Mechanistic Study of the Jacobsen Asymmetric Epoxidation of Indene

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The asymmetric epoxidation of indene using aqueous NaOCl, catalyzed by Jacobsen's chiral manganese salen complex, provides indene oxide in 90% yield and 85−88% enantioselectivity. The axial ligand, 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO), increases the rate of epoxidation without affecting enantioselectivity and also stabilizes the catalyst. These two effects afford a reduction in catalyst loading to <1%. The turnover-limiting step in the catalytic cycle has been determined to be the oxidation of the manganese catalyst, based on reaction orders of 0 in indene and 1 in catalyst and also based on the dependence of the rate on the hypochlorite concentration. In the presence of the ligand P_3NO, this rate-limiting oxidation occurs in the organic phase with HOCl as oxidant, as shown by the dependence of the rate on the NaOH concentration. P_3NO assists the transport of HOCl to the organic layer as demonstrated by titration studies and by measuring the rates of oxidation of a redox indicator, diphenylbenzidine. On the other hand, stirring speed studies indicate that, in the absence of the ligand, oxidation occurs at the interface. Thus, the axial ligand plays at least two roles in the epoxidation of indene: it stabilizes the catalyst, presumably by ligation, and it increases the epoxidation reaction rate by drawing the active oxidant, HOCl, into the organic layer.

Introduction

The versatility of asymmetric epoxides as intermediates in organic synthesis has sparked considerable effort in their synthesis over the past 2 decades. In the 1970s Sharpless[1] and others[2] discovered that achiral epoxides could be generated from alkenes using metal catalysts and alkyl peroxides. As an extension of this work, the first significant breakthrough in realizing asymmetric epoxidations came in 1980 when Sharpless and Katsuki reported that the reaction of allylic alcohols with *t*-BuOOH, Ti(O-*i*-Pr)$_4$, and (+)- or (−)-diethyl tartrate provided high yields of epoxides with enantioselectivities up to 90%.[3] Soon after, Groves discovered that chiral transition metal porphyrin complexes were able to epoxidize styrenes with enantioselectivities up to 51%.[4] Building on the work of Kochi[5] and Burrows[6] in the 1980s, who used achiral manganese salen catalysts for epoxidations, Jacobsen reported in 1990 that unfunctionalized alkenes could be epoxidized with high enantioselectivities using chiral manganese salen catalysts.[7] High ee's, straightforward catalyst preparation, use of simple oxidants such as aqueous hypochlorite, and success of the method with a wide variety of olefins have made the preparation of chiral epoxides practical and efficient using the Jacobsen protocol.[8]

The mechanism of the transition metal-catalyzed epoxidation has been the subject of speculation for the last decade. Recent controversy has centered on whether the reaction takes place as a direct transfer of the oxygen from the metal to the substrate or whether an intermediate oxametallocycle is formed. The hypothesis for the oxametallocycle was first advanced by Collman and co-workers and was based on kinetic measurements.[9a,b] The reactions were independent of olefin concentration, yet different olefins exhibited variable epoxidation rates. This suggested that the olefin and catalyst reversibly formed an intermediate that broke down in the rate-determining step, and as expected from this reasoning, the reactions followed Michaelis−Menten kinetics.[9a,b] However, the conclusions from this paper were later withdrawn as results from further experimental work demonstrated poor mass balance and instability of the oxidant under the conditions used for the kinetic experiments.[9b,c] On the other hand, Norrby and colleagues recently argued that the oxetane was a viable intermediate based on theoretical considerations,[10] and Katsuki observed nonlinearity in Eyring plots for the epoxidation of alkenes using modified chiral manganese salen catalysts,[11] which is consistent with an intermediate on the reaction pathway. However, these results were questioned by Jacobsen,[12] who noted that the variation in ee is less than 10%, making interpretation difficult. On the other hand, Jacobsen has demonstrated a linear temperature/ee

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(10) Norrby, P.-O.; Linde, C.; Akermark, B. *J. Am. Chem. Soc.* **1995,** *117,* 11035−11036.

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(12) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Hansen, K. B.; Jacobsen, E. N. Private communication.

relationship over a 100 °C range, which argues against an intermediate in the reaction.[12]
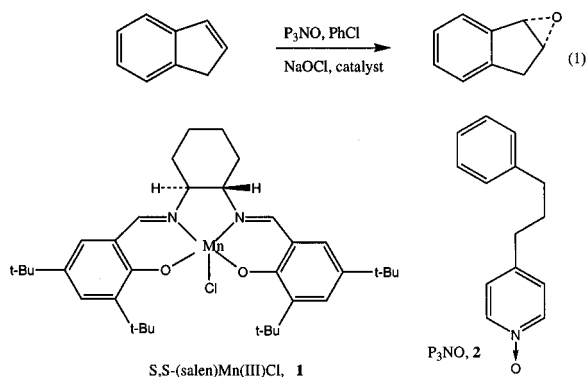
Another curious and ill-defined aspect of these epoxidations is the role of the cocatalysts, which include variously substituted pyridines, imidazoles, and *N*-oxides, that accelerate the reactions and sometimes increase the enantioselectivities. These additives are generally thought to act as axial ligands on the transition metal catalyst, which help to activate the catalyst either toward oxidation or toward reactivity with the olefin. Jacobsen has recently presented convincing evidence that the *N*-oxides behave as axial ligands, since the catalyst with a strapped *N*-oxide ligand is more active that the standard catalyst and is no longer affected by added *N*-oxide ligands.[12]

The asymmetric epoxidation of indene is a key step in the formation of 1,2-aminoindanol, a component of the HIV-protease inhibitor CRIXIVAN. Jacobsen reported that indene could be epoxidized in the presence of 4-phenylpyridine *N*-oxide with 1.5 mol % of the chiral manganese salen catalyst, providing an 80% yield and 84% ee of chiral indene oxide.[13] Recently, Senanayake and co-workers found that the use of 4-(3-phenylpropyl)-pyridine *N*-oxide as ligand allowed for a more reproducible reaction and the catalyst loading could be reduced to 0.4 mol %.[14]

The present contribution describes mechanistic studies of the asymmetric epoxidation of indene and the role of the *N*-oxide. The *N*-oxide is involved both in accelerating the epoxidation and in stabilizing the catalyst and, unexpectedly, in transporting the oxidant HOCl into the organic layer.

Results and Discussion

Reaction Overview. The standard epoxidation of indene (eq 1) is carried out in a two-phase mixture that includes (S,S)-(salen)Mn^{III}Cl catalyst (**1**), 4-(3-phenyl-propyl)pyridine *N*-oxide (P$_3$NO) (**2**), indene, and chlorobenzene as the organic components and 1.5 M aqueous sodium hypochlorite as the terminal oxidant. The cata-

lytic cycle is shown in Scheme 1. The optimum conditions for ee, yield, and productivity include the use of 0.75 mol % catalyst vs indene, 3 mol % P$_3$NO vs indene, 3 M indene in the chlorobenzene, and 1.5 M NaOCl in the aqueous phase; reaction is complete within 2.5 h at −5 °C with a yield of >90% and an ee of 85−88%. The ee values of the indene oxide taken at 0.5 h intervals
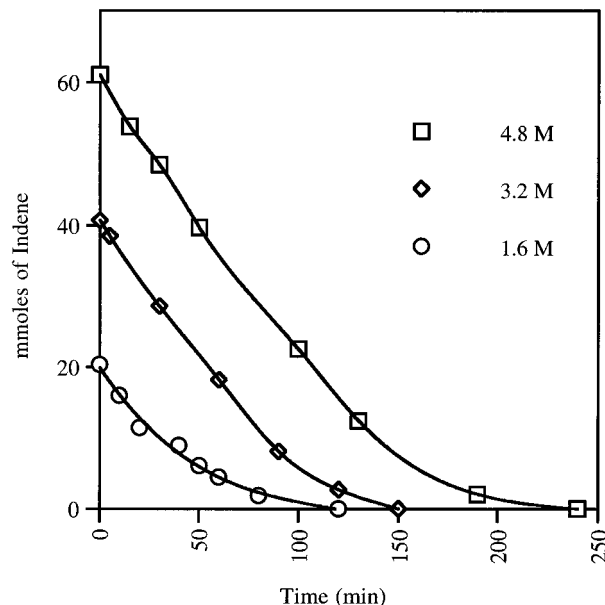
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Figure 1. Rate of epoxidation of indene with variable initial levels of indene. Reactions run with 25 mM catalyst and 100 mM P$_3$NO at 860 rpm, by method 2 as described in the Experimental Section.

Scheme 1. Catalytic Cycle for Epoxidation of Indene by Hypochlorite
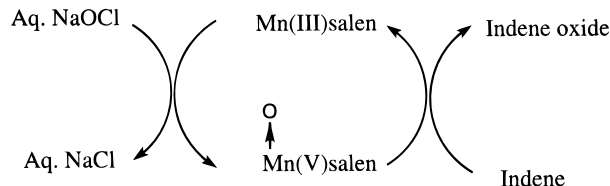
throughout the reaction were all measurably the same at 85−88%. All of the components of the reaction (indene, indene oxide, P$_3$NO, and catalyst) were monitored over the course of the reactions using both normal and reverse phase HPLC.

Since the catalyst degraded as the epoxidation reaction proceeded, it was vital to have in place an assay for the catalyst in order to interpret kinetic data. A normal phase HPLC assay was developed using a Whatman Partisil 10 PAC column, as described in the Experimental Section. Using this assay the catalyst levels were routinely determined in epoxidation experiments. The results are discussed in conjunction with the epoxidation kinetics in the following sections.
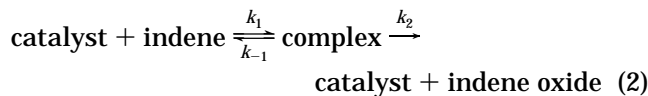
Reaction Orders. 1. Catalyst. Reactions run at variable catalyst levels indicated that the epoxidation is roughly first order in catalyst concentration.

2. Indene. A kinetic profile of indene concentrations for reactions run using 1.6, 3.2, and 4.8 M indene in chlorobenzene is shown in Figure 1. In each case, the catalyst (25 mM) and P$_3$NO (100 mM) levels were kept constant and the reaction was carried out at −5 °C. For each curve, the disappearance of indene was zeroth order for most of the reaction, with slowing only at the end. The abrupt disappearance of indene and the similarity in initial rates for the three concentrations examined were also consistent with an order of 0 for indene. The kinetic profile was also similar to those observed by Collman and co-workers for epoxidations of olefins using a manganese(III) porphyrin catalyst in a two-phase system with LiOCl as oxidant and a phase transfer agent.

They were able to fit their kinetic data to the Michaelis–Menton equation and determined K_m and V_{max} constants for several olefins.[9a,b] However, these results were subsequently retracted as further experimentation revealed that the hypochlorite was degrading under the conditions used for the kinetic experiments.[9c] In the event, we have been able to use the Michaelis–Menten kinetics (eq 2) to fit our data, with values of $K_m = (k_{-1} + k_2)/k_1 = 0.8$ M and $k_2 = 100$ h^{-1}.

$$\text{catalyst} + \text{indene} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex} \overset{k_2}{\longrightarrow}$$
$$\text{catalyst} + \text{indene oxide} \quad (2)$$

Using a kinetic model which takes into account the rate of catalyst degradation and avoids the steady state assumption for the complex, the values changed slightly to $K_m = 0.4$ M and $k_2 = 90$ h^{-1}. However, as discussed below, this validity of this model becomes a mute point, as we show that the rate-determining step is catalyst oxidation and therefore the kinetics can provide no information on steps occurring after the rate-determining step.

Effect of the *N*-Oxide P₃NO on Indene Epoxidation.

After surveying a wide range of additives for the epoxidation, Senanayake and co-workers found that the best results in terms of yield and conservation of catalyst were obtained with the lipophilic *N*-oxide **2**, termed P₃-NO.[14] Thus, this *N*-oxide was chosen for further investigations. A series of epoxidations was run using P₃NO at levels varying from 0 to 10 equiv vs the catalyst. The reaction profiles for indene epoxidation are shown in Figure 2a. For these reactions, the P₃NO, Mn salen catalyst, chlorobenzene, and indene were mixed at ambient temperature such that all solids dissolved. This solution was then cooled to −10 °C and added to the hypochlorite solution at −5 °C to initiate the reaction. Although the P₃NO was supersaturated in the mixture when P₃NO/catalyst > 1, it remained in solution for the duration of the experiments except for the case where P₃NO/catalyst = 10, where precipitation occurred after 30 min of reaction.[15] The curves in Figure 2a indicate that the epoxidation rate is increased with an increasing level of P₃NO. With 1 equiv or less of P₃NO, an initial burst is followed by a slower conversion to indene oxide, while with greater than 1 equiv the reactions stay near zeroth order in indene for most of the reaction. The enantioselectivity was unchanged within experimental error at 85−88%, indicating that the ee is not dependent on the P₃NO level. In another experiment, the reaction was started with no P₃NO present, then 4 equiv of P₃-NO vs catalyst was added at 3 h, and the epoxidation accelerated immediately (Figure 3). Thus, the effect of P₃NO on the indene epoxidation was felt instantaneously.

P₃NO also has a significant effect on the stability of the catalyst, as shown for the same set of reactions in Figure 2b. These data are consistent with a model in which P₃NO serves as an axial ligand for the catalyst, as depicted in **3**, where the ligand activates the catalyst for the epoxidation and also stabilizes the catalyst.

(15) If P₃NO is not dissolved at room temperature but added first to the cold aqueous NaOCl, the initial concentration of P₃NO is 6 mg/mL, which is equivalent to 1 mol/mol of catalyst at a catalyst loading of 0.75% vs indene. As the reaction proceeds, the concentration increases, since the indene oxide product increases its solubility. The kinetics in this case are somewhat different than those in which all P₃NO is dissolved initially, and interpretation is more complex since the level changes throughout the reaction.
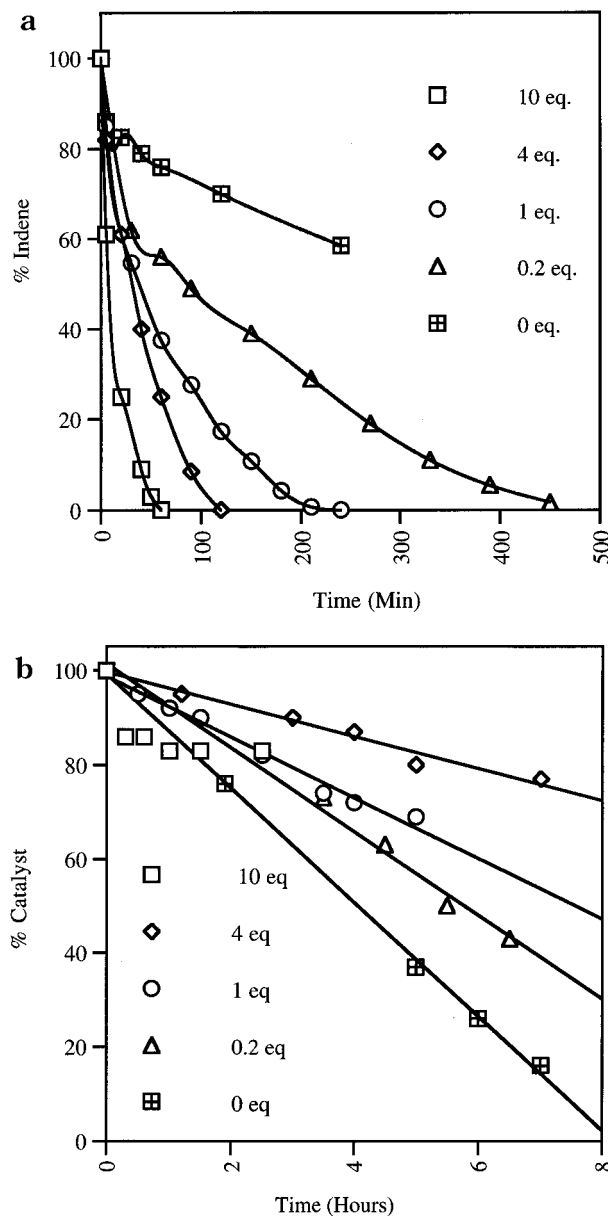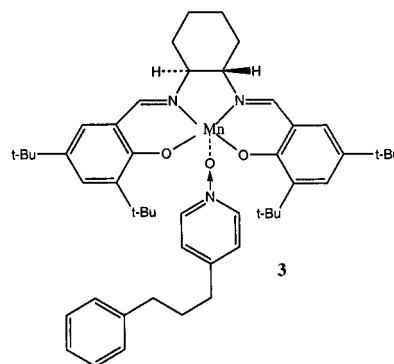
Figure 2. (a) Effect of variable P₃NO levels on the rate of indene epoxidation. Reactions run with 0.75 mol % catalyst vs indene at 860 rpm, by method 1 as described in the Experimental Section. (b) Effect of variable P₃NO levels on the rate of catalyst degradation.

However, experiments discussed below suggest that this is not the only role of P₃NO.

Effect of Hydroxide and Hypochlorite Concentrations.
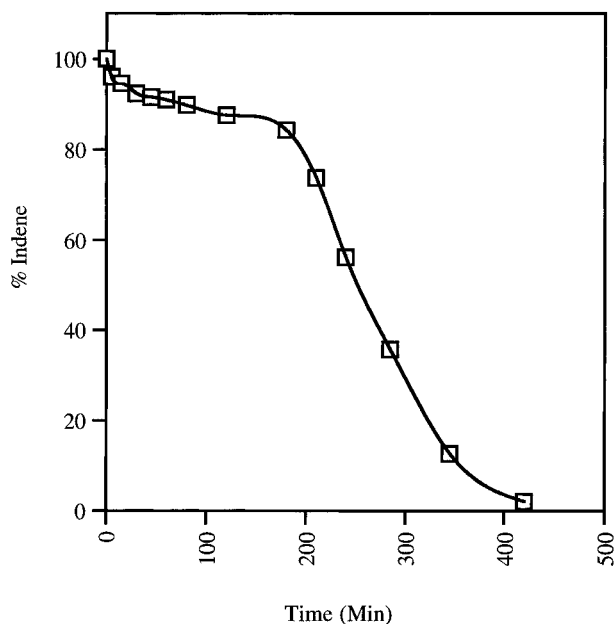
Prepared by reaction of molecular chlorine

Figure 3. Effect of addition of P_3NO to an indene epoxidation at 3 h time point. Conditions: catalyst, 0.75 mol % vs indene; stirring rate, 420 rpm; 3 mol % P_3NO added as a solid at 3 h point.
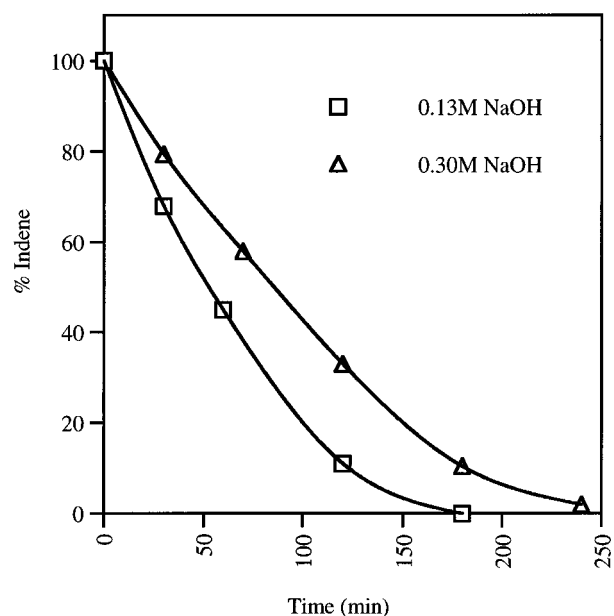

Figure 5. Effect of variation in catalyst, NaOH, and NaOCl levels on the rate of indene epoxidation in the absence of P_3-NO.

Figure 4. Effect of NaOH concentration on the rate of indene epoxidation. Reactions run with 0.75 mol % catalyst and 3 mol % P_3NO, both vs indene, at 860 rpm, by method 2 as described in the Experimental Section.

with aqueous NaOH, commercial aqueous sodium hypochlorite contains residual levels of hydroxide that vary among sources. The commercial material from Spectrum Chemicals consistently contained 0.13 M NaOH in the 1.5−1.6 M NaOCl. The effects of the hypochlorite and hydroxide concentrations on the epoxidation were determined both with and without P_3NO present. Figure 4 illustrates the effect of increasing the hydroxide concentration from 0.13 to 0.3 M in the presence of 4 equiv of P_3NO vs catalyst at a catalyst level of 0.75 mol % vs indene. At −5 °C the initial reaction rate was slowed by 1.7-fold when the NaOH concentration was increased. When the concentration of NaOCl was cut in half, but the NaOH kept constant at 0.13 M (by diluting NaOCl
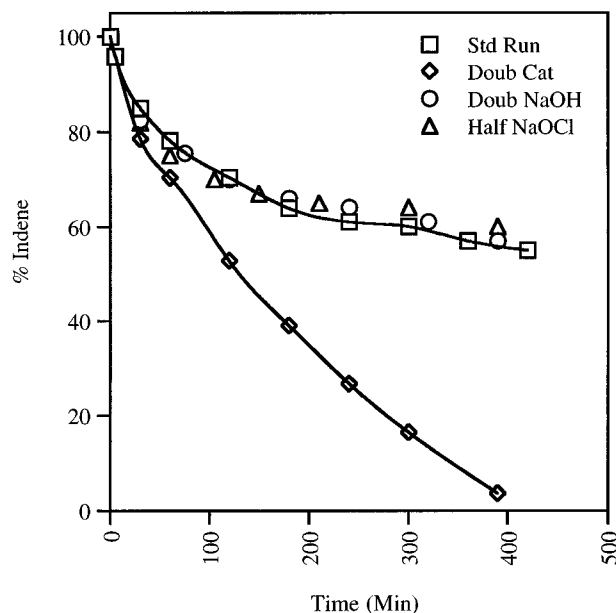
with water and then adding back NaOH), the reaction rate slowed by roughly 2-fold. In another experiment, both the NaOCl and NaOH concentrations were halved (by simply diluting with water), and this had no effect on the epoxidation rate. These data can be readily rationalized based on the equilibrium equations for HOCl and water dissociation (eqs 3, 4). They demonstrate that the rate of the epoxidation is directly proportional to the amount of HOCl present, *i.e.*, that HOCl is involved in the rate-determining step. From eq 5, the HOCl concentration is inversely proportional to the hydroxide concentration, which is consistent with the reaction profiles shown in Figure 4 that show the reaction slows with increasing NaOH. The HOCl concentation is also

$$HOCl \underset{}{\overset{K_{eq}}{\rightleftharpoons}} H^+ + OCl^- \tag{3}$$

$$H_2O \underset{}{\overset{K_w}{\rightleftharpoons}} H^+ + OH^- \tag{4}$$

$$[HOCl] = \frac{K_w[H_2O][OCl^-]}{K_{eq}[OH^-]} \tag{5}$$

proportional to the OCl^- concentration, and we observe a rate decrease when the OCl^- concentration is decreased if the NaOH concentration is held constant. In addition, when OCl^- and HO^- are decreased proportionally, as occurs with just a simple water dilution, then eq 5 predicts that there will be no effect on the HOCl concentration, and this is consistent with the observation that diluting the NaOCl by one-half with water causes no rate effect.

In contrast to the above results, reactions in the absence of P_3NO behaved completely differently. As shown in Figure 5, variation in the concentrations of hydroxide and hypochlorite had essentially no effect on the rate of epoxidation. However, increasing the concentration of catalyst increased the rate. These results suggest that, in the absence of the *N*-oxide, the catalyst is still involved in the rate-determining step, but [HOCl] no longer controls the reaction rate. As discussed in the

next section, these data along with the stirring speed studies suggested that the reaction in the absence of P$_3$-NO occurs at the liquid−liquid interface.

In the presence of P$_3$NO the above results indicated that the reaction rate was dependent on the level of HOCl. Thus, the oxidation of catalyst must be the turnover-limiting step, as it is the only step in the cycle in which hypochlorite is involved. These data are consistent with the reaction orders in indene and catalyst discussed above. Since the oxidation of catalyst is turnover limiting, the amount of catalyst present should affect the rate, and we find an order in catalyst close to unity. On the other hand, the epoxidation of indene is not the rate-limiting step, so we would expect a zeroth-order dependence on indene, as observed. This hypothesis is also consistent with results reported by Jacobsen, who found that the epoxidation of styrene using manganese salen catalysts could be carried out at −78 °C when an organic oxidant such as m-CPBA is used.[16] In this case, oxidation in the homogeneous organic solution is fast and the epoxidation of the alkene must also be rapid since the reactions readily occur at −78 °C. Thus, if the oxidation of the catalyst is rapid, then the overall epoxidation can occur at low temperature. If the oxidation of catalyst is slow, as in the two-phase system with NaOCl as oxidant, then the overall catalytic cycle is slow and requires temperatures near 0 °C for a suitable reaction rate. Our kinetic results, however, provide no information regarding the oxametallocycle pathway. Since the limiting step in the catalytic cycle is catalyst oxidation, the kinetics provide no information on the other steps in the cycle.

Effect of Stirring Speed. Since the epoxidation is a two-phase reaction, possible interfacial reactions were probed by variation of the agitation speed. In the first set of experiments, shown in Figure 6a, the epoxidation in the presence of 0.75 mol % catalyst and 3 mol % P$_3$-NO (both vs indene) was conducted at speeds of 420, 860, and 2180 rpm. In the runs shown in previous figures, the agitation speed had always been 860 rpm, so we chose a speed above and below our standard conditions.

The results shown in Figure 6a reveal that the stirring speed has only a small effect on the rate of epoxidation in the presence of P$_3$NO. Moderately faster epoxidation at higher stirring speed indicated some reaction at the liquid−liquid interface. At 860 rpm the rates of both the epoxidation and the catalyst decomposition were essentially unchanged when Aliquat 336 (tricaprylmethylammonium chloride) (4 mol/mol of Mn salen catalyst) was included in the reaction mixture (not shown). This result ruled out rate-determining phase transfer of OCl$^-$ and confirmed that HOCl reacts in the slow step of the epoxidation rather than OCl$^-$.

In runs with P$_3$NO, the rate at which catalyst disappeared was measurably independent of the stirring speed, indicating that the catalyst was decomposing only in the organic phase (Figure 6b).

The effect of stirring speed in runs without P$_3$NO was quite different. Strong dependence of the epoxidation rate and the catalyst decomposition rate on the stirring speed indicated the importance of both reactions at the liquid−liquid interface, Figure 7. At the medium stirring speed of 860 rpm, the rates of both reactions were essentially unchanged when Aliquat 336 (4 mol/mol of
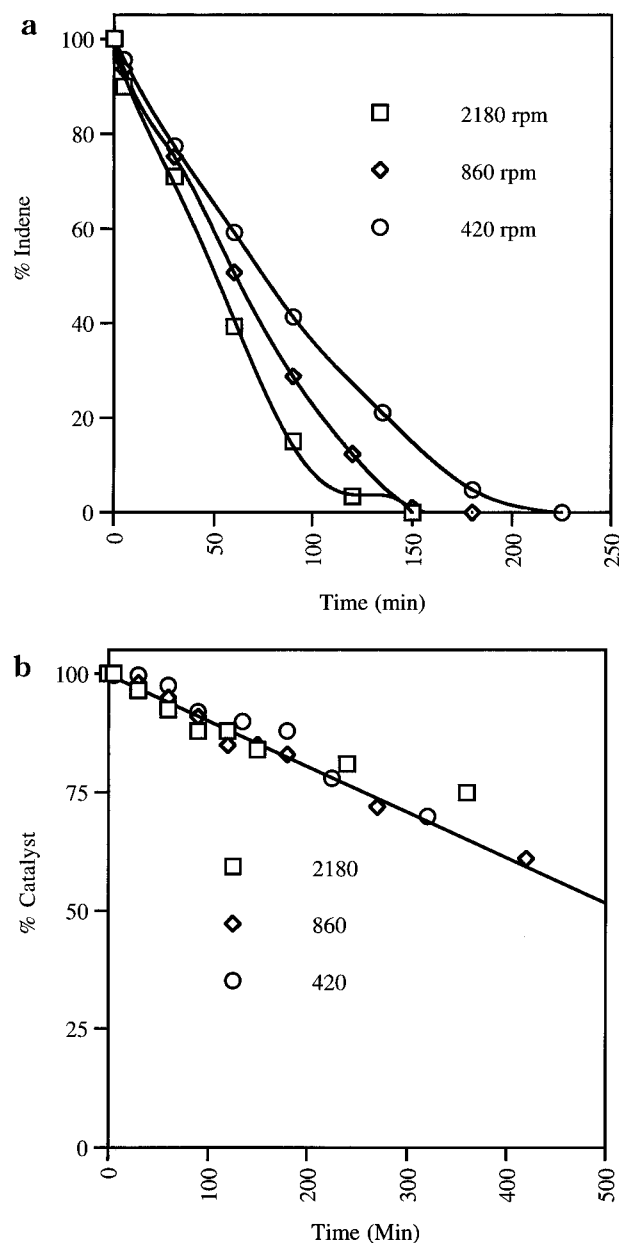
(16) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333−9334.

Figure 6. (a) Effect of stirring speed on the rate of indene epoxidation in the presence of P$_3$NO. Reactions run with 0.75 mol % catalyst and 3 mol % P$_3$NO, both vs indene, at 860 rpm, by method 2 as described in the Experimental Section. (b) Effect of stirring speed on the rate of catalyst degradation in the presence of P$_3$NO.

Mn salen catalyst) was included in the reaction mixture. Thus, rate-determining phase transfer of OCl$^-$ in either reaction was ruled out.

These data suggest that the turnover-limiting step in the epoxidation without P$_3$NO is a liquid−liquid interfacial oxidation of the catalyst, while the reaction in the presence of P$_3$NO occurs mainly in the organic phase with a small interfacial component.

Summary on the Role of P$_3$NO for the Epoxidation. Several lines of evidence point toward the role of P$_3$NO in accelerating the indene epoxidation as being to transport HOCl into the organic layer, where it oxidizes Mn(III) to the catalytically active Mn^V=O in the rate-determining step. The zeroth-order indene kinetics indicate that indene is not involved in the turnover-limiting step, and the dependence of the rate on hydroxide and hypochlorite concentrations indicates that HOCl
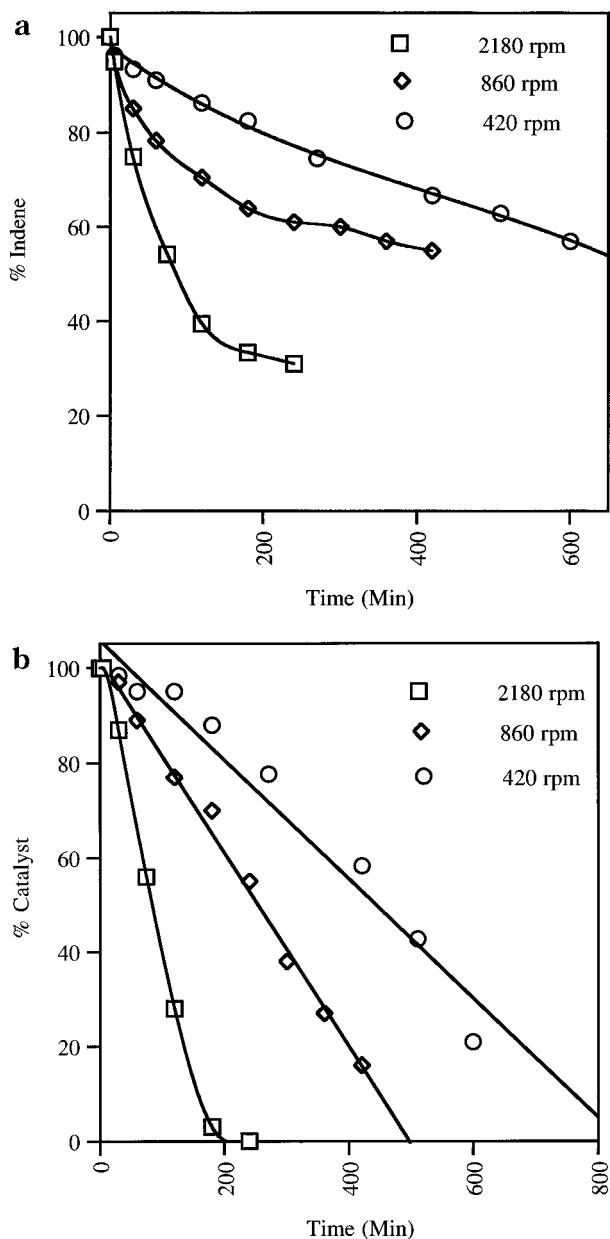
Figure 7. Effect of stirring speed on the rate of (a) indene epoxidation in the absence of P$_3$NO and (b) catalyst degradation in the absence of P$_3$NO.

is the active oxidant and that HOCl is involved in the rate-limiting step. Additionally, since the rate is nearly independent of stirring speed in the presence of P$_3$NO, the turnover-limiting step is occurring primarily in the organic phase.[17]

In the absence of P$_3$NO, the epoxidation exhibits quite different behavior. The reactions are now dependent on the rate of agitation, indicating that the turnover dependent step is occurring at the interface. Moreover, the epoxidation is no longer dependent on hydroxide or hypochlorite concentrations, so HOCl appears not to be

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(17) A reviewer has suggested that a synergistic effect between P$_3$-NO and HOCl may accelerate the catalyst oxidation; that is, complexation of P$_3$NO with catalyst, as in **3**, may result in the catalyst being more readily oxidized. On the other hand, as the structure **3** suggests, the oxygen from P$_3$NO may be transferred to the catalyst aided by HOCl as acid catalyst. However, experiments using 4-(3-phenylpropyl)-pyridine[14] indicated that the pyridine cannot be oxidized to the *N*-oxide under the reaction conditions, so it is unlikely that a catalytic cycle exists involving the pyridine and its *N*-oxide.

the active oxidant. These data suggest that the oxidation of the catalyst in the absence of P$_3$NO is occurring at the interface with NaOCl as oxidant.

Titration of HOCl in the Organic Layer. Since the kinetic experiments above suggested that P$_3$NO was transporting HOCl into the organic layer, we sought to quantitate the oxidant level in the organic layer by redox titration using thiosulfate/iodine. These experiments were run in the same manner as the kinetic experiments, except that the catalyst was omitted so that no epoxidation would take place. In the absence of P$_3$NO, no oxidant ($<10^{-5}$ M) could be measured in the organic layer after separation of the aqueous layer and centrifugation to remove all second-phase water. This is not surprising since the pK_a of HOCl is 7.5, and only very small amounts of HOCl would be expected to be found from an aqueous solution that contains 0.13 M NaOH even if the distribution coefficient for the organic layer was large. On the other hand, in the presence of the standard level of P$_3$-NO (3% vs indene), the quantity of oxidant in the organic phase was quantifiable at $(7 \pm 1) \times 10^{-5}$ M. Using one-quarter of the level of P$_3$NO (0.75% vs indene), the quantity of oxidant was too low to accurately measure. Control experiments showed that P$_3$NO itself was not titrated by the thiosulfate/iodine system. These experiments quantified the total amount of oxidant that P$_3$NO transports into the organic phase but provided no information on whether this oxidant is HOCl or OCl$^-$. However, the above kinetic experiments suggested that HOCl was the active oxidant in the indene epoxidation.

Kinetic Measurements Using a Redox Indicator. Since the level of oxidant measured by titration was small and there was no information as to the ionization of the oxidant (HOCl or ClO$^-$), a redox indicator was used to monitor the level of oxidant drawn into the organic phase by P$_3$NO. The indicator used was diphenylbenzidine, which is colorless in the reduced state but is oxidized to the violet-colored quinoid structure (eq 6). The oxidation was followed by monitoring the increase in absorbance at 437 nm.
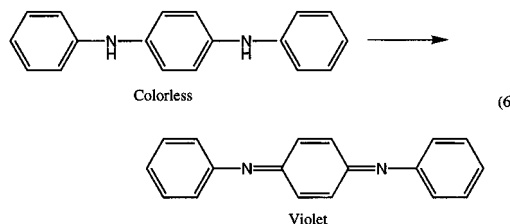
Experiments with this indicator were not definitive, but the results supported the argument that P$_3$NO transports HOCl to the organic phase. A number of probe experiments were conducted to establish conditions in which the oxidation was reproducible. Initial experiments carried out in aqueous NaOCl/PhCl or aqueous NaOCl/PhCl/indene were difficult to interpret because the oxidized form of the indicator was not stable in these media, as the color deepened initially and then faded. The best system found was aqueous NaOCl/dichloromethane, wherein the oxidized form of the indicator was stable long enough for valid kinetic measurements to be obtained. Previous work with the epoxidation of indene has shown that the epoxidation characteristics are very similar in PhCl and dichloromethane. The experiments described below were carried out at -5 °C with the indicator level at 1 mM in dichloromethane, which
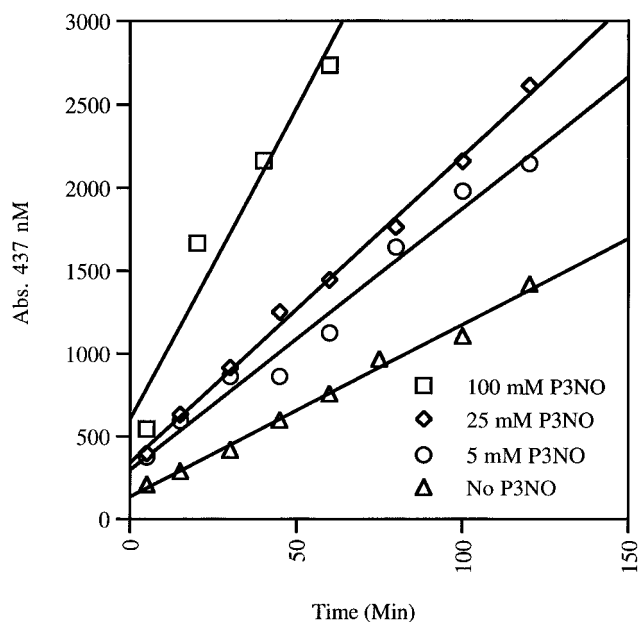
Figure 8. Effect of P$_3$NO levels on the rate of diphenylbenzidine oxidation in dichloromethane/aqueous NaOCl.
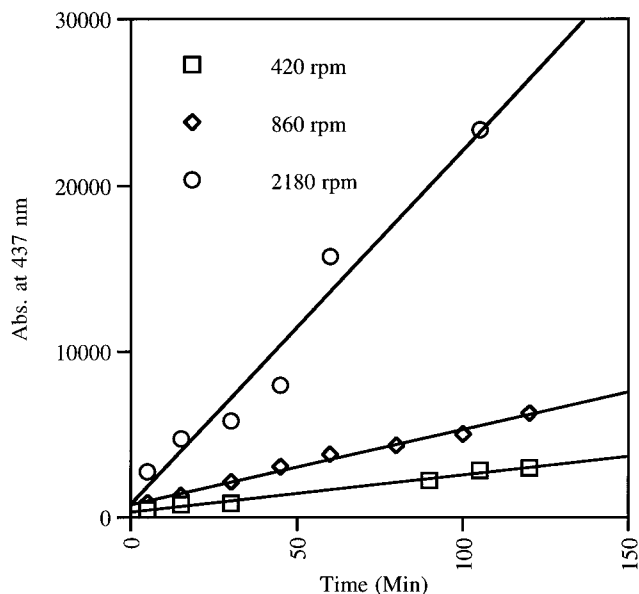

Figure 9. Effect of stirring speed on the rate of diphenylbenzidine oxidation in the presence of 0.1 M P$_3$NO in dichloromethane/aqueous NaOCl.

Figure 10. Effect of NaOH concentration on oxidation of diphenylbenzidine, with and without P$_3$NO.

result again opposite to what was observed in the epoxidation and consistent with the oxidation occurring by an interfacial mechanism.

Experiments conducted at a slower agitation speed of 420 rpm were more consistent with the results observed with the epoxidation. Displayed in Figure 10 are results for experiments run at two concentrations of hydroxide, 0.125 and 0.25 M. Without P$_3$NO present, there was no difference in oxidation rate between the two levels of hydroxide. However, with P$_3$NO, the rate was slowed as the concentration of hydroxide increased, a result in concert with the findings for the epoxidation. Moreover, reducing the concentration of NaOCl by one-half, but keeping the hydroxide constant, also reduced the rate by one-half, which is consistent with eq 5, where the concentration of HOCl is proportional to the hypochlorite concentration. Thus, the experiments at 420 rpm are consistent with P$_3$NO transporting HOCl to the organic layer, with oxidation of diphenylbenzidine occurring in the organic layer. However, these experiments also indicate that P$_3$NO serves as a surfactant, and at higher stirring speeds, it is this property that overwhelms the HOCl transportation in controlling the oxidation.

Conclusions

We have identified an unexpected role of an *N*-oxide in the epoxidation of indene in the two-phase system of aqueous NaOCl and chlorobenzene, which is to transport HOCl into the organic phase, where HOCl oxidizes Mn^{III} to Mn^V=O in the turnover-limiting step. This conclusion is supported by kinetic experiments on the epoxidation, which show that the epoxidation rate is not dependent on indene but is dependent on HOCl concentration, by titrations of the oxidant level in the organic layer and by the kinetics of oxidation of the redox indicator, diphenylbenzidine, that closely resemble the kinetics of the epoxidation. The transfer of HOCl to the organic phase may involve a hydrogen-bonded complex **4**. P$_3$NO itself crystallizes as a hydrate **5**, which provides some support for P$_3$NO as a hydrogen bond acceptor. The

is close to the solubility limit. The first set of experiments at the intermediate stirring speed of 860 rpm probed the effect of P$_3$NO on the rate of oxidation. As illustrated in Figure 8, P$_3$NO accelerated the oxidation, although not in a proportional fashion, since 5 and 25 mM solutions provided nearly the same level of rate increase. However, P$_3$NO was clearly capable of accelerating the oxidation reaction. How it accelerates the oxidation is more complicated. As shown in Figure 9, for the reactions at 0.1 M P$_3$NO, the rates were faster at higher stirring speed. This is opposite to what was observed in the epoxidation and suggests that the oxidation of diphenylbenzidine is occurring at least partially by an interfacial mechanism. Also supporting this conclusion were the results obtained with the phase transfer agent and surfactant Aliquat 336. Addition of Aliquat 336 to the reaction mixture also increased the rate of oxidation, a
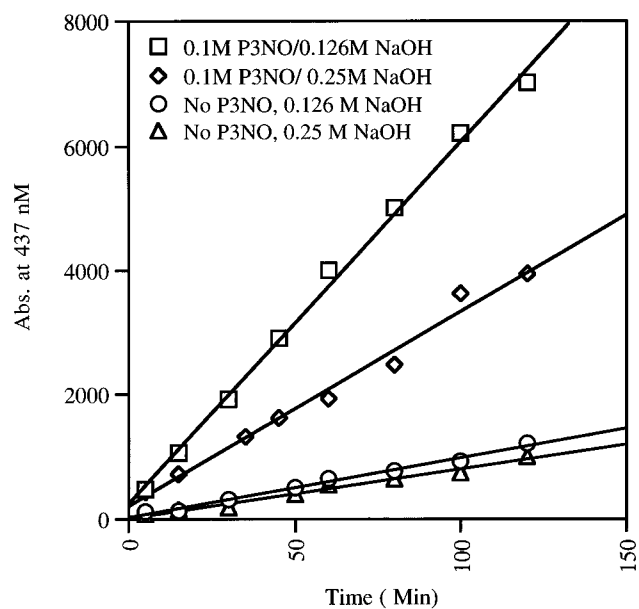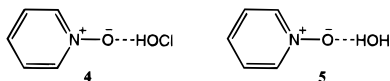
N-oxide also plays other roles in the epoxidation, including stabilization of the catalyst and as a surfactant.

Experimental Section

General. NaOCl (1.5 M) was purchased from Spectrum Chemicals, chlorobenzene and diphenylbenzidine were sourced from Aldrich, and the Mn(salen)Cl catalyst was provided by Sepracor. 4-(3-Phenylpropyl)pyridine *N*-oxide was prepared by Oxone oxidation of the corresponding pyridine,[14] which was available from Lancaster.

A normal phase HPLC assay for the Mn salen catalyst was developed using a Whatman Partisil 10 PAC column with a gradient elution from 10% ethanol in isooctane to 30% ethanol over 20 min, with a flow rate of 2 mL/min. Mn^{III}salen eluted at 8.5 min, while P_3NO eluted at 12 min. A diode array detector provided multiwavelength detection. A guard column of the same packing was found to be essential, as reaction samples fouled the column after 15−20 injections causing split peaks for the catalyst. With fresh packing in the guard column, the catalyst eluted as a fairly sharp peak, and quantitation of catalyst in reaction mixtures was readily accomplished.

Assays for indene, indene oxide, and P_3NO were accomplished by reverse phase HPLC using a Zorbax RX-C8 column, isocratic elution of 60% acetonitrile/40% 0.01 M aqueous KH_2PO_4, a flow rate of 1 mL/min, and detection at 220 nm. The asymmetric induction in indene oxide was determined by HPLC with a Chiracel-OB column with a mobile phase of 97% hexane/3% isopropyl alcohol, a flow rate of 1 mL/min, and detection at 254 nm.

General Procedure for Epoxidation Kinetic Experiments. Epoxidations were performed under nitrogen atmosphere at −5 °C on a 75-mL scale using a jacketed vessel equipped with a mechanical stirrer, whose stirring speed was calibrated using a tachometer. Ethylene glycol−water at −7 °C circulating from a constant temperature bath controlled the reaction temperature at −5 °C. For standard epoxidation runs, reaction mixtures were composed in two ways. In one all the organic components were mixed and dissolved at room temperature; in the other P_3NO was added as a solid to the cold aqueous NaOCl.

Method 1 Using 4 mol of P_3NO vs Catalyst. P_3NO (274 mg, 1.28 mmol), Mn salen catalyst (204 mg, 0.32 mmol), indene (5.0 mL, 40.7 mmol), and chlorobenzene (7.5 mL) were combined at room temperature, mixed to dissolve P_3NO and catalyst, and then cooled to −10 °C in the constant temperature bath. Aqueous 1.64 M NaOCl (60 mL, 98 mmol, 0.13 M in NaOH) was added to the reaction vessel and cooled to −5

°C; then the precooled organic mixture was added to initiate the reaction. The slight exotherm was compensated for by having the organic mixture at −10 °C before adding, such that the reaction temperature after addition was very close to −5 °C. Using this procedure, P_3NO was supersaturated in the organic layer at the reaction temperature of −5 °C but remained in solution for the duration of the run. Aliquots, about 0.5 mL, of the mixtures of the two liquid phases were removed periodically with the stirrer running and were centrifuged. Control experiments indicated that the reaction stopped once the aliquots were pulled, since the layers were no longer mixing. The upper organic layer was diluted 2000-fold with acetonitrile for reverse phase HPLC analysis and 100-fold with dichloromethane for the normal phase HPLC analysis.

Method 2 Using 4 equiv of P_3NO vs Catalyst. Aqueous 1.64 M NaOCl (60 mL, 98 mmol, 0.13 M in NaOH) and P_3NO (274 mg, 1.28 mmol) were charged to the vessel at ambient temperature and cooled to −5 °C. The Mn salen catalyst (204 mg, 0.32 mmol) was dissolved in chlorobenzene (7.5 mL), cooled to −5 °C, and then added to the reaction vessel. Then, indene (5.0 mL, 40.7 mmol), cooled to −5 °C, was added to the mixture to initiate the reaction. Sampling and assaying were done as described above. In this procedure, only 25% of the P_3NO is dissolved at the beginning of the run, but the percentage slowly increases as the reaction proceeds since it is more soluble in the product mixture than in the initial reaction mixture, as determined by control experiments.

Hypochlorite Titrations. Hypochlorite was titrated iodometrically. Chlorobenzene or chlorobenzene/indene (3:2, v:v), 15 mL, was stirred in the epoxidation vessel described above with 40 mL of 1.5 M aqueous NaOCl at room temperature. In one run, 274 mg of P_3NO was included, while none was added in another. In a control run, just chlorobenzene and P_3NO were combined, leaving out the NaOCl. After 15 min, the stirrer was stopped and the layers were allowed to separate. The organic layer was then centrifuged to further remove any second-phase water and then titrated. For the titrations, 5 mL of HOAc, 5 mL of water, and 5 mL of 10% aqueous potassium iodide were mixed and titrated using 0.001 M sodium thiosulfate. Then three 5-mL aliquots of the organic layer were added and titrated in succession, all in the same vessel. All operations were carried out under a nitrogen atmosphere to avoid autooxidation of KI to iodine.

Kinetic Experiments with Diphenylbenzidine. Runs were performed using the epoxidation vessel described above starting with 60 mL of aqueous 1.5 M NaOCl and adding 15 mL of dichloromethane containing 1 mM of diphenylbenzidine, at −5 °C. P_3NO was added in various amounts. Appearance of the oxidized form of the indicator was followed by visible spectroscopy (λ_{max} 445 nm) of samples diluted from 1- to 10-fold, depending on the extent of oxidation.