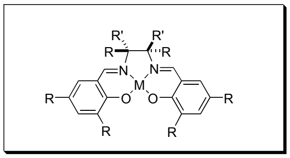
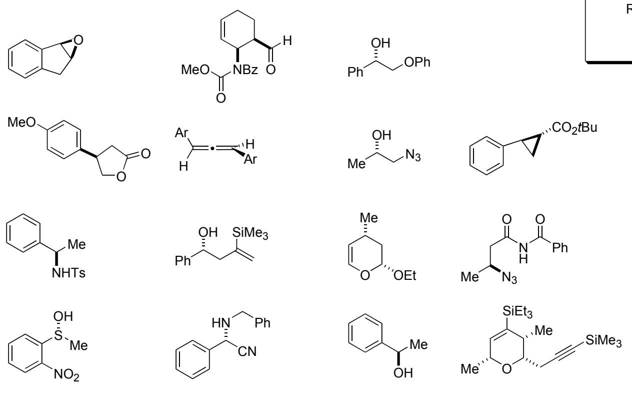
Mechanism and Application of Salen Ligands in Asymmetric Catalysis

Mike Brochu
MacMillan Group Meeting
July 9 2003

Salen Complexes: A Privileged Chiral Catalyst



Diverse family of accessible products



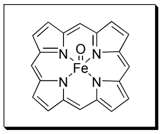
- Epoxidations
- Aziridinations
- Epoxide Ring Opening
- Hydrolytic Kinetic Resolution

Reviews and seminal papers:

Katsuki, T. *Synlett*, **2003**, 281
Comprehensive Asymmetric Catalysis, Vol II. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds; Springer: Berlin, 1999
Catalytic Asymmetric Synthesis, Second Edition. Ojima, I. Eds: Wiley-VCH. **2000**

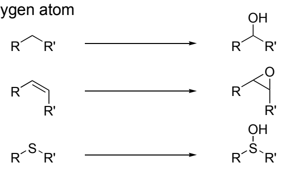
Zhang, W.; Loebach, J. L; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801
Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326

Interest Began in Understanding Biological Systems

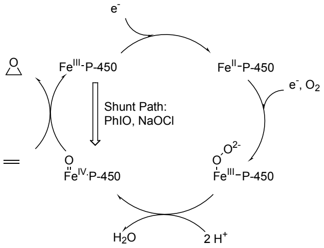


Cytochrome P-450

- Critical to hormone biosynthesis, drug metabolism, and detoxification of xenobiotics
- Suprafamily of cysteine thiolate-ligated heme iron enzymes that activate dioxygen for insertion or addition of a single oxygen atom

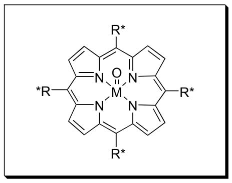


- Reactions proceed through cationic oxoiron (IV) species which are generated by the oxidation of Fe(III) with O_2



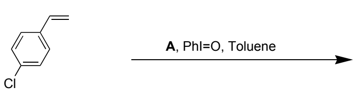
Sono, M.; Roach, M. P.;Coulter, E. D.; Dawson, J. H *Chem. Rev.* **1996**, *96*, 2841

Porphyrins: Active Site Mimics

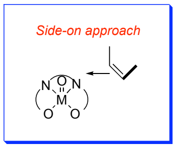


Groves Uses Metalloporphyrins for Epoxidations

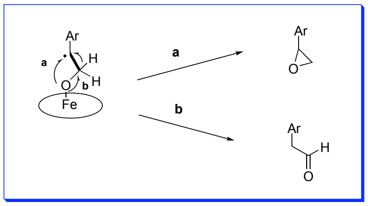
- In 1979 Groves found that treatment of Fe(III) complex with terminal oxidant provided cationic oxoiron(IV)-porphyrin complexes that epoxidize simple olefins.
- In 1983, Groves used a chiral iron porphyrin complex to promote the asymmetric epoxidations of olefins



51% ee
63 % yield



- Hypothesizes that olefin approach must be *side-on* in order for stereochemical information to be passed from porphyrin to olefin

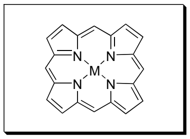


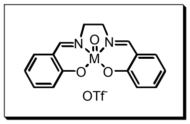
- Presence of aldehyde by-product and low enantioselectivity interpreted as evidence for radical mechanism

Groves, J.T.; Nemo, T. E.; Myers, R.S. *J. Am. Chem. Soc.* **1979**, *101*, 1032
Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, 105, 5786
Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791

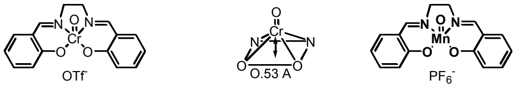
Kochi Begins Working with oxo Metal-salen Complexes

Successfully isolates oxo Cr-Salen Complex





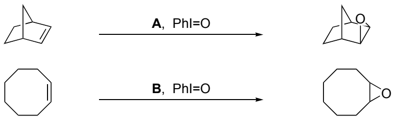
- Salen complex designed to mimic porphyrin core
- sp^3 C's now located 2 atoms away from metal center



A

B

- Oxo Cr-salen complex has square-pyramidal structure
- Unable to isolate oxo Mn species
- Participates in one oxygen atom transfer to olefins to provide epoxides



85% yield

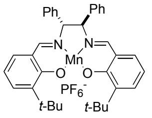
69% yield

- Radical Intermediate is postulated

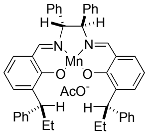
Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem Soc.* **1985**, *107*, 7606
Sriniviasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309

Jacobsen and Katsuki Enter the Game

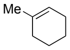
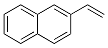
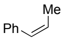
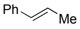
First moderately selective epoxidation of unfunctionalized olefins



A



B

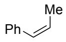
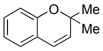
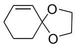
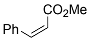
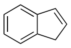
Olefin	Catalyst	yield,%	ee,%	previous best ee,%
	A	50	59	12
	A	72	67	36
	A	73	84	44
	B	26	44	
	A	93	20	16
	B	37	44	

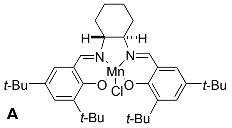
- Side-on approach of olefin is used to explain sense of enantioselection
- Superior enantioselectivity over porphyrin systems is attributed to chirotopic carbons in vicinity of metal

Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **1990**, *112*, 2801
Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345

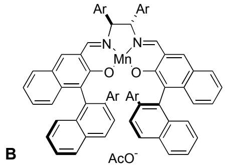
Jacobsen and Katsuki Achieve High Levels of Enantioselectivity

Ligand modification provides crucial difference

Olefin	Catalyst	yield,%	ee,%
	**A**	81	92
	B	16	90
	**A**	72	98
	B	60	>99
	**A**	63	94
	**A**	65	89
	**B**	82	94



A



B

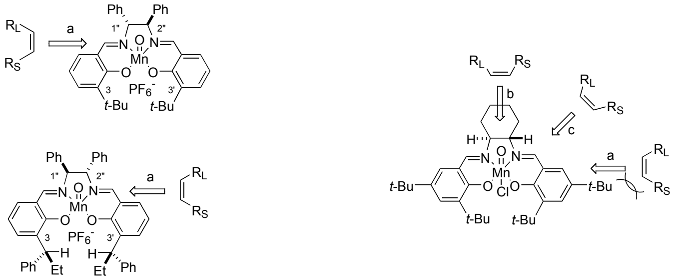
- Axially locked substituents on diimine bridge lead to more effective differentiation of olefin approach
- Locking the diimine bridge provides opposite sense of asymmetric induction
- Increased steric bulk at C_3 and C_5 enhances enantioselectivity

Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063
Sasaki, T.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827

Debate over Approach of cis-Olefins

Side-on approach is accepted model for oxo M-porphyrin and oxo M-salen complexes

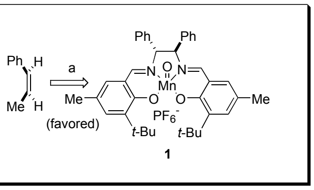
- First and second generation ligands discriminate olefin approach differently



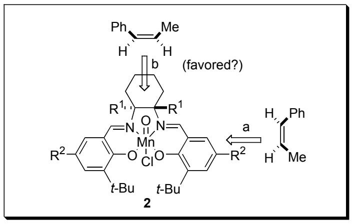
- Side-on approach allows for approach of incoming olefin by three pathways with second generation ligand

Jacobsen Rules Out Approach A for his Second Generation Ligand

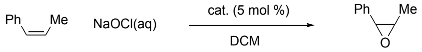
Argument is solely based on sterics



1



2



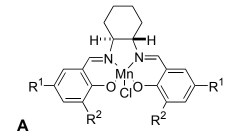
Catalyst	R^1	R^2	yield, %	ee, %	epoxide config
1	N/A	N/A	88	84	1*R*,2*S*-(+)
2	Me	Me	54	49	1*S*,2*R*-(-)
2	Me	*t*-Bu	56	55	1*S*,2*R*-(-)
2	H	Me	87	80	1*S*,2*R*-(-)
2	H	*t*-Bu	81	92	1*S*,2*R*-(-)

- Catalyst 2 is less hindered than 1 in the vicinity of approach b
- Replacement of Me groups at R^1 with H further opens approach b
- Increasing steric bulk at R^2 (Me v. *t*-Bu) partitions olefin approach away from path a

Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063

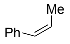
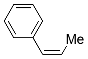
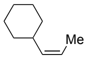
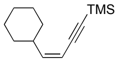
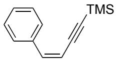
What Factors Contribute to Enantioselectivity?

Sterics alone do not explain enantioselectivity



A

- Electronic variation on substrate and ligand have pronounced effect on enantioselectivity and yield

Entry	Olefin	R^1	R^2	Yield(%)	ee (%)
1		NO_2	*t*-Bu		46
2		Me	*t*-Bu		80
3		OMe	*t*-Bu		86
4		*t*-Bu	*t*-Bu		90
5		*t*-Bu	*t*-Bu	81	92
6		*t*-Bu	*t*-Bu		50
7		*t*-Bu	*t*-Bu	65^a	98
8		*t*-Bu	*t*-Bu	34^a	35

electronic variation on ligand

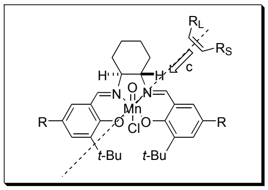
electronic variation on substrate

[a]Epoxide exists as a mix of cis and trans isomers. C_6H_{11}: 5.2:1, C_6H_5: 1:1

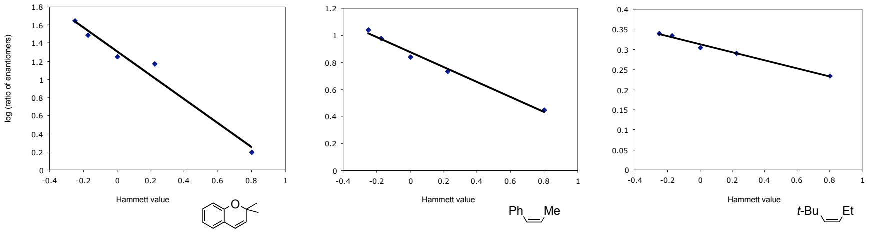
Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189

Katsuki Proposes a New Method of Olefin Approach

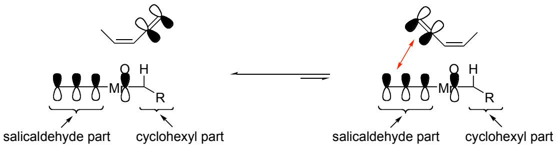
Electronic influence on olefin approach



- A linear correlation between ee and substituent sigma value indicates that substuent effects are electronic as well as steric.



- Olefins approaching along path c experience different electronic environments on different side of M-N axis

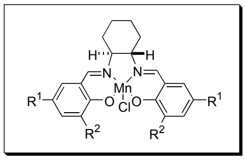


- Repulsive pi-pi electron interaction between the benzene ring of the salen ligand and the substituent are important

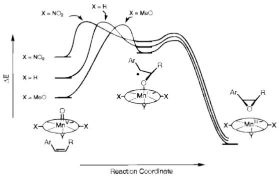
Hamada, T.; Irie, R. Katsuki, T. *Synlett*. **1994**, 479
Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189

Jacobsen Proposes a Different Interpretation

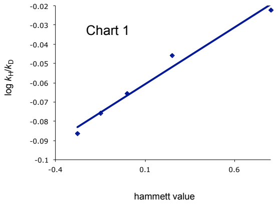
Ligand electronics modulate the reactivity of (salen)Mn oxo intermediate

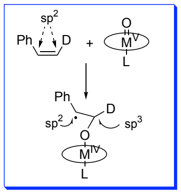


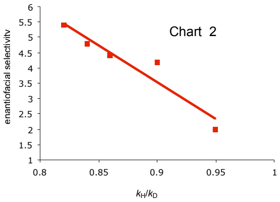
- Electron-donating groups lead to a less reactive (salen)Mn oxo intermediate, which results in a comparatively late transition state



- Since the transformation involves the encounter of two reactants which do not resemble each other at the origin of the reaction coordinate, more stereochemical communication can be passed in a later transition state





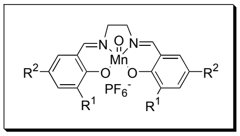


- The electronic character of the catalyst alters the degree of rehybridization of the ß-carbon and thus the position of the transition state (chart 1)
- Late transition states in the C-O bond forming step affords higher enantioselectivity in the epoxidation reaction (chart 2)

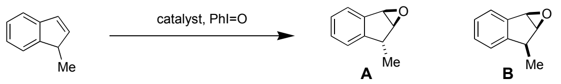
Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948

Case of 1-methylindene

Experimental Results do not fit model

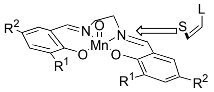


- Trans:cis ratio should improve with added steric bulk at R^1 and R^2



R^1	R^2	A:B
H	H	3:1
t-Bu	H	5.7:1
t-Bu	*t*-Bu	6.2:1

- *Is there a better model?*

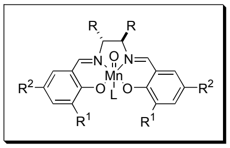


Salen ligand adopts a non-planar stepped conformation

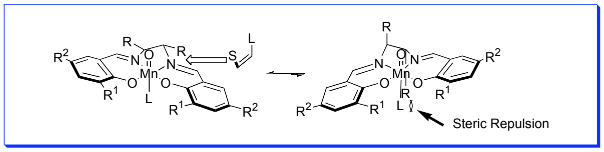
Noguchi, Y.; Irie, R.; Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4533

The Folded Structure

Explains sense of induction



- Salen complex exists in a equilibrium of two conformers which is controlled by axial and equitorial considerations of R groups on diimine bridge



- Olefin passes over benzene ring in the down position, thereby avoiding interaction with bulky group at R^2

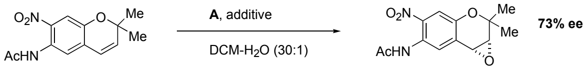
Oxo M-salen is known to exist in a non-planar, stepped conformation

- Kochi initially isolated an oxo(salen)chromium (V) complex as well as its pyridine *N*-oxide adduct and crystal structures of both species show a stepped comformation
- Oxo Cu(salen) complexes isolated in aziridinations are folded

Noguchia, Y.; Irie, R.; Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4523

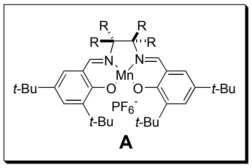
Experimental Support for Folded Structure

Use of achiral salen complex and a chiral ligand

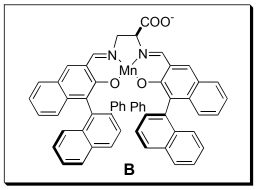


A: R= Me, Additive= (-)-Sparteine: 73% ee

- Presence of a chiral ligand in oxo Mn(salen) complex makes two conformations diastereotopic

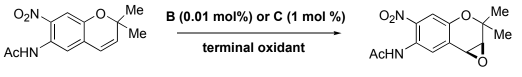


A



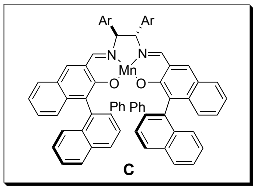
B

Carboxylate group on diimine bridge can lock ligand into one conformer

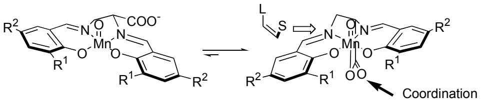


B: 99% ee, 92%, TON =9,200

C: >99% ee, 80%



C

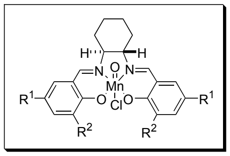


- **B** and **C** gives same sense of enantio-induction despite the opposite configurations of moieties on diimine bridge

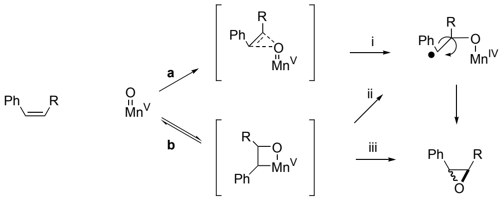
Hashiyata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**,1079
Hashiyata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541
Miura, K.; Katsuki, T. *Synlett*. **1999**, 783
Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1998**, *39, 4325*

Mechanism of Oxygen Transfer

Mechanism still in controversy

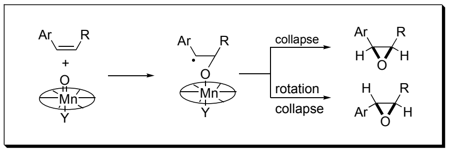


- **Path A -** Direct substrate attack at the oxo ligand with concerted C-O bond formation (i)
- **Path B -** Stepwise mechanism characterized by reversible formation of a metallaoxetane prior to epoxide formation either through a radical intermediate (ii) or through metallaoxetane decomposition (iii)



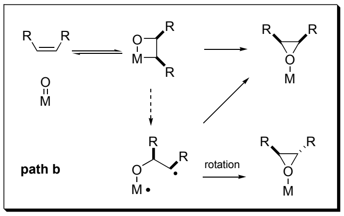
Initial evidence for path a

- Proposed by Groves and Kochi to explain early work
- *cis*- and *trans*-epoxides are formed from cis-olefins
- Conjugated olefins are isomerized to a greater extent than unstabilized olefins
- Mechanistic simplicity



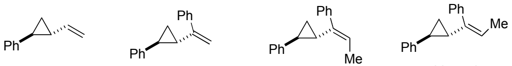
Katsuki, T.; *J. Mol. Cat. A* **1996**, *113*, 87

Evidence for Path B



1. Cyclopropane RAR

- Epoxidation of phenylvinylcyclopropanes gives corresponding epoxide without cleavage of cyclopropane ring

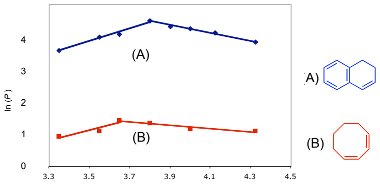


epoxide   epoxide   epoxide   epoxide and ring opened pdt

- Rate of rearrangement for phenylcyclopropane is very fast (>10^{10} s^{-1})

2. Non-linear relationship between enantioselectivity and temperature

- If a reaction involves reversible formation of diastereomeric intermediates and irreversible transformation of the intermediates to a product of another intermediate there is a possibility for a non-linear relationship between enantioselectivity and temperature
- The reversible formation of a metallaoxetane intermediate is a viable explanation for this observation



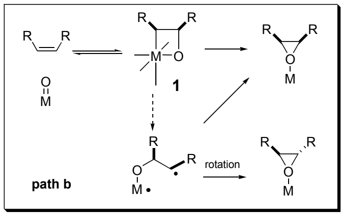
$P = \frac{\text{major enantiomer of epoxide}}{\text{minor enantiomer of epoxide}}$

3. Molecular modeling of transition state

- The enantioselectivity of the reaction can be explained by the energy difference between two diastereomeric metallaoxetane intermediates. The intermediate which leads to the major epoxide enantiomer is 11 kcal/mol more stable.

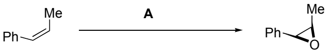
Norrby, P-O.; Linde. C.; Akermark. *J. Am. Chem. Soc.* **1995**, *117*, 11035
Katsuki, T.; *J. Mol. Cat. A:* **1996** (*113*) 87

Evidence Against Path B

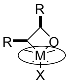


Metallaoxetane requires apical coordination site

- The formation of a metallaoxetane requires a coordination site adjacent to the oxo ligand for the M-C bond, **1**

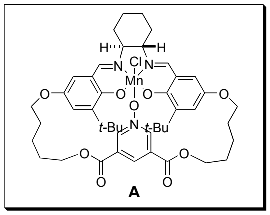


increased ee, rate, conversion and cis/trans ratio



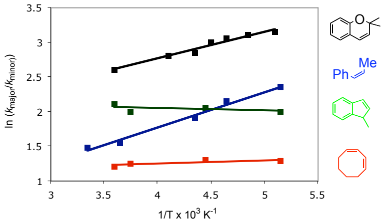
2

- Axial binding throughout the catalytic cycle implies that the adjacent sites required for metallaoxetane are unavailable and the reaction must proceed through a highly strained intermediate **2**



A

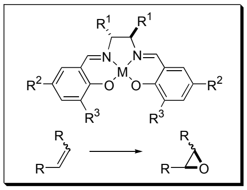
Jacobsen attempts to reproduce non-linear Eyring plots



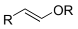
- Eyring plots for 4 olefins all showed linear behavior

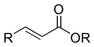
Finney, N.S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1997**, *36*, 1720

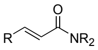
Salen Ligand Mediated Epoxidation - Scope

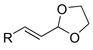


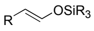
Functional group tolerance

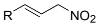

ethers

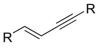

esters


amides

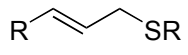

acetals

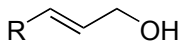

silyl ethers


nitros

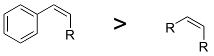

acetylines

Functional group intolerance


sulfides

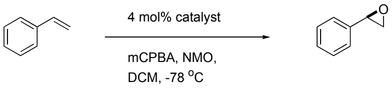

allylic alcohols

Conjugated vs. non-conjugated olefins



R= alkyl

Terminal Olefins

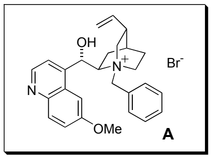

4 mol% catalyst

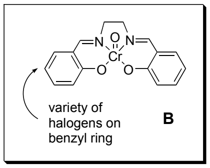
mCPBA, NMO, DCM, -78 ^oC

86% ee
88% yield

R^1: Ph
R^2: OTIPS
R^3: H

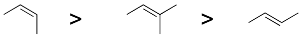
Salen Ligand Mediated Epoxidation- Scope



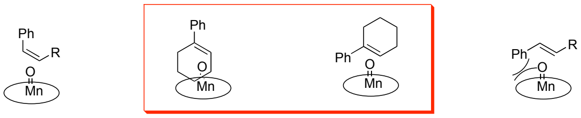


variety of halogens on benzyl ring

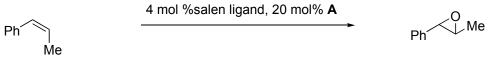
Olefin geometries



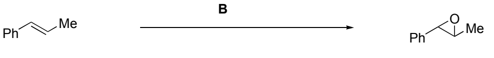
- Stereochemical induction for trisubstituted olefins is opposite of disubstituted olefins



Trans - olefins


4 mol %salen ligand, 20 mol% **A**

90% ee
27:1

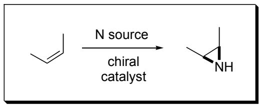

B

>88% ee
>80% yield

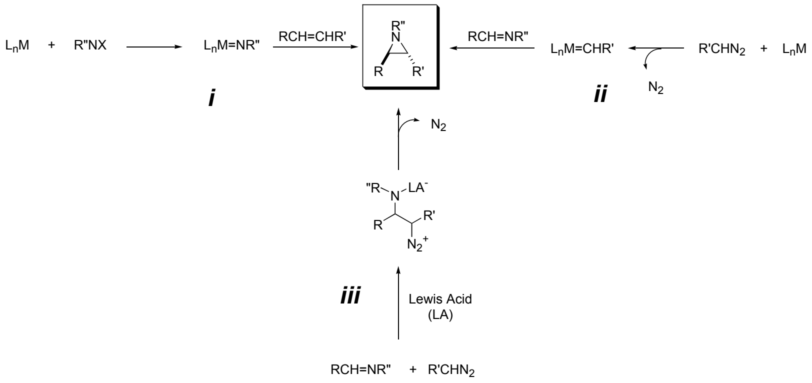
O'Mahony, C. P.; McGarrigle, E. M.; Renehan, M. F.; Ryan, K. M.; Kerrigan, N. J.; Bousquet, C.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 3435

Aziridination

Three mechanistically different approaches



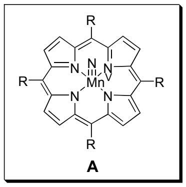
i - Azirdination via Imido Transfer Catalysis
ii - Azirdination via Carbene Transfer Catalysis
iii - Azirdination by Lewis Acid catalysis



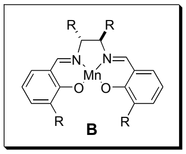
Jacobsen, E. N. *Comprehensive Asymmetric Catalysis...*

Historical Development of Salen Mediated Aziridination

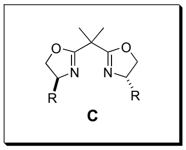
Groves and Evans provide scientific background



A

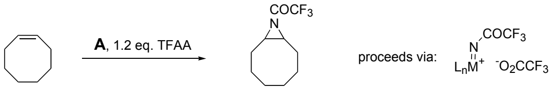


B

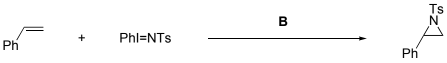


C

- 1983 Groves demonstrated stoichiometric azirdination of alkenes by way of *in situ* generated manganese-nitridocomplex

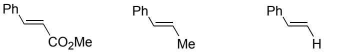


- 1992, Burrows reported aziridination using salen ligands, but without enantioselectivity



20% yield
0% ee

- In 1991 Evans discovered that low-valent copper can catalyze aziridinations by way of ligand **C**



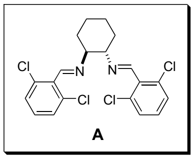
R=Ph	R=*t*-Bu	R=*t*-Bu
63%, 94% ee	62%, 70% ee	86%, 78% ee

- High levels of enantioselectivites with cinnamate esters, but difficulties with other substrate classes

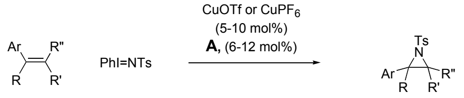
Groves, J.T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073
Evans, D.A.; Faul, M.M.; Bilodeau, M.T. *J. Org. Chem.* **1991**, *56*, 6744
O'Connor, K. J.; Wey, S. J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001
Evans, D.A.; Faul, M.M.; Bilodeau, M.T.; *J. Am. Chem. Soc.* **1994**, *116*, 2742

Jacobsen Discovers Cu(salen) Aziridination

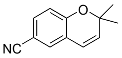
Offers synthetically useful levels of enantioselectivity



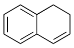
A



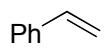
CuOTf or $CuPF_6$
(5-10 mol%)
A, (6-12 mol%)



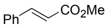
75%
>98% ee



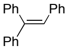
70%
87% ee



79%
(3:1 cis:trans)
66% ee cis
81% ee trans



92% ee



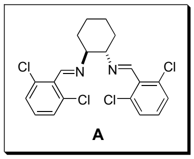
94% ee

- Reaction scope is limited: requires olefin to be in conjugated with aromatic group for high ee

Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326
Li, Z. PhD thesis, Harvard University **1997**

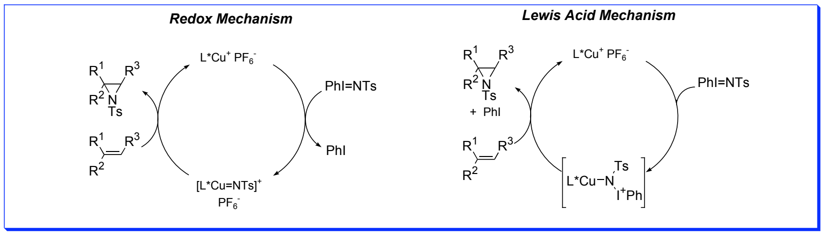
Mechanism of Cu(salen) Catalyzed Aziridination

Two reasonable mechanisms can be postulated

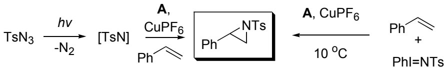


A

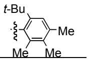
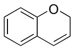
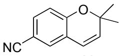
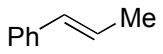
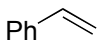
- **Redox Mechanism** - Analagous to cyclopropanation mechanism, involves discrete formation of Cu-nitroid intermediate
- **Lewis Acid Mechanism** - Copper complex functions as a Lewis Acid catalyst



- Two pieces of evidence for the redox mechanism:



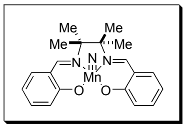
Both routes provide product with 41% ee

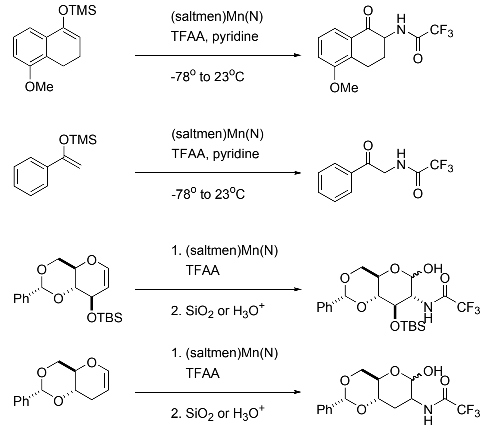
	Ar= Ph	
	62	63
	82-85	84
	71	70
	42	39-43

Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889

Carreira Discovers a Nitro-Transfer Amination of Enols

New class of L*Mn developed





(saltmen)Mn(N)
TFAA, pyridine
-78° to 23°C
78%

(saltmen)Mn(N)
TFAA, pyridine
-78° to 23°C
69%

1. (saltmen)Mn(N)
TFAA
2. SiO_2 or H_3O^+
75%
7:1 selectivity

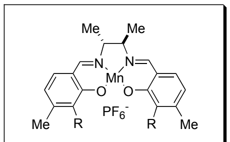
1. (saltmen)Mn(N)
TFAA
2. SiO_2 or H_3O^+
75%
1:1 selectivity

- All reactions involve stoichiometric imidotransfer to alkene
- Requires electron-rich olefins

Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *116*, 915
Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179

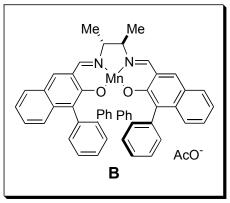
Recent Advances in Asymmetric Aziridination

Katsuki returns



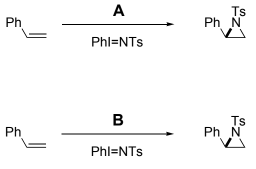
R: (*R*)-(4-*t*-BuC_6H_4)(Et)CH

A



B

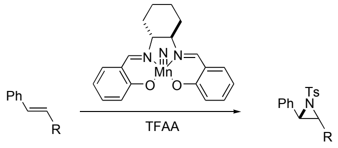
- Move to ligand with less bulky substituents on diimide bridge proves critical, but substrate scope is very limited



61% ee
9%

94% ee
76%

- Asymmetric version of Carreira's reactant

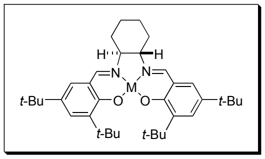


R=*i*-Pr: 96% ee, 53%
R=Me: 85% ee, 72%

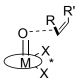
Noda, L.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993** 463
Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, 37, 9246
Minakata, S.; Ando, T.; Nishimura, M.; Ryu, I. Komatsu, M. *Angew. Chem. Int. Ed.* **1998**, 37, 3392

Ring-Opening of meso-Epoxides

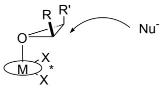
Metal selection provides key lead



- Epoxidation transition state resembles the ground state structure of coordinated epoxides

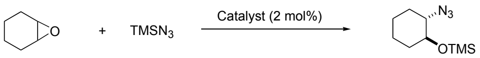


Epoxidation Catalysis



Lewis Acid Activation of Epoxides

- Would require a (salen)M complex that favored epoxide coordination

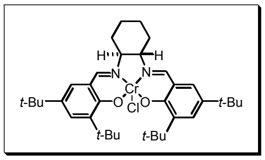


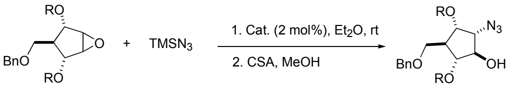
M	%conv	%ee
AlCl	73	5
$TiCl_2$	74	7
CrCl	95	88
MnCl	12	2
CoI	22	48

Martinez, L. E.; Leighton, J. L; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897
Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924

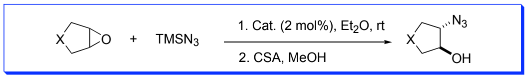
Scope of Epoxide Ring-Opening Reactions

Sensitive to local steric environment

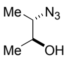




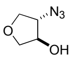
R=TMS, TBDMS: no reaction, R=Bn: 98% ee, >95%



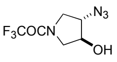
- Tolerant of a range of functionalities



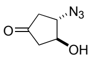
82% ee
65%



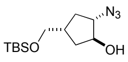
97% ee
96%



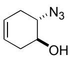
95% ee
87%



94% ee
77%

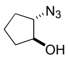


96% ee
95%

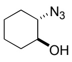


92% ee
85%

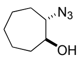
- Enantioselectivity decreases as ring size increases



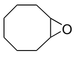
93% ee
97%



85% ee
96%



42% ee
99%

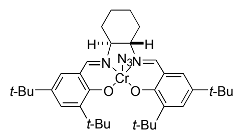


no reaction

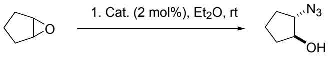
Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N.; *J. Am. Chem. Soc.* **1995**, *117*, 5897
Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7893
Martinez, L. E.; Nugent, W. A.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 7963
Kassab, D. J.; Ganem, B. *J. Org. Chem.* **1999**, *64*, 1782

Epoxide Ring-Opening Reaction

Kinetics and Implications

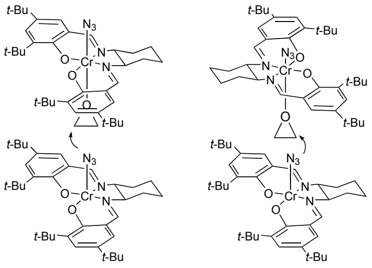


- Reaction is second order with respect to catalyst



rate=$k[\mathbf{Cat^{*}N_2}]^2[\text{epoxide}]^{-1}[HN_3]^0$

- Two geometries can be envisioned for selectivity-determining step

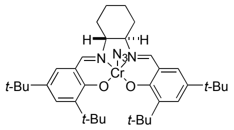


"head to head" "head to tail"

Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924

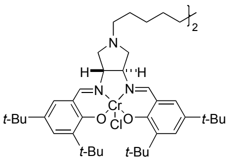
Dimeric Catalysts in Epoxide-Opening Reactions

Suggestive of geometry of enantiodetermining step

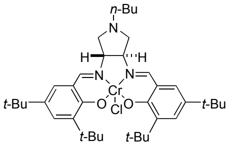


A

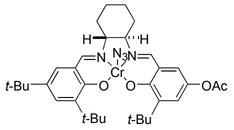
- Attempts to develop a "head to head" catalyst



8% ee



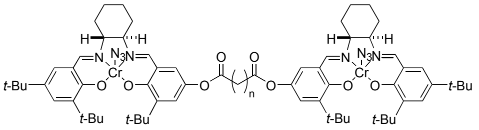
90% ee



B

- Attempts to develop a "head to tail" catalyst

Catalyst	n	%ee	k ($M^{-1}min^{-1}$)
A		93	0.6
B		94	1.2
C1	2	90	15.7
C2	4	90	15.1
C3	5	93	27.4
C4	6	93	15.8
C5	7	93	7.9
C6	8	94	10.5
C7	10	92	4.4

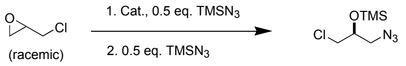


C1: n=2, **C2**: n=4, **C3**: n=5, **C4**: n=6, **C5**: n=7, **C6**: n=8, **C7**: n=10

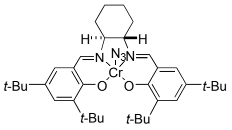
Konsler, R. G.; Karl. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780

Resolution of Terminal Epoxides

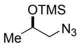
Practical Application of the ARO

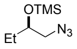


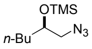
97% ee
76%

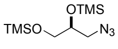


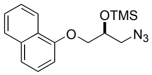
- Reaction is general for terminal epoxides

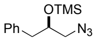

97% ee, 97%

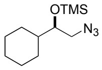

97%ee, 83%

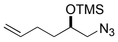

97% ee, 89%

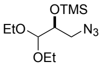

96% ee, 96%

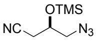

93%ee, 74%


93%ee, 94%


97% ee, 84%


98% ee, 94%


89% ee, 96%


92% ee, 80%

Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420

Conclusions

- **M(salen) system constitutes a privelidged class of catalsysts capable of participating in myriad of asymmetric reactions**
- **Efforts in salen ligand catalysis were pioneering in the field of ligand controlled asymmetric catalysis**
- **Enantioselectivity in M(salen) system is governed by a complicated interplay of electronic and steric variables**

Future Research Considerations

- **Develop a more thorough understanding of the mechanistic pathway of M(salen) systems**
- **Expand substrate scope: simple terminal olefins and *trans*-olefins remain a problem**
- **Make aziridinations synthetically feasible for non-conjugated olefins**