A mechanistically designed cinchona alkaloid ligand in the osmium catalyzed asymmetric dihydroxylation of alkenes

B B Lohray* S K Singh† & V Bhushan

Zydus Research Centre, Sarkhej-Bavla Highway, Moraiya, Ahmedabad-382210, India
Tel : 091-79-3750603, Fax : 091-79-3750606
E-mail: braj.lohray@zyduscadila.com

Received 15 November 2001; accepted 13 February 2002

A new ligand has been designed using dihydroquinine as the chiral controller for asymmetric dihydroxylation of alkenes. The purpose of this design of the ligand is to find out the transition state involved in the mechanism of asymmetric dihydroxylation, which may shed some light to differentiate between the hypothesis put forward by Sharpless et al. and Corey’s groups. The present study supports the hypothesis proposed by Sharpless et al. and it appears that the L shape d cleft may be involved in governing the high selectivity of asymmetric dihydroxylation of alkenes.

The cinchona alkaloid catalyzed asymmetric dihydroxylation (Sharpless Asymmetric Dihydroxylation) has emerged as one of the most powerful tools for the enantioselective functionalization of olefins. There have been variations in the structure of ligands, although they are all derived from cinchona alkaloid, for achieving highly selective dihydroxylation of different class of olefins. However, (DHQD)$_2$PHAL$^1$ or (DHQD)$_2$PYDZ$^2$ are more effective among the catalysts for highly enantioselective reactions of four to six possible class of olefins with respect to substitution. Despite these advances, there has been a debate regarding the origin of enantioselectivity emerging in the asymmetric dihydroxylation of alkenes. We had previously proposed a model to explain the possible origin of asymmetric dihydroxylation of alkenes, which triggered a lot of debate regarding the actual nature of the transition state responsible for the high enantioselectivity in this reaction leading to numerous publications. Despite this, a very clear cut understanding regarding the transition state which really governs the enantioselectivity in the asymmetric dihydroxylation reaction is still elusive. In our original proposition, we envisaged that the two-dihydrocinchona alkaloids linked together with the help of a spacer offer a suitable chair like platform. The reacting olefin could occupy a position on this chair like conformer, due to π-π interaction, which then undergoes oxygen transfer reaction with one of the OsO$_4$ bound to alkaloid (Figure 1).

Sharpless et al. carried out various kinetic as well as molecular mechanics calculations to arrive at the same conclusion, that the ligand OsO$_4$-complex operates from one of its more stable conformers to form a chiral L shaped binding cleft.

The stereo structure presented in Figure 2 illustrates how the aryl group of styrene can nestle snugly into the wedge of the binding platform. The arrangement allows simultaneous attractive face to face interactions with the highly polarized phthalazine or pyridazine floor, and edge to face interactions with the bystander aromatic quinoline group. This can be stabilized by a favorable π-π interaction between the olefin and the highly polarized phthalazine or pyridazine floor.

Subsequently, Corey and Noe proposed a model in which OsO$_4$ is co-ordinated to quinuclidine.

---

† ZRC Communication No. 104. Part of this work was done at Dr Reddy’s Research Foundation, Hyderabad, India. Dedicated to my mentor, Professor K. B. Sharpless, Nobel Laureate, 2001 on his 60th birthday.
nitrogens leading to a rigidified structure in which two methoxy quinoline moieties and the pyridazine spacer create a U-shaped cleft as shown in Figure 3. Modeling and MM2 energy minimization indicate the preferred structure to be U shape only. Corey and Noe proposed that the olefin stacks within the U shaped cleft due to Van der waals contacts between the two methoxy quinoline units.

In support of his argument Corey et al. \(^\text{2b}\) carried out an X-ray crystallographic as well as NMR studies of DHQ2-PYDZ 1a (Figure 3) as well as bis-methiodide salt of DHQ2-PYDZ 1b (Figure 3). The conformation of alkaloid complex in which osmium tetroxide is bound to alkaloid is expected to assume a U shaped structure like 1a, however, the X-ray as well as the modeling data resemble more to a Z shaped conformation. From Figure 3, it is clear that the bis methylammonium salt 1b resembles more with Z shaped conformation, whereas DHQ2-PYDZ 1a is near to a U shaped structure.

In order to support his claim, Corey and Noe \(^\text{2a,b}\) prepared a new ligand 2a in which the two quinuclidine moieties are tied together in such a way that the two methoxy quinoline moieties of DHQD or DHQ are forced to form a U shaped cavity (Figure 4). It is very clear from both the models (Figures 3 and 4) that there is a considerable change in the conformation of free ligand 1a or 2a and their bis methiodide salt 1b or 2b, respectively. It is believed that OsO\(_4\) bound to DHQ2-Pyridazine ligand 1a or 2a should adopt a conformation very close to DHQ2-Pyridazine bis methiodide complex 1b or 2b. However, comparison of the models shows that the bis methyl complex adopts a Z shaped conformation rather than a U shaped cavity. In fact, after quaternization, the ligand preferred a Z shaped conformation which is equivalent to two L shaped conformations facing opposite to each other, which is expected from C-2-symmetric ligands.

In order to differentiate between the two models and the transition state involved in the enantioselective dihydroxylation of alkenes, we designed a ligand which can lock the two quinoline moieties actually in a U shape. This will arrest the flexibility of the U shaped cavity both when the ligand (DHQ2-PYDZ 1) is free or co-ordinated with OsO\(_4\). This is only
possible by joining the two methoxy quinoline moieties with a suitable spacer. By doing so, the structure of the so-called U-shaped ligand would lose flexibility and form a very rigidified structure. We, in fact created a model and carried out MM2 energy minimization and we found that this molecule will be an ideal ligand having a locked U-shaped conformation (Figure 5).

Interestingly, the conformational structures of the ligand 3a as well as its bis methyl ammonium salt 3b did not change much as shown by modeling and MM2 energy minimization study. If Corey’s suggestion about U-shaped ligand is correct, then one would expect the following results in the AD reaction carried out with ligand 3a.

(a) If U-shaped cavity is essential for better interaction of the substrate with the catalyst, then the ligand with rigidified cavity should lead to increase in the % ee of the diol.

(b) The monosubstituted olefin, should give a better enantioselectivity than the trans-1,2-disubstituted alkenes, because of the fact that monosubstituted alkenes can get inside the rigidified U-shaped cavity only with one face, which is sterically less hindered when compared to trans-1,2-disubstituted alkenes.

In ligand 3 (Figure 5), both the methoxy groups of the two quinoline moieties are replaced by a -O-(CH₂)₅-O- group. The synthetic strategy for Ligand 3 is shown in Scheme 1.

The commercially available quinine sulfate monohydrate 4 was hydrogenated under hydrogen pressure using PdCl₂-H₂SO₄ to get dihydroquinine 5. Reaction of 5 with 3,6-dichloropyridazine in refluxing toluene in the presence of KOH afforded DHQ₂-PYDZ 1. The methoxy group on quinoline moieties were removed by heating with 47% HBr to get a bisphenolic intermediate 8. All attempts to connect the two OH group of quinoline moieties by
carrying out end to end alkylation using various dibromo alkanes for example 1,4-, 1,5-, 1,8-, and 1, 10-, were unsuccessful. The reactions were carried out in the presence of different bases like KOH, K₂CO₃, Cs₂CO₃, NaH either with or without using iodide catalyst at various temperatures. Use of bistosylates in the place of dibromoalkanes also did not yield the desired product 3. Even the bisacetylation reaction using succinoyl chloride and terephthaloyl chloride to connect the two OH of quinoline did not succeed to give the desired product (Scheme I).

Therefore, a different route was adopted for the synthesis of 3. The dihydroquinine 5 was converted into hydrocuprein 6 by reacting with 47 % HBr at 120-130° C for 6 hr in 90% yield. The hydrocuprein 6 underwent successful bisalkylation selectively at phenolic OH with 1,5 pentanebistosylate to furnish compound 7 in 82 % yield. The bisdihydrocupreinyl
penty l ether 7 was then treated with 3,6-dichloro-
pyridazine in refluxing toluene in the presence of
powdered KOH. Water was removed azeotropically to
furnish 19% yield the desired product 3. This
macrocyclic ether ligand 3 was fully characterized by
spectroscopy.

Asymmetric dihydroxylation of various mono and
disubstituted alkenes were carried out using ligand 3
as chiral controller. AD-reaction of these alkenes
were also carried out using DHQ2-PHAL, and
DHQ2-PYDZ-1. For comparison, we have also quoted
some of the examples from the work published by
Corey et al. using ligand 2 (Figure 4).

The % yield and % ee for these olefins are reported
in the Table 1. The results clearly indicate that the
yield of the diols remain unaffected under identical
conditions for the same olefins by using either of the
chiral ligands DHQ2-PHAL (Figure 2), DHQ2-PYDZ-
1 (Figure 3), 2 (Figure 4) or 3 (Figure 5). The rate of
the AD reaction did not change. However, the most interesting
fact was the dramatic drop in the % ee of the diol
using chiral ligand 3 when compared with the % ee of
the diol obtained using chiral ligand DHQ2-PHAL or
DHQ2-PYDZ 1 or the cyclic ligand 2. By replacing
the two methoxy groups on the quinoline moieties by
a single -O-(CH2)5-O-
ligand 3 (Table I). This is essentially due to the loss of the
flexibility to accommodate the incoming substrate in
the cleft provided by the ligand 3, despite having a U
shaped cavity locked in a rigidified macrocyclic ether
structure. The substrate can still undergo dihydroxy-
lization but with poor selectivity. This concept, in fact,
fits quite well with the enzyme-like nature of the
catalyst, wherein, enzyme can accommodate the
substrate of desired size or reject the substrate of undesired dimension. By locking the two-quinoline
moieties in a macrocyclic array, the flexibility of the
catalyst is lost which does not allow the catalyst to
adopt the desired enzyme-like cavity. In contrast,
when these quinoline moieties are free, the ligand has
flexibility to adopt the desired conformation suitable
for high enantioselectivity. Interestingly, the ligand 3
still accelerates the catalytic asymmetric dihydroxy-
lization of alkenes, nearly with the same rate as that of
ligand DHQ2-PHAL or DHQ2-PYDZ. However, the
drop in selectivity could be very well explained based
on a L shaped transition state, which is lost in the
present ligand 3. In ligand 3, the desired face from
which the high selectivity is expected is now the inner
surface of macrocyclic ether. The polar floor of
pyridazine joining the two alkaloid moieties is
covered from top by O-(CH2)5-O-
group by joining the two quinoline moieties. In fact, if the substrate
gets inside the macrocyclic ether cavity selectively
from one face, it would result in a very high
selectivity. However, this will have severe steric
constraints. In contrast, the other face of the ligand is
exposed which is the outer surface of the macrocyclic
erther. From the exposed face of the catalyst, interaction with substrate is still very much feasible in
which the bystander wall provided by quinoline
moiety is missing as shown in Figure 6. This
essentially leads to the loss of selectivity in AD
reaction with ligand 3. In contrast to the ligand 3, the
macrocyclic ligand 2 (Figure 4) made by Corey et al,
can still adopt a Z shaped conformation in which the
polar pyridazine floor and the bystander quinoline
moiety remain undisturbed as shown in Figure 4 and
therefore, there is no change in the selectivity of AD
reaction when compared with the corresponding open
ligand 3.

From this study it appears that the ligand be
flexible enough to adopt a suitable conformation
where the substrate could interact with the floor of the
polarized spacer (here pyridazine) due to weak Van
der Waals or π-π interaction between the substrate
and the catalyst.

In conclusion, it is quite unlikely that the shape of
the catalyst is an enzyme-like U-cavity, in which the
substrate can fit and give a highly selective

Figure 6 — Transition state model for poor selectivity in AD
reaction using ligand DHQ2-PYDZ-O-(CH2)5-O ligand 3.
asymmetric dihydroxylation of various alkenes. A more pragmatic view of the transition state is therefore, an open flexible L shaped floor and a bystander wall which is provided by the aromatic spacer joining the two alkaloids together and the quinoline moiety respectively. This would allow all class of olefins to interact with the catalyst quite effectively to give a high enantioselectivity in asymmetric dihydroxylation process.

**Experimental Section**

All melting points are uncorrected. Flash chromatography was carried out using silica gel SRL 230-400 mesh. $^1$H NMR spectra were recorded on a Varian Gemini (200MHz) FT-NMR instrument in CDCl$_3$. $^{13}$C NMR were recorded on the same instrument. IR spectra were recorded in KBr or as neat on a Perkin Elmer 1600 series FT IR spectrophotometer. Mass spectra were recorded on HP 5989A mass spectrometer. Optical rotations were measured on a JASCO DIP - 370 digital Polarimeter.

**Dihydroquinine 5.** Quinine sulfate monohydrate 4 (31g, 40.57 mmole) was dissolved in dilute sulfuric acid (77.5 mL, 10% w/w) and palladium chloride (310 mg, 1.75 mmole) was added. This mixture was hydrogenated in a Parr apparatus at a constant hydrogen pressure of 50 psi for 4 hr. After the completion of the reaction, activated charcoal powder (3.1 g, 10% w/w) was added. The reaction mixture, was stirred at room temperature for 10 min. and filtered through a celite pad. The filtrate was extracted with chloroform (2 × 100 mL) and rejected. The pH of the aqueous solution was adjusted to 8 - 8.5 by aqueous NaOH solution (10 %) to get a white precipitate. The precipitate was filtered, washed with water and dried to get the title compound 5 (22 g, 83%), m.p. 170-172°C (Lit 8, m.p. 171-172°C); IR (KBr): 3420, 2958, 1620, 1509, 1242, 1117 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz): 5 0.80 (t, 7.0 Hz, 3H), 1.15 – 1.30 (m, 2H), 1.45 – 1.52 (m, 3H), 1.70 – 1.85 (m, 3H), 2.25 – 2.40 (m, 1H), 2.50 – 2.70 (m, 1H), 2.90 – 3.15 (m, 2H), 3.45 – 3.60 (m, 1H), 3.85 (s, 3H), 4.98 (bs, 1H, exchangeable), 5.60 (s, 1H), 7.10 (s, 1H), 7.20 – 7.30 (m, 1H), 7.55 (d, J = 4.4 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 8.53 (d, J = 4.6 Hz, 1H); Mass (m/z): 327 (M$^+$+1), 311, 297, 269, 214, 201, 189, 174, 160, 138 (100 %), 110.

**Hydrocuprein 6.** A mixture of dihydroquinine 5 (4 g, 12.26 mmole) and aqueous HBr (26 mL, 47 %) was refluxed for 5 hr, cooled to room temperature and poured into cold water (100 mL). Carefully, the pH was adjusted to 8 using saturated aqueous sodium bicarbonate solution and then added solid ammonium chloride to bring to pH 6.5 - 7. The aqueous solution was extracted with 10 % methanol-chloroform mixture (3 × 100 mL), dried (Na$_2$SO$_4$) and evaporated to get a brown solid which on trituration from ether afforded hydrocuprein 6 (4.6g, 90%); m.p. 167 – 69 °C; IR (KBr): 3427, 2926, 1618, 1465, 1242, 1116, 855 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz, CDCl$_3$): 5 0.55 (t, J = 6.5 Hz, 3H), 0.9 – 1.05 (m, 2H), 1.25 – 1.50 (m, 3H), 1.8 (bs, 1H), 1.85 – 2.1 (m, 2H), 2.60 – 2.80 (t, J = 10.2 Hz, 1H), 3.00-3.15 (t, J = 8.2 Hz, 1H), 3.90 - 4.10 (m, 1H), 6.0 (s, 1H), 7.30 – 7.35 (d, J = 6.5 Hz, 2H), 7.50 - 7.60 (d, J = 4.2 Hz, 1H), 7.90 – 8.00 (d, J = 9.2 Hz, 1H), 8.60 (d, J = 6 Hz, 1H); Mass (m/z): 313 (M$^+$+1), 312, 295, 283, 255, 175, 138 (100%), 126, 110.

**Pentane 1.5- bistosylate.** To a solution of 1.5-pentane diol (1g, 9.62 mmole) in THF (20 mL) at 0-5 °C, sodium hydride (0.60 g, 25 mmole, 100 %) was added in five portions under argon. The reaction mixture was stirred for 15 min from 0 °C to room temperature and re-cooled to 0-5°C. Freshly crystallized p-toluene sulfonyl chloride (4.60 g, 24.14

---

**Table I — Comparative studies in asymmetric dihydroxylation of alkene using various ligands.**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Substrate</th>
<th>DHQ$_2$-PHAL</th>
<th>Ligand 1 % yield(% ee)</th>
<th>Ligand 2 % yield(% ee)</th>
<th>Ligand 3 % yield(% ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-Stilbene</td>
<td>99 (99 %)</td>
<td>99(99%)</td>
<td>99 (99 %)</td>
<td>95 (72%)</td>
</tr>
<tr>
<td>2</td>
<td>Styrene</td>
<td>95 (97 %)</td>
<td>95(96%)</td>
<td>91 (97 %)</td>
<td>91 (30%)</td>
</tr>
<tr>
<td>3</td>
<td>Allyl p-ethoxybenzoate</td>
<td>Not done</td>
<td>99(98%)</td>
<td>Not done</td>
<td>85 (5%)</td>
</tr>
<tr>
<td>4</td>
<td>Ethyl trans Cinnamate</td>
<td>90(97 %)</td>
<td>Not done</td>
<td>Not done</td>
<td>90 (12%)</td>
</tr>
<tr>
<td>5</td>
<td>1-Decene</td>
<td>95 (80 %)</td>
<td>95(79%)</td>
<td>92 (88 %)</td>
<td>88 (38%)</td>
</tr>
<tr>
<td>6</td>
<td>trans-3-hexene</td>
<td>88 (93%)</td>
<td>58(93%)</td>
<td>71 (88 %)</td>
<td>87 (53%)</td>
</tr>
</tbody>
</table>

(a) ref 1c (b) ref. 2a (c) % ee were determined by using chiral HPLC chromatography or by $^1$H NMR
mmole) was added in portions keeping the temperature around 5-10 °C, and the reaction mixture was stirred at room temperature for 24 hr. The reaction mixture was evaporated on a rotavapour and ice water was added to get a solid, which was stirred, filtered, triturated with diethyl ether and dried to get the pure bistosylate, m.p. 68-70°C (1.6 g, yield 40%); IR (KBr); 2941, 1597, 1364, 1191, 1170, 1097, 923 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz); δ 1.25 – 1.45 (m, 2H), 1.65 (q, J = 6.0 Hz, 4H), 2.45 (s, 6H), 4.0 (t, J = 6.2 Hz, 4H), 7.36 (d, J = 8.0 Hz, 4H), 7.80 (d, J = 8.0 Hz, 4H); ¹³C NMR (CDCl₃, 50 Hz); δ 21.4, 21.5, 28.1, 69.9, 127.7, 129.8, 132.9, 144.7; Mass (m/z) 413 (M⁺+1), 398, 358, 241, 204, 176, 144, 102.

1.5 – Bis-[6-Hydrocupreinyl]-pentan-2-ol ether 7.
A well dried and argon flushed flask, was charged with hydrocuprein (3 g, 9.61 mmole), dry DMF (18 mL), molecular sieves (3 g, 4 Å) and Cs₂CO₃ (8 g, 24.53 mmole). The mixture was stirred at room temperature for 30 min when the reaction mixture turned greenish. Pentane 1,5-bistosylate (1.90 g, 4.60 mmole) dissolved in 4 mL dry DMF was slowly added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was slowly warmed to 80°C and was stirred at 80°C for 20 hr. The reaction was monitored by TLC. After the reaction was complete, it was cooled to room temperature, diluted with CH₂Cl₂ (3 x 10 mL). The combined extracts were dried over Na₂SO₄ and filtered and the solvent was evaporated under reduced pressure. Distilled water (100 mL) was added to the residue and extracted with chloroform (3 x 50 mL), dried (Na₂SO₄) and the solvent was evaporated to get a viscous liquid which was purified over silica gel using 3% MeOH in CHCl₃ to afford the desired ligand 3 (0.55 g, yield 19%), m.p. 154-156°C; [c]δ²⁵ = -20.6 °C (C = 12.6%, CH₂OH); IR (KBr); 2959, 2870, 1621, 1659, 1590, 1508, 1434, 1259, 1223 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz); δ 0.78 (t, J = 6.7 Hz, 6H), 1.25-1.44 (m, 1OH), 1.60-1.97 (m, 12H), 2.35 (d, J = 11.62 Hz, 2H), 2.56 (m, 2H), 3.03 (m, 4H), 3.29 (q, J = 6.5 Hz, 2H), 4.20-4.34 (m, 4H), 6.95 (s, 2H), 7.15 (d, J = 5 Hz, 2H), 7.26-7.42 (m, 4H), 7.73 (s, 2H), 8.00 (d, J = 9.4 Hz, 2H), 8.70 (d, J = 5 Hz, 2H); ¹³C NMR (CDCl₃, 50 MHz); δ 11.9, 22.5, 23.2, 25.2, 27.4, 27.6, 28.6, 29.6, 36.9, 42.6, 57.6, 59.7, 68.3, 73.3, 118.2, 121.2, 122.5, 127.5, 131.3, 144.2, 144.4, 147.1, 157.6, 160.7. Mass (m/z) 770 (M⁺+2), 475, 411, 369, 325, 285, 257, 228, 201, 175, 165.

General procedure for asymmetric dihydroxylation. To a mixture of t-butanol and distilled water (1:1, 10 mL), was added potassium ferricyanide (0.259 g, 0.78 mmole) and K₂CO₃ (0.109 g, 0.78 mmole). After 10 min, osmium-tetroxide (1.33 mg, 0.005 mmole) was added, followed by ligand 3 (4 mg, 0.005 mmole). After 20 min of stirring at room temperature, the reaction mixture was cooled to 0°C and charged with alkene (0.26 mmole). The stirring was continued at 3-6°C for several hours till the completion of the reaction depending upon the substrate. The reaction was monitored by TLC for the consumption of starting material. The reaction was quenched by careful addition of NaHCO₃ (caution; exothermic reaction with effervescence) and extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were washed with saturated NaHCO₃ (10 mL), dried...
(Na$_2$SO$_4$), filtered and the filtrate was evaporated under reduced pressure to furnish the diol. The % enantiomeric excess of diol was determined using chiral HPLC method reported in the literature (see Table I for reference).

Acknowledgement
We are thankful to Dr Reddy’s Research Foundation, Hyderabad, where part of this research work was carried out and the encouragement provided by the DRF & ZRC management.

References