Kinetics of Osmium Tetraoxide Catalyzed Trimethylamine *N*-Oxide Oxidations of Cyclohexene and α-Pinene to Diols

Ender Erdik

Ankara University Science Faculty, Besevler, Ankara 06100, Turkey

Donald S. Matteson*

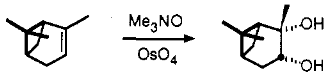
Department of Chemistry, Washington State University, Pullman, Washington 99164-4630

Received February 14, 1989

The kinetics of the osmium tetraoxide catalyzed oxidation of cyclohexene and of α-pinene with trimethylamine *N*-oxide in aqueous *tert*-butyl alcohol are first order in total osmium species, first order in trimethylamine *N*-oxide, and zero order in alkene but are strongly dependent on which alkene is used. Thus, the rate-determining step is attack of the trimethylamine *N*-oxide on the osmium(VI) ester, which is the major reservoir of osmium in the system. The reaction of cyclohexene is inhibited by pyridine with an inverse first-order dependence. Addition of α-pinene in slight excess of the osmium tetraoxide inhibits the oxidation of cyclohexene by more than 2 orders of magnitude, but additional α-pinene has no further effect. The oxidation of α-pinene is not inhibited by pyridine or cyclohexene. Oxidation of *trans*-stilbene in the presence of α-pinene results in slight (3%) but mechanistically significant asymmetric induction. A side reaction in the dihydroxylation of α-pinene, overoxidation to α-hydroxy ketone, is suppressed by increasing the concentration of trimethylamine *N*-oxide.

The syn dihydroxylation of sterically hindered alkenes such as α-pinene (1) is accomplished especially cleanly by the osmium tetraoxide catalyzed procedure of Ray and Matteson,[1] which utilizes trimethylamine *N*-oxide as the oxidizing agent and pyridine as a catalyst modifier. *N*-Methylmorpholine *N*-oxide had previously been shown to be an excellent oxidizing agent by VanRheenen and coworkers.[2] Other useful oxidizing agents include *tert*-butyl hydroperoxide[3] or organic selenoxides,[4] but highly hindered trisubstituted alkenes react very slowly and tend to overoxidize to α-hydroxy ketones. This side reaction is minimal in the trimethylamine *N*-oxide–pyridine system.[1]

Osmium tetraoxide oxidations have been reviewed.[5] In spite of the importance of the catalytic process, this review cites only one prior kinetic study, which concerned maleic and fumaric acids with chlorate ion in water.[6] The traditional method for avoiding overoxidation has been the use of a stoichiometric amount of osmium tetraoxide, followed by reductive cleavage of the osmium(VI) ester,[7] which is impractical for preparative scale syntheses. In view of the importance of pinanediol (2) in our directed chiral synthesis with boronic esters,[8] as well as the utilization of our new dihydroxylation conditions by others for synthetic purposes,[9-11] the present kinetic study was undertaken in order to obtain a better understanding of the osmium tetraoxide catalysis.



1 2

There have been several mechanistic studies of stoichiometric osmium tetraoxide oxidation.[5,7,12-15] Cyclic osmium(VI) intermediates are a universal feature and are generally isolable as monomers or their pyridine complexes[7] or as dimers.[15] Rates are typically first order in alkene and first order in osmium tetraoxide.[12-14] If pyridine or bipyridyl is added, an additional term appears in the rate law that is first order in the amine as well as the other reactants, and considerable acceleration results.[12,13] This rate law plus observations that optically active amines lead to optically active diols[16-18] indicate that the amine complexes of osmium tetraoxide react directly with alkenes. It has been suggested that the initial attack on the double bond involves the osmium atom directly.[17,19] Although this intriguing idea has not been accessible to proof,[15] it is in agreement with stereochemical observations.[20]

Recent communications from Sharpless' group[18] describe a highly significant chiral-catalyzed hydroxylation of unhindered olefins. Attack of osmium tetraoxide on an unhindered olefin (styrene) was found to be the rate-limiting

---

(1) (a) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450. (b) Ray, R.; Matteson, D. S. *J. Indian Chem. Soc.* **1982**, *59*, 119–123.

(2) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.

(3) (a) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986–1987. (b) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063–2066.

(4) Abatjoglu, A. G.; Bryant, D. R. *Tetrahedron Lett.* **1981**, *22*, 2051–2054.

(5) Schröder, M. *Chem. Rev.* **1980**, 80–187.

(6) Zelikoff, M.; Taylor, H. A. *J. Am. Chem. Soc.* **1950**, *72*, 5039–5042. The data were interpreted as indicating rate-determining attack of OsO_4 on the unsaturated substrates. However, the relative rates (fumarate ion 3.3, fumaric acid 1, maleic acid 0.17) are so similar as to suggest osmium(VI) ester hydrolysis might be rate determining, and there are insufficient data for critical reevaluation. Chlorate is not as efficient an oxidizing agent as trimethylamine *N*-oxide with a substrate similar to α-pinene,[1] and water is not the typical solvent for reactions of alkenes.

(7) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99–133.

(8) (a) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819. (b) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics* **1983**, *2*, 1536–1543. (c) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300.

(9) (a) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378–6386. (b) Hauser, F. M.; Ellenberger, S. R.; Rhee, R. P. *J. Org. Chem.* **1987**, *52*, 5041–5044.

(10) Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1983**, *48*, 4144–4147.

(11) Takeuchi, Y.; Sudani, M.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 4151–4152.

(12) (a) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972**, *11*, 2621–2627. (b) Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425–1426.

(13) Hartman, R. F.; Rose, S. D. *J. Org. Chem.* **1981**, *46*, 4340–4345.

(14) Deetz, J. S.; Behrman, E. J. *J. Org. Chem.* **1980**, *45*, 135–140.

(15) Casey, C. P. *J. Chem. Soc., Chem. Commun.* **1983**, 126–127.

(16) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265.

(17) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213–6215.

(18) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (b) Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737–739. (c) **Note Added in Proof:** Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125.

(19) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120–3127.

(20) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573–576.

0022-3263/89/1954-2742$01.50/0

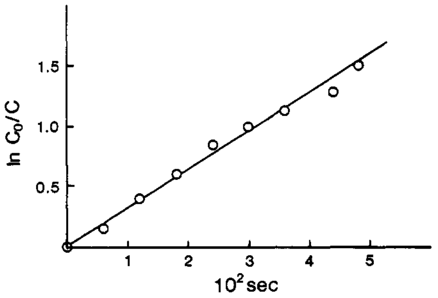


Figure 1. Typical first-order plot of the osmium tetraoxide catalyzed oxidation of cyclohexene with trimethylamine *N*-oxide in aqueous 90% *tert*-butyl alcohol at 50 °C; [cyclohexene] = 0.439 M, [Me_3NO] = 0.454 M, [OsO_4] = 2.36 × 10^{-3} M, no pyridine.

step in the catalytic process, although with some other alkenes at high concentrations other steps were said to be turnover limiting.

In this paper, we show that with α-pinene and cyclohexene the oxidation of the osmium(VI) ester is rate-determining.

Experimental Section

Chemicals. *tert*-Butyl alcohol was fractionated and traces of isobutylene were removed by bubbling nitrogen through it for several hours at 50 °C before use. Osmium tetraoxide, trimethylamine *N*-oxide, and cyclohexene were obtained from Fluka. (+)-α-Pinene from Aldrich Chemical Company was redistilled. All other chemicals were reagent grade.

Kinetic Measurements. The kinetics were followed by measuring the concentration of remaining alkene by GC with a silicone fluid column on a Perkin-Elmer F-11 gas chromatograph with an electronic integrator or with an OV-101 column on a Hewlett-Packard 5890A gas chromatograph. (Attempts to measure the diol produced have yielded somewhat erratic results.) In a jacketed reaction vessel of approximately 50-mL capacity capped with a rubber septum, equipped with a magnetic stirrer, and flushed with nitrogen, 5 mL of an aqueous *tert*-butyl alcohol solution of trimethylamine *N*-oxide and internal standard was thermostated. Alkene and pyridine were added, followed by osmium tetraoxide in aqueous solution. Beginning 1 min after injection of the osmium tetraoxide, aliquots were withdrawn at appropriate times by removing 0.2 mL of the reaction mixture by syringe and adding it slowly to a vial containing a quenching solution of 10% aqueous sodium bisulfite and ether. The vial was capped and shaken. Extraction of alkene and internal standard to the ethereal phase was found to be essentially quantitative. In each kinetic experiment, 7–16 aliquots were withdrawn and the ethereal phase was analyzed by GLPC. Generally, self-consistent data could be obtained over 2 half-lives. Observed pseudo-zero-order rate constants (k_0) or pseudo-first-order rate constants (k_1) were calculated by the method of least squares from plots of ($c_0 - c_t$) versus time or ln (c_0/c_t) versus time, respectively, where c_0 and c_t were the concentrations of alkene initially and at time *t*. Reproducibility was generally ±3%.

Oxidation of *trans*-Stilbene in the Presence of (+)-α-Pinene. A 3.60-g (20-mmol) portion of *trans*-stilbene was added to a solution of 2.31 g (20.7 mmol) of trimethylamine *N*-oxide, 0.5 mL (0.04 mmol) of 2% osmium tetraoxide in *tert*-butyl alcohol, and 0.1 mL (1 mmol) of (+)-α-pinene in 50 mL of *tert*-butyl alcohol and 5 mL of water. The solution was kept at 50 ± 5 °C for 7 days and then worked up with ether and water. The crude mixture of stilbene and hydrobenzoin, 3.56 g, was chromatographed on silica with 5% ether/petroleum ether to separate stilbene. Elution with ether yielded 2.24 g (52%) of hydrobenzoin; after sublimation, $[\alpha]^{22.5}{}_{546}$ +3.5° (*c* 12, EtOH); $[\alpha]^{22.5}{}_{577}$ +3.0°; extrapolated $[\alpha]^{22.5}{}_{589}$ +2.8° [lit.[21] $[\alpha]_D$ +94°, *R,R* isomer]. A control reaction was run in the absence of α-pinene with half the above concentrations of stilbene, trimethylamine *N*-oxide, and osmium tetraoxide 40 h at 20 °C, 24 h at 38–40 °C. Chromatography yielded 40% unchanged stilbene and 55% hydrobenzoin.

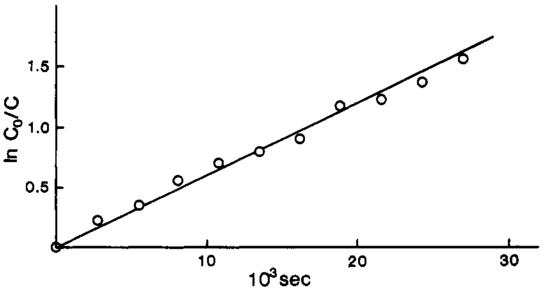


Figure 2. Typical first-order plot of the osmium tetraoxide catalyzed oxidation of α-pinene with trimethylamine *N*-oxide in aqueous 85.7% *tert*-butyl alcohol at 70 °C; [α-pinene] = [Me_3NO] = 0.375 M, [OsO_4] = 7.85 × 10^{-3} M, [pyridine] = 0.465 M.

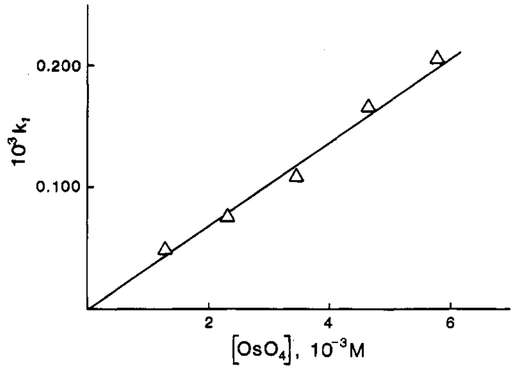


Figure 3. Effect of osmium tetraoxide concentration on the pseudo-first-order rate constants for the osmium tetraoxide catalyzed oxidation of cyclohexene with trimethylamine *N*-oxide in aqueous 90% *tert*-butyl alcohol at 50 °C. Data are from Table I.

Table I. Effect of OsO_4 Concentration on the Rate of Oxidation of Cyclohexene with Me_3NO in 90% *t*-BuOH and 10% Water (v/v) at 50.0 °C[a]

$10^3[OsO_4]$, M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
1.29	0.0483	37.4
2.36	0.0753	32.0
3.51	0.1095	31.2
4.65	0.1685	36.6
5.77	0.2053	35.7

[a] Cyclohexene, 0.436 M; trimethylamine *N*-oxide, 0.451 M; pyridine, 0.092 M; $k_2 = k_1/[OsO_4]$.

Table II. Effect of OsO_4 Concentration on the Rate of Oxidation of α-Pinene with Me_3NO in 85.7% *tert*-Butyl Alcohol and 14.3% Water at 70.0 °C[a]

$10^3[OsO_4]$, M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
3.93	0.0325	8.27
7.85	0.0548	7.00
11.78	0.0868	7.40
15.70	0.1105	7.15
19.63	0.1402	7.15

[a] α-Pinene, 0.375 M; trimethylamine *N*-oxide, 0.375 M; pyridine, 0.645 M; $k_2 = k_1/[OsO_4]$.

Results

Reaction Order. The first rate data were taken with nearly equal concentrations of alkene and trimethylamine *N*-oxide and were plotted as pseudo first order in one reactant, which was subsequently interpreted as the amine oxide. Typical first-order plots for cyclohexene and (+)-α-pinene are shown in Figures 1 and 2, respectively. The osmium tetraoxide concentration was varied by a factor of 5 while keeping all other concentrations constant

---

[21] (a) Berti, G.; Bottari, F. *J. Org. Chem.* **1960**, *25*, 1286–1292. (b) Eisenlohr, F.; Hill, L. *Chem. Ber.* **1937**, *70*, 942–947.

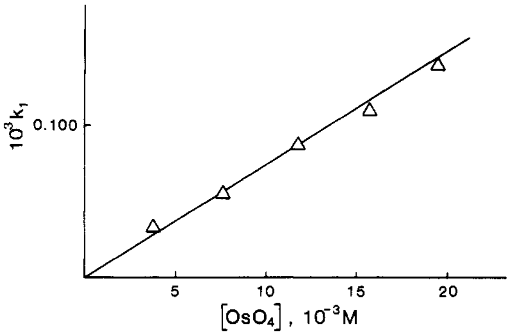


Figure 4. Effect of osmium tetraoxide concentration on the pseudo-first-order rate constants for the osmium tetraoxide catalyzed oxidation of α-pinene with trimethylamine *N*-oxide in aqueous 85.7% *tert*-butyl alcohol at 0 °C. Data are from Table II.

Table III. Effect of Trimethylamine *N*-Oxide Concentration on the Rate of Oxidation of Cyclohexene with Me_3NO in 90% *t*-BuOH and 10% Water (v/v) at 50.0 °C[a]

$[Me_3NO]$, M	10^3k_0, M-s^{-1}	10^3k_2, M^{-1} s^{-1}
0.163	0.0023	13.7
0.245	0.0040	15.9
0.326	0.0051	15.1
0.408	0.0059	14.1
0.489	0.0071	14.1

[a] Cyclohexene, 0.010 M; OsO_4, 1.03 × 10^{-3} M; pyridine, 0.082 M; $k_2 = k_0/([Me_3NO][OsO_4])$.

Table IV. Effect of Trimethylamine *N*-Oxide Concentration on the Rate of Oxidation of α-Pinene with Me_3NO in 87.5% *tert*-Butyl Alcohol and 12.5% Water at 70.0 °C[a]

$[Me_3NO]$, M	10^3k_0, M-s^{-1}	10^3k_2, M^{-1} s^{-1}
0.151	0.0027	9.5
0.226	0.0038	8.9
0.302	0.0046	8.0
0.377	0.0063	8.8

[a] α-Pinene, 0.009 M; OsO_4, 1.89 × 10^{-3} M; pyridine, 0.339 M; $k_1 = k_0/([Me_3NO][OsO_4])$.

in order to test the effect of catalyst concentration on k_1 values. The results are shown in Tables I and II, and the data are plotted in Figures 3 and 4. The rate is first order in osmium tetraoxide. Least-squares analyses of the log k_1 values versus log $[OsO_4]$ yielded slopes of 0.93 for cyclohexene and 0.91 for α-pinene.

The correct reaction order was discovered by plotting the dependence on alkene in the presence of large excesses of trimethylamine *N*-oxide. First-order plots curved, but plots zero order in alkene proved linear to 100% reaction, as shown in Figures 5 and 6. Zero-order k_0 values are given in Tables III and IV, and the linearity with trimethylamine *N*-oxide concentration is illustrated in Figures 7 and 8. Plots of log k_0 versus log $[Me_3NO]$ yielded slopes of 0.99 for cyclohexene and 0.88 for α-pinene, respectively, confirming the first-order dependence on trimethylamine *N*-oxide concentration. Thus, the total rate law is expressed by eq 1.

$$-d[\text{alkene}]/dt = k_2[\text{total Os}][Me_3NO] \qquad (1)$$

"Total Os" is indicated rather than "OsO_4" in eq 1 because the osmium tetraoxide is largely converted to other species at the outset of the reaction. It should be emphasized that even though the alkene does not appear in the rate law, the reaction of cyclohexene is much faster than that of α-pinene.

Table V. Effect of Pyridine on the Oxidation of Cyclohexene in 90% *tert*-Butyl Alcohol and 10% Water at 50.0 °C[a]

[pyridine], M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
0.184	0.0701	29.7
0.092	0.0753	32.0
0.086	0.128	54.3
0.072	0.135	74.3
0.054	0.256	108
0.036	0.275	117
0.018	0.681	288
0.000	3.10	1310

[a] Cyclohexene, 0.436 M; Me_3NO, 0.451 M; OsO_4, 2.36 × 10^{-3} M; $k_2 = k_1/[OsO_4]$.

Table VI. Effect of 2,2′-Bipyridyl on Rates of Oxidation of Cyclohexene in 90% *tert*-Butyl Alcohol and 10% Water at 50.0 °C[a]

[bipyridyl], M × 10^3	10^3k_1, s^{-1}	k_2, M^{-1} s^{-1}
22.8	0.0675	0.0144
15.2	0.0861	0.0185
11.4	0.1173	0.0252
7.6	0.1879	0.0404

[a] Cyclohexene, 0.436 M; Me_3NO, 0.451 M; OsO_4, 4.65 × 10^{-3} M.

Table VII. Effect of Pyridine on the Rate of Oxidation of α-Pinene in 85.7% *tert*-Butyl Alcohol and 14.3% Water at 70.0 °C[a]

[pyridine], M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
0.000	0.0618	5.35
0.222	0.0711	6.00
0.465	0.0795	6.75
0.645	0.0868	7.40
0.699	0.0883	7.60
0.897	0.0962	8.20

[a] α-Pinene, 0.375 M; Me_3NO, 0.375 M; OsO_4, 11.78 × 10^{-3} M; $k_2 = k_1/[OsO_4]$.

Table VIII. Effect of 2,2′-Bipyridyl on the Rate of Oxidation of α-Pinene in 85.7% *tert*-Butyl Alcohol and 14.3% Water at 70 °C[a]

[bipyridyl], M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
0.000	0.0600	5.35
0.200	0.0323	2.88
0.400	0.0309	2.76
0.600	0.0286	2.55
0.800	0.0315	2.81

[a] α-Pinene, 0.360 M; Me_3NO, 0.360 M; OsO_4, 11.21 × 10^{-3} M.

Table IX. Effect of Triethylamine on the Rate of Oxidation of α-Pinene in 85.7% *tert*-Butyl Alcohol and 14.3% Water at 60 °C[a]

$[Et_3N]$, M	10^3k_1, s^{-1}	10^3k_2, M^{-1} s^{-1}
0.000	0.0299	2.67
0.125	0.0191	1.70
0.250	0.0186	1.66
0.500	0.0187	1.67

[a] α-Pinene, 0.375 M; Me_3NO, 0.375 M; OsO_4, 11.2 × 10^{-3} M.

Effect of Amines. Amines greatly retard the catalytic osmium tetraoxide oxidation of cyclohexene. Rate constants were found to vary linearly with the reciprocal of pyridine concentration (Table V, Figure 9). Least-squares slopes of plots of log k_2 versus log [pyridine] were −1.04. 2,2′-Bipyridyl caused an even greater rate retardation (Table VI, Figure 6). Triethylamine had a slight retarding effect at relatively high concentrations (not illustrated).

α-Pinene behaved differently. Pyridine slightly increased the reaction rate in a linear manner, $k = k_0 + k'[\text{pyridine}]$ (Table VII, Figure 10). The usual least-

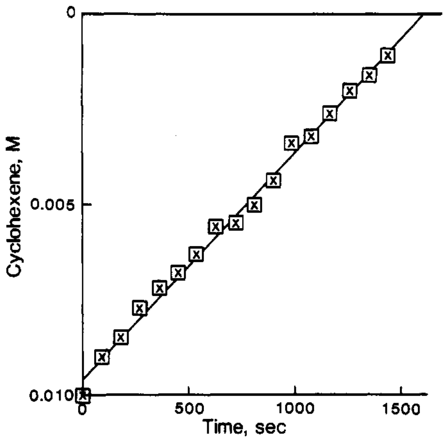


Figure 5. Typical pseudo-zero-order plot of the osmium tetraoxide catalyzed oxidation of cyclohexene with trimethylamine *N*-oxide in aqueous 90% *tert*-butyl alcohol at 50 °C; [cyclohexene] = 0.010 M, $[Me_3NO]$ = 0.408 M, $[OsO_4]$ = 1.03×10^{-3} M, [pyridine] = 0.082 M.

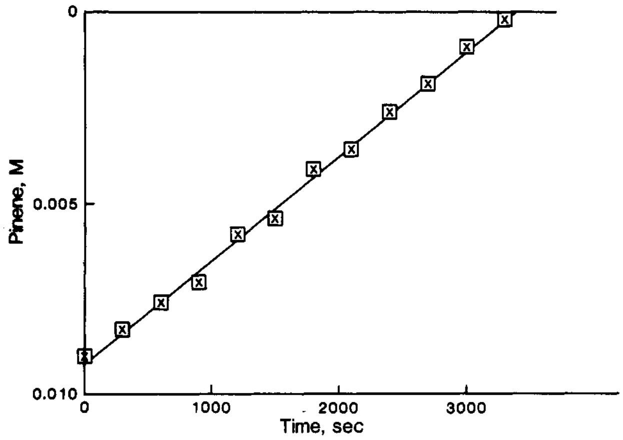


Figure 6. Typical pseudo-zero-order plot of the osmium tetraoxide catalyzed oxidation of α-pinene with trimethylamine *N*-oxide in aqueous 87.5% *tert*-butyl alcohol at 70 °C; [α-pinene] = 0.009 M, $[Me_3NO]$ = 0.151 M, $[OsO_4]$ = 1.89×10^{-3} M, [pyridine] = 0.339 M.

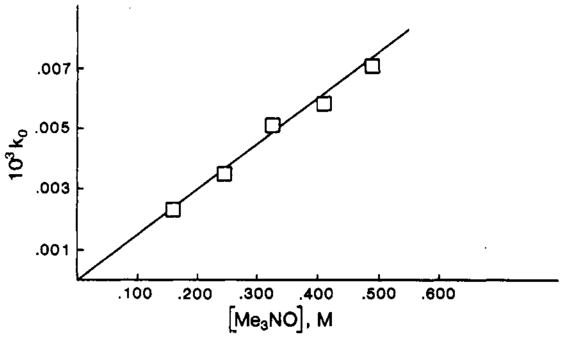


Figure 7. Effect of trimethylamine *N*-oxide concentration on the pseudo-zero-order rate constants for the osmium tetraoxide catalyzed oxidation of cyclohexene in aqueous 90% *tert*-butyl alcohol at 50 °C. Data are from Table III.

squares analysis of log/log plots yielded a pyridine-dependent slope of 1.07. In contrast to pyridine, 2,2′-bipyridyl and triethylamine slightly retarded oxidation of α-pinene, but after addition of 0.1–0.2 M amine halved the rate, further increases to 0.5–0.8 M had no effect (Tables VIII and IX).

Effect of Water. The effect of increasing the amount of water in the oxidation of cyclohexene in *tert*-butyl alcohol is summarized in Table X. The reaction shows a somewhat less than first-order relationship to the amount

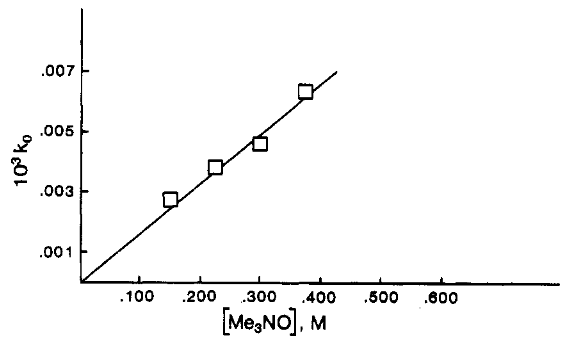


Figure 8. Effect of trimethylamine *N*-oxide concentration on the pseudo-zero-order rate constants for the osmium tetraoxide catalyzed oxidation of α-pinene in aqueous 87.5% *tert*-butyl alcohol at 70 °C. Data are from Table IV.

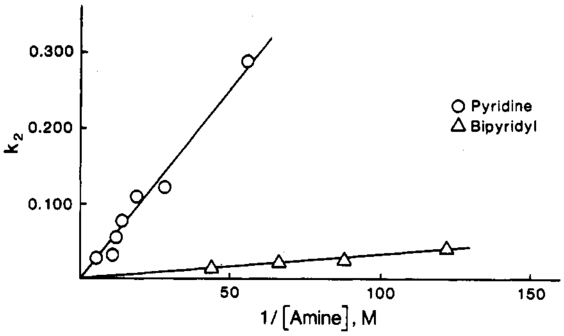


Figure 9. Plot of k_2 versus 1/[amine] for the osmium tetraoxide catalyzed oxidation of cyclohexene with trimethylamine *N*-oxide in aqueous 90% *tert*-butyl alcohol at 50 °C. Circles are with pyridine, triangles are with 2,2′-bipyridyl; [cyclohexene] = 0.436 M; $[Me_3NO]$ = 0.451 M; $[OsO_4]$ = 4.65×10^{-3} M.

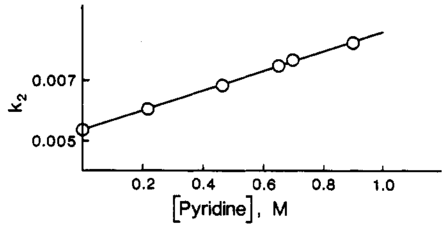


Figure 10. Plot of k_2 versus pyridine concentration for the osmium tetraoxide catalyzed oxidation of α-pinene with trimethylamine *N*-oxide in aqueous 85.7% *tert*-butyl alcohol at 70 °C. Data are from Table VII.

Table X. Effect of Water on the Rate of Oxidation of Cyclohexene in *tert*-Butyl Alcohol at 50.0 °C[a]

% water	mol fractn H_2O	k_2, M^{-1} s^{-1}
5.0	0.215	0.909
10.0	0.368	1.312
15.0	0.507	2.103
18.0	0.540	3.149

[a] Cyclohexene, 0.436 M; Me_3NO, 0.451 M; OsO_4, 1.44×10^{-3} M; no pyridine.

Table XI. Effect of Water on the Rate of Oxidation of α-Pinene in *tert*-Butyl Alcohol at 70 °C[a]

% water	mol fractn H_2O	10^3k_2, M^{-1} s^{-1}
2.9	0.135	0.45
4.3	0.191	2.27
5.7	0.239	5.23
10.0	0.368	5.55
14.3	0.468	5.35

[a] α-Pinene, 0.390 M; Me_3NO, 0.390 M; OsO_4, 8.16×10^{-3} M; no pyridine.

Table XII. Competitive Oxidations of Cyclohexene and α-Pinene in 85.7% *tert*-Butyl Alcohol and 14.3% Water at 60.0 °C[a]

	separate k_2's, M^{-1} s^{-1}		competitive k_2's, M^{-1} s^{-1}	
pyridine, M	cyclohexene	α-pinene	cyclohexene	α-pinene
0	2.22	0.00267	0.0105	0.00267
0.465	0.024	0.00383	0.0077	0.00367
0.897	0.010	0.00383	0.0093	0.00333

[a] Cyclohexene = α-pinene = Me_3NO = 0.361 M; OsO_4, 7.57 × 10^{-3} M.

Table XIII. Effect of α-Pinene on the Rate of Oxidation of Cyclohexene in 87.1% *tert*-Butyl Alcohol and 12.9% Water at 60.0 °C[a]

[α-pinene], M	cyclohexene k^2, M^{-1} s^{-1}	[α-pinene], M	cyclohexene k^2, M^{-1} s^{-1}
0	6.89	0.018	0.089
0.001125	0.527	0.036	0.086
0.00225	0.280	0.072	0.088
0.0045	0.136	0.216	0.081
0.009	0.124	0.432	0.085

[a] Cyclohexene = Me_3NO = 0.072 M; OsO_4, 0.9 × 10^{-3} M; no pyridine.

Table XIV. Effect of Trimethylamine *N*-Oxide Concentration on the Production of α-Hydroxy Ketone (Ketol) and Diol in the OsO_4-Catalyzed Oxidation of α-Pinene in 90% *t*-BuOH and 10% Water (v/v) at 66 °C[a]

[Me_3NO], M	% yield of ketol	% yield of diol
0.151	14	65
0.226	9	73
0.302	0	90

[a] α-Pinene, 0.006 M; pyridine, 0.339 M; OsO_4, 1.89 × 10^{-3} M.

of water in the range 5–18%. Below 5%, rate measurements became erratic, and above 18%, separation into two phases occurred.

With α-pinene, the rate increased markedly as the water was increased from 2.9 to 5.7%, but there was little further rate increase when the water was increased to 14% (Table XI).

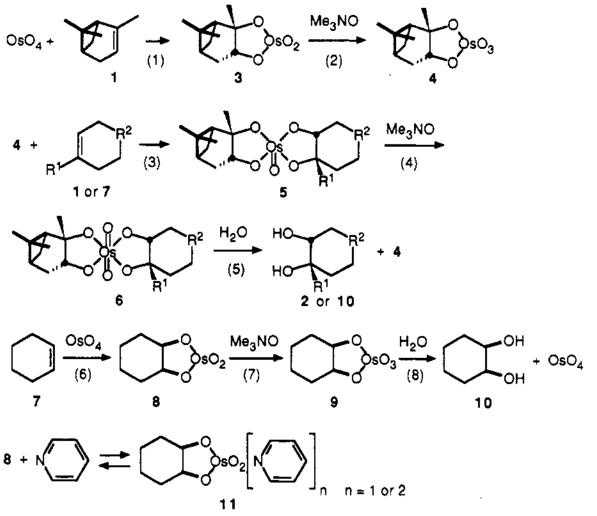
Competitive Oxidation of Cyclohexene and α-Pinene. Rate of reaction of mixtures of cyclohexene and α-pinene were measured. In a competitive oxidation of 0.36 M cyclohexene and 0.36 M α-pinene without pyridine, the rate of oxidation of the cyclohexene was greatly retarded but that of the α-pinene was unaffected. In the presence of pyridine up to 0.9 M, the rate of oxidation of the cyclohexene showed slight further lowering (Table XII).

In another series of experiments, the concentration of the α-pinene was varied and the rate of cyclohexene oxidation was measured. The dependence was inverse first order in α-pinene between 1.1 × 10^{-3} and 4.5 × 10^{-3} M, log/log slope −0.98, and zero order above 0.018 M, when the osmium tetraoxide was 0.9 × 10^{-3} M (Table XIII).

Cholesterol also inhibited the oxidation of cyclohexene. In the presence of 0.113 M cholesterol, the rate of reaction of 0.436 M cyclohexene was one-sixth the usual value.

The ratio of diol to α-hydroxy ketone was improved by increasing the trimethylamine *N*-oxide concentration (Table XIV). The α-hydroxy ketone from α-pinene was positively identified by isolation and comparison of its NMR spectrum with literature data.[22] The diol is clearly the major product. The α-hydroxy ketone must be formed by a mechanistically distinct pathway with a different rate law. None of our data provide information regarding such a pathway, but the formation of α-hydroxy ketone in our synthetic process[1] has appeared to be erratic, as if adventitious radical reactions might be involved.

Scheme I



Pyridine also appeared to increase the ratio of diol to α-hydroxy ketone. For example, the ratio of pinanediol to α-hydroxy ketone at 66 °C when no pyridine was present was 5:1, and when 0.72 M pyridine was present rose to 21:1 (initial conditions: 0.35 M α-pinene, 0.35 M trimethylamine *N*-oxide, 0.0146 M osmium tetraoxide, 90% *tert*-butyl alcohol/10% water; 50–70% conversion). At 76 °C the ratio fell to 5:1 with 0.72 M pyridine and was increased to 30:1 by 1.44 M pyridine. Under the conditions used for synthetic purposes, we have previously noted that keeping the temperature below 70 °C helps prevent overoxidation to α-hydroxy ketone.[8a]

Asymmetric Induction by α-Pinene in the Oxidation of *trans*-Stilbene. After the report of asymmetric dihydroxylation of *trans*-stilbene in the presence of cinchona alkaloids,[18a] we recognized that verification of direct hydroxylation by pinanediol–osmium(VIII) complex would be provided if asymmetric induction were observed. Reaction of *trans*-stilbene [(*E*)-1,2-diphenylethene] with osmium tetraoxide in the presence of a small amount of α-pinene at 50 °C yielded (+)-*threo*-hydrobenzoin [(*R*,*R*)-1,2-diphenyl-1,2-ethanediol], 3% enantiomeric excess (ee) after chromatographic separation from the unchanged stilbene.[23] Cinchona alkaloids accelerate the reaction,[18] but pinanediol greatly retards it, as shown by the control without α-pinene in which the same conversion was achieved at a lower temperature and concentration in a shorter time.

Discussion

Mechanism. The discussion that follows will relate the kinetic data to processes summarized in Scheme I. Oxidation step 4 or 7, depending on the reactants, will be shown to be rate determining.

Rate Law. The rate law expressed by eq 1 in the Results section may seem surprising, especially in view of the previously reported first-order dependence on alkene.[6] However, steady-state kinetics provide a straightforward explanation. The concentration of OsO_4 is low. If it is

---

[22] Carlson, R. G.; Pierce, J. K. *J. Org. Chem.* **1971**, *36*, 2319–2324.

[23] Although the degree of asymmetric induction was small, the product was pure by 200-MHz ^1H NMR analysis and the rotation was unambiguous. The rotation of pinanediol, the only other likely optically active product, would be very small and, in ethanol, opposite in sign to that observed.

assumed that the osmium(VI) ester is not hydrolyzed but attacked directly by trimethylamine *N*-oxide, then eq 2 results.

$$0 = d[OsO_4]/dt = k_2[\text{Os(VI) ester}][Me_3NO] - k_2'[OsO_4][\text{alkene}] \quad (2)$$

If the reaction of OsO_4 with alkene (k_2') were rate determining, the reaction would be first order in alkene, first order in total osmium (mostly OsO_4), and zero order in trimethylamine *N*-oxide or any other reagent that might oxidize the osmium(VI) or hydrolyze the osmium(VI) ester. Observation requires that the trimethylamine *N*-oxide (k_2) and not the alkene be included in the rate law, which leads to eq 3.

$$d[\text{diol}]/dt = k_2[\text{Os(VI) ester}][Me_3NO] \quad (3)$$

This assumption requires that essentially all of the osmium be present as osmium(VI) ester (**3**, **5**, or **8**), so that [Os(VI) ester] = [total Os], and eq 3 is therefore equivalent to the experimentally observed rate law, eq 1. The osmium(VI) ester must be relatively substitution-inert at osmium.[24]

If this interpretation is correct, the oxidation of α-pinene (**1**) must be rapid compared to the overall catalytic process. In the classic study of stoichiometric OsO_4 oxidations by Criegee and co-workers,[7] α-pinene was one of the faster reacting substrates, 0.005 M solutions in chloroform at 20 °C having a half-life of 1.5 min, in ethyl acetate 2 min, corresponding to $k_2 \sim 4\ M^{-1}\ s^{-1}$. Pinanediol osmate(VI) (**3**) as well as its bis(pyridine) complex were isolated.[7] These k_2's for $[OsO_4]$[pinene] have roughly the same magnitude at 20 °C that the k_2's for [Os(VI) ester]$[Me_3NO]$ in the catalytic process have at 70 °C. Thus, not only would all of the OsO_4 react with α-pinene within seconds at the outset of our reactions, but the rate constant for reaction of any regenerated OsO_4 with α-pinene would be substantially greater than that for the rate-determining step.

Although the rate law has been derived as if oxidation of osmium(VI) ester yields OsO_4 directly, it seems more likely that the rate-determining step is transfer of an oxygen atom from Me_3NO to oxidize osmium(VI) ester to osmium(VIII) ester (steps 2, 4, and 7). The osmium(VIII) ester of cyclohexanediol hydrolyzes rapidly (step 8), but as discussed in the next paragraphs, the 1:1 ester of pinanediol (**4**) evidently does not.

Retardation by α-Pinene. If α-pinene sequesters the osmium as a relatively inert osmium(VI) ester, it should inhibit the oxidation of cyclohexene, as it has been shown to do. Intuitively, inverse dependence of the rate on the α-pinene concentration might be expected.[25] The contrary observation that the rate of cyclohexene oxidation falls rapidly with introduction of a small amount of α-pinene but then becomes independent of the α-pinene concentration above a certain low level (Table XIII) was initially anomalous.

Our results suggest that the osmium(VIII) ester of pinanediol (**4**) is the oxidizing agent that attacks cyclohexene when the free OsO_4 has been sequestered. There is good UV spectroscopic evidence that osmium(VIII) esters are formed in a reversible reaction with diols and osmium tetraoxide.[26] Pinanediol forms unusually stable cyclic esters with boron compounds, replacing all other tested diols essentially irreversibly,[8] and it would not be surprising if **4** had an unusually high stability constant.

Although we are not aware of precedent for attack of diol osmium(VIII) esters on alkenes, there is clear evidence that amine–osmium(VIII) complexes attack alkenes.[5,7,12-14,16-18] There are also several known examples of guidance of osmylation stereochemistry by neighboring polar groups in which it appears that direct bonding of the osmium(VIII) to the neighboring group may be involved, including sulfoximines (but not sulfones),[27] chiral sulfoxides,[28] and an allylic hydroxyl.[29] (Other examples of stereodirection may involve steric repulsions rather than bonding to the attacking osmium.[30]) Several bis(diol) osmate(VI) esters analogous to **5** have been prepared by esterification of osmate(VI),[7] and although more recent work suggests that these may be polymeric,[31] their existence is well established. We conclude that there are ample precedents for attack of osmium(VIII) species other than OsO_4 itself on double bonds.

Although our limited kinetic data (Table XII) suggest that the rate of oxidation of α-pinene is not affected by the presence of cyclohexene, considerable further investigation would be required in order to define the possibly complex relationships involving the two types of intermediates **5** and **6** postulated, $(\text{pinanediol})_2$Os and (pinanediol)(cyclohexanediol)Os. The two alternatives of steps 3 and 4 involve four rate constants that may affect relative rates of formation of pinanediol (**2**) and cyclohexanediol (**10**). The differences between calculated *k*'s in Tables XII and XIII, which involve significantly different reactant concentrations, may reflect this oversupply of uninvestigated parameters. Because the data were gathered in different apparatus at remote times and places, nothing can be deduced from direct comparison.

The asymmetric induction in the reaction of *trans*-stilbene with osmium tetraoxide and trimethylamine *N*-oxide in the presence of α-pinene leaves no doubt that a species containing the pinene unit is involved in the product-determining step. Although the strictest interpretation of the small ee only requires 3% reaction via such a pathway, there is no reason to believe that pinanediol should be a good chiral director in this system, and it could well be that nearly 100% of the reaction proceeds via this path.

Self-consistent interpretation requires that pinanediol osmium(VIII) ester **4** attack α-pinene, analogous to the

---

(24) If the osmium(VI) ester were hydrolyzed rapidly to free osmate(VI) before osmate(VI) was oxidized by trimethylamine *N*-oxide in the rate-determining step, then the empirical rate law would still have the form [total Os]$[Me_3NO]$ and be indistinguishable from eq 1 and 3, except that the major osmium species present would be osmate(VI) and the nature of the alkene substrate would have no effect whatever on the rate, clearly contrary to observation. It may also be noted that stoichiometric preparative procedures call for reduction, not hydrolysis, of osmium(VI) esters,[5] although osmium(VI) esters have been cleaved with potassium hydroxide.[7] The rate of hydrolysis of an osmium(VI) ester has been found to be 0.03 that of its formation, and the hydrolysis of the bis(pyridine) complex ~0.03 as fast as hydrolysis of the free ester.[12] Finally, it may be noted that if hydrolysis of the osmium(VI) ester were rate determining, then the oxidizing agent would not appear in the rate law.

(25) Steady-state treatment requires that eq 2 must apply to each alkene separately as well as to the sum of the reactions. The major osmium species must be α-pinene osmium(VI) ester, since the rate of reaction of α-pinene is unaffected by the presence of cyclohexene. The derived rate law for the cyclohexene reaction, which is inconsistent with our results, would require rate-limiting attack of trimethylamine *N*-oxide on cyclohexene osmium(VI) ester, the concentration of which would be proportional to [α-pinene-Os(VI)][cyclohexene]/[α-pinene].

(26) Milas, N. A.; Trepagnier, J. H.; Nolan, J. T., Jr.; Iliopulos, M. I. *J. Am. Chem. Soc.* **1959**, *81*, 4730–4733.

(27) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459–2461.

(28) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458–2459.

(29) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *37*, 3951–3954.

(30) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *37*, 3943–3946. (b) Selnick, H. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1987**, *28*, 4955–4958.

(31) Griffith, W. P.; Rosetti, R. *J. Chem. Soc., Dalton Trans.* **1972**, 1449.

attack on cyclohexene, in the major pathway. The rate law would not be altered if the major osmium species were bis(pinanediol) osmate(VI) [**5** as $OsO(O_2C_{10}H_{16})_2$] instead of the monoester **3**. In accord with this interpretation, oxidations of α-pinene result in a very dark purplish solution, in contrast to the much lighter yellows or browns characteristic of the cyclohexene or stilbene reactions.

Effects of Amines. The retardation of the oxidation of cyclohexene by pyridine and the even greater retardation by 2,2′-bipyridyl must be attributed to the formation of relatively unreactive amine complexes (**11**) of the osmium(VI) ester intermediates. The alternative hypothesis that the amines retard the cyclohexene reaction by diminishing the free OsO_4 concentration is contradicted by the observations that these amines accelerate the stoichiometric addition of osmium tetraoxide to alkenes.[5,7,12,13] The resistance of amine complexes of osmium(VI) esters to oxidation is in accord with the observations that pyridine and especially 2,2′-bipyridyl complexes of these esters are stable compounds.[7,13,14,32]

The lack of effect of pyridine on the rate of oxidation of α-pinene or of cyclohexene in the presence of α-pinene is consistent with the possibility that both processes involve 2:1 diol/osmium(VI) esters (**5**) and that these do not complex with pyridine.

The fact that triethylamine only slightly retards the reaction of either alkene provides assurance that the trimethylamine evolved in the reaction probably did not have a gross effect on the kinetics. Even so, the amount of trimethylamine escaping from the solution, which depends on the void volume of the container and leakiness of the seal, could lead to some minor differences. This as well as other unidentified variables make it impossible to compare sets of data from one table with those in another.

It would have been desirable to measure the production of diol as well as the consumption of alkene, but gas chromatographic analyses for diols and α-hydroxy ketones were relatively difficult and somewhat erratic. We have never observed the α-hydroxy ketone production to approach that of diol and consider this potential source of error in our kinetics to be minor.

Conclusions

The observed kinetics require that the mechanism of the osmium tetraoxide catalyzed reactions of α-pinene and cyclohexene with trimethylamine *N*-oxide involve oxidation of a relatively substitution-inert osmium(VI) ester to a substitution-labile osmium(VIII) species in the rate-determining step. Reaction of osmium(VIII) with the alkene to form osmium(VI) ester must be rapid.

The observation that the trimethylamine *N*-oxide directly attacks osmium(VI) esters is in accord with earlier findings that amine oxides are superior to other oxidizing agents for preparative purposes.[1,2] If the oxidizing agent merely converted inorganic osmium(VI) to osmium(VIII), the differences in performance between different oxidizing agents would be difficult to rationalize.

Pyridine and similar amine additives greatly retard the reaction of cyclohexene, and for that reason these additives are undesirable for preparative reactions involving relatively unhindered alkenes. Pyridine promotes the reaction of α-pinene enough to provide significant shortening of reaction time, and our results indicate a beneficial effect on the diol to α-hydroxy ketone ratio. Higher concentrations of trimethylamine *N*-oxide also appear to be beneficial for suppressing overoxidation of α-pinene to α-hydroxy ketone.

Reactions in which α-pinene is present appear to involve a catalytic cycle having hydrolytically stable pinanediol osmium(VIII) ester **4** as the active oxidizing agent and osmium(VI) bis(diol esters) **5** as the major osmium species. The relative slowness of osmium tetraoxide catalyzed oxidations of highly substituted alkenes may be attributed to the intermediacy of bis(diol esters) resembling **5**, which are sterically hindered at osmium and provide opportunities for other modes of oxidative attack leading to side products.

Acknowledgment. We thank NATO for grant No. 038.80 and the National Science Foundation for grant No. CHE8400715.

Registry No. **1**, 7785-70-8; **2**, 18680-27-8; **2** (ketone), 1845-25-6; **7**, 110-83-8; **10**, 1792-81-0; Me_3NO, 1184-78-7; O_sO_4, 20816-12-0; Et_3N, 121-44-8; *trans*-stilbene, 103-30-0; (+)-hydrobenzoin, 52340-78-0; 2,2′-bipyridyl, 366-18-7; cholesterol, 57-88-5.

---

[32] (a) Daniel, F. B.; Behrman, E. J. *J. Am. Chem. Soc.* **1975**, *97*, 7352–7358. (b) Chang, C. H.; Beer, M.; Marzilli, L. G. *Biochemistry* **1977**, *16*, 33–38.

Notes

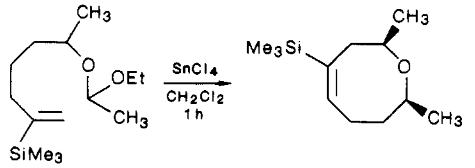
Preparation of Cyclic Ethers via a Transacetalization–Cationic Cyclization Sequence

Nikola A. Nikolic, Elizabeth Gonda,
C. P. Desmond Longford, Nancy T. Lane, and
David W. Thompson*

Department of Chemistry, College of William and Mary, Williamsburg, Virginia 23185

Received July 12, 1988

There is current interest in the preparation of cyclic ethers by way of Lewis acid promoted carbon–carbon bond-forming cyclizations of unsaturated acetals. An illustrative example reported by Overman et al.[1] of the facility and selectivity of these reactions is shown in eq 1



(1)

where the cyclization proceeds rapidly under mild conditions to give essentially a single diastereomeric eight-membered cyclic ether. Itoh,[2] Kay,[3] Kocienski,[4] Overman,[5]

---

[1] Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516.

0022-3263/89/1954-2748$01.50/0