Ligand-Dependent Reversal of Facial Selectivity in the Asymmetric Dihydroxylation

Koen P. M. Vanhessche[1] and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

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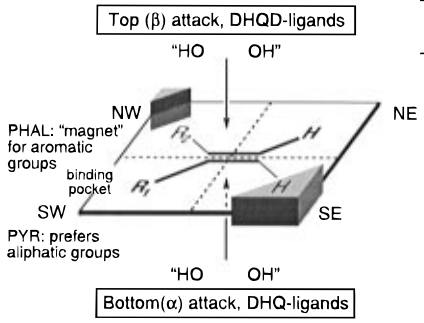
Though the mechanism of even the "simple" reaction of osmium tetraoxide with an olefin remains uncertain,[2] there has been considerable controversy over the mechanism of the process when a chiral cinchona alkaloid ligand is also involved.[3] While it is certainly risky to build the "superstructure" of a mechanism on such an insecure foundation, the extensive use of the asymmetric dihydroxylation (AD) process[4] has fueled substantial interest and speculation on this topic. On the basis of a large body of enantioselectivity data, an empirical, but reliable, predictive mnemonic has evolved.[3a]

This device has proven suitable for interpreting most of the AD results using both the phthalazine spacer (PHAL and related "1,4-substituted spacers"[5]) and the pyrimidine (PYR) spacer. For the present study, the most important feature of the AD mechanism to appreciate is the "binding pocket" phenomenon. We have established the existence of a binding pocket effect by kinetic studies,[3a] and despite the controversy over its location, both camps[3] support its existence. In our mnemonic this binding pocket (Figure 1) resides in the SW quadrant. With PHAL ligands, this pocket is a "magnet" for flat aromatic groups, whereas with PYR ligands, aliphatic groups are preferentially attracted to the "SW binding pocket". Taken together with the "rule" that the group *cis* to the substituent in the binding pocket is ideally a hydrogen (the SE quadrant is sterically the most crowded),[3a] these preferences lead to an interesting prediction for AD applications involving α-alkylstyrenes (Figure 1): Namely, that for a given pseudoenantiomer of the alkaloid [*e.g.*, dihydroquinidine (DHQD)] the PHAL and PYR heterocyclic spacers should give opposite enantiofacial selectivity. The systematic study presented in Table 1 reveals that this prediction is borne out by experiment.[6] The phenomenon was discovered independently by Krysan, and his recent report[7] prompted us to publish our study.

All results for the series of α-aliphatic substituted styrenes in Table 1 were obtained using DHQD-based ligands. The enantioselectivities observed with the PHAL ligand drop gradually with increasing chain length (Table 1, entries 1−6), but the expected π-facial selectivity is maintained. With the PYR ligand the ee drops dramatically from α-methylstyrene (69% ee) to α-ethylstyrene (20% ee), and beginning with α-propylstyrene (−16% ee), reversed selectivities are observed, reaching −35% ee for α-hexylstyrene. In retrospect, these results are anticipated by the known poor selectivity (80% ee) for styrene and the good selectivity (89% ee) for 1-hexene with the $(DHQD)_2$−PYR ligand (*cf.* 97% ee and 80% ee, respectively, with the $(DHQD)_2$−PHAL ligand).



Substitution pattern	Best Ligand
R_1= aromatic R_2= H	PHAL
R_1= aliphatic R_2= H	PYR
R_1 = aromatic R_2 = aliphatic	PHAL
R_1 = aliphatic R_2 = aromatic	PYR

Figure 1. Modified mnemonic for PHAL and PYR-ligands with mono- and 1,1-disubstituted olefins.

Entries 7−11 of Table 1 show the effect of α-branching[9] in both acyclic and cyclic systems. Changing from isopropyl to *tert*-butyl (Table 1, entries 7 and 8) causes a remarkable drop in ee with the PHAL ligand, from 82 to 8% ee. Calculations reveal that with at least one hydrogen at the point of attachment of the alkyl group [*e.g.*, $(Me)_2HC$−, Table 1, entry 7] the phenyl can still be positioned nicely in the PHAL binding pocket. However, when this last hydrogen becomes a methyl (*e.g.*, $(Me)_3C$−, Table 1, entry 8), rotation of the phenyl group, in relation to the rest of the structure, is restricted to conformers that allow only very poor presentation of the phenyl to the binding pocket.[3a]

High enantioselectivities were obtained for the exomethylene substrates (Table 1, entries 9 and 11, 95% and 92% ee, respectively) with PHAL, and no reversal occurred with PYR. Introducing *gem*-dimethyl groups in the allylic position (Table 1, entry 10) produces a small drop for PHAL (to 82% ee) and a strong reversal of facial selectivity for PYR (to −59% ee). In other words, these fairly rigid cyclic cases mainly follow the same trends as the acyclic analogs. The informative exception here is that, unlike entry 8, entry 10, being cyclic, still fits fairly well into the PHAL binding pocket. We attribute the origin of this difference to the fact that in the cyclic cases the key torsional angles are locked close to the favorable conformation needed to fit into the PHAL binding pocket.[10]

The patterns that emerge for the α-cycloalkyl-substituted series (Table 1, entries 12−15) are the same as those for their acyclic alkyl analogs (Table 1, entries 3−6). The PHAL ligand exhibits a slight decline in enantio-

(1) Current address: Firmenich, S. A., Research Laboratory, 1, route des Jeunes, CH-1211 Geneva, Switzerland.

(2) A [3 + 2] mechanism was originally proposed by Böseken for reactions of permanganate and adopted by Criegee for osmium tetraoxide: (a) Böseken, *J. Recl. Trav. Chim.* **1922**, *41*, 199. For the [2 + 2] mechanism, see: (b) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120. (c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (d) Gable, K. P.; Juliette, J. J. J. *J. Am. Chem. Soc.* **1995**, *117*, 955. (e) Gable, K. P.; Phan, T. N. *J. Am. Chem. Soc.* **1994**, *116*, 833. (f) Jørgensen, K. A.; Schiøtt, B. *Chem. Rev.* **1990**, *90*, 1483.

(3) (a) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278. (b) Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35. (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319 and references cited therein.

(4) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(5) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940.

(6) A general procedure for the AD of α-alkylstyrenes is given in the Supporting Information.

(7) Krysan, D. J. *Tetrahedron Lett.* **1996**, *37*, 1375.

(8) Related reversals of enantiofacial selectivity have also been observed for α-arylstyrenes; Loren, S.; Sharpless, K. B. unpublished results.

(9) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu., D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

(10) We have also been able to rationalize the trends in facial selectivity for α-alkylstyrenes using molecular mechanics calculations (see ref 3b for parameters). This approach is of course much more complicated than the simple "binding pocket" mnemonic, but it is especially informative for the exceptional cases 8 and 16 in Table 1: Becker, H.; Loren, S.; Vanhessche, K.; Sharpless, K. B. Unpublished results.

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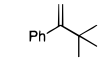
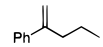
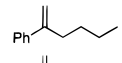
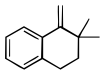
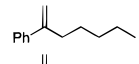
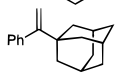
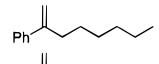
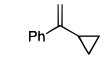
Table 1[a] Enantioselectivities,[b] Configurations,[c,d] and Signs of Optical Rotations of the Diols from the AD of α-Alkylstyrenes with $(DHQD)_2$−PHAL and $(DHQD)_2$−PYR as the Ligands

entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR	entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR	entry	olefin	$(DHQD)_2$-PHAL	$(DHQD)_2$-PYR
1		94 *(R)*-(–)	69 *(R)*-(–)	8		8 *(R)*-(+)	**–37** *(S)*-(–)	13		58 *(R)*-(+)	**–59** *(S)*-(–)
2		78 *(R)*-(+)	20 *(R)*-(+)	9		95 *(R)*-(–)	60 *(R)*-(–)	14		55 *(R)*-(+)	**–66** *(S)*-(–)
3		60 *(R)*-(+)	**–16** *(S)*-(–)					15		57 *(R)*-(+)	**–68** *(S)*-(–)
4		56 *(R)*-(+)	**–28** *(S)*-(–)	10		82 *(R)*-(–)	**–59** *(S)*-(+)				
5		48 *(R)*-(+)	**–30** *(S)*-(–)	11		92 *(R)*-(–)	78 *(R)*-(–)	16		**–53** *(S)*-(–)	**–77** *(S)*-(–)
6		37 *(R)*-(+)	**–35** *(S)*-(–)								
7		82 *(R)*-(+)	**–8** *(S)*-(–)	12		70 *(R)*-(+)	**–24** *(S)*-(–)				

[a] The isolated yields of diols were 85−95%, except for entries 8, 10, and 16 (20−40%). [b] Enantiomeric excesses were determined by HPLC analysis of the diols or their respective derivatives; see the supporting information. [c] The absolute configurations of the diols were determined by comparison of their optical rotations with literature values; see the supporting information. [d] The assignment of "negative" ee values is just a convenient device for making the reversal of face selectivity obvious at a glance. As a further aid, the "negative" values are also bolded.

selectivity down the series, whereas the PYR ligand gives reversed enantiofacial selectivities and with consistently higher ee values than seen for their acyclic counterparts (*e.g.*, Table 1, entries 3−6). These results clearly support the preference of the PHAL pocket for aromatic groups and of the PYR pocket for aliphatic groups, especially those with α-branching. Earlier evidence[3a] suggests that both pockets benefit from a hydrophobic effect, but the latter must be the dominant factor for the PYR pocket.

The result in Table 1 that stands out from all the others is the dramatic switch in enantiofacial selectivity for α-(1-adamantyl)styrene using the PHAL ligand (first column, entry 16, *cf.* entries 12−15). At first, the only thing certain was that the PHAL and PYR ligands had given the same enantiomer. We believed that it was the PYR case that had switched faces and given the (*R*)-diol, perhaps, because in this sterically demanding case, the phenyl group had for some reason replaced the alkyl group in the PYR-binding pocket. However, the absolute configuration of the diol was then proven to be *S* by an X-ray crystal structure determination on the mono-(1*S*)-camphanic ester derivative.[14] This result established that it was the adamantyl substituent that occupied the SW quadrant in both cases (*i.e.*, with PYR *and* PHAL ligands). In hindsight, the "strange" results in entries 8 and 16 (Table 1) are consistent with the good results for 1-adamantylethylene using either $(DHQD)_2$−PHAL (87% ee, (*R*)-diol) or $(DHQD)_2$−PYR (97% ee, (*R*)-diol)[11] and, above all, with the massive drop in ee between entries 7 and 8 (Table 1) with the PHAL ligand (rationale for this drop, *vide supra*).

The recent[11] 87% ee result for 1-adamantylethylene using $(DHQD)_2$−PHAL requires further explanation. It seemed out-of-line since *tert*-butylethylene was known to give only 64% ee under identical conditions,[9] and a similar branched alkyl substituent that, like 1-adamantyl, is much larger "at a distance," might have been expected to result in an even poorer ee. At present we can only speculate on causes for this "adamantyl phenomenon" (*i.e.*, counter to trend for the PHAL ligand, wherein ee is poor when a *tert*-alkyl group is the best "offering" available for the binding pocket). Perhaps it is due to additional attractive interactions with the ligand at a greater distance from the reaction center, which offset the deleterious effects in close. Another possibility is that hydrophobic binding effects, which will certainly be greater for adamantyl than for *tert*-butyl, override the negative "in-close" effects. These latter steric effects must be very similar for the two substituents, yet are calculated to be slightly larger for *tert*-butyl than for 1-adamantyl (*i.e., A* value for *tert*-butyl *ca.* 0.2 kcal mol^{-1} larger than for 1-adamantyl).[12] Continuing the analysis along these lines, one notes that the increase from 64% ee to 87% ee between the *tert*-butyl and the adamantyl cases (both performed at 0 °C) represents an increase in $\Delta\Delta G^{\ddagger}$ of *ca.* 0.6 kcal mol^{-1}, which leads to the, admittedly, highly speculative conclusion that the observed ee increase could be due to small steric (1/3) and hydrophobic (2/3) effects acting in concert.

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Supporting Information Available: A general experimental procedure for the AD reactions, characterization data for all the diols, as well as the methods for their ee determination, optical rotation, and absolute configuration, and an ORTEP for the mono-(1*S*)-camphanate ester of the diol derived from α-(1-adamantyl)styrene (entry 16, Table 1) (10 pages).

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(11) Vanhessche, K.; Sharpless, K. B. *Chem. Eur. J.*, in press.

(12) The *tert*-butyl and adamantyl substituents are generally regarded as having similar steric demands in the regions of space where their structures are homologous (*i.e.*, referred to here as "in-close"). Yet, the calculated (MacroModel 5.0) *A* values—*i.e.*, the free energy differences between the equatorial and axial conformations for substituted cyclohexanes (*tert*-butyl: calculated 5.0 kcal mol^{-1}, experimental 4.9 kcal mol^{-1};[13] 1-adamantyl: calculated 4.8 kcal mol^{-1})—indicate slightly lower "in-close" steric demands for the 1-adamantyl substituent. If these small calculated differences are real, it is interesting to speculate on the origin of the effect. The adamantane structure is rigid and compact, and significant bond angle variations are impossible. If one now *imagines* the creation of the *tert*-butyl group by formal hydrogenolysis of the three appropriate C−C bonds in adamantane, what remains, in place of the very polycyclic framework that made deformations a nonissue, are three new C−H bonds, one on each of the methyls of what is now a *tert*-butyl group. Hence, cyclic constraint has in a sense been exchanged for nonbonded repulsion in the acyclic analog, and even a very slight spreading of the methyls (angle bending) could account for the *tert*-butyl group's larger size apparent.

(13) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267.

(14) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.