Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1739-1742, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00162-1

Position and Enantioselective Dihydroxylation of 2-Hydroxymethyl- and 2-Hydroxyethyl-1,3-butadiene Derivatives Using Bis-cinchona Alkaloid Catalysts

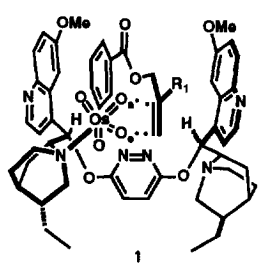
Mark C. Noe and E. J. Corey*

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Summary: *The asymmetric dihydroxylation of p-methoxybenzoate esters or p-methoxyphenyl ethers of 2-hydroxymethyl-1,3-butadienes or 2-hydroxyethyl-1,3-butadienes proceeds with excellent position and enantioselectivity using bis-cinchona alkaloid catalysts. The regioselectivity of these reactions is strongly influenced by binding interactions between the aromatic ether or ester group and the catalyst as predicted from a previously proposed transition state model.*

Methodology has been developed earlier for the highly efficient asymmetric dihydroxylation of appropriate allylic alcohol derivatives using the Sharpless catalytic system.[1] This work demonstrated that although the Sharpless asymmetric dihydroxylation proceeds with poor enantioselectivity in the case of various allylic alcohols or their silyl ethers, the dihydroxylation of the corresponding 4-methoxybenzoate esters affords products of high enantiomeric purity.[1-3] The use of these derivatives was suggested by the mechanistic model for the bis-cinchona-OsO_4 system which has been advanced previously.[4] The proposed transition state assembly for the face selective dihydroxylation of allyl 4-methoxybenzoate using the $(DHQD)_2PYDZ$–OsO_4 system is shown in stereo formula **1** (R_1=H). The interactions between the substrate and the catalyst which operate to favor this pathway have been described in detail elsewhere.[1c,4] During the course of these studies, it was noted that the enantioselectivity obtained in the asymmetric dihydroxylation of various allylic, homoallylic and bishomoallylic 4-methoxybenzoates was sensitive to the length of the aliphatic chain connecting the 4-methoxybenzoyl group to the olefin. Thus, while the asymmetric dihydroxylation of allyl and bishomoallyl 4-methoxybenzoate gives products of high enantiomeric purity (>96% and 82% ee, respectively), the corresponding reaction of homoallyl 4-methoxybenzoate affords the corresponding diol in only 40% ee.[1c] In contrast, the dihydroxylation of the corresponding homoallylic 4-methoxyphenyl ether derivatives produces the corresponding diols in high enantiomeric purity.[1b] These results can be understood in terms of unfavorable electron repulsion involving the carbonyl group of the homoallylic 4-methoxybenzoate and the pyridazine spacer group of the catalyst that is absent in the case of the allylic and bishomoallylic esters and the homoallylic 4-methoxyphenyl ethers.[1c] The proposed transition state assemblies for the asymmetric dihydroxylation of each of these substrates is shown in expressions **1** (R_1=H), **2** (R_1=H), **3** (R_1=H) and **4** (R_1=H) below (the methoxy group of the substrate is omitted for clarity).

The dependence of enantioselectivity on the position of the 4-methoxybenzoyl group relative to the substrate double bond suggested that this group might be effective in directing the position selectivity of the dihydroxylation of polyunsaturated substrates. While substituent steric and electronic factors are known to direct regioselective dihydroxylation of polyunsaturated substrates, the use of a removable directing group that would influence both position selectivity and enantioselectivity has been less well studied.[5] A series of polyunsaturated dienyl alcohol derivatives was prepared and tested with the results shown in Table 1.[6] Although each reaction was carried to *ca.* 90% total conversion, less than 10% of the corresponding tetraols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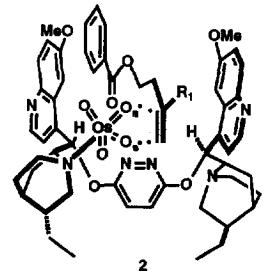
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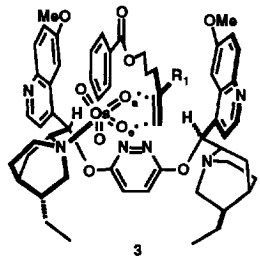
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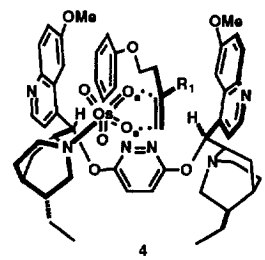
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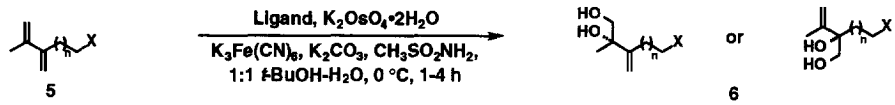
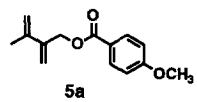
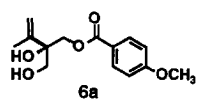
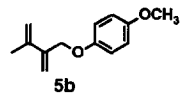
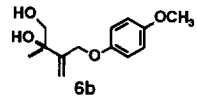
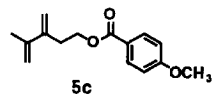
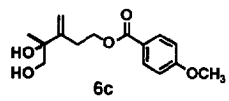
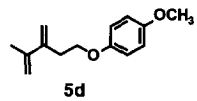
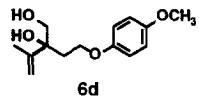
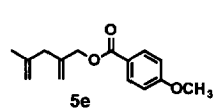
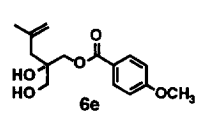
Table 1. Enantioselective Dihydroxylation of Bis-unsaturated Alcohol Derivatives **5a-e** Using Bis-cinchona Alkaloid Catalysts $(DHQD)_2PYDZ$ (ligand **A**) and $(DHQD)_2PYDZ$•AntCl (ligand **B**).



Olefin	Ligand	Major Product	Yield	Position Selectivity	ee	$[\alpha]_D^{23}$ (*c* 1, $CHCl_3$)
 5a	A	 6a	80%	33:1	84%[1]	+13°
 5b	A	 6b	70%	8:1	93%[2]	+5.5°
 5c	B	 6c	74%	12:1	97%[3]	-1.8°
 5d	A	 6d	70%	8:1	74%[2]	-19°
 5e	A	 6e	72%	17:1	93%[2]	+6.7°

[1] Determined by Chiral HPLC (Chiralpak AD, 7.5% isopropanol in hexane, λ=254 nm, 1 mL/min, 23 °C).

[2] Determined by ^1H NMR integration of the corresponding mono-MTPA ester derivative.

[3] Determined by Chiral HPLC of the corresponding acetonide (Chiralcel OD, 5% isopropanol in hexane, λ=254 nm, 1 mL/min, 23 °C).

were observed. The structure (and position selectivity) of each diol was assigned by comparison of the ^1H NMR chemical shifts of the terminal methyl groups in $CDCl_3$ solution at 23 °C (for **6a**, **6d**, and **6e** δ = 1.8 ppm; for **6b** and **6c**, δ = 1.3 ppm). The absolute configurations of the diols **6** were assigned based on the absolute stereochemistry previously demonstrated for the asymmetric dihydroxylation of allylic[1a] or homoallylic[1b] alcohol derivatives. The planar conformation of these substrates, which is expected to be crucial for binding of the substrate to the U-shaped pocket of the catalyst, should be favored by *s-trans*-coplanarity of the diene. The conformational preferences of allylic and homoallylic 4-methoxybenzoates and 4-methoxyphenyl ethers have been described previously.[1c,7]

In each case, the position- and enantioselectivity of the asymmetric dihydroxylation is directed by the 4-methoxyaryl group of the substrate. Since the oxidation of the homoallylic double bond of the polyunsaturated 4-methoxybenzoate esters is unfavorable, the dihydroxylation of the allylic double bond of **5a** and the bishomoallylic double bond of **5c** occurs preferentially. This observation is consistent with the mechanistic model proposed previously in that unfavorable electrostatic interactions between the ester carbonyl group of the substrate and the pyridazine linker group of the catalyst disfavor reaction of the homoallylic double bond as shown in **2** (R_1=2-propenyl for **5c**). The corresponding dihydroxylation of the allylic or bishomoallylic double bond of the substrate occurs with high selectivity, as the ester carbonyl group is oriented out the top of the U-shaped binding pocket toward solvent, while the 4-methoxyphenyl ring is oriented to allow face and edge interactions with the U-shaped pocket, as shown in **1** (R_1=2-propenyl for **5a**) and **3** (R_1=Me for **5c**). The corresponding reaction of 1,3-dienyl 4-methoxyphenyl ethers, however, favors oxidation of the homoallylic double bond over the corresponding allylic or bishomoallylic olefins. Unlike the corresponding 4-methoxybenzoate esters, the dihydroxylation of the homoallylic double bond of **5b** and **5d** allows the 4-methoxyphenyl group to reside in the U-shaped binding pocket with face and edge interactions without imparting unfavorable electrostatic interactions between an electron rich atom of the substrate and the pyridazine nitrogen atoms of the catalyst. The unconjugated dienyl 4-methoxybenzoate **5e** possesses both an allylic and a bishomoallylic double bond. While each of these groups in the mono-unsaturated substrates can effectively bind to the catalyst and are dihydroxylated with high enantioselectivity, the substrate **5e** is oxidized selectively at the allylic double bond. This observation can be understood in terms of a substrate conformational preference that minimizes sterically unfavorable *H,H*-repulsion between the two proximate vinylic methylene protons of **5e** and that forces one of the two olefin units to be out of plane relative to the remainder of the substrate. Co-planarity of the allylic double bond with the substrate 4-methoxybenzoyl group clearly favors the dihydroxylation of this group in preference to the bishomoallylic double bond.

Further examination of Table 1 indicates a dependence of the degree of enantioselectivity on the substitution pattern of the double bond that is oxidized for the 1,3-dienes. Oxidation of the internal double bond results in slightly lower enantioselectivity than the corresponding dihydroxylation of the terminal double bond of these substrates (compare **5a** with **5b** and **5c** with **5d**). Each double bond carries two carbon substituents that compete for binding within the U-shaped pocket of the catalyst, and the two binding modes lead to opposite enantioface selectivity. For the dihydroxylation of **5b** and **5c**, the 4-methoxyaryl group and the attached aliphatic chain bind more strongly than the terminal methyl group, leading to high enantioselectivity in the asymmetric dihydroxylation. The lower enantioselectivity in the case of **5a** and **5d** may be due to an appreciable affinity for the terminal isopropenyl group for the binding pocket, which clearly would be greater than for a methyl group.

In summary, the use of the 4-methoxybenzoyl ester or 4-methoxyphenyl ether derivative of doubly unsaturated alcohols such as **5a**-**5d** leads to highly regioselective and enantioselective dihydroxylation. The opposite directing effects of these groups and the regularities established by our results can be used to design

routes to numerous unsaturated 1,2-diols with position and enantiocontrol. The following procedure provides experimental detail.

General Procedure for the Asymmetric Dihydroxylation of 5. A solution of K_2CO_3 (0.089 g, 0.64 mmol), $K_3Fe(CN)_6$ (0.21 g, 0.64 mmol), $K_2OsO_4 \cdot 2H_2O$ (0.0008 g, 0.002 mmol), $(DHQD)_2PYDZ$ (0.0016 g, 0.0021 mmol) for **5a**, **5b**, **5d**, **5e**, or $(DHQD)_2PYDZ \cdot AntCl$ (0.0021g, 0.0021 mmol) for **5c**, and methanesulfonamide (0.020 g, 0.21 mmol) in *tert*-butyl alcohol-water 1:1 (2.7mL) was cooled to 0°C. The resulting suspension was treated with the corresponding olefin **5** (0.213 mmol). The mixture was stirred for 3 h and quenched by addition of Na_2SO_3. 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 the crude mixture of diols **6**. Purification by radial chromatography (2 mm plate, EtOAc–hexane 1:2 to 1:1) afforded the pure diols as colorless oils.

References and Notes

1. (a) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481. (c) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. (d) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817. (e) Corey, E. J.; Noe, M. C.; Ting, A. Y., preceding paper.
2. Although the dihydroxylation of terminal allylic alcohols proceeds with poor enantioselectivity, it has been shown that reaction of tertiary or *cis*-allylic alcohols can proceed with good levels of enantioselectivity: (a) Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 8225, (b) VanNieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 843 and (c) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 2495. For a recent review, see Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
3. The dihydroxylation of a series of substituted allyl aryl ethers has been reported to give products with ee's averaging 70%; see: (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267. On the other hand, allyl *p*-methoxyphenyl ether afforded the corresponding diol of 90-92% ee; see: (b) Vilchèze, C.; Bittman, R. *J. Lipid Res.* **1994**, *35*, 734 and (c) Byun, H.-S.; Kumar, E. R.; Bittman, R. *J. Org. Chem.* **1994**, *59*, 2630.
4. (a) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Letters* **1994**, *35*, 2861. (c) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (d) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427.
5. For leading references to methods for the position selective dihydroxylation of polyunsaturated substrates using the Sharpless asymmetric dihydroxylation, see (a) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron*, **1995**, *51*, 1345. (b) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.
6. Compounds **5a**, **5b** and **5e** were prepared from the corresponding known allylic alcohols. See (a) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *J. Chem. Soc. Perkin Trans. I* **1989**, 77. (b) Frangin, Y.; Gaudemar, M. *J. Organomet. Chem.* **1977**, *142*, 9. Compound **5c** was prepared from 3-butyn-1-yl 4-methoxybenzoate by: (1) iodoboration with 1.2 equiv of *B*-I-9BBN in CH_2Cl_2 at -20 °C for 1 h to give the corresponding vinyl iodide in 92% yield, followed by (2) coupling with 2.0 equiv of *bis*-(2-propenyl)copper(I)lithium•PBu_3 in ether at -45 °C to 0 °C for 45 min to give **5c** in 67% yield. Compound **5d** was prepared from **5c** by sequential deprotection with K_2CO_3 in methanol, followed by coupling with 3.0 equiv of *p*-methoxyphenol, 1.3 equiv of PPh_3 and 1.3 equiv of diethylazodicarboxylate in THF at reflux for 2 h to give **5d** in 85% yield. See (c) Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291.
7. For conformational studies of allylic systems, see (a) Bothner-By, A. A.; Castellano, S.; Ebersole, S. J.; Günther, H. *J. Am. Chem. Soc.* **1966**, *88*, 2466. (b) Gung, B. W.; Wolf, M. A.; Zhu, Z. *J. Org. Chem.* **1993**, *58*, 3350. (c) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1993**, *58*, 7038. A theoretical treatment appears in (d) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035.

8. This research was assisted financially by a graduate fellowship to M.C.N. (NSF) and a grant from the National Science Foundation.

(*Received in USA* 2 *January* 1996; *accepted* 18 *January* 1996)