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Experimental Test of the [3+2]- and [2+2]-Cycloaddition Pathways for the bis-Cinchona Alkaloid-OsO_4 Catalyzed Dihydroxylation of Olefins by Means of $^{12}C/^{13}C$ Kinetic Isotope Effects

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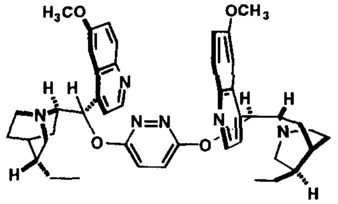
Summary: *The $^{12}C/^{13}C$ kinetic isotope effects for the bis-cinchona-OsO_4 catalyzed dihydroxylation of 4-nitrostyrene, 4-methoxystyrene and allyl 4-methoxybenzoate have been measured at the olefinic carbons by the method of Singleton. For each olefin, the $^{12}C/^{13}C$ kinetic isotope values are substantial and similar at the two olefinic carbons. These results accord well with prediction based on a [3+2] cycloaddition pathway but not with expectations for a [2+2] cycloaddition process.* Copyright © 1996 Elsevier Science Ltd

The detailed mechanism of the OsO_4-bis-cinchona alkaloid catalyzed enantioselective dihydroxylation of olefins has been the subject of intensive study, especially with regard to the origin of enantioselectivity.[1,2] Most recently, a detailed analysis has been presented of possible transition states for this process in terms of [3+2] (Criegee) and [2+2] (Sharpless osmaoxetane) cycloaddition paths.[3] It was concluded that one particular [3+2] transition state is consistent with all the available experimental data. In contrast, it was not possible to reconcile much of the experimental evidence with a metallaoxetane-like transition state. The preferred [3+2] transition state (Criegee-Corey-Noe (CCN) model[3]) is shown in Scheme 1 for the substrate styrene and the catalytic ligand **1**, [$(DHQD)_2PYDZ$]. The essential structural elements of the [3+2] transition state which is presented in Scheme 1 have been described in detail elsewhere.[2] One prediction which can be made on the basis of this transition state is that the $^{12}C/^{13}C$ kinetic isotope effect for the dihydroxylation of olefins should be significant and approximately the same at each of the carbon atoms of the olefinic linkage. This communication presents the results of a test of this prediction which utilized ^{13}C NMR measurements by the method of Singleton for the accurate determination of $^{12}C/^{13}C$ kinetic isotope effects.[4]

The kinetic isotope effects for the catalytic dihydroxylation with ligand **1** were measured for three substrates which produce 1,2-diols with high enantioselectivity: 4-nitrostyrene,[2c] 4-methoxystyrene[2c] and allyl 4-methoxybenzoate.[2f] The asymmetric dihydroxylation was carried out with approximately 5.0 g of substrate to 97-99% conversion (determined accurately[4] by HPLC or GC analysis of the reaction mixture using naphthalene or α-



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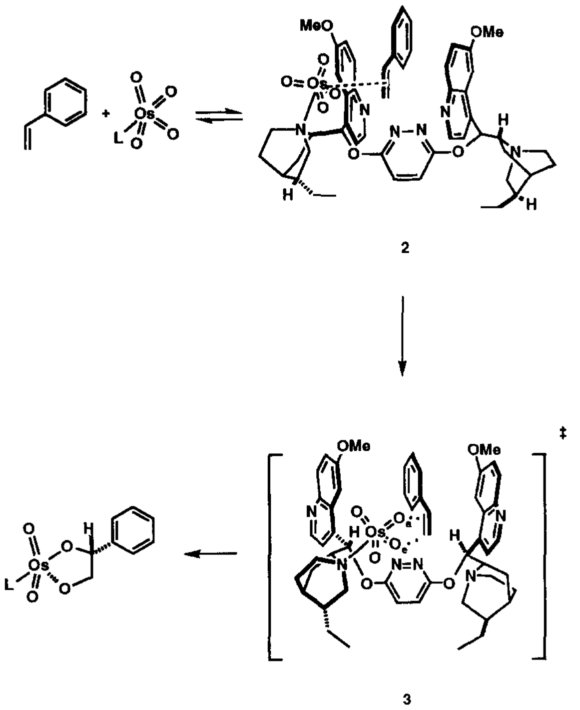


Scheme 1. CCN [3+2] cycloaddition pathway for the asymmetric dihydroxylation of styrene catalyzed by $1 \cdot OsO_4$.

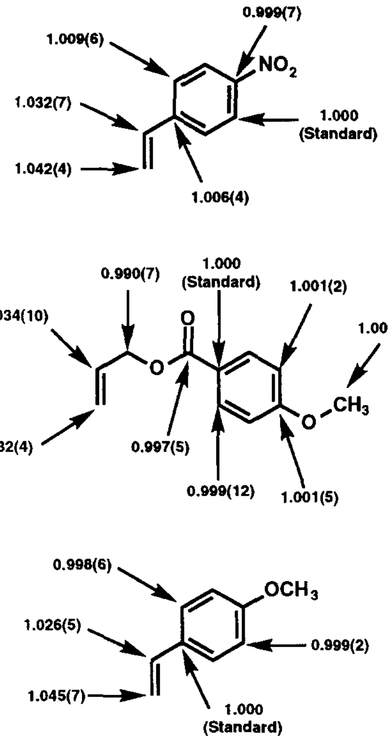
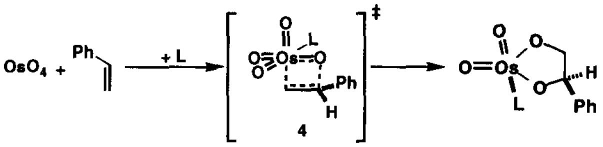


Figure 1. Measured $^{12}C/^{13}C$ kinetic isotope effects for the asymmetric dihydroxylation of monosubstituted olefins.

tetralone as internal standards).[5] In the case of the substituted styrenes, the unreacted olefin was isolated, purified and subjected directly to NMR analysis.[6] In the case of allyl 4-methoxybenzoate, the recovered olefin was epoxidized, and then the rigorously purified epoxide was submitted to NMR analysis.[7] The peak areas from averaged ^{13}C NMR spectra were scaled to an internal reference carbon atom and were compared to averaged control spectra to obtain the area ratios, R/R_0. For each substrate, three individual asymmetric dihydroxylations were performed, and two spectra were taken of each sample, including the control, producing a total of eight spectra. The individual $^{12}C/^{13}C$ kinetic isotope effects and their standard deviations were calculated from the measured values of R/R_0 and the fractional conversion, F, using the equations of Singleton.[4b]

The $^{12}C/^{13}C$ kinetic isotope effects for the catalytic asymmetric dihydroxylation of each substrate are shown in Figure 1. For each substrate, significant and similar primary $^{12}C/^{13}C$ kinetic isotope effects were observed at each of the olefinic carbon atoms. No other significant $^{12}C/^{13}C$ kinetic isotope effects were found. These results are fully consistent with the CCN [3+2] cycloaddition model for the bis-cinchona alkaloid catalyzed enantioselective dihydroxylation. In the transition state arrangement for this process, depicted in Scheme 1, the



Scheme 2. The [2+2] cycloaddition pathway for the asymmetric dihydroxylation of styrene.

two carbon atoms of the olefinic linkage are involved in simultaneous formation of carbon-oxygen bonds. A significant and similar $^{12}C/^{13}C$ primary kinetic isotope effect on this process is expected for each of these carbon atoms. The observed difference in the magnitude of the isotope effect for 4-methoxystyrene at the benzylic methine and terminal methylene carbons of the double bond is consistent with the anticipated greater degree of bonding to the electron rich terminal methylene in the transition state.

It is more difficult to estimate the $^{12}C/^{13}C$ kinetic isotope effect for a [2+2] pathway, especially because there has been no clear proposal for the transition state structure.[1e,8] Assuming that the transition state resembles the metallaoxetane structure (**4**, Scheme 2) (occurring either just before or just after the metallaoxetane intermediate), significantly different $^{12}C/^{13}C$ isotope effects are expected at each olefinic carbon atom because of the large difference in C-O and C-Os stretching frequencies. For example, the following analysis can be made for the dihydroxylation of 4-methoxystyrene. The most reasonable [2+2] pathway is that which attaches the electrophilic Os to the terminal methylene and the O to the benzylic methine of the substrate, as shown in Scheme 2. The stretching frequencies for the C-Os and C-O bonds can be estimated as approximately 500-600 cm^{-1} [9]and 1000 cm^{-1}, respectively. The $^{12}C/^{13}C$ kinetic isotope effect for the methylene position is therefore expected to be lower than that at the methine position by a significant amount rather than larger, as is observed.[10]

In the event that metallaoxetane formation is rapid and reversible with subsequent slow rearrangement to the [3+2] adduct, it seems likely that a relatively small, perhaps insignificant, $^{12}C/^{13}C$ kinetic isotope effect would be expected at the carbon atom which is bound to oxygen in the metallaoxetane, contrary to the above summarized data. Thus, this possibility is also difficult to reconcile with our experimental results.

The experimental results currently available, including the kinetic isotope effect data summarized above, favor the π-complex/[3+2] mechanism for the *bis*-cinchona alkaloid catalyzed dihydroxylation of olefins. As discussed in detail in a recent paper, the experimental evidence which is inconsistent with a [2+2] transition state model includes: (1) enantioselectivity as a function of olefin structure for a wide range of olefinic substrates, (2) enantioselectivity as a function of catalyst structure for a variety of catalysts in the cinchona series, and (3) observed Michaelis-Menten kinetics which demonstrate rapid reversible formation of an intermediate prior to the rate limiting step.[3] The [3+2] CCN model not only accords well with the experimental facts, but also leads to useful predictions which have been confirmed in practice.[11]

References and Notes:

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4. (a) Singleton, D. A.; Thomas, A. A. *J. Am. Chem. Soc.* **1995**, *117*, 9357. (b) Kinetic isotope effects were calculated using the following equation:

$$\mathrm{KIE} = \frac{\ln(1\text{-}F)}{\ln[(1\text{-}F)R/R_0]}$$

5. A suspension of $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $K_2OsO_4 \bullet 2H_2O$ (0.0013 equiv), and $(DHQD)_2PYDZ$ (**1**) (0.0025 equiv) in 330 mL of 1:1 *tert*-butyl alcohol-water was cooled to 0 °C. The corresponding olefin (5.0 g, 1.0 equiv) and the appropriate internal standard (1-2 weight % based on olefin) were added to the mixture, and the resulting suspension was stirred vigorously at 0 °C for 3 to 4 hours, at which point HPLC or GC analysis indicated *ca.* 97-99% conversion. The mixture was treated with 300 mL of saturated aqueous Na_2SO_3 and was stirred at 0 °C for 10 min. The aqueous suspension was extracted with pentane (3 x 500 mL), and the combined organic layers were washed with water (3 x 250 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The substituted styrenes were purified chromatographically. Allyl 4-methoxybenzoate was purified after conversion to the corresponding epoxide.
6. ^{13}C NMR analysis was performed with a Bruker AM 400 spectrometer. Raw data were acquired using inverse gated decoupling and calibrated $2\pi/9$ ^{13}C pulses. A 180 second delay between pulses was included to ensure complete relaxation of all carbon atoms. The sweep width was adjusted to allow at least 20 ppm of free space on either edge of the spectral window. Zero filling of the 64K spectrum to 128K afforded a digital resolution of 0.2 Hz/pt for the substituted styrenes and 0.38 Hz/pt for allyl 4-methoxybenzoate. The raw data were processed using trapezoidal multiplication from 0 to 63K, followed by Lorentzian multiplication (LB=Hz/pt), Fourier transformation and zero-order baseline correction. Spectra processed in this manner had measured signal to noise ratios between 40 and 110 and contained between 3 and 5 data points per peak width at half-height. Integration of the signals was carried out so as to include at least 2.6 Hz of baseline on each end of a peak.
7. Due to the presence of a small amount (*ca.* 0.4%) of *n*-propyl 4-methoxybenzoate in the allyl 4-methoxybenzoate, the unreacted olefin was converted to the corresponding epoxide (see: Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887), which was purified by silica gel chromatography and subjected to ^{13}C NMR analysis.
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9. See, for example, (a) Cai, S.; Hoffman, D. N.; Wierda, D. A. *J. Chem. Soc. Chem. Commun.* **1988**, 313. (b) Polzer, T.; Kiefer, W. *J. Organometal. Chem.* **1994**, *472*, 303.
10. For a basic discussion of the underlying principles, see Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, Harper and Rowe, New York, 1976, pp. 105-112.
11. This research was supported by grants from the National Institutes of Health and the National Science Foundation.

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