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Note

Asymmetric dihydroxylation of olefins by osmium tetroxide coordinated with chiral Cinchona alkaloid

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Bisesters of cinchonine, cinchonidine, dihydrocinchonine and dihydrocinchonidine with terephthalic acid and isophthalic acid are used as chiral auxiliaries for osmium tetroxide-catalyzed asymmetric dihydroxylation of olefins such as styrene, α-methylstyrene, methyl cinnamate, ethyl cinnamate, isopropyl cinnamate, cinnamyl alcohol, cyclohexene, 1-methylcyclohexene, 1-phenylcyclohexene, cycloheptene, cyclooctene, 3-chloro-1-propene, 1-hexene and methyl fumarate, and the enantiomeric excess in every case has been determined.

Asymmetric induction has been frequently used in the synthesis of optically active natural products and biologically active compounds, since the asymmetric centers present in these compounds may be provided by chiral transfer to readily available prochiral moieties[1]. Among the most prominent examples of asymmetric reactions, the "Sharpless process" for the asymmetric dihydroxylation of olefinic compounds is widely recognized in recent years[2]. With the development of more effective chiral Cinchona alkaloid derived ligands reported by Sharpless[3] group, today a large class of olefinic substances can be transformed to enantiometrically pure or enriched diols, useful as intermediates in drug synthesis, e.g. chloroamphenicol[4] and Taxol side chain[5]. Sharpless[3,6] and Lohray[7] have recently reported the use of C-2 symmetric bisether and bisester derivatives of dihydroquinidine (DHQD) and dihydroquinine (DHQ) in highly efficient dihydroxylation process. The enantioselectivity was mainly influenced by the nature of O-9 substituent[8], but deeply seated structural variations of the alkaloid cage had only minor effect on the selectivity[8].

In this report, we describe the enantioselective oxidation of olefins with osmium tetroxide coordinated by chiral Cinchona alkaloid, viz. cinchonine and cinchonidine and their dihydro analogues as bisesters with terephthalic and isophthalic acids. These esters are easily prepared in one-step starting with the corresponding acid in the presence of triethylamine, as compared with diphenylpyrimidine and phthalazine ligands[8a]. Osmium tetroxide was used in an stoichiometric amount for effective *cis*-dihydroxylation of olefins and the use of it was proved to be more reliable than any other oxidant[9] despite its high cost and toxicity. Inorganic cooxidants like sodium chlorate and hydrogen peroxide were also examined, but in some cases these reagents gave less yields of the products due to overoxidation[10]. Subsequently, some organic cooxidants such as alkaline *tert*-butylhydroperoxide[11] and *N*-methylmorpholine-*N*-oxide[12] were introduced which afforded comparatively better results. But, the use of potassium ferricyanide in combination with potassium carbonate has been demonstrated to be a powerful system for osmium-catalyzed asymmetric dihydroxylation of olefins[13].

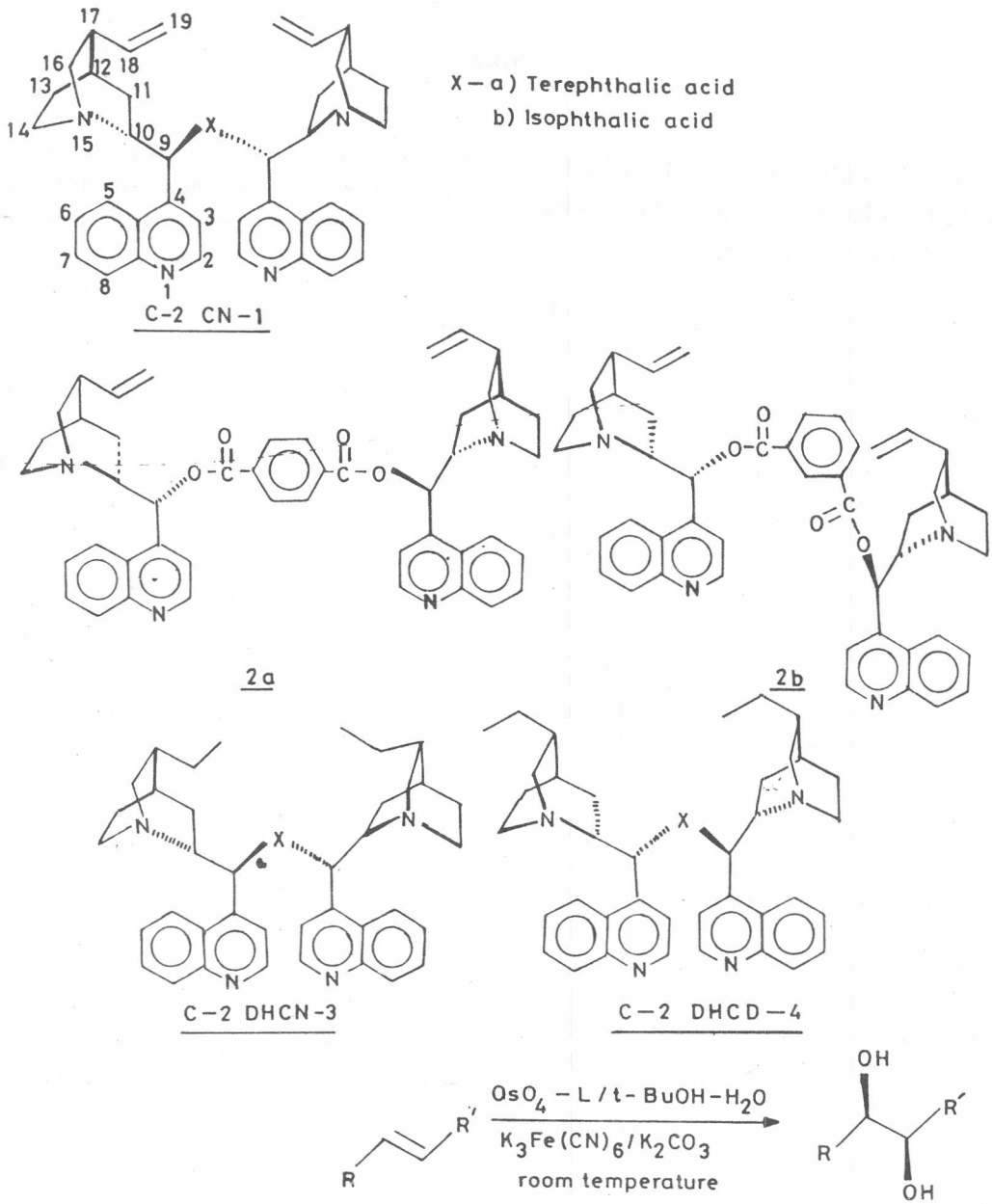
The olefin dihydroxylation enantioselectivities derived from allylic ligands, viz $(CN)_2TP$ **1a**, $(CN)_2IP$ **1b**, $(CD)_2TP$ **2a** and $(CD)_2IP$ **2b** are summarized in Table I, which shows less enantiomeric excess. So, we prepared the dihydro products of the above ligands by reducing the allylic double bond on cinchona base alkaloids using palladium on charcoal in ethyl acetate at 200 psi pressure. The enantiomeric excess of olefins obtained by the dihydro products of the above ligands, viz. $(DHCN)_2TP$ **3a**, $(DHCN)_2IP$ **3b**, $(DHCD)_2TP$ **4a** and $(DHCD)_2IP$ **4b** are summarized in Table II.

From the results given in Tables I and II we conclude that the dihydroligands are preferred over allylic ligands for better enantiomeric excess. At the same time terephthalic acid ligands give better enantiomeric excess because of the fact that the two alkaloid moieties present on the terephthalic acid are at *para*-position, wide apart from each other having no steric hindrance.

The spectral data of all the new compounds were in conformity with the assigned structures.

Experimental Section

General. Melting points are uncorrected. IR



spectra were recorded on a Perkin-Elmer spectrophotometer and ^{1}H NMR spectra on a Bruker AC 80 instrument using TMS as internal standard (chemical shift in δ, ppm).

Synthesis of 1,4-bis(cinchonine)terephthalate. Thionyl chloride (4 mL, 0.052 mole) was added slowly to terephthalic acid (1.66 g, 0.01 mole) and the mixture refluxed for 5 hr. The progress of reaction was monitored by TLC, and when the reaction was over, excess of thionyl chloride was removed under pressure to get terephthaloyl chloride. To the stirred suspension of cinchonine (4.528 g, 0.0154 mole) in dry 1,2-dichloroethane (30 mL) containing triethyl amine (1.96 mL, 0.014 mole), a solution of terephthaloyl chloride (1.41 g, 0.007 mole) in dry 1,2-dichloroethane (20 mL) was added through a syringe over 10 min at 0°C. Temperature was gradually increased to room temperature, and dimethyl formamide (1 mL) and 4-dimethylaminopyridine (50 mg) were added, and the reaction mixture was stirred for 15 hr at room temperature and then refluxed for 1 hr, cooled, solid sodium bicarbonate (1.5 g) added and stirred for another 20 min. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution, water and brine.

Table I—Enantiomeric excess (%) of olefins[a] using ligands $(CN)_2TP$ **1a**, $(CN)_2IP$ **1b**, $(CD)_2TP$ **2a** and $(CD)_2IP$ **2b**

Olefin	Ligand **1a**	Ligand **1b**	Ligand **2a**	Ligand **2b**
Styrene[c]	32 (98.7)[b]	28 (99.0)	34 (99)	32 (98.4)
α-Methylstyrene[c]	79.66 (81)	79 (80)	80.22 (83.4)	78.1 (89.1)
Methyl cinnamate[c]	42 (87)	35 (84)	46 (92)	41 (71)
Ethyl cinnamate[d]	20 (85)	15 (81)	10 (86)	11 (83)
Isopropyl cinnamate[d]	20 (89)	12 (87)	21 (93)	17 (88)
Cinnamyl alcohol[d]	58 (82)	50 (80)	60 (85)	57 (84)
Cyclohexene[c]	71.43 (95)	63.78 (92)	76.53 (95)	68.88 (90)
Methylcyclohexene[c]	85.27 (90)	83.48 (87)	90.16 (90.79)	84.7 (87)
Phenylcyclohexene[c]	90.21 (94.76)	73.2 (90.88)	92.27 (94.99)	77.84 (90)
Cycloheptene[c]	90.07 (88)	81.1 (85)	90.73 (89.2)	84 (85.5)
Cyclooctene[c]	61.32 (90)	57.66 (93)	64.92 (91)	59.2 (89.4)
3-Chloropropene[c]	66.52 (89.9)	56.37 (89)	68.4 (88.15)	57.8 (90)
1-Hexene[c]	67.23 (83)	65.06 (80.7)	73.94 (83.8)	65.72 (80)
Methyl fumarate[c]	84.87 (92.12)	70.94 (90.12)	89(93)	74.69 (90)

[a]All the reactions were run in *t*-butanol-water (1:1) at room temperature and all the products showed similar spectral and elemental data with literature values.
[b]Figure in parentheses indicates % yield.
[c]Enantiomeric excess was calculated by comparing optical rotation with literature value.
[d]Enantiomeric excess was calculated by chiral HPLC of the corresponding acetate derivative.

Table II—Enantiomeric excess (%) of olefins[a] using ligands $(DHCN)_2TP$ **3a**, $(DHCN)_2IP$ **3b**, $(DHCD)_2TP$ **4a** and $(DHCD)_2IP$ **4b**

Olefin	Ligand **3a**	Ligand **3b**	Ligand **4a**	Ligand **4b**
Styrene[c]	74 (98)	68 (99)	77 (95)	70 (92)
α-Methylstyrene[c]	98.6 (97.1)	97.38 (98.8)	99.05 (98.7)	97.49 (97.8)
Methyl cinnamate[c]	84 (92)	79 (89.5)	91 (93)	89 (89)
Ethyl cinnamate[d]	95 (94)	93 (89)	97 (91)	91 (90)
Isopropyl cinnamate[d]	57 (91)	50 (84)	60 (94)	53 (90)
Cinnamyl alcohol[d]	85 (89)	50 (85)	60 (90)	53 (89)
Cyclohexene[c]	98.8 (97)	79 (98.2)	99.2 (98)	85.5 (97)
Methylcyclohexene[c]	94.29 (95)	90.16 (94)	97.87 (98.89)	93.73 (94)
Phenylcyclohexene[c]	93.3 (95)	88.6 (92)	98.46 (98)	78.36 (92.7)
Cycloheptene[c]	93.3 (97)	88.51 (90)	97.1 (99)	90.05 (91)
Cyclooctene[c]	93.79 (95.6)	91.35 (94)	97.77 (96.2)	93.66 (94.21)
3-Chloropropene[c]	91.44 (96)	73.04 (95)	95.5 (96.8)	85.36 (94)
1-Hexene[c]	98.61 (97)	74.14 (94)	99.8 (97.5)	79.6 (94.5)
Methyl fumarate[c]	96.23 (98)	85 (92)	98.15 (98)	84.31 (95)

[a]All the reactions were run in *t*-butanol-water (1:1) at room temperature and all the products showed similar spectral and elemental data with literature values.
[b]Figure in parentheses indicates % yield.
[c]Enantiomeric excess was calculated by comparing optical rotation with literature value.
[d]Enantiomeric excess was calculated by chiral HPLC of the corresponding acetate derivative.

The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude compound was purified over neutral alumina column using dichloromethane as eluent, yield 3.3 g (65.47%), mp 146°C; $[\alpha]_D$–69.81° (1%, $CHCl_3$); IR(KBr): 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): 7.4-8.4 (m, 16H, Ar-H), 6.7-6.8 (d, 2H, C9-H), 5.93-6.10 (m, 2H, C18-H), 5.04-5.15 (m, 4H, C19-H), 3.40-3.48 (dd, 2H, C10-H), 2.82-2.92 (m, 4H, C14-H), 2.67-2.78 (m, 4H, C16-H), 2.17-2.31 (dd, 2H, C13-H), 1.5-2.0 (m, 5H, C11-H, C12-H and C17-H). Anal. Calcd for $C_{46}H_{48}N_4O_4$: C, 76.66; H, 6.66; N, 7.77. Found: C, 76.34; H 6.74; N, 7.99%.

All other ligands, e.g. $(CN)_2IP$, $(CD)_2TP$ and $(CD)_2IP$ were synthesized by similar method.

Typical procedure for synthesis of diols: Synthesis of 1-phenyl-1,2-ethanediol. A mixture of potassium ferricyanide (988 mg, 3 mmoles, 3 eq) and potassium carbonate (416 mg, 3 mmoles, 3 eq) in *t*-butanol-water (1:1, 10 mL) was stirred at room

temperature for 10 min. The ligand 1,4-bis(cinchonine)terephthalate (9.267 mg, 0.0128 mmole) and osmium tetroxide (0.5 mL, 0.04 *M* in *t*-BuOH, 0.002 mmole) were added and the mixture was stirred vigorously. To this reaction mixture styrene (0.115 ml, 1 mmole) was added and the whole mixture stirred for 24 hr. The reaction was finally quenched with sodium metabisulfite (2 g) and stirred at room temperature for another 30 min. The two layers were separated and the aqueous layer was extracted with dichloromethane (2×15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude mass was purified over silica gel (60-120 mesh) column using hexane-ethyl acetate (90:10) as eluent, yield 120 mg (98%); IR(KBr): 3300-3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$): 7.3 (s, 5H, Ar-H), 4.70-4.76 (t, 1H, C-H), 3.56-3.70 (d, 2H, CH_2). Anal. Calcd for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.56; H, 7.24%.

All other diols were synthesized in similar fashion.

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