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Improved Enantioselective Dihydroxylation of Bishomoallylic Alcohol Derivatives Using a Mechanistically Inspired Bis-cinchona Alkaloid Catalyst

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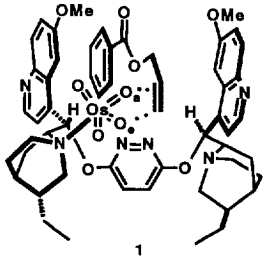
Summary: *The catalytic dihydroxylation of p-methoxybenzoate esters of various bishomoallylic alcohols proceeds with excellent enantioselectivity and, in the case of diolefins, with improved regioselectivity using a designed catalyst that incorporates an N-anthracenylmethyl group to enhance catalyst-substrate binding interactions.*

Although the Sharpless asymmetric dihydroxylation of terminal olefinic allylic and homoallylic alcohols (or their silyl ethers) proceeds with poor enantioselectivity,[1-3] much improved results are obtained with 4-methoxybenzoate esters of allylic alcohols and 4-methoxyphenyl ethers of homoallylic alcohols.[1] The use of these derivatives was suggested by the mechanistic model for the bis-cinchona–OsO_4 catalytic dihydroxylation system which has been advanced previously.[4] The proposed transition-state assembly for the face-selective dihydroxylation of allyl 4-methoxybenzoate (>96% ee), for example, in the $(DHQD)_2PYDZ$–OsO_4 system is depicted in expression **1**. The factors which operate to favor this pathway and the stereochemical / structural features of this model have been described in detail earlier.[4] In contrast to the excellent enantioselectivities which can be realized in the dihydroxylation of the above mentioned allylic and homoallylic alcohol derivatives, the corresponding transformations of *bishomoallylic* alcohol derivatives occur with substantially lower facial selection.[1c] This result is consistent with the mechanistic model which predicts diminished binding of bishomoallylic 4-methoxybenzoate esters to the U-shaped region of the catalyst, due principally to a reduction in aryl-aryl contacts. In order to improve the enantioselectivity in the asymmetric dihydroxylation of these substrates, the modified bis-cinchona alkaloid catalyst **3** which possesses an additional aromatic contact juxtaposed to the hydrophobic U-shaped binding pocket was prepared. The following ^1H NMR observations (500 MHz, CD_3OD, 23 °C) provide support for the conformation shown in formula **3**: (1) a 3.6% NOE from H_a to H_g and an 8.9% NOE from H_g to H_d, supporting the orientation of the anthracene ring shown, (2) H_d (δ 7.6 ppm) is shielded relative to H_c (δ 8.4 ppm) due to its proximity to the face of the pyridazine ring, (3) a 5.3% NOE from H_a to H_e and a 9.2% NOE from H_i to H_h supporting the orientation of the methoxyquinoline rings shown, and (4) J (H_iH_j) and J (H_aH_b) = 0-2 Hz, suggesting a *ca.* 90° dihedral angle between each set of protons and supporting the orientation of the quinuclidine rings shown.[5] It is important to note that the bulk of the 9-anthracenyl group serves to rigidify structure **3** by severely limiting the rotational movements about the two bonds which connect this tricyclic unit with the quinuclidine nitrogen.



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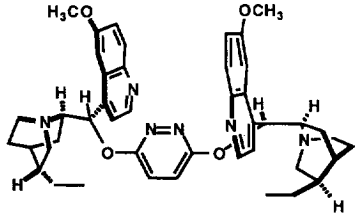

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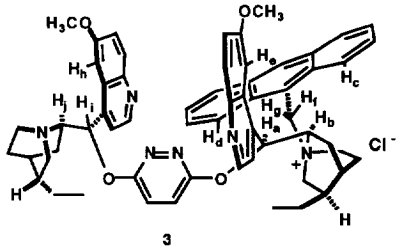

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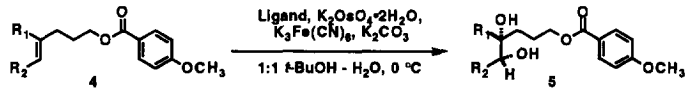
Table 1. Enantioselective Dihydroxylation of 4-Penten-1-ol Derivatives **4a-g** Using Bis-cinchona Alkaloid Catalysts **2** and **3**.



Olefin	Enantiopurity (%Yield) Ligand 2	Enantiopurity (%Yield) Ligand 3	$[\alpha]_D^{23}$
4a	82 (99)[1]	86 (91)[1]	+2.4° (*c* 1.0, $CHCl_3$)
4b	79 (95)[2]	90 (99)[2]	-1.0° (*c* 0.40, $CHCl_3$)
4c	33 (99)[2]	82 (99)[2]	-0.2° (*c* 1.9, $CHCl_3$)
4d	92 (88)[2,3]	92 (91)[2,3]	+0.5° (*c* 2.1, $CHCl_3$)
4e	89 (97)[2,3]	90 (98)[2,3]	+12° (*c* 0.47, $CHCl_3$)
4f	89 (100)[2,3]	91 (94)[2,3]	-3.5° (*c* 1.9, $CHCl_3$)
4g	86 (73)[2,3] 3.4:1 Position Selectivity	97 (74)[2,3] 12:1 Position Selectivity	-1.8° (*c* 1.2, $CHCl_3$)

[1] Enantioselectivity determined by ^1H NMR analysis of the bis-Mosher ester derivative.
[2] Enantioselectivity determined by chiral HPLC analysis of the acetonide derivative (Chiralcel OD, 2-10% 2-propanol in hexane as appropriate, 1 mL/min, λ=254 nm, at 23 °C).
[3] Methanesulfonamide (1.0 equiv) was added to this reaction.

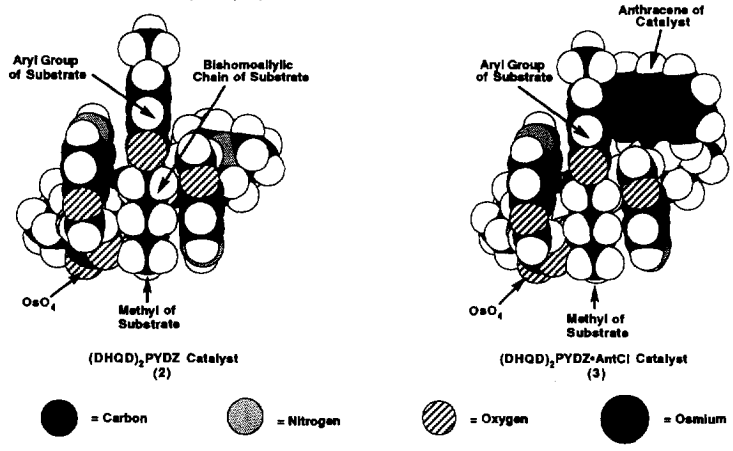


Figure 1. Proposed transition-state geometries for the catalytic asymmetric dihydroxylation of **4b** using the *bis*-cinchona alkaloid catalysts **2** and **3**.

A comparative study of ligands **2** and **3** in the catalytic dihydroxylation of a series of bishomoallylic 4-methoxybenzoates was carried out with the results shown in Table I. The absolute stereochemistry of **5b** was demonstrated rigorously by chemical correlation[6]; the absolute configurations of **5a** and **5c-5g** were assigned by analogy based on the mechanistic model.[1c,4] In general, it is evident that ligand **3** is clearly superior to ligand **2** with terminal olefins, where low enantioselectivity is usually observed with **2**. Thus, although the catalytic dihydroxylation of **4b** using the $(DHQD)_2PYDZ$ ligand (**2**) proceeded with only 8.5:1 facial selectivity, the corresponding reaction using the ligand **3** proceeded with 19:1 facial selectivity to afford the (*R*)-glycol **5b** in 99% yield. For the *trans*-disubstituted or trisubstituted substrates shown in Table I, very good enantioselectivities were obtained for both ligands **2** and **3**. The doubly unsaturated substrate **4g** is more rapidly dihydroxylated at the bishomoallylic double bond, whereas the corresponding oxidation using OsO_4–*N*-methylmorpholine *N*-oxide is non-selective. The effect of the anthracenylmethyl group of the catalyst on the enantio- and regioselectivity of these dihydroxylations is completely consistent with our proposed transition-state model, which is shown for the dihydroxylation of **4b** using ligands **2** and **3** in Figure 1. In this model, the 4-methoxybenzoate subunit, the bishomoallylic double bond and the propyl linker group of the substrate are all involved in binding to the catalyst leading to face-selective accelerated dihydroxylation. For the asymmetric dihydroxylations of these substrates using ligand **3**, enhanced hydrophobic and aryl-aryl stacking interactions between the bishomoallylic 4-methoxybenzoyl group of the substrate and the anthracenylmethyl group of the catalyst lead to better binding interactions and improved enantioselectivity. The importance of the anthracenyl group in imparting higher facial selectivity was indicated by control experiments using the mono-methyliodide salt of **2** which, for substrates **4a**, **4b** and **4d**, gave enantioselectivities that were comparable to those obtained using the ligand **2** (**4a**: 81% ee, **4b**: 77% ee, **4d**: 86% ee). The β-naphthylmethyl quaternary ammonium derivative of **2** was found to be only slightly more effective than the *N*-methyl analog with regard to enantioselectivity (**4b**: 82% ee).

In summary, the enantio- and regioselective dihydroxylation of bishomoallylic 4-methoxybenzoate esters can be accomplished with higher levels of selectivity using the rationally designed ligand **3**. The following procedures provide experimental detail for the preparation of **3** and the asymmetric dihydroxylation of **4b**.[7]

3,6-Bishydroquinidylpyridazine - mono 9-anthracenylmethylchloride salt (3). To a solution of 3,6-bishydroquinidylpyridazine (**2**) (1.6 g, 2.2 mmol) in 4.4 mL of acetonitrile was added 9-chloromethylanthracene (0.50 g, 2.2 mmol), and the resulting mixture was stirred for 12 h at 40 °C. After concentration *in vacuo*, the residue was purified by flash column chromatography (90:10:1 $CHCl_3$-MeOH-NH_4OH), followed by radial chromatography (4 mm plate, $CHCl_3$-MeOH-NH_4OH 98:2:0.2 - 90:10:1), giving 0.85 g (40%) of **3** as a light yellow solid: R_f = 0.28 (85:15:1.5 $CHCl_3$-MeOH-NH_4OH); $[\alpha]_D^{23}$ +48° (*c* 0.18, $CHCl_3$); FTIR (film) 2955, 2934, 2873, 1622, 1509, 1475, 1435, 1257, 1228, 1027, 989 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 8.73 (d, 1H, *J* = 4.6 Hz), 8.67 (s, 1H), 8.39 (d, 1H, *J* = 9.0 Hz), 8.34 (d, 1H, *J* = 4.6 Hz), 8.27 (s, 1H), 8.10 (m, 3H), 7.88-7.82 (m, 2H), 7.72-7.66 (m, 2H), 7.64 (d, 1H, *J* = 9.3 Hz), 7.61 (d, 1H, *J* = 2.2 Hz), 7.58-7.52 (m, 3H), 7.51 (d, 1H, *J* = 4.6 Hz), 7.44 (t, 1H, *J* = 8.2 Hz), 7.34 (d, 1H, *J* = 1.9 Hz), 7.17 (dd, 1H, *J* = 2.5, 9.2 Hz), 7.00 (t, 1H, *J* = 7.4 Hz), 6.91 (s, 1H), 5.96 (d, 1H, *J* = 14.0 Hz), 5.66 (d, 1H, *J* = 14.0 Hz), 4.53 (m, 1H), 4.09 (s, 3H), 4.05 (m, 1H), 3.75 (s, 3H), 3.59 (m, 1H), 3.18 (m, 1H), 2.92-2.67 (m, 6H), 2.28 (m, 1H), 1.94 (s, 1H), 1.79 (m, 2H), 1.67-1.53 (m, 11H), 1.37 (m, 1H), 0.94 (t, 3H, *J* = 7.1 Hz), 0.79 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ 164.5, 163.3, 161.5, 160.3, 159.7, 148.1, 148.0, 147.8, 145.3, 145.1, 144.8, 140.9, 134.0 (2C), 133.6, 132.6, 132.5, 132.2 (2C), 131.2, 129.3, 128.8, 128.1 127.4, 126.5, 126.2, 124.7, 124.1, 123.8, 123.6,

123.3, 121.4, 121.3, 119.5, 117.9, 103.0, 102.4, 77.3, 72.5, 68.9, 60.4, 59.4, 59.2, 57.0, 56.5, 56.4, 51.9, 51.0, 37.9, 36.9, 27.1, 26.2, 25.6, 25.5, 25.0, 23.1, 22.1, 12.2, 11.5 ppm; FABMS 919 $[M\text{-}Cl]^+$, 309; HRMS calcd for $[C_{59}H_{63}N_6O_4Cl\text{-}Cl]^+$: 919.4911, found: 919.4936.

Asymmetric dihydroxylation of 4-methyl-4-penten-1-yl 4-methoxybenzoate (4b): A solution of K_2CO_3 (0.531 g, 3.84 mmol), $K_3Fe(CN)_6$ (1.26 g, 3.84 mmol), $K_2OsO_4{\cdot}2H_2O$ (0.0048 g, 0.013 mmol) and **3** (0.012 g, 0.013 mmol) in *tert*-butyl alcohol-water 1 : 1 (16 mL) was cooled to 0°C. The resulting suspension was treated with 4-methyl-4-penten-1-yl 4-methoxybenzoate (**4b**) (0.30 g, 1.28 mmol). The mixture was stirred for 4 h and quenched by addition of Na_2SO_3 (0.670 g, 4.7 mmol). The resulting mixture was stirred for 5 min, warmed to 23°C over 5 min and partitioned between EtOAc and minimal water. The organic extract was washed twice with brine, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a silica gel plug eluting with EtOAc. The filtrate was concentrated *in vacuo* to afford 0.34 g (99% yield) of **5b** as a colorless liquid of 90% ee (determined by HPLC analysis of the acetonide derivative): R_f = 0.16 (1:1 EtOAc-hexane); $[\alpha]_D^{23}$ -1.0° (*c* 0.40, $CHCl_3$); FTIR (film) 3600-3200, 2938, 1708, 1600, 1512, 1463, 1318, 1281, 1258, 1169, 1108, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (m, 2H), 6.91 (m, 2H), 4.30 (t, 2H, *J* = 6.6 Hz), 3.85 (s, 3H), 3.48 (dd, 1H, *J* = 4.5, 10.6 Hz), 3.43 (dd, 1H, *J* = 4.4, 10.8 Hz), 2.40 (b, 1H), 2.29 (s, 1H), 1.82 (m, 2H), 1.65 (m, 2H), 1.19 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 163.3, 131.6, 122.6, 113.6, 72.6, 69.8, 65.0, 55.4, 34.7, 23.3, 23.2 ppm; EIMS 268 $[M]^+$, 237, 152, 135 $[An]^+$; HRMS calcd for $[C_{14}H_{20}O_5]^+$: 268.1311, found: 268.1321. HPLC (chiral, on acetonide) Chiralcel OD at 23 °C, λ = 254 nm, hexane-isopropanol 90:10; retention times: 10.8 (major), 15.7 min (minor) at 1 mL/ min flow rate.

References and Notes

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