Catalytic Asymmetric Dihydroxylation of Tetrasubstituted Olefins

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We report here that tetrasubstituted olefins (*vi* in Scheme I) are also good substrates for the asymmetric dihydroxylation (AD) process. As shown in Table I the enantiomeric excesses are generally in the fair to excellent range for the cases examined. Moreover, the best ligands for the tetrasubstituted olefins are the PYR-[1] and PHAL-[2] classes, which taken together are also the best ligands for four (*i*, *ii*, *iv* and *v*) of the five remaining olefin types. Only *cis*-olefins (*iii*) require a unique ligand (IND,[3] Scheme I) and still have yielded no examples exceeding the 90% ee mark.

These successful catalytic AD's of tetrasubstituted olefins are noteworthy on two counts: 1) catalytic osmylations of tetrasubstituted alkenes, asymmetric or otherwise have been extremely rare[4] due to turnover problems at the osmate ester stage of the cycle; and 2) we had long believed that at least one of the olefinic substituents had to be a hydrogen atom in order to fit into a crowded region of the AD transition state.[5]

The turnover problem is largely overcome by a combination of the earlier discovered "methanesulfonamide additive" effect,[6] along with an increase in the osmium catalyst loading to 1 mol %, and also by operating at room temperature in the most sluggish cases. One equivalent of $CH_3SO_2NH_2$ at 0 °C is adequate for the tetrasubstituted enol ethers,[7] but 3 equivalents of the sulfonamide and operation at room temperature are needed for the all-carbon substituted examples.

The general experimental procedure we found to be superior for the asymmetric dihydroxylation of tetrasubstituted olefins was as follows: the reactions were run in the presence of 3 molar equiv of $K_3Fe(CN)_6$, 3 molar equiv of K_2CO_3, 1 mole % of OsO_4, 5 mole % of ligand and 3 molar equiv (for olefins) or 1 molar equiv. (for enol ethers) of $CH_3SO_2NH_2$,[8] in *t*-BuOH/H_2O 1/1 (5 mL of each/mmol olefin) at r. t. (for olefins) or at 0 °C (for enol ethers). The diols obtained from dihydroxylation of tetrasubstituted olefins were isolated in 51–87 % yields for acyclic olefins (entries 1–3) and 16–31 % yields[9] for cyclic olefins (entries 4–6). The α-hydroxy ketones obtained from tetrasubstituted enol ethers were isolated in 23–97 % yields for cyclic enol ethers (entries 7–11) and 15–60 % yields for acyclic enol ethers (entries 12 and 13).[10]

Scheme I. Ligand Preference as a Function of Olefin Substitution Patterns

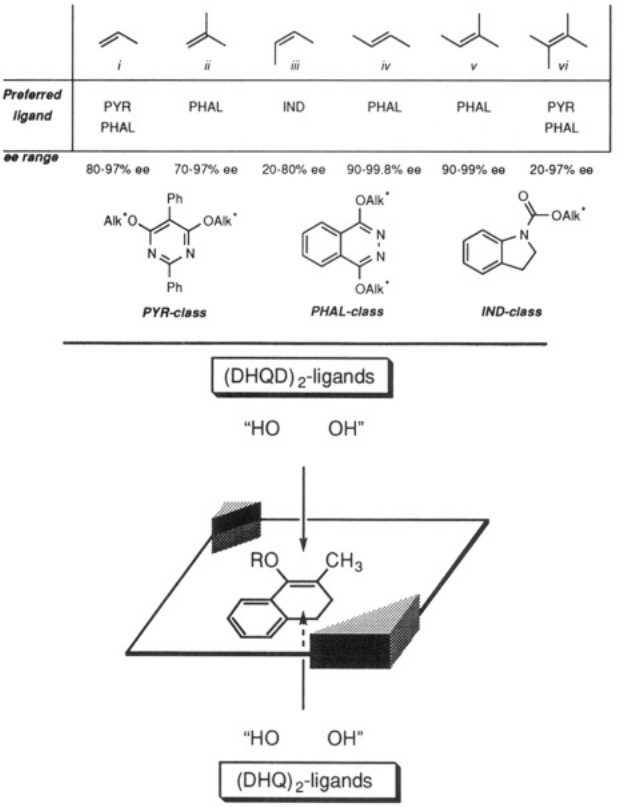

Figure 1.

With these improvements the AD of some tetrasubstituted olefins now gives the corresponding diols and α-hydroxy ketones in fair to good yields and with moderate to excellent ee's (Table I). The ligands which were found to give best results for this new class of substrates were the phthalazine [$(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL[11]] and the pyrimidine [$(DHQD)_2$-PYR and $(DHQ)_2$-PYR[1]] ligands. The inclusion of the PYR-ligand class among the preferred ligands for the tetrasubstituted olefins seems odd when one realizes that the only other olefin type for which it gives good results is the monosubstituted type (*i*) (see Scheme I).

Our mnemonic device shown in Figure 1, has been developed based on the stereochemical outcome of the AD for the five hitherto successful classes of olefins (mono-, 1,1-di-, *cis*-, *trans*- and trisubstituted). The smallest substituent on the olefin (hydrogen) is always placed in southeast quadrant which is the most hindered space in the putative asymmetric environment created by protuberances from the oxygen-donating surface.[1,2] In the case of tetrasubstituted olefins and enol ethers, the one among the four substituents which is recognized as the smallest is now placed in this quadrant as a hydrogen surrogate. For the tetrasubstituted enol ethers this device gives successful predictions in all but one case (entry 8 with $(DHQD)_2$-PYR), and the selectivities reveal that the cyclic methylene is more suitable for the hindered space than -OR and resides in the southeast quadrant as shown in Figure 1.

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

(2) 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*, 2768.

(3) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.

(4) (a) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986. (b) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

(5) (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (b) 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*, 2768.

(6) The presence of $CH_3SO_2NH_2$ leads to shorter reaction times for non-terminal olefins, occasionally as much as fifty times shorter. See ref. 2.

(7) Recently we reported that trisubstituted enol ethers are excellent substrates for the AD, giving α-hydroxy ketones with high enantiomeric purities (Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067).

(8) For the substrate in entry 9, the AD with $(DHQD)_2$-PHAL was complete within 24 hours at 0 °C when 1 molar equiv. of $CH_3SO_2NH_2$ was added (97% isolated yield and 93% ee). Without $CH_3SO_2NH_2$ after 70 hours the isolated yield was only 53% (92% ee) and 44% of the starting material was recovered.

(9) Even with added $CH_3SO_2NH_2$ the reaction rates for these cyclic olefins were very slow. The reactions were worked up after 48 hours. Higher conversions can be obtained if the reaction time is prolonged.

(10) Competitive oxidative cleavage reduced the yields for these acyclic enol ethers.

(11) Dihydroquinidine (DHQD) and dihydroquinine (DHQ) are diastereomers in that they have the opposite chirality at only 4 of the 5 stereogenic centres. However, as ligands in the AD, they behave like enantiomers, giving diols and α-hydroxy ketones of opposite configuration.

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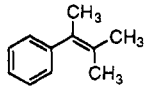
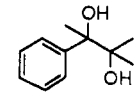
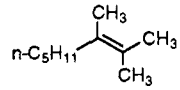
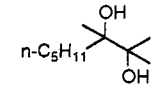
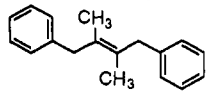
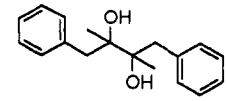
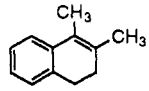
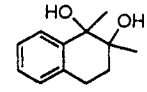
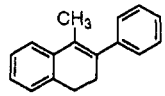
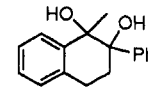
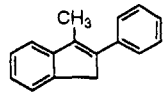
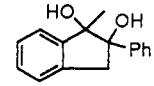
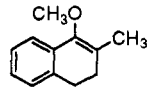
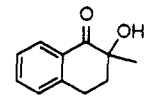
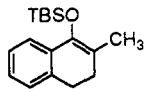
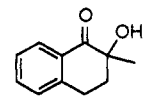
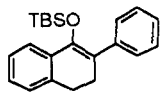
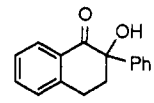
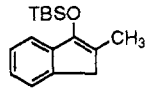
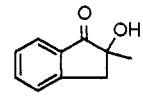
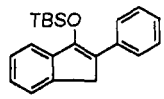
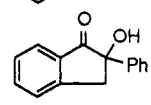
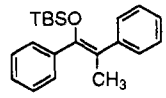
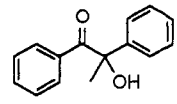
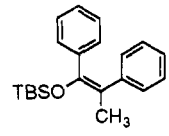
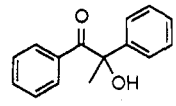
Table I. Enantiomeric Excesses[a] and Yields of the Diols and α-Hydroxy Ketones Resulting from the AD[b] of Tetrasubstituted Olefins

		ee (%)					
		PHAL		PYR			
entry	substrate	$(DHQD)_2$	$(DHQ)_2$	$(DHQD)_2$	$(DHQ)_2$	product	yield[c] (%)
1[d]		39 (*R*)		47 (*R*)			80–82*
2[e]		20 (*R*)		22 (*R*)			51–55*
3[e]		29 (*R*)		31 (*R*)			85–87*
4[e]		59 (1*R*,2*S*)		56 (1*R*,2*S*)			23–24*
5[e]		83 (1*R*,2*R*)	85 (1*S*,2*S*)	85 (1*R*,2*R*)	89 (1*S*,2*S*)		29–31*
6[e]		75 (1*R*,2*R*)		82 (1*R*,2*R*)			16–19*
7[d]		64 (*S*)	60 (*R*)	41 (*S*)	62 (*R*)		79–95
8[d]		67 (*S*)	65 (*R*)	6 (*R*)	37 (*R*)		89–92
9[e]		93 (*R*)	95 (*S*)	95 (*R*)	97 (*S*)		94–98
10[d]		85 (*S*)	81 (*R*)	59 (*S*)	80 (*R*)		64–85
11[e]		89 (*R*)		84 (*R*)			23–32*
12[d]		75 (*R*)	81 (*S*)	79 (*R*)	79 (*S*)		15–22
13[d]		53 (*R*)	63 (*S*)	60 (*R*)	33 (*S*)		46–60

[a] Enantiomeric excesses were determined by HPLC analysis of the diols and α-hydroxy ketones (entries 1 and 4–13) and by NMR using a chiral shift reagent (entries 2 and 3) (see supplementary material). [b] The ADs were run at room temperature (entries 1–6) or at 0 °C (entries 7–13). [c] All yields are isolated yields. The presence of an asterisk indicates an incomplete reaction where the only other product detected is recovered starting material. [d] Absolute configurations were determined by comparison of optical rotations with literature values (see supplementary material). [e] Absolute configurations are tentatively assigned following the AD face-selection mnemonic.[5]

With the extension of the AD's scope to include tetrasubstituted olefins, all of the six olefin substitution patterns now fall into the "good substrate" classification. Admittedly, the inclusion of *cis*-olefins in this category is streching a point since only a few types give useful ee's. Nevertheless, it is remarkable that the other five olefin types have given enantiomeric excesses in the mid- to high-nineties using only two different ligands.

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Supplementary Material Available: General experimental procedures for the preparation of olefins and enol ethers, details for determination of enantiomeric excesses and absolute configurations of the products (10 pages). Ordering information is given on any current masthead page.