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A Mechanistically Guided Design Leads to the Synthesis of an Efficient and Practical New Reagent for the Highly Enantioselective, Catalytic Dihydroxylation of Olefins

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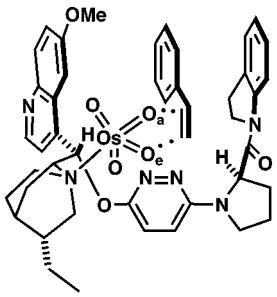
ABSTRACT



The catalytic asymmetric dihydroxylation of olefins has been accomplished with high enantioselectivities using a proline-based catalyst. The pre-transition-state assembly for styrene is shown.

The high enantioselectivity and broad applicability of the biscinchona alkaloid-catalyzed dihydroxylation of olefins by osmium tetraoxide have made this reaction a synthetic tool of extraordinary utility.[1,2] Although initially the underlying reasons for its effectiveness were obscure, a series of mechanistic studies generated a transition-state model that has turned out to be both rational and powerfully predictive.[3−7] The model can be illustrated by the proposed pre-transition-state assembly, **1**, for the enantioselective dihydroxylation of styrene by OsO_4 using a pyridazine-linked bisdihydroquinidine catalyst. On the basis of this model, several new and useful catalysts have been designed, including the Noe−Lin (**2**)[5d] and Zhang (**3**)[8] systems for the position-selective and enantioselective terminal dihydroxylation of oligoprenols (e.g., farnesyl acetate).

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

(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.

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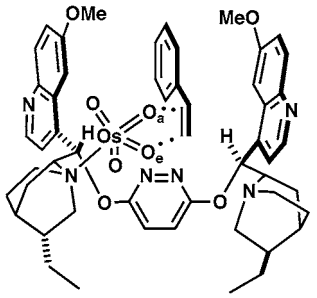

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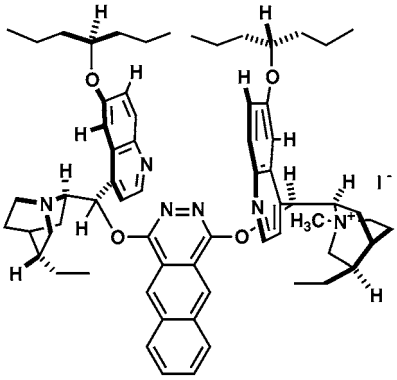

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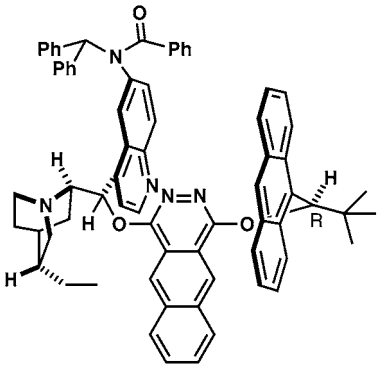

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In this paper, we describe the synthesis and successful application of a new ligand for the enantioselective dihydroxylation of olefins that was based on guidance from the mechanistic model. On the basis of the model, we expected that the (*R*)-proline-derived catalyst **4** would be effective whereas the (*S*)-proline diastereomer (**5**) would not be.

A simple two-step synthesis of the (*R*)-proline-based catalyst **4** is summarized in Scheme 1. Conversion of dihydroquinidine (**6**) to the sodium salt with NaH in dimethylformamide followed by reaction with 1 equiv of 3,6-dichloropyridazine afforded the cross-coupling product **8**. A second coupling of **8** with the (*R*)-proline amide **9** under palladium catalysis produced catalyst **4** as a crystalline solid, mp 131−132 °C, $[\alpha]^{22}_{D}$ +29.0 (c = 1.2, $CHCl_3$). The (*R*)-proline amide **9** was prepared by coupling of the acid chloride of *N*-carbobenzyloxy-(*R*)-proline with dihydroindole followed by hydrogenolysis of the Cbz protecting group, as shown in Scheme 1 (bottom). The (*S*)-proline-derived diastereomer of **4** (**5**) was also prepared by the route shown in Scheme 1 starting from (*S*)-proline.

Ligand **4** dramatically accelerated the dihydroxylation of a series of olefins under the same conditions that have been employed previously for catalytic reactions with the biscinchona alkaloid−OsO_4−$K_3Fe(CN)_6$−*t*-BuOH−H_2O system. The results obtained for the catalytic dihydroxylation of 12 olefinic substrates under promotion by ligand **4** are summarized in Table 1. Both the rates and enantioselectivities observed using ligand **4** (0.7 mol %) with these substrates are at least equal to the best that have been reported for any other ligand, including the popular Sharpless biscinchona ligand $(DHQD)_2PHAL$. The synthetic accessibility of ligand **4**, the requirement for only 0.7 mol % in the catalytic dihydroxylation, the ease of recovery of **4** for reuse, and the exceptional catalytic efficiencies and enantioselectivities that are documented in Table 1 all combine to recommend the use of this new reagent.

The use of ligand **5**, the diastereomer of **4** derived from (*S*)-proline, in the catalytic dihydroxylation of olefins led to only poor enantioselectivity as expected from the mechanistic model. The enantioselectivity was in fact no better than with

Scheme 1

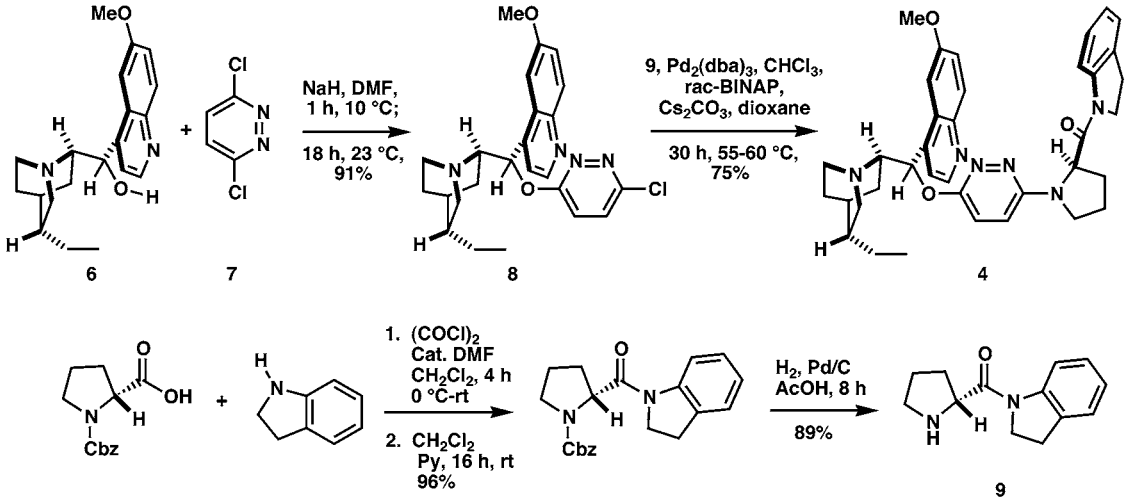

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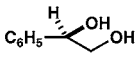
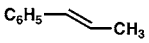
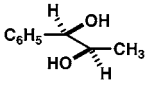
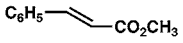
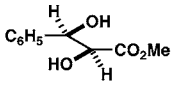
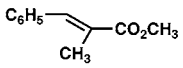
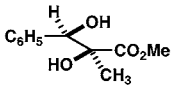
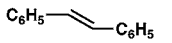
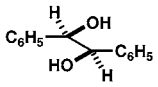
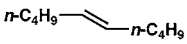
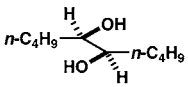
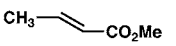
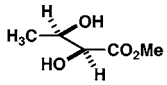
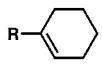
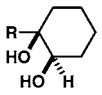
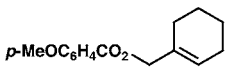
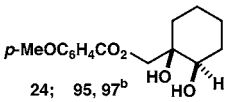
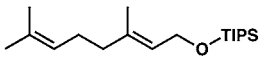
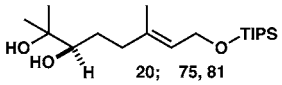
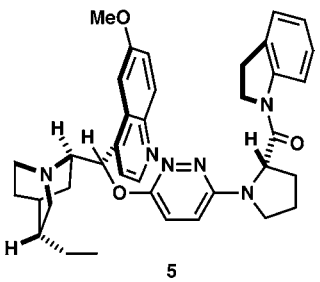
Table 1. Enantioselective Dihydroxylation of Olefins Catalyzed by **4** (0.7 mol %)

olefin	diol[a] time (h); yield, ee (%)
	 8; 94, 93
	 18; 94, 97
	 28; 76, 96
	 40; 86, 85
	 20; >99, 99.5
	 16; 95, 78
	 18; 67, 84
	 R = C_6H_5, 18; 90, >99[b] R = *n*-C_4H_9, 16; 96, 79 R = CO_2Me, 16; 72, 89
	 24; 95, 97[b]
	 20; 75, 81

[a] Reaction performed at 0 °C following the general procedure in the ref 9; ees were determined by ^{1}H NMR analysis of Mosher diesters. [b] Ees determined in these two cases by HPLC analysis using a Chiracel OJ column.

the simpler dihydroquinidine **8** (Scheme 1). Thus, with styrene as a substrate and **5** and **8** as chiral ligands, the OsO_4-mediated dihydroxylation produced styrenediol of 56 and 53% ees, respectively. Similarly, much lower ees were observed with **5** as ligand and either *trans*-stilbene or 1-phenylcyclohexene as a substrate than those recorded in Table 1 for ligand **4**.



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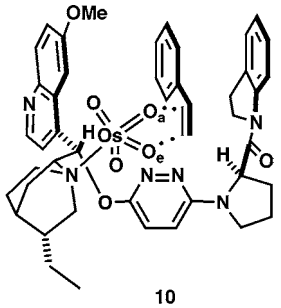
The pre-transition-state assembly for the enantioselective dihydroxylation of styrene by OsO_4 and ligand **4** that was anticipated from the mechanistic model[3,4] is shown in **10**. This structure contains the following elements, in common with other highly enantioselective chiral ligand−OsO_4 complexes: (1) a U-shaped conformation that allows attack by the axial oxygen and one equatorial oxygen of OsO_4 on the π-bond of the substrate, as it is bound within the pocket that forms from the structural subunits of the U, and (2) a minimum motion pathway from this arrangement for the [3 + 2]-cycloaddition, which directly produces the pentacoordinate osmate(VI) ester in the energetically most favorable geometry.[3,4] The rate acceleration for the observed enantioselective pathway relative to other modes of reaction is due to a lowering of $\Delta G^{\ddagger}$ that results from increased binding to ligand **4** in the transition state and to initial precomplexation of the reactants (these reactions follow saturation, i.e., Michaelis−Menten kinetics[4d]). [3 + 2]-Cycloaddition to the opposite π-face of the olefin is unfavorable because there is no comparably stable three-dimensional transition-state arrangement. The pyridazine ring at the bottom of the U-shaped binding pocket is oriented to allow coplanarity of the O−C and N−C subunits attached at positions 3 and 6 (for maximum conjugation of O and N into the electron-attracting pyridazine ring). The prolyl amide linkage is coplanar in **10**, and the planes of the proline and dihydroindole rings are approximately at a 90° angle. Two-dimensional NOE ^{1}H NMR studies of the monomethiodides of **4** and **5** confirm that the proline α-C−H and indoline methylene protons at C(2) are juxtaposed as indicated in the depictions **4**, **5**, and **10** shown herein. The mechanistic model predicts that **5**, the diastereomer of ligand **4**, cannot form a similar favorable U-shaped binding pocket and, thus, should not lead to the level of enantioselectivity realized with ligand **4**. We believe that the experimental results disclosed herein for ligands **4** and **5** add additional weight to the already strong case[4d] for the mechanistic model.

In conjunction with the development of **4** as a useful reagent for the asymmetric dihydroxylation of olefins, we undertook to find a more practical substitute for $K_3Fe(CN)_6$ as the stoichiometric oxidant in the Sharpless procedure. In larger scale reactions, the huge amount of $K_3Fe(CN)_6$ that is normally required (3 mol/mol of olefin) and the attendant workup and disposal issues represent major drawbacks. Some years ago, we observed that sodium chlorite ($NaClO_2$), an inexpensive oxidant, could replace $K_3Fe(CN)_6$ in catalytic enantioselective oxidations with biscinchona catalysts.[10]

(9) **General Procedure for Catalytic Asymmetric Dihydroxylation.** A mixture of ligand **4** (5 mg, 0.008 mmol), $K_2OsO_4{\cdot}2H_2O$ (1.0 mg, 0.0027 mmol), $K_3Fe(CN)_6$ (1.18 g, 3.57 mmol), K_2CO_3 (0.493 g, 3.57 mmol), and $MeSO_2NH_2$ (113 mg, 1.19 mmol, only when 1,2-disubstituted or trisubstituted olefins were used as substrates) in 12 mL of 1:1 *t*-BuOH−H_2O was stirred at 0 °C for 0.5 h. The olefin (1.19 mmol) was added to the suspension, and the resulting mixture was stirred vigorously at 0 °C for

However, a major disadvantage of the $NaClO_2$ system was the oxidation of the catalytic ligand (resulting in its loss) and also overoxidation of the olefinic substrate. A recent reinvestigation of $NaClO_2$ as an oxidant has led to the development of an excellent dihydroxylation system consisting of 0.7 mol % OsO_4, 10 mol % $K_3Fe(CN)_6$, 50 mol % $NaClO_2$, and 4 equiv of K_2CO_3 with 1:1 *t*-BuOH−H_2O as the solvent. The best results are obtained when the $NaClO_2$ is added slowly to the reaction mixture. A representative procedure appears below.[11] In general, enantioselectivities were very good and reaction rates were satisfactory, as shown for the five examples in Table 2.



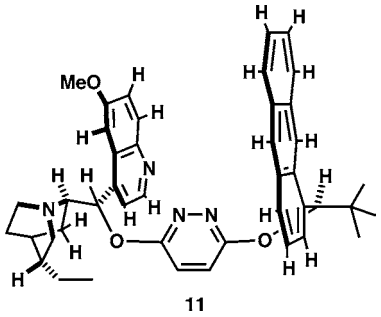
10

The yields of product diol were also good but somewhat lower than those for the conventional Sharpless procedure. In the case of stilbene as the substrate, the lower yield was accounted for by the coproducts benzil (15%) and benzoic acid (~5%), both of which appear to be formed by further oxidation of the intermediate Os(VI) ester. The chiral ligand **4** could be recovered efficiently from the $NaClO_2$-promoted dihydroxylations under the conditions employed.[11] We believe that the $NaClO_2$ procedure described herein is at least as practical as any currently available.[12]

Catalyst **4** is structurally quite distinct from the monoquinidine dihydroxylation catalyst **11**[4c] that has previously been designed and shown to be at least the equal of the best biscinchona catalysts such as $(DHQD)_2PHAL$. Though the noncinchona elements in **11** and **4** are very different, these catalysts are both excellent reagents for the asymmetric dihydroxylation of a variety of olefins, and the enantioselectivity vs olefin structure profiles are essentially the same. From a practical standpoint, however, **4** is superior to **11**

Table 2. Enantioselective Dihydroxylation of Olefins Catalyzed by **4** (0.7 mol %) with $NaClO_2$ as a Cooxidant

olefin	diol time (h); yield, ee (%)
C_6H_5	16; 97, 90
C_6H_5 CO_2CH_3	24; 75, 90
C_6H_5 C_6H_5	16; 73, 99
C_6H_5	16; 85, 91
p-$MeOC_6H_4CO_2$	16; 85, 94



11

because of the greater ease of synthesis. The experimental results obtained with **11**[4c] and **4**, by themselves, provide strong support for our three-dimensional transition-state model,[3,4] which is as aesthetically pleasing as it is powerfully predictive.

Acknowledgment. We are grateful to Pfizer, Inc., for generous support of this research.

Supporting Information Available: Experimental procedures and physical data are given for compounds **4**, **8**, and **9** and characterization data for chiral 1,2-diols. This material is available free of charge via the Internet at http://pubs.acs.org.

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8−24 h. The reaction was monitored by TLC (20−50% EtOAc/hexane). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with Na_2SO_3 (1.5 g) at 0 °C and then allowed to warm to room temperature and stirred for 45 min. The reaction mixture was extracted three times with ethyl acetate (3 × 25 mL). The combined organic extract was washed with 1 N KOH (to remove methanesulfonamide when necessary) and 15 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give the diol (10−70% EtOAc in hexane) as a colorless solid or colorless oil and the ligand **4** (5% TEA/EtOAc for elution; quantitative recovery). The enantiomeric excess (ee) of diols was determined either by chiral-column HPLC analysis or ^1H NMR analysis of the corresponding MTPA esters.

(10) Corey, E. J.; Noe, M. C. Unpublished work, 1994.

(11) **Representative Procedure for Catalytic Asymmetric Dihydroxylation Using $K_3Fe(CN)_6$ and $NaClO_2$ as Cooxidants.** A mixture of ligand **4** (8 mg, 0.013 mmol), $K_2OsO_4 \cdot 2H_2O$ (1.0 mg, 0.0027 mmol), $K_3Fe(CN)_6$ (17 mg, 0.05 mmol), and K_2CO_3 (0.276 g, 2.0 mmol) in 5.0 mL of 1:1 *t*-BuOH−H_2O was stirred at 0 °C for 0.5 h. Styrene (0.057 mL, 0.5 mmol) was added to the suspension. To the resulting stirred mixture was added a solution of $NaClO_2$ (31 mg in 0.2 mL of H_2O) over 5 h by syringe pump. Stirring was continued at 0 °C until the reaction was complete as indicated by TLC. The reaction mixture was treated with Na_2SO_3 (0.7 g) and then allowed to warm to room temperature and stirred for 45 min. The reaction mixture was extracted three times with ethyl acetate (3 × 25 mL). The organic extract was washed with 15 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to give styrenediol (50% EtOAc in hexane) as a colorless solid, yield = 134 mg (97%), and the ligand **4** (5% TEA−EtOAc, 100%). The enantiomeric purity was determined to be 90% by ^1H NMR integration analysis of the corresponding bis-MTPA ester ($CDCl_3$, 500 MHz): δ 6.28 ppm (dd, 1 H, (*R*, major)), 6.18 ppm (dd, 1 H, (*S*, minor)).

(12) See: Wirth, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 334.