interfacial exchange) of DHQD–PHN **1a** as the hydrochloride (108 mg, 0.2 mmol, 2 mol %, 0.004 M in the organic phase),[14] $K_3Fe(CN)_6$ (9.88 g, 30 mmol, 3 equiv), and K_2CO_3 (4.15 g, 30 mmol, 3 equiv) in a *t*-BuOH–H_2O mixture (50 mL/50 mL) was added potassium osmate(VI) dihydrate[15] (7.4 mg, 0.02 mmol, 0.2 mol %). The resulting yellow solution was cooled to 0 °C, and vinylcyclooctane (1.64 mL, 1.38 g, 10 mmol) was then added. The reaction mixture was stirred for 18 h at 0 °C, Na_2SO_3 (7.5 g) was added, and the resulting mixture was stirred for 30 min at room temperature. The two phases were separated, and the aqueous phase was then extracted (2 × 50 mL) with CH_2Cl_2. The combined organic phases were evaporated, and the residue was diluted with 200 mL of ethyl acetate, washed with 1 M H_2SO_4 (acid must be H_2SO_4, ligand·HCl is poorly soluble in H_2O), aqueous $NaHCO_3$, and brine, and finally dried with $MgSO_4$. Concentration and flash chromatography (silica gel) using ethyl acetate–CH_2Cl_2 (2:1) afforded 1.63 g (95% yield) of (*R*)-2-cyclooctylethane-1,2-diol as a colorless oil; $[\alpha]^{22}_D$ −10.8° (*c* 1.3, $CHCl_3$). The ee of the diol was determined to be 93% by HPLC analysis of the derived bis-MTPA ester. The alkaloid ligand was recovered in 82% yield by adjusting the acidic aqueous washes to pH 11 with Na_2CO_3 and extracting with CH_2Cl_2. **B. (*E*)-5-Decene** (and other internal olefins, e.g. entries 8-13) [The key difference from procedure A above is that the process is run at room temperature, necessitating increased ligand concentration]. The following stoichiometry was employed: DHQD–PHN **1a** as the hydrochloride (108 mg, 0.2 mmol, 13 mol %, 0.02 M), $K_3Fe(CN)_6$ (1.47 g, 4.5 mmol, 3 equiv), K_2CO_3 (0.62 g, 4.5 mmol, 3 equiv), *t*-BuOH–H_2O mixture (10 mL/10 mL), potassium osmate(VI) dihydrate[15] (5.6 mg, 0.015 mmol, 1 mol %), (*E*)-5-decene (210 mg, 1.5 mmol). After 24 h of reaction at room temperature, workup afforded the (*R*,*R*)-5,6-decanediol in 78% yield (206 mg) and 95% ee $[\alpha]^{24}_D$ 27.7° (*c* 0.98, $CHCl_3$) (mp 48–49 °C). **C. Other General Points.** (1) To achieve acceptable rates with di- and trisubstituted olefins, a higher reaction temperature (up to ca. 25 °C) is usually required since the more substituted osmate(VI) esters can be slow to hydrolyze, generating a bottleneck in the catalytic cycle. The rate is also enhanced by increasing the osmium concentration 20-fold to 1 mol %. (2) These are conservative guidelines based on (*E*)-5-decene, a "worst case" internal olefin whose osmate ester is very slow to hydrolyze. However, other internal olefins, especially those with polar groups (even aromatic substituents are helpful), often exhibit good turnover rates below 25 °C. In such cases, optimization studies should be pursued. Since the concentration of ligand needed decreases rapidly with dropping temperature, optimization studies should vary not only the temperature, but also ligand and Os concentration, using procedures A and B as approximate boundaries for the ranges explored.

(14) We have recently found that the hydrochloride salts of the alkaloids are completely equivalent sources of the chiral ligand (the free alkaloid is generated in situ by the excess base in the aqueous phase). In the case of the PHN–ligands, **1a** and **2a**, the HCl salts are now preferred since they are an integral part of the isolation procedure employed in the synthesis of these ligands.

(15) We have established that $K_2OsO_2(OH)_4$ [Aldrich, potassium osmate(VI) dihydrate, no. 20,910-4)] is completely equivalent to OsO_4 in these applications. In fact, $K_2OsO_2(OH)_4$ was shown to be an intermediate in the catalytic cycle of these ADH processes (Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* In press).

(16) Yun Gao, Sepracor Inc., Marlborough, MA, unpublished results.

(17) (a) Here and elsewhere in this paper the molarities are based on the volume of the organic phase which is approximated as the volume of the *t*-BuOH added. (b) Several effects acting in concert with the ligand acceleration phenomenon are believed responsible for this happy situation. These effects will be discussed in detail elsewhere.

proximately 90 different olefins. This means of predicting/rationalizing the outcome, both regarding approximate ee and the absolute sense of enantiofacial recognition, has proven extremely useful. It is the best planning tool we can offer the synthetic chemist until such time that the mechanistic details of osmylation in general, and asymmetric osmylation in particular are better understood.[18]

In Scheme III, the osmium–ligand ensemble is represented as a chiral yellow oxygen-donating surface. In addition, one of the olefin's prochiral faces is shown as approaching the chiral disklike entity from above, such that the axis along which the two olefinic carbons lie is roughly parallel to the east–west direction. The central area of this asymmetric yellow surface then delivers the two oxygen atoms to the bottom face of the olefin. The enantiofacial selectivity consequently arises from interactions of the olefin's substituents with the putative asymmetric protuberances on the oxygen-donating surface.[19] With quinidine (left side in Scheme III), this is represented by open northwest and southeast quadrants with a relatively proximate steric barrier in the northeast quadrant (deduced from the fact that only a hydrogen atom seems able to fit there) and with the southwest quadrant flat and open near the center but characterized by a rising surface at a greater radial distance. Thus, in the southwest region, the barrier encroaches less closely than the steeply inclined wall in the diagonal northeast quadrant, so that a small (e.g. CH_3, CH_2R, etc.) substituent can be accommodated (entries 12 and 13). Analysis of the predicted outcomes for each of the six olefin substitution patterns is left to the reader. The quinine surface (right side in Scheme III) is simply represented as the mirror image of the quinidine surface and the inversion of the enantiofacial preference follows from this assumption.[20]

The catalytic ADH has now reached levels of enantioselectivity that are commensurate with those realized in other highly effective catalytic asymmetric processes such as the asymmetric epoxidation and asymmetric hydrogenation. However, these latter two systems require the presence of an ancillary functional group to act as a binding tether to the catalytic metal center.[21] Such a requirement introduces a massive restriction in the pool of possible substrates. This point stands out clearly upon comparing the outcomes of the ADH and AE processes with the *E* isomers of the following members of a closely related olefin family:

$PhCH{=}CHCH_3$	$PhCH{=}CHCH_2OCH_2Ph$
$PhCH{=}CHCH_2OH$	$PhCH{=}CHCH(OCH_3)_2$
$PhCH{=}CHCH_2OAc$	$PhCH{=}CHCO_2CH_3$

All are excellent substrates for the catalytic ADH,[22] but only the alcohol reacts in the titanium-catalyzed AE process.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-8903218), the National Institutes of Health (GM 28384), and Eli Lilly & Co. We are grateful to Lisa Wang for helpful discussions. We are also indebted to Professor Timothy Dowling and Albert Fischer of MIT's Earth and Planetary Sciences Department for carving up the planet Neptune to produce Scheme III. W.A. and J.H. thank the Deutsche Forschungsgemeinschaft (DFG) for providing fellowships. M.B. thanks the Fonds der Chemischen Industrie for a Liebig Stipendium. Y.K. is grateful to the Ministry of Education, Science, and Culture of Japan for a research fellowship.

Supplementary Material Available: Detailed synthetic procedures and physical data for the new ligands (**1a,b, 2a,b**) and details for the determination of the enantiomeric excesses and absolute configurations of the diols (9 pages). Ordering information is given on any current masthead page.

(18) See: Jørgensen, K. A.; Schiøtt, B. *Chem. Rev.* **1990**, *90*, 1483–1506 and references cited therein.

(19) In the absence of a detailed mechanism, we have tried to eschew the natural tendency to identify elements of the asymmetric OsO_4·alkaloid complex with the two- and/or three-dimensional domains of this imaginary surface.

(20) Dihydroquinine and dihydroquinidine are actually diastereomers. They have opposite absolute configurations at four of the five stereogenic centers; only the center bearing the ethyl group is the same in both series. As ligands in the ADH, they behave almost like enantiomers and hence the appellation "pseudoenantiomers" seems appropriate (Wynberg, H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S., Allinger, N. L., Eds.; John Wiley and Sons: New York, 1986; Vol. 16, p 87).

(21) Catalytic asymmetric epoxidation of simple olefins (i.e. lacking a tethering group) is a recent dramatic breakthrough: (1) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L., submitted for publication in *J. Am. Chem. Soc.* (2) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

(22) Sharpless, K. B.; Park, C. Y.; Marko, I.; Wai, J. S. M., unpublished results.