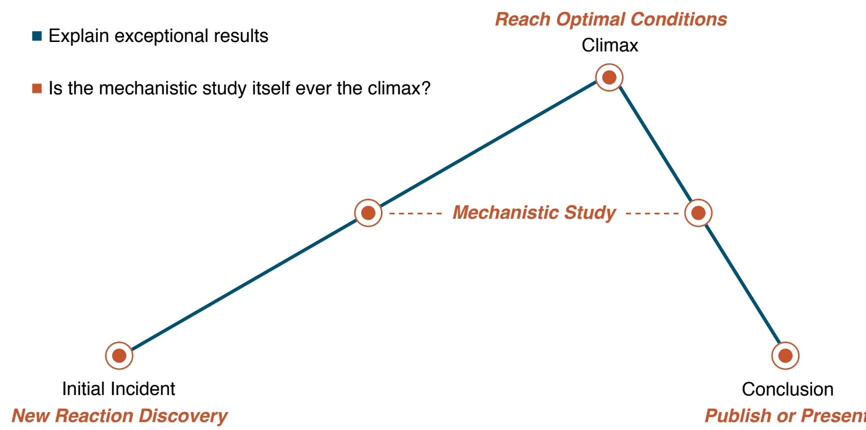
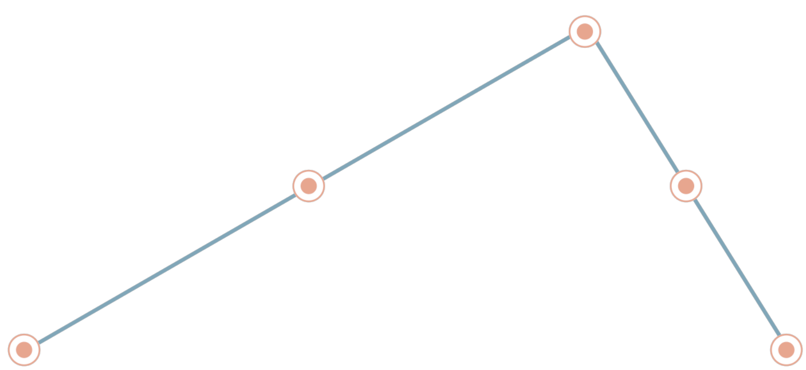
A Thought Exercise - Mechanistic Study in the MacMillan Group

Why (and When) do we do mechanistic studies?

- Aid with reaction development
- Explain exceptional results
- Is the mechanistic study itself ever the climax?

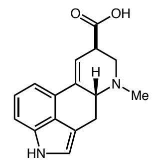


Houk/Martinelli Ergot Alkaloid Oxidations

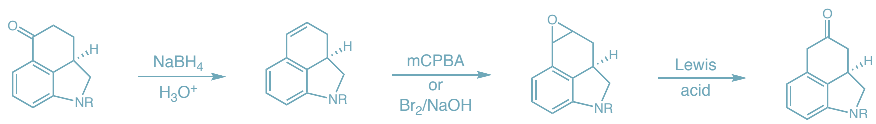


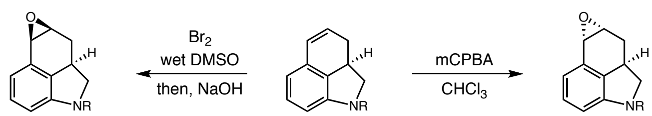
High Selectivity in Ergot Epoxidation

- Kornfeld-Woodward ketone
- Widely used in ergot alkaloid synthesis
- Often converted to 2-keto isomer



Kornfeld, Woodward *et al.*
J. Am. Chem. Soc. **1956**, *78*, 3087.

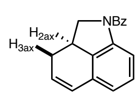




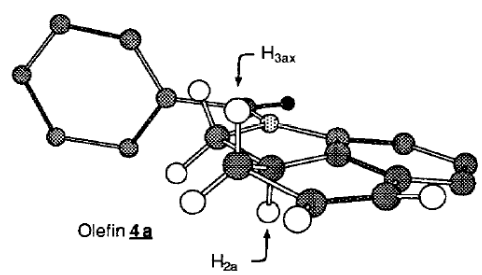
99 : 1 dr **98 : 2 dr**

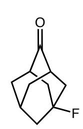
Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30*, 3935.

Steric Arguments are Minimal

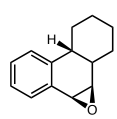


- Axial hydrogen atoms are conflicting
- Electronic nature of diastereoselectivity

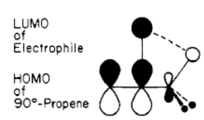




le Noble
J. Org. Chem. **1989**, *54*, 997



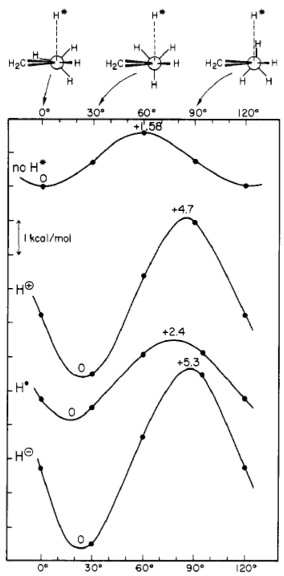
Jerina
J. Am. Chem. Soc. **1982**, *104*, 1972



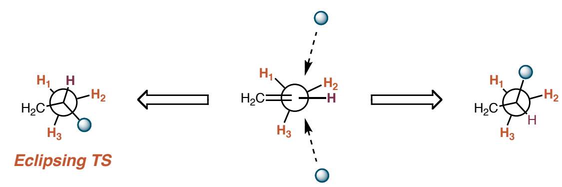
Houk
J. Am. Chem. Soc. **1981**, *103*, 2438

Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30*, 3935.

Torsional Effects on Transition States



- Inherent barrier to rotation around propene: 1.58 kcal/mol
- Barrier to rotation is significantly larger in transition state
- Consider addition to opposite faces of same rotamer



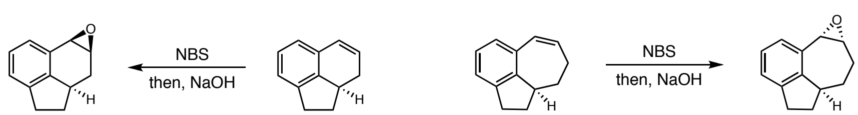
". . . the stereochemical rule found here can be stated

. . . to be a result of magnified torsional effects occuring

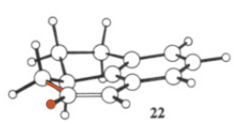
in the transition states of addition reactions."

Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438.

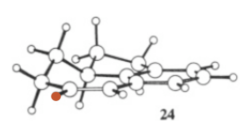
Houk/Martinelli Home Run Experiment

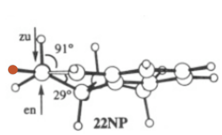


99:1 dr ***Differ by one –CH_2– unit*** **98:2 dr**

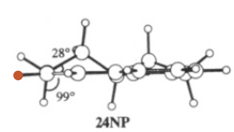


- No change in axial H



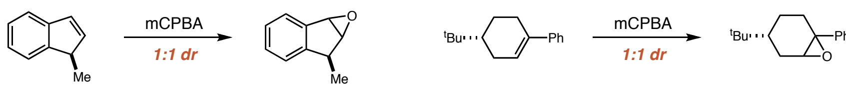


- Opposite torsional steering



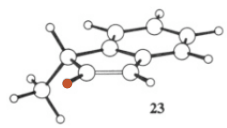
Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Leanna, M. R.; Audia, J. E.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204

Torsional Effects - A Word of Caution

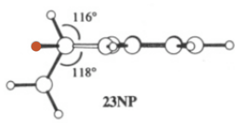


■ No torsional bias

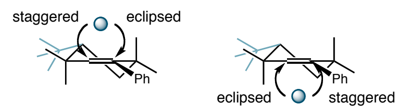
■ Equal and opposite torsional bias



23



23NP

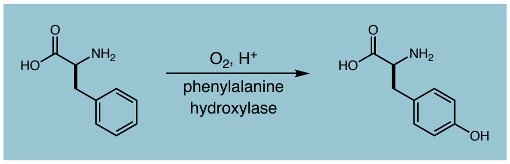


"These results provide powerful examples of the magnitude of torsional steering upon the stereoselectivities of additions to π-bonds."

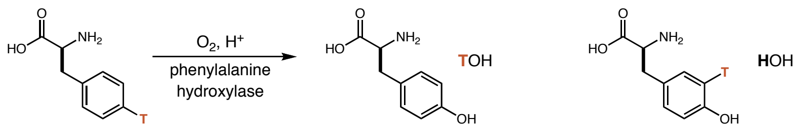
Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchinson, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J. *J. Org. Chem.* **1994**, *59*, 2204

The NIH Shift

In-Situ Reaction Monitoring - Historic Methods



- First phenolase discovered 1955
- Oxygen atom from $^{18}O_2$
- How to direcly measure kinetics?

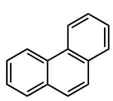


- Minute amounts of tritium can be measured in aliquots

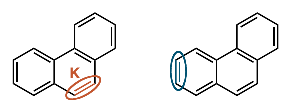
"NIH-Shift"

Mason, H. S.; Fowlks, W. L.; Peterson, E. *J. Am. Chem. Soc.* **1955**, *77*, 2914.
Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science* **1967**, *157*, 1524.

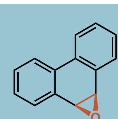
Mechanistic Basis of Carcinogenicity



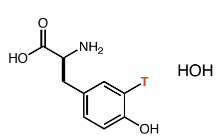
- Cancer of chimney sweeps



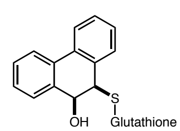
- "K-region" of highest toxicity



Arene Oxides



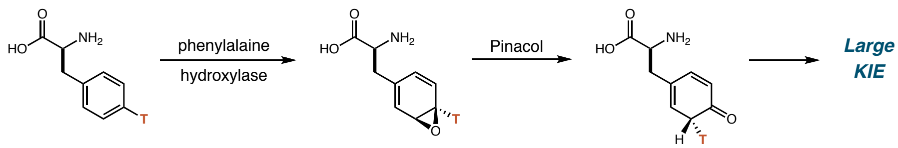
- NIH Shift



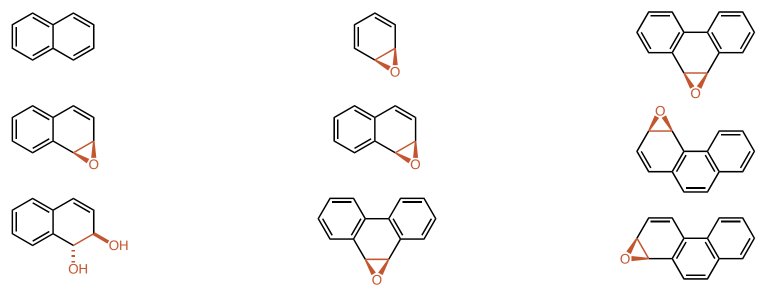
- Biological conjugates

Jerina, D. M.; Daly, J. W. *Science*, **1974**, *185*, 573.

NIH Shift – Pinacol Rearrangement

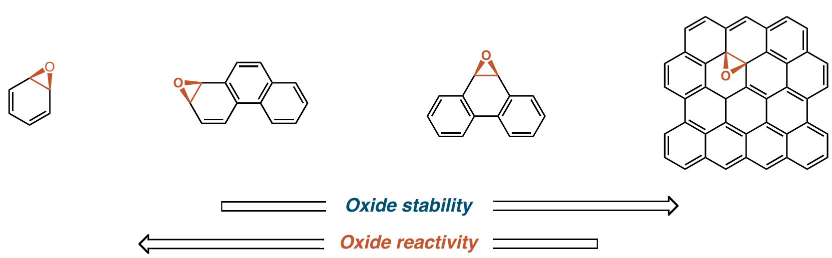


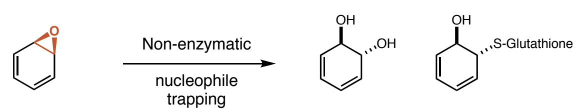
- Compare arene vs. oxide
- Compare arene series
- Compare arene isomers

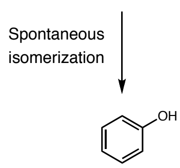


Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science*, **1967**, *157*, 1524.

'Goldilocks' Postulate for Carcinogenicity



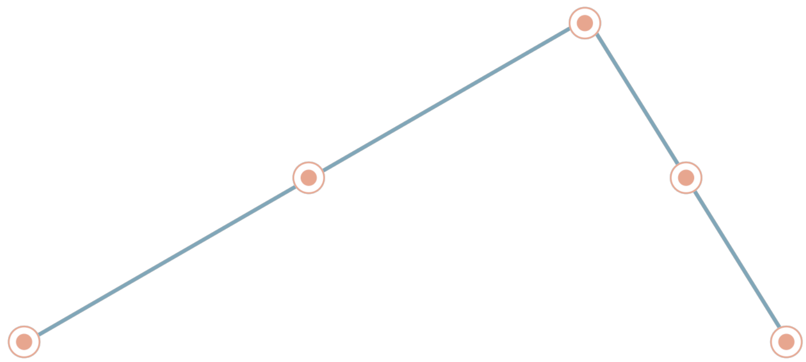




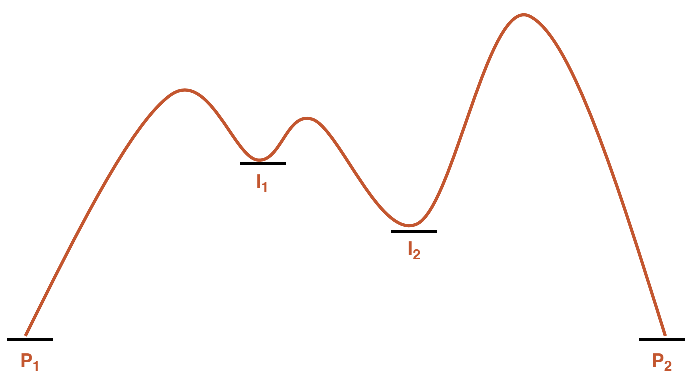
- Lifetime of highly reactive oxides too short for high carcinogenicity
- K-region oxides reactive enough to alkylate important biomolecules
- K-region oxides stable enough to require enzymatic degredation

Jerina, D. M.; Daly, J. W. *Science*, **1974**, *185*, 573.

Halpern Mechanism for Hydrogenation



Curtin-Hammett Principle

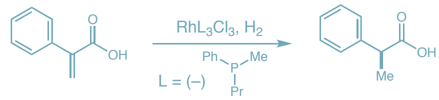


- A kinetic (mathematical) concept
- If I_1/I_2 interconversion is rapid, selectivity is determined by I to P transition state
- To what extent would this affect important catalytic systems?

Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111.

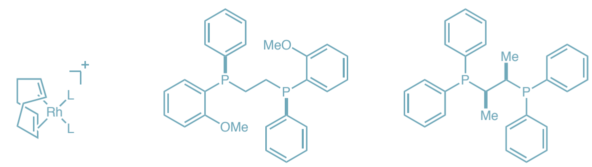
Knowles' Hydrogenation of Enamides

- Knowles' original system

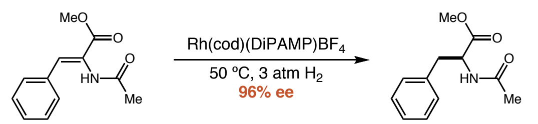


15% ee
(60% ee ligand)

- Finalized system



(R,R)–DiPAMP (R,R)–CHIRAPHOS

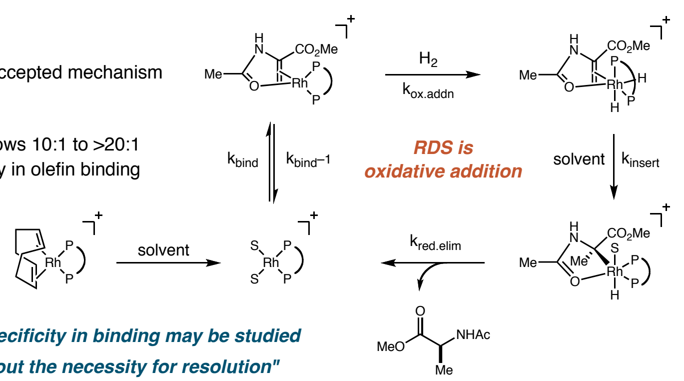


- Requires multi-point binding
- Z-olefin much more selective

Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445.
Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.

Original Mechanistic Studies

- Widely accepted mechanism
- NMR shows 10:1 to >20:1 selectivity in olefin binding



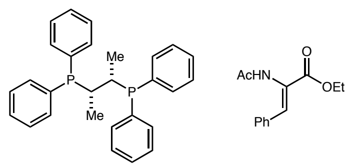
". . diastereospecificity in binding may be studied by NMR without the necessity for resolution"

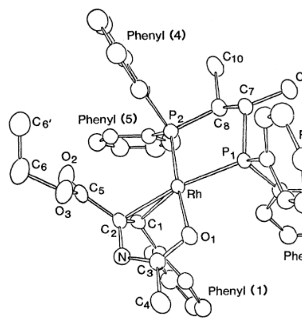
Upon addition of H_2 at –50 °C only minor diastereomer in NMR reacts

Brown, J. M.; Chaloner, P. A. *Tetrahedron Lett.* **1978**, *21*, 1877.
Brown, J. M.; Chaloner, P. A. *Chem. Commun.* **1978**, 321.
Brown, J. M.; Chaloner, P. A. *Chem. Commun.* **1980**, 344.

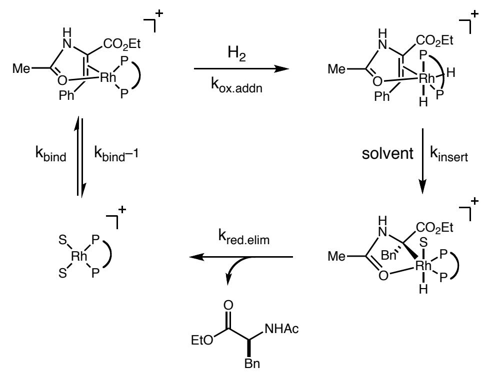
Halpern's X-Ray Structure

- Halpern solves structure of related complex

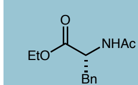




19



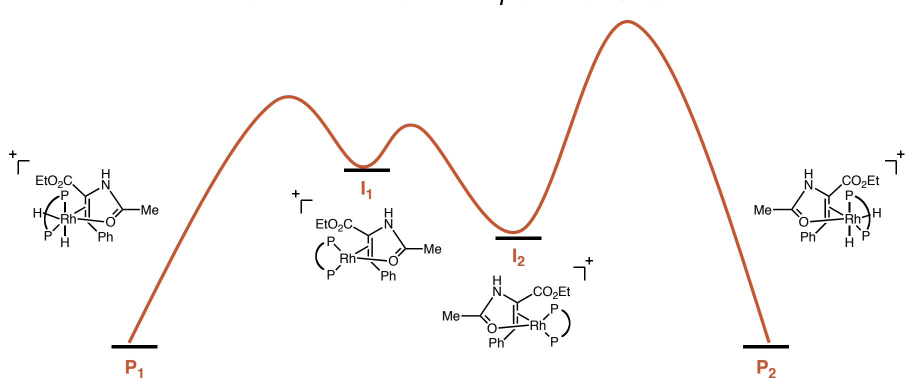
Not formed



Major product
>95% ee

Halpern, J. *Science*, **1982**, *217*, 401.

Curtin-Hammett Principle – Revisited

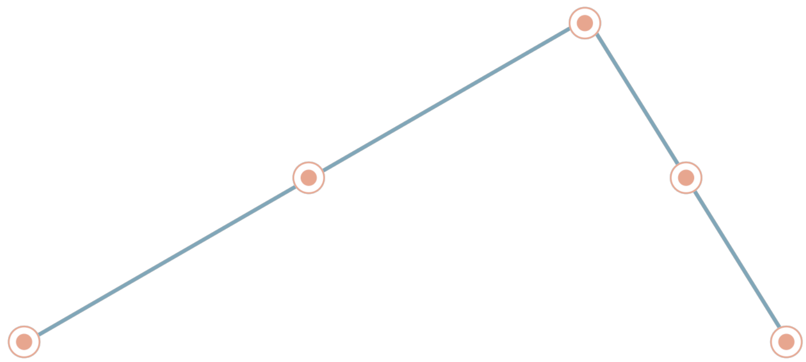


- Predicted effect of increasing p_{H2}?
- Eventually, outcompete isomerization
- Inverse temperature effects

p_{H2}(atm)	%ee (S,S-BPPM)
1	84
5	62
20	21
50	5
100	8

Halpern, J. *Science*, **1982**, *217*, 401.
Sinou, D. *Tetrahedron Lett.* **1981**, *22*, 2987.

Olah's Structure of Non-Classical Carbocations



Symposium-In-Print

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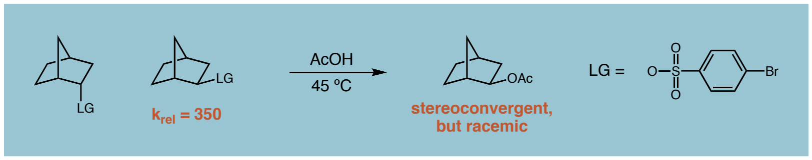
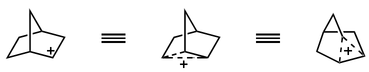
VOLUME 16 NUMBER 12 DECEMBER, 1983

"The Great Carbocation Problem"	Joseph F. Bunnett, editor-in-cheif of Accounts
"Inductivity and Bridging in Carbocations"	Cyril A. Grob
"The Energy of the Transition States and the Intermediate Cation in the Ionization of 2-Norbornyl Derivatives. Where is the Nonclassical Stabilization Energy?	Herbert C. Brown
"Conclusion of the Classical-Nonclassical Ion Controversy Based on the Structural Study of the 2-Norbornyl Cation"	George A. Olah, G. K. Surya Prakash Martin Saunders
"An Innocent Bystander Looks at the 2-Norbornyl Cation"	Cheves Walling, editor-in-cheif JACS

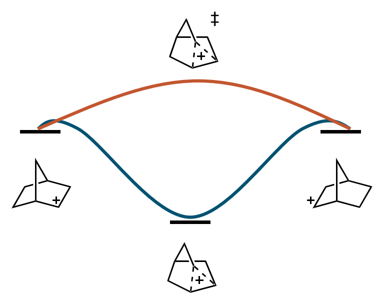
Winstein's Norbornyl Solvolyses



■ Proposed delocalized cation intermediate



True Question: Intermediate vs T.S.



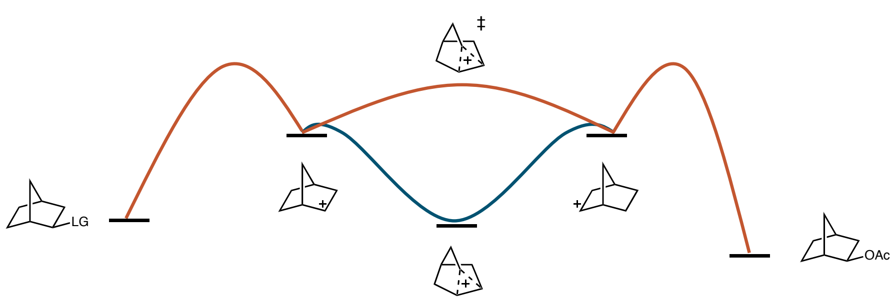
H. C. Brown's Objections

■ Endo solvolysis is sterically encumbered

■ Substitution to make 3º cation skews results

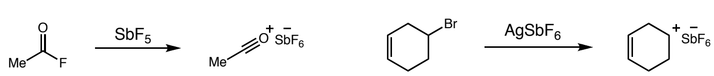
Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.

True Problem: Observing Reactive Intermediates



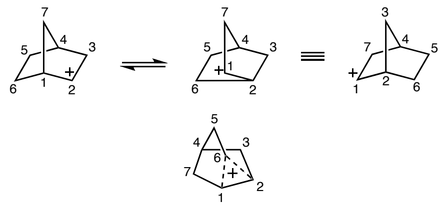
■ Effect of substitution on LG ionization/OAc capture

■ Development of non-protic stable ion media

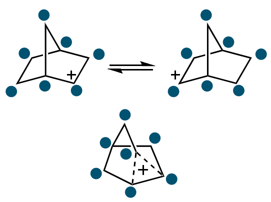


Olah, G. A.; Tolgyesi, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 5031.
Olah, G. A.; Kuhn, S. J.; Tolgyesi, W. S.; Baker, E. B. *J. Am. Chem. Soc.* **1962**, *84*, 2733.

^{1}H NMR of Norbornyl Carbocations

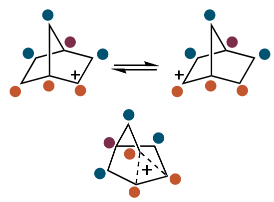


Room Temperature



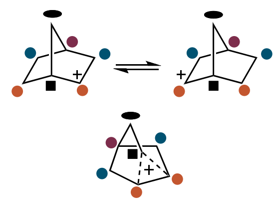
3.10

−100 ºC (2,3-H shift frozen)



1.93 2.82 4.92

−156 ºC (1,2,6-H shift frozen)



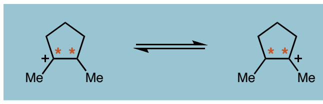
2.13 2.82 6.75

3.17 1.37

C(1)–C(6) to C(1)–C(2) Wagner-Meerwein shift would have to be ≤3 kcal/mol

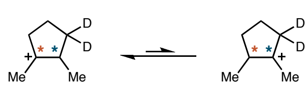
Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M.; Anet, F. A. L. *J. Am. Chem. Soc.* **1982**, *104*, 7105.

Isotopic Perturbation of Chemical Shift



- 1,2-hydride degenerate shift is rapid even at −130 ºC
- δ200 ppm (Avg. 50% 350 ppm, 50% 50 ppm for e.g.)

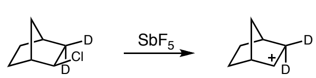
Isotopic Substitution



- Equilibrium isotope effect: 2 signals in ^{13}C

If 50.1:49.9 equilibrium: δ200.3, 199.7 (Δ0.6 ppm)

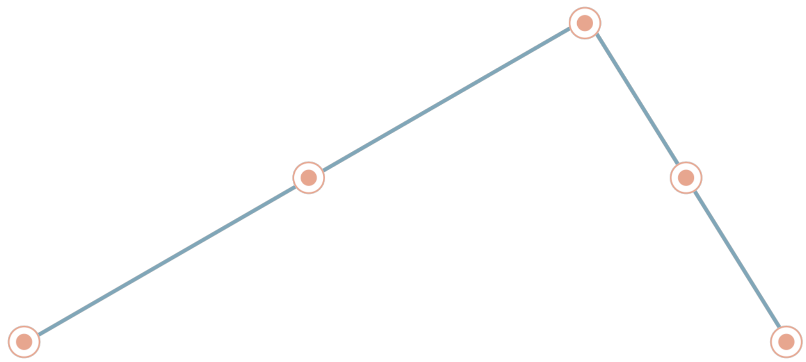
In reality: Δ105.3 ppm



2-norbornyl: no peak splitting

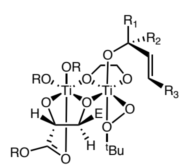
Saunders, M.; Kates, M. R. *J. Am. Chem. Soc.* **1983**, *105*, 3571.
Saunders, M.; Telkowski, L.; Kates, M. R. *J. Am. Chem. Soc.* **1977**, *99*, 8070.
Saunders, M.; Jaffe, M. H.; Vogel, P. *J. Am. Chem. Soc.* **1971**, *93*, 2558.

Jacobsen's Mechanism for Epoxidation



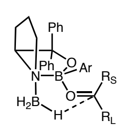
Asymmetric Induction Strategies (Early)

Dual activation (covalent)

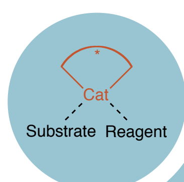


Titanium-catalyzed epoxidation

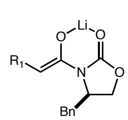
Dual activation (coordination)



Boron-catalyzed reduction

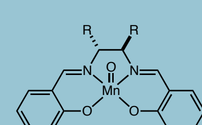


Oxazolidinone alkylation



Activation of substrate

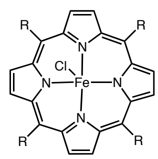
Mn-catalyzed epoxidation

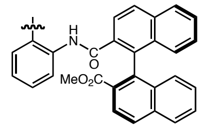


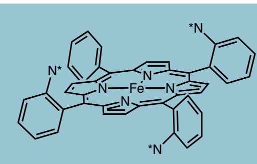
Activation of reagent

What methods are available to increase asymmetry when the substrate is not bound to catalyst?

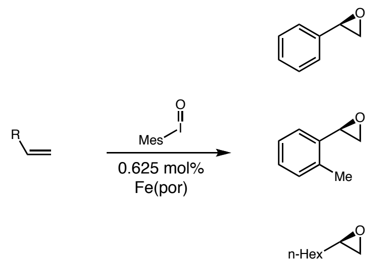
Groves' Chiral Porphyrin Catalysts







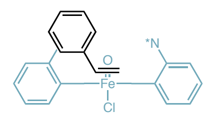
αβαβ–diastereomer



67% yield
48% ee

58% yield
16% ee

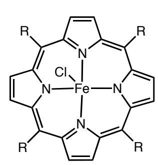
31% yield
20% ee

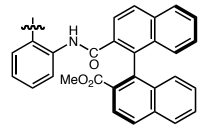


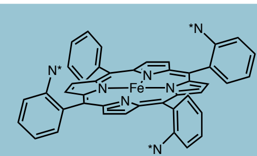
Model for stereoinduction?

Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

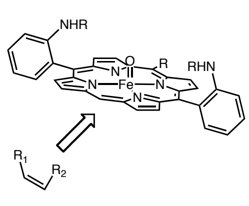
Groves' Chiral Porphyrin Catalysts





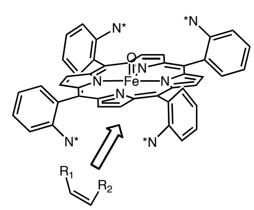


αβαβ–diastereomer



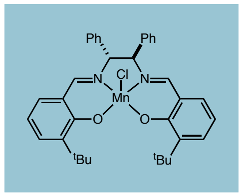
αβαβ–diastereomer facial selectivity
$\Delta\Delta G^{\ddagger}$ = 0.34 kcal/mol

ααββ–diastereomer yields racemic product

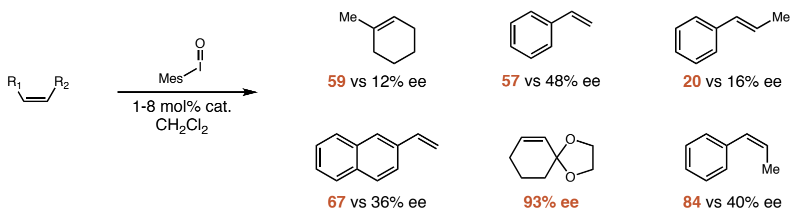


Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.

Original Salen Catalyst a Modest Improvement



- Chiral information closer to Mn center
- Simplified synthesis
- Ability to easily tune steric/electronic properties

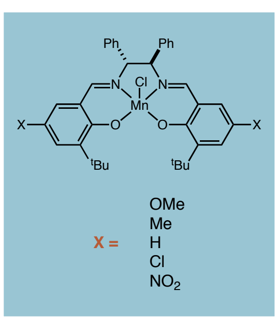


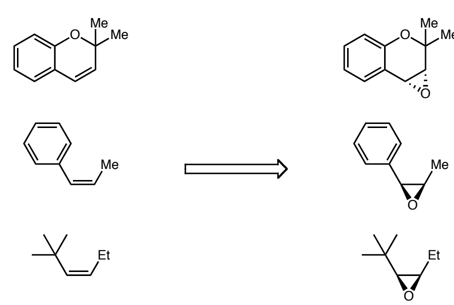
Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

Electronic Tuning of Asymmetric Catalysis

Electronic Tuning of Asymmetric Catalysts

Eric N. Jacobsen,* Wei Zhang, and Mehmet L. Güler

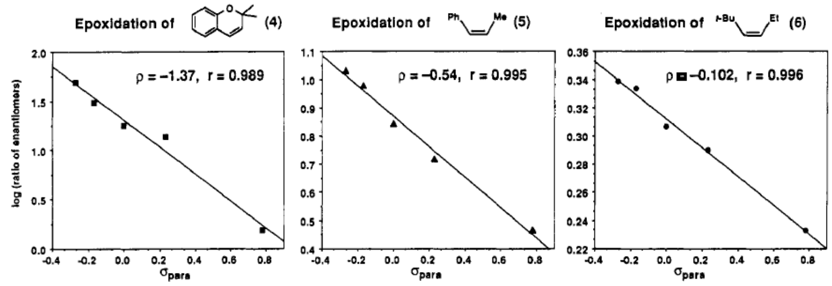




"To our knowledge, the effect of varying the electronic properties of chiral catalysts has never been systematically assessed in practical systems."

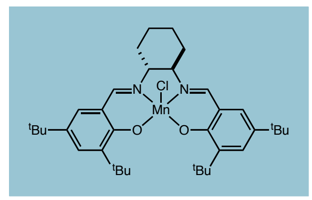
Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.

Linear Free-Energy Effects of Substitution



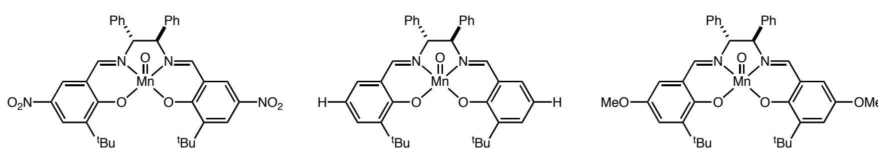
- Direct relationship – donating ability increases ee

"If changes in enantioselectivity are interpreted according to a simple Hammond postulate argument, this also raises an important general consideration for catalyst design."



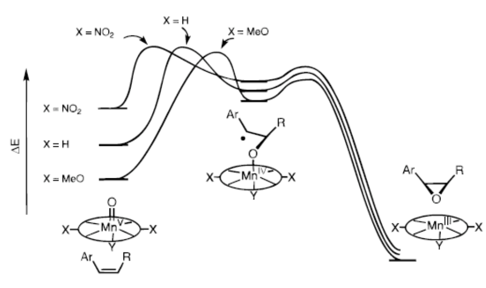
Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.
Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.

Hammond Analysis of Epoxidation



Mn-oxo stability

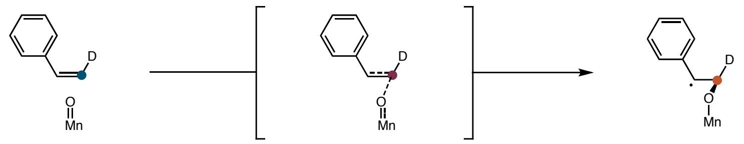
Mn-oxo reactivity



- Less reactive oxo = later TS
- Later TS = better chiral relay
- How could this ever be proven?

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

Secondary Isotope Effects

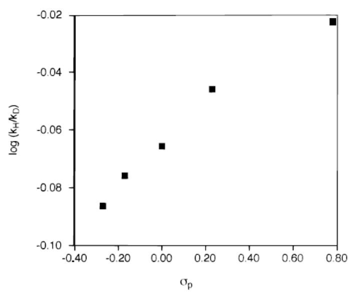


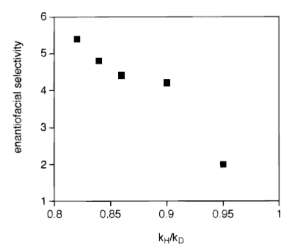
More sp^2-like
Smaller KIE

Position
of
transition state

More sp^3-like
Greater KIE

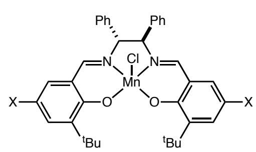
- KIE values correlate with σ
- KIE values correlate with **facial selectivity**



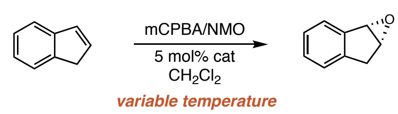


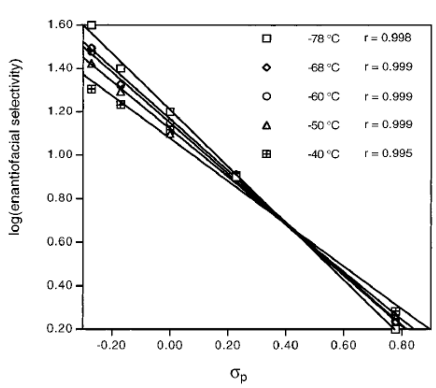
Paluck, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

Jacobsen's Home-Run Experiment



X = OTIPS, OMe, Me, H, Br, NO_2



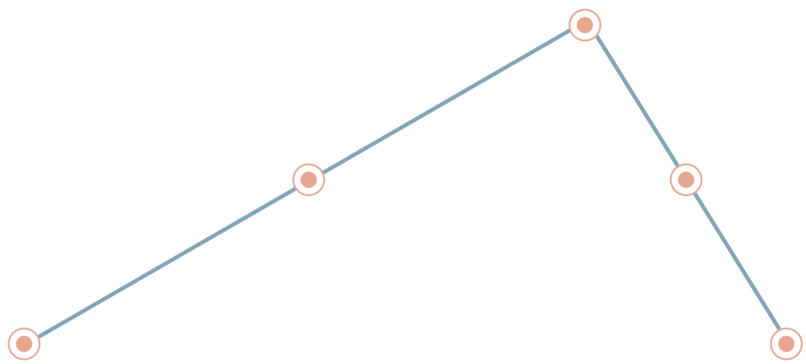


- "Isoelectronic" point shows selectivity depends on 1 variable
- Position of TS is only variable that could explain all results

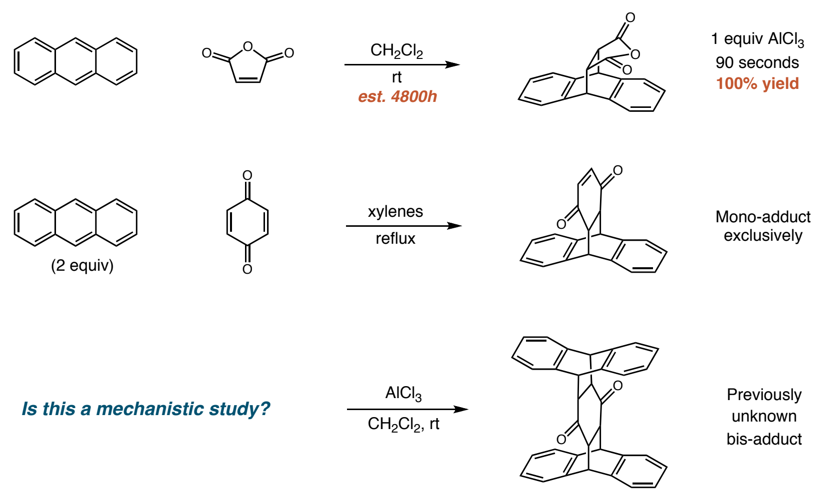
"The observations made in this study may therefore hold general implications for the design of asymmetric catalysts, particularly those that proceed without substrate precoordination"

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

Yates' Lewis Acid Catalysis



Lewis-Acid Accelerated Diels-Alder Reaction



Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.