Kinetic Resolution by Enantioselective Dihydroxylation of Secondary Allylic 4-Methoxybenzoate Esters Using a Mechanistically Designed Cinchona Alkaloid Catalyst

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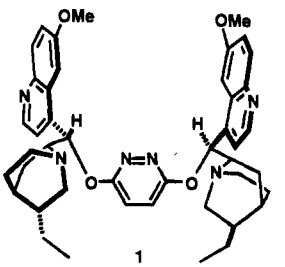
Abstract: The OsO_4−cinchona alkaloid catalyzed asymmetric dihydroxylation process has been applied successfully to the kinetic resolution of 1-substituted allylic alcohols by the use of the 4-methoxybenzoyl derivatives in conjunction with the specifically designed DHQD-PYDZ-(*S*)-anthryl catalyst (**5**·OsO_4). Thus, (±)-3-buten-2-yl 4-methoxybenzoate (**4a**) and (±)-1-phenyl-2-propen-1-yl 4-methoxybenzoate (**4b**) have been kinetically resolved with relative rate constants of 20 and 79, respectively. These values are among the best reported for the kinetic resolution of racemic compounds using non-enzymatic catalyst systems. The design of this resolution process was accomplished under mechanistic guidance using the transition state model proposed recently for the asymmetric dihydroxylation process. The specially selected ligand **5** possesses a deep U-shaped binding pocket with both the methoxyquinoline and the 1-anthryl walls projecting rearward of the pyridazine linker group at the floor. This catalyst not only recognizes the 4-methoxybenzoyl group of these substrates, which extends into the distant binding pocket of the catalyst, but also provides an open space adjacent to one of the allylic α-substituents of the substrate which allows for enantiomeric selection in the dihydroxylation. The magnitude of the kinetic resolution and the absolute stereopreference for the dihydroxylation reaction provide strong evidence for the guiding mechanistic model. The utility of this process is clearly demonstrated by the selective dihydroxylation of 1,4-pentadien-3-yl 4-methoxybenzoate (**10**) to give diol **11** in 70% isolated yield with >98% ee and >96% de.

Introduction

In the previous paper,[1] we described an extension of the Sharpless asymmetric dihydroxylation[2] to the enantioselective oxidation of allylic 4-methoxybenzoates and related substrates.[3] Bis-cinchona alkaloids, such as $(DHQD)_2PYDZ$ (**1**), are effective catalysts for the reaction, giving high levels of enantioselectivity for allylic 4-methoxybenzoates, benzamides, 9-fluorenimines, thiobenzoates, and homoallylic 4-methoxyphenyl ethers and ketones. The chiral 1,2-diols produced using this methodology are well suited to the preparation of several types of chiral glycerol derivatives including β-adrenergic blocker drugs,[4] and should be useful starting materials for carbohydrate synthesis. The development of this extension of the Sharpless asymmetric dihydroxylation was guided by the mechanistic model recently advanced for this process by our group.[5] The proposed transition state assembly for the face-selective dihydroxylation of allyl 4-methoxybenzoate (**2**), for example, in the $(DHQD)_2PYDZ$·OsO_4 system is depicted in Figure 1. The following catalyst features are crucial for high face-selectivity



1

in the reaction: (1) a preference for the U-shaped conformation as in **3** for the OsO_4 complex, which has the ability to hold olefinic substrates such as allyl 4-methoxybenzoate in a binding pocket composed of the two parallel methoxyquinoline units, OsO_4 and the pyridazine connector, as shown, (2) staggered geometry about the Os−N bond of the bis-cinchona−OsO_4 complex, (3) the proximity of one axial oxygen (O_a) and one equatorial oxygen (O_e) of the complexed OsO_4 unit to the olefinic carbons of the bound substrate, as shown, and (4) a minimum motion pathway from this arrangement for the [3 + 2] cycloaddition which directly produces the pentacoordinate osmate ester in the energetically most favorable geometry. Additionally, the following substrate features have emerged as essential: (1) the presence of a suitable binding group on the substrate that allows extensive π-contact and other favorable binding interactions with the U-shaped binding pocket of the catalyst, (2) accessibility of the s-*cis*-allylic conformation of the substrate that places this binding group in the correct spatial orientation for interaction with the catalyst, and (3) stability of the protecting group with regard to potential acyl migration reactions of the product that can lead to racemization and reduced yield. The rate acceleration for the observed enantioselective pathway relative to other modes is due to the favorable free energy of activation for the reaction from complex

[⊗] Abstract published in *Advance ACS Abstracts*, October 15, 1995.

(1) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. Preceding paper in this issue.

(2) For a recent review on the Sharpless asymmetric dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(3) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109.

(4) For leading references to the synthesis of β-adrenergic blocker drugs including (*S*)-atenolol, see: Bevinakatti, H. S.; Banerji, A. A. *J. Org. Chem.* **1992**, *57*, 6003.

(5) (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (d) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427.

0002-7863/95/1517-10817$09.00/0

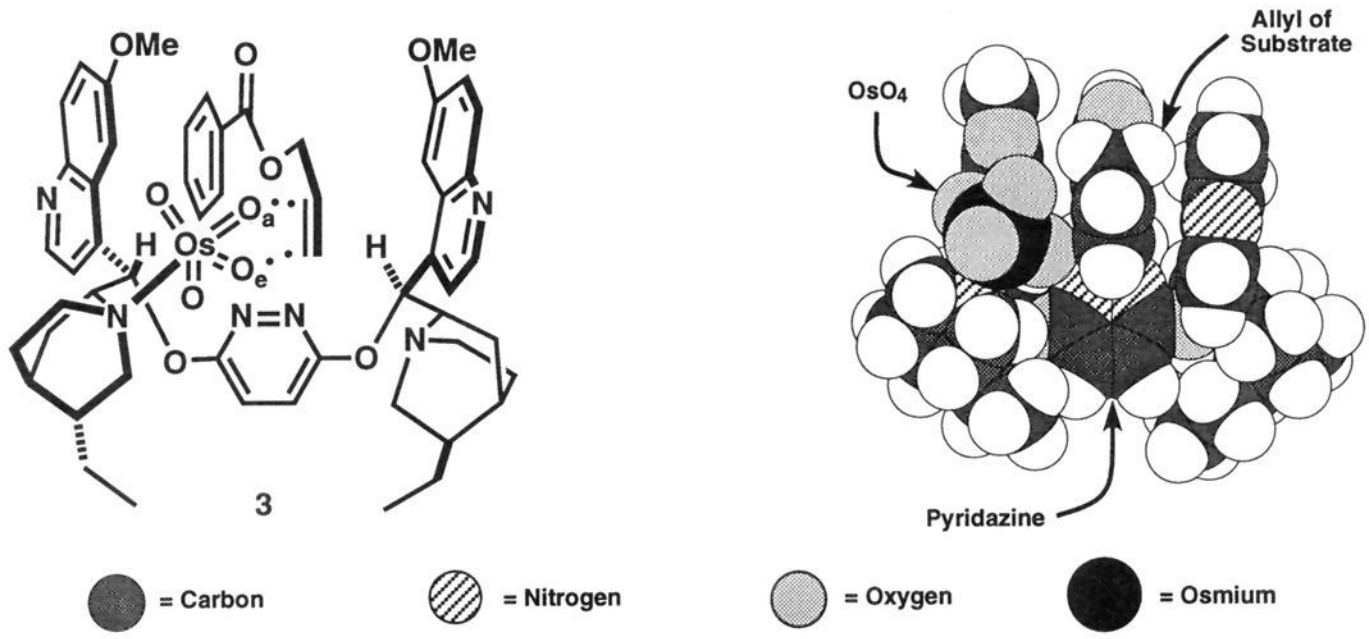


Figure 1. Proposed geometry for the complex between the s-*cis*-allylic form of allyl 4-methoxybenzoate (**2**), OsO_4, and ligand **1**. The methoxy group of **2** was omitted for clarity in **3**. The catalyst geometry was based on the X-ray crystal structure of **1**·CH_3I[5b] with the following modifications: (a) the methyl group of the methiodide salt was replaced by OsO_4 with the staggered arrangement about the N−Os bond and the bond distances demonstrated from X-ray studies[5c] and (b) the H(8)−C(8)−C(9)−H(9) dihedral angle was adjusted to *ca.* 90°.[5b]

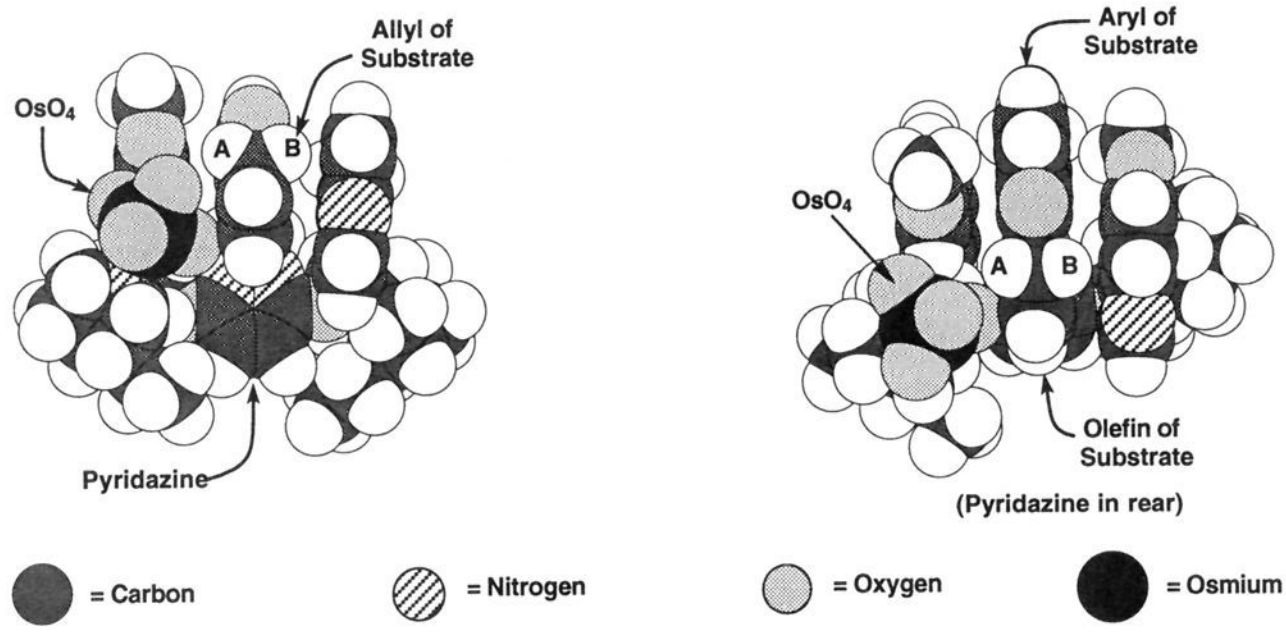


Figure 2. Two views of the complex of allyl 4-methoxybenzoate (**2**) bound to the $(DHQD)_2PYDZ$·OsO_4 catalyst in the geometry indicated in Figure 1. The prochiral hydrogen atoms are labeled A and B. As indicated, the catalyst cannot accommodate a substituent at either of these positions of the prochiral methylene group of the substrate.

3 in which the reactants are held in a manner which is ideal for the formation of the thermodynamically more stable osmate ester. Dihydroxylation of the opposite olefin face to that shown in **3** is unfavorable due to the fact that there is no three-dimensional arrangement for simultaneous π-facial approach of the olefin to the oxygens labeled as O_a and O_e and favorable interaction with the binding pocket.[1,5]

Although the bis-cinchona alkaloid catalyzed asymmetric dihydroxylation reaction of achiral olefins has been of great value in synthesis because of its wide scope and high enantioselectivity, relatively little progress has been made on the kinetic resolution of racemic olefins.[6] In view of the success achieved in the asymmetric dihydroxylation of allylic 4-methoxybenzoates, we have extended the enantioselective dihydroxylation to the kinetic resolution of racemic allylic alcohol derivatives[7] using the insights provided by the mechanistic model outlined above. The results of this study, which led to a very useful kinetic resolution method, are described herein.

(6) For references on the application of the asymmetric dihydroxylation to kinetic resolution of racemic olefins, see: (a) VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864. (b) Ward, R. A.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3363. (c) Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1993**, *34*, 3911. (d) Hawkins, J. M.; Meyer, A. *Science* **1993**, *260*, 1918. (e) Reference 2.

Results and Mechanistic Discussion

The rational design of an effective kinetic resolution system using the cinchona alkaloid catalyzed asymmetric dihydroxylation is based on the following analysis of catalyst and transition state geometry. Initial molecular modeling studies under mechanistic guidance indicated that the $(DHQD)_2PYDZ$ ligand (**1**) was unlikely to be effective for the kinetic resolution of racemic olefins such as **4**.[8] A good catalyst for this process must be able to accommodate the allylic substituent R for only one enantiomer of the substrate. As shown in Figure 2, the $(DHQD)_2PYDZ$ catalyst obstructs an additional allylic substituent at *either* position A or B of the substrate. The validity of

(7) The Sharpless asymmetric epoxidation is also effective for the kinetic resolution of racemic allylic alcohols. See: (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1985; Vol. 5, p 247. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (c) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(8) The parallelism in structure and enantioselectivity of the $(DHQD)_2PYDZ$ and $(DHQD)_2PHAL$ ligands suggest that both ligands would perform similarly in the kinetic resolution of racemic olefins. For detailed comparisons of these ligands in the asymmetric dihydroxylation reaction see: (a) ref 5c. (b) Crispino, G. A.; Makita, A.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 543.

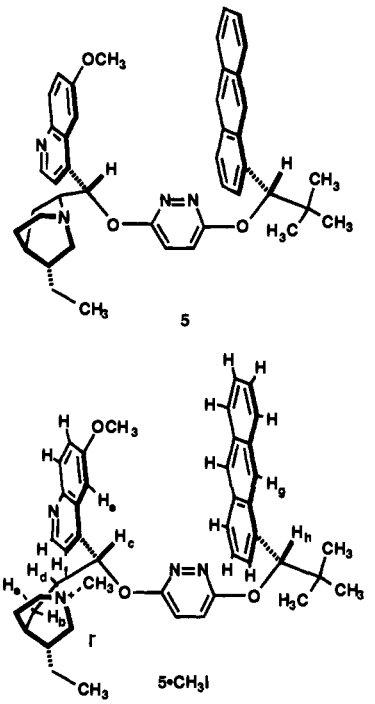
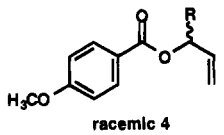


Figure 3. The structure of **5**·CH_3I as a model for the OsO_4 complex of **5** as shown by 500 MHz ^1H NMR studies in degassed $CDCl_3$ solution at 23 °C. The corresponding conformation of free DHQD-PYDZ-(*S*)-anthryl ligand **5** is also shown.

this analysis was subsequently confirmed by the data presented below.

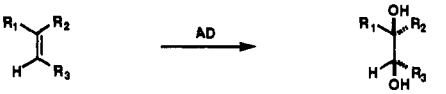


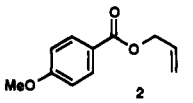
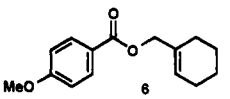
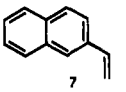
racemic **4**

Examination of Figure 2 suggests that a different ligand class possessing an open space to accommodate an allylic substituent at site B would be more suitable for the kinetic resolution of this type of substrate. The previously described DHQD-PYDZ-(*S*)-anthryl ligand **5** (Figure 3)[5d] would afford an OsO_4 complex with the required geometry. ^1H NMR observations revealed that the DHQD-PYDZ-(*S*)-anthryl catalyst (**5**·OsO_4) possesses structural features similar to those reported earlier for the corresponding DHQD-PYDZ-(*R*)-anthryl catalyst.[5d] The predominance of the U-shaped conformation of **5**·CH_3I, shown in Figure 3, is supported by the observation in the ^1H NMR spectrum of (a) an 8.2% NOE between H_c and H_e (7.0% in the other direction) and a 2.5% NOE between H_b and H_f (consistent with the orientation of the methoxyquinoline ring shown), (b) J (H_cH_d) = 0−2 Hz (indicating a *ca.* 80−90° dihedral angle), (c) $\delta(H_a)$ = 1.28 ppm, $\delta(H_b)$ = 2.48 ppm (consistent with shielding and deshielding effects of the methoxyquinoline ring expected for the structure shown), and (d) a 13.0% NOE between H_g and H_h (demonstrating the orientation of the anthracene ring shown).[9] The (*S*)-anthryl catalyst possesses a deeper binding pocket than any previously reported cinchona alkaloid asymmetric dihydroxylation catalyst, with both aromatic walls projecting rearward of the pyridazine linker group as shown.[10]

(9) For a related NMR study of cinchona alkaloid catalysts, see: Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.

Table 1. Asymmetric Dihydroxylation of Selected Substrates Using DHQD-PYDZ-anthryl Ligands and **1**



Substrate	$(DHQD)_2PYDZ$ (1) ee (yield)	DHQD-PYDZ-(*R*)-anthryl ee (yield)	DHQD-PYDZ-(*S*)-anthryl (5) ee (yield)
 2	98% ee (>99%)	95% ee (>99%)	90% ee (98%)
 6	98% ee (>99%)	98% ee (>99%)	95% ee (>99%)
 7	99% ee (98%)	98% ee (93%)	91% ee (99%)
 8	96% ee (95%)	91% ee (76%)	80% ee (82%)

A comparison of these ligands for the asymmetric dihydroxylation of selected olefins appears in Table 1. As a consequence of the more distant binding pocket of **5**·OsO_4, as compared to that of **1**·OsO_4, only substrates possessing extended binding groups are dihydroxylated with high enantioselectivity. The allylic 4-methoxybenzoates (**2** and **6**) and 2-vinylnaphthalene (**7**) possess extended binding groups capable of interacting favorably with the deep binding pocket of **5**·OsO_4, resulting in high enantioselectivity in the asymmetric dihydroxylation of these substrates with this catalyst. However, substrates such as styrene (**8**), which do not possess binding groups capable of reaching the binding pocket of **5**·OsO_4, give relatively lower enantioselectivity.[5d] In these cases competitive, non-enantioselective dihydroxylation pathways become significant. A representation of the proposed transition state for the asymmetric dihydroxylation of allyl 4-methoxybenzoate using **5**·OsO_4 as catalyst appears in Figure 4. As indicated in this figure, the catalyst can not only recognize the 4-methoxybenzoyl group of substrate **2**, which extends into the distant binding pocket of the catalyst, but can also provide an open space on one face of the prochiral methylene group of the substrate at position B where a second allylic substituent could reside.

These observations led to the idea that **5**·OsO_4 might be an effective catalyst for the kinetic resolution of racemic secondary allylic 4-methoxybenzoates using the asymmetric dihydroxylation reaction. A systematic investigation of this reaction was conducted with the results shown in Table 2. The efficiency of the kinetic resolution is denoted by the k_{rel} term, which is the ratio of the rates of reaction of each enantiomer of the olefin.[11] As expected, kinetic resolution using $(DHQD)_2PYDZ$ (**1**) as ligand afforded poor results, whereas the DHQD-PYDZ-(*S*)-anthryl ligand (**5**) displayed excellent differentiation between

(10) The Sharpless group has previously reported the use of phthalazine-linked catalysts containing a diarylmethyl group coupled to a mono-cinchona alkaloid unit for enantioselective dihydroxylation (ee's reported from 78−84%; no examples were given of kinetic resolution); see: Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226.

(11) For reviews on kinetic resolution, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695.

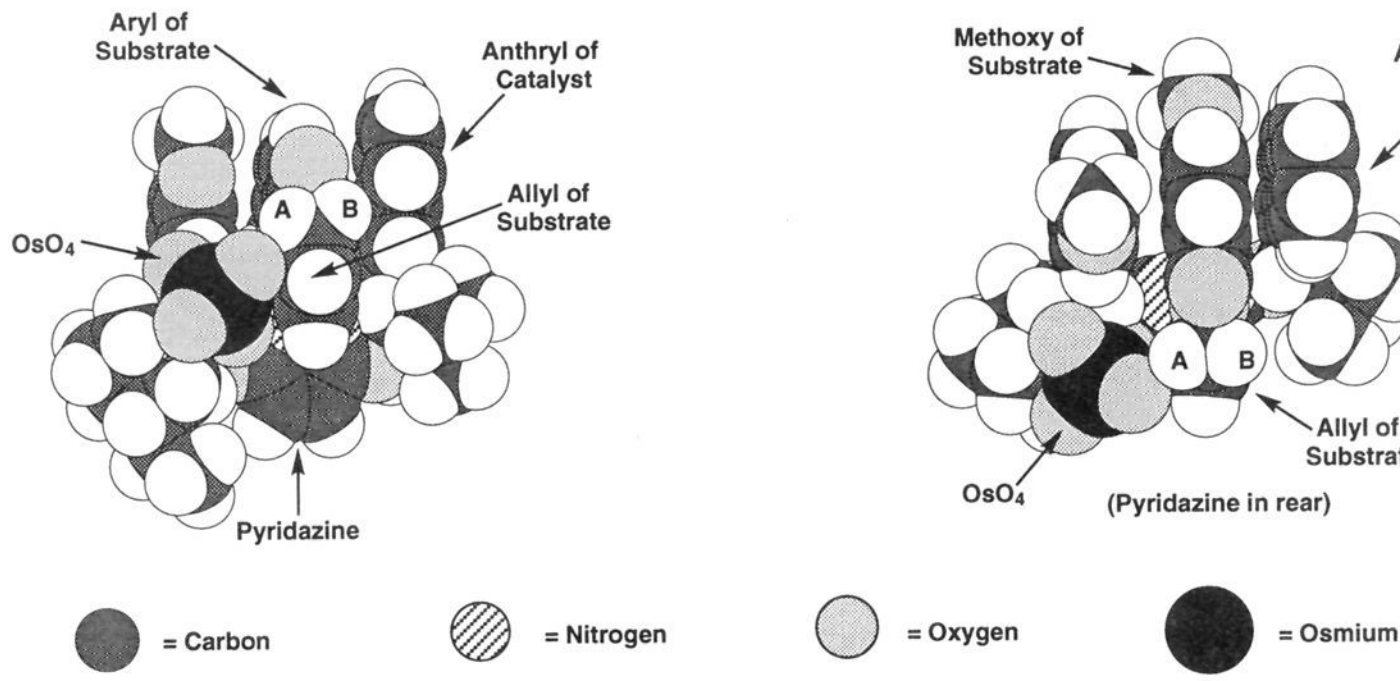
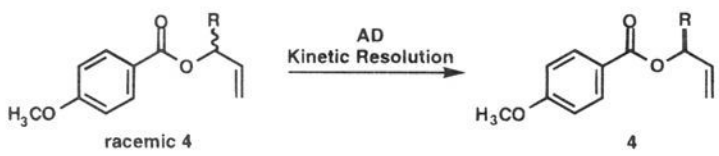
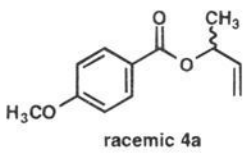
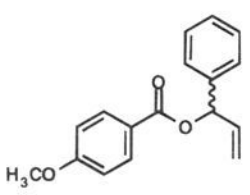


Figure 4. Two views of the complex of allyl 4-methoxybenzoate (**2**) bound to the DHQD-PYDZ-(*S*)-anthryl catalyst (**5**·OsO_4) which has the geometry indicated in Figure 3. The prochiral hydrogen atoms are labeled A and B. As indicated, the catalyst can accommodate a substituent at site B of the prochiral methylene group of the substrate.

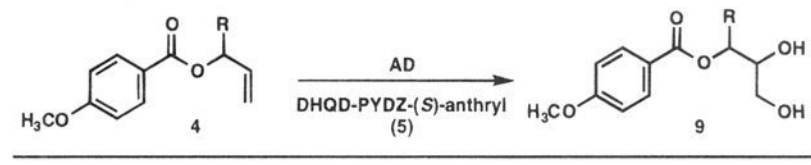
Table 2. Kinetic Resolution of Racemic Secondary Allylic 4-Methoxybenzoates Using Catalytic Asymmetric Dihydroxylation Conditions

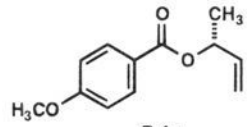
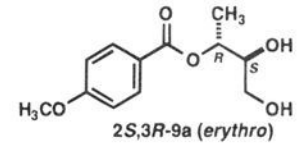
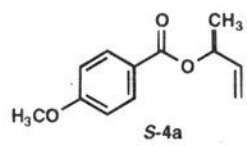
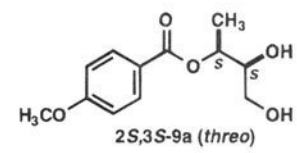
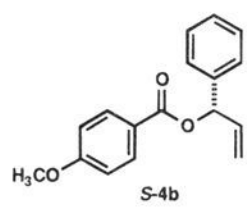
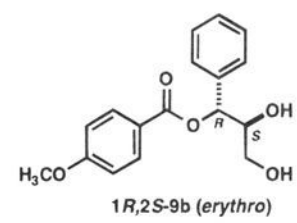
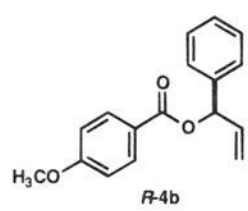
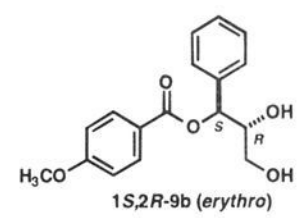


Substrate	Ligand	$k_{rel} = k_{ent4} / k_4$[a]
 racemic 4a	$(DHQD)_2PYDZ$ (1)	3.1
	DHQD-PYDZ-(*S*)-anthryl (5)	20
 racemic 4b	$(DHQD)_2PYDZ$ (1)	1.9
	DHQD-PYDZ-(*S*)-anthryl (5)	79

[a] Relative rates of reaction of ent **4** and **4**.

Table 3. Double Diastereoselection in the Asymmetric Dihydroxylation of Enantiomerically Pure Secondary Allylic 4-Methoxybenzoates[a]



Substrate	Main product	Diastereomeric ratio
 *R*-4a	 2*S*,3*R*-9a (*erythro*)	>100 : 1
 *S*-4a	 2*S*,3*S*-9a (*threo*)	approx. 1.7 : 1
 *S*-4b	 1*R*,2*S*-9b (*erythro*)	>100 : 1
 *R*-4b	 1*S*,2*R*-9b (*erythro*)	approx. 1.9 : 1

[a] The reaction of racemic **4a** with OsO_4/NMO in aqueous acetone gave a *ca.* 2:1 mixture of *erythro*-**9a** and *threo*-**9a**. The corresponding reaction of racemic **4b** gave a *ca.* 2:1 mixture of *erythro*-**9b** and *threo*-**9b**.

the enantiomers of the racemic substrates. The levels of differentiation are comparable to the highest levels of efficiency obtained in other non-enzymatic kinetic resolutions, and are certainly of practical utility.[7,11] Moreover, a marked difference in diastereofacial selectivity was noted in the asymmetric dihydroxylation of each enantiomer of **4a** and **4b**. Thus, in both cases, asymmetric dihydroxylation of the matched enantiomer (***R*-4a** and ***S*-4b**) afforded >100:1 diastereoselectivity, while the corresponding reactions of the mismatched enantiomers (***S*-4a** and ***R*-4b**) afforded <2:1 diastereoselection, as indicated in Table 3.[12]

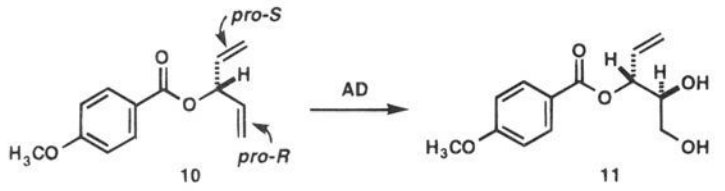
As an extension of this methodology, the asymmetric dihydroxylation of 1,4-pentadien-3-yl 4-methoxybenzoate (**10**), which possesses two potentially reactive enantiotopic vinyl groups, was investigated with the result shown in Table 4. As indicated, ligand **5** affords higher yield, enantiomeric and diastereomeric purity of the diol **11** than $(DHQD)_2PYDZ$ (**1**). Deprotection of **11** gives D-erythropentenitol, a versatile intermediate for carbohydrate synthesis.[13]

The kinetic resolution of racemic olefins offers a unique mechanistic probe resulting from two levels of stereodifferentiation: the enantiomeric sense of kinetic resolution and the sense of diastereofacial selection in the resulting reaction

(12) For other work on double diastereoselection in the Sharpless asymmetric dihydroxylation, see: (a) Morikawa, K.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 5575. (b) Wade, P. A.; Cole, D. T.; D'Ambrosio, S. G. *Tetrahedron Lett.* **1994**, *35*, 53. (c) Reference 6a. (d) Reference 2, pp 2497−2502 and references cited therein.

(13) (a) Jäger, V.; Schröter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195. (b) Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108 and references cited therein.

Table 4. Asymmetric Dihydroxylation of 1,4-Pentadien-3-yl 4-Methoxybenzoate (**10**)



10 11

Ligand	Isolated Yield[a]	Enantiomeric excess of 11 (ee)	Diastereomeric excess (de)
$(DHQD)_2PYDZ$ (1)	58%	92%	60%
DHQD-PYDZ-(*S*)-anthryl (5)	70%	>98%	>96%

[a] Isolated yield of compound **11** with the diastereomeric excess indicated above. Approximately 13% yield of products of acyl migration were also isolated.

products. Examination of the molecular models in Figure 5 indicates several features essential for obtaining effective kinetic resolution: (1) the ability of the catalyst to interact with the substrate 4-methoxybenzoyl group in a binding pocket composed of the methoxyquinoline ring, the 1-anthryl ring, and the pyridazine spacer of the catalyst, and (2) the participation of the stereogenic allylic substituent in binding to the anthryl moiety through hydrophobic and edge−face aryl−aryl interactions in the case of the fast-reacting enantiomer (***S*-4b**) and in repulsive steric interactions with the quinuclidine bound OsO_4 portion of the catalyst in the case of the unreactive enantiomer (***R*-4b**). From this model, it is clear why conventional ligands, such as $(DHQD)_2PYDZ$ (**1**), have not afforded more general and efficient kinetic resolutions. Topological constraints within the binding pocket of this catalyst preclude efficient differentiation between enantiotopic allylic substituents. On the other hand, a ligand such as DHQD-PYDZ-(*S*)-anthryl possesses an open space on one side of the binding pocket where an allylic substituent can reside. The efficiency of the kinetic resolution of racemic olefins by the DHQD-PYDZ-(*S*)-anthryl ligand as compared with the $(DHQD)_2PYDZ$ ligand validates the design principles for this process and should encourage further developmental work in this area.

The efficiency of the kinetic resolution of secondary allylic 4-methoxybenzoates is sensitive not only to catalyst structure but also to the nature of the substrate. The kinetic differentiation between the substrate enantiomers in this process results both from stabilizing interactions between the catalyst and substrate for one enantiomer and destabilizing interactions between the two for the other enantiomer. The fast-reacting enantiomer of **4a** (***R*-4a**) exhibits favorable hydrophobic interactions between its allylic methyl group and the anthryl ring of the catalyst in the transition state of the asymmetric dihydroxylation reaction. The rapidly reacting enantiomer of **4b** (***S*-4b**) presents not only the hydrophobic interactions discussed for **4a** but also stabilizing edge−face aryl−aryl interactions between its phenyl substituent and the anthryl ring of the catalyst, as shown in Figure 5. The slow-reacting enantiomers of **4a** (***S*-4a**) and **4b** (***R*-4b**) both exhibit unfavorable interactions between their corresponding allylic substituents and the quinuclidine bound OsO_4 portion of the catalyst in the asymmetric dihydroxylation transition state, but these repulsions are probably greater in the latter case. This analysis not only predicts the sense of enantiomeric differentiation in the kinetic resolution for both substrates but also explains the greater k_{rel} observed in the kinetic resolution of **4b** as compared to **4a**.

The observed sense and magnitude of diastereoselection in the asymmetric dihydroxylation of enantiomerically pure **4a** and **4b** is also consistent with the model presented in Figure 5. The matched substrates (***R*-4a** and ***S*-4b**) exhibit very high diastereoselectivity corresponding to dihydroxylation of the *si* face of the olefin as shown for ***S*-4b** in Figure 5. Favorable binding interactions between both allylic substituents and elements of the catalyst binding pocket direct the dihydroxylation through this selective pathway. The mismatched substrates ***S*-4a** and ***R*-4b** *give much lower levels of diastereoselection. These* compounds would exhibit prohibitive steric interactions between the secondary allylic substituent and the catalyst on binding the 4-methoxybenzoyl group and probably react through competing less selective pathways.

The asymmetric dihydroxylation of the symmetric substrate **10**, which possesses two enantiotopic vinyl groups, represents a mechanistically related case to the kinetic resolutions presented above. In the transition state for the asymmetric dihydroxylation of the *pro-R* olefin using **5**·OsO_4, the other vinyl group of the substrate resides in the open space adjacent to the anthryl ring of the catalyst in a manner analogous to the dihydroxylation of ***S*-4b** shown in Figure 5. Dihydroxylation of the *pro-S* olefin is unfavorable due to high-energy steric interactions between the other vinyl group of the substrate and the quinuclidine-bound OsO_4 portion of the catalyst in the transition state. The efficiency of the dihydroxylation in this case is measured by the yield, enantioselectivity, and diastereoselectivity of the reaction, all of which are higher for **5** as opposed to **1** as ligand. The sense and magnitude of enantioselection and diastereose-

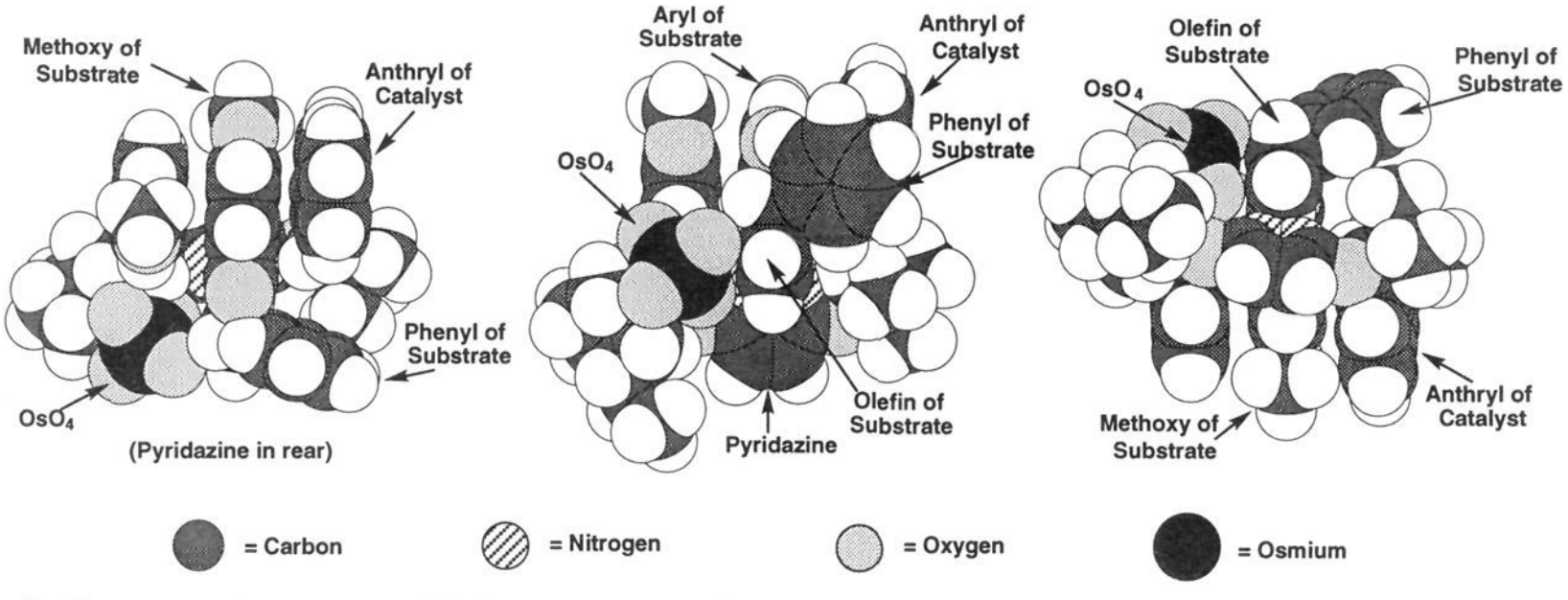


Figure 5. Three views of the complex of ***S*-4b** bound to the DHQD-PYDZ-(*S*)-anthryl catalyst (**5**·OsO_4) which has the geometry indicated in Figure 3.

lection are fully consistent with the guiding mechanistic considerations which are summarized in the Introduction.

Conclusions

The Sharpless asymmetric dihydroxylation process has been applied successfully to the kinetic resolution of 1-substituted allylic alcohols by the use of the 4-methoxybenzoyl derivatives in conjunction with the specifically designed catalyst **5**·OsO_4. The selection of the appropriate derivative and catalyst was made possible by the availability of the transition state model derived from earlier studies. Relative rate factors for the kinetic resolution of enantiomers as high as 79:1 have been attained. This level of efficiency in kinetic resolution approaches the best observed in any non-enzymatic reaction system. The magnitude of the kinetic resolution, the absolute configuration of the recovered olefins, and the relative configuration of the dihydroxylation products provide strong evidence for our mechanistic model for the bis-cinchona alkaloid catalyzed asymmetric dihydroxylation and again demonstrate its heuristic value. The results of these studies could not have been anticipated by application of the mechanistic model proposed by Sharpless *et al.*[14] The insight obtained from this study provides a basis for the rational design of new catalysts and additional subtle applications for the asymmetric dihydroxylation reaction.

Experimental Section

General Methods. All moisture- and air-sensitive reactions were performed in oven- or flame-dried glassware equipped with rubber septa under a positive pressure of nitrogen or argon. When necessary, solvents and reagents were distilled prior to use and were transferred using a syringe or cannula. Reaction mixtures were magnetically stirred. Thin layer chromatography was performed on Merck precoated silica gel F-254 plates (0.25 mm). Concentration *in vacuo* was generally performed using a Büchi rotary evaporator. Kugelrohr distillation temperatures are reported as oven temperatures. Flash column chromatography was performed on Baker 230–400 mesh silica gel. Melting points were determined with a Fisher-Johns hot stage apparatus and are reported uncorrected for all crystalline products. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Nuclear magnetic resonance spectra were recorded on Bruker AM500, AM400, AM300, and AM250 instruments. Proton NMR spectra were recorded in ppm using the residual solvent signal as an internal standard: $CDCl_3$ (7.26 ppm), C_6D_6 (7.15 ppm), or $(CD_3)_2CO$ (2.05 ppm). Carbon NMR were recorded in ppm relative to solvent signal: $CDCl_3$ (77.07 ppm), C_6D_6 (128.0 ppm), or $(CD_3)_2CO$ (29.8 ppm). Mass spectra and high resolution mass spectra (HRMS) were recorded on JEOL Model AX-505 or SX-102 spectrometers and are reported in units of mass to charge (*m/e*). Chiralcel and Chiralpak HLPC columns were obtained from Daicel Chemical Industries, Ltd.

1-Anthryl *tert*-Butyl Ketone (12). To a suspension of 1-anthracenecarboxylic acid (3.00 g, 13.5 mmol)[15] in 125 mL of dry CH_2Cl_2 was added oxalyl chloride (1.24 mL, 14.2 mmol) and *N,N*-dimethylformamide (DMF, *ca.* 100 μL). The mixture was stirred for 1 h at 23 °C, during which time vigorous gas evolution occurred, and a yellow solution formed. After the solvent was removed *in vacuo*, the residual yellow solid was used immediately in the coupling below. In a separate flask, *n*-butyllithium (1.53 M in hexane, 11.5 mL, 17.5 mmol) was added to a solution of *tert*-butyl alcohol (1.7 mL, 18 mmol) in 11.5 mL of THF at −78 °C. The solution was warmed to 23 °C and was then added to a suspension of cuprous iodide (3.4 g, 18 mmol) in 11.5 mL of THF. After the resulting brown suspension was stirred for 20 min at 23 °C, it was cooled to −78 °C, and a solution of *tert*-butyllithium (1.70 M in pentane, 10.3 mL, 17.6 mmol) was slowly added. This mixture was stirred for 5 min at −78 °C, and the acid chloride prepared above was rapidly added as a solution in 200 mL of THF. The resulting mixture was stirred for 30 min at −78 °C and was then quenched by addition of 10 mL of methanol. The mixture was warmed to 23 °C and diluted with 150 mL of saturated aqueous NH_4Cl, and the aqueous layer was extracted three times with 150 mL of ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was filtered through a small plug of silica gel with 4:1 hexane–ethyl acetate, and the residue after concentration was recrystallized from hexane, giving **12** as a yellow solid (2.75 g, 78%): mp 97–98 °C; FTIR (film) 3054, 2968, 2933, 2905, 2870, 1688, 1478, 1280, 1193, 1070, 879, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.45 (s, 1H), 8.20 (s, 1H), 8.00 (m, 3H), 7.44 (m, 2H), 7.43 (t, 1H, J = 7.01 Hz), 7.34 (d, 1H, J = 6.7 Hz), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.4, 138.8, 131.9, 131.6, 131.5, 129.4, 128.5, 128.2, 127.9, 126.9, 125.9, 125.8, 124.4, 123.5, 121.9, 45.6, 27.3; CIMS (NH_3) 280 $[M + NH_4]^+$; HRMS calcd for $[C_{19}H_{18}O]^+$ 262.1358, found 262.1365.

(*S*)-1-Anthryl-*tert*-butylcarbinol (13). To a solution of **12** (1.0 g, 3.8 mmol, dried twice by azeotropic removal of water with toluene *in vacuo*) in 7.6 mL of toluene was added freshly prepared CBS catalyst obtained from (*S*)-diphenylprolinol and *n*-butylboronic acid (3.81 mL of a 0.2 M solution in toluene, 0.76 mmol).[16] A solution of BH_3·DMS in toluene (2.3 mL, 1 M, 2.3 mmol) was added dropwise at 23 °C to this solution over 20 min, and the resulting mixture was stirred for 12 h. A solution of HCl in methanol (2 mL, 0.5 M) was added, and the mixture was stirred for 30 min. Addition of 100 mL of ether resulted in precipitation of (*S*)-diphenylprolinol·HCl for reuse. After filtration of the solid, the filtrate was washed twice with 0.1 M aqueous HCl, twice with $NaHCO_3$ (saturated aqueous), and once with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography (4:1 hexane–ethyl acetate) to afford 0.60 g (60%) of **13** as a yellow syrup of 84% ee (determined by chiral HPLC). Two recrystallizations from hexane gave 0.32 g (32%) of **13** of 98% ee: mp 115 °C; $[\alpha]^{23}_D$ −48.3° (*c* 0.18, $CHCl_3$); FTIR (film) 3450, 3055, 2954, 2869, 1478, 1407, 1364, 1316, 1235, 1056, 1009, 876 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.72 (s, 1H), 8.44 (s, 1H), 8.01 (m, 3H), 7.69 (d, 1H, J = 7.0 Hz), 7.48 (m, 3H), 5.61 (s, 1H), 2.05 (s, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.8, 131.8, 131.3, 131.0, 130.4, 128.6, 128.2, 127.8, 127.0, 125.5, 125.4, 125.0, 124.4, 122.8, 76.7, 37.0, 26.6; EIMS 265 $[M + H]^+$, 207, 178; HRMS calcd for $[C_{19}H_{20}O]^+$ 264.1514, found 264.1519. HPLC (chiral) Chiralcel OD at 23 °C, 10% 2-propanol–hexane, 1 mL/min flow rate, λ = 254 nm, retention times 11.8 (*S*), 14.3 min (*R*).

(*S*)-1-(1-Anthryl)-2,2-dimethylprop-1-yl 6-Chloro-3-pyridazyl Ether (14). To a suspension of potassium hydride (0.016 g, 0.40 mmol) in 2 mL of 1,2-dimethoxyethane (DME) was added **13** (0.10 g, 0.38 mmol). The resulting mixture was stirred for 20 min at 23 °C. 3,6-Dichloropyridazine (0.056 g, 0.38 mmol) (Aldrich) was added, and the mixture was stirred for 30 min at 23 °C. The mixture was cautiously quenched with a little water. The resulting mixture was further diluted with 20 mL of water and extracted three times with 30 mL of ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 0.141 g (99%) of **14** as a light tan solid: mp 120 °C; $[\alpha]^{23}_D$ +460° (*c* 0.40, $CHCl_3$); FTIR (film) 3057, 2972, 2908, 2870, 1582, 1419, 1395, 1287, 1140, 974 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.91 (s, 1H), 8.41 (s, 1H), 8.10 (d, 1H, J = 7.3 Hz), 7.97 (m, 1H), 7.92 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 6.9 Hz), 7.47 (m, 2H), 7.38 (m, 1H), 7.29 (d, 1H, J = 9.2 Hz), 7.19 (s, 1H), 7.04 (d, 1H, J = 9.2 Hz), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1, 150.6, 134.8, 131.6, 131.1, 130.5, 128.9, 128.6, 127.7, 127.0, 125.5, 125.3, 124.5, 124.0, 122.8, 120.1, 80.2, 36.9, 26.6; FABMS 399 $[M + Na]^+$, 376 $[M+H]^+$, 247; HRMS calcd for $[C_{23}H_{21}N_2OCl + Na]^+$ 399.1240, found 399.1249.

(14) The Sharpless model invokes stabilizing interactions between the substrate and a catalyst L-shaped binding pocket in the transition state for a [2 + 2] cycloaddition reaction to form a postulated metallaoxetane intermediate which ultimately produces the product diol. See: (a) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1329. (b) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278. (c) Becker, H.; Ho, P. T.; Kolb, H. C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 7315. (d) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470.

(15) Golden, R.; Stock, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 3080.

(16) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

DHQD-PYDZ-(*S*)-anthryl Ligand (5). To a suspension of hydroquinidine (0.114 g, 0.350 mmol) and 3 mL of toluene was added potassium hydroxide (0.070 g, 1.3 mmol, pulverized prior to use) and **14** (0.12 g, 0.32 mmol). The resulting mixture was heated at reflux (140 °C bath temperature) for 45 min (larger scale reactions require azeotropic removal of water using a Dean Stark trap). After the mixture was cooled to 23 °C, 15 mL of water were added, and the mixture was extracted three times with 30 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (3:97:0.3 MeOH−$CHCl_3$−NH_4OH) to give 0.19 g of **5** (88%) as a light yellow syrup: $[\alpha]^{23}_D$ +188.5° (*c* 0.20, MeOH); FTIR (film) 3054, 2955, 2935, 2871, 1622, 1508, 1474, 1438, 1394, 1364, 1347, 1263, 1243, 1226, 1046, 1004, 877 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.85 (s, 1H), 8.53 (dd, 1H, J = 1.5, 4.4 Hz), 8.37 (s, 1H), 8.06 (d, 1H, J = 5.7 Hz), 7.95 (d, 1H, J = 7.4 Hz), 7.84 (m, 2H), 7.56 (d, 1H, J = 4.9 Hz), 7.45 (m, 2H), 7.36 (m, 2H), 7.27 (d, 1H, J = 7.2 Hz), 7.18 (d, 1H, J = 8.5 Hz), 7.08 (s, 1H), 7.00 (d, 1H, J = 8.9 Hz), 6.91 (d, 1H, J = 9.4 Hz), 6.88 (s, 1H), 3.50 (s, 3H), 3.35 (m, 1H), 2.81 (m, 2H), 2.63 (m, 2H), 1.90 (m, 1H), 1.71 (s, 1H), 1.47 (m, 6H), 1.08 (s, 9H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 160.6, 157.5, 147.3, 144.6, 131.4, 131.3, 131.0, 128.8, 128.3, 127.7, 127.1, 126.9, 125.4, 125.3, 124.8, 124.1, 123.0, 121.8, 121.5, 121.1, 118.9, 102.0, 79.1, 76.2, 59.4, 55.3, 50.8, 50.0, 37.5, 37.1, 27.3, 26.7, 26.1, 25.3, 23.1, 12.0; FABMS 667 $[M + H]^+$, 309, 247; HRMS calcd for $[C_{43}H_{46}N_4O_3 + H]^+$ 667.3648, found 667.3652.

(±)-3-Buten-2-yl 4-Methoxybenzoate (4a). To a solution of 3-buten-2-ol (1.04 mL, 0.865 g, 12 mmol) in 100 mL of CH_2Cl_2 was added triethylamine (1.81 mL, 1.31 g, 13 mmol), DMAP (0.15 g), and 4-methoxybenzoyl chloride (2.0 g, 12 mmol). The mixture was stirred for 24 h at 23 °C and then diluted with 100 mL of CH_2Cl_2. The organic phase was washed with 30 mL of 1 M HCl and 50 mL of $NaHCO_3$ (saturated aqueous), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (250 °C (0.3 mmHg)), giving 1.9 g (79%) of **4a** as a colorless liquid: R_f = 0.58 (4:1 hexane−EtOAc); FTIR (film) 2981, 2935, 2841, 1712, 1607, 1511, 1459, 1335, 1301, 1181, 1102, 1047, 1009, 929, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.01 (dt, 2H, J = 2.8, 9.7 Hz), 6.92 (dt, 2H, J = 2.8, 9.7 Hz), 5.95 (ddd, 1H, J = 5.7, 10.6, 16.3 Hz), 5.57 (m, 1H), 5.31 (ddd, 1H, J = 1.3, 2.6, 17.2 Hz), 5.17 (ddd, 1H, J = 1.3, 2.5, 10.6 Hz), 3.86 (s, 3H), 1.43 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 163.3, 137.9, 131.6, 123.0, 115.6, 113.5, 71.1, 55.4, 20.1; EIMS 206 $[M]^+$, 135 [4-methoxybenzoyl (An)]$^+$; HRMS calcd for $[C_{12}H_{14}O_3]^+$: 206.0943, found 206.0949. A sample of (*R*)-(−)-**4a** was obtained by preparative HPLC (Chiralcel OD at 23 °C, 1% 2-propanol−hexane): $[\alpha]^{23}_D$ −66.3° (*c* 0.73, EtOH). A sample of (*S*)-(+)-**4a** was obtained similarly: $[\alpha]^{23}_D$ +64.4° (*c* 0.71, EtOH). These compounds were stereochemically correlated with 2-butyl 4-methoxybenzoate (**15**) as detailed below.

Kinetic Resolution of (±)-3-Buten-2-yl 4-Methoxybenzoate (4a). A mixture of $K_3Fe(CN)_6$ (0.24 g, 0.73 mmol), K_2CO_3 (0.10 g, 0.73 mmol), DHQD-PYDZ-(*S*)-anthryl ligand (**5**) (0.0016 g, 0.0024 mmol) or $(DHQD)_2PYDZ$ ligand (**1**) (0.0018 g, 0.0024 mmol), (±)-3-buten-2-yl 4-methoxybenzoate (**4a**) (0.05 mL, 0.05 g, 0.24 mmol), and 0.01 mL of α-tetralone (as an internal standard) in 3 mL of 1:1 *tert*-butyl alcohol−water was stirred for 20 min at 0 °C. Approximately 0.025 mL of this mixture was quenched with 0.05 mL of saturated aqueous Na_2SO_3 and extracted with 0.1 mL of EtOAc. The organic layer was concentrated (reduced pressure, 23 °C bath temperature) and analyzed by HPLC (Chiralcel OD at 23 °C, 1% 2-propanol−hexane, 1 mL/min flow rate, λ = 254 nm, retention times (*S*)-(+) (less reactive olefin) 7.3, (*R*)-(−) (more reactive olefin) 8.8, α-tetralone 10.9 min). The reaction was initiated by the addition of $K_2OsO_4{\cdot}2H_2O$ (0.45 mg, 0.0012 mmol), and aliquots were taken and analyzed as indicated above every 5−10 min. Calculation of k_{rel}, the relative rates of reaction of olefin enantiomers, was accomplished using the following equation:[11]

$$k_{rel} = \ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$$

where c = conversion of the reaction and ee = percent enantiomeric excess/100. A plot of $\ln[(1 - c)(1 - ee)]$ vs $\ln[(1 - c)(1 + ee)]$ is linear, with slope equal to k_{rel}.

(*S*)-(+)-2-Butyl 4-Methoxybenzoate (15). To a solution of (*S*)-(+)-3-buten-2-yl 4-methoxybenzoate (**4a**) (0.050 g, 0.24 mmol) in 3 mL of EtOAc was added 5% Rh/C (5 mg) and the resulting mixture was stirred for 20 min at 23 °C under 1 atm of hydrogen. The catalyst was removed by filtration, and concentration of the filtrate afforded 0.050 g (100%) of **15** as a colorless oil: R_f = 0.73 (4:1 hexane−EtOAc); $[\alpha]^{23}_D$ +34.8 ° (*c* 0.61, EtOH); FTIR (film) 2973, 2937, 1709, 1607, 1512, 1462, 1355, 1316, 1302, 1257, 1168, 1101, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (dt, 2H, J = 2.8, 9.6 Hz), 6.91 (dt, 2H, J = 2.7, 9.6 Hz), 5.07 (m, 1H), 3.82 (s, 3H), 1.72 (m, 2H), 1.32 (d, 3H, J = 6.3 Hz), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 163.1, 131.5, 123.3, 113.5, 72.4, 55.4, 29.0, 19.6, 9.7; EIMS 208 $[M]^+$, 152, 135 $[An]^+$; HRMS calcd for $[C_{12}H_{16}O_3]^+$ 208.1099, found 208.1108. An authentic sample of **15** was prepared by 4-methoxybenzoylation of (*S*)-(+)-2-butanol (Fluka) as described above for the preparation of **4a**. Data for authentic **15**: $[\alpha]^{23}_D$ +30.8 ° (*c* 1.13, EtOH).

General Procedure for the Asymmetric Dihydroxylations of Allylic 4-Methoxybenzoates. A mixture of K_2CO_3 (3.00 equiv), $K_3Fe(CN)_6$ (3.00 equiv), $K_2OsO_4{\cdot}2H_2O$ (0.005 equiv), and DHQD-PYDZ-(*S*)-anthryl ligand (**5**) (0.01 equiv) in 1:1 *tert*-butyl alcohol−water was cooled to 0 °C. The resulting suspension was treated with the corresponding olefin (0.08 M olefin concentration with respect to total reaction volume), stirred for the indicated time, and quenched by addition of Na_2SO_3 (12 equiv). The resulting mixture was stirred for 5 min, warmed to 23 °C over 5 min, and partitioned between EtOAc and minimal water. The organic extract was washed twice with brine, dried with Na_2SO_4, and concentrated *in vacuo*. The residue was filtered through a silica gel plug eluting with EtOAc. The filtrate was concentrated *in vacuo* to afford the indicated yield of product.

(2*S*,3*R*)-1,2-Dihydroxybut-3-yl 4-Methoxybenzoate (2*S*,3*R*-9a). Asymmetric dihydroxylation according to the above general procedure on 0.050 g (0.24 mmol) of ***R*-4a** for 2 h gave 0.058 g (99%) of **2*S*,3*R*-9a** of > 100:1 diastereomeric purity (determined by ^1H NMR integration in $CDCl_3$, major diastereomer: 5.11 (1H), minor diastereomer 5.26 (1H)): R_f = 0.25 (2:1 EtOAc−hexane); $[\alpha]^{23}_D$ −25.9° (*c* 1.22, EtOH); FTIR (film) 3600−3000, 2938, 1708, 1607, 1512, 1458, 1318, 1278, 1259, 1170, 1105, 1051, 1030, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96 (dt, 2H, J = 2.6, 9.6 Hz), 6.89 (dt, 2H, J = 2.8, 9.8 Hz), 5.11 (m, 1H), 3.84 (s, 3H), 3.72 (m, 2H), 3.61 (m, 1H), 3.03 (br s, 2H), 1.39 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 163.7, 131.8, 122.2, 113.7, 74.2, 71.1, 62.6, 55.5, 16.5; EIMS 240 $[M]^+$, 202, 153, 135; HRMS calcd for $[C_{12}H_{16}O_5]^+$ 240.0998, found 240.1008. The stereochemistry of **2*S*,3*R*-9a** was verified by (1) conversion to the acetonide with excess 2-methoxypropene and $POCl_3$ in CH_2Cl_2, addition of K_2CO_3, and concentration followed by (2) addition of methanol and stirring for 4 h under nitrogen. The resulting suspension was concentrated and filtered through a small plug of silica gel (1:1 EtOAc−hexane) to afford (2*S*,3*R*)-1,2-*O*-isopropylidinebutane-1,2,3-triol: $[\alpha]^{23}_D$ −36.8° (*c* 0.4, C_6H_6), lit. for the (2*R*,3*S*)-enantiomer: $[\alpha]^{23}_D$ +33.8° (*c* 1.6, C_6H_6).[17]

(±)-1-Phenyl-2-propen-1-yl 4-Methoxybenzoate (4b). To a solution of 1-phenyl-2-propen-1-ol (1.54 mL, 1.57g, 11.7 mmol) in 48 mL of CH_2Cl_2 was added triethylamine (3.07 mL, 2.23 g, 22 mmol) and a catalytic amount of DMAP. After 4-methoxybenzoyl chloride (2.0 g, 12 mmol) was added, the mixture was stirred for 2 h at 23 °C and for 3 h at reflux (60 °C bath temperature). The mixture was cooled to 23 °C, diluted with 50 mL of CH_2Cl_2, and washed with 30 mL of 1 M HCl and 30 mL of $NaHCO_3$ (saturated aqueous). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (8:1 hexane−EtOAc), giving 2.7 g (87%) of **4b** as a colorless liquid: R_f = 0.57 (4:1 hexane−EtOAc); FTIR (film) 3065, 3033, 3009, 2963, 2936, 2840, 1715, 1607, 1582, 1511, 1316, 1256, 1168, 1099, 1030, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.06 (dt, 2H, J = 2.8, 9.8 Hz), 7.44 (d, 2H, J = 7.2 Hz), 7.37 (t, 2H, J = 6.2 Hz), 7.33 (m, 1H), 6.93 (dt, 2H, J = 2.8, 7.3 Hz), 6.48 (d, 1H, J = 5.8 Hz), 6.13 (m, 1H), 5.40 (ddd, 1H, J = 1.3, 2.5, 17.2 Hz), 5.30 (ddd, 1H, J = 1.1, 2.5, 10.4 Hz), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 163.5, 139.2, 136.5, 131.7, 128.5, 128.1,

(17) Mulzer, J.; Angermann, A.; Münch W.; Schlichthörl, G.; Hentzschel, A. *Liebigs Ann. Chem.* **1987**, 7.

127.1, 122.6, 116.8, 113.6, 76.3, 55.4; EIMS 268 $[M]^+$, 135 $[An]^+$, 117; HRMS calcd for $[C_{17}H_{16}O_3]^+$ 268.1100, found 268.1110. HPLC (chiral) Regis Whelk O1 column at 23 °C, 5% 2-propanol−hexane, 1 mL/min flow rate, $\lambda = 254$ nm, retention times 9.9 (*R*)-(−), 16.6 min (*S*)-(+). A sample of (*R*)-(−)-phenylpropenyl 4-methoxybenzoate (***R*-4b**) was prepared from (*R*)-(−)-1-phenyl-2-propen-1-ol (Fluka) as described above: $[\alpha]^{23}_D$ −23.8° (*c* 0.94, EtOH). A sample of (*S*)-(+)-**4b** was prepared similarly from (*S*)-(+)-1-phenyl-2-propen-1-ol (Fluka): $[\alpha]^{24}_D$ +26.5° (*c* 7.44, EtOH).

Kinetic Resolution of (±)-1-Phenyl-2-propen-1-yl 4-Methoxybenzoate (4b). A mixture of $K_3Fe(CN)_6$ (0.24 g, 0.73 mmol), K_2CO_3 (0.10 g, 0.73 mmol), DHQD-PYDZ-(*S*)-anthryl ligand (**5**) (1.6 mg, 0.0024 mmol) or $(DHQD)_2PYDZ$ ligand (**1**) (1.8 mg, 0.0024 mmol), (±)-1-phenyl-2-propen-1-yl 4-methoxybenzoate (**4b**) (0.065 g, 0.24 mmol), and 0.05 mL of dibutyl phthalate (added as an internal standard) in 3 mL of 1:1 *tert*-butyl alcohol−water was stirred for 20 min at 0 °C. Approximately 0.025 mL of this mixture was quenched with 0.05 mL of saturated aqueous Na_2SO_3 and extracted with 0.1 mL of EtOAc. The organic layer was concentrated (reduced pressure, 23 °C bath temperature) and analyzed by HPLC (Regis Whelk O1 column at 23 °C, 5% 2-propanol−hexane, 1 mL/min flow rate, $\lambda = 235$ nm; retention times (*R*) 9.9, (*S*) 16.6, dibutyl phthalate 11.9 min). The reaction was initiated by addition of $K_2OsO_4 \cdot 2H_2O$ (0.45 mg, 0.0012 mmol) to the reaction mixture, and aliquots were taken and analyzed using the above procedure every 5−10 min. The data were analyzed as described for the kinetic resolution of (±)-**4a**. After all of one enantiomer of **4b** had reacted, the mixture was quenched with 2 mL of saturated aqueous Na_2SO_3 and extracted three times with EtOAc. The combined organic layers were washed twice with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (1:1 EtOAc−hexane to elute olefin **4b**, followed by EtOAc to elute diols **9b**) gave 0.026 g of recovered **4b** (41%), which was determined to be the (*R*)-(−)-enantiomer by comparison of its optical rotation ($[\alpha]^{23}_D$ −21.7° (*c* 0.35, EtOH)) with that of an authentic sample prepared as indicated above, and 0.036 g of diols **9b** (50%).

(1*R*,2*S*)-2,3-Dihydroxy-1-phenylprop-1-yl 4-Methoxybenzoate (1*R*,2*S*-9b). Asymmetric dihydroxylation according to the above general procedure on (*S*)-**4b** (0.089 g, 0.332 mmol) for 2.5 h gave a 0.098 g (98%) yield of (**1*R*,2*S*)-9b** of >100:1 diastereomeric purity (determined by ^1H NMR in $CDCl_3$, major diastereomer 5.95 (1H), minor diastereomer 6.09 (1H)): $R_f = 0.37$ (2:1 EtOAc−hexane); $[\alpha]^{23}_D$ +82.1° (*c* 0.42, EtOH); FTIR (NaCl Plate) 3600−3200, 2933, 1712, 1606, 1511, 1458, 1319, 1258, 1169, 1103, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (dt, 2H, $J = 2.4$, 11.1 Hz), 7.45 (d, 2H, $J = 9.1$ Hz), 7.39 (m, 3H), 6.94 (dt, 2H, $J = 2.5$, 12.2 Hz), 5.95 (d, 1H, $J = 9.1$ Hz), 4.07 (m, 1H), 3.84 (s, 3H), 3.80 (dd, 1H, $J = 3.9$, 14.8 Hz), 3.72 (dd, 1H, $J = 6.9$, 14.7 Hz), 2.41 (br s, 1H), 1.65 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 163.7, 137.3, 131.8, 128.6, 128.4, 127.3, 122.0, 113.7, 75.7, 74.0, 62.7, 55.4; CIMS (NH_3) 320 $[M + NH_4]^+$, 303, 244; HRMS calcd for $[C_{17}H_{18}O_5 + NH_4]^+$ 320.1498, found 320.1484. The stereochemistry was verified by (1) conversion to the acetonide with excess 2-methoxypropene and $POCl_3$ in CH_2Cl_2, addition of K_2CO_3, and concentration followed by (2) addition of methanol and stirring for 4 h under nitrogen. The resulting suspension was concentrated and filtered through a small plug of silica gel (1:1 EtOAc−hexane) to afford (1*R*,2*S*)-2,3-*O*-isopropylidine-1-*C*-phenylglycerol: $[\alpha]^{23}_D$ −3.45° (*c* 0.81, MeOH), lit. for (1*S*,2*R*)-enantiomer: $[\alpha]^{23}_D$ +4.5° (*c* 4, MeOH).[18]

1,4-Pentadien-3-yl 4-Methoxybenzoate (10). To a solution of 1,4-pentadien-3-ol (2.0 mL, 1.73 g, 20.6 mmol) in 20 mL of CH_2Cl_2 was added triethylamine (5.6 mL, 4.0 g, 40 mmol), DMAP (234 mg), and 4-methoxybenzoyl chloride (3.43 g, 20 mmol). The mixture was stirred for 18 h at 23 °C. The resulting mixture was diluted with 200 mL of ether, and the organic layer was washed twice with 50 mL of 1 M HCl and once with 30 mL of $NaHCO_3$ (saturated aqueous), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by Kugelrohr distillation (170 °C (0.3 mmHg)), followed by filtration through a silica gel plug eluting with 4:1 hexane−EtOAc, to afford 2.4 g (53%) of **10** as a colorless liquid: $R_f = 0.63$ (4:1 hexane−EtOAc); FTIR (film) 3013, 2988, 2964, 2937, 2841, 1716, 1606, 1512, 1320, 1257, 1168, 1101, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (dt, 2H, $J = 2.7$, 9.7 Hz), 6.92 (dt, 2H, $J = 2.8$, 9.7 Hz), 5.98 (m, 1H), 5.92 (m, 2H), 5.37 (ddd, 2H, $J = 1.6$, 2.9, 15.6 Hz), 5.26 (ddd, 2H, $J = 1.5$, 3.6, 5.5 Hz), 3.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 163.4, 135.3, 131.7, 122.7, 117.3, 113.6, 75.1, 55.4; EIMS 218 $[M]^+$, 135 $[An]^+$; HRMS calcd for $[C_{13}H_{14}O_3]^+$ 218.0943, found 218.0945.

(3*R*,4*S*)-4,5-Dihydroxy-1-penten-3-yl 4-Methoxybenzoate (11). Asymmetric dihydroxylation according to the above general procedure on 0.106 g (0.486 mmol) of **10** gave 0.085 g (70%) of **11** with a >98% ee (determined by HPLC of the bis-benzoate derivative) and >96% de (determined by ^1H NMR analysis). Additionally, 0.017 g (14%) of products from acyl migration (separated by flash chromatography, 1:1 EtOAc−hexane) were also isolated. Data for **11**: $R_f = 0.33$ (1:1 EtOAc−hexane); $[\alpha]^{23}_D$ +66.4° (*c* 0.9, EtOH); FTIR (film) 3600−3300, 2937, 1712, 1606, 1512, 1421, 1320, 1259, 1170, 1104, 1029, 990, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (dt, 2H, $J = 2.8$, 9.7 Hz), 6.91 (dt, 2H, $J = 2.1$, 8.9 Hz), 6.02 (m, 1H), 5.51 (m, 1H), 5.46 (d, 1H, $J = 17.3$ Hz), 5.35 (d, 1H, $J = 10.6$ Hz), 3.87 (m, 1H), 3.84 (s, 3H), 3.75 (dd, 1H, $J = 3.2$, 11.8 Hz), 3.66 (dd, 1H, $J = 5.8$, 11.8 Hz), 2.6 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 163.8, 133.1, 131.9, 122.0, 119.0, 113.8, 74.9, 73.1, 62.6, 55.5; CIMS (NH_3) 253 $[M + H]^+$ 235, 135 $[An]^+$; HRMS calcd for $[C_{13}H_{16}O_5 + H]^+$ 253.1076, found 253.1074. Data for **16** (the diastereomer of **11**, obtained from a 1:1 diastereomeric mixture derived from NMO/OsO_4 oxidation of **10**): ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03 (m, 2H), 6.92 (m, 2H), 5.96 (m, 1H), 5.60 (m, 1H), 5.48 (m, 1H), 5.35 (m, 1H), 3.92 (m, 1H), 3.84 (s, 3H), 3.76 (m, 1H), 3.66 (m, 1H), 2.7 (br s, 2H). HPLC of the bis-benzoate derivatives: Chiralpak AD at 23 °C, 1 mL/min flow rate, 10% 2-propanol−hexane, $\lambda = 254$ nm, retention times for enantiomers of **11** 23.3 (3*S*,4*R*), 25.2 min (3*R*,4*S*) and enantiomers of **16** 20.7, 27.3 min. The diastereomeric purity was determined by ^1H NMR integration of **16** at 5.95 ppm (1H) and **11** at 6.03 ppm (1H) in $CDCl_3$ solution. The stereochemistry was verified by treatment with K_2CO_3 in MeOH for 2 h at 23 °C. The resulting suspension was concentrated and filtered through a small plug of silica gel (1:1 EtOAc−hexane to elute methyl benzoate, followed by 1:1 acetone−MeOH to elute the product) to afford D-erythropentenitol: $[\alpha]^{23}_D$ +22.3° (*c* 0.56, MeOH), lit. $[\alpha]^{23}_D$ +27.4° (*c* 1.16, MeOH).[13]

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