downshift in $\nu$(Fe–O) and implies a substantial weakening of the Fe–O linkage. Finally, it should be pointed out that Spiro and co-workers have shown that conversion of vandyloctaethylporphine to the corresponding radical leads to an *upshift* of $\nu$(V–O) of 13 cm$^{-1}$.[13] We note that this latter complex forms an "$a_{1u}$-like" radical, whereas (OFe)TMP$^{\bullet+}$ and HRP-I are considered to be "$a_{2u}$-like" radicals.[8c,14] While further studies will be needed to investigate this issue in detail, the weakening of Fe–O in "$a_{2u}$-like" and strengthening in "$a_{1u}$-like" systems may prove to hold generally, as was noted in our recent work on HRP-I.[2d]

(13) Oliver Su, Y.; Czernuszewicz, R. S.; Miller, L. A.; Spiro, T. G. *J. Am. Chem. Soc.* **1988**, *110*, 4150-4157.

(14) Browett, W. R.; Gasyna, Z.; Stillman, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 3633-3640.

(15) The extreme photolability of this species in the presence of methanol prevented us from obtaining good quality spectra of the nonphotolyzed material. Further experiments to obtain this spectrum are planned.

# Kinetic Role of the Alkaloid Ligands in Asymmetric Catalytic Dihydroxylation

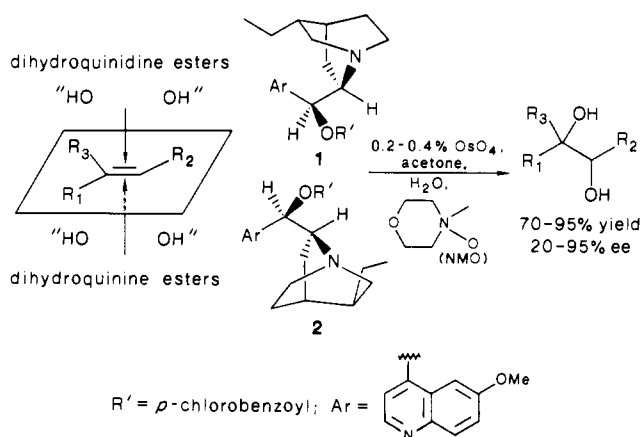Eric N. Jacobsen, Istvan Marko, Marcia B. France, John S. Svendsen, and K. Barry Sharpless*

*Department of Chemistry*
*Massachusetts Institute of Technology*
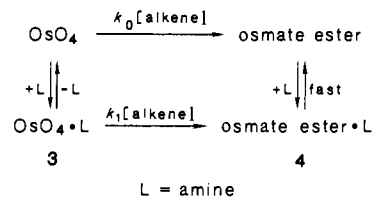*Cambridge, Massachusetts 02139*

Simple ester derivatives of dihydroquinidine (**1**) and dihydroquinine (**2**) play a complex role as ligands in the osmium-catalyzed dihydroxylation process (Scheme I).[1] In addition to imparting fair to high levels of asymmetry into the diol products, these *cinchona* alkaloid ligands accelerate the rate of addition of olefins to OsO$_4$ by 1-2 orders of magnitude. A major current research goal is to determine the various interactions which occur between the amine ligands and the different osmium species present in the catalytic cycle. Specific aspects which we address in the present study include (a) the number of alkaloid ligands present in the rate-limiting and ee-determining step(s); (b) the role of amines in the reoxidation/hydrolysis steps; and (c) the level of alkaloid required to achieve optimal enantioselectivities. We find that due to the ligand-acceleration phenomenon, ee maximization takes place with extremely low levels of alkaloid, well below the levels required to achieve rate saturation. The kinetic basis for this observation is described.

The number of alkaloid ligands present in the olefin addition step is a crucial mechanistic question, for this is the step in which both the asymmetric induction and the rate acceleration arise. Osmium tetroxide forms coordinatively saturated 18-electron 1:1 complexes with a variety of 3° amines ($K_{eq} = 10$–$50$ M$^{-1}$ at 25 °C in toluene or acetone/water (10:1) for the derivatives of **1** and **2** we have examined),[2] and no evidence has ever been obtained

(1) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(2) Binding constants were determined from Scatchard plots or from Benesi–Hildebrand plots of UV–vis data. While derivatives of **1** and **2** each contain two different amine moieties, solution and solid-state studies of OsO$_4$·alkaloid complexes show that binding occurs exclusively through the quinuclidine N and that chelation by coordination of the quinoline N is geometrically impossible. Details of our structural studies will be reported separately: Jacobsen, E. N.; Lippard, S. J.; Markó, I.; Pulla Rao, Ch.; Sharpless, K. B.; Svendsen, J. S., Manuscript in preparation.

**Scheme I**



$R' = p$-chlorobenzoyl; Ar =

**Scheme II**



$$OsO_4 \xrightarrow{k_0[\text{alkene}]} \text{osmate ester}$$

$$OsO_4 \cdot L \xrightarrow{k_1[\text{alkene}]} \text{osmate ester} \cdot L$$

L = amine

by us or by others[3] for a bis-amine adduct (formally a 20-electron complex). On the other hand, stoichiometric olefin oxidations by OsO$_4$ in the presence of pyridine or ammonia, the only kinetically well-characterized amine-promoted osmylation systems described in the literature, have been shown to obey rate laws with a second-order amine component.[3a,b] In addition, Tomioka and Koga recently proposed a stereochemical model for their stoichiometric asymmetric osmylations in which the rate-limiting and asymmetry-inducing step involves attack, intramolecularly by virtue of chelation, of a second amine.[4] Therefore the question of whether one or two molecules of the alkaloid ligand are involved in these systems was examined.

The rate expression predicted for the pathway outlined in Scheme II involving a single amine ligand is

$$\Delta k = k_2 - k_0 = \frac{(k_1 - k_0)K_{eq}[\text{amine}]}{K_{eq}[\text{amine}] + 1} \tag{1}$$

where $K_{eq}$ is the binding constant between amine and OsO$_4$, and $k_2$ is the measured second-order rate constant.[5] Kinetic measurements of both the stoichiometric reaction and the catalytic reaction were performed for nine different olefins with varying concentrations of **1** or **2**.[6] Quinuclidine was also examined as a model ligand. In all cases, the relationship in eq 1 was obeyed, as plots of $1/\Delta k$ vs $1/[\text{alkaloid}]$ were strictly linear, rigorously establishing the involvement of only a single amine ligand in the rate/turnover limiting step. Enantiomeric excesses obtained in the catalytic reaction also approached a maximum value with increasing amine concentration, obeying the equation

$$ee = \frac{(k_f - k_s)K_{eq}[\text{amine}]}{k_1 K_{eq}[\text{amine}] + k_0} \tag{2}$$

where $k_f$ and $k_s$ are the rate constants for the major and minor enantiomeric pathways, respectively.[5] This behavior, too, is
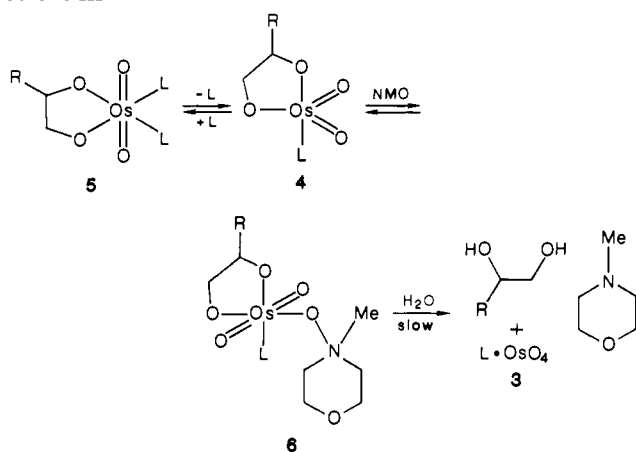
(3) (a) Clark, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425. (b) Burton, K. *Biochem. J.* **1967**, *104*, 686. (c) Griffith, W. P.; Rossetti, R. *J. Chem. Soc., Dalton Trans.* **1972**.

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

(5) Derivation of eq 1 and 2 is provided as Supplementary Material.

(6) Kinetics of the stoichiometric reaction were measured by UV–vis spectroscopy under pseudo-first-order conditions with limiting OsO$_4$. In the catalytic reaction, rates were determined by monitoring changes in starting olefin concentration by GC.

**Scheme III**





**Figure 1.** Plot of the concentration of alkaloid ligand **1** vs observed rate constant $k_{obsd}$ (●) and % ee (▲) for the catalytic dihydroxylation of *trans*-stilbene. Conditions: 25 °C, $[OsO_4]_0 = 3.8 \times 10^{-4}$ M, $[NMO]_0 = 0.2$ M, $[stilbene]_0 = 0.1$ M.

consistent with only a single amine ligand present in the ee-determining step.

Attention thus far has focused on the addition step (Scheme II), which is, of course, common to both stoichiometric and catalytic osmylation processes. We now consider the equilibria and reactions which are peculiar to the catalytic system. The events proposed in Scheme III taken together with those in Scheme II constitute a closed catalytic cycle along with its associated nonproductive equilibria.

While a single alkaloid ligand is involved in the addition reaction, at elevated amine concentrations the resulting osmate ester intermediate **4** appears to bind a second ligand (in a kinetically fast step) to afford a coordinatively saturated 18-electron complex. Direct measurement of the second binding constant was possible by UV–vis spectroscopy, with observed values lying in the range of $K_2 = 0.8$–$2.1$ $M^{-1}$ at 25 °C in acetone/$H_2O$, depending on the identity of the olefin precursor. Osmate esters form octahedral bis-amine complexes with pyridine[7] as well as with several chelating amines, Tomioka's chiral linked bis-pyrrolidine ligand being an important, structurally characterized example.[4] We have found that such coordinatively saturated osmate ester complexes are completely unreactive toward *N*-methylmorpholine *N*-oxide (NMO) in acetone/$H_2O$ at 25 °C, so it appears that an open coordination site on the Os(VI) ester is required to achieve reoxidation/hydrolysis. Chelating amines evidently shut down this reaction pathway because the entropically favored second binding constant is very high. Similarly, bis-alkaloid adducts become the predominant osmate ester species in the presence of high concentrations of **1** or **2**, with the result that the rate of catalysis is retarded as the reoxidation/hydrolysis phase of the catalytic cycle is inhibited and becomes turnover-limiting.[8,9] Low levels of **1** or **2** do not inhibit the reoxidation/hydrolysis of osmate esters; in fact we have observed that process to be somewhat accelerated (by a factor of ≈2 or 3) relative to the alkaloid-free system. Reoxidation/hydrolysis therefore appears to be accessible from an osmate ester bound to a single alkaloid ligand (e.g., **4** and/or **6**).

Further mechanistic insight was provided by kinetic analysis of the decomposition of the osmate ester of styrene in the presence of varying concentrations of NMO. These studies revealed sat-
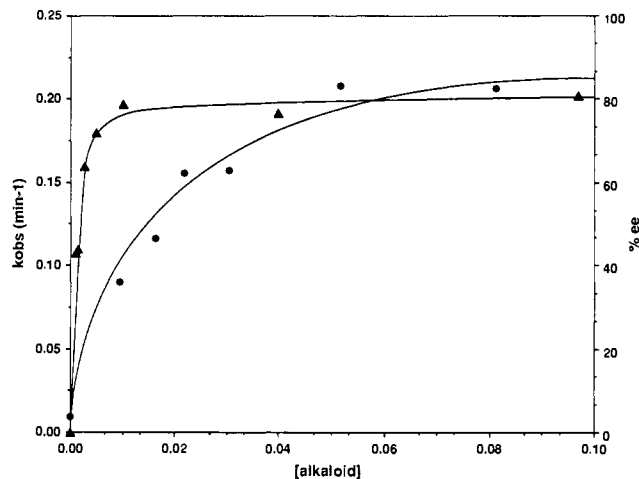
uration dependence on this stoichiometric oxidant, indicative of the formation of an $Os^{VI}$·NMO intermediate (such as **6**) on the reaction pathway. We propose that NMO reversibly binds to the alkaloid·osmate ester complex **4** and that reoxidation/hydrolysis takes place from the resulting intermediate **6**. The mechanism for the reoxidation/hydrolysis of osmate esters outlined in Scheme III accommodates our experimental data. A concentration window for alkaloid therefore exists for which the rate of catalysis is highest. Enough alkaloid is required to achieve rate saturation in the addition step, but too much alkaloid inhibits the reoxidation/hydrolysis steps which are also an essential part of the catalytic cycle.

Given that both the enantioselectivity and the rate acceleration are due to the formation of the $OsO_4$·amine complex, we initially believed that the alkaloid concentration necessary to achieve rate saturation in the addition step would be the same as that required for the ee to level off at a maximum value. However, as depicted graphically in Figure 1, the ee obtained for stilbene (as well as for other olefins examined) approaches a maximum value at alkaloid concentrations which are well below those which produce rate saturation.[10] This phenomenon is actually an artifact of ee being defined as a ratio of rates and can be explained by comparison of eq 1 and 2. The rate becomes independent of ligand concentration (i.e., saturates) when $K_{eq}[amine] \gg 1$. Inspection of eq 2 shows that the ee of the reaction reaches saturation when $k_1 K_{eq}[L] \gg k_0$, that is when $(k_1/k_0)K_{eq}[L] \gg 1$. Thus, when plotted as a function of alkaloid concentration, *the enantiomeric excess of the reaction approaches its maximum value* $k_1/k_0$ *times sooner than does the rate, with* $k_1/k_0$ *being the direct measure of the ligand acceleration effect* (*Scheme II*).

While a nonlinear relationship between rate and ee is not unknown,[11] this is nonetheless an extremely practical feature of asymmetric ligand-accelerated reactions and to our knowledge has never been described.[12] Since eq 1 and 2 are general for any

(7) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75. Criegee, R.; Marchand, B.; Wannowius, B. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.

(8) In our initial report[1] we stated that, at least in the case of styrene, the alkaloid ligands did not appear to interfere with the turnover steps in the catalytic cycle. We have since found that, at high (>0.5 M) concentration of alkaloid, rate inhibition does in fact occur. Other olefins, such as stilbene or β-methylstyrene, display an onset of rate inhibition at lower alkaloid concentrations (≈0.2 M).

(9) We also originally reported that quinuclidine inhibited catalyst turnover. In fact, at very low concentrations (≤8 × 10⁻³ M) quinuclidine enhances the rate of catalysis in a manner analogous to the behavior of **1** and **2**. The onset of inhibition at lower ligand concentration (≈1 × 10⁻² M) in the case of quinuclidine is attributable to a substantially higher second binding constant for this amine, as would be expected on steric grounds.

(10) It must be noted that in the context of the catalytic cycle the rate saturation in fact corresponds to a rate maximization due to the drop-off in rate at higher ligand concentrations. With regard to this discussion, however, we can disregard the kinetic contribution of the reoxidation/hydrolysis steps since the addition step is usually turnover-limiting in the ligand concentration range in Figure 1.

(11) (a) A similar, although inverse, correspondence between hydrogen concentration and ee has been observed in asymmetric hydrogenations. Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. (b) As pointed out by a referee, any relationship between ee and rate should not be interpreted to bear any physical significance. However, while these two parameters have different units, they are the ones of greatest interest to the synthetic chemist planning on running an asymmetric reaction, and we believe it is useful to show how they correspond as a function of alkaloid concentration. From a kinetic perspective, it may be more valid to compare $k_{obsd}$ with the mole fraction of the major enantiomer or $k_{obsd}$ with $k_f$ and $k_s$. Plots of these parameters are included in the Supplementary Material.

reaction analogous to the one in Scheme II, it is also expected to occur in other known ligand-promoted systems.[13] The implications for the OsO$_4$/alkaloid system are that low levels of alkaloid may be employed with nearly optimal enantioselectivity. Typical $k_1/k_0$ values lie in the range of 15–50 at 25 °C, and these increase substantially (up to ≈100 for styrene) at 0 °C. Further synthetic and mechanistic implications of ligand-accelerated catalysis are under current investigation.[14]

**Supplementary Material Available:** Derivation of eq 1 and 2 and Figures S1 and S2 containing plots of the concentration of **1** vs $k_{obsd}$ and mole fraction of the major diol enantiomer (Figure S1) and $k_{obsd}$, $k_f$, and $k_s$ (Figure S2) for the catalytic dihydroxylation of *trans*-stilbene (5 pages). Ordering information is given on any current masthead page.

(12) Blaser and co-workers at Ciba-Geigy have recently observed a remarkably similar effect in *cinchona* alkaloid-modified heterogeneous platinum hydrogenation catalysts for the asymmetric reduction of α-keto esters. Blaser, H. U.; Jalett, H. P.; Monti, D. M.; Reber, J. F.; Wehrli, J. T. Heterogeneous Catalysis and Fine Chemicals. *Stud. Surf. Sci. Catal.* **1988**, *41*, 153.

(13) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247. Wynberg, H.; Staring, E. C. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6072. Smaardijk, A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(14) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* In press.

## Reductive Cyclizations. The Electrochemical Generation of Cyclopropanes via the Double Intramolecular Cyclization of Initially Formed Vinyl Radicals

Paul G. Gassman* and Changjin Lee

*Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455*

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Numerous examples of the intramolecular addition of alkyl radicals to carbon–carbon double bonds have appeared in the literature.[1] However, much less is known about the analogous behavior of vinyl radicals.[2] The facile reduction of enol phosphates[3] and the alkylation[4] of β-dicarbonyl enol phosphates with dialkyl cuprates indicates that vinyl radicals derived from β-

(1) For some pertinent reviews, see: Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553. Stork, G. In *Selectivity: A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; Verlag Chemie: Basel, 1984; p 281. Hart, D. J. *Science* **1984**, *223*, 883. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(2) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986**, *27*, 4525. Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3720. Marinovic, H. N.; Ramanathan, H. *Tetrahedron Lett.* **1983**, *24*, 1871. Knight, J.; Parsons, P. J.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, *78*. Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *Tetrahedron Lett.* **1985**, *26*, 957. Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

(3) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145.

**Table I.** Products and Yields from the Double Reductive Cyclization of β-Dicarbonyl Enol Phosphates

| example no. | starting material | product | % yield |
|---|---|---|---|
| (1) | | | 58 |
| (2) | | | 55 |
| (3) | | | 38 |
| (4) | | | 63 |
| (5) | | | 53 |
| (6) | | | 51 R$_1$ = H, R$_2$ = CH$_3$ <br> 10 R$_1$ = CH$_3$, R$_2$ = H |
| (7) | | | 41 R$_1$ = H, R$_2$ = CH$_3$ <br> 18 R$_1$ = CH$_3$, R$_2$ = H |
| (8) | | | 26 R$_1$ = CO$_2$C$_2$H$_5$, R$_2$ = H <br> 22 R$_1$ = H, R$_2$ = CO$_2$C$_2$H$_5$ |

phosphonylated α,β-unsaturated carbonyl compounds can be generated with ease. However, when β-dicarbonyl enol phosphates were reductively alkylated in the presence of pendant olefinic linkages, no intramolecular addition occurred.[4,5] As part of our continuing interest in reductive cyclization reactions,[6] we have studied the electrochemical reduction of a series of 1,3-dicarbonyl enol phosphates bearing attached olefinic linkages. We now wish to report that, under controlled potential conditions, a variety of 1,3-dicarbonyl enol phosphates[7] were reduced to give reactive intermediates which, in a double cyclization process, gave bicyclo[*n*.1.0]alkanes where *n* was 3 or 4.

In a typical procedure, the β-dicarbonyl enol phosphate, **1**, in
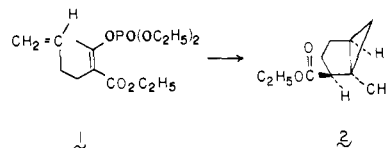
dimethylformamide, was added via syringe to an H-cell which contained a platinum gauze anode, a mercury pool cathode, a saturated calomel reference electrode, and a solution of 0.2 M tetra-*n*-butylammonium perchlorate in dimethylformamide, under a nitrogen atmosphere. The potential of the cathode was maintained at −2.05 V vs SCE, and **1** was added to the cathodic compartment at a rate sufficient to maintain the current between

(4) (a) Alderdice, M.; Spino, C.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1643. (b) Sum, F. W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431. (c) Sum, P. E.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1475. Lombardo, D. A.; Weedon, A. C. *Tetrahedron Lett.* **1986**, *27*, 5555.

(5) Assuming that a vinyl radical was generated as an intermediate, these data indicate that alkylation is much more facile than intramolecular addition.

(6) Gassman, P. G.; Rasmy, O. M.; Murdock, T. O.; Saito, K. *J. Org. Chem.* **1981**, *46*, 5455.

(7) Satisfactory elemental analyses and/or exact mass molecular weights have been obtained on all new compounds. All compounds exhibited IR, $^{13}$C NMR, and $^1$H NMR spectra which were consistent with the assigned structures.