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A Dramatic Reversal of Facial Selectivity in the Sharpless Asymmetric Dihydroxylation of a Sterically Hindered 3-Methylidene-benzofuran

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Abstract: A dramatic reversal of π-facial selectivity in the osmium-catalyzed asymmetric dihydroxylation (AD) of an exocyclic olefin is reported; wherein, switching from a phthalazine-linked ligand to a pyrimidine-linked ligand led to the opposite enantiomer using the same psuedo-enantiomer of the cinchona alkaloid.

In the course of a process research project, the osmium-catalyzed asymmetric dihydroxylation (AD) of olefin **1** was studied using Sharpless' heterocycle linked, bis-cinchona alkaloid ligand system.[1] As detailed below, a remarkable dependance of the π-facial selectivity on the nature of the heterocyclic linker was discovered.

Table. Asymmetric Dihydroxylation of 1

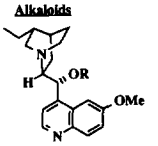
1 2

Entry	Alkaloid	Linker	ee(%)[b]	Abs. Conf.[c]
1	DHQ	PHAL	32	*S*
2	DHQD	PHAL	36	*R*
3	DHQ	PYR	86	*R*
4	DHQD	PYR	93	*S*

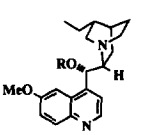
a) 1 mol% $K_2OsO_2(OH)_4$, 3.0 eq $K_3Fe(CN)_6$, 2.0 eq *p*-$TolSO_2NH_2$, 3.0 eq K_2CO_3, 1 mol% ligand, $^tBuOH/H_2O$, rt.
b) Determined by ^1H NMR of the mono Mosher's ester derivative.
c) See text for absolute configuration assignment.

Ligands

Alkaloids

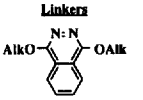


DHQ (dihydroquinine)

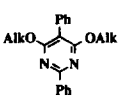


DHQD (dihydroquinidine)

Linkers



PHAL-class (AD-mix)



PYR-class

3-Methylidene-4-methoxy-2,2,3,5,6-pentamethyl-(*2H*)-benzofuran (**1**) was prepared according to a procedure described elsewhere.[2] Treatment of **1** with the commerically available, phthalazine based AD-mix α or β® under standard conditions resulted in minimal conversion after 48 hr. Fortification of the AD-mix® with additional osmium (total loading 1 mol%) and addition of *p*-toluenesulfonamide[3] (2.0 eq relative to olefin) did, however, lead to smooth conversion of this sterically demanding olefin to the desired diol **2** in good yield (85-90%). The enantiomeric excess (ee) of the respective dihydroxylations was, however, far from satisfactory with

the DHQ-ligand (AD-mix α) giving a 32% ee and the DHQD ligand (AD-mix β) providing only a marginally improved 36% ee.

Much better results were observed when the dihydroxylation was performed in the presence of the pyrimidine based ligands (DHQD$_2$PYR and DHQ$_2$PYR).[4] The DHQD$_2$PYR reaction gave a 93% ee while the DHQ$_2$PYR gave a slightly reduced 86% ee. Surprisingly, the *major enantiomer* in the pyrimidine (DHQD$_2$PYR and DHQ$_2$PYR) catalyzed reactions was the *minor enantiomer* in the phthalazine catalyzed (DHQD$_2$PHAL and DHQ$_2$PHAL) reactions. In other words, *changing the heterocyclic spacer from phthalazine to pyrimidine while keeping the chiral, cinchona alkaloid constant reversed the sense of the π-facial selectivity of the dihydroxylation.*

Attempts to unequivocally assign the absolute configuration of the diol products (**2**) have not been successful. The absolute stereochemical assignments indicated in the table are tentatively based on the assumption that the PHAL ligands follow the facial selection rules established by Sharpless' mnemonic[5] while the PYR ligands generate the opposite facial selectivity. Concurrent results from the Sharpless lab concerning the AD of a series of sterically hindered 1,1-disubstituted styrenes related to **1** have confirmed the generality of the observed heterocycle-dependant reversal of facial selectivity and support the absolute configuration assignments in the table.[6] Among the several olefins that have been shown to undergo linker-dependant reversal of facial selectivity, olefin **1** displays the largest change in ee yet observed.[6a]

Any attempts to rationalize these results based upon the models and mnemonics developed to predict the enantioselectivities of the AD are beyond the scope of this Letter.[7] Still, it seems quite clear that the dramatic, linker-dependant reversal of facial selectivity in the osmylation of this 1,1-disubstituted olefin must represent profound changes in the binding of the olefin (**1**) to the OsO$_4$L complex. We hope that these data will be useful in the further refinement of such models and will be of use in future synthetic applications of the cinchona alkaloid based AD technology.

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References and Notes

1. Kolb, H.C.; VanNieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* **1994**, *94*, 2483.
2. Ayers, T.A.; Marciniak, G.; Schnettler, R.N. manuscript in preparation.
3. The sterically hindered nature of **1** is most likely the reason for the sulfonamide requirement in this case.[1] The use of the less costly *p*-toluenesulfonamide in place of the usual methanesulfonamide did not affect the ee.
4. Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* **1993**, *58*, 3785.
5. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
6. (a) Vanhessche, K.P.M. and Sharpless, K.B., personal communication. (b) Sharpless and Vanhessche were able to unambiguously determine the absolute stereochemistry of some of their diols and show that the facial selectivity of the PHAL ligand was consistent with the published mnemonic[5] while the PYR ligand selecitivity was counter to that predicted by the mnemonic.
7. (a) Kolb, H.C.; Andersson, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1994**, *116*, 1278. (b) Norrby, P.-O.; Kolb, H.C.; Sharpless, K.B. *J.Am. Chem. Soc.* **1994**, *116*, 8470. (c) Corey, E.J.; Noe, M.C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427 and references therein.

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