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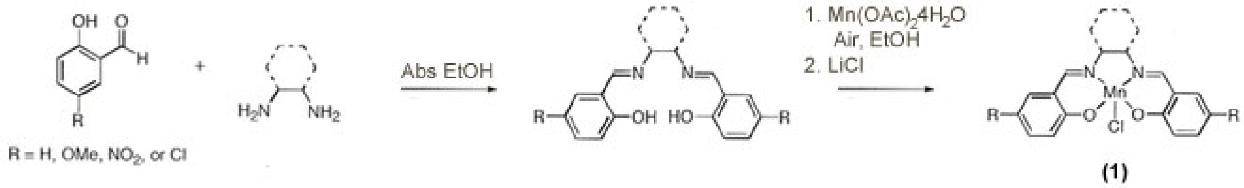
5.301 Final Report

Effects of 5,5'-position substitutions on the Mn(salen) catalyzed epoxidation of stilbene

1. Objective:

Easily prepared manganese salen complexes have been shown to be versatile and effective catalysts for the epoxidation of olefins.[1] In this investigation, we follow the basic procedure for the synthesis of the Mn(salen) complex **1** developed by Jacobsen *et al.* using several salicylic acid derivatives and diamine bridges (Scheme I), in order to probe for the electronic effects pertinent to catalytic activity arising from the various substituents in the 5,5'-position of the salen ligand.

Scheme I: Preparation of Mn(salen) catalyst



Much attention has already been given to the enantioselective nature of Jacobsen's catalyst **1**, a property controlled by the steric bulk in the 3,3'-position of the salen ligand.[2] In this report, we disregard enantioselectivities entirely and seek corresponding experimental conversion ratios of stilbene by the various complexes. In particular, we attempt to verify whether Cavallo and (Heiko) Jacobsen's recent computational study on the topic[3] is matched with experimental agreement.

$$\text{Conversion} \equiv \frac{\text{mols of } \mathbf{2b}}{\text{mols of } \mathbf{2a} + \text{mols of } \mathbf{2b}}$$

2. Background

Jacobsen's preparation of **1** is reproduced here:

> The salicylic acid derivative (2.0 equiv) is added as a solid to a 0.2M solution [of the diamine] (1.0 equiv) in absolute ethanol. The mixture is heated to reflux for 1h and then

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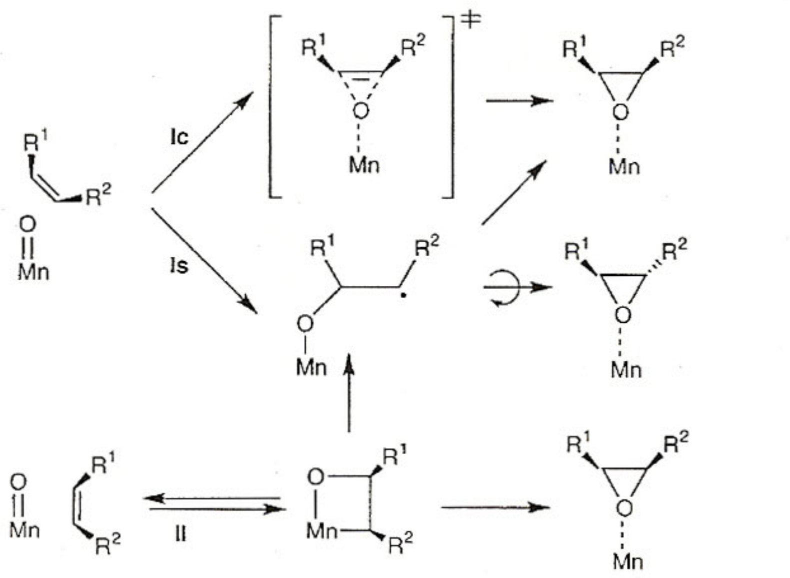
[1] Zhang, Wei, Jacobsen, E.N. *J. Org. Chem.* **1991.** *56*, 2296-2298.
[2] Cavallo, Luigi, Jacobsen, Heiko. *Angew. Chem. Int. Ed.* **2000**. *39*, 589-592.
[3] Ibid.

> H_2O is added to the cooled bright yellow solution. The resulting yellow crystalline solid [salen ligand] is collected by filtration, washed with small portion of 95% ethanol… The ligand is redissolved in hot absolute ethanol to give a 0.1M solution. Solid $Mn(OAc)_2 4H_2O$ (2.0 equiv) is added in one portion and the solution is refluxed for 1 h. Approximately 3 equiv of solid LiCl are then added and the mixture is heated to reflux for an additional 0.5 h. Cooling the mixture to 0°C affords the Mn (III) complex **1** as dark brown crystals that are washed thoroughly with H_2O and isolated by filtration.

The above procedure serves as a guide to our investigation.



Scheme 2. Possible mechanisms for oxygen transfer in the Jacobsen–Katsuki epoxidation. For **Is**, rotational collapse leads to the *trans* epoxide, whereas direct collapse leads to the same *cis* product as pathway **Ic**.

A recent computational study by Cavallo and Jacobsen examined the possible mechanisms of action for the Mn(salen) catalysis. In particular, two probable pathways – one involving a direct attack of the olefin at the oxo ligand and the other via an oxametallacycle – were compared. Their investigation concluded that, due to energy considerations, the Jacobsen-Katsuki epoxidation occurs by an electrophilic attack at the HOMO of the olefin system (Pathway I in Scheme II).[4]

With this mechanistic model in mind, a follow-up study investigating the effects of 5,5' substitutions on the reactivity of the oxo ligand reported high correlation between Hammet constants σ^{+}_{para} (a measure of the substituents' electrophilicty) and Mulliken charges at the oxo ligand, Mn=O bond strength ΔE_{Ox} and critical distances for the evolving C-O bond (d_{CO}).[5]

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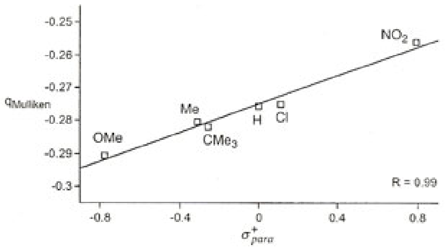
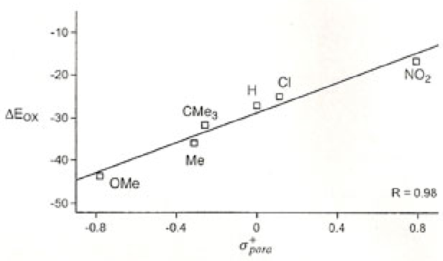
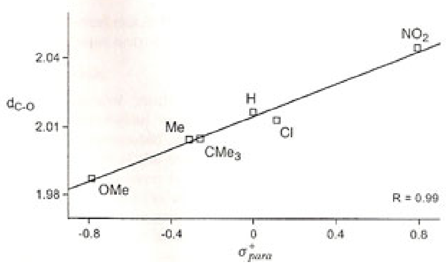
[4] Cavallo, Luigi, Jacobsen, Heiko. *Angew. Chem. Int. Ed.* **2000**. *39*, 589-592.
[5] Cavallo, Luigi, Jacobsen, Heiko. *J. Org. Chem.* **2003**. *68*, 6202-6207.

Overall, the study revealed that electron-donating substitutions (low σ^{+}_{para} ; *i.e.* OMe) attenuate catalytic activity through the following factors: higher negative charge at the oxygen, a stronger Mn=O bond (both of which disfavor electrophilic attack of the olefin), and the resultant closer proximity requirement (d_{CO}) for reaction.







In our investigation, we utilize the same substituents (OMe, H, Cl and NO_2) in order to verify the computational predictions.

3. Experimental procedure:

A. Synthesis of Mn(salen) complex.

The quantities of the reactants used were aimed towards synthesizing 1.0 g of the Mn(salen) catalyst, assuming a 70% yield.[6] 0.529mL of 3-methoxy salicylic acid (0.645g; 4.24 mmol) and 0.26mL 1,2-diaminocyclohexane (0.242g; 2.12mmol) were added to a 50mL R.B. flask via syringe. Immediately afterwards, the flask was filled approximately halfway with absolute ethanol. Following 1 h reflux, the flask was placed in an ice bath, and chilled H_2O was added dropwise to induce crystallization.

The bright yellow solid was obtained by vacuum filtration, yielding 0.886g of the salen ligand after an overnight drying in a desiccator. NMR spectroscopy data for the salen ligand (R: OMe) is available in Appendix I.

The dry salen ligand solid (~0.886g) was added to a 100mL R.B. flask, rinsed with approximately 23mL of absolute ethanol (which yields a roughly 0.1M solution). Immediate change in color was observed (yellow to muddy brown) with the addition of 1.1938g of $Mn(OAc)_2 4H_2O$ (2 equiv). The ligand appeared largely insoluble in the alcohol solution. In order to dissolve the solid, approximately 4 mL of warm toluene was added via pipet into the flask. The resulting mixture was refluxed for 1 h.[7]

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[6] In his paper, Jacobsen reports ~75% yield of the catalyst.

[7] At the end of the 1 h reflux, the mixture bumped, resulting in an appreciable loss of solution.

While the solution was still warm, 0.3629g of LiCl (approximately 3 equiv) was added and was refluxed for an additional 0.5 h.

Finally, the mixture was cooled in an ice bath to assist in recrystallization. A *very wet,* dark brown crystals were obtained by vacuum filtration. (For instance, the wet mass of the product was 2.619g; following four days in a desiccator, the mass was reduced to 0.9602g.)

B. Epoxidation of stilbene and purification of product.

In order to be able to readily compare conversion ratios as a function of the substitution, we standardized several reaction parameters such as reaction time at 3 h, and the quantity of catalyst at 4 mmol. In addition, the solutions were prepared as stock to reduce variability.

The aqueous layer, which includes commercial bleach (NaOCl) as the oxygen source, was prepared in the following ratio: 10mL of 0.05M Na_2HPO_4 was combined with 25mL NaOCl. The pH of the resulting solution was adjusted to 11.3 by addition of NaOH, and the solution was cooled to 0°C.

The organic solution was prepared by adding 0.1850g of catalyst into a 100mL R.B. flask, rinsing with 10mL of the stock organic solution composed of 10mmol stilbene per 10.0mL CH_2Cl_2. In the transfer, some stilbene crashed out of solution.

35mL of the aqueous stock solution was added to the flask. The two layers were immiscible, and a light brown aqueous layer was above the very dark brown organic solution. The two-phase mixture was placed in an ice bath for approximately 2 minutes.

The flask was removed from the ice bath, and was allowed to reach room temperature. The reaction was allowed to proceed for three hours after taking the mixture out of the ice bath. Vigorous stirring thoroughly mixed the two phases, which blended into a creamy, brown mixture. Every fifteen minutes or so, however, the stirring was halted so that the extent of the reaction could be monitored by TLC. Because the species of interest – stilbene and stilbene oxide – exist in the organic layer, the stirring was temporarily stopped to allow the two phases to separate. The approximate R_f values of stilbene and stilbene oxide in a 1% ether/pentane system were 0.37 and 0.17 respectively. For R: OMe, no stilbene oxide was observed by TLC until after 2.25 h after beginning the reaction.

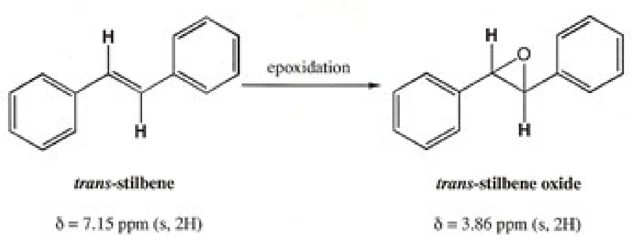
After 3 h, any solids in the biphasic mixture were filtered off by gravity filtration, and the solution was transferred to a 250mL separatory funnel and rinsed with 100mL of hexane. At this point, the CH_2Cl_2/hexane organic layer was less dense than and hence was above the aqueous layer. Initially, the aqueous layer was clear and the organic layer was slightly brown. However, after vigorous shaking, the colors began to blend and eventually the organic layer became almost clear.

After extracting stilbene and stilbene oxide into the organic layer, the solution was washed twice with approximately 50mL of H_2O and then once with saturated NaCl. Drying agent was then added until solution was cloudy when stirred. Also, by this time, the solution became almost completely clear.

The CH_2Cl_2/hexane solvent was then evaporated via rotovap, which yielded a yellowish solid. This crystalline product – stilbene, stilbene oxide, and (presumably) the bright yellow salen ligand – was placed in a desiccator overnight.

C. Determination of conversion ratio.

Due to the one-to-one correspondence between the hydrogen in stilbene and its epoxide, it is possible to directly utilize NMR spectra of the crude sample to determine the conversion ratio.



trans-stilbene

δ = 7.15 ppm (s, 2H)

trans-stilbene oxide

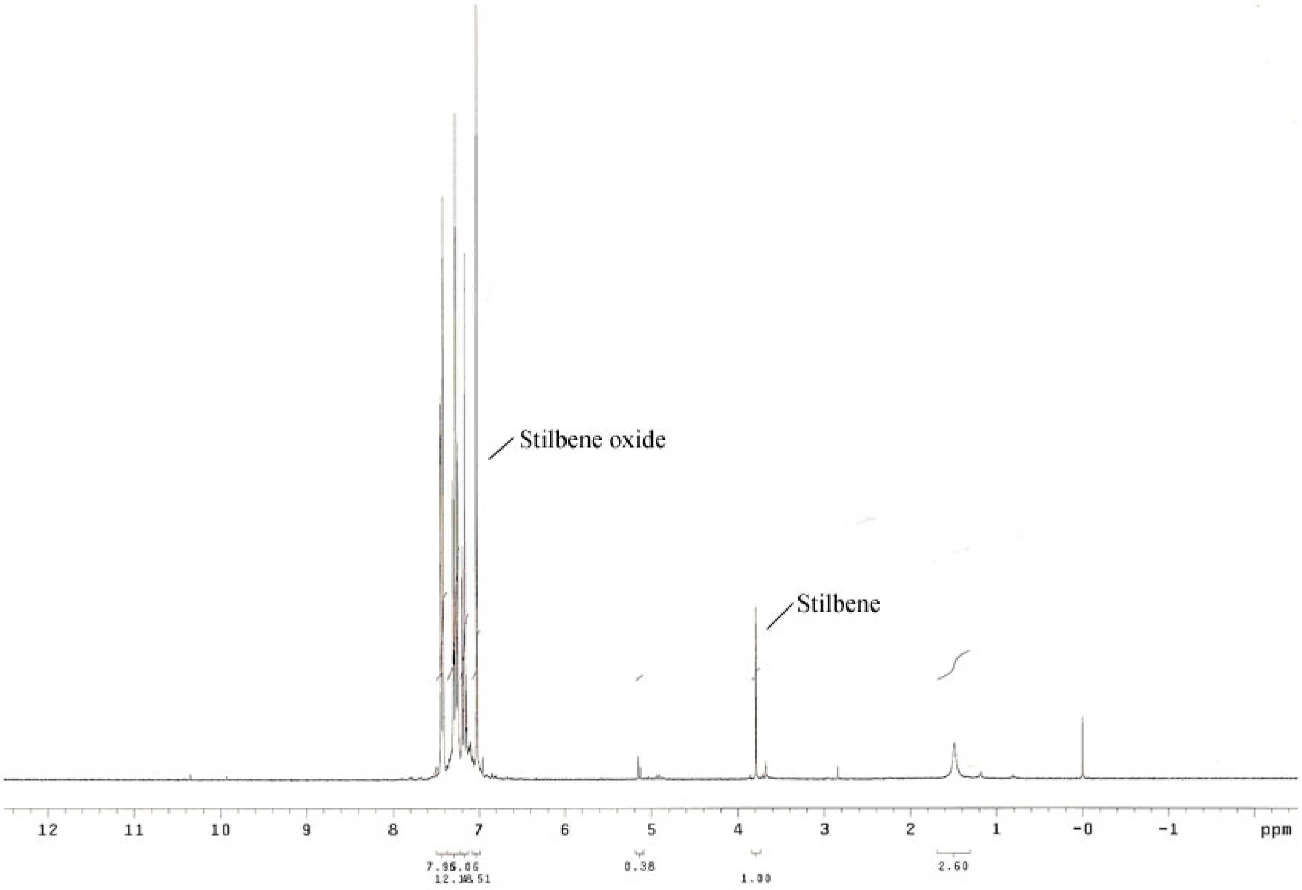
δ = 3.86 ppm (s, 2H)

$$\text{Conversion} = \frac{\text{Mols stilbene oxide}}{\text{Mols stilbene oxide} + \text{Mols stilbene}}$$

$$= \frac{\text{Area under peak at 3.86}}{\text{Area under peak at 3.86} + \text{Area under peak at 7.15}}$$

For instance, in the spectra of the OMe crude mixture (Figure I) obtained by the procedure above, the conversion ratio is: $Conversion = \frac{1.00}{4.51 + 1.00} \approx 18.1\%$

Figure 1: NMR spectra of the crude reaction mixture



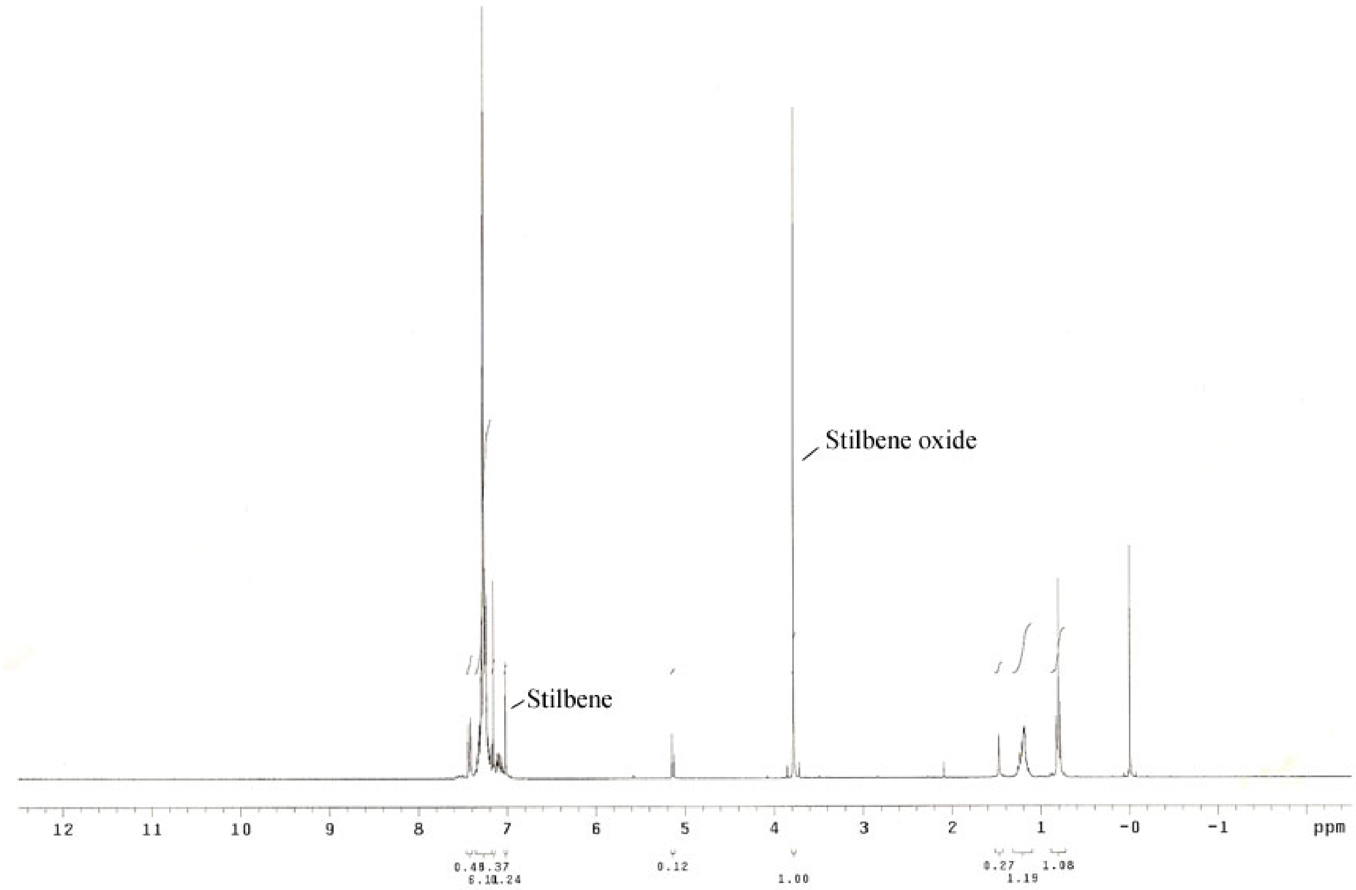
A more comprehensive NMR data for the mixture is given in Appendix II.

D. Purification of stilbene oxide.

The yellowish solid was composed of stilbene, stilbene oxide, and the decomposed salen ligand. By TLC in pure pentane and 1%, 2% and 5% ether/pentane systems, it was revealed that the ligand behaves as if it were highly polar and remained at the initial point for all solvent systems that were attempted. Hence, the purification of stilbene oxide by flash column chromatography was conducted as if the ligand were not present.

Organic material was collected in 22 continuous fractions with, unfortunately, no fraction that contained pure epoxide. However, by TLC it was determined that the last five fractions contained both stilbene and stilbene oxide. They were collected into a R.B. flask and the solvent was evaporated via rotovap to yield white crystalline solid. By a procedure completely analogous to the determination of conversion ratio, the final product was shown to be 80.6% pure. (The NMR spectra of the purified epoxide is reproduced below. Again, more comprehensive data can be found in Appendix III.)

Figure 2: NMR spectra of purified stilbene oxide



4. Results and Discussion

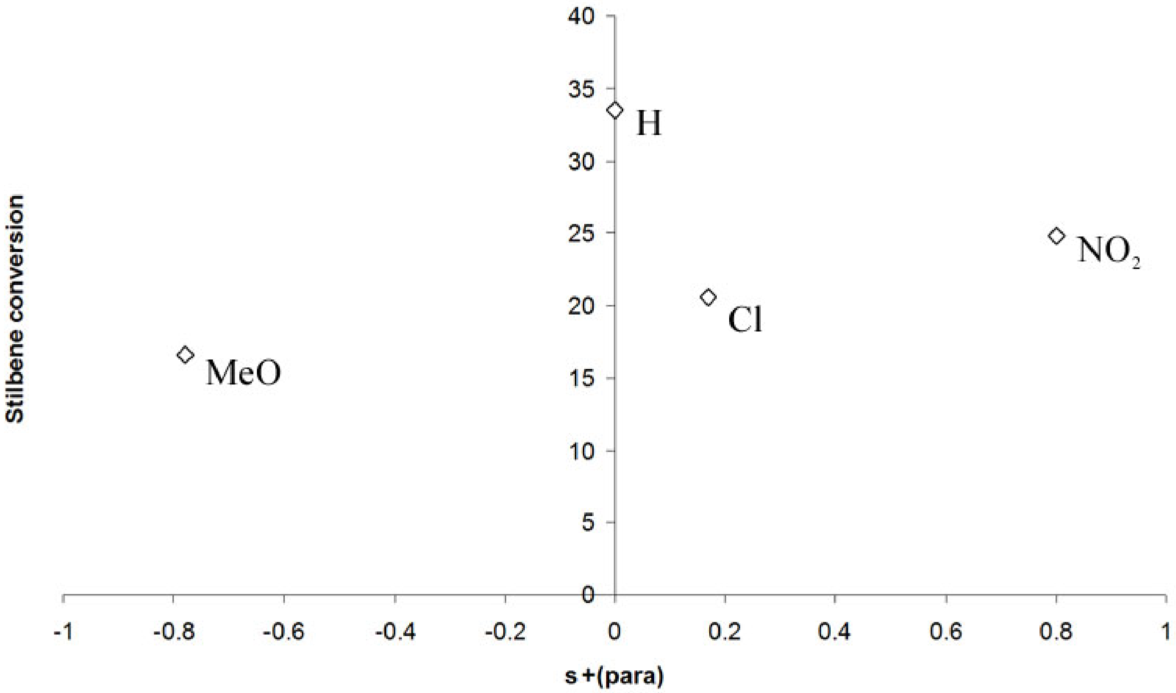
Extent of conversion.

Table 1: Conversion ratios

	OMe	H	Cl	NO_2
Conversion	17.2%	34.0%	20.6%	24.8%
	14.6%	32.9%		
	18.1%			
Average	16.6%	33.5%	20.6%	24.8%

Table I shows the conversion results for the various substitutions that were attempted; averages are given where appropriate. In the Figure 3 below, the average conversion values are plotted against corresponding σ^{+}_{para} values of the four R groups.[8]

Figure 3: Stilbene conversion as a function of substituent electrophilicty



From the graph, it is readily apparent that the data disagrees with Cavallo and Jacobsen's hypothesis that the reactivity of the oxo group increases as a function of the electrophilicity of the substituent. The anomalies (according to the theoretical model) can be seen as an overestimation of the conversion ratios for R: H, and/or an underestimation of the ratios for R: Cl and R: NO_2.

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[8] σ^{+}_{para} values are approximately equivalent to those found in Cavallo and Jacobsen's paper. The origin of the values is: Leffler, J. E., Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963.

Rate of conversion.

Due to the irregular amounts of solvent (pentane) used to dilute the sample, TLC does not offer a very quantitative method for determining the extent or rate of reaction. However, by recording the time bracket in which the epoxide spot is first observed, it is possible to gain a qualitative understanding of the relative effectiveness of the catalysts in terms of the speeds.

Table 2: Time bracket in which epoxide is first observed by TLC

	OMe	**H**	**Cl**	**NO_2**
Stilbene oxide first observed	1:50-2:15	N/A	Within the first thirty minutes	N/A

Table 2 lists the (very limited) data regarding the relative rates of catalysis for the various complexes. The chlorinated salen is apparently *several times faster* than the OMe substitution in the epoxidation of stillbene. This result is consistent with the theoretical background provided by Cavallo and Jacobsen. As discussed previously, an electron density withdrawing substituent is expected to decrease the local charge of the oxo group and to weaken the Mn=O bond.

Limitations.

A major setback to the validity of the experimental data is the variable amount of catalyst that was employed in the reactions. For instance, due to the thick, slurry consistency of the Mn(salen) crystals, it was difficult to remove the solvent. (This was observed as early as in the filtration process where the solvent pooled on top of the filter paper creating a muddy slurry with the solid instead of being filtered through.) Even after four days of drying in a desiccator, my sample (R: OMe) consisted of large, clearly wet “chunks” instead of free flowing powder. Many of my colleagues had similar difficulties.

The amount of catalyst in solution is vital for this investigation as, according to the proposed mechanism, the complex is directly responsible for coordinating the oxo group towards the olefin in a 1:1 ratio. As NaOCl and stilbene were in excess, the likely rate-limiting “reactant” was the catalyst itself.

In addition, in order to perform TLC during the reaction, a pipet had to be plunged into the bottom layer of the biphasic mixture (since the organic layer was on the bottom). This procedure almost invariably resulted in a loss of solid catalyst that clung onto the glassware. Considering the differing solubilities of the various Mn(salen) complexes and the variable frequency of TLC testing employed by each member, a loss of catalyst over the course of the reaction may be a significant source of error.

In the workup of the reaction, many of us collected crystals that were *yellow*, instead of white in color, most likely indicating the presence of the salen ligand. (Stilbene and its epoxide are both colorless compounds.) This indicates that over the course of the reaction the Mn catalyst decomposed and/or the initial sample of catalyst actually contained a portion of pure ligand, in addition to the catalyst.

The uneven amount of catalyst used is most likely to result in incorrect values for the total *extent* of conversion, rather than the *rate* of conversion, since TLC will report the presence of *any* amount of the epoxide present. Hence, considering the qualities of the conversion and rate data, the error in catalyst measurement appear to be a highly likely source of error.

Interestingly, if more information regarding the relative rates of the reactions were available, it would be possible to *logically conclude* that the conversion ratios are in error due to uneven quantities of catalyst tested. If, for example, theoretically consistent data were obtained regarding the rates were obtained (OMe, H, Cl, NO_2. In order from slowest to fastest), we could immediately ask the question: given that there is excess oxygen and stilbene, and Cl-substituted Mn(salen) forms stilbene oxide more rapidly than the complex with the hydrogen group, how could the Cl achieve a lower overall conversion ratio? It may be due to a more complicated, time-dependent catalysis rate, which seems highly unlikely given the theoretical understanding of the catalytic mechanism. The most plausible response is that uneven quantities of Mn(salen) was present. As stated before, because the rate determination should be much less sensitive to the quantity of catalyst present, subsequent experiments on the topic should take greater care in TLC data collection.

5. Conclusion

The conversion results obtained in this study, taken at face value, refute the theoretical framework proposed by Cavallo and Jacobsen. However, the limited rate data – which are less sensitive to the initial concentrations of the catalyst – are consistent with the model. As such, a repeat of the same investigation may be worthwhile, taking additional time to dry the ligands/catalysts to ensure purity. Also, more extensive TLC data should be compiled, in order to verify consistency with the conversion ratios.