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The Role of 4-(3-Phenylpropyl)pyridine *N*-Oxide (P3NO) in the Manganese-Salen-Catalyzed Asymmetric Epoxidation of Indene

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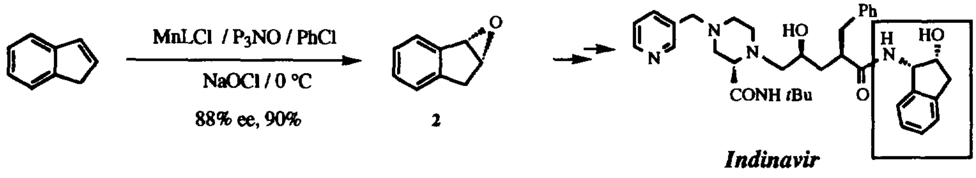
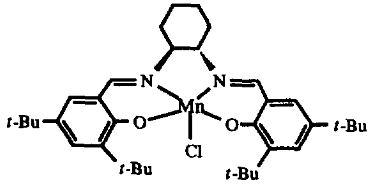
Abstract: 4-(3-Phenylpropyl)pyridine N-Oxide (P$_3$NO) has provided a more active and stable catalytic media for manganese-salen complex 1 in the asymmetric epoxidation of indene. Copyright © 1996 Elsevier Science Ltd

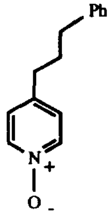
During the development of the chiral synthesis of *cis*-aminoindanol,[1a] which is a key building block of the HIV protease inhibitor Indinavir,[1b] we required a reproducible and large-scale procedure to prepare chiral indene oxide (**2**) (Scheme 1). Jacobsen has shown the tremendous application of chiral manganese-salen complexes in the catalytic asymmetric epoxidation of unfunctionalized olefins.[2] In these salen systems the addition of a pyridine *N*-oxide activates and stabilizes the catalytic system.[3] We explored the reactivity of Jacobsen's catalyst (MnLCl, **1**) in the presence of various *N*-oxides in the hope of obtaining a stabilized and more efficient catalyst system that could be utilized in a practical process for the epoxidation of indene. Herein, we report on the development of 4-(3-phenylpropyl)pyridine *N*-oxide (P$_3$NO) as an additive for the MnLCl/ NaOCl system.

Scheme 1



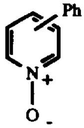


MnLCl (Jacobsen's catalyst, 1)

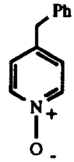


P$_3$NO

We examined a variety of pyridine *N*-oxides in the epoxidation of indene using 1.5 mol% of MnLCl with 12% aqueous NaOCl as the terminal oxidant at 0 °C in chlorobenzene.[4] The lipophilic *N*-oxides of 4-phenylpyridine, quinoline, and methyl quinoline led to a 2-3 fold increase in the reaction rate.[5] On the other hand, water soluble *N*-oxides, such as pyridine, nitropyridine, methoxypyridine, picoline or lutidine provided no significant rate enhancement.



PPNO



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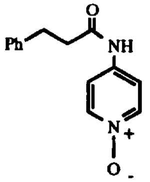

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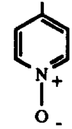

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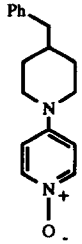

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The *N*-oxides that exhibited rate acceleration were tested to optimize the catalytic loading. Only with 4-phenylpyridine *N*-oxide (4-PPNO) could the charge of MnLCl be decreased from 1.5 mol% to 0.75 mol% without affecting the yield (88%) or the e.e. (86%).[6] The 3-isomer behaved identically; whereas, the 2-isomer caused the reaction rate to decrease two-fold. In the latter case, steric hindrance probably interfered with ligation. Increasing the length of the chain by one (**3**) or three carbons (P_3NO) decreased the reaction time from 2h to 1.75h or 1h, respectively. The electronics at the 4-position of the *N*-oxide indicated that an electron withdrawing group, as in 4-(hydrocinnamamido)pyridine *N*-oxide (**4**), dramatically decreased the rate (only 75% conversion after 20h) and the enantioselectivity (74%). In contrast, the electron-donating ether in 4-benzyloxypyridine *N*-oxide (**5**) had no effect on the enantioselectivity and only slightly slowed the reaction; however, substitution with an amino group (**6**) provided lower enantioselectivity (82%), yield (56%) and rate (24 h).

Of the *N*-oxides tested, P_3NO was optimal.[7] Most importantly, the catalytic loading could be reduced to 0.25 mol% in chlorobenzene at 0 °C with no effect on yield (90%) or optical purity (88% e.e.) of the indene oxide, with a reaction time of 4h.

The efficacy of P_3NO in the MnLCl catalytic epoxidation is striking. Therefore we examined the role of P_3NO in the catalytic cycle. The kinetic study indicates that at -5 °C, the initial rates are the same with P_3NO to MnLCl ratio of 2 to 8. However, a ratio of 4 is sufficient to complete the epoxidation (2h). Next, the stabilization and activation effects of the P_3NO were examined. The stabilizing effect of P_3NO on the catalyst can be seen in **Figure 1**.[8] With P_3NO, the catalyst decomposition is minimal. On the other hand, without P_3NO the catalyst decomposed rapidly with time in NaOCl. These results suggest that P_3NO slows the catalyst decomposition, thereby, providing a more stable catalyst system. The activation effect of P_3NO is represented by the kinetics as shown in **Figure 2**.[5] In the presence of 3 mol% of P_3NO, 0.75 mol% of MnLCl afforded indene oxide in 90% yield with 89% e.e. within 2.0 h. In contrast, without P_3NO the epoxidation did not go to completion. The immediate stabilization and activation effect of P_3NO on catalyst was illustrated by the delayed addition of P_3NO to the epoxidation mixture. Addition of P_3NO to the catalyst after 1 h ceased the rapid decomposition (Figure 1). Similarly, upon addition of P_3NO, the rate immediately increased and the reaction was complete within 2.5h (Figure 2). These experiments suggest that a rapid coordination of P_3NO with the catalyst occurs. Evidently, a Mn^VL-P_3NO oxo species (**7**) is the active catalyst, being much more active than the MnL oxo species alone. A React-IR experiment with MnLCl in dichloromethane was run at 0 °C. When P_3NO was added at 0 °C the characteristic stretch at 1613 cm^{-1} for the C=N shifted immediately to 1623 cm^{-1} suggesting that MnLCl (**1**) became ligated to P_3NO as **8**. This solution was then treated with NaOCl at 0 °C. The IR spectrum of the organic phase displayed further shifting of the C=N stretch from 1623 to 1630 cm^{-1}. Presumably, this new C=N shift was due to the formation of the Mn-oxo species **7**.

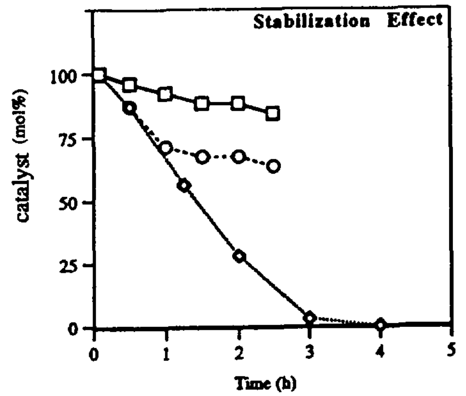


Figure 1. Disappearance of catalyst in runs at -5 °C stirred at 2180 rpm. Key: (□) P3NO present initially; (◇) P3NO absent; (O) P3NO was added after 1 h.

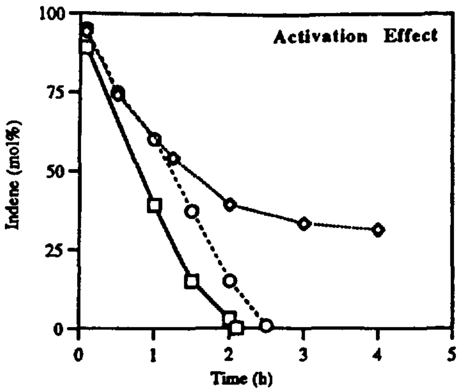
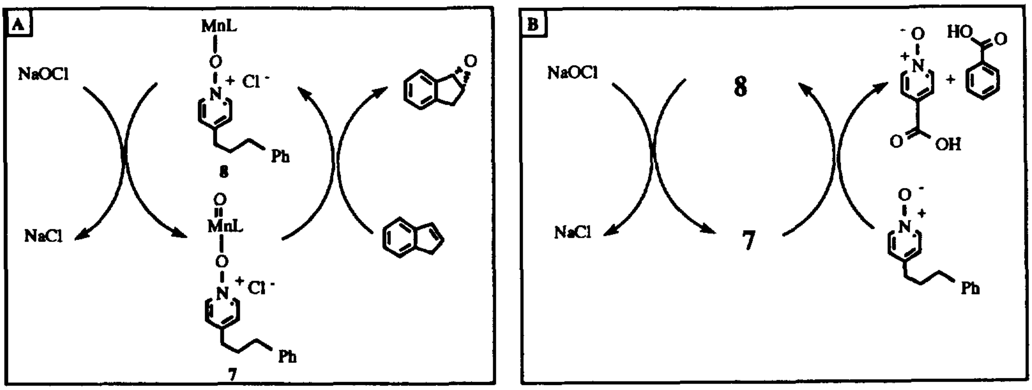


Figure 2. Disappearance of indene in runs at -5 °C stirred at 2180 rpm. Key: (□) P3NO present initially; (◇) P3NO absent; (O) P3NO absent initially but was added at 1 h.

Scheme 2 **Mechanism for indene oxide formation**



During the development of the epoxidation of indene (Scheme 2A), NaOCl was observed to decompose throughout the course of the reaction, which presented potential problems with reagent stability and stoichiometry. Furthermore, P_3NO was oxidized to isonicotinic acid and benzoic acid (Scheme 2B).[9] The cause of this decomposition was due to insufficient hydroxide content in the NaOCl. By increasing the hydroxide ion concentration of commercial 2M NaOCl from the 0.03 - 0.18 M range to 0.3 M the hypochlorite was stabilized.[10] With this reagent mixture the epoxidation of indene only required a charge of 1.3 equivalents of NaOCl. The concentration of NaOH was unchanged throughout the reaction and 0.15 equivalents of NaOCl remained at the end of the epoxidation.

A typical epoxidation was conducted in the following manner:[11] A 2 M solution of sodium hypochlorite (26.5 mmol) was cooled to 0 °C. The MnLCl (0.56 mmol) and P_3NO (2.32 mmol) were dissolved in chlorobenzene (10 mL) and the mixture was added to the hypochlorite under N_2. The solution was stirred for 15 min at 0 °C, then simultaneously indene (10 mL) and the remaining hypochlorite (79.5 mmol) were added over 30 min with syringe pumps. The reaction was complete within one hour at 0 °C. The viability of this process for the catalytic epoxidation of indene was successfully demonstrated on a multi-kilogram scale to afford indene oxide in 89% yield with an optical purity of 88% e.e.[12]

The use of 4-(3-phenylpropyl)pyridine *N*-oxide (P3NO) offers an effective catalytic media for manganese-salen-catalyzed epoxidations by stabilizing and activating the catalyst. Furthermore, by adjusting the hydroxide ion concentration in the reagent system a practical process for indene epoxidation was accomplished.

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† New address: Sepracor Inc., 33 Lock Drive, Marlborough, MA 01752.

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(4) In the comparison study of pyridine *N*-oxides the hydroxide ion concentration in NaOCl was 0.13M.

(5) Kinetic data were obtained using HPLC with a reverse phase HPLC assays on a Zorbax RX-C8 column, 4.6 mm x 25 cm at 254 nm, mobil phase; aqueous(0.01M KH_2PO_4)/acetonitrile = 65 /35 over 20 min; 1.5 mL/min. Aliquots of the reaction mixture were removed periodically and analyzed for unreacted indene and the product, indene oxide.

(6) For comparison of the reactivity of the *N*-oxides, 0.75mol % of MnLCl and 3 mol % of *N*-oxide in PhCl at 0 °C were used in the epoxidation.

(7) (a) Preparation of 4-(3-phenylpropyl)pyridine *N*-oxide with Oxone®. A 500-mL, three-necked flask equipped with an overhead paddle stirrer, thermocouple, condenser, nitrogen atmosphere and cooled by means of a water bath, was charged with water (63.5 mL), methanol (125 mL), and Oxone® (37.5 g). The pH of the slurry was 1.4 due to the bisulfate salts in Oxone®. To this slurry 4-(3-phenylpropyl)-pyridine (12.5 g) was added over 5 min. The mixture was then maintained at pH = 5.5 by addition of 5 N sodium hydroxide solution while controlling the temperature at ≤ 35 °C. The temperature was controlled by water cooling and by the rate that sodium hydroxide was added: The progress of the reaction was monitored by HPLC assay. Upon completion of the reaction (< 1 area % by HPLC), the salts were removed by filtration and the cake was washed with 50 mL of methanol. The combined filtrate and washes were treated with 1 M sodium metabisulfite solution (12 mL) and stirred for 0.5 h. The quenched solution was then adjusted to pH = 10.0 with 5 N sodium hydroxide solution and further aged for 1 h. The solution was concentrated *in vacuo* (26 in Hg, 50 °C) to a final volume of 75 mL. The resulting slurry was cooled to 20 °C, the product was filtered, washed with 50 mL of water, and dried under nitrogen. The yield of 4-(3-phenylpropyl)pyridine *N*-oxide was 93%: m.p.60 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 1.81.98(2H, m), 2.3-2.6(4H, m), 7.05(2H, m), 7.12-7.30(5H, m), 8.11(2H, m). (b) 4-Phenylpyridine *N*-oxide is widely used, however, the reagent is expensive and difficult to obtain in large quantities.[2]

(8) The unstable MnL-oxo species converts to the MnLCl in the chromatography media. This was established by UV-LC and LC-MS methods.Therefore, the true catalyst amount is propotional to MnLCl which was determined by the A% of HPLC at 8.69 min with comparison to the MnLCl standard (normal-phase on a Whatman Partisil 10 PAC column (4.6 mm x 25 cm, Hewlett-Packard model 1040A UV-visible diode array at 254 nm, 2 mL/min; mobile phase isooctane and ethanol; gradient elusion 90:10 to 70:30 over 20 min. The retention time (RT) of MnLCl is 8.69 min). The assay of complex **7** is directly proportional to the MnL-oxo species because of the high dilution (100 times) of the sample preparation for the HPLC analysis. Complex **7** disassociates from the Mn-oxo species and P_3NO (RT=12.5 min).

(9) The by-products of decomposition were detected by NMR and the epoxidation mixture was prepared without indene: 2M sodium hypochlorite (26.5 mmol) was cooled to 0 °C. The MnLCl (0.56 mmol) and P_3NO (2.32 mmol) were dissolved in chlorobenzene (10 mL) and the mixture was added to the hypochlorite under N_2. Interestingly, minimal decomposition of P_3NO took place once indene was added. Apparently, indene epoxidation is faster than the oxidation of P_3NO. The decomposition phenomenon was not only unique to P_3NO but was also observed with 4-PPNO. A full disclosure of these findings are planned.

(10) **Caution!** When $[OH^-] \leq 0.09$, the heat generated in the epoxidation is difficult to contain. The decrease in concentration of the hydroxide ion affects the concentration of HOCl. HOCl is a powerful oxidant and weak acid (pKa = 7.54), with HOCl and OCl^- in equilibrium. Initially the aqueous phase contains NaOCl and NaOH; the organic phase contains the catalyst and a low concentration of HOCl. The acidic by-products (benzoic acid, isonicotinic acid N-oxide), which are generated as a result of P_3NO oxidation, will decrease the hydroxide concentration and, as a result, increase the amount of HOCl. This in turn provides a greater amount of HOCl in the organic phase which increases the rate of decomposition of hypochlorite.

(11) Indene epoxidation is exothermic. The controlled addition of the indene and hypochlorite to the catalyst system is necessary in order to dissipate the heat generated in the reaction.

(12) Large quantities of *S,S*-Mn(salen) chloride (MnLCl) was purchased from Sepracor.

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