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The Asymmetric Dihydroxylation of *cis*-Allylic and Homoallylic Alcohols

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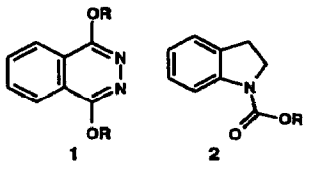
Abstract: The asymmetric dihydroxylation of several cis allylic alcohols is reported. The reactions proceed with moderate to good enantioselectivity. The enhanced enantioselection observed relative to other cis-olefin classes is believed to be dependent on the presence of the free hydroxyl group. A cis-homoallylic alcohol also gave a useful level of enantioselection in the AD.

The osmium tetroxide-cinchona alkaloid catalyst system has proven to be very efficient for the asymmetric dihydroxylation (AD) of most classes of prochiral olefins.[1] The *cis*-disubstituted and tetrasubstituted classes have been the most difficult olefin classes to dihydroxylate with high enantioselectivity. Recently, it was discovered that some tetrasubstituted olefins afford high levels of enantioselectivity in the AD reaction.[2] In our continuing studies on the scope of the AD process we have found that *cis*-allylic and homoallylic alcohols are also useful substrates.



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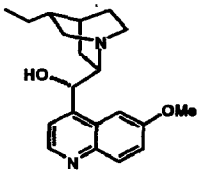
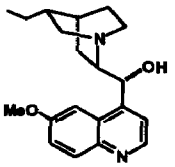


Dihydroquinidine (DHQD)



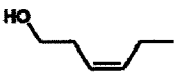
Dihydroquinine (DHQ)

Several *cis*-allylic alcohols having different steric and electronic environments were studied. The experiments were carried out using the commercially available AD-mixes which utilize the $(DHQD)_2$-PHAL [1,4-bis-9-O-dihydroquinidinephthalazine] (**1a**, R = DHQD) and $(DHQ)_2$-PHAL [1,4-bis-9-O-dihydroquininephthalazine] (**1b**, R = DHQ) ligands. In a few cases, the results were compared to those obtained in dihydroxylation experiments employing the DHQD-IND [(9-O-indolinylcarbamoyl)-dihydroquinidine] (**2**, R = DHQD) ligand which was previously shown to be the ligand of choice for the catalytic asymmetric dihydroxylation of *cis*-olefin substrates.[3] The

reactions were performed at 0°C in the t-BuOH-H_2O solvent system (1 : 1) at a substrate concentration of 0.1 M. The results of these experiments are summarized in Table 1.

Fair to good enantioselectivities were achieved in most cases with the phthalazine ligand system. Previous investigations in this laboratory had shown this

Table 1. Enantiomeric excesses obtained in the AD of cis-allylic alcohols with various chiral ligands.

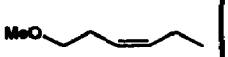
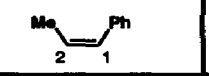
Substrate	$(DHQD)_2$-PHAL	$(DHQ)_2$-PHAL	DHQD-IND
	64[a] (2S,3R)[4]	57 (2R,3S)	31 (2S,3R)
	71[b] (2S,3R)[5]	73 (2R,3S)	72 (2S,3R)
	74[c] (2S,3R)[6]	64 (2R,3S)	51 (2S,3R)
	64[d] (2S,3R)[7]	--	--
	54[e] (3S,4R)[8]	45 (3R,4S)	--

Methods for determining enantiomeric excesses: a) Chiral HPLC analysis of derived triacetate (Chiralcel® OG, 2.5% IPA in hexanes, 0.5 mL/min). b) Chiral HPLC analysis of derived triacetate (Chiralcel® OJ, 10% IPA in hexanes, 1.0 mL/min). c) ^1H NMR analysis (400 MHz, $CDCl_3$) of tris-(R)-MTPA ester. d) Chiral HPLC of derived tribenzoate (Chiralcel® OD, 1% IPA in hexanes, 0.5 mL/min). e) ^1H NMR analysis (400 MHz, C_6D_6) of *tris* (R)-MTPA ester.

ligand to be very poor for simple hydrocarbon *cis*-olefins, especially those bearing alkyl groups at each terminus.[9] We believe that hydrogen bonding by the free hydroxyl to an oxo group on osmium may be responsible for the enhanced enantioselection seen with this special class of *cis*-olefins. Investigations are underway to identify the origin of this phenomenon. The final entry in Table 1 also appears to support the hydrogen bonding-hypothesis. The enantioselectivity displayed by this substrate is modest [54% ee with $(DHQD)_2$-PHAL] yet surprising considering that the environment near the olefin unit is very nearly symmetric.[10] The catalyst is able to differentiate the olefin termini even though the hydroxyl group is somewhat remote from the reaction center.

Further support for the beneficial effect of the terminal hydroxyl group was obtained when AD experiments were carried out on the corresponding methyl ethers of selected substrates. The data obtained from these experiments are summarized in Table 2. When compared to the data for the corresponding alcohols in Table 1, a dramatic drop in enantioselectivity is evident in each case.

Table 2. AD data of methyl ether derivatives and cis-β-methyl-styrene with $(DHQD)_2$-PHAL

Substrate	% Enantiomeric Excess	Major Product
	23[a]	(2S,3R)[11]
	13[b]	(2S,3R)[12]
	0[c]	–
	35[d]	(1R,2S)

Methods for determining enantiomeric excesses: a) Chiral HPLC of derived tris-methyl ether (Chiralcel® OB 2.5% IPA in hexanes, 0.5 mL/min). b) Chiral HPLC of derived diacetate (Chiralcel® OJ, 10% IPA in hexanes, 1.0 mL/min). c) ^{19}F NMR (400 MHz, C_6D_6) of *bis*-MTPA ester d) Data taken from reference 3.

An attractive feature of this methodology is that the crude triol products tend to be crystalline and thus present the opportunity for enantiomeric enrichment. For example, the enantiomeric purity of the triol obtained from the AD of *cis*-2-hexen-1-ol increased from 74% to 96% after a single recrystallization.[13]

In summary, we have demonstrated that cis-allylic alcohols hold considerable promise as substrates in the AD reaction. Current efforts are underway to determine the role of the free hydroxyl group and to examine the possibility that other properly placed acidic functional groups may also have beneficial effects on the enantioselectivity.

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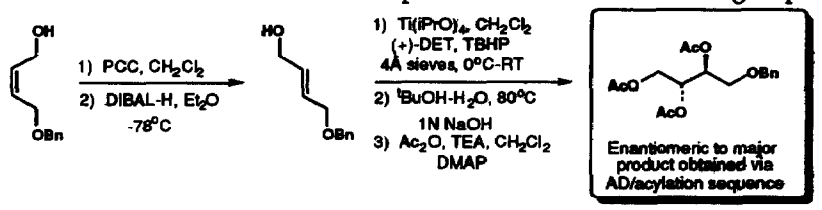
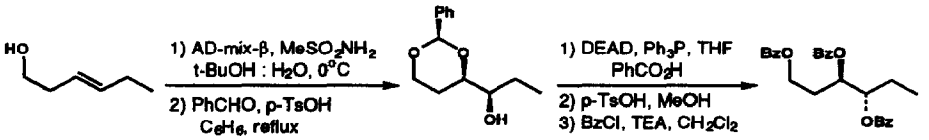
References

1. a) Jacobsen, E.N.; Marko, I.; Mungall, W. M.; Schroder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. b) Ogino, Y.; Chen, H.; Kwong, H. -L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965. c) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, Y.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, *J. Org. Chem.* **1991**, *56*, 4585. d) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong, H. -L.; Morikawa, K.; Wang, Z. -M.; Xu, D.; Zhang, X. -L. *J. Org. Chem.*. **1992**, *57*, 2769.
2. Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463.
3. Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.
4. The absolute configuration was proven by comparing the optical rotation of the triacetate with that of an authentic sample obtained via the following sequence :



5. The absolute configuration was established by comparison to commercially available L-(-)-*erythro*-1-C-phenylglycerol.
6. The absolute stereostructure was established by comparison to an authentic sample prepared via an asymmetric epoxidation/Payne rearrangement sequence starting from commercially available *trans*-2-hexen-1-ol.
7. The absolute configuration was assigned by application of the AD mnemonic.
8. The absolute configuration was established by comparing optical rotations of a sample prepared via benzoylation of the AD product obtained from *cis*-3-hexen-1-ol using $(DHQD)_2$-PHAL with that of an authentic sample prepared via the following sequence:



9. The best results with this ligand are obtained when one of the olefin substituents is a phenyl group. See reference 3.
10. Replacement of the terminal -OH group by a hydrogen would give a nonprochiral olefin and, therefore, a meso diol in the AD reaction.
11. The absolute stereostructure was assigned by comparison of the *tris*-methyl ether with an authentic sample made via the sequence cited in reference 4.
12. The absolute configuration was assigned by application of the AD mnemonic.
13. The AD reaction was run on a 2.0 g scale and proceeded in 80% overall yield. The crude triol product was recrystallized from ethyl acetate: hexanes (1 : 1). $[\alpha]_D^{25}$= +20.9° (c = 1.9, EtOH); mp 80-82°C.

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