Tetrahedron Letters,Vol.30,No.16,pp 2041-2044,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

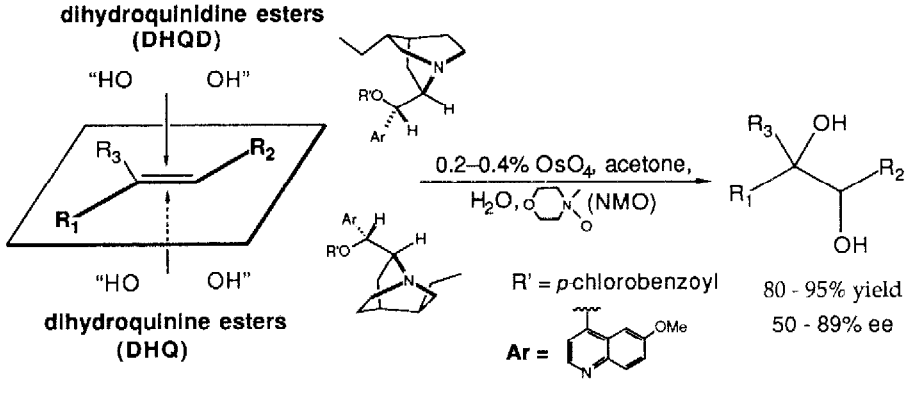
DOCUMENTING THE SCOPE OF THE CATALYTIC ASYMMETRIC DIHYDROXYLATION

B. Bhushan Lohray, Thomas H. Kalantar, B. Moon Kim, Christine Y. Park
Tomoyuki Shibata,† John S. M. Wai and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, MA 02139

Summary: A wide variety of functionalized and unfunctionalized olefins are efficiently converted to the corresponding cis vicinal diols in moderate to good enantiomeric excess via the "slow addition" enhanced catalytic asymmetric osmylation process.

About a year ago we described an osmium-catalyzed asymmetric dihydroxylation process employing cinchona alkaloid derivatives as the chiral ligands.[1] We subsequently discovered the presence of two diol-generating catalytic cycles in this process.[2] The first cycle turns over faster and produces diol in high enantiomeric excess, while the second proceeds slower and exhibits low, to opposite enantiofacial selectivity. Slow addition of the olefin to the reaction mixture minimizes production of diol by the second cycle, thereby increasing the enantiomeric excess of the product. Under such "slow addition" conditions, the scope of the asymmetric dihydroxylation process is greatly enhanced and includes simple hydrocarbon olefins, aromatic olefins, allylic alcohols and their esters, allylic chlorides, α,β-unsaturated esters, acetals of α,β-unsaturated aldehydes, ketals of α,β-unsaturated ketones, and water sensitive trimethylsilyl enol ethers, etc.. Reported here are some representative examples selected from the over 60 olefins examined to date (Table 1), general procedures for running the reaction,[3] and methods for determination of the enantiomeric excesses of the diols produced (Table 1).



The examples in Table 1 reveal that this catalytic asymmetric dihydroxylation, even at its present level of development, proceeds with moderate to good levels of asymmetric induction across a wide range of olefins. Its most striking feature is the lack of requirement for a directing functional group. The process

Table 1. Percentage enantiomeric excesses of diols obtained in the asymmetric dihydroxylation of olefins under stoichiometric and catalytic conditions.

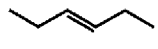
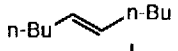
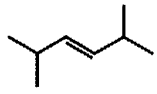
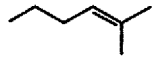
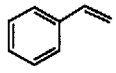
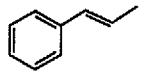
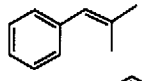
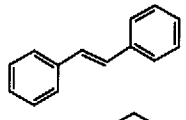
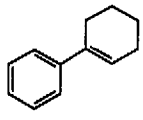
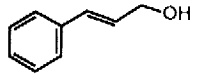
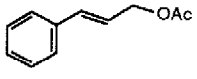
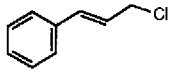
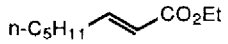
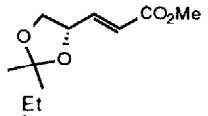
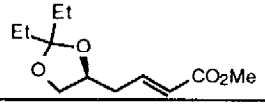
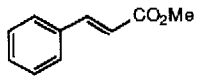
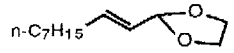
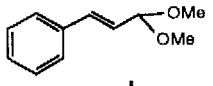
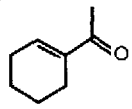
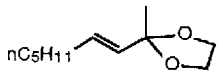
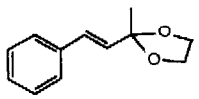
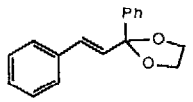
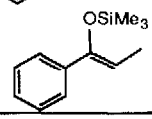
entry	olefins	stoichiometric[a]	catalytic[b] (slow addition)	method of ee & de determination[c]
1		69	70 (10h)	I[d]
2		71	69 (40h)[e]	II (δ 5.20, 5.12)
3		80	76 (24h)[e]	III
4		55	54 (24h, rt)[f]	IV
5		61	60 (5h)	IV
6		87	86 (5h)	IV
7		55	53 (12h)	IV
8		99	80[g]	V
9		79	78 (26h); 81 (16h)[e]	I[h]
10		66	66 (16h)	VI
11		82	79 (16h)[i]	II (δ 2.01, 1.99)
12		79	78 (10h)	III
13		66	67 (31h)	IV
14		77	76% de (42h)[j]	VII (δ 1.38, 1.36)
15		54	52% de (48h)[j]	IV

Table 1. continued

entry	olefins	stoichiometric[a]	catalytic[b] (slow addition)	method of ee & de determination[c]
16		89	86 (18h)	II (δ 6.62, 6.59)
17		83	56 (20h); 66 (20h)[e]	VI
18		82	75 (18h); 83 (18h)[e]	IV
19		56	54 (24h, rt)[f]	IV
20		50	46 (18h); 50 (18h)[e]	VI
21		85	60 (10 h); 89 (10h)[e]	IV
22		86	84 (20h); 87 (20h)[e]	VI
23		85	72 (23h); 78 (23h)[e,k]	VI

a. All stoichiometric reactions were carried out in acetone-water, 10:1 v/v, at 0 °C and at a concentration of 0.15M in each reagent except entries 8, 17, 20 which were performed in toluene under otherwise identical conditions. b. All reactions were carried out at 0 °C (unless otherwise cited) as described in the general procedure (note 3), and the period of addition of olefin is indicated in parentheses. All the ee's shown in the table were obtained with dihyroquinidine *p*-chlorobenzoate as ligand. All ten cases for which literature correlations exist, entries 1, 5, 6, 8, 9, 10, 11, 14, 16, 23, abide by the face selection rule in the Scheme, the others are expected to do likewise. c. Methods of ee & de determination: I. GLC analysis of the bis- or mono-Mosher esters[5] of diols on a 29m 5% phenylmethylsilicone capillary column. II. ^{1}H NMR of bis-Mosher esters of diols. Entries 2, 11 as solutions in $CDCl_3$, entry 16 in benzene-d_6. III. ^{1}H NMR of diols as a solution in $CDCl_3$ in the presence of tris[(3-trifluoromethylhydroxymethylene)-d-camphorato], europium(III) derivative. IV. HPLC of bis- or mono-Mosher esters of diols on Pirkle IA Ionic D-phenylglycine column (25 cm x 10 mm I.D.). Entries 4, 5, 6 eluted with 0.5% i-PrOH in hexane (3 mL/min), entries 7, 18, 19 eluted with 2.5% i-PrOH in hexanes (2 mL/min), entry 13 with 0.5% i-PrOH in hexanes (2 mL/min), entries 15, 21 with 2.5% i-PrOH in hexanes (3mL/min). V. HPLC of bis-acetate of diols on Pirkle IA Ionic D-phenylglycine column (25 cm x 10 mm I.D.), eluted with 5% i-PrOH in hexanes (2mL/min). VI. HPLC of mono-, bis- or tris-Mosher esters on Pirkle covalent D-phenylglycine column (25 cm x 10 mm I.D.). Entry 10 eluted with 10% i-PrOH in hexanes (2mL/min), entries 17, 20, 23 eluted with 2.5% i-PrOH in hexanes (2mL/min), entry 22 with 2.5% i-PrOH in hexanes (3mL/min). VII. ^{1}H NMR of diols as a solution in $CDCl_3$. d. GLC conditions: 220 °C for 4 min, then 2 °C/min to 300 °C. e. This reaction was carried out in the presence of 2 equiv. of $Et_4NOAc{\cdot}4H_2O$ for 1 equiv. of olefin. In the case of α,β-unsaturated esters and allylic alcohols, the presence of acetate results in lower ee's. f. This reaction was carried out in the presence of 2 equiv. of $Me_4NOH{\cdot}5H_2O$ and 2 equiv. AcOH. g. See note 4. h. GLC conditions: 200 °C for 4 min, then 2 °C/min to 250 °C. i. The 2,6-dichlorophenyl analog of entry 11 gave diol of ~75% ee under the old conditions.[1] j. The inherent diastereofacial selectivities exhibited in osmylation of olefin entries 14 and 15 in the absence of alkaloid are 2.1:1 (2S:2R) and 1:1.1 (2S:2R), respectively. k. The α-hydroxyketone was the product isolated.

is also exceedingly easy to perform and can be run very concentrated, the latter consideration greatly simplifies large scale applications. An immediate goal is to further improve the enantioselectivity of the reaction, but in the meantime most of the enriched diols can be raised to enantiomeric purity by recrystallization, either of the diol itself [6] or of a crystalline intermediate encountered during subsequent required synthetic steps. The resulting homochiral diols are proving useful as chiral synthons, for example they can be readily converted into the corresponding cyclic sulfates which exhibit epoxide-like reactivity.[7,8] Asymmetric syntheses employing these cyclic sulfates and related diol-derived synthons will be the subject of future reports.

Acknowledgments: Financial support was provided by the National Institutes of Health (GM 28384). We are grateful to Dr. Istvan Markó for a preliminary investigation of the scope of the catalytic asymmetric dihydroxylation under the original conditions.[1] T.H.K. thanks the Natural Sciences and Engineering Research Council (Canada) and the Alberta Heritage Scholarship Fund for financial support.

References and Notes:

† Sankyo Co. Ltd., Tokyo, Japan.

1. E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, and K. B. Sharpless, *J. Am. Chem. Soc.*, **1988**, *110*, 1968.
2. J. S. M. Wai, I. Markó, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, and K. B. Sharpless, *J. Am. Chem. Soc.*, **1989**, *111*, 1123.
3. General procedure: To a well-stirred mixture of 0.465 g (1 mmol, 0.25 equiv. = 0.25 M in L) dihydroquinidine *p*-chlorobenzoate (Aldrich, 98%), 0.7 g (6 mmol, 1.5 equiv.) *N*-methylmorpholine *N*-oxide (NMO) (Aldrich, 97%) and 32 μL of a 0.5 M toluene solution of osmium tetroxide (16 μmol, 0.004 equiv.) in 4 mL of an acetone-water mixture (10:1, v/v) at 0 °C, neat (0.5 mL, 0.34 g, 4 mmol) trans-3-hexene (Wiley, 99.9%) was added slowly, with a gas-tight syringe controlled by a syringe pump and with the tip of the syringe needle immersed in the reaction mixture, over a period of 10 h. The mixture gradually changed from heterogeneous to homogeneous. After the addition was complete the resulting clear orange solution was stirred at 0 °C for an additional hour. Solid sodium metabisulfite ($Na_2S_2O_5$, 1.2 g) was added, and the mixture was stirred for 5 min at rt, then diluted with dichloromethane (8 mL) and dried (Na_2SO_4). The solids were removed by filtration and washed three times with dichloromethane. The combined filtrates were concentrated, and the residual oil flash column chromatographed (silica gel, 25 g; elution with diethyl ether-dichloromethane, 2:3 v/v, R_f 0.33) affording 0.43 g (92% yield) of 70% ee R,R-(+)-hexanediol, $[\alpha]^{22}_D$ +20.0° (*c* 2.50, H_2O). Lit. $[\alpha]^{25}_D$ +22.7° (*c* 2.50, H_2O): A. C. Cope and T. Y. Shen, *J. Am. Chem. Soc.*, **1956**, *78*, 5916. [When the above reaction was repeated with 1.2 mL (6mmol, 1.5 eq) 60% aqueous NMO (Aldrich) in 4mL acetone, diol of 71% ee was obtained.]
4. Stilbene is only sparingly soluble in aqueous acetone. As the reaction proceeds it gradually dissolves in the reaction mixture thereby approximating "slow addition" conditions. The experimental procedure for dihydroxylation of stilbene is given in reference 1.
5. J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **1969**, *34*, 2543.
6. Many diols are crystalline, but we have found that they only occasionally exhibit the felicitous behavior of crystalline epoxy alcohols (i.e. undergo rapid ee improvement upon recrystallization). Fortunately, several classes of simple derivatives, from which the diols are easily regenerable, are showing much more promise for ee enrichment through recrystallization. D. G. Gilheany and K. B. Sharpless, unpublished results.
7. Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, **1988**, *110*, 7538.
8. B. M. Kim and K. B. Sharpless, *Tetrahedron Lett.*, in press.

(Received in USA 9 February 1989)