On the Mechanism of Osmium Catalyzed Asymmetric Dihydroxylation (ADH) of Alkenes^{**}

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Abstract: Dihydroquinidine and dihydroquinine bisesters of malonic acid, adipic acid and terephthalic acids are used as chiral auxiliaries for osmium tetroxide catalyzed asymmetric dihydroxylation of alkenes. Highly stereoselective osmylation of alkenes has been rationalized on the basis of π - π interaction of the alkenes with the ligand.

During the past few years, a number of reports have appeared on the asymmetric dihydroxylation of alkenes employing either stoichiometric¹ or catalytic ² amount of osmium tetroxide-ligand complexes and since then continuous efforts have been made to improve the optical purity of the resulting diols.^{2b-g} Despite extensive NMR³, kinetic⁴ and X-ray⁵ studies, the mechanism of the catalytic asymmetric dihydroxylation reaction catalyzed by osmium tetroxide in the presence of dihydroquinidine (DHQD) and dihydroquinine (DHQ) derivatives has remained unsolved.

Recently, Corey and Lotto ⁶ have suggested an interesting possibility of dimerization of OsO_4 , L^{*} to afford Os_2O_8 , L_2^* 5 as the actual catalyst which might determine the enantiofacial approach of the alkenes. With the view to examine the validity of this model, we prepared ligands 1a, 1b and 1c⁷ and examined their effect on the osmium catalyzed asymmetric dihydroxylation of alkenes using $K_3Fe(CN)_6$ - K_2CO_3 as secondary oxidant in *tert*-butanol-water (1:1) system.



Ligand 1a can only form either a very crowded *cis*-dimer 3 (which is highly improbable as suggested by Corey⁶) or may bind to the same osmium tetroxide as a bidentate ligand as shown in 4 like other *tert*-diamines.¹ In the latter case, the reaction should not undergo catalytic turnover (like diamines¹) as it was found to be the case (Table 1, entries 1 & 2). On the other hand, in the case of 1b, it is possible that the two quinuclidine moieties may occupy *trans* position in the dimeric species 5 as proclaimed by Corey and Lotto or each quinuclidine moiety may co-ordinate to OsO₄ separately as indicated in the structure 6 and function as a pedestal for the dihydroxylation independently. Using 1b as the chiral

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controller, the enantiomeric excess of the hydrobenzoin was found to be > 90% ee (Table 1, entries 1 & 2). High stereoselectivity could be explained either through the intermediacy of 5 or 6.



Table 1: Enantiomeric Excess of the Diols Using C,-Symmetry-DHQD-1a,1b and 1c.*

Entry	Alkenes	Temperature	la	1b	1c ^b	Config	^c [α] _D ²²
1	E-Stilbene	25° C	NR	90	97	RR	
2	E-Stilbene	0° C	NR	92	>98	RR	+94.74 (1.0, EtOH)
3	E-Stilbene ^d	0° C	-	-	>98	SS	-92.5 (1.2, EtOH)
4	E-ß-Methylstyrene	0° C	-	-	>98	RR	-35.6 (1.19, EtOH)
5	E-3-Hexene	20° C	-	-	93	RR	+20.8 (1.48, H ₂ O)
6	E-Methyl cinnamate	20° C	-	-	94	SR	-10.4 (1.52,CHCl ₃)
7	Styrene	0° C	-	-	92	R	-64.4 (1.18, CHCl ₃)
8	Styrene ^d	0° C	-	-	85	S	+56.6 (1.24, CHCl ₃)
9	2-Methylstyrene	0° C	-	-	76	R	-70.3 (0.91, CHCl ₃)
10	3,3-Dimethylbutene	0° C	-	-	48	R	-13.3 (0.8, CHCl ₃)
11	1-Decene	0° C	-	-	45	R	+5.96 (0.94, EtOH)

a) Yield of diols varies between 80-95 %. b) Enantiomeric excess of the diols were determined by ¹H NMR (200 MHZ) by (i) shift method on bisacetate derivatives using Eu(hfc)₃; (ii) bis-MTPA-derivatives and comparison of optical rotations. c) Configurations were assigned based on optical rotation of the known compounds.^{1,2} NR = No reaction, d) DHQ deriv. was used.

To examine this possibility, we investigated 1c in which two units of DHQD are coupled together via a terephthaloyl moiety. We expected a decrease in enantioselectivity, if Corey's suggestion that the dimer being the actual catalyst is true since 1c cannot form dimeric species 5. On the contrary, the

enantiomeric excess of the hydrobenzoin resulting from this reaction was >98 % (Table 1, entry 2), supporting our surmise that each quinuclidine moiety in 1c is functioning independently during the facial discrimination of alkenes.



We believe that the presence of sterically demanding and electron rich (π -cloud) substituent is playing a pivotal role, in addition to the chirality information from the alkaloid in governing the stereoselectivity of the reaction. We envisage a model in which the olefin is held over the π -cloud of the ligand (either CO or aromatic substituents) due to π - π interaction and the osmium tetroxide co-ordinated to the quinuclidine moiety can approach it from only one face of the alkene as shown in A via the interaction of axial oxygen O₁ and equatorial oxygen O₃.⁸ The possibility of π - π interaction with the other face of the olefin will suffer from severe steric repulsion as shown in B. Such a π - π interaction has been recently invoked by Corey and Loh⁹ to explain the high diastereofacial selectivity in Diels-Alder reaction. This model explains the similar selectivity in the case of monosubstituted alkenes and superior selectivity in the case of *trans* disubstituted olefins than with dihydroquinidine 4-chlorobenzoate.²¹ This also accounts for the poor selectivity observed in the case of dihydroquinidine and 9-methoxy dihydroquinidine ^{2e} as well as the excellent selectivity for 9-phenanthryl and naphthyl ether derivatives of DHQD and DHQ as reported by Sharpless & co-workers.^{21,g} Any perturbation of this π - π interaction due to substituents would result in the decrease in enantiomeric excess.^{2g}

To ascertain our hypothesis of π - π interaction of alkene and aromatic ring at the 9-position of the alkaloid, we have investigated the effect of ligand 1c in the case of other olefins and the results are collected in the table 1 (entries 2 - 10). Most of the alkenes show respectable level of asymmetric induction even with trace amount of OsO₄ and C₂-DHQD-1c.¹⁰ We propose that the presence of more electron rich aromatic rings with C₂-symmetry structure would help to improve the enantiofacial discrimination. To support our assumption, we are investigating ligands similar to 1c containing anthracene-9,10-dicarboxylate and anthracene 9,10-bishydroquinidine ether and the corresponding quinine derivatives.

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- 7. Bisesters 1a,1b and 1c/2c were prepared by the reaction of the corresponding acid chlorides (0.5 equiv.) in CH₂Cl₂ at ca. 0 ° C in the presence of triethylamine (1.5 equiv.) and they showed satisfactory spectral data and elemental analysis. 1c, mp 114-116°C. [α]_p²² = -100.4° (c, 1.02, EtOH); ¹H NMR (200 MHz, CDCl₃): δ 8.73 (d, J = 4.6 Hz, 2 H); 8.18 (S, 4 H), 8.02 (d, J = 9.2 Hz, 2 H), 7.5 (d, J = 2.56 Hz, 2 H); 7.4 (m, 4 H); 7.35 (d, J = 2.6 Hz, 2 H), 6.75 (d, J = 7.44, 2 H), 3.98 (s, 6 H), 2.9-2.6 (m, 8 H), 1.93-1.76 (m, 4 H), 1.65-1.48 (m, 12 H), 1.26 (t, J = 6.55, 6 H); ¹³C NMR (50 MHz, CDCl₃); δ 165.0, 158.29, 147.69, 145.10, 143.82, 134.26, 132.16, 130.05, 127.33, 122.14, 118.90, 101.76, 75.07, 59.75 55.84, 51.08, 50.18, 37.64, 27.43, 26.40, 25.72, 23.92, 12.14. 2c, mp 126-128 ° C. [α]_p²² = +219° (c, 1.05, EtOH).
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- A typical experimental procedure is as follows: In a double jacketed reaction flask attached to a cooling system was placed a mixture of K₃Fe(CN)₆ (2.47 g, 7.5 mmol, 3 equiv.); K₂CO₃ (1.04 g, 7.5 mmol, 3 equiv.) in tert-butanol-water (1:1, 25 mL) and stirred at ca. 20 °C for 10 min. Organic and aqueous layers get separated. Ligand (0.032 mmol; 0.013 equiv) and osmium tetroxide (10 µL, 0.5 M in toluene, 0.005 mmol, 0.002 equiv.) were added and stirred vigorously. The reaction mixture was cooled to the desired temperature and the olefin (2.5 mmol) was added in one portion. The reaction was followed by TLC and finally was quenched with sodium metabisulfite (5g, 26.3 mmol) cautiously and stirred vigorously at room temperature for 30 min. Work-up of the reaction mixture furnished diols in high yields (80-95%).

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