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A Comparison of Ligands Proposed for the Asymmetric Dihydroxylation

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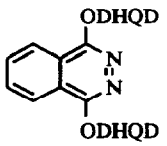
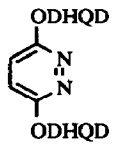
Abstract: Comparative data for several ligands proposed recently for use in the osmium-catalyzed asymmetric dihydroxylation (AD) are presented.

1,4-*Bis*(dihydroquinidyl)phthalazine **1a**, and its dihydroquinine analog, have greatly increased the scope of the osmium-catalyzed asymmetric dihydroxylation (AD), giving high enantioselectivities for five out of the six classes of olefins.[1] During the time that has elapsed since the earliest communication of these results,[2] reports from two laboratories have appeared proposing the use of other ligands[3] in the AD, namely, 1,4-dihydroquinidylpyridazine **2a**,[4] and dihydroquinidylterephthalate **3a**.[5] The purpose of this letter is to compare the enantioselectivities displayed by the latter with those obtained with the phthalazine class in the AD.



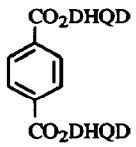
$(DHQD)_2$-PHAL

1a



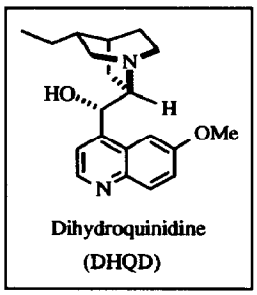
$(DHQD)_2$-PDZ

2a



$(DHQD)_2$-TP

3a



Dihydroquinidine
(DHQD)

Tables 1 and 2 compare the enantioselectivities obtained for several substrates of interest using the dihydroquinidine (Table 1) and dihydroquinine (Table 2) versions of the ligands in question. The terephthalate ligand **3a** and its dihydroquinine analog gave substantially lower enantioselectivities in every case (Table 1). In fact, the terephthalate ligands give enantioselectivities comparable to the dihydroquinidyl and dihydroquinyl-*para*-chlorobenzoate ligands (**4a** and **4b**) which were the first ligands introduced for the catalytic AD.[6]

Dihydroquinylpyridazine **2b** also gives results inferior to dihydroquinylphthalazine **1b** (Table 2). This is especially evident in the *trans*-disubstituted and trisubstituted olefin classes. As shown in Table 1, dihydroquinidylpyridazine **2a** gives results virtually identical within experimental error (± 1%) to the phthalazine **1a** for the substrates shown in Table 1.[7]

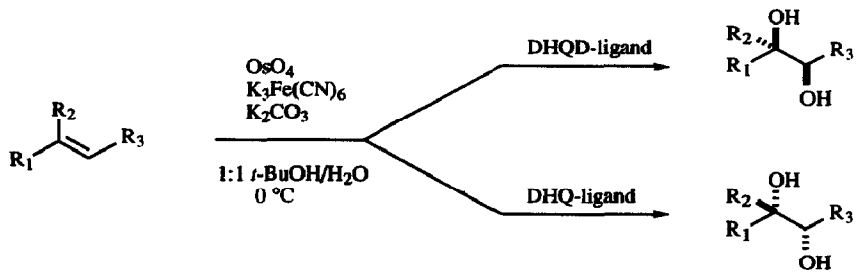
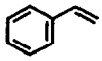
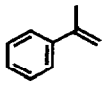
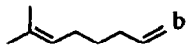
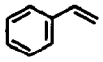
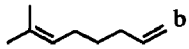


Table 1: Enantioselectivities obtained using *dihydroquinidyl* substituted ligands[a]

		1-decene	*(E)*-5-decene		 b
$(DHQD)_2$-PHAL, **1a**	**97%**	**84%**	**97%**	**94%**	**98%**
$(DHQD)_2$-PDZ, **2a**	96%	83%[c]	96%	93%	95%
$(DHQD)_2$-TP, **3a**	80%[d]	39%[d]	82%	72%	77%

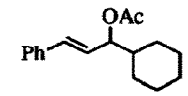
a) The AD's were run as described in ref. 2. The ee's were measured using HPLC and GLC analysis of the diols or MTPA esters as described in refs. 2 and 8. The configuration of the resulting diols are all *R* (or *R,R* for decane-5,6-diol). b) The product is 2-methyl-7-octene-2,3-diol, see ref. 8. c) Corey[4] reports 71% ee. d) Lohray[5] reports 92% ee for styrene and 45% ee for 1-decene. The enantiomeric excesses were determined by comparison of measured optical rotation values with reported literature values, by ^{1}H NMR analysis of the corresponding bis-MTPA esters, or by ^{1}H NMR (200 MHz) using a chiral shift reagent with the corresponding bis-acetate derivatives.

Table 2: Enantioselectivities obtained using *dihydroquinyl* substituted ligands[a]

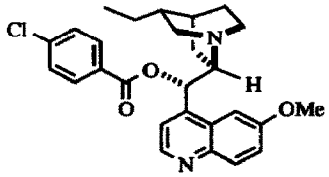
		*(E)*-5-decene	 b
$(DHQ)_2$-PHAL, **1b**	**97%**	**93%**	**94%**
$(DHQ)_2$-PDZ, **2b**	93%	83%	81%
$(DHQ)_2$-TP, **3b**	79%[c]	75%	65%

a) The AD's were run as described in ref. 2. The ee's were obtained using HPLC and GLC analysis of the diols or MTPA esters as described in refs. 2 and 8. The configuration of the resulting diols are all *S* (or *S,S* for decane-5,6-diol). b) The product is 2-methyl-7-octene-2,3-diol, see ref. 8. c) Lohray[5] reported 85% ee using the methods described in the legend for Table 1.

Finally, Lohray has proposed the use of the terephthalate **3a** for the kinetic resolution of allylic acetates.[9] His report that the terephthalate **3a** gives better resolution of 1-acetoxy-1-cyclohexyl-3-phenyl-2-propene than does the phthalazine **1a** was confirmed by us, however, we observed (Table 3) a lower relative rate than he reported (7.4 compared to 10.7[10]). Of more significance is the observation that dihydroquinidyl-*para*-chlorobenzoate **4a** gives slightly better kinetic resolution than the terephthalate **3a**.[12]

Table 3: Kinetic resolution[a] of: 

	ee[b] at 60% conversion	k_{rel}
$(DHQD)_2$-PHAL, **1a**	38%	2.3
$(DHQD)_2$-TP, **3a**	79%[c]	7.4
DHQD-CLB, **4a**	**81%**	**8.0**



DHQD-CLB
4a

a) The kinetic resolutions were performed as described by Lohray in ref. 9. b) The ee of the recovered allylic acetate was determined with a Chiralcel OF HPLC column using an eluent of 1.0% iPrOH in hexane and a 0.75 mL/min flow rate. The configuration is *S*, see ref. 9. c) Lohray reports 88% ee as determined by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent.

In conclusion, we have demonstrated that the phthalazine ligand class is superior to the other ligand classes reported recently for use in the AD. Since it is virtually certain that new ligands will be found which will eclipse even the present best ones ,[13] the search for new ligands should continue.

Acknowledgments

We thank Dr. Marcos Soler for preparing $(DHQD)_2$-TP **3a**. This work was supported by a grant from The National Institutes of Health (GM-28384).

References and Notes

1. Morikawa, K., Park, J., Andersson, P. G., Hashiyama, T., Sharpless, K. B., *J. Am. Chem. Soc.* **1993**, 115, 8463 and references cited therein.
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.
3. Both of the ligands in question (**2a** and **3a**) were prepared and tested by the Sharpless group at MIT, as part of the general ligand screening process. They were subsequently rejected due to the observed superiority of the phthalazine class of ligands in virtually all applications of the AD process: Hartung, J., Jeong, K.-S., Sharpless, K. B. unpublished results. (Pyridazine ligands **2a** and **2b** are included in MIT's U.S. Pat. Appl. No. 077/775, 683, Oct. 10, 1991.)

4. Corey, E. J., Noe, M. C., Sarshar, S. *J. Am. Chem. Soc.*, **1993**, *115*, 3828.
5. Lohray, B. B., Bhushan, V. *Tetrahedron Lett.* **1992**, *33*, 5113.
6. Jacobsen, E. N., Markó, I., Mungall, W. S., Schröder, G., Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.
7. Since the enantioselectivities obtained with dihydroquinidylpyridazine **2a** and the phthalazine **1a** are very close for most substrates, cost considerations may make this pyridazine attractive for β-face selective AD on a large scale.
8. Crispino, G. A., Sharpless, K. B. *Synlett* **1993**, 47.
9. Lohray, B. B., Bhushan, V. *Tetrahedron Lett.* **1993**, *34*, 3911.
10. The relative rate can be calculated by application of the following equation:[11]

$$k_{rel} = \ln(1-C)(1-ee)/\ln(1-C)(1+ee)$$

where C is the percent conversion/100 and ee is the enantiomeric excess of the recovered olefin/100, respectively. A relative rate of 10.7 can be calculated with C = 0.60 and ee = 0.88 as reported in ref. 9.
11. This equation is an adaptation of one presented by Kagan where the variables have been changed to those most applicable to synthetic problems. Balavoine, G.; Moradpour, A.; Kagan, H. B. *J. Am. Chem. Soc.* **1974**, *96*, 5152.
12. It is not clear at present why $(DHQD)_2$-PHAL **1a** gives kinetic resolution inferior to either $(DHQD)_2$-TP **3a** or DHQD-CLB **4a**. This unexpected result is currently under investigation. For examples of kinetic resolution with the phthalazine class of ligands see: VanNieuwenhze, M. S., Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864.
13. A recent report from these laboratories describes a new class of diphenylpyrimidine ligands which give higher enantioselectivies than phthalazine **1** for terminal olefins, especially those with branching in the substitutent: Crispino, G. A., Jeong, K.-S., Kolb, H. C., Wang, Z.-M., Xu, D., Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

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