Pergamon

Tetrahedron Letters, Vol. 35, No. 35, pp. 6427-6430, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01348-9

A Mechanistically Designed Mono-cinchona Alkaloid Is An Excellent Catalyst for the Enantioselective Dihydroxylation of Olefins

E. J. Corey*, Mark C. Noe and Michael J. Grogan

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: *On the basis of ideas recently advanced regarding the origin of enantioselectivity in the OsO_4-promoted dihydroxylation of olefins catalyzed by bis-cinchona alkaloid derivatives such as 1, specifically strong evidence for reaction via transition state assembly 2, the mono-quinidine derivative 3 was selected as a promising catalytic ligand. The experimental observation of high enantioselectivity promoted by 3 provides additional evidence in favor of transition-state 2.*

A detailed explanation has recently been provided of the basis for high enantioselectivity in the dihydroxylation of many olefins in the presence of catalytic amounts of osmium tetraoxide and certain bis-cinchona alkaloid derivatives.[1-3] For the example of dihydroxylation of styrene with the bis-cinchona catalyst **1**, the following factors have emerged as crucial for enantioselectivity: (1) a preference for the U-shaped conformation **2** for the OsO_4 complex of **1** (*but not for free 1 which is relatively flexible*), (2) the ability of **2** to hold olefinic substrates such as styrene in a binding pocket composed of the two parallel methoxyquinoline units and the pyridazine connector, as shown, (3) the proximity of one axial oxygen and one equatorial oxygen of the complexed OsO_4 unit to the olefinic carbons of the bound substrate, as shown in **2**, and (4) a minimum motion pathway from this arrangement for the [3+2] cycloaddition which directly produces the pentacoordinate osmate ester in the energetically most favorable geometry.[4] The rate acceleration for the observed enantioselective pathway relative to other modes is due to the favorable free energy of activation for reaction from the complex **2** in which the reactants are held in a manner which is ideal for formation of the thermodynamically more stable osmate ester. Dihydroxylation of the opposite olefin face to that shown in **2** is unfavorable due to the fact that there is no three-dimensional arrangement for simultaneous π-facial approach of the olefin to the oxygens labeled as O_a and O_e and favorable interaction with the binding pocket. X-ray crystallographic data suggest that the pyridazine ring at the bottom of the U-shaped cavity tends to be oriented so as to allow conjugation of the ring and the two alkoxy substituents, with the N-N side of the ring participating in binding to the substrate,[2] though the exact tilt of this ring during reaction probably varies with substrate.

On the basis of this model it was predicted that the mono-cinchona alkaloid derivative **3** should be an excellent catalyst for the enantioselective OsO_4-mediated dihydroxylation of olefins—comparable to the highly effective bis-cinchona derivative **1**. The essential features of **3** include the presence of a large tertiary butyl substituent to maintain the *s*-trans geometry between it and the pyridazine unit and to ensure the perpendicularity between planes passing through the pyridazine and anthracene rings. Molecular mechanics calculations using the CHARMm force field indicated that the most stable conformation of the (3-pyridazinyl)-(*t*-butyl-1-anthracenylmethyl) ether moiety of **3** corresponds to that shown. This preference and the geometrical constraints within the OsO_4 complexed cinchona subunit result in the U-shaped geometry depicted by stereoformula **3**. This paper describes the synthesis of **3** and its study with regard to preferred conformation and catalytic behavior in the asymmetric dihydroxylation reactions.

Ligand **3** was prepared from acid **4**[5] as follows. Conversion of **4** to the acid chloride, followed by treatment with $[t\text{-BuOCu}t\text{-Bu}]^- Li^+$ (prepared from *t*-BuOCu and *t*-BuLi)[6] in THF at -78 °C for 30 min, gave the ketone **5** in 78% yield as a yellow crystalline solid (m.p. 97-98 °C). CBS reduction[7] using the oxazaborolidine

Table 1. Enantioselective Dihydroxylation of Olefins Catalyzed by **1** and **3**[a]

Olefin	Cat. **1**, ee, (% yield)	Cat. **3**, ee, (% yield)
E-stilbene	> 99 (99)	> 98 (92)
E-3-hexene	93 (58)[b]	96 (74)[b]
styrene	96 (95)	91 (76)
2-vinylnaphthalene	99 (98)	98 (93)
1-decene	79 (95)	78 (86)
1-phenylcyclohexene	98 (88)	93 (99)

[a] Reactions were conducted according to footnote 10. All 1,2-diols were of the (*R*) or (*R*, *R*) configuration. [b] Yields not optimum because of less efficient extractive isolation.

Table 2. Enantioselective Dihydroxylation of Olefins Catalyzed by **1** and **3**

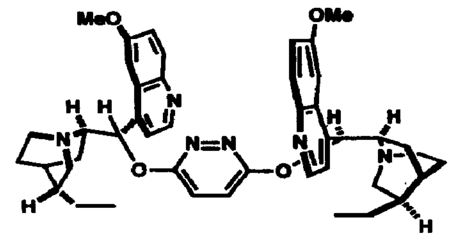
Olefin	Cat. **1**, ee, (% yield)	Cat. **3**, ee, (% yield)
Styrene	96 (95)	91 (76)
4-Methoxystyrene	98 (98)	97 (88)
4-Nitrostyrene	98 (78)	99 (79)
3-Nitrostyrene	96 (89)	95 (99)
3,5-Dinitrostyrene	94 (83)	96 (90)

derived from (*R*) diphenylprolinol and *n*-butylboronic acid gave the carbinol **6** in 88% yield with 78% ee. This was subsequently enriched to 98% ee after two recrystallizations from hexane (m.p. 115 °C, $[\alpha]^{23}_{D}$ +42° (c=0.20, $CHCl_3$). Deprotonation of **6** using KH in DME, followed by reaction with 3,6-dichloropyridazine gave the chloropyridazine ether **7** as a tan solid (m.p. 120 °C) in 99% yield. Coupling with dihydroquinidine using powdered KOH (4 equiv) in refluxing toluene with azeotropic removal of water gave **3** as a light yellow syrup in 88% yield.

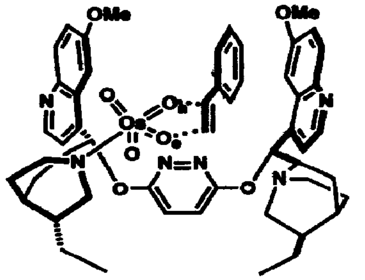
Structural studies of ligand **3**, which were carried out on the stable, crystalline mono-CH_3I salt as a model of the non-crystalline OsO_4 complex, have confirmed the expected molecular geometry. ^1H NMR comparison of the methiodide derivative of **3** with the methiodide derivatives or OsO_4 complexes of bis-cinchona alkaloids[8] such as **1** reveals a close conformational similarity. Both the solid state and solution structures of **3** are strikingly similar to the recently reported structures of bis-cinchona alkaloid ligands.[2] Crystals of the methiodide salt of **3** were obtained from a CH_3CN solution of the free base and 1 equiv of CH_3I at 23 °C.[9] X-ray crystallographic analysis of **3**•CH_3I revealed structure **8** in which the pyridazine ring is oriented to allow conjugation of the ring and its two alkoxy substituents with the N-N side pointing into the binding pocket. The anthracene and 6-methoxyquinoline rings are oriented in parallel planes perpendicular to the plane of the pyridazine ring. This conformation is also predominant in solution as indicated by the following NMR observations (500 MHz, $CDCl_3$, 23 °C): (1) a 7.3% NOE between H_a and H_b and a 3.0% NOE between H_a and H_c supporting the orientation of the methoxyquinoline ring shown in **3**; (2) J H_bH_c = 0-2 Hz, indicating a *ca.* 90 ° dihedral angle between them (66 ° in the solid state); (3) δ H_e = 1.28 ppm, δ H_d = 2.48 ppm consistent with shielding and deshielding effects of the methoxyquinoline ring expected for structure **3**; (4) an 11.6% NOE between H_f and H_g supporting the orientation of the anthracene ring shown in **3**.

The olefin dihydroxylation enantioselectivities observed for the anthracene derived ligand **3** and the bis cinchona ligand **1**, as summarized in Table I, are nearly identical, a striking validation of our design principles.[10] Further, the rates of the catalytic reactions with ligands **1** and **3** are essentially the same as shown by competitive rate experiments. Thus, using 1 mol% of the dihydroquinine PYDZ analog of **1** (which converts styrene to the (*S*) glycol) and 2 mol% of **3**, styrene was oxidized to (*R*) styrene glycol in 31% ee (calc'd for identical rates, 33%).

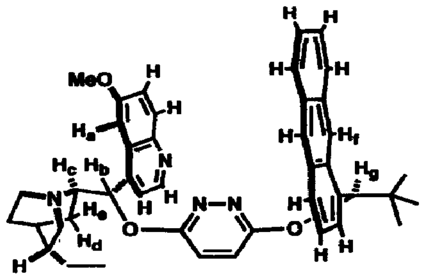
The close similarity of the catalytic ligands **1** and **3** was also evident from a comparison of enantioselectivities in the dihydroxylation of a number of ring-substituted styrenes, as shown in Table II. These data also reveal the persistence of excellent enantioselectivity with either electron accepting or donating substituents.



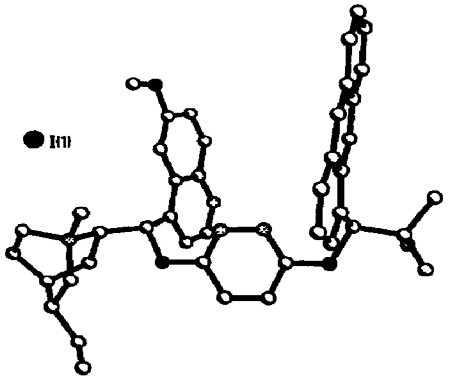
1



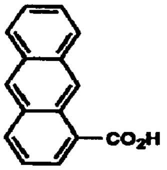
2



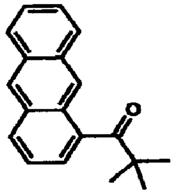
3



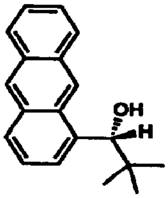
X-Ray Crystal Structure (8) of CH_3I Salt of 3



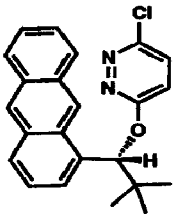
4



5



6



7

The diastereomer of ligand **3** at the 1-anthryl-bearing carbon (**3a**) was also synthesized from *ent*-**6** and dichloropyridazine and studied as a ligand in the catalytic olefin dihydroxylation, as described above for **3**. Although ligand **3a** was expected to possess a U-shaped binding pocket with parallel methoxy-quinoline and anthracene rings on the same side of the pyridazine spacer and perpendicular to it, the anthracene component of the binding pocket is attached by the bond corresponding to H_g in **3** and hence projects rearward relative to **3**. This is expected to lead to a less effective binding pocket. In accord with this analysis, enantioselectivity in the catalytic dihydroxylation using **3a** was generally poorer than with **1** or **3**, (2-vinylnaphthalene, 91% ee; styrene, 80% ee; 1-decene, 44% ee; (E)-stilbene, >98% ee; (E)-3-hexene, 78% ee; 1-phenylcyclohexene, 90% ee).

The results of the experiments described herein are completely consistent with the mechanism which has been proposed for the olefin asymmetric dihydroxylation using cinchona alkaloid derivatives.[1,2] More importantly, they encourage the rational design of new catalytic systems containing only a single alkaloid unit. As stated earlier[2] these enantioselective catalysts are remarkably close to enzymes in terms of general function since they provide specific binding sites for OsO_4 and the olefin, the latter being a pocket which involves non-covalent, shape / size - selective interactions, and since they accelerate and control the stereochemistry of the reaction by means of a favorable 3-dimensional arrangement in the transition state.[11]

References and Notes

1. Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579-12580.
2. Corey E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861-2864.
3. For key references to the work of the Sharpless group which developed this methodology see, (a) 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. (b) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463-8464. (c) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226. (d) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278-1291 and refs. cited therein.
4. Cartwright, B. A.; Griffith, W. P.; Schröder, M.; Skapski, A. C. *J. Chem. Soc. Chem. Commun.* **1978**, 853-854.
5. Golden, R.; Stock, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 3080.
6. (a) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.*, **1973**, 1815. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.
7. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
8. Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.
9. The deep orange crystals of **8** were found to contain 2 molecules of **8** per unit cell: empirical formula $C_{44}H_{49}IN_4O_3$ (808.8); crystal size 0.8 x 0.8 x 0.5 mm^3; space group $P2_1$; a = 11.781(4) Å, b = 10.304(2) Å, c = 17.435(4) Å, β = 102.86(2); V = 2063.6(11) $Å^3$; d = 1.302 g/cm^3; (MoK_α radiation, 23 °C); 6955 reflections collected, of which 4718 with $F_o > 4.0\ \sigma\ (F_o)$ were used in the solution of structure; R_w = 0.0587; GOF = 1.30. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U. K.
10. The following procedure was used for the catalytic dihydroxylations summarized in Tables 1 and 2. To 1 mol% of ligand **1**, **3** or **3a** in 1 : 1 *tert*-butyl alcohol - water was added 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 0.1 mol% of K_2OsO_4, and 1 equiv of $CH_3SO_2NH_2$ (omitted for terminal olefins), and the mixture was stirred at 0 °C for 20 min. The olefin was added, and the mixture was stirred at 0 °C for 6 - 12 h. The product was isolated by addition of Na_2SO_3, extraction with CH_2Cl_2 and filtration through a small plug of silica gel.
11. This research was supported by a grant and a graduate fellowship from the National Science Foundation.

(*Received in USA* 29 *June* 1994; *accepted* 11 *July* 1994)