Syntheses and Crystal Structures of the Cinchona Alkaloid Derivatives Used as Ligands in the Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins

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Experimental procedures for the preparation of two classes of derivatives of the cinchona alkaloids dihydroquinine and dihydroquinidine are described. Ligands $(DHQ)_2$-PHAL, 1a, and $(DHQD)_2$-PHAL, 2a, are conveniently synthesized in good yield by the reaction of the corresponding alkaloid with 1,4-dichlorophthalazine in the presence of K_2CO_3 and KOH in refluxing toluene. Derivatives DHQ-PHN, 1b, and DHQD-PHN, 2b, are prepared through an Ullmann-type coupling between the 9-O-alkaloid sodium alkoxide and 9-iodophenanthrene in the presence of CuI and pyridine. Crystal structures for derivatives 2a and 2b are also presented. These four alkaloid derivatives serve as highly enantioselective ligands for the osmium tetraoxide catalyzed asymmetric dihydroxylation (AD) of olefins.

The osmium tetraoxide catalyzed asymmetric dihydroxylation (AD) of olefins has reached high levels of enantioselectivity and practicality in large part due to the development of more effective chiral cinchona alkaloid derived ligands.[1] Since our original report of the stoichiometric[2] and later catalytic[3] variant of this reaction, much effort has been devoted to the design of better ligands for the AD process (Scheme I). Enantiomerically pure or enriched diols obtained through this catalytic process are useful in organic synthesis.[4]

Reported here are the crystal structures and the preparations for the two best ligand pairs found to date.

Quinine and its pseudoenantiomer quinidine have received much attention over the years;[5] their availability and unique properties as drugs, chiral auxiliaries and ligands in asymmetric catalysis have maintained for these famous alkaloids a prominent position throughout the history of organic chemistry.[6] In the course of our continuing effort to provide the optimum conditions for the AD, we have synthesized and evaluated over 300 derivatives of quinine, quinidine and/or their analogs dihydroquinine, 1, and dihydroquinidine, 2 (Chart I).[7,8]

Efforts directed at screening a variety of derivatives of 1 and 2 for the AD at (a) the 6'-O-position of the quinolyl moiety, (b) the C(10)–C(11) vinyl group in the quinine/quinidine series, and/or (c) the 9-O-position of the free hydroxyl group led us to conclude that the latter type of modification is the most promising. Thus, on changing the 9-*O*-DHQD (or 9-*O*-DHQ) substituents from *p*-chlorobenzoate to phenyl (**A**), naphthyl (**B**), 4-methyl-quinolyl, phenanthryl (**C**), and many others (Chart II), we noticed

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(1) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

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(4) (a) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538. (b) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295. (c) Ko, S. Y.; Lee, A. M. M.; Masamune, S. A.; Reed, L. A.; Sharpless, K. B. *Tetrahedron* **1990**, *46*, 245. (d) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623. Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2041. (e) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 2095. (f) Ireland, R. E.; Winpf, P.; Roper, T. D. *J. Org. Chem.* **1989**, *54*, 2284. (g) Rao, A. V. R., Gurjar, M. K., Joshi, S. V. *Tetrahedron Asymmetry* **1990**, *1*, 697. (h) Schreiber, S. L.; Ikemoto, N. *J. Am. Chem. Soc.* **1992**, *114*, 2524. (i) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515. (j) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570. (k) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Asymmetry*, in press.

(5) (a) 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 AD, they behave almost like enantiomers, and hence Wynberg's appellation "pseudo-enantiomers" seems appropriate (see: Wynberg, H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Allinger, N. L., Eds.; John Wiley and Sons: New York, 1986; Vol. 16, p 87). (b) Cordell, G. *Introduction to Alkaloids: A Biogenetic Approach*; Wiley: New York, 1981; p 708. (c) *Drug Information for the Health Care Professional*; U.S. Pharmacopeial Convention: Maryland, 1988, pp 1866 and 1870. (d) For a general review on the chemistry of cinchona alkaloids, see: Grethe, G.; Uskokovic, M. R. In *Heterocyclic Compounds, The Monoterpenoid Indole Alkaloids*; John Wiley and Sons: New York, 1983; Vol. 25, Part 4, Chapter XII, p 729 and references cited therein.

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(7) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585 and references cited therein.

(8) A different class of ligands, for example, the 9-*O*-carbamoyl derivatives, provide up to 80% ee for aromatic cis-olefins: Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

(9) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761.

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Scheme I

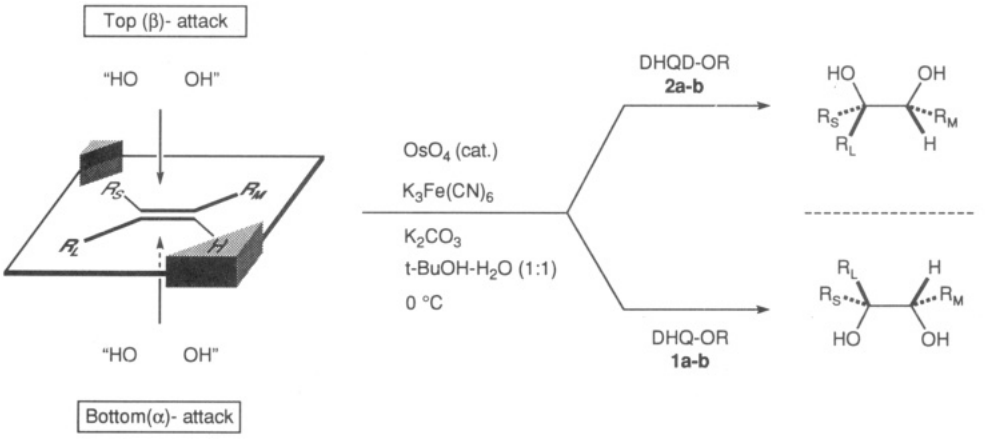
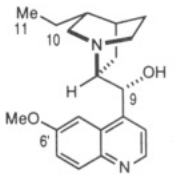
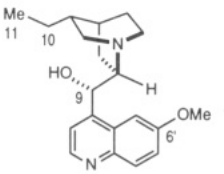


Chart I



Dihydroquinine (DHQ) **1**



Dihydroquinidine (DHQD) **2**

a steady improvement of the levels of enantioselectivity in the dihydroxylation of olefins. In light of these observations we concluded that the larger the group occupying the upper left quadrant[9] the better the ligand and that a bi- or tricyclic planar aromatic group at the 9-O-position of the alkaloid is necessary to achieve optimum enantioselectivity in the AD process. This ligand structure–enantioselectivity relationship[9] (LSER) has proven useful in guiding the ligand improvement task.

A big jump in effectiveness came with the discovery of the phthalazine class of ligands,[1] $(DHQ)_2$-PHAL, **1a**, and $(DHQD)_2$-PHAL, **2a**, which have two dihydroquinine (or dihydroquinidine) entities attached at the 1,4 positions of a phthalazine ring (Chart II (**D**) and Scheme II). This class of ligands has proven to be excellent for the AD reaction, providing a number of 1,2-diols from four different olefin classes with ee's >95%.

Strong evidence that each quinuclidine moiety in the phthalazine class of ligands is operating independently is provided by the observation that quaternization of *one* of the quinuclidine groups ($PhCH_2Br$, EtOH) gave a monoquat-salt ligand that proved to be just as effective as the parent phthalazine ligand **2a** (AD of 1-decene at 0 °C gave 1,2-decanediol in 85% yield and 84% ee).[1] Thus, it appears that in these nominally C_2 symmetrical ligands the phthalazine ring and its bystander alkaloid substituent provide helpful steric blocking for the other operative alkaloid moiety and vice versa (i.e., these phthalazine ligands are operating as C_1 symmetrical ligands). In addition, the bis benzyl-quat salt of **2a** was prepared and found to give only the racemic diol with 1-decene.

Dihydroquinine, **1**, and dihydroquinidine, **2**, are obtained in quantitative yield from the commercially available hydrobromide dihydrate and hydrochloride, respectively, by aqueous ammonia-CH_2Cl_2 extraction. $(DHQ)_2$-PHAL, **1a**, and $(DHQD)_2$-PHAL, **2a**, have been prepared in good yields (76–95%) from reaction of the lithium (n-BuLi, toluene, 0 °C to reflux) or sodium (NaH, DMSO, Cs_2CO_3, 0 °C to reflux) alkoxides of DHQ or DHQD with 1,4-dichlorophthalazine **3**.[10] However, we have recently found a simpler method which involves mixing the free-base alkaloid **1** or **2**, K_2CO_3, 1,4-dichlorophthalazine, and KOH (pellets)[11] in refluxing toluene with azeotropic removal of water to provide the corresponding ligand **1a** or **2a** in 68–88% isolated yields on a 50-g scale (Scheme II). Ligand **1a** is isolated from the crude reaction mixture by simple recrystallization from EtOAc, while **2a** is precipitated as its tetrasulfate salt from acidic ethanol. The salt is then neutralized using a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 to give the free-base ligand. We have found that this tetrasulfate salt could also be used in the AD without affecting the outcome of the reaction (same yield and enantioselectivity as the free-base ligand **2a**). The chemical purity of these ligands is usually >98% (by spectroscopic and elemental analyses), which is satisfactory for use in the AD.[1]

Crystals of ligand $(DHQD)_2$-PHAL, **2a**, suitable for X-ray diffraction, were obtained from an EtOAc–toluene mixture. An ORTEP[12] drawing of its crystal structure is presented in Figure 1.

The structure was solved by direct methods using the SHELX program.[13,14] The cell dimensions and experimental parameters are summerized in Table I. All the bond distances and angles are in the expected range.[13] From all the available crystallographic evidence and after a number of refinement cycles, we concluded that one and a half molecules each of water and toluene are loosely held in the lattice and are undergoing rapid thermal motion.

(10) 1,4-Dichlorophthalazine is commercially available from Aldrich, Inc.; however, for optimal purity, it is preferable to prepare it in one step from phthalhydrazide and PCl_5 and catalytic DMF (see Experimental Section): Hirsch, A., Orphanos, D. *Can. J. Chem.* **1965**, *43*, 2708.

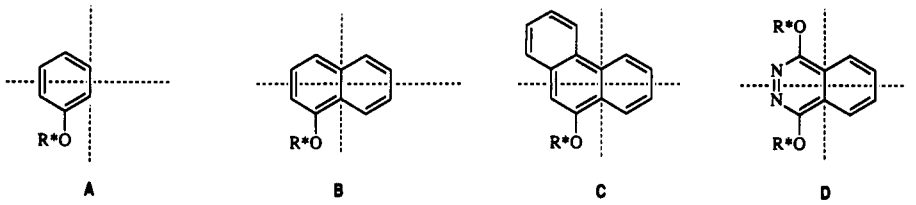
(11) Similar conditions (NaOH) are used by Merck Sharp & Dohme, Inc. for the preparation of a commercial drug: Grabowsky, E. J. J. and Grenda, V. J. Personnal communication. For use of K_2CO_3 with 1-chlorophthalazine see: Hartman, M.; Druey, J. *Chem. Abstr.* **1950**, *46*, 4046; U.S. 2,484,029, Oct 11, 1949.

(12) Johnson, C. K. ORTEP, 1976, Report ORNL-3794, Oak Ridge National Laboratory, TN.

(13) The author has deposited experimental details, solution and refinement parameters, atomic coordinates and equivalent isotropic temperature factors, bond lengths and bond angles, anisotropic temperature factors,and hydrogen atoms coordinates along with the observed and calculated structure factors for the crystal structures of both DHQD-PHN, **1a**, and $(DHQD)_2$-PHAL, **2a**, with the Cambridge Crystallographic Data Centre. This material can be obtained, on request, from the director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

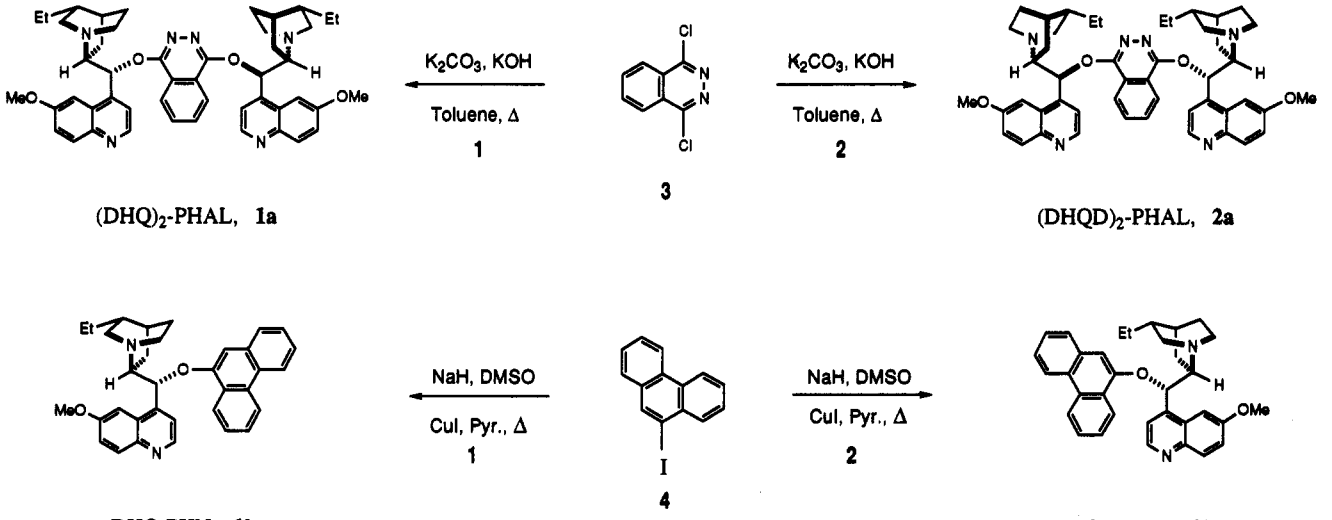
(14) Sheldrick, G. M. SHELXS86, Program for Crystal Structure Determination, University of Cambridge, England, 1986.

Chart II



R*= DHQD or DHQ

Scheme II



This structure also reveals that both quinuclidine rings in (DHQD)$_2$-PHAL, **2a**, are hydrogen bonded to water molecules at 2.875 (6) Å and 2.763 (5) Å, respectively, setting the ligands in an "open-type conformation".[15] A transoid conformation of the dihydroquinidine moieties is adopted in the crystal lattice [both quinolyl (and quinuclidine) rings are anti to each other with respect to the phthalazine ring plane]. The anticipated C_2 symmetry aspect in this ligand seems to be slightly disturbed in the crystal lattice due to both the presence of toluene molecules and to packing forces.

Ligands DHQ-PHN, **1b**, and DHQD-PHN, **2b**, were synthesized using an Ullmann reaction.[16] Thus, 9-*O*-DHQ- or 9-*O*-DHQD-sodium alkoxides[17] were coupled with 9-iodophenanthrene, **4**,[18] in the presence of equimolar amounts of copper(I) iodide[19] and 2 molar equiv of pyridine.[20] Phenanthryl ethers **1b** and **2b** were isolated as their hydrochloride salts in 70–73% yield without the need for chromatography. These salts are also equivalent to their free bases for direct use in the AD. A single-crystal X-ray diffraction analysis of ligand **2b** was carried out. The crystallographic structure was solved by the direct method using MITHRIL[21] and DIRDIF[22] and is presented in Figure 2.

The cell dimensions and experimental parameters are also summarized in Table I.[13] This crystal structure reveals that all the atomic distances and bond angles are in the normal range.[13] It also shows that one molecule of water is hydrogen bonded to the quinuclidine ring at a 2.875 (7) Å distance; thus, an "open-type conformation" is present in this structure as well.[15]

(15) (a) See ref 7o. (b) Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 639 and references cited therein. (d) Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H. *J. Org. Chem.* **1990**, *55*, 6121. (d) Karle, J. M.; Karle, I. L.; Gerena, L.; Milhous, W. K. *Antimicrob. Agents and Chemother.*, in press.

(16) Ullmann, F.; Ochsner, P. *Liebigs Ann. Chem.* **1911**, *1*, 381. Brewster, R. Q.; Goering, T. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 445.

(17) The commercially available 80% suspension of sodium hydride in mineral oil (Aldrich) was thoroughly washed with pentane before use in order to remove the oil. The use of the corresponding potassium salt led to a small increase in yield (~3%). However, this advantage is eroded by an increase in the price of potassium hydride compared to sodium hydride.

(18) (a) Goldberg, M. A.; Ordas, E. P.; Carsch, G. *J. Am. Chem. Soc.* **1947**, *69*, 260. (b) Dougherty, T. K.; Lau, K. S. Y. *J. Org. Chem.* **1983**, *48*, 5273. (c) Suzuki, H.; Kondo, A.; Inoue, M.; Ogawa, T. *Synthesis* **1986**, 121. For a comparison of the efficiency of aromatic iodides versus bromides in the syntheses of dihydroquinidine 9-*O*-aryl ethers: the synthesis of dihydroquinidine 9-*O*-(1′-naphthyl) ether gave 36% yield from 1-bromonaphthalene and 62% yield from 1-iodonaphthalene (with CuCl as mediator, 70% with CuI/1-iodonaphthalene). Synthesis of dihydroquinidine 9-*O*-(9′-phenanthryl) ether **2b** from 9-bromophenanthrene gave 23–50% yield depending on the scale of the reaction. For syntheses of aryl iodides see: (d) Datta, R. C.; Miller, H. K. *J. Am. Chem.* **1919**, *41*, 287. (e) Coad, P.; Coad, R. A.; Clough, S.; Hyepock, J.; Salisbury, R.; Wilkins, C. *J. Org. Chem.* **1963**, *28*, 218. (f) Suzuki, H.; Kondo, A.; Ozawa, T. *Chem. Lett.* **1985**, 411. (g) Diercks, R.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 3150. (h) Meyer, G.; Rollin, Y.; Perichon, J. *Tetrahedron Lett.* **1986**, *27*, 3497.

(19) CuI has been proven to be superior to CuCl as mediator in the coupling reaction of the sodium alkoxide derived from **2** and bromophenanthrene and was therefore selected for the synthesis of the phenanthryl ether **2b** via 9-iodophenanthrene **4** as alkylating reagent. CuBr has not been tested. See also: Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097. For a review on copper(I)-assisted nucleophilic substitutions of aryl halogens, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(20) Running the reaction in neat pyridine resulted in low yields (15–20%).

(21) Gilmore, C. J. MITHRIL—An Integrated Direct Computer Program. *J. Appl. Cryst.* **1984**, *17*, 42.

(22) Beurskens, P. T. *DIRDIF—Direct Methods for Difference Structures—An Automatic Procedure for Phase Extension and Refinement of Difference Structure Factors*; Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed., Nijmegen, Netherlands.

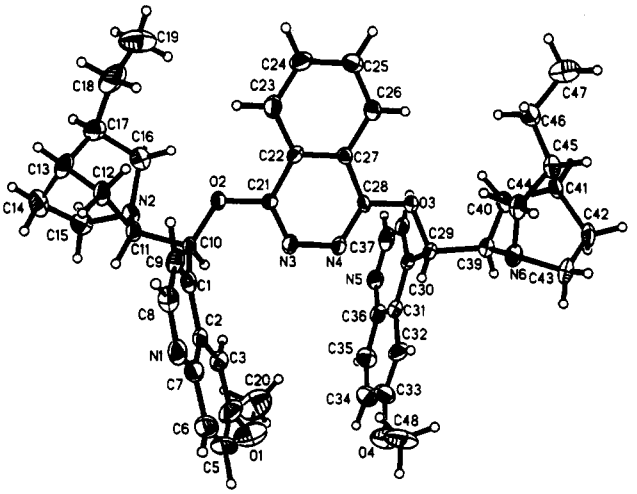


Figure 1.

Table I. Cell Dimensions and Experimental Parameters of $(DHQD)_2$-PHAL 2a and DHQD-PHN 2b

	$(DHQD)_2$-PHAL, 2a	DHQD-PHN, 2b
expl mol formula	$C_{58.5}H_{67.5}N_6O_{5.5}$	$C_{34}H_{36}N_2O_3$
mol wt	942.70	520.67
color; habit	colorless, block-shaped	colorless, prismatic
crystal size (mm)	0.23 × 0.29 × 0.46	0.20 × 0.20 × 0.20
crystal system	orthorhombic	orthorhombic
space group	$P2_12_12$ (No. 18, D_2^3)	$P2_12_12_1$ (No. 19, D_2^4)
unit cell dimen	a = 22.701 (2) Å	a = 16.958 (6) Å
	b = 24.907 (2) Å	b = 18.275 (9) Å
	c = 8.830 (2) Å	c = 9.127 (4) Å
unit cell vol	4993 (1) Å^3	2829 (2) Å^3
Z	4	4
density (calcd) (Mg/m^3)	1.254	1.222
radiation	Cu Kα	Mo Kα
temp (°C)	23	23
obsd reflns (m)	2702	2703
final R	0.081	0.060
final wR	0.112	0.081

From the preparative aspect, both ligands are easily obtained in good yields by using readily available reagents and their purification does not require chromatography.[23] In the absence of a general accepted mechanism for the ligand-assisted osmylation of olefins, a sensible explanation for the "LSER" effects remains out of reach and thus a rational approach to designing better ligands for the AD is not yet possible. At present, our best contenders, **1a–b** and **2a–b** (Chart II), have allowed the asymmetric dihydroxylation of four of the six patterns of olefins in high yields (80–99%) and good to excellent enantiomeric excesses (ee) (65–99%).[1,8] Although the phthalazine-based ligands [$(DHQ)_2$-PHAL, **1a**; $(DHQD)_2$-PHAL, **2a**] have surpassed ligands **1b** and **2b** for most substrates,[1] we have found some cases where the phenanthryl class of ligands are still superior.[4e] The terminal olefins class remains a difficult challenge for these ligands, and ee's of less than 80% are not uncommon. Our current efforts are directed toward the search for better ligands for the AD of terminal olefins—perhaps the single most important class of substrates.[24]

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus in open glass capillaries; the values are uncorrected. Elemental analyses were performed by Robertson Laboratories Inc., Madison, NJ. Analytical thin-layer chromatography (TLC) was performed on Merck precoated glass plates (silica gel 60, F-254, 0.25-mm thick). Preparative column chromatography was performed using EM Reagents silica gel 60, 230–400 mesh. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (75.0 MHz) spectra were recorded on a Brucker AMX 400, Varian XL 300, and Bruker AC 250. IR spectra were obtained on a Perkin-Elmer FTIR 1600 series and a Nicolet 510. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and a Rudolph Autopol III.

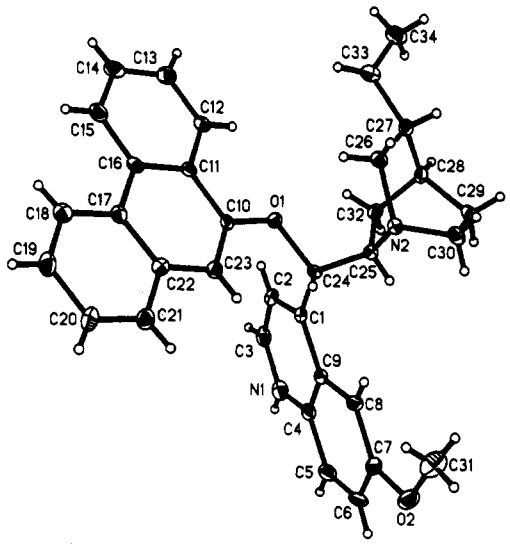


Figure 2.

Improved Procedure for the Preparation of 1,4-Dichlorophthalazine,[10] 3. A 1-L three-necked round-bottomed flask was equipped with a condenser and a mechanical stirrer. The system was flame-dried under a strong flow of nitrogen and then cooled to room temperature. The flask was charged with 81.0 g (0.50 mol) of phthalhydrazide (Aldrich), and 218.40 g (1.05 mol) of phosphorus pentachloride, and 2 drops of DMF. The condenser was fitted with a calcium chloride drying tube (4 × 1 in. of $CaCl_2$ having a cotton plug on each side and directly connected to the condenser to prevent moisture contamination and allow HCl evolution), and the solid mixture was gently heated from room temperature to 145 °C (oil bath temperature) over a 60-min period upon which a steady (over ~3 h) moderatly strong evolution of hydrogen chloride through the condenser-drying tube occurred. The mixture slowly liquified, and the orange solution was heated for an additional 4 hours. The condenser was then replaced with a distillation apparatus, and the phosphorus oxychloride was distilled off. The residual off-white solid was cooled to room temperature, crushed to a fine powder, and then dissolved in 1.2 L of methylene chloride with stirring. After 1 h the solution was filtered and the filtrate was added to 250 g of neutral alumina. After being stirred for an additional hour, the solution was filtered through a 3 in. deep pad of alumina (in a 5-in. diameter sintered glass funnel), and the pad was washed with more methylene chloride (~3 L). The organic layers were combined, dried over $MgSO_4$, and then evaporated to give a white solid. Recrystallization from 750 mL of THF (OmniSolv, EM Science) gave 58.2 g; concentration of the mother liquor and crystallization gave an additional 20.0 g of pure white needles (78%) (R_f 0.35, CH_2Cl_2), mp 162–163.5 °C (lit.[10] mp 164 °C).

Preparation of 1,4-Bis(9-*O*-dihydroquinidinyl)phthalazine, 2a. The dihydroquinidine free base was obtained as follows: 500 mL of ammonium hydroxide (NH_4OH) was added to 75.0 g of the hydrochloride salt [Buchler (Braunschweig), imported by TRAXX Inc. (Pine Brook, NJ)] to give a suspension which was extracted with methylene chloride (3 × 200 mL). The combined extracts were washed with ammonium hydroxide (200

(23) These ligands have been prepared on a 250 g or larger scale by Michigan State University, Department of Chemistry Synthesis Laboratory and by C^3 Inc., OR.

(24) We are currently investigating new ligands which have allowed the AD of 1-decene to proceed with up to 92% ee at 0 °C; N.B. the phthalazine ligand **2a** gives 1,2-decadiol in 84% ee:[1] Sharpless, K. B. et al. Unpublished results.

mL) and then water (200 mL) and finally dried over $MgSO_4$. Concentration provided 55.0 g of the free base.

A 1-L flame-dried one-neck round-bottom flask was charged with 50.02 g (0.153 mol) of dihydroquinidine, 15.55 g (0.078 mol) of 1,4-dichlorophthalazine, **3**, 31.75 g (0.229 mol) of K_2CO_3, and 500 mL of anhydrous toluene. The flask was flushed with nitrogen and then equipped with a Dean-Stark-condenser. Under nitrogen atmosphere, the mixture was refluxed (oil bath temperature 135 °C) for 2 h. Then, 14.54 g (0.229 mol) of KOH pellets (87%) were added and the mixture refluxed (with azeotropic removal of water) and under nitrogen atmosphere for an additional 12 h. [The reaction can be followed by TLC using 20:1 CH_2Cl_2/MeOH (saturated with NH_3 gas) on silica gel. The R_f of the ligand is 0.22.] The light orange solution was cooled to room temperature, mixed with water (100 mL), and then extracted with EtOAc (3 × 150 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and evaporated to dryness. The crude slightly yellow solid was dissolved in absolute EtOH (250 mL), and a solution of 51 g of concentrated H_2SO_4 in 500 mL of absolute EtOH was added over a 10-min period with vigorous stirring. The clear solution was refrigerated (−5 °C) for 2 h, and the resulting white precipitate of the tetrasulfate salt was collected by filtration through a 10–20-μm sintered glass funnel and washed first with cold EtOH (100 mL) and then with diethyl ether (200 mL). If difficulty occurs during the filtration, the ethanolic precipitate solution should be heated until clear and cooled at −5 °C to provide a salt easier to filter.

Physical data: mp 203–205 °C. Anal. Calcd for $C_{48}H_{62}N_6O_{20}S_4$: C, 49.22; H, 5.34; N, 7.18; S, 10.95. Found: C, 48.95; H, 5.54; N, 6.89; S, 10.71.

The free base was easily prepared by dissolving the off-white tetrasulfate salt in water (200 mL) and adding saturated sodium bicarbonate until the solution became basic (pH 9–10). This was then extracted with EtOAc (3 × 200 mL), dried over $MgSO_4$, and concentrated to yield a solid which was dried in vacuo to give 52.30 g (88%) of pure ligand.

Physical data: MS (FAB+) Calcd for $C_{48}H_{54}N_6O_4 + Cs^+$ 911.3261, found 911.3270; mp 133–135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.5 Hz, 2 H), 8.31 (m, 2 H), 7.97 (d, J = 9.2 Hz, 2 H), 7.91 (m, 2 H), 7.55 (d, J = 2.6 Hz, 2 H), 7.43 (d, J = 4.6 Hz, 2 H), 7.35 (d, J = 9.2 Hz, 1 H), 7.34 (d, J = 9.2 Hz, 1 H), 6.96 (d, J = 6.6 Hz, 2 H), 3.9 (s, 6 H), 3.39 (q, J = 15.7 Hz, 2 H), 2.81–2.60 (m, 8 H), 2.34 (s, 1 H), 2.20 (s, 1 H), 1.94 (t, J = 11.1 Hz, 2 H), 1.68 (s, 2 H), 1.58–1.50 (m, 4 H), 1.46–1.38 (m, 6 H), 0.79 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.52, 156.40, 147.36, 145.03, 144.70, 132.09, 131.55, 127.38, 122.79, 122.42, 121.77, 118.54, 102.09, 76.30, 60.26, 55.56, 50.87, 49.96, 37.45, 27.32, 26.28, 25.29, 23.56, 11.88; IR (KBr) ν 2933, 2871, 1623, 1509, 1474, 1455, 1393, 1354, 1262 cm^{-1}; $[\alpha]_D$ −262.5° (c 1.15, MeOH). Anal. Calcd for $C_{48}H_{54}N_6O_4$: C, 74.00; H, 6.99; N, 10.79. Found: C, 73.81; H, 6.89; N, 10.57.

Preparation of 1,4-Bis(9-*O*-dihydroquininyl)phthalazine, 1a. The dihydroquinine free base was obtained as follows: 500 mL of ammonium hydroxide (NH_4OH) was added to 70.0 g of the hydrobromide salt dihydrate [Buchler (Braunschweig), imported by TRAXX Inc. (Pine Brook, NJ)] to give a suspension which was extracted with methylene chloride (3 × 200 mL). The combined extracts were washed with ammonium hydroxide (200 mL) and then water (200 mL) and finally dried over $MgSO_4$. Concentration provided 50.0 g of the free base.

This ligand was prepared starting from 49.6 g of free base dihydroquinine to give 40.0 g of **2a** following the same procedure described in the section above except that methylene chloride was used in the extraction step. The crude product from the reaction mixture was then recrystallized from 1 L of EtOAc, and a second crop of crystals was obtained from the mother liquor (68% total recrystallized yield). (The ligand could not be purified through the tetrasulfate salt method.)

Physical data: MS (FAB+) calcd for $C_{48}H_{54}N_6O_4 + Cs^+$ 911.3261, found 911.3270; mp 176.5–178 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.5 Hz, 2 H), 8.31 (m, 2 H), 7.97 (d, J = 9.21 Hz, 2 H), 7.93 (m, 2 H), 7.57 (d, J = 2.6 Hz, 2 H), 7.42 (d, J = 4.5 Hz, 2 H), 7.353 (d, J = 9.2 Hz, 1 H), 7.346 (d, J = 9.2 Hz, 1 H), 7.00 (d, J = 5.7 Hz, 2 H), 3.91 (s, 6 H), 3.45 (m, 2 H), 3.10 (m, 2 H), 3.01 (d, J = 13.5 Hz, 1 H), 2.99 (d, J = 13.7 Hz, 1 H), 2.53 (m, 2 H), 2.31 (d, J = 13.1 Hz, 2 H), 2.00 (s, 1 H), 1.78 (d, J = 6.1 Hz, 6 H), 1.70 (m, 2 H), 1.39–1.27 (m, 7 H), 0.82 (t, J = 7.21 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.61, 156.38, 147.33, 144.77, 144.72, 132.24, 131.50, 127.22, 122.78, 122.46, 121.80, 118.41, 101.98, 76.31, 60.00, 58.45, 55.63, 42.79, 37.46, 28.59, 27.67, 25.35, 23.52, 12.08; IR (KBr) ν 2919, 2867, 1623, 1594, 1477, 1374, 1306, 1223 cm^{-1}; $[\alpha]_D$ +336.0° (c 1.22, MeOH). Anal. Calcd for $C_{48}H_{54}N_6O_4$: C, 74.00; H, 6.99; N, 10.79. Found: C, 73.01; H, 6.47; N, 10.23.

Dihydroquinidine 9-*O*-(9′-Phenanthryl) Ether, 2b. A 2-L three-necked round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and inert gas in- and outlet was charged with dihydroquinidine, **2** (48.9 g, 0.15 mol) (ground in a mortar). The flask was flushed for 30 min with a gentle stream of argon. Anhydrous dimethyl sulfoxide (600 mL, Fisher Chemicals, anhydrous grade) was added, and the reaction mixture was stirred at room temperature until all the dihydroquinidine dissolved (~45 min). Sodium hydride (4.0 g, 0.17 mol) was added in small portions over 45 min yielding an orange, slightly cloudy solution of the corresponding sodium alkoxide. Upon addition of pyridine (24.2 mL, 0.30 mol) and copper(I) iodide (28.6 g, 0.15 mol) to the reaction mixture at room temperature, the reaction mixture changed color from orange to dark green. After 30 min all of the precipitate dissolved, and a clear solution was formed. 9-Iodophenanthrene, **4** (45.6 g, 0.15 mol), was added, and the reaction mixture was kept at 113 °C for 70 h (oil bath, temperature: 120 °C). The reaction mixture was allowed to cool to room temperature. Water (400 mL), methylene chloride (400 mL), and diethyl ether (200 mL) were successively added to the brown solution followed by ethylenediaminetetraacetate disodium salt dihydrate (83.8 g, 0.23 mol) and concentrated aqueous ammonia solution (60 mL, 29%, w/w). The argon inlet was removed, and a gentle stream of air was flushed through the well-agitated reaction mixture for about 1 h. The reaction mixture was transferred to a separatory funnel and the turquoise blue aqueous phase separated from the dark brown organic phase. The aqueous layer was washed twice with methylene chloride (200 mL), and the combined organic phases were extracted three times with aqueous ammonia solution (200 mL, 5%, w/w) until the aqueous phase remained colorless. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The remaining brown oily residue was dissolved in methylene chloride (500 mL) and extracted twice with hydrochloric acid (200 mL, 5%, w/w) and three times with water (200 mL) in order to remove the remaining dihydroquinidine hydrochloride (dihydroquinidine 9-*O*-(9′-phenanthryl) ether hydrochloride is almost insoluble in water whereas the dihydroquinidine hydrochloride is very readily soluble in the aqueous phase). An additional portion of water (200 mL) was added to the methylene chloride layer followed by concentrated aqueous ammonia in order to obtain a pH value of 9 in the aqueous phase and to neutralize the dihydroquinidine-9-*O*-(9′-phenanthryl) ether hydrochloride which is readily soluble in methylene chloride. The organic layer was separated and dried ($MgSO_4$), and the solvent was removed in vacuo yielding the crude product **2b** as a brown crystalline foam. This crude produce was dissolved in 1 L of anhydrous diethyl ether and treated dropwise with 0.95 equiv of 1.0 M solution of hydrogen chloride in diethyl ether (Aldrich) in order to precipitate the dihydroquinidine 9-*O*-(9′-phenanthryl) ether hydrochloride and to separate the product from remaining 9-iodophenanthrene, **4**.

The slightly brown precipitate was collected and dried in vacuo to yield 59.0 g of the crude dihydroquinidine 9-*O*-(9′-phenanthryl) ether hydrochloride. Further purification is achieved by recrystallization from a minimum volume of hot acetonitrile (~10 mL of solvent per 1 g of hydrochloride salt) yielding block-shaped crystals which melted at 194–195 °C. The yield of this crystallization process was about 60%, but the mother liquor could be further worked up to yield ~10% of slightly impure hydrochloride salt. The dihydroquinidine 9-*O*-(9′-phenanthryl) ether hydrochloride salt may be used directly in the AD process. However, if desired, the free base **2b** can be obtained in quantitative yield from the corresponding hydrochloride by simple neutralization of a solution in methylene chloride with concentrated aqueous ammonia solution (29%, w/w) and thorough extraction of the aqueous phase with methylene chloride.

Physical data: mp 98–100 °C; ^1H NMR (250 MHz, $CDCl_3$) 8.70 (m, 2 H), 8.38 (dd, J = 3.1, 9.3 Hz, 1 H), 8.07 (d, J = 9.2 Hz,

1 H), 7.75 (m, 2 H), 7.57 (d, J = 2.6 Hz, 1 H), 7.4 (m, 6 H), 6.63 (s, 1 H), 6.33 (d, J = 3.8 Hz, 1 H), 4.03 (s, 3 H), 3.38 (m, 1 H), 3.16 (m, 1 H), 2.97 (m, 2 H), 2.78 (m, 1 H), 2.55 (m, 1 H), 2.39 (m, 1 H), 1.81 (s, 1 H), 1.6 (m, 6 H), 0.98 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR ($CDCl_3$) 158.2, 150.4, 147.5, 144.6, 143.7, 132.3, 132.0, 131.5, 127.4, 127.2, 126.7, 126.6, 126.5, 126.4 (2 C), 124.5, 122.8, 122.2, 121.9, 118.1, 104.8, 100.9, 78.8, 60.3, 55.8, 51.0, 50.1, 37.4, 27.1, 26.6, 25.2, 21.7, 11 ppm; IR (KBr) ν 1622, 1508, 1452, 1227 cm^{-1}; $[\alpha]_D$ = −281.3° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{34}H_{34}N_2O_2$ (502.7): C, 80.92; H, 6.99; N, 5.27. Found: C, 81.24; H, 6.82; N, 5.57.

Physical data for dihydroquinidine 9-*O*-(9′-phenanthryl) ether hydrochloride: mp 194–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 13.41 (s, br, 1 H), 8.66 (d, 1 H), 8.56 (m, 3 H), 8.11 (m, 2 H), 8.00 (s, 1 H), 7.76 (m, 2 H), 7.60 (d, 1 H), 7.49 (m, 4 H), 7.18 (s, 1 H), 4.33 (s, 3 H), 3.86 (m, 1 H), 3.70 (t, 1 H), 3.50 (m, 2 H), 3.23 (q, 1 H), 2.96 (m, 1 H), 2.20 (m, 1 H), 1.90 (m, 2 H), 1.56 (m, 1 H), 0.99 (t, 3 H) ppm; ^{13}C NMR ($CDCl_3$) 159.2, 148.4, 146.9, 144.5, 140.2, 131.8, 131.4, 128.0 (2C), 127.1, 126.7, 126.4, 126.1, 126.0, 124.9, 123.1, 122.9 (2C), 121.9, 121.0, 117.6, 106.3, 100.7, 72.7, 59.6, 57.6, 49.4, 49.1, 35.1, 25.5, 24.4, 23.8, 18.9, 11.1 ppm; IR (KBr) ν 3055, 2960, 2320, 2260, 1620, 1590, 1440, 1315, 1315, 1240, 1220, 1220, 1180 cm^{-1}; $[\alpha]_D$ −398.0° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{34}H_{35}N_2O_2Cl$ (539.1): C, 75.69; H, 6.54; N. 5.20; Cl, 6.58. Found: C, 74.71; H, 6.57; N, 5.53; Cl, 6.55.

Dihydroquinine 9-*O*-(9′-Phenanthryl) Ether, 1b. Dihydroquinine 9-*O*-(9′-phenanthryl) ether, **1b**, was prepared from dihydroquinine, **1**, and 9-iodophenanthrene, **4**, according to the same protocol as described for dihydroquinidine 9-*O*-(9′-phenanthryl) ether, **2b**, except of the following changes: The crude product **1b** was further purified by careful addition of 0.95 equiv of hydrogen chloride in anhydrous diethyl ether to an ethereal solution **1b** to yield a light yellow powder. The hydrochloride is collected by filtration and dried in vacuo at 40 °C (dec 236–238 °C).

Free base dihydroquinine 9-(*O*-9′-phenanthryl) ether **1b** was obtained from the corresponding hydrochloride in quantitative yield by simple neutralization of a solution in methylene chloride with concentrated aqueous ammonia solution (29%, w/w) and thorough extraction of the aqueous phase with methylene chloride.

Physical data: mp 95–98 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 8.68 (m, 3 H), 8.60 (d, J = 4.0 Hz, 1 H), 8.53 (d, J = 7.6 Hz, 1 H), 8.09 (d, J = 9.0 Hz, 1 H), 7.75 (m, 2 H), 7.40 (m, 5 H), 6.67 (s, 1 H), 6.43 (d, J = 2.4 Hz, 1 H), 4.04 (s, 3 H), 3.45 (m, 2 H), 3.18 (dd, J = 10.1, 13.4 Hz, 1 H), 2.71 (m, 1 H), 2.49 (m, 1 H), 2.24 (dd, J = 7.7, 13.3 Hz, 1 H), 1.95 (m, 2 H), 1.69 (m, 1 H), 1.51 (m, 2 H), 1.28 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 158.3, 150.0, 147.6, 144.7, 143.2, 132.3, 132.2, 131.5, 127.5, 127.3, 127.0, 126.9, 126.6, 126.5, 126.4, 124.6, 122.9, 122.6, 122.3, 122.0, 118.0, 105.0, 100.8, 78.2, 60.2, 58.8, 56.0, 43.5, 37.4, 28.4, 27.7, 25.6, 21.4, 12.0; IR (KBr) ν 1618, 1508, 1452, 1228 cm^{-1}; $[\alpha]_D$ +248.C (c 0.61, $CHCl_3$). Anal. Calcd for $C_{34}H_{34}N_2O_2$ (502.7): C, 80.92; H, 6.99; N, 5.27. Found: C, 80.50; H, 7.24; N, 5.23.

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