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 NONLINEAR EFFECTS INVOLVING TWO COMPETING PSEUDO-ENANTIOMERIC CATALYSTS:
 EXAMPLE IN ASYMMETRIC DIHYDROXYLATION OF OLEFINS

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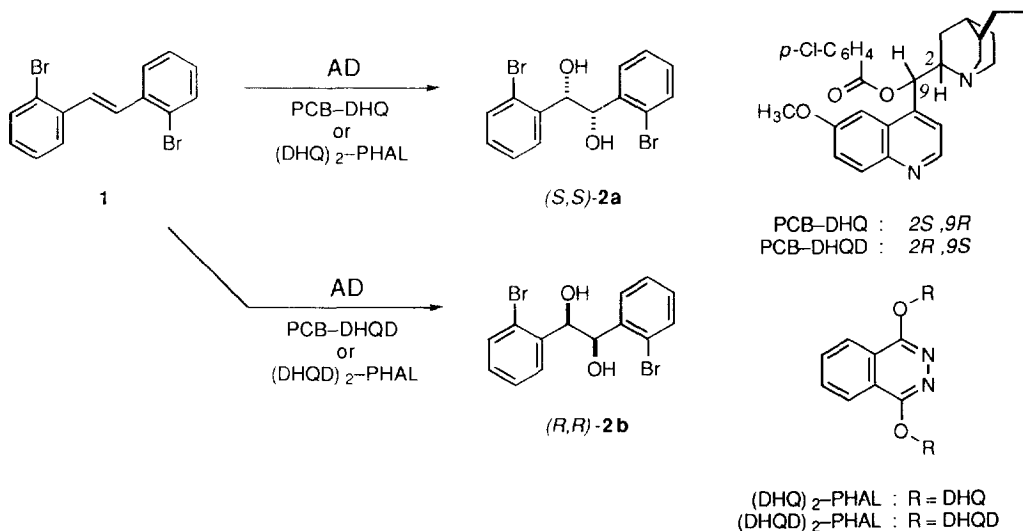
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Abstract: Asymmetric catalysis in the case of a mixture of pseudo-enantiomeric ligands has been studied in the Sharpless asymmetric dihydroxylation of bis-(*ortho*-bromo)stilbene. Nonlinear behaviours were observed in this situation, one spectacular case being evidenced ((DHQD)₂-PHAL / PCB-DHQ mixtures).

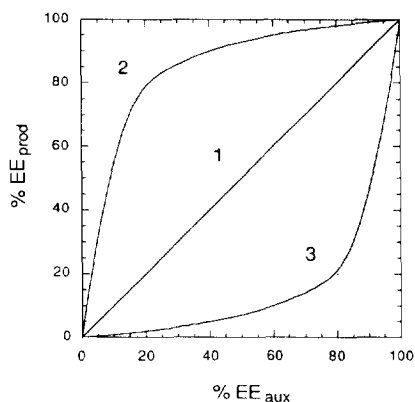
In the course of current work in our group, we needed to apply the efficient Sharpless asymmetric dihydroxylation¹ to the case of dibromostilbene **1**. This asymmetric hydroxylation (AD) has been described by Kelly *et al*, with formation of (*S,S*)-**2a** (79%*ee*) in 94% yield, using dihydroquinine *para*-chlorobenzoate (PCB-DHQ) as ligand for osmium². We could optimize the formation of diol **2a** (98% *ee*) or **2b** (98% *ee*) by using the chiral ligand (DHQ)₂-PHAL or (DHQD)₂-PHAL respectively (10 eq. by respect to OsO₄)³. Thus the chiral ligands behave as pseudo-enantiomers in the reaction (Scheme 1). The use of PCB-DHQ of the first generation of Sharpless ligands, gave in the same conditions³ lower *ee*'s in **2a** (91% *ee*).



Scheme 1

Owing our interest in the study of nonlinear effects in asymmetric catalysis⁴⁻⁶ (Scheme 2), we were intrigued to see if a similar phenomena could occur in organometallic catalysis by replacing a mixture of enantiomeric ligands by a mixture of diastereomeric ligands (giving asymmetric catalysts leading to products of opposite absolute configuration). For that purpose, we decided to study the above asymmetric

dihydroxylation (**1**→**2**) by replacing the chiral auxiliary by a mixture of two chiral auxiliaries (10 eq. by respect to OsO₄) in various proportions, accordingly to the previously cited procedure³. Experiments were performed with the mixtures (DHQ)₂-PHAL / (DHQD)₂-PHAL and PCB-DHQ / (DHQD)₂-PHAL. A similar study was recently reported by Noyori *et al* regarding alkylation with dialkylzinc catalyzed by a mixture of diastereomeric aminoalcohols^{6h}.



Curve 1: Proportionality between ee of the chiral auxiliary (EE_{aux}) and ee of the product (EE_{prod})

Curve 2: Positive nonlinear effect

Curve 3: Negative nonlinear effect

Scheme 2

EE_{prod} is linearly correlated to the diastereomer composition (percentage of a given diastereomer in the mixture) of catalysts when assuming strict independence of the diastereomeric and enantiopure catalysts. The results are depicted in Table 1 and Scheme 3.

In a first series of experiments, mixture of (DHQ)₂-PHAL and (DHQD)₂-PHAL of different proportions were used to perform the osmylation. In that case, there is only a slight departure from linearity (Scheme 3A). For a 1:1 mixture of the two ligands, the diol **2** is of (*R,R*)-configuration (with an ee of 23%). This is an indication of a slight predominance of dihydroxylation through the (DHQD)₂-PHAL / osmium complex. The linear behavior is expected for a 1:1 mixture of (DHQD)₂-PHAL and (DHQ)₂-PHAL complexes if they have the same reactivity.

The dihydroxylation of **1** using a mixture of (DHQD)₂-PHAL and PCB-DHQ gives however a strong departure from linearity (Scheme 3B). It is the (DHQD)₂-PHAL complex which is operating almost all the time. It is interesting to see that even for a 90 : 10 mixture of PCB-DHQ/(DHQD)₂-PHAL the diol **2** nevertheless remains of (*R,R*) configuration (77% ee), a clear indication that in these experimental conditions most of the dihydroxylation of **1** has been realized through the (DHQD)₂-PHAL / osmium channel⁷.

This type of experiments should be useful to extract quantitative informations on the behavior of catalytic species⁸. It can be a tool for the study of the interaction between complexes since mixed species could give rise to anomalies by respect of independent complexes.

We are currently investigating in that area for extending the scope of this method.

Acknowledgments

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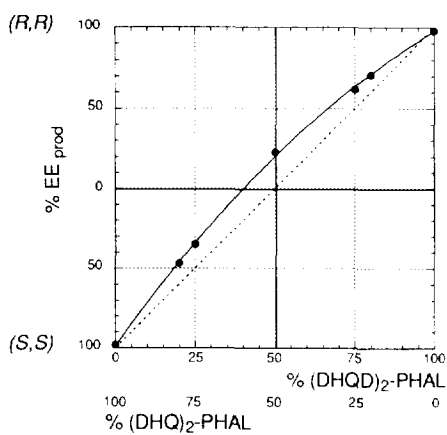
Table 1: Asymmetric Dihydroxylation of (*E*)-bis-(*o*-bromo)stilbene (**1**)

(DHQD) ₂ -PHAL	(DHQ) ₂ -PHAL	Diol	EE _{prod} ^a
%	%	—	%
100	0	(<i>R,R</i>)	98 ^b
80	20	(<i>R,R</i>)	71
75	25	(<i>R,R</i>)	62
50	50	(<i>R,R</i>)	23
25	75	(<i>S,S</i>)	35
20	80	(<i>S,S</i>)	47
0	100	(<i>S,S</i>)	98 ^b

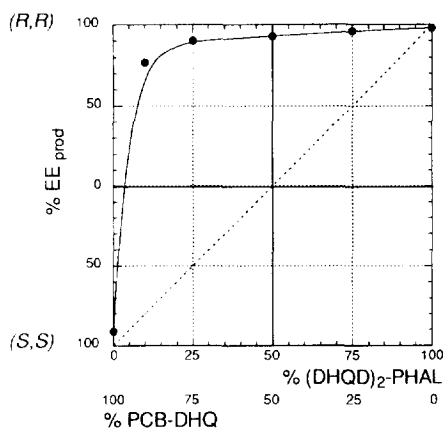
(DHQD) ₂ -PHAL	DHQ-PCB	Diol	EE _{prod} ^a
100	0	(<i>R,R</i>)	98 ^b
75	25	(<i>R,R</i>)	96
50	50	(<i>R,R</i>)	93
25	75	(<i>R,R</i>)	90
10	90	(<i>R,R</i>)	77
0	100	(<i>S,S</i>)	91

a) HPLC: (*S,S*)-WheIk-01 (Pirkle-type, Regis Technologies), hexane/*i*-PrOH - 9/1, 0.5 ml/min. UV 254 nm detection. (*R,R*)-Diol: $R_f = 16$ min.; (*S,S*)-Diol: $R_f = 20$ min.

b) Based on $[\alpha]_D^{\max} = +39.9$ (*c* 1, EtOH) (ref 2).



A



B

Scheme 3

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3. 0.23 g (0.3 mmol) of (DHQD)₂-PHAL (*or mixture of chiral auxiliaries*), 2.94 g (9 mmol) of K₃Fe(CN)₆, 1.24 g (9 mmol) K₂CO₃, OsO₄ (0.03 mmol) and 0.28 g (3 mmol) of CH₃SO₂NH₂ are mixed in 40 mL *t*-BuOH/H₂O (1:1). After cooling at 0°C, 1.02 g (3 mmol) of (*E*)-**1** is added. Following a 20 h of stirring at 0°C, one adds 0.5 g of sodium metabisulfite. Usual work up and flash chromatography on silica gel (CH₂Cl₂:Et₂O, 4:1) afforded 0.95 g of (*S,S*)-(+)-**2a** (87% yield). [α]_D = +39.2 (*c* 1, EtOH). 98 % ee based on [α]_D^{max} = +39.9 (*c* 1, EtOH) (ref 2).
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7. When the chiral auxiliary is ligand of a metal one needs to take into account, in the competition experiments, the association constants and the catalytic activity. A kinetic study of dihydroxylation of **1** in presence of either (DHQD)₂-PHAL or PCB-DHQ in the experimental conditions of Table 1 indicates that (DHQD)₂-PHAL gives a catalyst slightly faster than PCB-DHQ. The strong departure from linearity (curve of Scheme 3B) could be indicative of an higher association between (DHQD)₂-PHAL to osmium in the competition with PCB-DHQ.
8. Mechanism of asymmetric dihydroxylation is under active investigation⁹⁻¹³, especially for explaining the high efficiency of the new generation of Sharpless ligands (PHAL and related series). The detailed analysis of curves such as in Scheme 3 in various experimental conditions should be useful in that context.
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