Improved Enantioselectivity in Asymmetric Dihydroxylations of Terminal Olefins Using Pyrimidine Ligands

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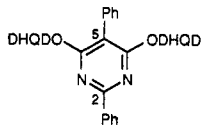
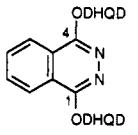
Summary: Bis-cinchona alkaloid substituted pyrimidine ligands were found to give improved enantioselectivity in the osmium-catalyzed asymmetric dihydroxylation (AD) of monosubstituted terminal olefins.

Recently, we reported that a class of ligands employing the 1,4-phthalazine spacer gives exceptional ee's in the osmium-catalyzed asymmetric dihydroxylation of olefins (AD).[1] However, the generally poorer results obtained for terminal olefins, especially those with branching in the substituent, prompted us to continue the search for even better ligands.[2] In this paper we describe a new class of ligands which shows great promise for terminal olefins.

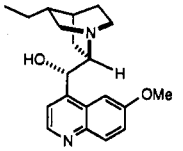
After an initial screen involving many variously substituted pyrimidines, we found that 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinidyl)pyrimidine, **1**, gave 92% ee for 3,3-



1
$(DHQD)_2$-PYR



3
$(DHQD)_2$-PHAL



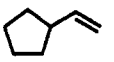
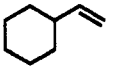
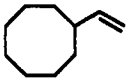
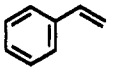
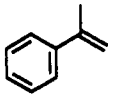
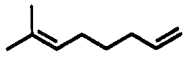
Dihydroquinidine
(DHQD)

dimethyl-1-butene,[3] a poor substrate (only 64% ee) for the dihydroquinidine–phthalazine ligand **3**. Evaluation of **1** with other monosubstituted terminal olefins quickly revealed its superiority (see Table I). Of special note is the complementary nature of the pyrimidine and phthalazine ligands: the pyrimidine class gives poorer results with 1,1- and 1,2-disubstituted and trisubstituted olefins. Several representative results obtained using the pseudoenantiomer of **1**, 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl)pyrimidine, **2**, are also shown in Table I. The drop in ee's observed for **2** compared with **1** are generally larger than in the phathalazine class.

The diphenylpyrimidine ligands **1** and **2** are easily prepared in three steps starting with condensation of commercially available ethyl phenylmalonate and benzamidine hydrochloride in the presence of sodium methoxide[4] (Scheme I). The resulting 2,5-diphenyl-4,6-dihydroxypyrimidine is converted to the 4,6-dichloride with $POCl_3$[4] or PCl_5 and finally condensed with dihydroquinidine or dihydroquinine in the presence of KOH/K_2CO_3 in toluene to afford the pure ligand after recrystallization. The steps are high yielding and require no chromatography, making them practical on a large scale.

Molecular modeling studies[5] of the new diphenylpyrimidine ligand reveal that the 5-phenyl group is twisted almost 90° relative to the pyrimidine ring, while the 2-phenyl group is nearly planar with the pyrimidine ring (Figure 1).[6] We believe that this configuration, with one of the dihydroquinidine portions acting as a steric barrier,

Table I[a]

	olefin	% ee[b] and configuration[c] of the resulting diol: $(DHQD)_2$-PYR **1**	$(DHQD)_2$-PHAL **3**
1		**89**, *R* (76% *S*)[d]	84, *R*
2		**92**, *R* (87% *S*)[d]	64, *R*
3		**93**, *R*	80, *R*
4		**96**, *R*	88, *R*
5		**94**, *R* (87% *S*)[d]	87, *R*
6[e]		80, *R*	**97**, *R*
7		69, *R*	**94**, *R*
8		88, *R*,*R*	**98**, *R*,*R*
9[f]		87, *R*	**98**, *R*

[a] These AD's were run with 1.0 mol % of OsO_4 and 1.0 mol % of ligand; see ref 3. [b] Enantiomeric excesses were determined by HPLC or GLC analysis of the diols or MTPA esters; see supplementary material. [c] The relative configurations of the diols were determined by comparison of their optical rotations with literature values; see supplementary material. [d] The AD was run with $(DHQ)_2$-PYR, **2**. [e] See ref 8. [f] The product is 2-methyl-7-octene-2,3-diol; see ref 10.

(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.

(2) Sharpless, K. B.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Ho, P. T.; Jeong, K.-S. Unpublished results.

(3) Representative procedure for the AD of 3,3-dimethyl-1-butene with $(DHQD)_2$-PYR, **1** (Table I, entry 2): To a well stirred solution of $(DHQD)_2$-PYR (8.8 mg, 1.0 mol %), $K_3Fe(CN)_6$ (990 mg, 3 mmol), K_2CO_3 (420 mg, 3 mmol), and OsO_4 (42 μL of a 0.25 M solution in toluene, 1.0 mol %) in 1:1 *tert*-butyl alcohol/water (5 mL of each) at 0 °C was added 3,3-dimethyl-1-butene, (84 mg, 1.0 mmol). The mixture was stirred for 3 h, and then $Na_2S_2O_5$ (1.5 g) was slowly added and the suspension warmed to room temperature. CH_2Cl_2 (10 mL) was added, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and then concentrated. The crude product was flash chromatographed on silica with 7:3 ethyl acetate/hexane as eluent to give (*R*)-3,3-dimethyl-1,2-butanediol (94 mg, 80%) as a clear colorless oil. The ee was determined by analysis of the bis-MTPA ester. The single difference between this and the general procedure described in ref 1 is that five times the amount of Os is used which results in a much faster reaction.

(4) Schubert, H.; Zaschke, H. *J. Prakt. Chem.* **1970**, *312*, 494.

(5) Molecular modeling studies were carried out with the MacroModel program using the modified MM2 force field (MacroModel V3.5×): Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(6) A preliminary crystal structure of the OsO_4 complex of **1** shows the same conformation of the phenyl groups with respect to the pyrimidine ring: Sharpless, K. B.; Bennani, Y. L., unpublished results.

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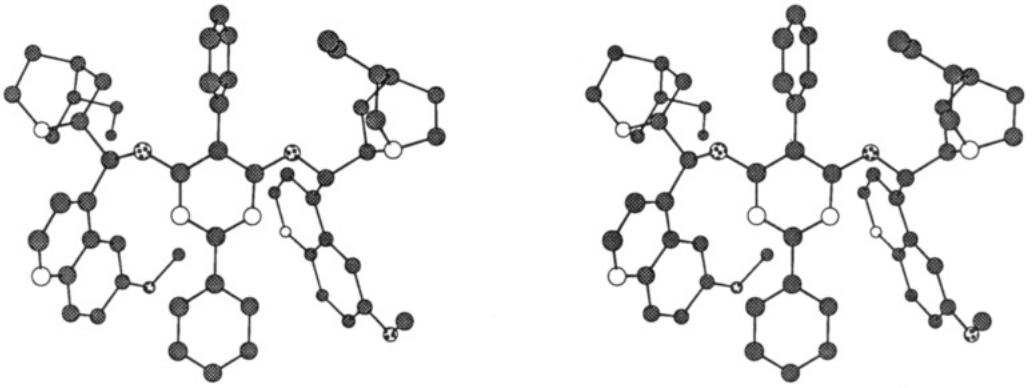
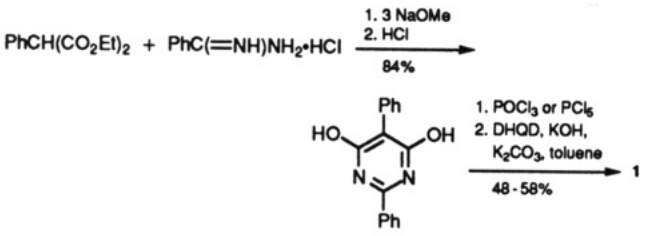
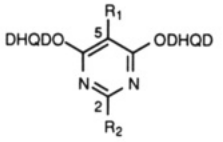


Figure 1. Stereoview of the lowest energy conformation of **1**. The alkaloid on the left of the pyrimidine ring is in the closed conformation (cannot bind), while the alkaloid on the right is in the open conformation (binds Os). Nitrogen atoms are represented by open circles, carbon atoms by darkened circles, and oxygen atoms by dotted circles.

Scheme I



sets up a cavity for the approach of the olefin. Experimental evidence supports the modeling studies.[7] Thus, replacement of the 5-phenyl by *tert*-butyl (ligand **4**) gives



4 (R_1 = *t*-butyl, R_2 = Ph)
5 (R_1 = Ph, R_2 = *t*-butyl)

results very similar to the 2,5-diphenylpyrimidine **1**, indicating the 5-substitutent simply acts as a steric barrier. In contrast, replacement of the 2-phenyl with *tert*-butyl (ligand **5**) has a disasterous effect on the ee, perhaps due to disruption of the putative cavity.

In conclusion, the phthalazines, **3** and its DHQ analog, are still the ligands of choice for the 1,1- and 1,2-*trans*-disubstituted as well as the trisubstituted classes of olefins. However, the results shown in Table I demonstrate the general[8] superiority of diphenylpyrimidine ligands **1** and **2** for monosubstituted terminal olefins, especially those with branching in the substitutent,[9] making them the preferred ligands for this challenging class of substrates.

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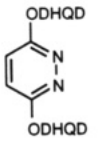
Note Added in Proof. Pyridazine ligand ***i*** has been proposed for the AD (Corey, E. J.; Noe, M. C.; Sarahar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828). This ligand was phthalazine **3**'s inspiration and immediate predecessor (both are included in MIT's U.S. Pat. Appl. No. 07/775, 683, Oct. 10, 1991), but we have never recommended pyridazine ***i*** for research use because it gives ee's inferior to those obtained with phthalazine **3**. In an industrial application cost considerations might make this pyridazine attractive, so it remains under investigation by Dr. Yun Gao of Sepracor, Inc., Marlborough, MA.



i
(DHQD)$_2$-PDZ

Supplementary Material Available: Experimental procedures and spectral data for ligands **1** and **2**, enantiomeric excess determinations for the diols or their MTPA esters, and the optical rotations of the diols (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Kinetic data are consistent with the occurrence of attractive interactions between the olefin and 9-*O*-substituent in the transition state: Andersson, P. G.; Kolb, H. C.; Sharpless, K. B. Manuscript in preparation.

(8) As shown in Table I (entry 6), the phthalazine ligand **2** gives much higher ee for styrene than the pyrimidine ligand **1** (97% ee compared to 80% ee). Insofar as styrene can be regarded as a branched monosubstituted olefin, its anomalous position here can not be explained at present.

(9) Table I shows only simple hydrocarbon branching. We also have substantial experience with vinyl substrates involving heteroatom branching, especially those involving double asymmetric synthesis. Please FAX us at (619) 554-6406 if you would like advice on a specific case.

(10) Crispino, G. A.; Sharpless, K. B. *Synlett* **1993**, 47.