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A Dramatic Ligand Effect on the Relative Reactivities of Substituted Alkenes with Osmium Tetroxide

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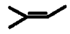
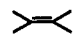
Implicit in our recent synthetic paper on the selective asymmetric dihydroxylation of dienes[1] is that the rate of oxidation can be a sensitive function of the olefin substitution pattern. We now report a quantitative study which reveals that this substitution/rate relationship is strikingly dependent on the nature of the accelerating ligand used.

The olefins chosen for the study are simple hydrocarbon representatives of the six olefin classes.[2] The rates were measured[3] under the three sets of conditions shown in Table I. The only variable in the conditions is the presence or absence of ligand: column 1, no ligand; column 2, quinuclidine[4] as ligand; and column 3, 1,4-bis(9-*O*-dihydroquinidyl)phthalazine [$(DHQD)_2PHAL$[4]] as ligand. Each column is arranged in order of decreasing rate of reaction, with the most reactive olefin at the top, and the absolute rate for each olefin is given below the structure.

In examining the results in Table I, it is important to realize that all reactions in the presence of ligand are much faster than those without. Comparing columns 1, 2, and 3 reveals that quinuclidine speeds the osmylation rate by about 2 orders of magnitude and that $(DHQD)_2PHAL$ adds another factor of 7 to the quinuclidine rates. The range of rates recorded in Table I differ by a factor of over 18 000.[5]

Table I. Ligand Effects on the Reactivity Hierarchy as a Function of Olefin Substitution Pattern[a]

OsO_4 alone	OsO_4 + Quinuclidine	OsO_4 + $PHAL(DHQD)_2$
 14 ± 10% (29)	 1200 ± 5% (18)	 8800 ± 5% (23)
 2.5 ± 10% (5.1)	 320 ± 5% (4.8)	 4100 ± 5% (11)
 1.5 ± 10% (3)	 210 ± 5% (3.2)	 1400 ± 5% (3.7)
 0.58 ± 10% (1.2)	 100 ± 5% (1.5)	 690 ± 5% (1.8)
 0.58 ± 10% (1.2)	 73 ± 5% (1.1)	 560 ± 5% (1.5)
 0.48 ± 10% (1)	 66 ± 5% (1)	 380 ± 5% (1)

[a] Rates in $M^{-1}\ min^{-1}$. Relative rates in parentheses. It is important to note that the relative rates only apply within a single column. The absolute rates can, of course, be compared throughout the table.

The relative rates for oxidation of the olefins in the absence of ligand (column 1) correspond well to what was already known from an earlier study.[6] The tetrasubstituted olefin is the most reactive, and the others follow suit on the basis of decreasing level of substitution. The presence of quinuclidine has no effect on the relative rate order (cf. columns 1 and 2). With these data in hand, it was a surprise to see the impact which the cinchona alkaloid-based ligand $(DHQD)_2PHAL$ had on the relative rates. In column 3 of Table I, every olefin occupies a different position from that in the hierarchy established in columns 1 and 2, where the orders are identical. In column 3 the trisubstituted olefin is by far the most reactive, and the previously dominant tetrasubstituted olefin has been demoted to fourth place, with only a small rate advantage over the monosubstituted entry.

Another helpful way to view the data in Table I is to compare the ligand acceleration effect (LAE) as shown in Figure 1. The points in this graph are simply the rate ratios for the olefin in the presence and in the absence of a ligand (i.e., the LAE). The LAEs for quinuclidine are relatively constant for all the olefin types (range = 90–170). In contrast, $(DHQD)_2PHAL$ exhibits more varied behavior with LAEs ranging from 50 to 3520. The accelerations are especially pronounced for tri- and *trans*-disubstituted alkenes. This is surprising, since one might have expected more substituted (i.e., bulkier) olefins to react slower in a sterically more congested ligand–osmium environment. In any case, the latter expectation is at least satisfied by the outcome for the tetrasubstituted olefin, which with $(DHQD)_2PHAL$ is one of the slowest cases, experiencing a dramatic shutdown compared to its very fast reacting trisubstituted relative. With the much less hindered ligand quinuclidine, the tetrasubstituted olefin returns to its position of primacy in the reactivity sequence (column 2).

Figure 1 demonstrates that *trans*-di- and trisubstituted olefins constitute an especially good fit for the $(DHQD)_2PHAL$ system. Moreover, these rate accelerations are coupled to the enantioselectivity trends in the $(DHQD)_2PHAL$ ligand system: *trans*-

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[1] Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.

[2] The representatives of the six olefin classes studied herein are the following:

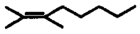

1-Undecene


2-Methyl-1-undecene


2-Methyl-2-octene

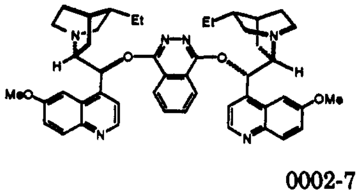

cis-5-Decene


trans-5-Decene


2,3-Dimethyl-2-octene

[3] The absolute rates were determined using a Cary 4 spectrophotometer equipped with a Cary temperature controller and interfaced to a Compac PC as follows: to a well-stirred solution of alkene and ligand in *t*-$BuOH/H_2O$ (6:1, the same ratio as in the organic phase in the catalytic AD) at 0 °C in a quartz cuvette was added OsO_4, and the change in absorbance vs time at 700 nm was followed. Concentrations of ligand, olefin, and OsO_4 were 0.04, 0.04, and 0.004 M respectively, imposing pseudo-first-order kinetics for the buildup of osmate ester. The relative rates for the dihydroxylation of the olefins were determined by observing the product distribution when a 1:1 mixture of two olefins was catalytically oxidized using the same reaction conditions as in the AD but with only enough reoxidant to effect about 5% conversion. All the olefins were then compared pairwise in these competitions by observing the ratio of the diol products and thereby establishing the relative reactivity between them. These competition studies were performed as follows: to a well-stirred solution of $K_3Fe(CN)_6$ (80 mg, 0.24 mmol), K_2CO_3 (180 mg, 1.3 mmol), $MeSO_2NH_2$ (12 mg, 0.13 mmol), OsO_4 (15 μL of a 0.393 M stock solution, 0.006 mmol), and, in some cases, ligand (0.025 mmol) in 10 mL of *t*-$BuOH/H_2O$ at 0 °C was added a mixture of the two dienes to be studied, 1.2 mmol of each. After 24 h the reaction mixture was diluted with EtOAc (10 mL), and the resulting two phases were separated. The aqueous phase was extracted with EtOAc (15 mL), and the combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the product ratio of the two diols was determined by ^1H NMR. It should be noted that the rate-limiting step in these catalytic reactions is in most cases the hydrolysis of the osmate ester. Nevertheless, the product distribution from the two alkenes must reflect the relative rates for the first irreversible step, which is the formation of the osmate ester.

[4] The structures of the ligands $(DHQD)_2PHAL$ (left)[1] and quinuclidine (right) are shown below:



[5] In fact, this rate differential is underestimated by a factor of 2 in cases where the chiral phthalazine ligand gives almost 100% ee. The reason for this is that in the achiral osmylation systems (columns 1 and 2) the concentration of olefin is essentially doubled since attack on either prochiral face is equienergetic. In column 3 this is true only for the one nonprochiral olefin (i.e., *cis*-5-decene).

[6] Sharpless, K. B.; Williams, D. R. *Tetrahedron Lett.* **1975**, 3045.

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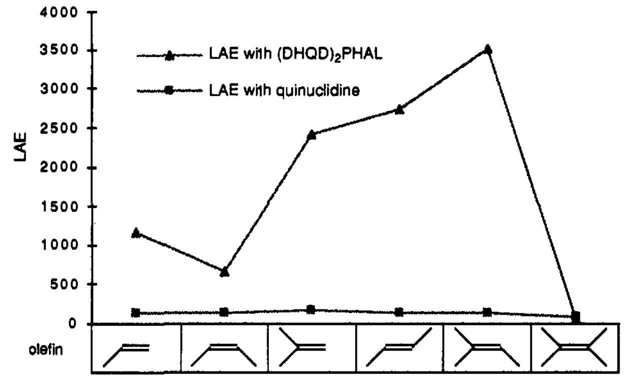

Figure 1. Ligand acceleration effects (LAE) for osmylation of various olefins with (DHQD)$_2$PHAL and with quinuclidine as a function of olefin substitution pattern.

di-, and trisubstituted olefins generally give higher ees than do their mono-, 1,1-di-, tetra-, or *cis*-disubstituted analogs. The unusually selective perhydroxylation of squalene that we observed previously[7] is no doubt due to its having six trisubstituted double bonds. The reactivity correlations revealed in Figure 1 must have important implications for how the olefin, osmium tetroxide, and ligand assemble in the rate- and/or enantioselectivity-determining transition state(s). The mechanistic implications of these observations will be discussed elsewhere.[8]

The immediate value of these new ligand-relative rate effects is that several hitherto unknown selective oxidations of polyenes are now possible. For instance, without ligand the tetrasubstituted[9] double bond is oxidized 6 times faster than the trisubstituted one. In the presence of (DHQD)$_2$PHAL, the selectivity is reversed, and the trisubstituted double bond is now oxidized about 13 times faster than the tetrasubstituted analog. Many other selective polyene oxidation scenarios can be planned and expected to succeed on the basis of the *relative* rate data given in parantheses in each column of Table I.

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(7) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993**, *259*, 64.

(8) Andersson, P. G.; Kolb, H. C.; Sharpless, K. B., manuscript in preparation.

(9) During this study it was found possible to partly overcome the turnover problem normally encountered when using tetrasubstituted olefins in the catalytic dihydroxylation process. As a result, the asymmetric dihydroxylation of tetrasubstituted olefins is now possible under certain conditions, and the corresponding diols can be obtained in enantiomeric excesses of 20–95%. Morikawa, K.; Park, J.-H. Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.*, in press.