

□

Ready; Catalysis

Nonlinear Effects

Outline

Definitions

Origins of nonlinear effects in enantioselective reactions

ML2 model

Reservoir model

Transition-state model

Kinetic aspects of nonlinear effects

Asymmetric amplification

Cool tricks

Origin of biotic asymmetry?

Key reviews

Kagan, ACIEE, 1998, 2922 (a pretty complete review, source of many of my figures)

Kagan, Advanced Syn. Cat., 2001, 227 (an overview)

Blackmond, Accts, 2000, 402 (kinetic aspects)

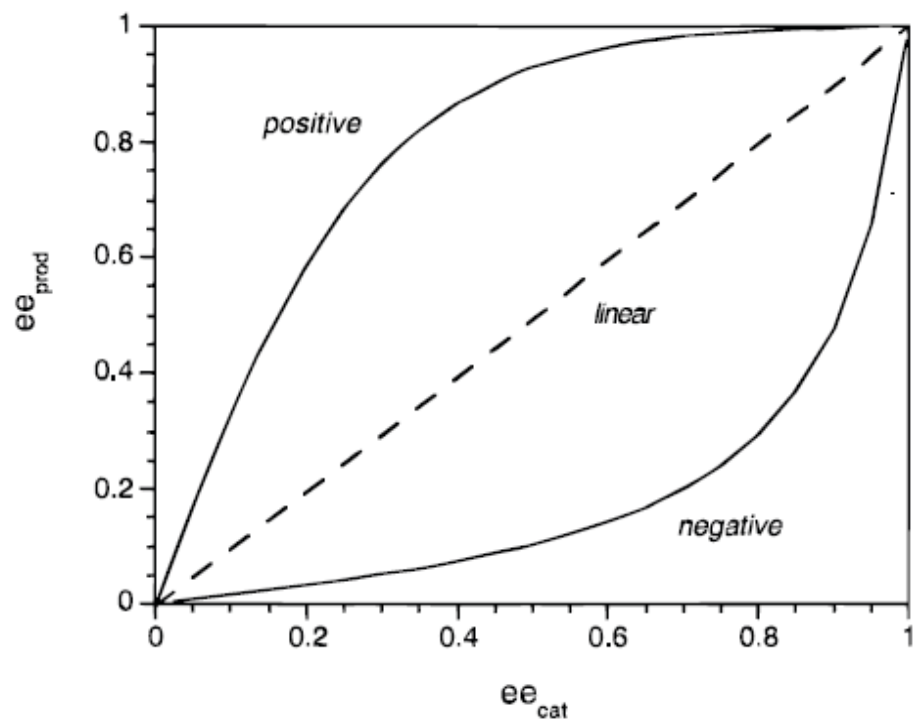
Soai, Accts, 2000, 382 (asymmetric amplification)

In an enantioselective reaction, expect product ee to be linearly related to catalyst ee:

$$ee_{\text{prod}} = ee_{\text{max}} * ee_{\text{cat}}$$

ee_{max} is maximal ee, i.e. when 100% ee cat is used

But sometimes linear relationship does not hold:



Relationship between product ee and catalyst (or reagent) ee:

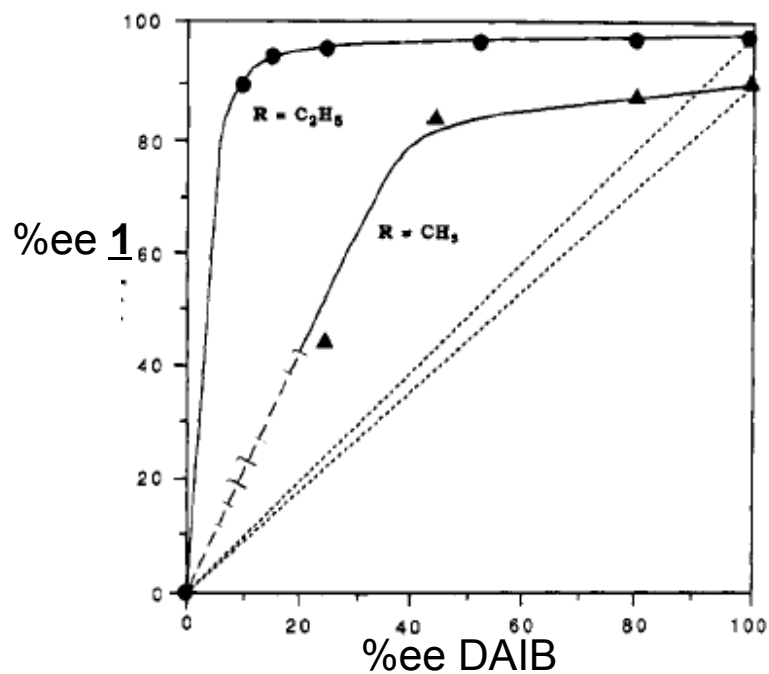
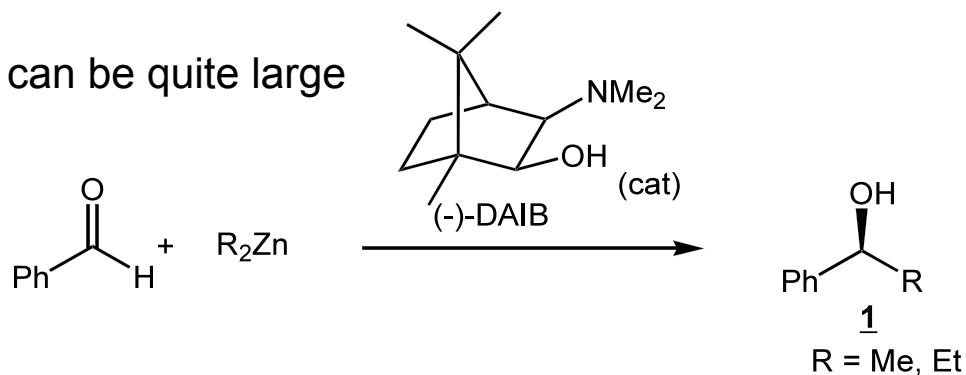
Called positive nonlinear effect (+NLE) if $ee_{\text{product}} > ee_{\text{catalyst}}$

Called negative nonlinear effect (-NLE) if $ee_{\text{product}} < ee_{\text{catalyst}}$

Ready; Catalysis

Nonlinear Effects

These effects can be quite large



21% ee DAIB gives 96% ee product!

Reasons to care:

Practical consequences:

If low ee cat way cheaper than high ee (+NLE)

If optically pure cat unavailable (+NLE)

Danger of extrapolating from low ee cat (-NLE)

Can have large impact on rates

Fundamental issues:

Can support or refute a mechanism

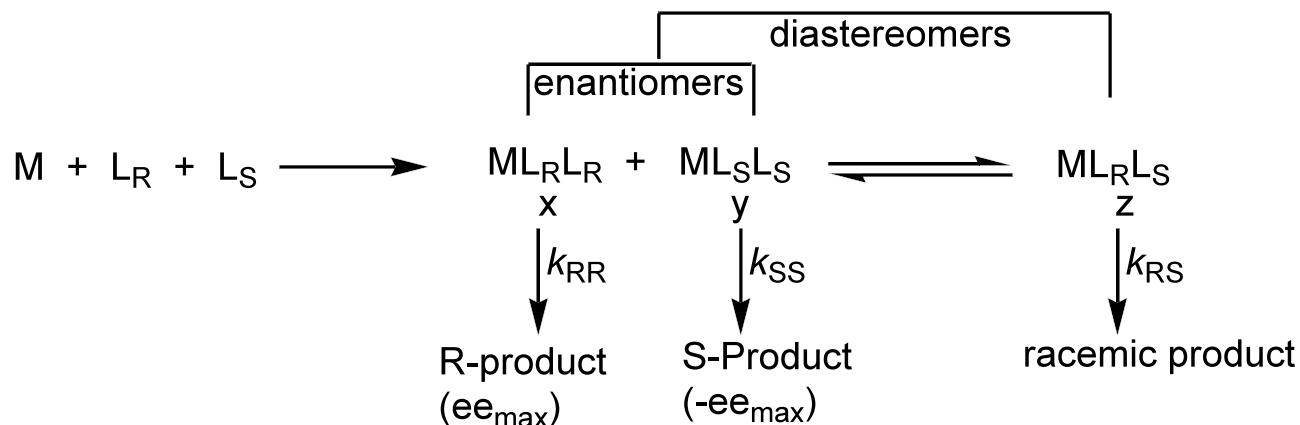
Provides more complete picture of reaction

May relate to origin of biological asymmetry

The ML₂ model

Most popular model to describe nonlinear effects; metrics even used for other models (e.g. reservoir)

Assume M is metal, L_R is (R)-Ligand, L_S is (S)-Ligand, and active species is ML₂
The following equilibrium is established:



x, y and z are mol%

$$K = z^2/xy$$

$$ee_{prod} = ee_{max} * ee_{cat} \frac{1 + \beta}{1 + g\beta}$$

$$\beta = z/(x+y) = \frac{-Kee_{cat}^2 + [-4Kee_{cat}^2 + K(4ee_{cat}^2)]^{1/2}}{4 + Kee_{cat}^2}$$

$$g = k_{RS}/k_{RR}$$

Important points:

β describes relative *stability* of homo and hetero chiral catalyst (but K is more useful)

g describes relative *reactivity* of homo and hetero chiral catalyst

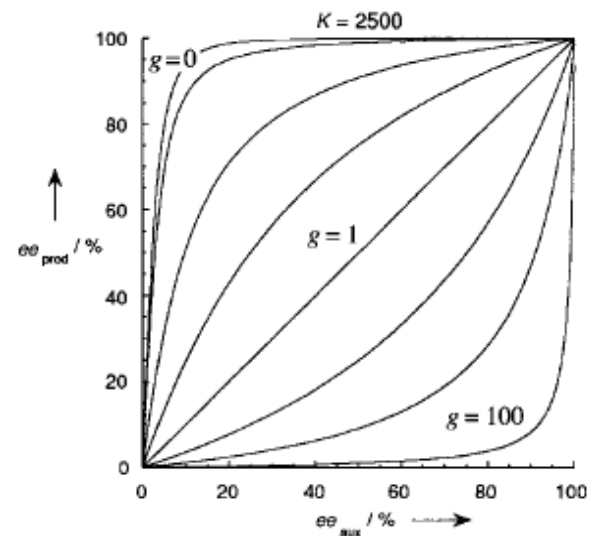
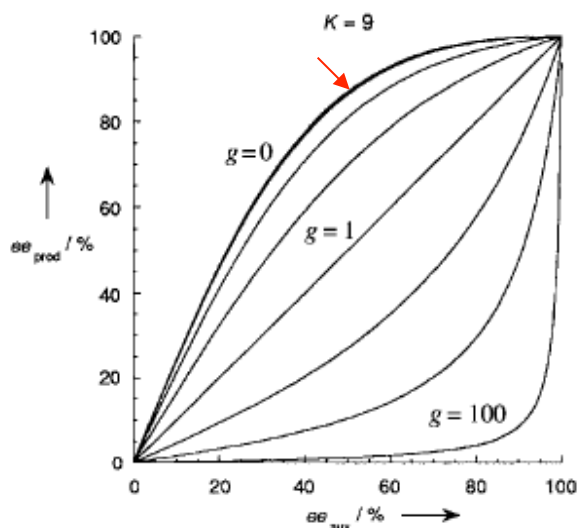
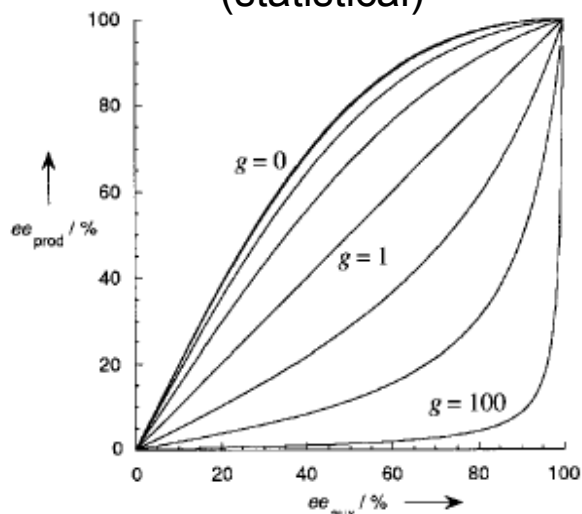
β and x,y,z depend on ee_{cat} and K

The origin of nonlinearity is g. The reactivity of the meso catalyst *must* be different to see a NLE, i.e. $g < 1$ (+NLE) or $g > 1$ (-NLE)

$$ee_{\text{prod}} = ee_{\text{max}} \cdot ee_{\text{cat}} \frac{1 + \beta}{1 + g\beta}$$

g – reactivity
 β – stability
 K – related to β

K = 4
 (statistical)



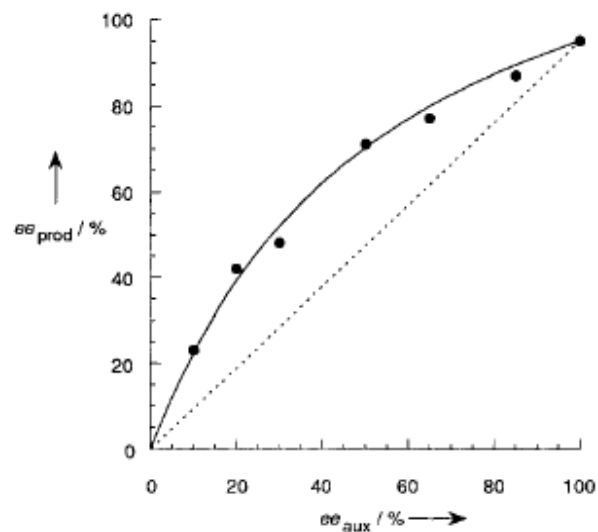
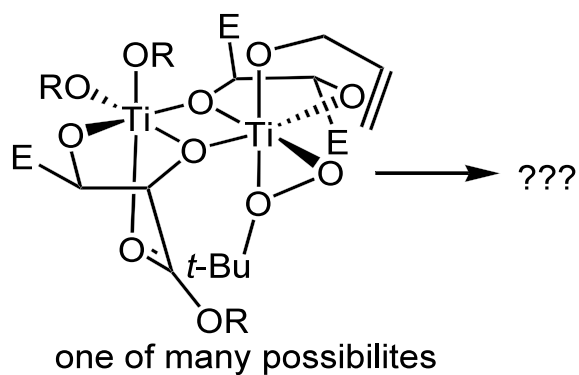
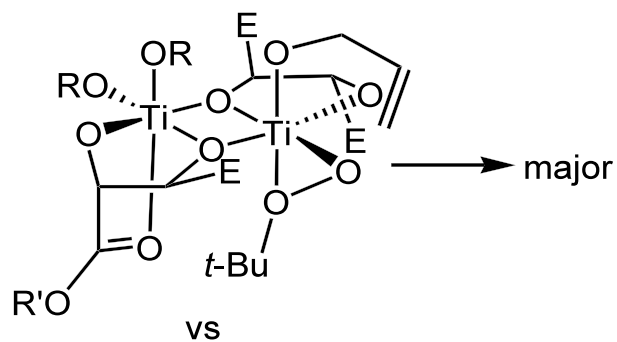
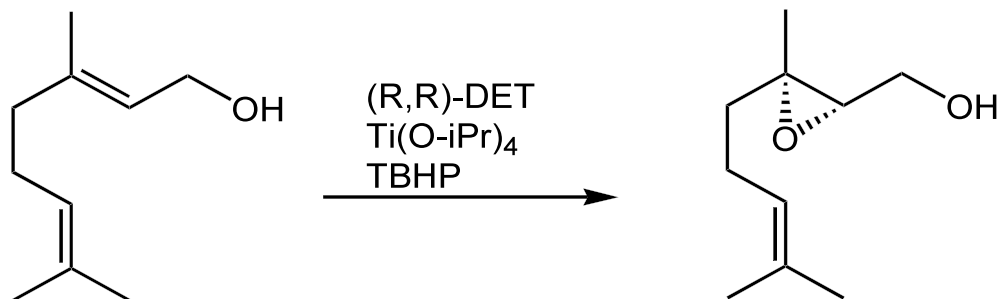
Biggest +NLE when g = 0 (inactive meso form)

K affects +NLE more than -NLE

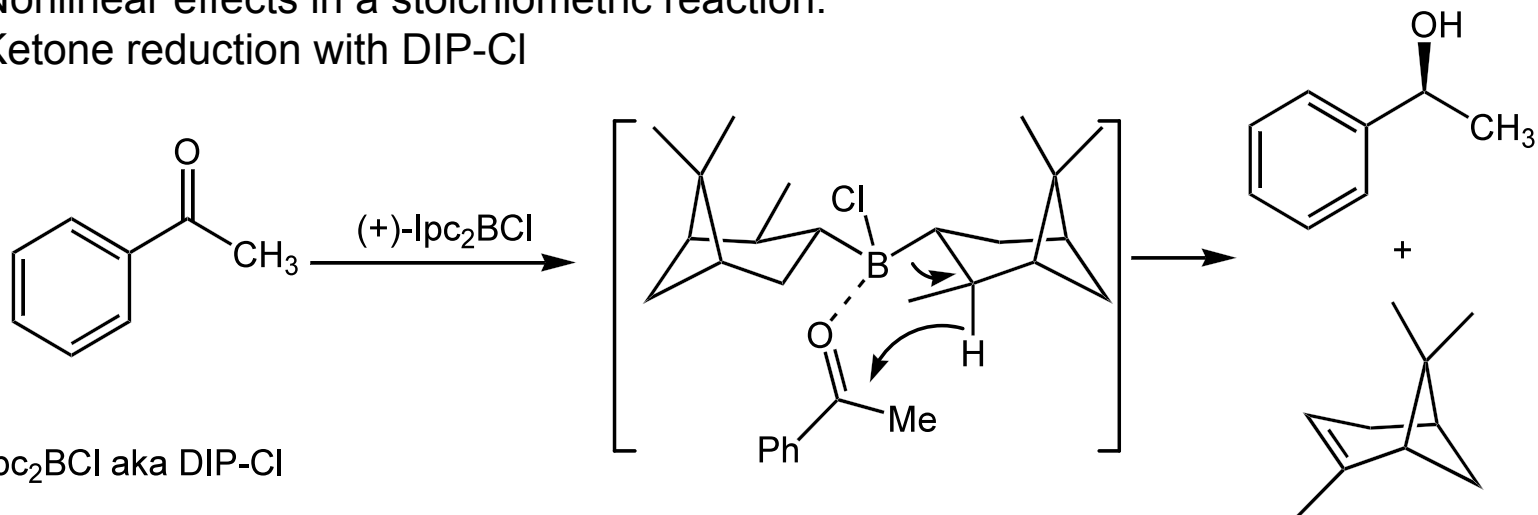
Can use curves to determine 'effective ee'

e.g. if for K = 9, g = 0, nominally 50% ee catalyst performs like 87% ee catalyst

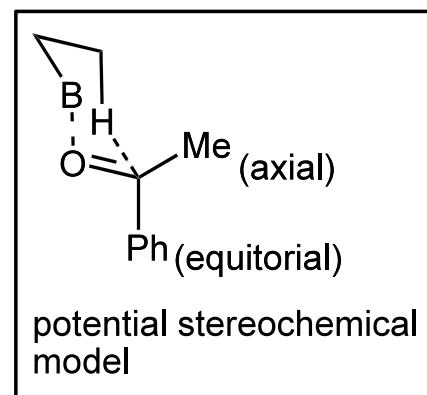
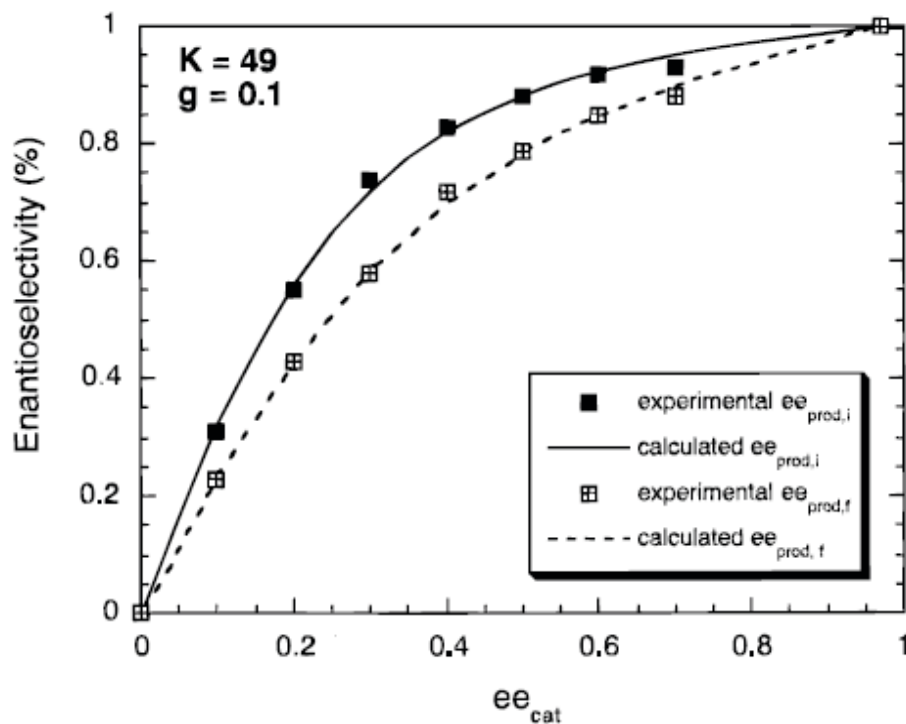
Example: Sharpless asymmetric epoxidation

Data fits to $K = 1000$ $ee_{max} = 95$ $g = k_{SR}/k_{RR} = 0.35$

Nonlinear effects in a stoichiometric reaction:
Ketone reduction with DIP-Cl



Ipc₂BCl aka DIP-Cl



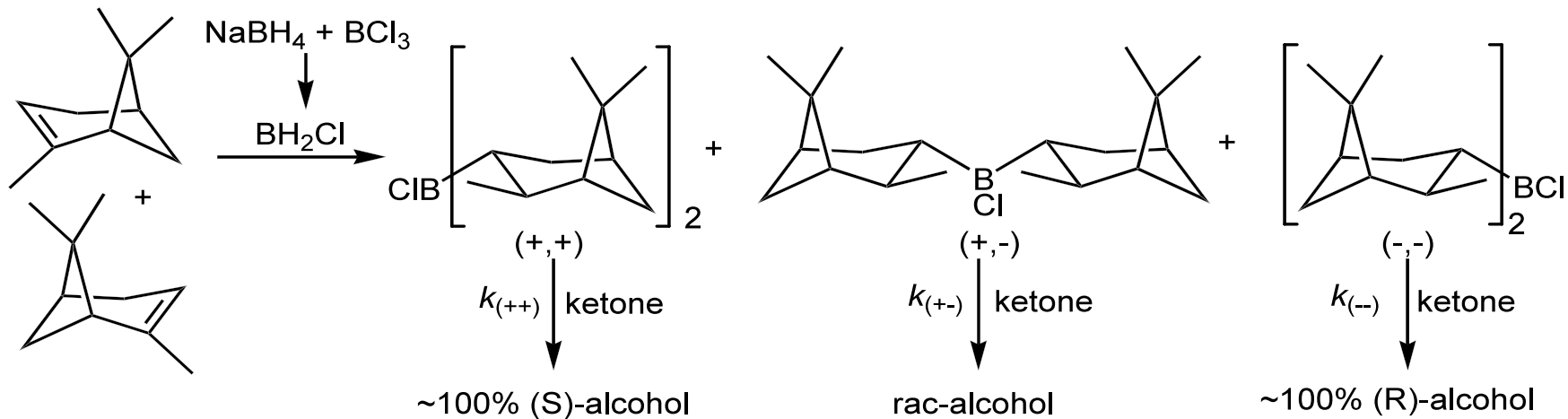
Original reduction: Brown, JOC, 1985, 5446

NLE Data: Merck process, TL, 1997, 2641

NLE analysis: Blackmond, JACS, 1998, 13349

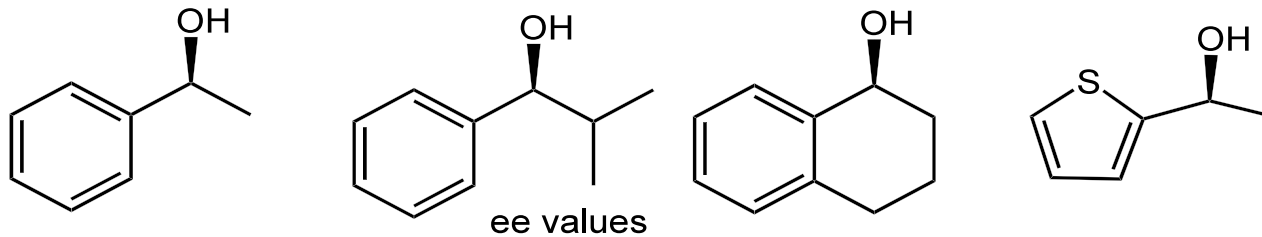
Ready; Catalysis

Nonlinear Effects



$$K = 49 = \frac{[(+,-)]^2}{[(+,+)] [(-,-)]} \quad g = k_{(+,-)}/k_{(++)} = 0.1$$

examples:



ee values

DIP-Cl from >99% ee pinene:
From from 85% ee pinene:

97
96

90
89

87
88

91
93

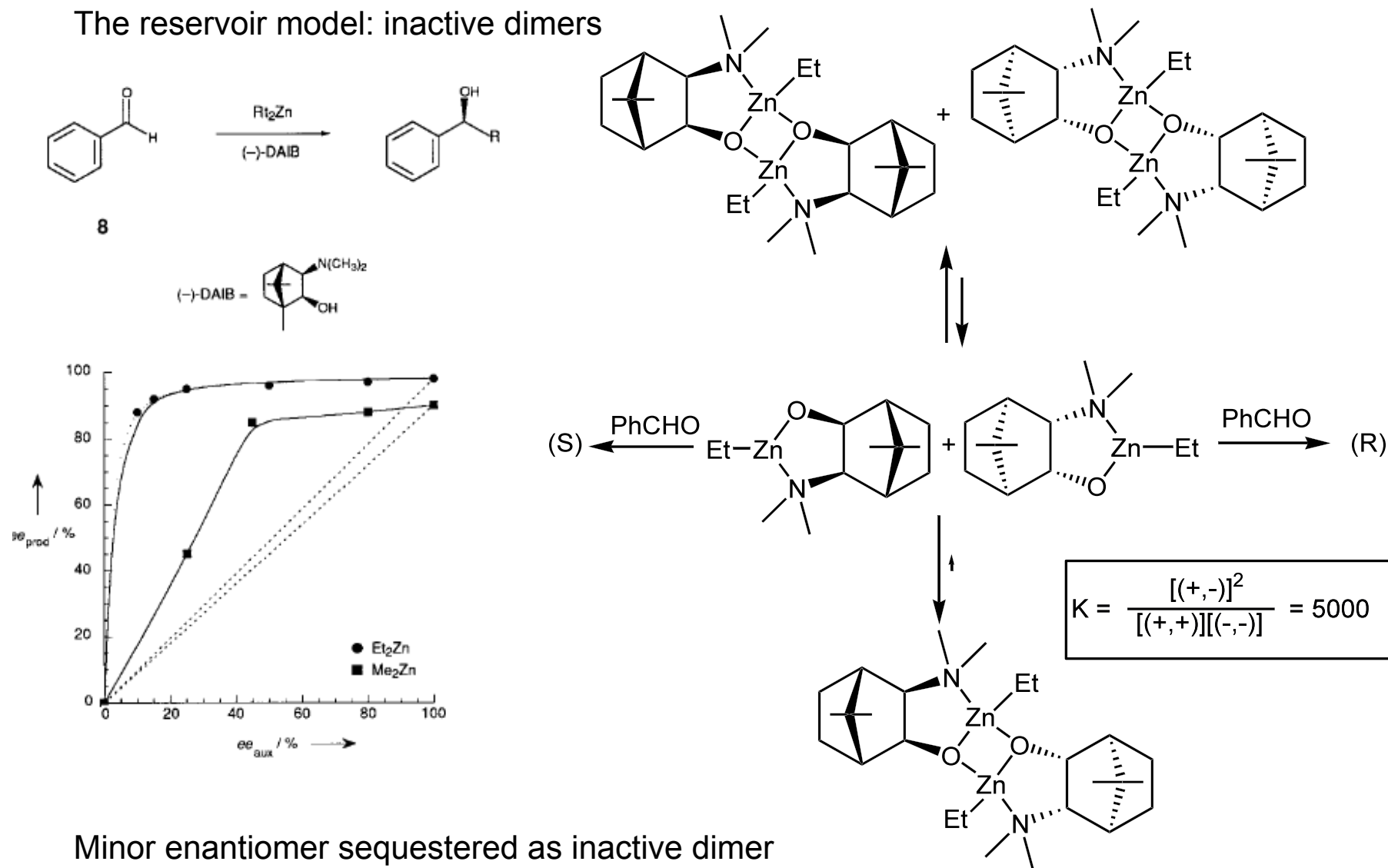
Notes: mixtures of (+,+) and (-,-) DipCl do not show NLE

97% ee pinene: \$500/100g; 87% ee pinene: \$60/100g

Product ee will decrease with conversion in stoichiometric reaction displaying +NLE

Model 2

The reservoir model: inactive dimers



Minor enantiomer sequestered as inactive dimer
 Monomer is active catalyst
 95% ee product from 15% ee catalyst!!

Structural basis for dimer stability

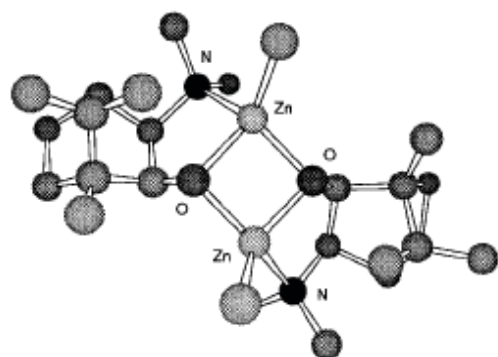
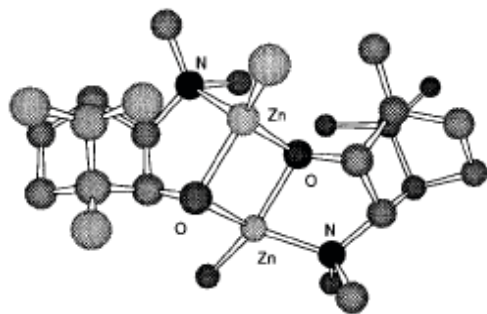
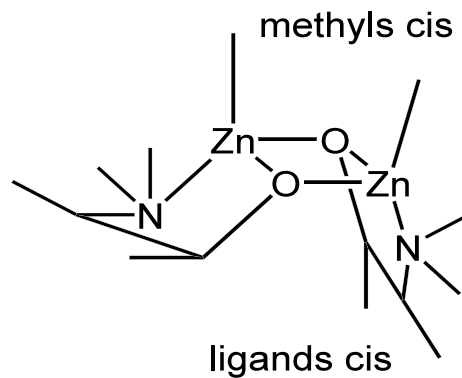
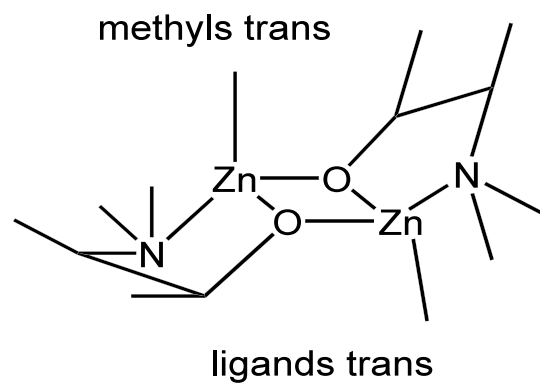
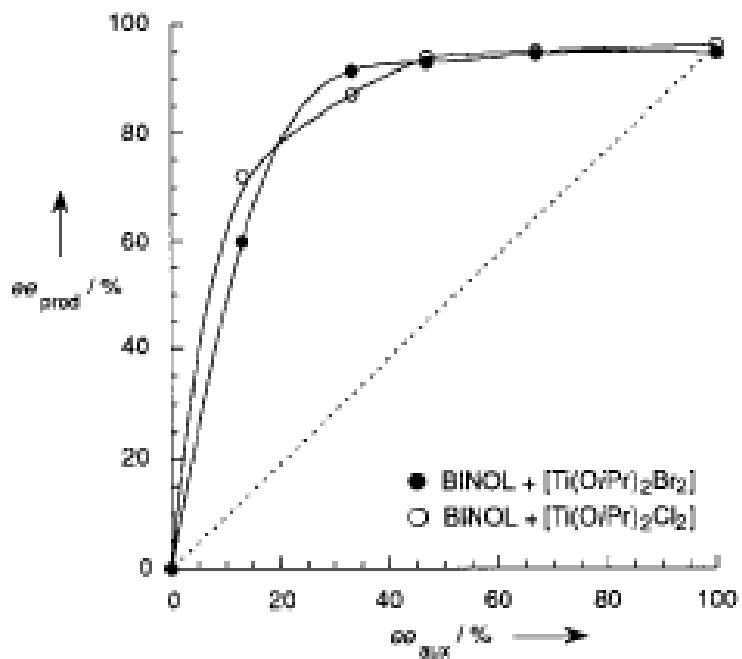
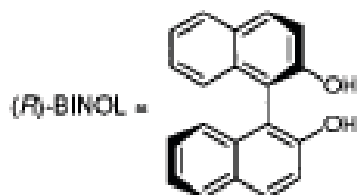
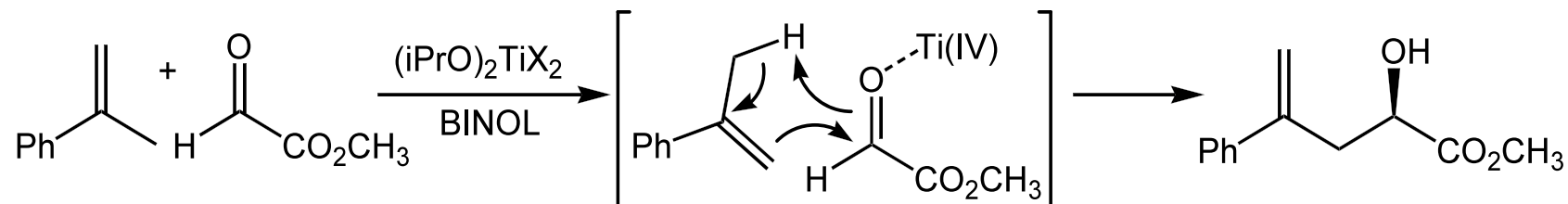
 $(-)\cdot(-)\text{-10}$  $(+)\cdot(-)\text{-10}$

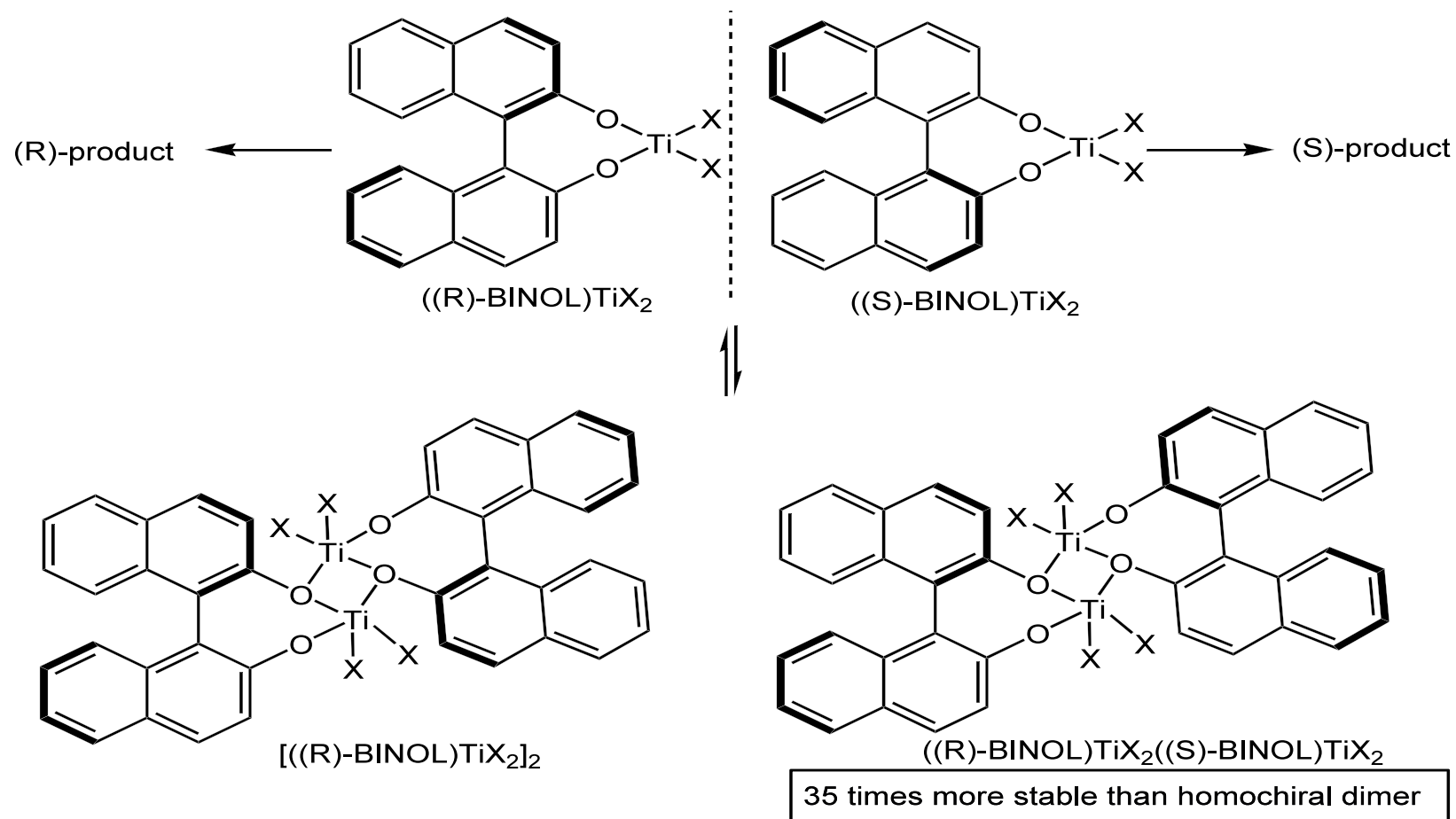
Figure 19. Three-dimensional models of the dimers of (-)-DAIB-methylzinc: (-)·(-)-10 (homochiral) and (-)·(+)-10 (heterochiral).

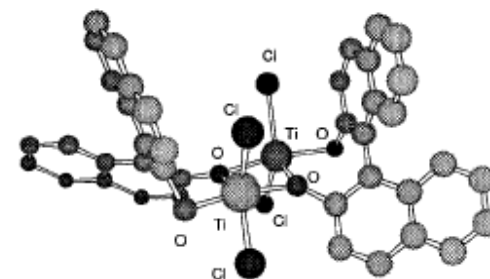
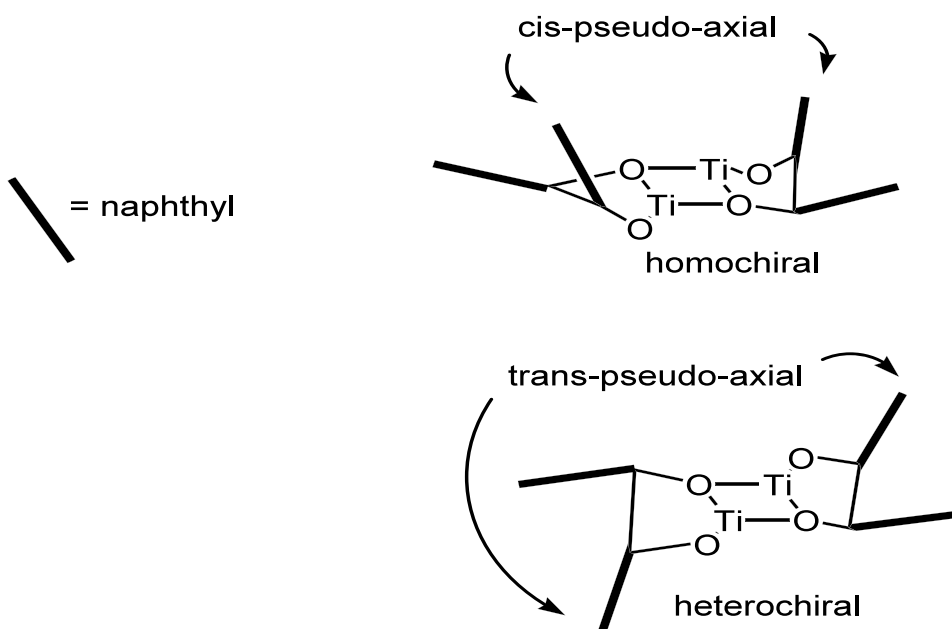
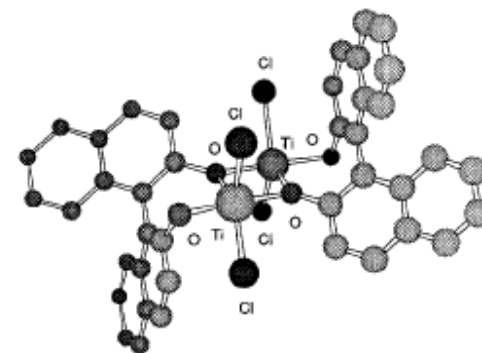
Homochiral dimer
(less stable)**Heterochiral dimer**
(more stable)

Reservoir model in glyoxylate ene reactions



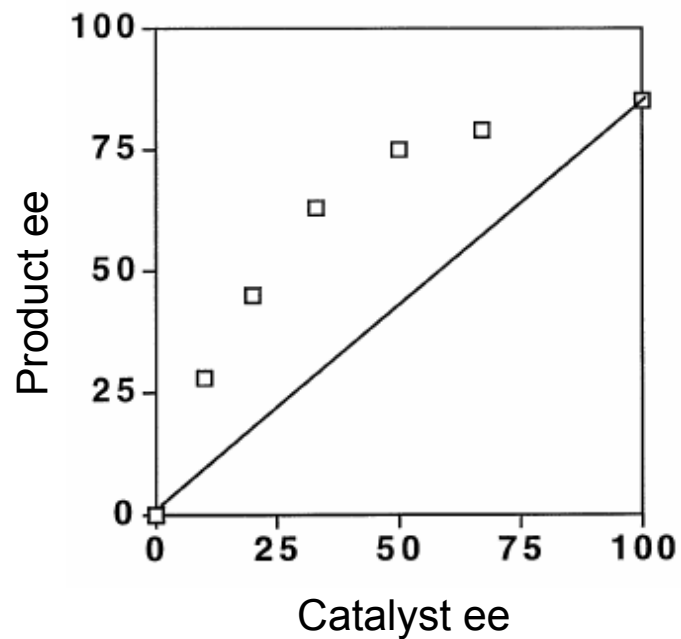
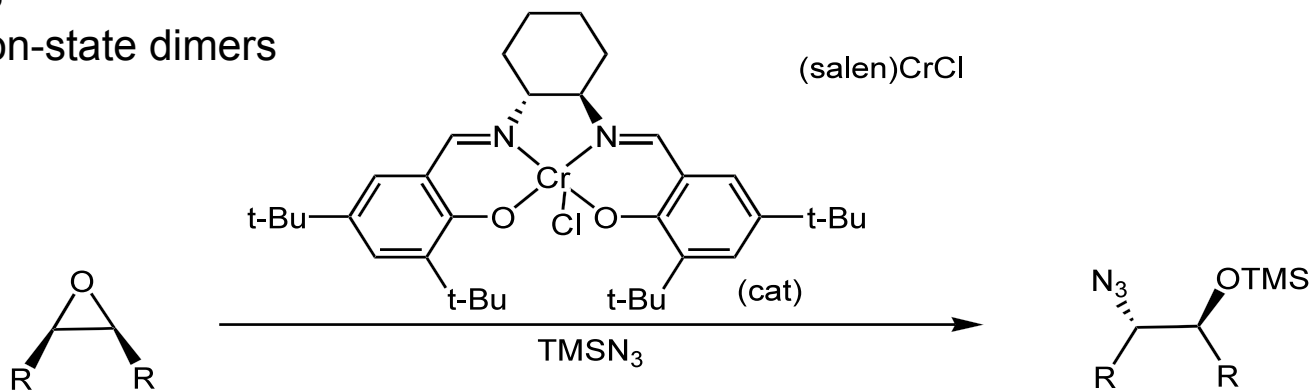
Equilibrium between active monomer and inactive dimer. Minor enantiomer is sequestered.



Structural basis for dimer stability with (BINOL)TiX₂*(R)*-*(R)*-25*(S)*-*(R)*-25Calculated structures for [(BINOL)₂TiCl₂]₂

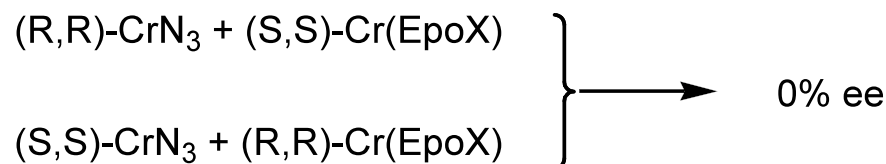
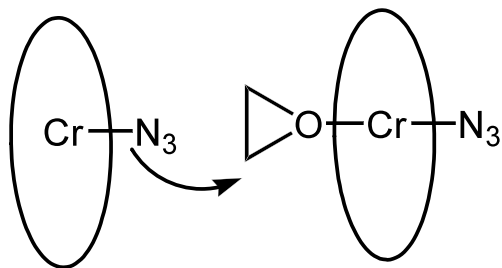
Model 3

Transition-state dimers



For ee < 100%, 4 possible transition states:

Recall bimetallic mechanism:



Imagine the following:

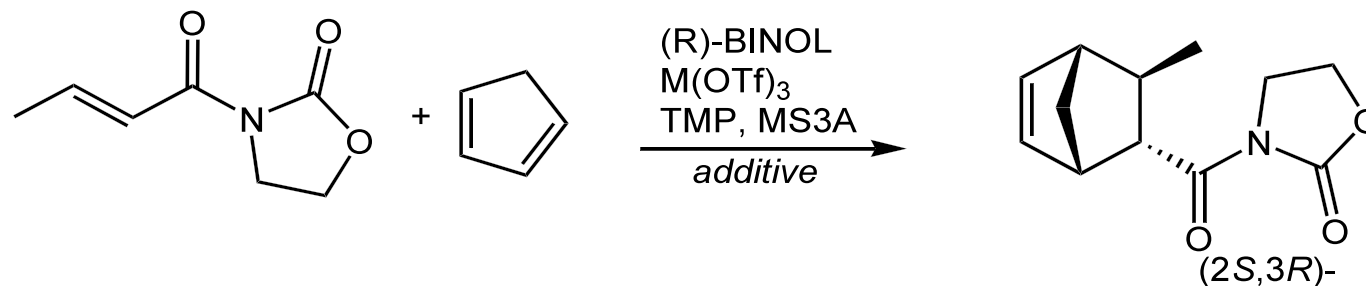
Meso reactions very slow
catalyst e.e. = 70% (85:15)

$$\frac{\left(\frac{d[(+)\text{-product}]}{dt}\right)}{\left(\frac{d[(-)\text{-product}]}{dt}\right)} = \frac{[.85]^2}{[0.15]^2} = 32.1 \implies 94\% \text{ ee!}$$

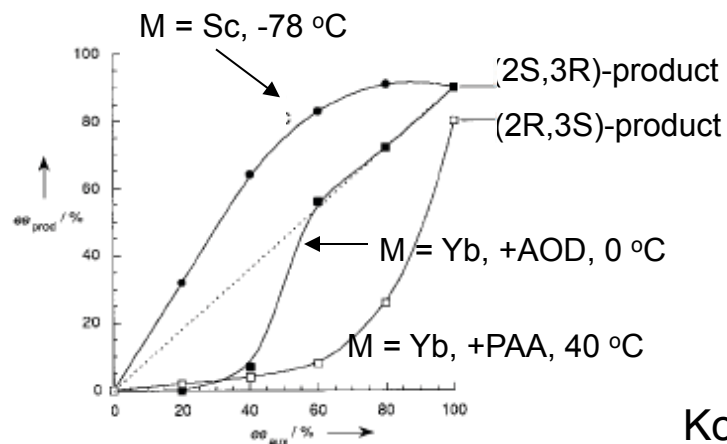
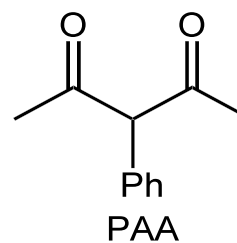
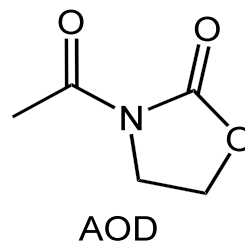
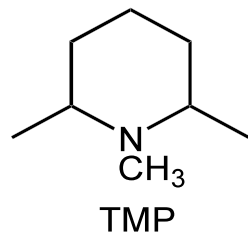
note k_{cat} , [epox], [azide] same for both homo-chiral transition states

In practice, 70% ee catalyst gives ~80% ee product, so significant, but minor, contribution from meso T.S.

Not all examples fit neatly into the models

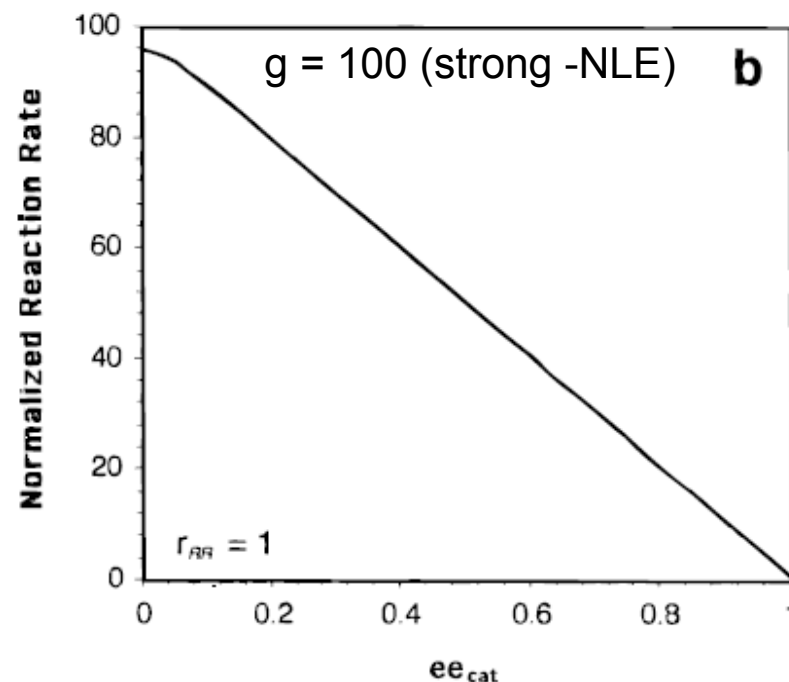
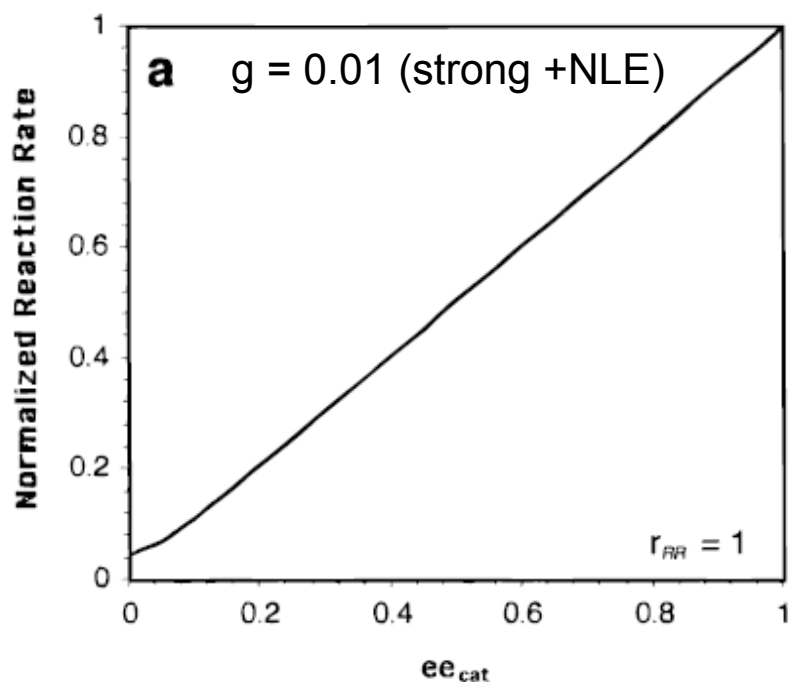


Additives:



Paying the piper: Kinetic repercussions of NLE's

Relationship between Rate and EE in ML_2 Model



Positive NLE will be associated with decrease in rate.

Rate drop and +NLE both a result of less-active dimeric species – i.e. you sacrifice one (R)-cat to sequester one (S)-cat
(note: %ee = %optically pure; remainder racemic)

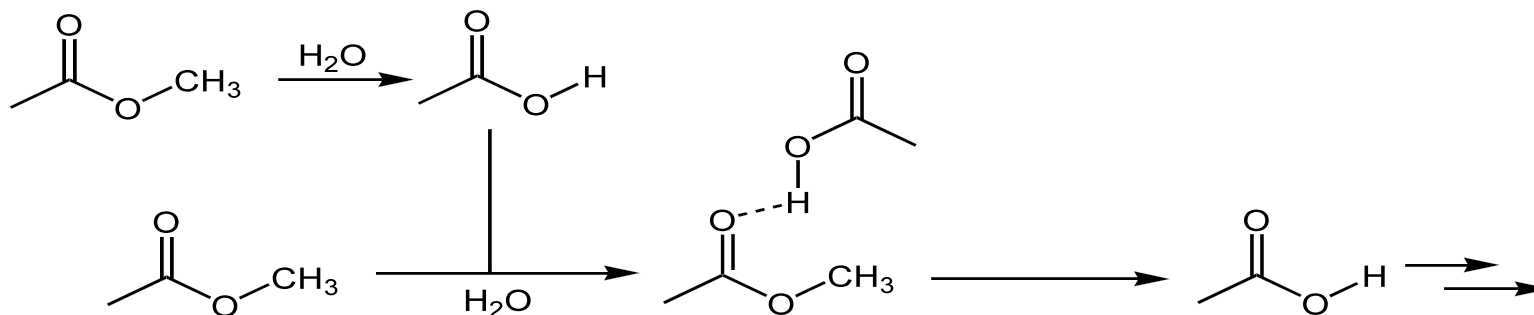
Negative NLE will be associated with increase in rate.

-NLE comes from more-active dimers – i.e. (rac)-catalyst is faster than optically pure

Asymmetric amplification and Autocatalysis

Autocatalytic reactions are one in which the product catalyzes its own formation.

A simple example: Ester hydrolysis yields an acid; ester hydrolysis is acid-catalyzed. Expect exponential increase in rate with time.



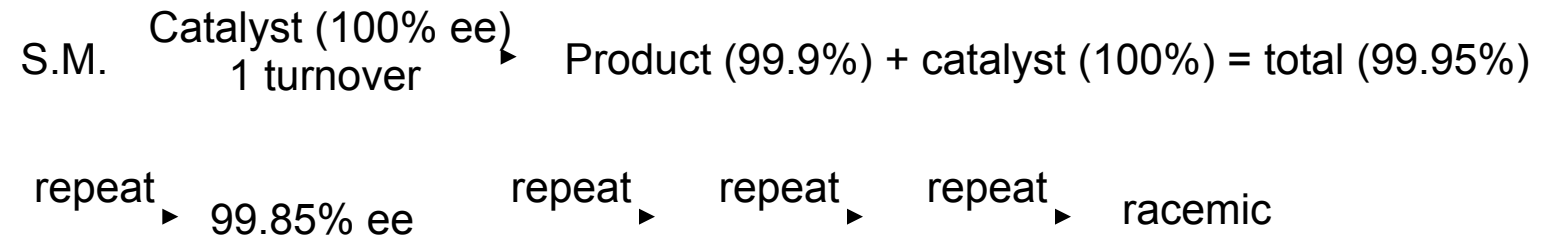
□

Ready; Catalysis

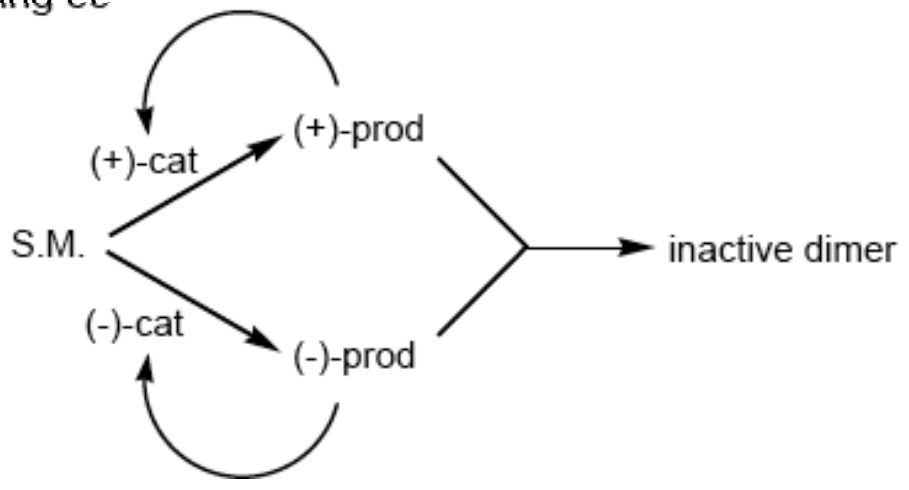
Nonlinear Effects

Might think this could be a mechanism for propagating optical activity. Small amount of high ee material leads to high ee catalyst catalyzes formation of more high ee catalyst...
Not so.

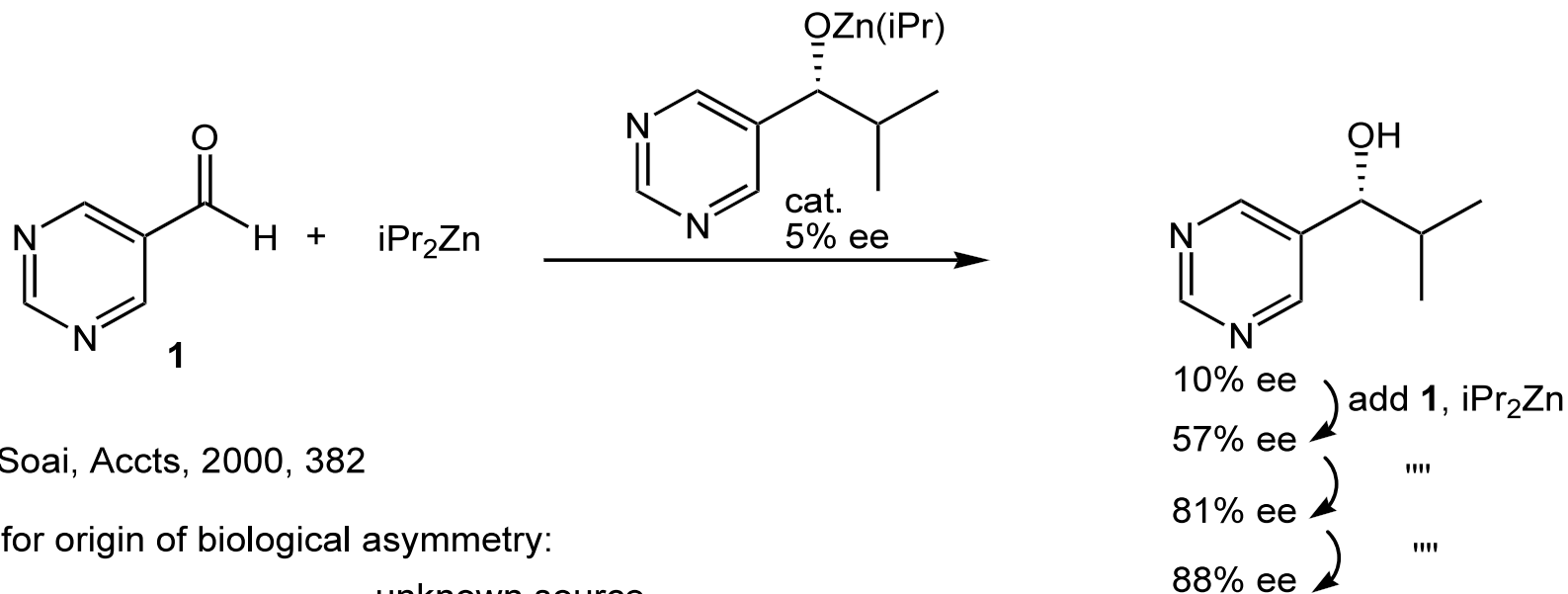
Consider a reaction in which 100% ee catalyst gives 99.9% ee product and the reaction is autocatalytic



If autocatalysis is coupled to a positive nonlinear effect, can see increasing rate and increasing ee

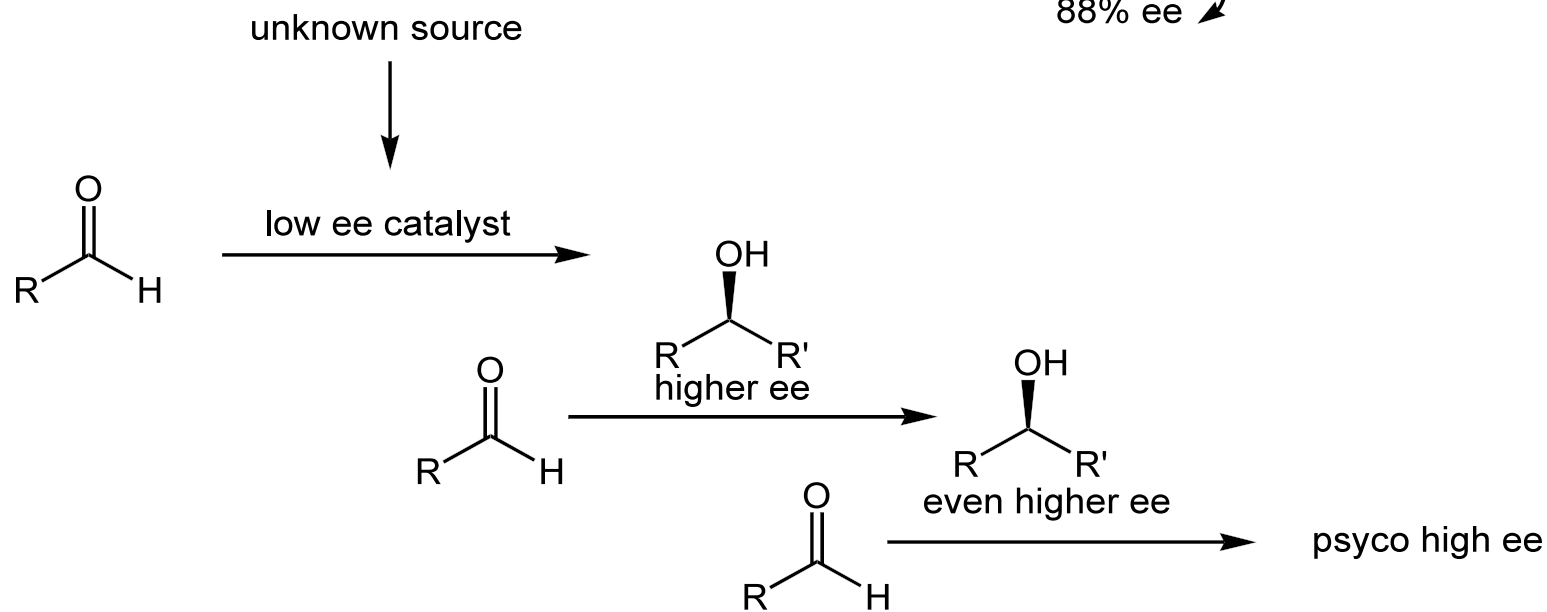


Pyrimidine carboxaldehyde/ R_2Zn system shows asymmetric amplification:

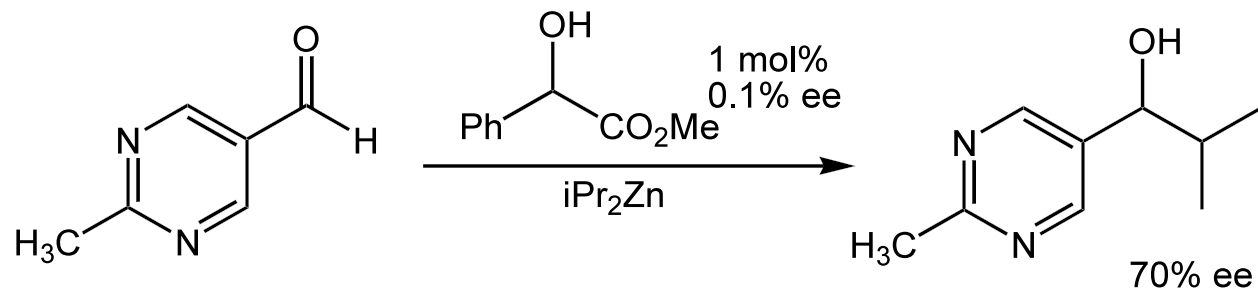


Soai, *Accts*, 2000, 382

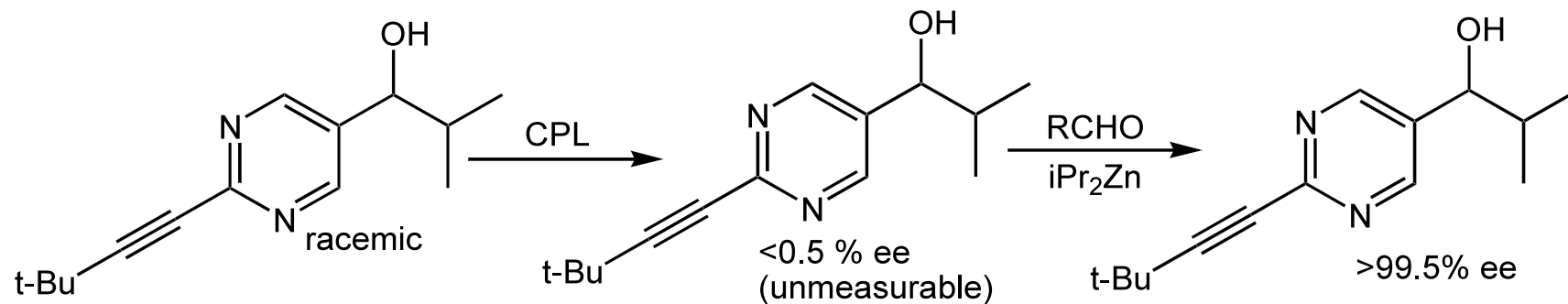
Idea for origin of biological asymmetry:



Extreme examples of asymmetric amplification



Connection between high ee and extraterrestrial chirality source:



CPL = circularly polarized light
asymmetric photolytic destruction of alcohol

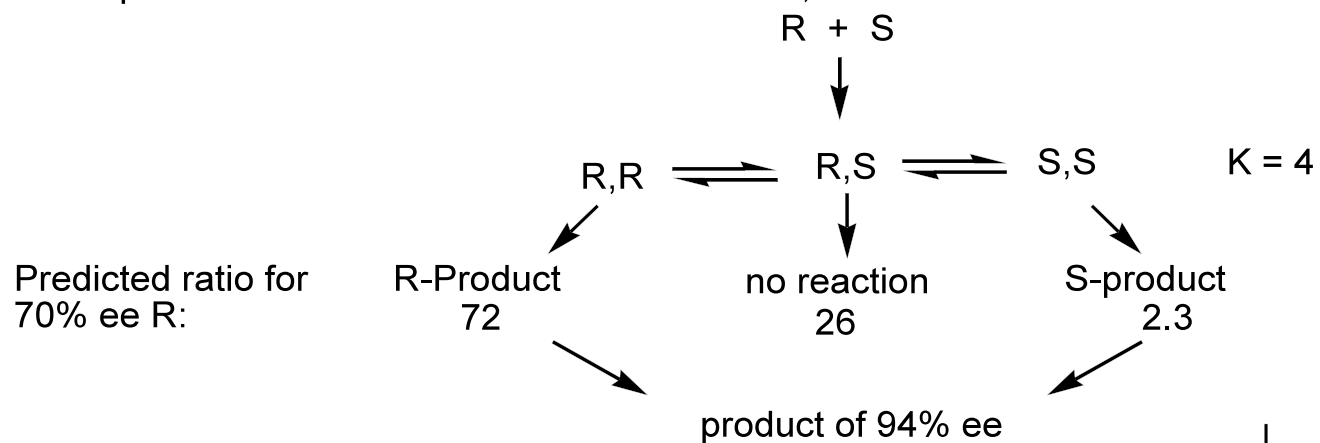
Origin of Asymmetric Amplification in Soai's system
Blackmond, JACS, 2001, 10103

experimental data

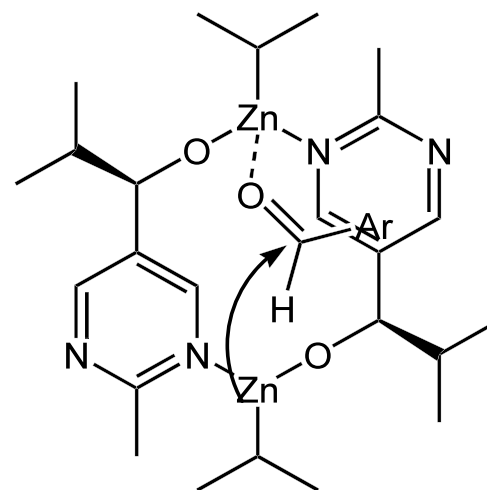
$$\text{Rate}_{(100\% \text{ ee})} = 2 \times \text{Rate}_{(\text{racemic})}$$

Inconsistent with reservoir model (postulates reactive monomers, preferential formation of inactive meso dimers)

Propose statistical mixture of reactive dimers; meso is unreactive:

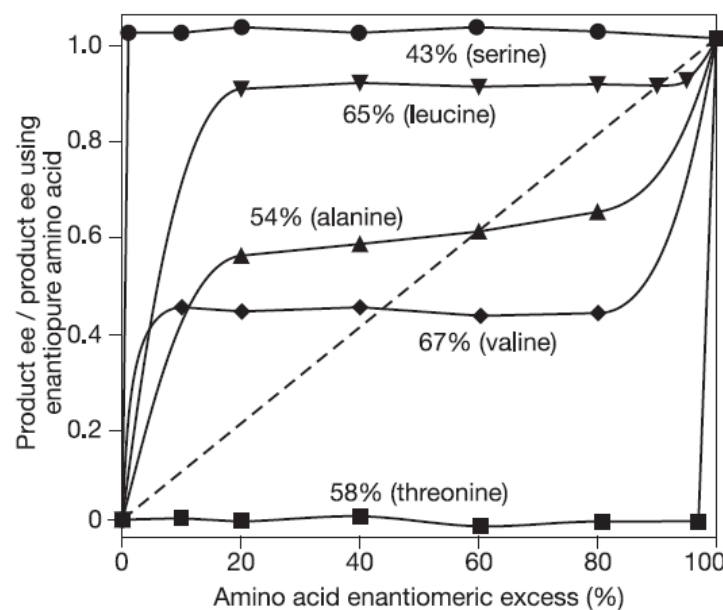
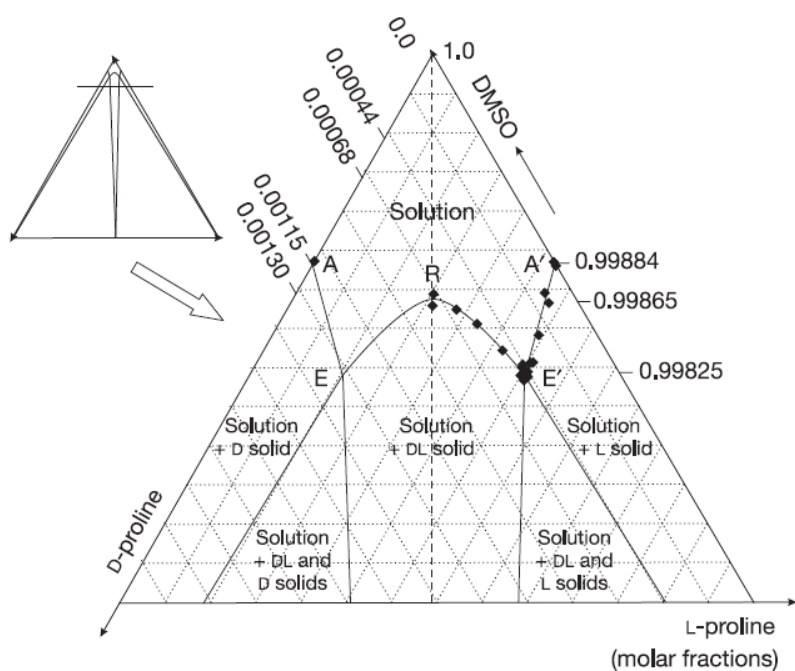


Both requirements for asymmetric amplification fulfilled:
-autocatalytic
-+NLE



Thermodynamic control of asymmetric amplification in amino acid catalysis

Martin Klussmann¹, Hiroshi Iwamura^{1†}, Suju P. Mathew¹, David H. Wells Jr^{1†}, Urvish Pandya¹, Alan Armstrong¹ & Donna G. Blackmond^{1,2}



Nature, 2006, 441, 621

See also Hayashi, *ACIEE*, 2006, 4593