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Catalytic asymmetric dihydroxylation of substituted *trans*-stilbene derivatives: implications of the variation of enantioselectivities on the mechanism of OsO_4 addition to olefins

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ABSTRACT

The OsO_4 catalyzed asymmetric dihydroxylation of substituted *trans*-stilbene derivatives using 9-*O*-acetyldihydrocinchonidine as chiral ligand gives the corresponding diols with lower enantioselectivity in the case of substrates containing electron-donating and electron-withdrawing substituents. The Hammett correlations of the enantiomeric ratios exhibit non-linear plots, in accordance with the conclusion that the reaction involves a 1,3-dipolar type [3+2] cycloaddition transition state.

The Sharpless catalytic asymmetric dihydroxylation (AD) of olefins using OsO_4 and cinchona alkaloid derivatives is a very useful synthetic transformation.[1] Though the stereochemical outcome of the AD reaction can be readily predicted,[1] the mechanism of this useful reaction is not clearly understood.[2–10] Most of the mechanistic proposals advanced for this reaction are based on two basic themes: a concerted [3+2] cycloaddition[7,8] and a stepwise process involving a [2+2]-like insertion with subsequent rearrangement[6] (Scheme 1). There has been overwhelming evidence in support of the [3+2] mechanism.[6] We report here evidence for the [3+2] mechanism for the AD reaction, which is in accordance with the proposal that the origin of the ligand acceleration is due to the ability of the ligand to make OsO_4 an efficient 1,3-dipole.[8]

The effect of substituents on the double bond of olefins on the stereochemical outcome has been reported for catalytic asymmetric dihydroxylation reactions.[1] The effect of the size of substituents on the regioselectivity of Sharpless AD reactions has also been reported.[11] However, the enantioselectivities in these cases would be subjected to unpredictable steric effects. Very recently, AD reactions of a series of substituted styrenes were studied and a concave-type Hammett plot was interpreted on the basis of a change in the mechanism of the hydrolysis of the osmate ester intermediate going from electron-donating to electron-withdrawing substituents.[12] We investigated the mechanism of the AD reaction using substituted *trans*-stilbene derivatives.

Initially, we studied the substituent effects on the mechanism of the AD reaction with different *trans*-stilbenes (**5a–d**) using the excellent ligand $(DHQD)_2$–PHAL (**1**) (Scheme 2). This ligand gives the diols (**6a–d**) with maximum enantioselectivities in the case of electron-donating as well as electron-withdrawing substituents. These selectivities might be due to the reaction proceeding through a ligand-assisted pathway to the maximum extent. The results are summarized in the Table 1. Since the Sharpless ligand $(DHQD)_2$–PHAL leads to the saturation point of enantioselectivities, we chose the 9-*O*-acetyldihydrocinchonidine[13] (**2**) (Fig. 1) as the chiral ligand, (Scheme 3, Table 2). Previously, it was reported that the corresponding cinchonine derivatives gave substantially lower enantioselectivities under stoichiometric conditions but these authors did not report the % ee of the products.[14]

We first examined the dihydroxylation of *trans*-stilbene under various conditions (Scheme 3). It was observed that on using 5 mol % of **2** along with 2 mol % of $K_2OsO_2(OH)_4$, the selectivity was better (91% ee, Table 2, entry 4) when the reaction was carried out at 25 °C in the solvent mixture of ^{t}BuOH (15 ml) and H_2O (15 ml). Lower selectivity was realized in the solvent mixture of ^{t}BuOH (70 ml) and H_2O (35 ml) (Table 2, entry 5), indicating that the ligand-unassisted (direct dihydroxylation) addition of OsO_4 to the olefin would take place to a greater extent under these conditions. Previously, Sharpless et al.[10a] noted the poor solubility of substituted stilbenes in the ^{t}BuOH/H_2O solvent system during their

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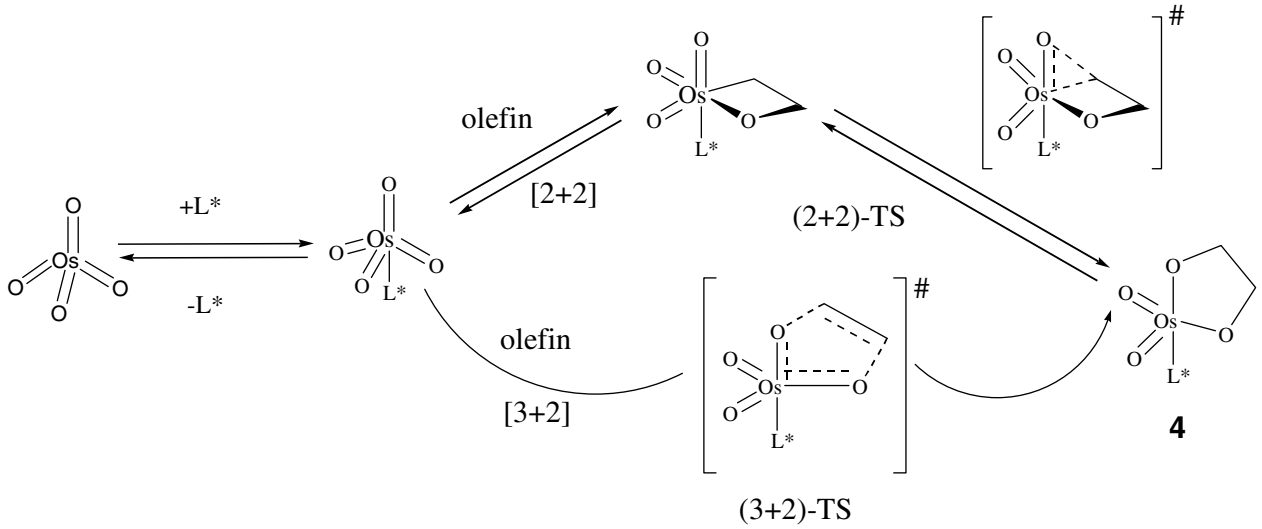
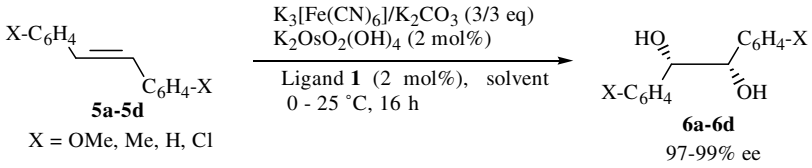


Scheme 1. Schematic representation of the concerted [3+2] mechanism and the stepwise osmaoxetane mechanism.



Scheme 2. Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using ligand **1**.

Table 1
Asymmetric dihydroxylation of *trans*-stilbenes using $(DHQD)_2$–PHAL as ligand[a,b,c]

Entry	product	ee[d] (%)	Yield[e] (%)
1	**6a**	97	93
2	**6b**	>98	95
3	**6c**	99	90
4	**6d**	99	89

[a] All the reactions were carried out using *trans*-stilbene (1 mmol).
[b] In each case 2 mol % of potassium osmate and 2 mol % of ligand were used.
[c] All the experiments were carried out using ^{t}BuOH (5 mL)/H_2O (5 mL) at 25 °C for 16 h.
[d] All the enantiomeric purities were based on HPLC analysis.
[e] Yields are of isolated and purified products.

kinetic studies of the dihydroxylation of olefins. We also encountered such difficulties during the present studies and hence we ran these reactions using increased quantities of solvents compared to those used in synthetic asymmetric dihydroxylation reactions. Also, we used another organic solvent in addition to ^{t}BuOH/H_2O to dissolve the stilbene derivatives (Scheme 4).

We ran the reaction in three different solvent systems. The diols were obtained in 64–90% ee at 25 °C using the toluene/^{t}BuOH/H_2O.[16] Whereas, the reaction in acetone/^{t}BuOH/H_2O gave the diols in 26–56% ee and the reaction using THF/^{t}BuOH/H_2O solvent system gave the diols in 20–82% (Table 3). The selectivities were low in these reactions. Previously, it was reported that use of the *t*-butyl methyl ether/H_2O solvent system gave a lower ee in the asymmetric dihydroxylation of allyl bromide.[1]

Though the diol was obtained in reasonable chemical yields, substantially lower enantioselectivities were realized with electron-donating and electron-withdrawing derivatives in all the solvent systems (Table 3). A possible explanation is that in these

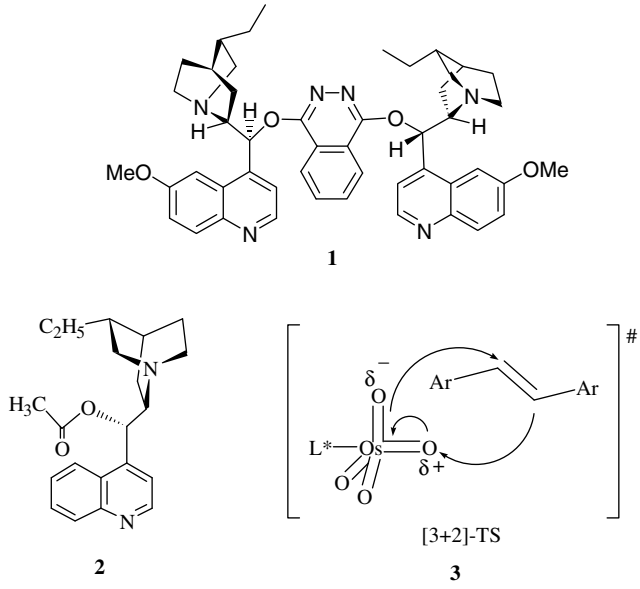
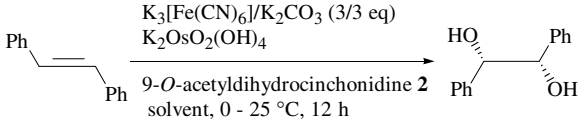


Figure 1.



Scheme 3. Asymmetric dihydroxylation of *trans*-stilbene using ligand **2.**

Table 2
Asymmetric dihydroxylation of *trans*-stilbene[a,b,c,d]

Entry	$K_2OsO_2(OH)_4$ (mol %)	Ligand **2** (mol %)	Diol-**6c** % ee[e]	Yield[f] (%)
1	1.2	3	(1*S*,2*S*),74	75
2	2.0	5	(1*S*,2*S*),82	82
3	2.8	7	(1*S*,2*S*),82	83
4	2.0	5	(1*S*,2*S*),91	91
5	2.0	5	(1*S*,2*S*),38	80

[a] In entries 1–5, *trans*-stilbene (1 mmol) was used.
[b] In entries 1–3, the experiments were carried out at 0 °C for 12 h and in entries 4 and 5 the experiments were carried out at 25 °C for 12 h.
[c] A mixture of ^{t}BuOH (15 ml) and H_2O (15 ml) was used as solvent in entries 1–4.
[d] In entry 5, a mixture of ^{t}BuOH (70 ml) and H_2O (35 ml) was used as solvent.
[e] ee = enantiomeric excess, (based on $[\alpha]_D$ −94.5 (*c* 0.998, EtOH), (1*S*,2*S*)-(−)-diphenyl-1,2-ethane-1,2-diol[15] and HPLC analysis).
[f] Yields are of isolated and purified products.

cases, direct dihydroxylation of the olefin by OsO_4 could have taken place to a greater extent compared to unsubstituted olefins, leading to lower selectivity.[1] Another possibility is that the secondary catalytic cycle (proposed by Sharpless et al.[1a]) involving the corresponding osmate ester intermediate **4** could have taken place to a greater extent in these cases, leading to lower enantioselectivity.[1] These parallel processes would take place to a greater extent, if the ligand-accelerated AD reaction path becomes difficult. The 1,3-dipole would find it difficult to react with the stilbene derivatives containing electron-withdrawing substituents as transfer of electrons from the olefin to the dipole is difficult in these cases (T.S. **3**, Fig. 1). In the case of stilbene derivatives containing electron-donating substituents, the transfer of electrons from the dipole to the olefin would become difficult. Therefore, the ligand-unassisted dihydroxylation or reaction through the secondary catalytic cycle would take place to a greater extent in these cases, resulting in lower enantioselectivities.

The lower enantioselectivities realized in these cases would also lead to non-linearity in the correlation of log (enantiomeric ratio) vs σ (Fig. 2).[17] Hammett correlations of the enantioselectivities realized in different organic reactions have been reported.[18] For example, in the case of specific asymmetric diethylzinc addition to aromatic aldehydes, a linear Hammett plot was realized, with more reactive substrates giving higher enantioselectivities.[18c]

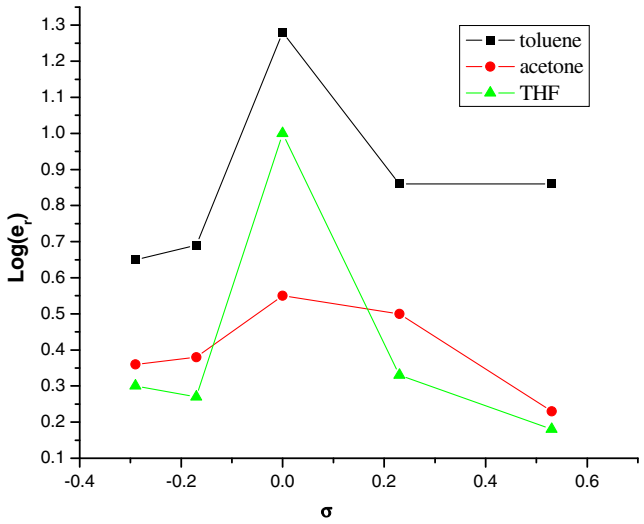
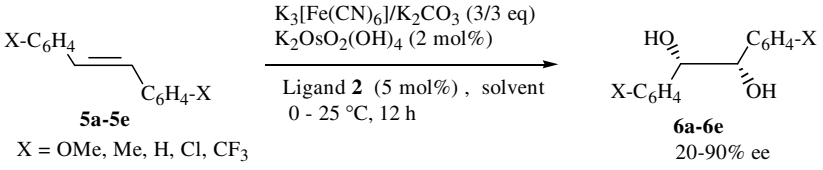


Figure 2. Plots of log (enantiomeric ratio) vs Hammett σ values.

In the present case, non-linear Hammett plots were realized. The concave-shaped plot clearly indicates a change in mechanism for the unsubstituted and substituted *trans*-stilbenes[19] (Fig. 2). This would be expected if the diols are produced through the L. OsO_4 1,3-dipole (T.S **3**) to a greater extent in the case of unsubstituted stilbene and to a lesser extent in the case of stilbenes substituted with electron-donating and electron-withdrawing substituents. Thus, the results obtained in the present studies are in accordance with the conclusion that the ligand acceleration effect on the catalytic asymmetric dihydroxylation of olefins is due to the ability of the ligand to convert OsO_4 into an efficient 1,3-dipole upon complexation for reaction with olefins.[8,9]



Scheme 4. Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using ligand **2**.

Table 3
Asymmetric dihydroxylation of 4-substituted *trans*-stilbenes using 9-*O*-acetyldihydrocinchonidine (**2**) as the chiral ligand[a,b,c]

Olefin (X=)	Product	Solvent (A)			Solvent (B)			Solvent (C)		
		Yield[f] (%)	ee[d] (%)	e_r^f	Yield[e] (%)	ee[d] (%)	e_r^f	Yield[e] (%)	ee[d] (%)	e_r^f
OMe, **5a**	**6a**	80	64	4.55	65	40	2.33	68	34	2.03
Me, **5b**	**6b**	76	66	4.88	60	40	2.33	70	30	1.86
H, **5c**	**6c**	92	90	19.0	85	56	3.54	92	82	10.1
Cl, **5d**	**6d**	85	76	7.33	62	52	3.17	72	36	2.12
CF_3, **5e**	**6e**	79	76	7.33	56	26	1.70	65	20	1.5

[a] In all the experiments olefin (1 mmol) was used.
[b] In each case 2 mol % of potassium osmate and 5 mol % of ligand were used.
[c] All the experiments were carried out at 25 °C for 12 h and solvent (A): toluene (20 mL)/^{t}BuOH (20 mL)/H_2O (20 mL), solvent (B): acetone (20 mL)/^{t}BuOH (20 mL)/H_2O (20 mL) and solvent (C): THF (20 mL)/^{t}BuOH (20 mL)/H_2O (20 mL) were used.
[d] The enantiomeric excesses were based on HPLC analysis.
[e] Yields are of isolated and purified products.
[f] e_r = enantiomeric ratio {(1*S*,2*S*)/(1*R*,2*R*)}.

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13. *Preparation of 9-O-acetyldihydrocinchonidine*: Dihydrocinchonidine[20] (4.2 mmol, 1.24 g) was dissolved in CH_2Cl_2 (20 mL). Acetyl chloride (5 mmol, 0.36 mL) was added dropwise over a period of 0.5 h with stirring at 0 °C. The reaction mixture was brought to 25 °C and stirring was continued for 12 h followed by reflux for 2 h. The contents were cooled to 25 °C, solid K_2CO_3 was added and the mixture stirred for 0.5 h. Water was added and the organic layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (100–200 mesh) using methanol/chloroform/hexane (0.15/3/6.85) to elute a viscous sample of **2**. Yield: 0.88 g (62%); $[\alpha]_D^{25}$ −28.2 (*c* 0.5, EtOH); IR (neat): 2935, 2862, 1745, 1593, 1230, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.2 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.55–7.79 (m, 2H), 7.36 (m, 1H), 6.60 (d, *J* = 4.2 Hz, 1H), 3.28–3.46 (m, 1H), 2.98–3.25 (m, 2H), 2.59–2.78 (m, 1H), 2.23–2.30 (m, 1H), 2.11 (s, 3H), 1.66–1.94 (m, 2H), 1.40–1.65 (m, 3H), 1.18–1.38 (m, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 149.9, 148.7, 145.1, 130.4, 129.2, 125.9, 123.5, 118.5, 73.8, 59.4, 58.2, 42.6, 37.2, 28.1, 27.6, 25.3, 23.7, 21.0, 12.0.
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16. *General procedure for the asymmetric dihydroxylation of trans-stilbenes in the presence of 9-O-acetyldihydrocinchonidine ligand using the toluene/^{t}BuOH/H_2O solvent system:* To a mixture of potassium ferricyanide (3 mmol, 990 mg), potassium carbonate (3 mmol, 420 mg), ligand **2** (5 mol %, 16.9 mg) and potassium osmate dihydrate (2 mol %, 7 mg) was added toluene (20 mL)/^{t}BuOH (20 mL)/H_2O (20 mL) and the reaction mixture was stirred vigorously at 0 °C for 0.5 h. To this solution was added *trans*-stilbene (1 mmol) and the mixture stirred for 12 h at 25 °C. The reaction mixture was quenched with sodium sulfite (1.5 g). After stirring for 3 h, the organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed successively with 3 N hydrochloric acid, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude stilbene diol was purified by column chromatography on silica gel using ethyl acetate/hexane (3/7) as eluent. Compound **6a**: Yield: 0.220 g (80%); mp: 118–119 °C (lit.[21a] 118–119 °C); IR (KBr): 3489, 3398, 2890, 1448, 1193, 1043, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, 4H, *J* = 8.8 Hz), 6.75 (d, 4H, *J* = 8.4 Hz), 4.63 (s, 2H), 3.76 (s, 6H), 2.83 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 132.2, 128.2, 113.5, 78.8, 55.2. Enantiomeric excess by HPLC: Chiralcel–OJ–H (hexane/2-propanol = 70:30, flow rate = 1 mL/min). Compound **6b**: Yield: 0.186 g (76%); Mp: 108–110 °C (lit.[21b] 110 °C); IR (KBr): 3490, 3400, 2892, 1450, 1197, 1043, 776, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (br s, 8H), 4.65 (s, 2H), 2.82 (br s, 2H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.0, 128.8, 126.8, 78.8, 21.1. Enantiomeric excess by HPLC: Chiralpak-AS-H (hexane/2-propanol = 90: 10, flow rate = 1 mL/min). Compound **6c**: Yield: 0.196 g (92%); mp: 145–148 °C (lit.[14] 148–150 °C); IR (KBr): 3499, 3400, 2893, 1452, 1197, 1043, 777, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.22 (m, 10H), 4.68 (s, 2H), 3.05 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 128.1,127.9, 126.9, 79.1. Enantiomeric excess by HPLC: Chiralcel-OJ-H (hexane/2-propanol = 90:10, flow rate = 1 mL/min). Compound **6d**: Yield: 0.240 g (85%); mp: 126–128 °C (lit.[21c] 127 °C); IR (KBr): 3486, 3399, 2890, 1448, 1198,1042, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 4H, *J* = 8.4 Hz), 6.98 (d, 4H, *J* = 8.4 Hz), 4.56 (s, 2H), 3.16 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 133.8, 128.4, 78.5. Enantiomeric excess by HPLC: Chiralpak-AS-H (hexane/2-propanol = 70:30, flow rate = 1 mL/min). Compound **6e**: Yield: 0.228 g (79%); mp: 128–130 °C; IR (KBr): 3400, 3344, 2928, 1928, 1622, 1331, 1122, 1070, 839, 763, 609, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 4H, *J* = 8.4 Hz), 7.22 (d, 4H, *J* = 8.0 Hz), 4.74 (s, 2H), 3.18 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 143.3, 130.3, 127.3, 125.2, 122.5, 78.3. Enantiomeric excess by HPLC: Chiralcel–OD–H (hexane/2-propanol = 85:15, flow rate = 1 mL/min). The same procedure as mentioned above was followed for the acetone/^{t}BuOH/H_2O and THF/^{t}BuOH/H_2O solvent systems.
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