New Ligands and Improved Enantioselectivities for the Asymmetric Dihydroxylation of Olefins†

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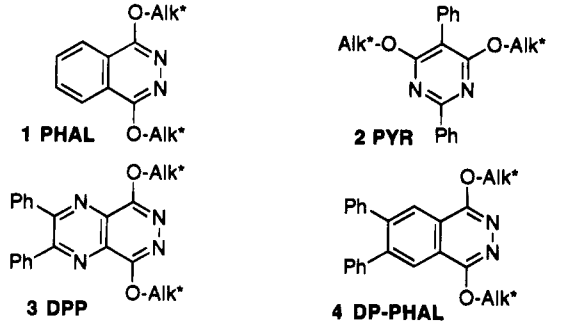
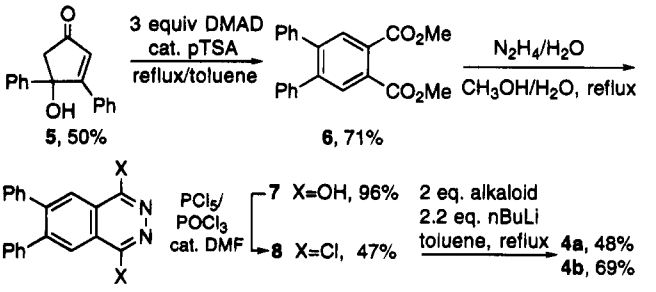
In recent years, the osmium tetraoxide-mediated catalytic asymmetric dihydroxylation (AD) of olefins has become one of the most useful and reliable organic reactions.[1] Bis-cinchona alkaloid ligands employing the 1,4-phthalazine spacer (PHAL, **1a,b**) were first reported to give exceptional enantiomeric excesses (ee's) in the AD's of a variety of olefins.[2] Subsequently, bis-cinchona alkaloid ligands with a pyrimidine spacer (PYR, **2a,b**) were shown to be superior for the AD of terminal olefins, especially those with branching in the substituent.[3] A bis-cinchona alkaloid ligand employing a diphenyl pyrazinopyridazine spacer (DPP, **3a**) was prepared earlier and shown to give improved enantioselectivities for the few olefins with which it was tried.[4] On the basis of these results, we chose to prepare and evaluate the close analogs of **3a,b** having a diphenyl phthalazine spacer (i.e. DP-PHAL, **4a,b**) as AD ligands. In addition, the full scope of ligands **3a,b** was also determined.



a. Alk* = DHQD (Dihydroquinidine)
b. Alk* = DHQ (Dihydroquinine)

The preparation of $(DHQD)_2$-DPP (**3a**) has previously been described[4a,5] and a similar sequence using dihydroquinine gave $(DHQ)_2$-DPP (**3b**).[6] Ligands **4a** and **4b** were prepared by the sequence depicted in Scheme 1 by constructing phthalate diester **6** followed by conversion to hydrazide **7** and dichloride **8**.[7,8] Reaction of the dichloride with the lithium alkoxide of dihydroquinidine or dihydroquinine gave the bis-cinchona ligands $(DHQD)_2$-DP-PHAL (**4a**) and $(DHQ)_2$-DP-PHAL (**4b**).

Scheme 1



Asymmetric dihydroxylations using **3a** and **4a** as ligands were performed on a series of olefins representing five of the six substitution classes of olefins and the results are collected in Table 1.[9] Except for the terminal alkyl olefins (entries 1, 2, 4, and 5) where **2a** remains the ligand of choice, ee's for ligands **3a** and **4a** were generally greater than or equivalent to those for ligands **1a** and **2a**. For example, allyl iodide (entry 3), a potentially useful precursor of a three-carbon chiral synthon,[10] was dihydroxylated in 77% ee using ligand **4a**. Asymmetric dihydroxylations of olefins containing aromatic groups (entries 6, 7, and 9) proceeded with exceptionally high enantioselectivities using ligand **3a**. Using **3a** and **4a**, the AD of an alkyl 1,1-disubstituted olefin (entry 8), a *trans*-disubstituted olefin (entry 10), and a trisubstituted olefin (entry 11) all proceeded with an enantioselectivity equal to or slightly greater than that seen with **1a** and **2a**. Especially noteworthy are the modest to large increases in the ee's observed in the AD of *cis*-olefins (entries 12–15). The enantioselectivities of this group using **3a** and **4a** as ligands are in some cases comparable to the best results to date and are approaching the useful range.[11]

Several representative examples using the diastereomeric ligands **3b** and **4b** were obtained and the results are collected in Table 1. In general, the drop in ee typically observed upon changing from the DHQD to DHQ ligands is small to nonexistent with these new ligands. In fact, the ee actually increased in one case (entry 4). Of special note is the result with 1-decene (entry 2) where **4b** gave a higher ee than even ligand **2b**.

A single crystal X-ray diffraction analysis of ligand **4b** was performed[14] and the structure is shown in Figure 1. This crystal structure is C_2 symmetric with the phenyl rings being twisted 70° relative to the phthalazine ring and is similar to the X-ray structure found for **1a**.[8]

† Dedicated to Professor Hans-Dieter Scharf on the occasion of his 65th birthday.

(1) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(2) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(3) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786.

(4) (a) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Asymmetry* **1993**, *4*, 133–141. (b) Arrington, M. P.; Bennani, Y. L.; Göbel, T.; Walsh, P.; Zhao, S.-H.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 7375–7378. (c) Bennani, Y. L.; Vanhessche, K. P. M.; Sharpless, K. B. *Tetrahedron Asymmetry* **1994**, *5*, 1473–1476.

(5) (a) Körmendy, K.; Ruff, F. *Acta Chim. Hung.* **1990**, *127*, 587–599. (b) Körmendy, K.; Ruff, F. *Acta Chim. Hung.* **1990**, *127*, 253–262.

(6) Full experimental details for an improved synthesis of ligands **3a,b** are given in the supporting information.

(7) For a general procedure to prepare phthalates by this route see, (a) Johnson, J. R.; Grummitt, O. *Organic Syntheses;* Wiley: New York, 1955; Collect. Vol. III, pp 806–807. (b) Grummitt, O. *Organic Syntheses;* Wiley: New York, 1955; Collect. Vol. III, pp 807–808. (c) Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261–367.

(8) For a general synthesis of the PHAL ligands see, Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K.-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844–849.

(9) The AD procedure is the same as for the ligands **1a,b**; a typical procedure is given in the supporting information.

(10) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469–3472.

(11) Using the (9-*O*-indolinylcarbamoyl)dihydroquinidine (DHQD-IND) ligand, the following ee's were observed: entry 12 = 72% ee, entry 13 = 16% ee, entry 15 = 31% ee. (a) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568–7570. (b) VanNieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843–846.

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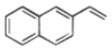
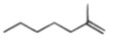
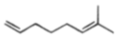
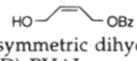
Table 1. Asymmetric Dihydroxylation of Selected Olefins with Ligands 1-4a,b[a]

		Ligand (%ee;[b] absolute configuration)[c]			
Entry	Olefin	**1a (1b) (PHAL)**	**2a (2b) (PYR)**	**3a (3b) (DPP)**	**4a (4b) (DP-PHAL)**
1		79; *R*	**88**; *R*	78; *R*	80; *R*
2		84; *R* (80; *S*)	**89**; *R* (76; *S*)	**89**; *R* (81; *S*)	87; *R* (**85**; *S*)
3[d]		63; *S*	70; *S*	68; *S*	**77**; *S*
4		64; *R* (66; *S*)	**92**; *R* (**87**; *S*)	59; *R* (65; *S*)	67; *R* (73; *S*)
5		88; *R*	**96**; *R*	89; *R*	91; *R*
6		97; *R* (**97**; *S*)	80; *R*	**99**; *R* (**97**; *S*)	98; *R* (96; *S*)
7		99; *R*		>**99.5**; *R*	97; *R*
8		78; *R*	76; *R*	78; *R*	**81**; *R*
9		94; *R* (93; *S*)	69; *R*	**96**; *R* (92; *S*)	94; *R* (**94**; *S*)
10		**97**; *R,R* (93; *S,S*)	88; *R,R*	96; *R,R* (94; *S,S*)	**97**; *R,R* (**97**; *S,S*)
11[e]		98; *R* (**95**; *S*)	87; *R*	98; *R* (94; *S*)	**99**; *R* (91; *S*)
12[f]		35; *1R, 2S*		**68**; *1R, 2S*	63; *1R, 2S*
13[f]		15; *1R, 2S*	7; *1R, 2S*	40; *1R, 2S*	**56**; *1R, 2S*
14		42; *1R, 2S*	35; *1R, 2S*	20; *1R, 2S*	**53**; *1R, 2S*
15[g]		64; *1S, 2R*		**82**; *1S, 2R*	73; *1S, 2R*

[a] The ee's of the asymmetric dihydroxylation reactions are found to be highly reproducible. For example, the AD reaction of styrene in the presence of $(DHQD)_2PHAL$ was repeated 5 times under the same conditions and the ee was determined 3 times for each reaction; all ee's were found between 97.3% and 97.6%. [b] For ee determination of the product diols, see *supporting information*. [c] For absolute configuration determination of the product diols, see *supporting information*. [d] AD run under buffered conditions (3 mmol $NaHCO_3$ added to normal recipe). [e] Product is 2-methyl-7-octene-2,3-diol. [f] See ref 11a for a comparison to (DHQD)-IND. [g] See ref 11b for a comparison to (DHQD)-IND.

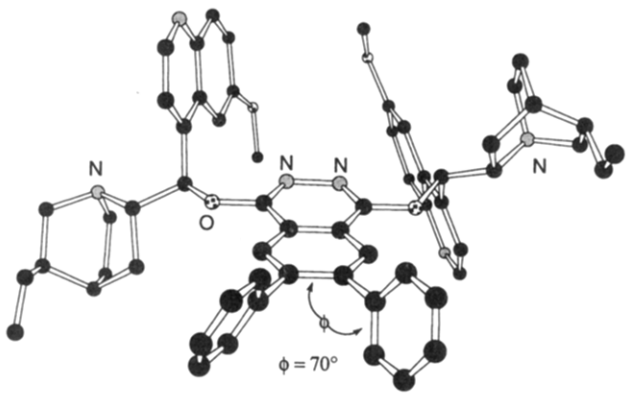


Figure 1. X-ray structure of ligand **4b**.

In summary, ligands **3a,b** and **4a,b** have been prepared and found to give excellent enantioselectivities in the AD of olefins. Except for the terminal alkyl olefins where **2a,b** usually remain the ligands of choice, ee's using the new diphenyl substituted ligands **3a,b** and **4a,b** are generally greater than or equivalent to those of ligands **1a,b** and **2a,b**. Taken together with the improved enantioselectivities observed for the *cis*-olefin class, ligands **3a,b** and **4a,b** are the most general ligands for the AD described to date.[12-14]

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Supporting Information Available: General experimental procedures, including synthesis and characterization of the new ligands **3a,b** and **4a,b**. Determination of ee and absolute configuration of the product diols (11 pages).

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(12) The new ligands described here not only give superior ee's, but also accelerate the AD reaction even more than ligand **1a**. A relative rate study shows that styrene reacts about 1.9 and 1.4 times faster in the presence of **3a** and **4a**, respectively, than in the presence of **1a**. For details, see supporting information.

(13) We feel that the observed changes in enantioselectivity upon increasing the steric bulk at the "backside" of the phthalazine spacer can be explained by our current mechanistic proposal. (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291. (b) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1994**, *116*, 8470–8478. (c) Becker, H.; Ho, P. T.; Kolb, H. C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 7315–7318. The observed changes in enantioselectivity upon phthalazine structural modification are not consistent with the current Corey–Noe mechanistic proposal. Structural changes to this part of the ligand should not significantly change the enantioselectivity according to that model. (a) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am Chem. Soc.* **1994**, **116**, 12109–12110. (b) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427–6430. (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579–12580.

(14) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.