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Ready; Catalysis Intro

Advanced Synthesis and Catalysis, Spring 2011

Or: How to make more molecules more complex more quickly with less effort/material/waste

Objective: Provide detailed description of the fundamental principles of catalysis
Enable students to apply known catalysts to or develop new catalysts for the synthesis of complex molecules

Required Text:
Transition Metals in the Synthesis of Complex Organic Molecules, Hegedus

Helpful Texts:
Principles and Applications of Organotransition Metal Chemistry, Collman, Hegedus, Norton, Fink
The Organometallic Chemistry of the Transition Metals, Crabtree; Prof. M-Christina White's lecture notes: http://www.courses.fas.harvard.edu/~chem153/ (many of my notes are taken from these, with permission)

Class Requirements and Format:
26 lectures – most with reading assignments
2 exams
5 problem sets
3 brief presentations
Grading: 25% for each exam, 25% total for problem sets, 25% presentations

Brief presentations. This assignment serves three purposes. To successfully complete it, you will need to (1) diligently read the current literature and identify the most practically or mechanistically important papers (2) critically evaluate a selected paper (3) prepare a well-researched, insightful analysis of the paper you choose.

Assignment: From the current literature (2009+) select a publication describing important advances in the field of catalysis. The paper should be related to the topic(s) that we are discussing in class. Present a brief (~5 min) talk focused on the paper. These should be done on the white board unless complex figures need to be projected. The overview should include the following items:

<u>Background</u>: put this paper into context. What question are the trying to answer? What problem are they trying to solve? What answers/solutions have appeared previously. Describe relevant result from the authors' lab as well as from other groups.

<u>Results</u>: Describe the authors' approach, results and conclusions.

<u>Analysis/Proposals</u>: Critically analyze the paper. Does their data support their conclusions? Are their results truly significant or just a parlor trick? Imagine you are the author. What's next? What experiments do you propose to address questions raised/left unanswered by the results in the paper. How could you expand or apply the approach or information from the this paper to other problems? Think about both immediate and long-term directions.

The 'Highlights' section of *Angewante Chemie* is a good model for the style of presentation.

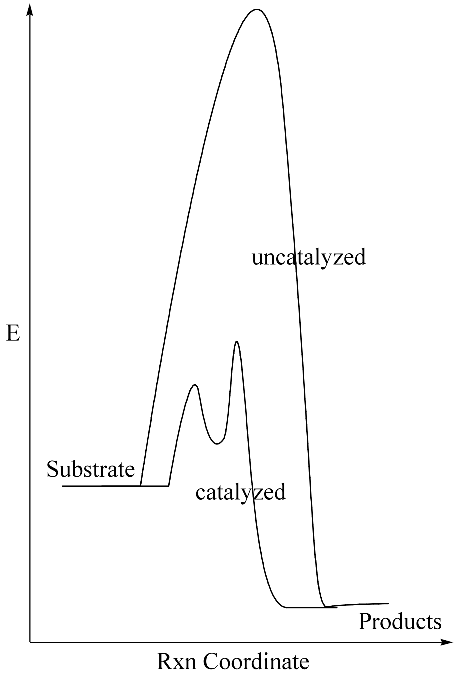
You will give three of these presentations throughout the semester according to the schedule provided.

Feel free to consult me, Prof Chen or Prof De Brabander on your paper selection.

Some useful definitions:

Catalyst: a substance that increases the rate of a reaction but is not changed by the reaction.

- •Light, heat, stirring, sonication and fire are not catalysts (they are not substances)
- •The definition does not say anything about stoichiometry, but in practice, less that 1 equiv (‘catalytic amounts’) of a catalyst is usually used.
- •A catalyst can only change rate, not thermodynamics. Corollary: A catalyst will increase the forward *and* reverse reaction
- •A catalyst can (and usually does) change the mechanism



TON: turn over number. Moles product formed per mole catalyst, a measure of catalyst stability

TOF: turn over frequency. Number of moles product per mole catalyst per unit time. A measure of catalyst efficiency.

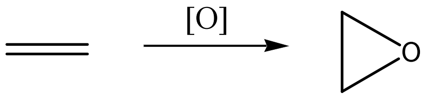
Inhibitor: A substance that decreases the TOF. Can be competitive (aka reversible) or non-competitive (not reversible, usually covalent modification of catalyst, AKA **poison**).

E.e.: enantiomeric excess. Measurement of optical purity
= %R-%S = (R-S)/(R+S)

E.r.: enantiomeric ratio. Measurement of optical purity
= R:S. Note value of e.r. always looks higher than ee (94:6 vs 88% ee)
e.r. less common, but more intuitive (e.r. reflects GC or HPLC reading; ee reflects optical rotation measurement)

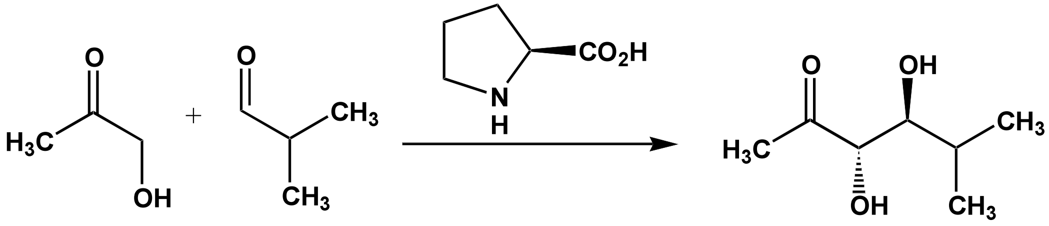
Advantages of Catalysis:

$$$$



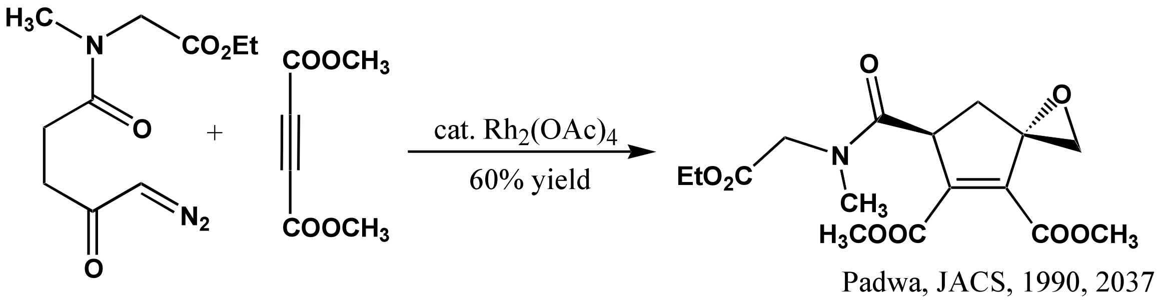
[O] = mCBPA, \$80/mol
[O] = H_2O_2, \$1.80/mol

Faster reaction rate
Milder reaction conditions
Control of reaction selectivity



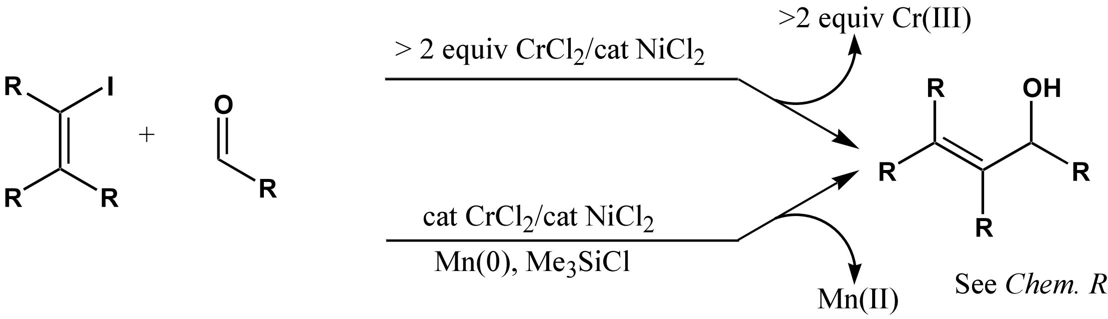
62% yield
>20:1 dr
>99% ee
List, *JACS*, 2000, 7386

Otherwise impossible reactions



Padwa, JACS, 1990, 2037

Environmental concerns



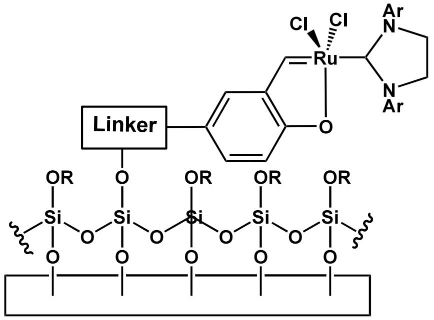
See *Chem. Rev.* **1999**, 991

Classes of Catalysis

Homogeneous — Most often used class for small scale synthesis

Heterogeneous — Very important for large scale
Pd/C (hydrogenations)
Zeolites (separations, oxidations)
Amberlyst (solid acid)
Supported metals (Haber process: NH_3 synthesis; Fischer-Tropsch: hydrocarbons from CO and H_2

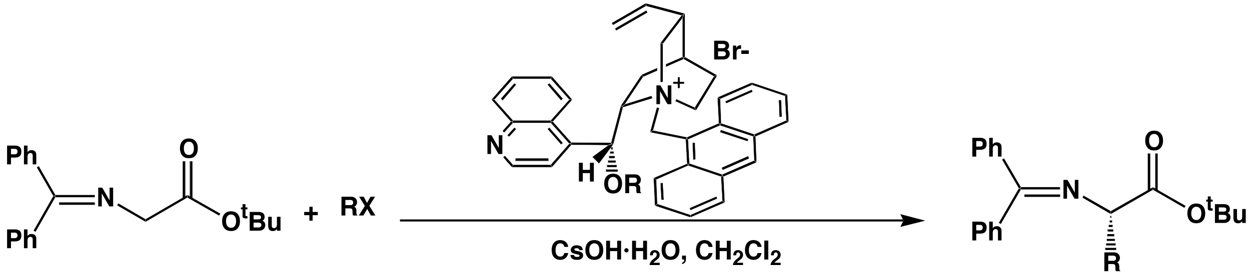
Polymer bound



Hoveyda, *ACIEE*, 2001, 4251

Many papers, few applications

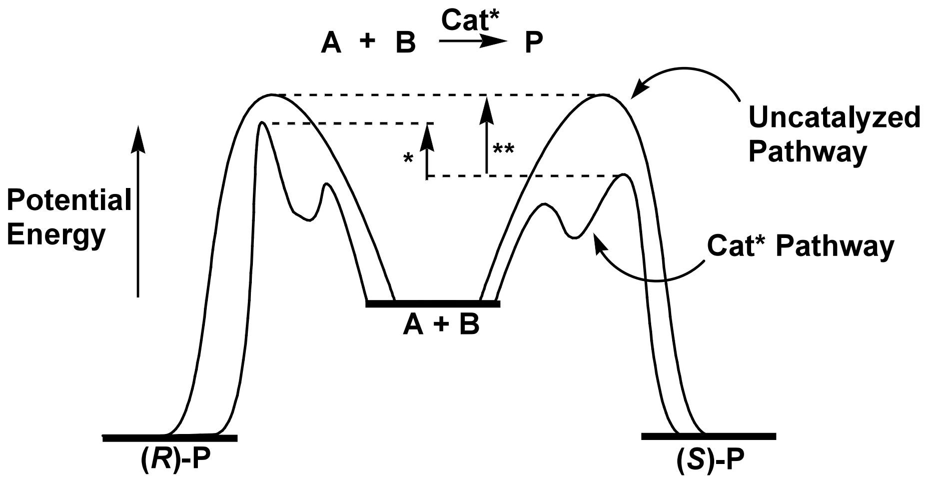
Phase transfer



72-99% ee
Corey, *JACS,* **1997**, 12414
Lygo, *TL*, **1997**, 8595

Biological — Enzymes, catalytic antibodies

Asymmetric Catalysis



$*$ = $\Delta\Delta G^{\ddagger}_{(R\text{-}S)}$ = **Energy difference between TS leading to (*R*)-P and (*S*)-P**

$**$ = $\Delta\Delta G^{\ddagger}_{(R\text{-bkgd})}$ = **Energy difference between TS's for catalyzed and uncatalyzed rxns**

Important points

Note R and S product have same energy, and uncatalyzed pathway has same $\Delta G^{\ddagger}$ for both

For good ee (%S-%R), need big $\Delta\Delta G^{\ddagger}_{(R\text{-}S)}$. (Approx 1.4 kcal/mol per order of magnitude diff in ratio. E.g., 1.4 kcal = 91:9 = 82% ee, 2.8 = 99% ee)

Catalyzed pathways are usually mechanistically more complex than uncatalyzed pathways

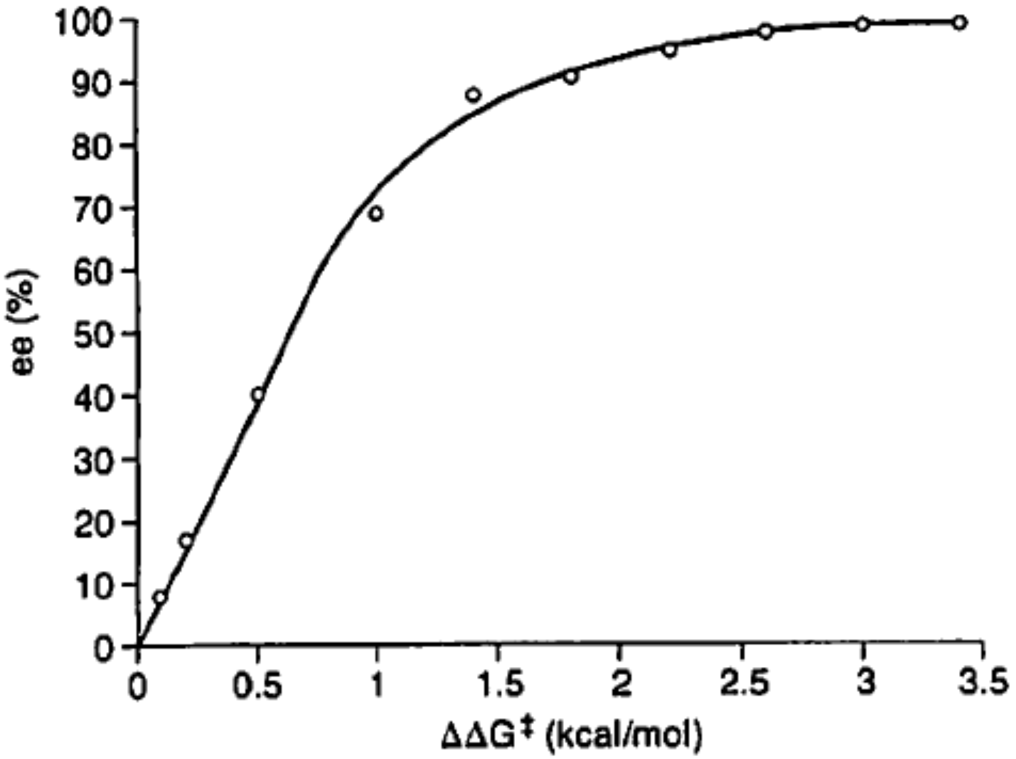


Figure 14.9.
Enantioselectivity as a function of the energy differences between the diastereomeric transition states ($\Delta\Delta G^\ddagger$) at 25 °C.

- Small $\Delta\Delta G^\ddagger$ required for good ee, esp compared to strength of C-C bond (~50-85 kcal/mol) or even H-bond (2-10 kcal/mol)

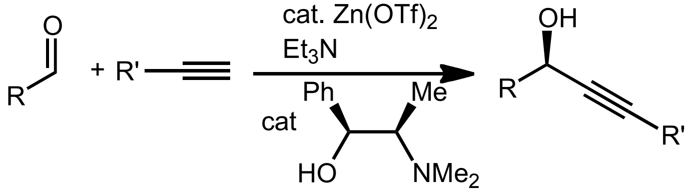
- Still, very hard to get good ee.

- Diminishing returns: 0 → 1.4 kca/mol: ~80% increase; 1.4 → 2.8: ~20% increase; 2.8 →4.2 ~1% increase

- Figure from Organotransitionmetal Chemistry, Hartwig

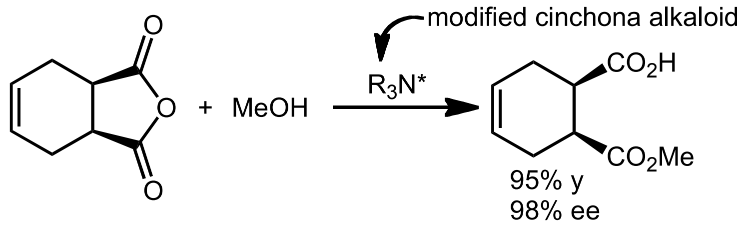
Classes of Asymmetric Catalysis

Reaction at prochiral centers:



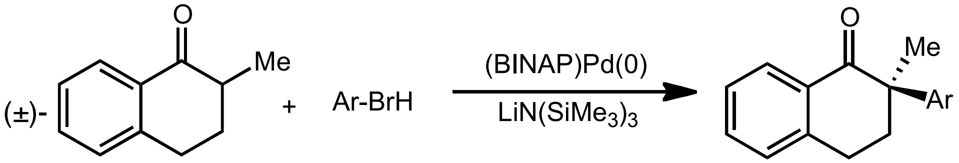
Carreira, *JACS,* 2001, 9687

Desymmetrization



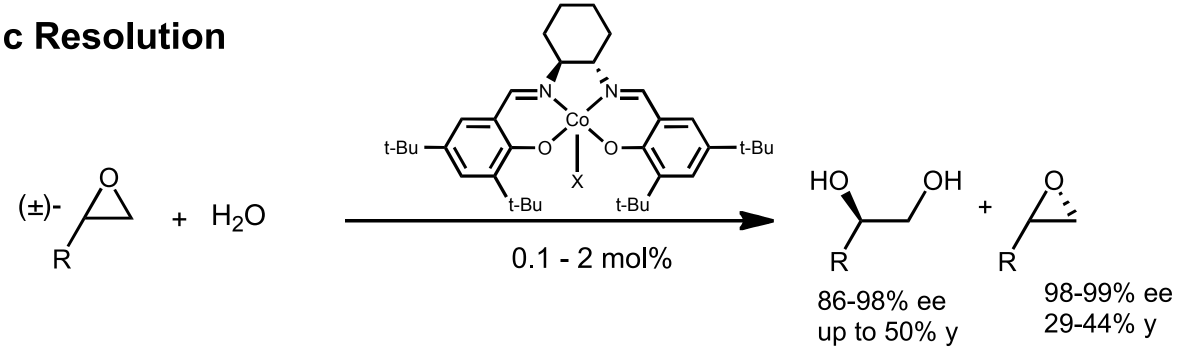
Li Deng, *JACS,* 2000, 9542

Stereoconvergent Processes



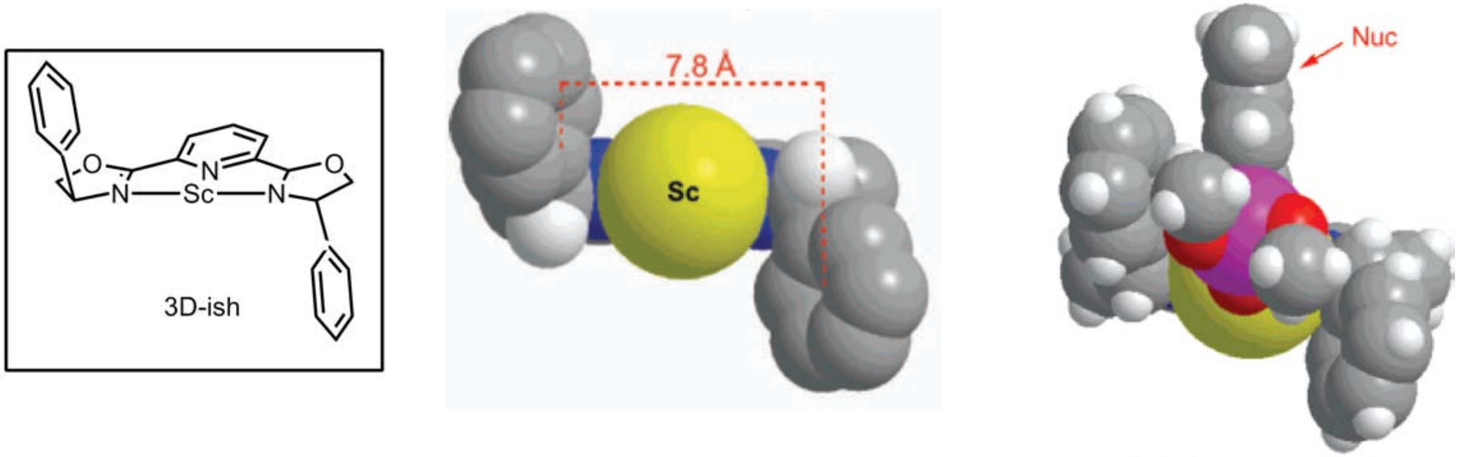
Buchwald, *JACS,* 1998, 1918

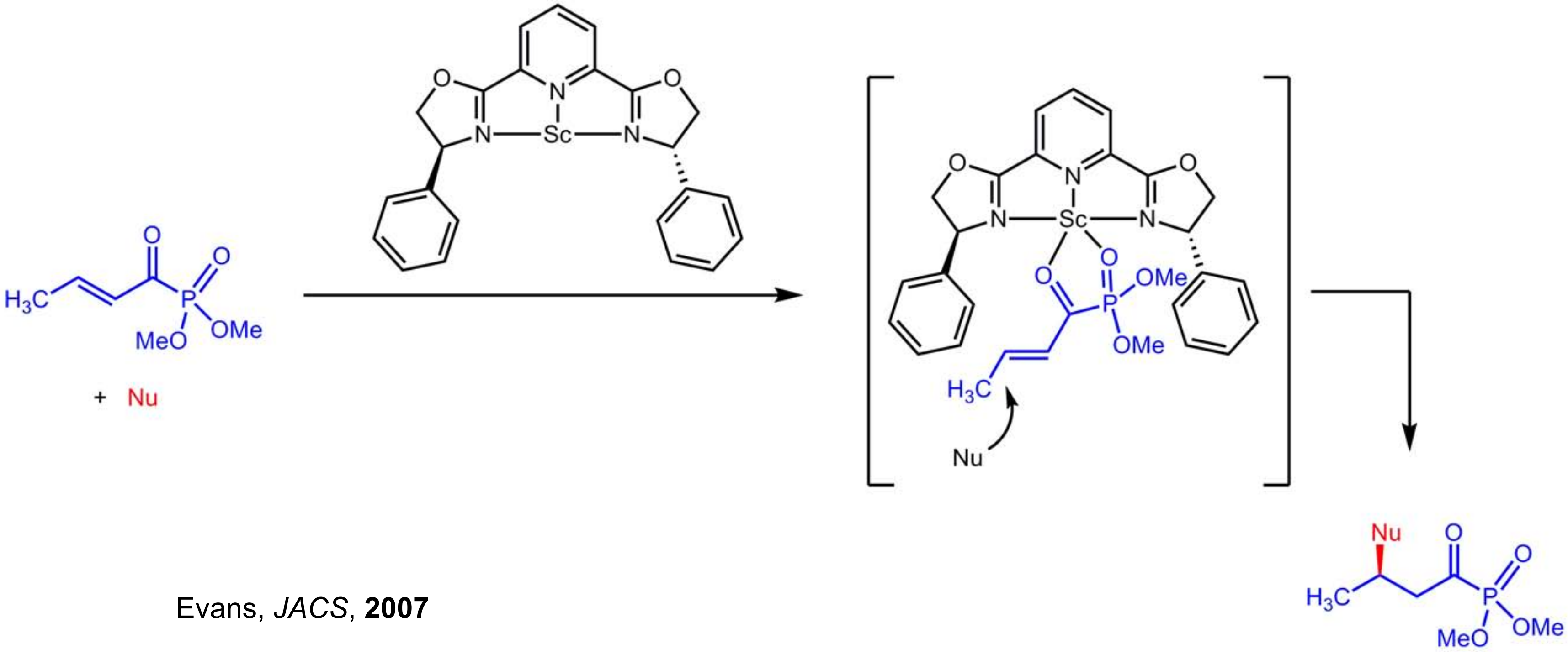
Kinetic Resolution



Jacobsen, *Science,*
1997, *277,* 936

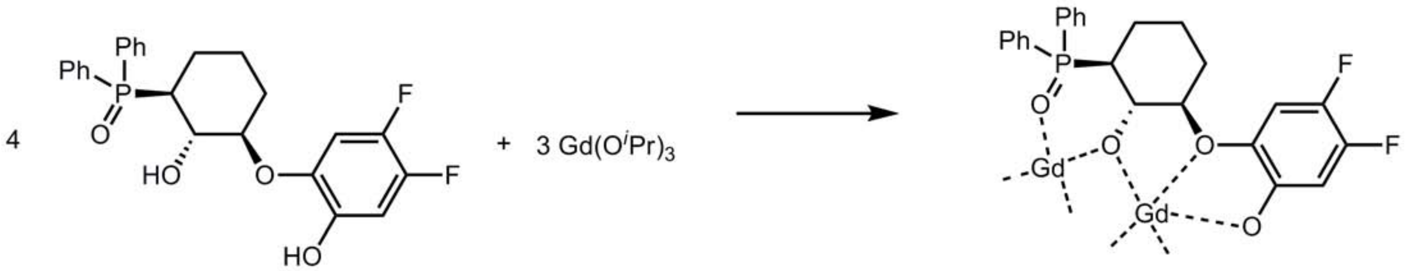
Some Examples of Asymmetric Catalysis are well Understood…

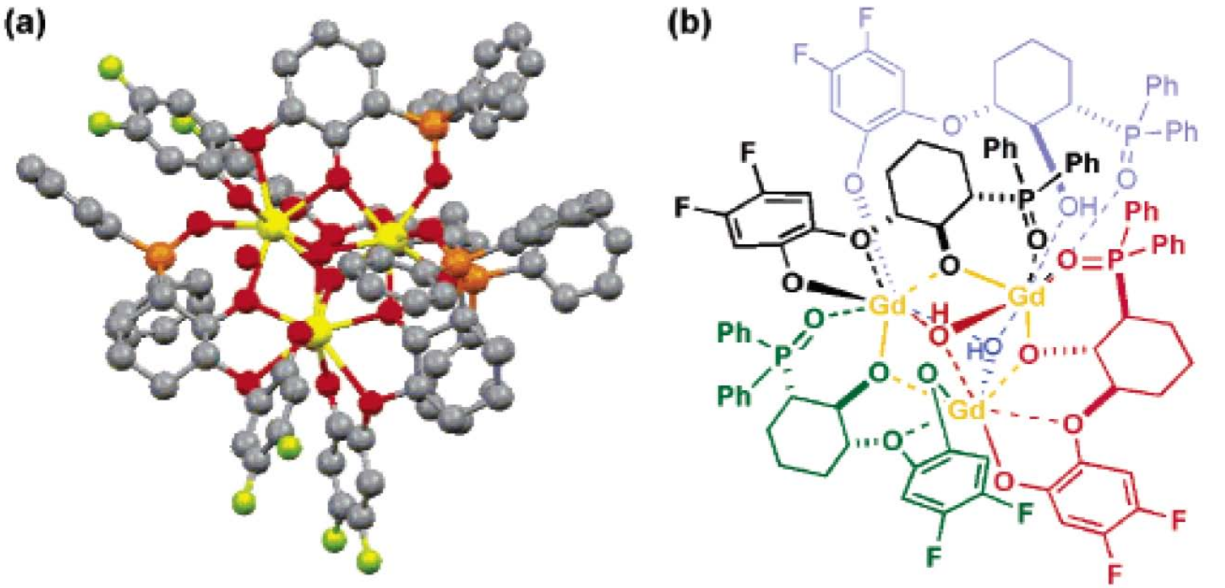


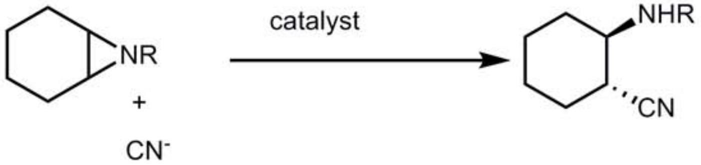


Evans, *JACS*, **2007**

…but Some Examples are not Understood Well

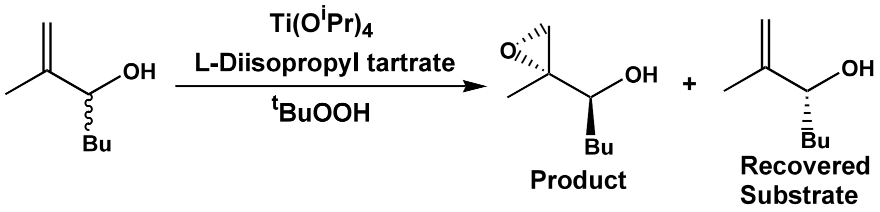






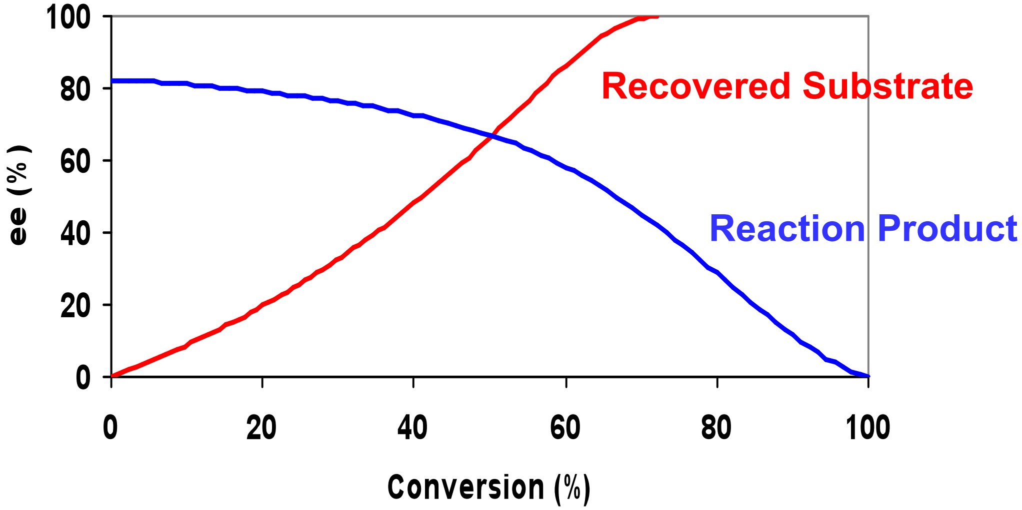
Shibasaki, *JACS*, **2006**

Kinetic Resolutions



Ee of substrate increases with conversion – can get as high as you want, but at the expense of yield

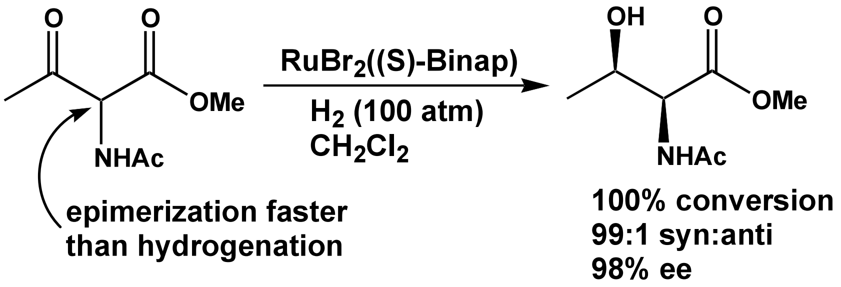
Ee of product decreases with conversion.



$$k_{rel} = \frac{k_{fast}}{k_{slow}} = \frac{\ln[(1-c)(1-ee_{sub})]}{\ln[(1-c)(1+ee_{sub})]} = \frac{\ln[1-c(1+ee_{prod})]}{\ln[1-c(1-ee_{prod})]}$$

%conv.	k_{rel} for 95% ee	k_{rel} for 99% ee
50	146	1057
55	29	49
60	16	24
75	8	9

Dynamic Kinetic Resolution

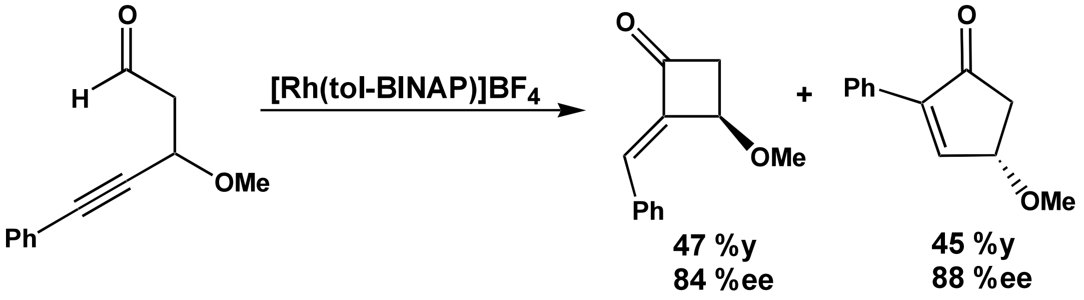


epimerization faster than hydrogenation

100% conversion
99:1 syn:anti
98% ee

Noyori, JACS, 1989, 9134

Parallel Kinetic Resolution



47 %y
84 %ee

45 %y
88 %ee

Fu, JACS, 2003, 8078

Criteria for useful KR's:

Rac substrate cheap, enatio enriched substrate hard to make
Can achieve theoretical ee's
Catalyst is accessible, selective and reactive (low loadings)
Substrate and product easy to separate
Product is useful
Resolving agent is cheap
Need extremely high ee's