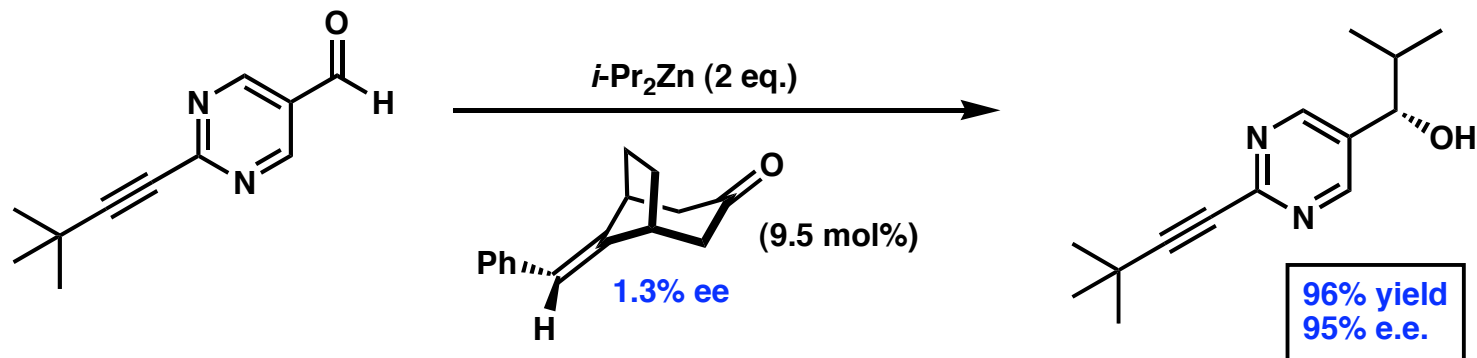


Asymmetric Amplification



and Autocatalysis



Literature Group Meeting
by Dan Caspi

Monday January 10, 2005 • 147 Noyes, 8 PM

Outline of Topics



- I. Introduction
 - a. Definitions
 - b. Biological Implications

- II. Asymmetric Amplification
 - a. Non-Linear Effects
 - b. Examples
 - c. Kinetic Models

- III. Autocatalysis
 - a. Explanation
 - b. Soai Reaction
 - c. Kinetic Models and Mechanism

IV. Conclusion

Additional Reviews:

- H. Kagan. *Angew. Chem. Int. Ed.* **1998**, 37, 2922-2959.
- K. Soai. *Acc. Chem. Res.* **2000**, 33, 382-390.
- H. Kagan. *Synlett* **2001**, SI, 888-899.
- M. Todd. *Chem. Soc. Rev.* **2002**, 31, 211-222.
- K. Mikami. *Chem. Rev.* **2003**, 103, 3369-3400.
- K. Soai. *Bull. Chem. Soc. Jpn.* **2004**, 77, 1063-1073.



Terms Organic Chemists Take For Granted

From a Molecular Perspective!

Racemate:

An equimolar mixture of a pair of enantiomers. It does not exhibit optical activity.

Enantiopure:

A sample all of whose molecules have (within limits of detection) the same chirality sense.

Enantiomer:

One of a pair of molecular entities which are mirror images of each other and non-superposable.

reproduced from:

*IUPAC Compendium of Chemical Terminology
2nd Edition (1997)*

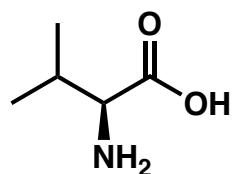
Enantiopure compounds can have *different*...

- Melting points
- Boiling points
- NMR spectra
- Chromatographic behavior
- Solubility properties
- **Reactivities**

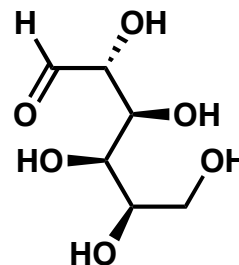
...than racemates

A Brief Interlude About the Origins of Life

Each of life's crucial biomolecules - amino acids, sugars, and biopolymers exist in essentially complete enantiomeric homogeneity



L-Valine



D-Glucose

Homochirality is a precondition for life, so...

- How did life choose its handedness?
- How was high optical activity achieved from a racemic or prochiral prebiotic environment?

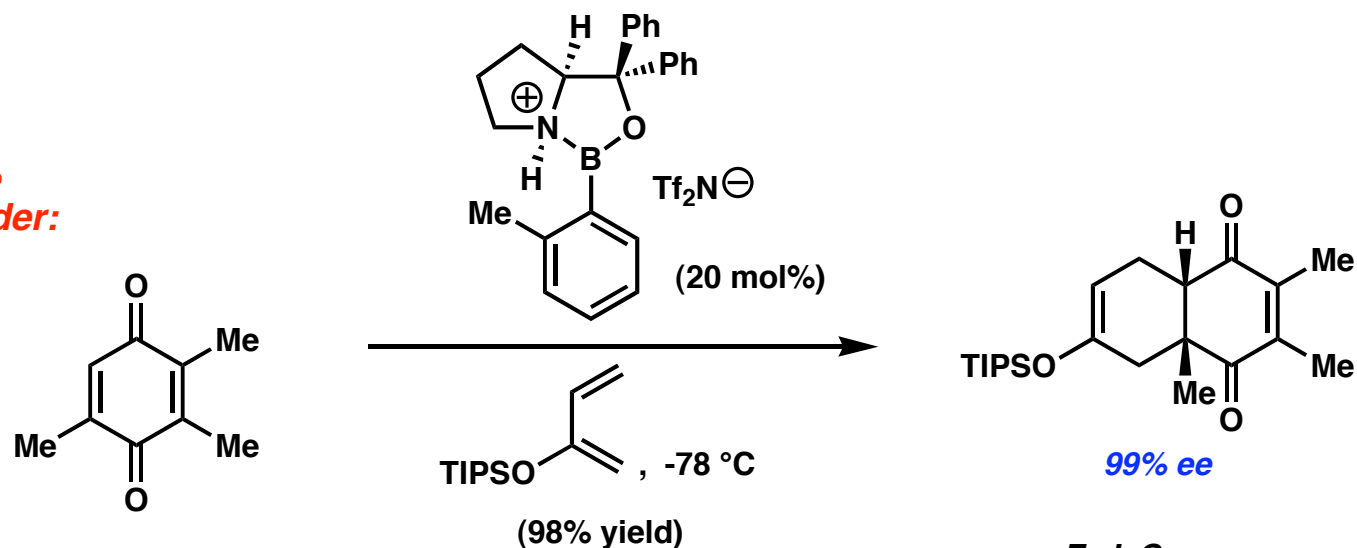
"A laboratory demonstration may not be impossible."

F. C. Frank
Biochim. Biophys. Acta **1953**, 11, 459-463.

How Do Chemists Prepare Enantioenriched Compounds?

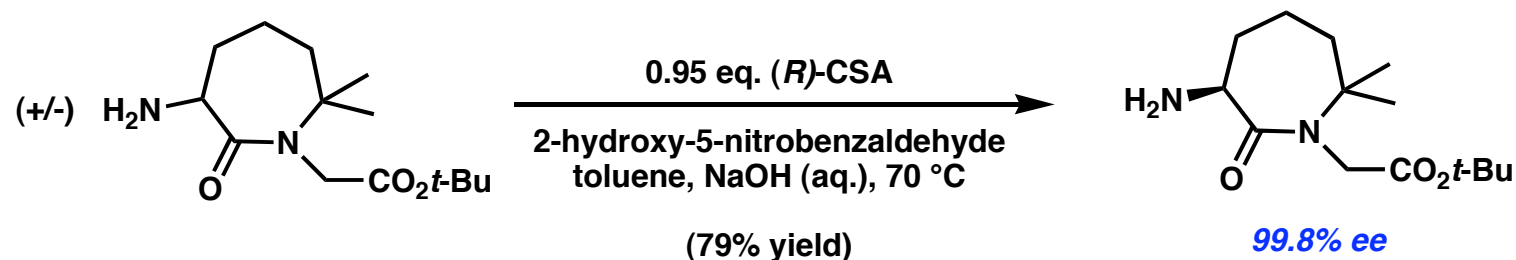
Typically accomplished using a chiral reagent or catalyst

Quinone Diels-Alder:



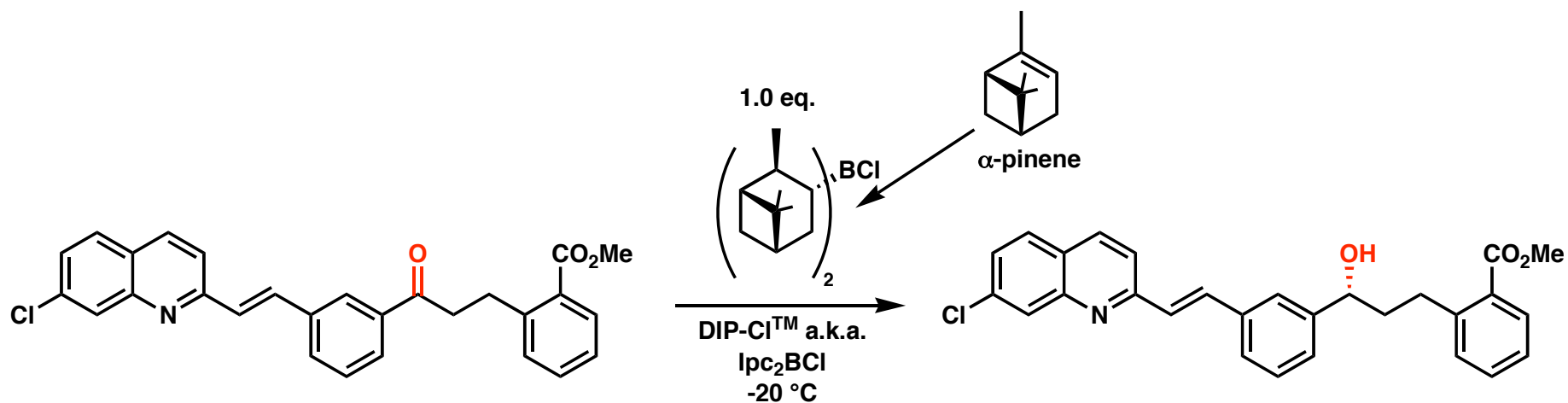
E. J. Corey
J. Am. Chem. Soc. **2004**, 126, 4800-4802.

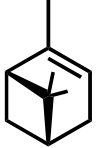
Crystallization-Induced Dynamic Kinetic Resolution:

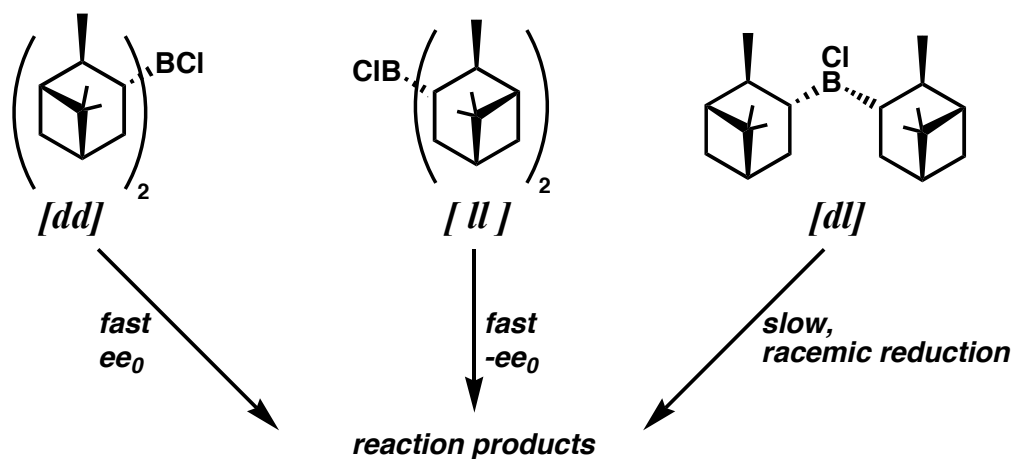


Bristol-Myers Squibb Process Group
Org. Lett. **2003**, 5, 3155-3158.

Case Study: Merck Process Development of Singulair



	98% ee	→	97% ee
α -pinene	70% ee (85:15) 1.8 eq. lpc_2BCl	72 : 2 : 26 → dd: ll : dl	95% ee (72 : 2 or 94% ee predicted)
	racemic	→	52% conversion



Merck Process

Tetrahedron Lett. **1997**, 38, 2641-2644.

Pure & Appl. Chem. **1994**, 66, 1551-1556.

Donna Blackmond (Detailed Kinetics)

J. Am. Chem. Soc. **1998**, 120, 13349-13353.

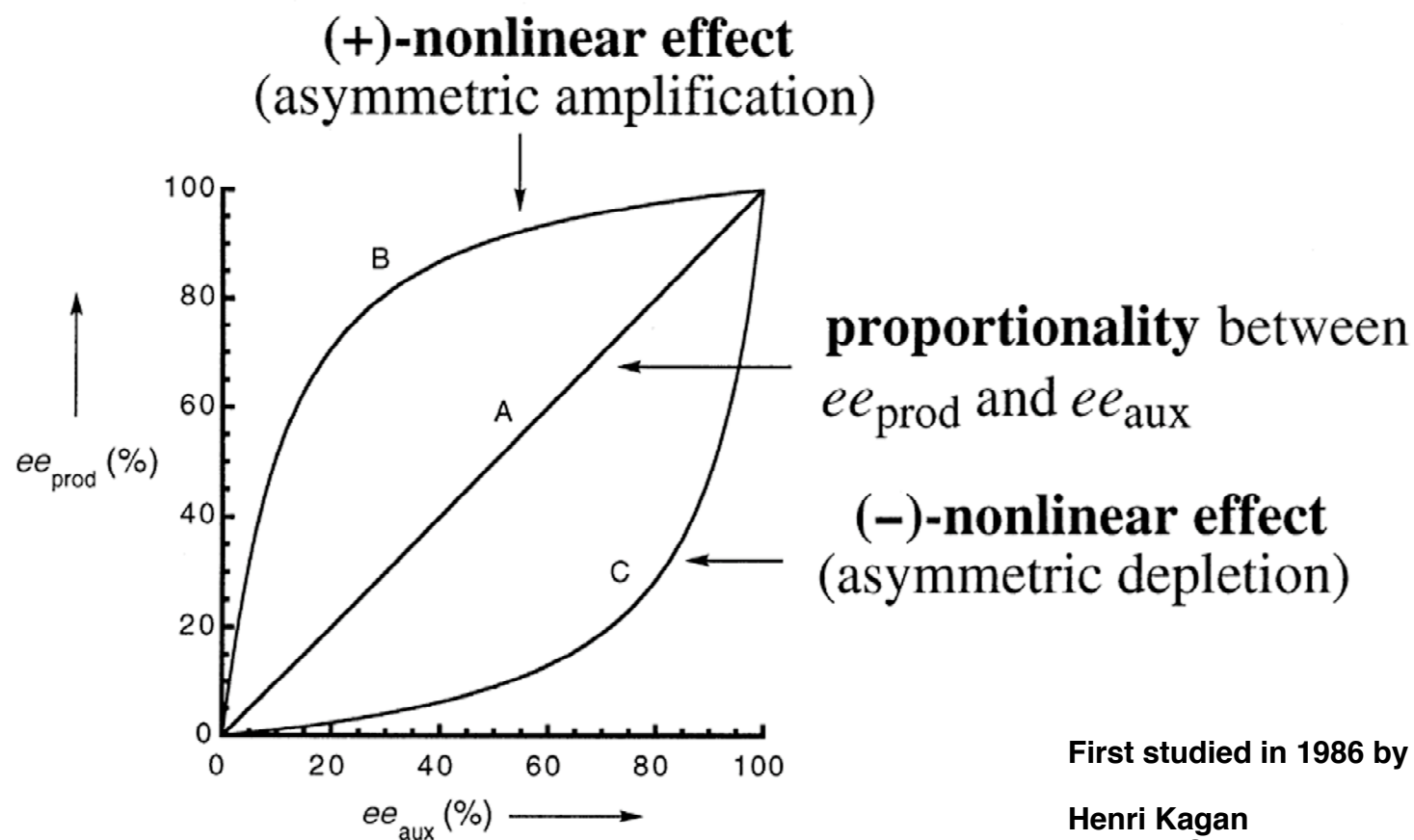
Non-Linear Effects (NLE) and How They Can Arise

$$ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}}$$

ee_{prod} Final ee of the product
 ee_0 ee_{prod} obtained using enantiopure auxilliary ($ee_{\text{aux}} = 1$)
 ee_{aux} Catalyst or auxilliary ee

These nonlinear interactions occur as a result of diastereomeric perturbations.

Three systems were studied in 1986 to confirm this experimentally, one of which was the Sharpless asymmetric epoxidation.

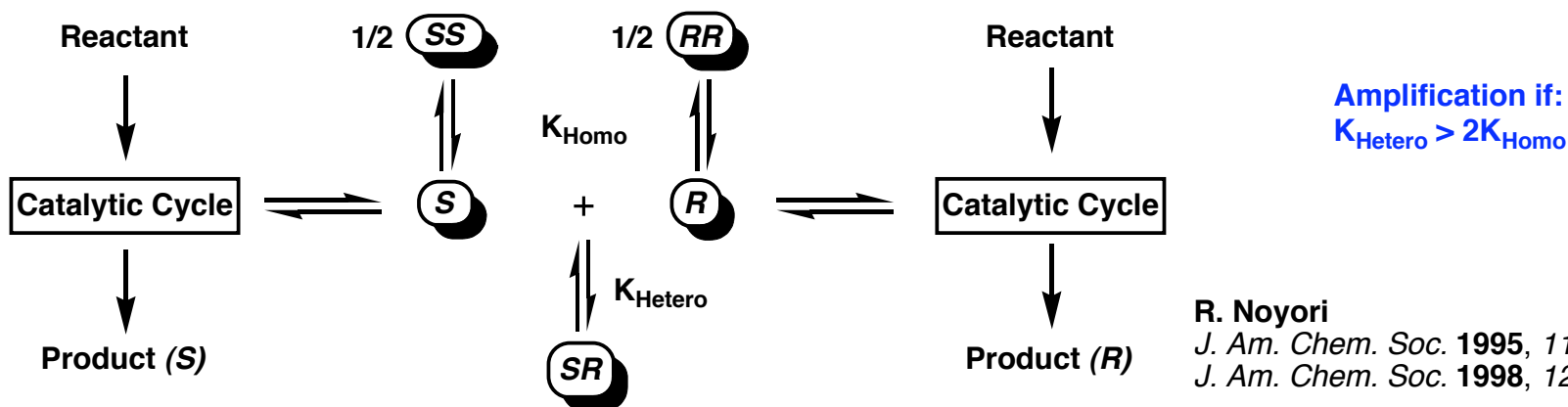


First studied in 1986 by Kagan.

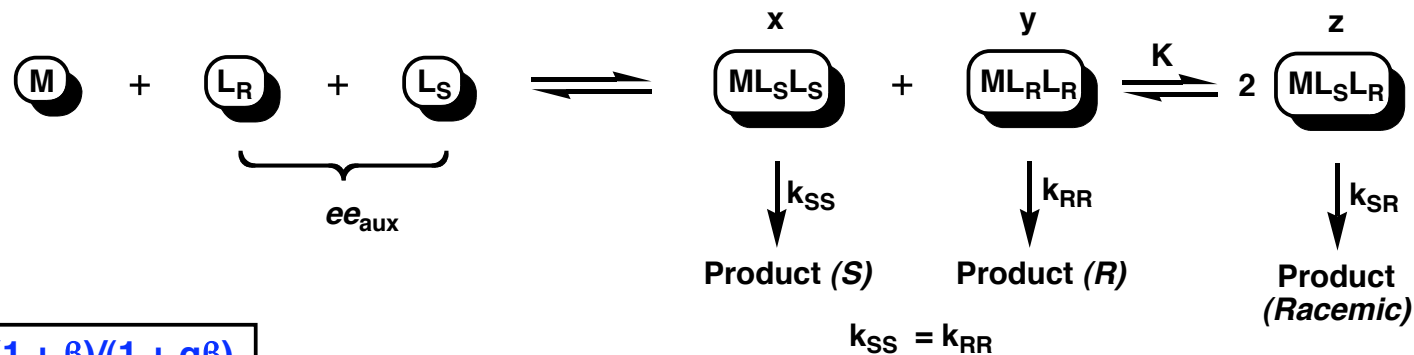
Henri Kagan
Angew. Chem. Int. Ed. **1998**, 37, 2922-2959.

Models for Asymmetric Nonlinear Effects

Noyori's Model:



Kagan's ML_2 Model:



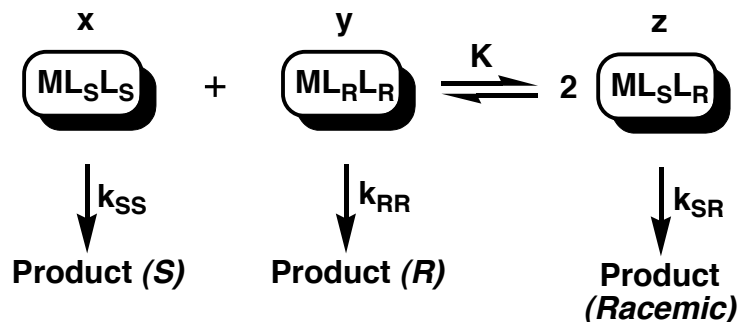
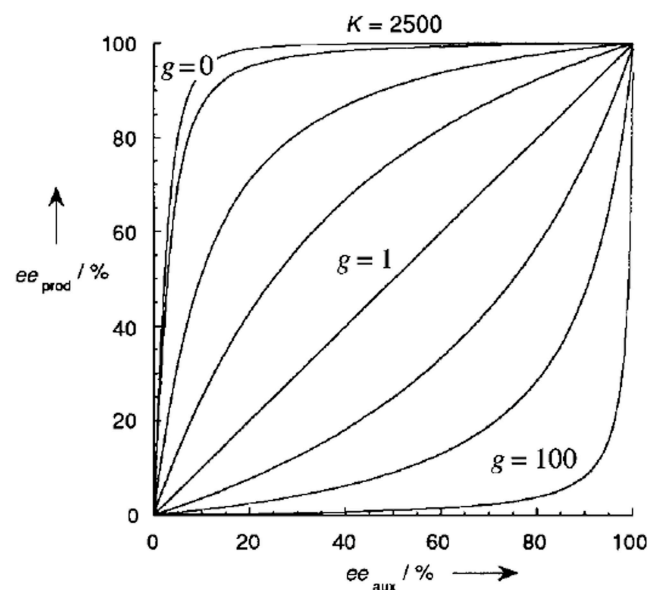
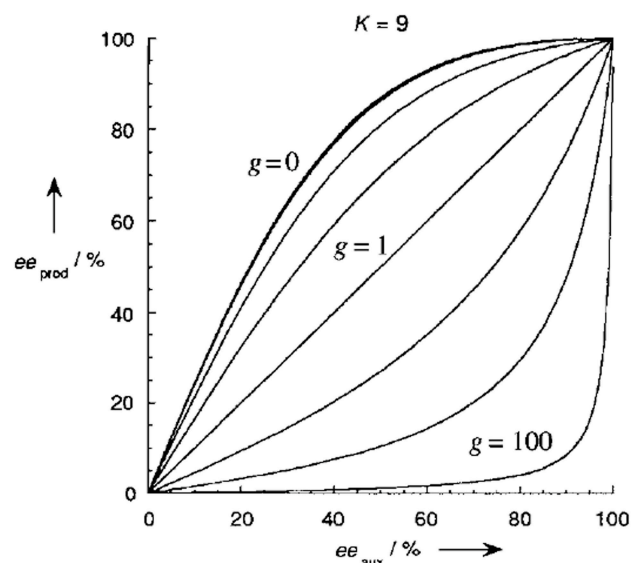
$$ee_{prod} = ee_0 \cdot ee_{aux} \cdot (1 + \beta)/(1 + g\beta)$$

- ee_{prod} Final ee of the product
- ee_0 ee_{prod} obtained using enantiopure auxilliary ($ee_{aux} = 1$)
- g k_{SR}/k_{RR} or relative activities of hetero and homo complexes
- β $z / (x + y)$ or relative amounts of hetero and homo complexes
- K z^2 / xy or the equilibrium constant between hetero and homo complexes

H. Kagan
J. Am. Chem. Soc. **1994**, 116, 9430-9439.
Angew. Chem. Int. Ed. **1998**, 37, 2922-2959.

Models for Asymmetric Nonlinear Effects

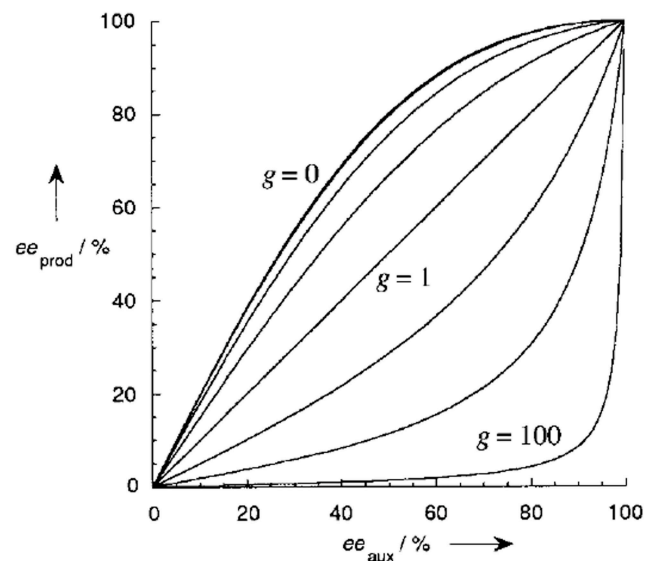
Kagan's ML_2 Model:



$$ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}} \cdot (1 + \beta) / (1 + g\beta)$$

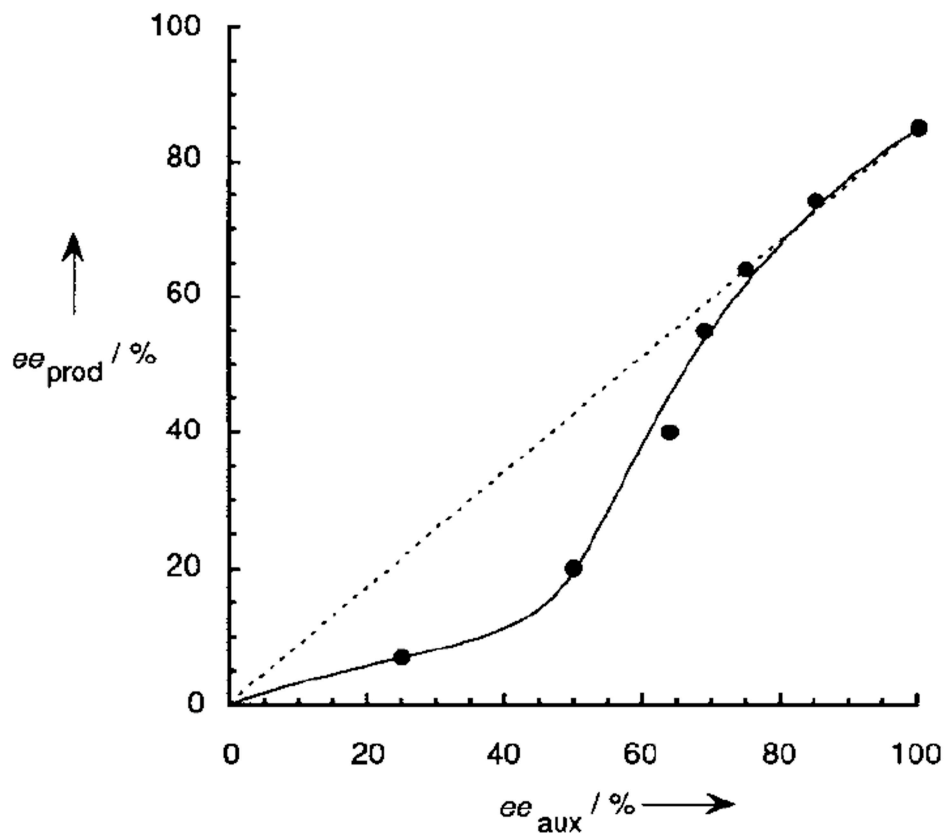
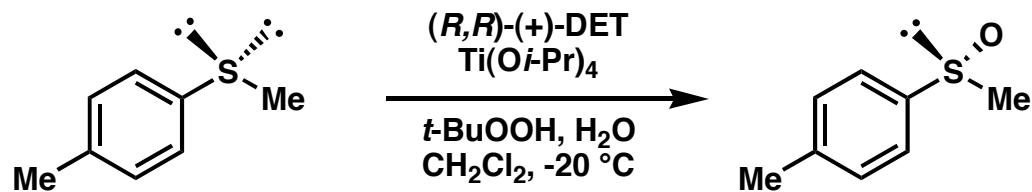
- ee_{prod} Final ee of the product
- ee_0 ee_{prod} obtained using enantiopure auxiliary ($ee_{\text{aux}} = 1$)
- g k_{SR}/k_{RR} or relative activities of hetero and homo complexes
- β $z / (x + y)$ or relative amounts of hetero and homo complexes
- K z^2 / xy or the equilibrium constant between hetero and homo complexes

Statistical
Distribution
($K = 4$):



Early Experiments by Kagan

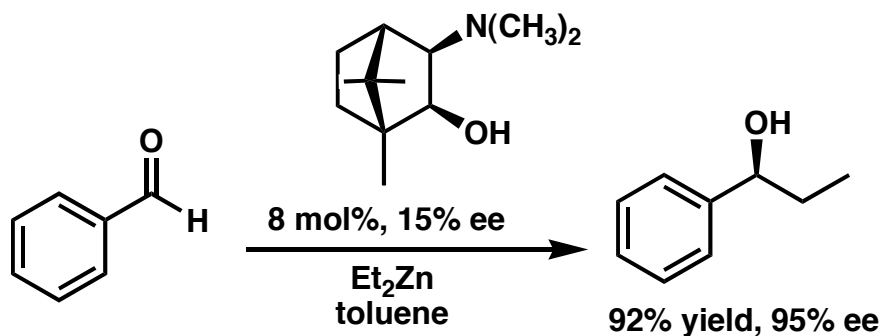
Asymmetric Oxidation of Sulfides:



This behavior indicates a quite complicated structure for the water-modified Sharpless reagent.

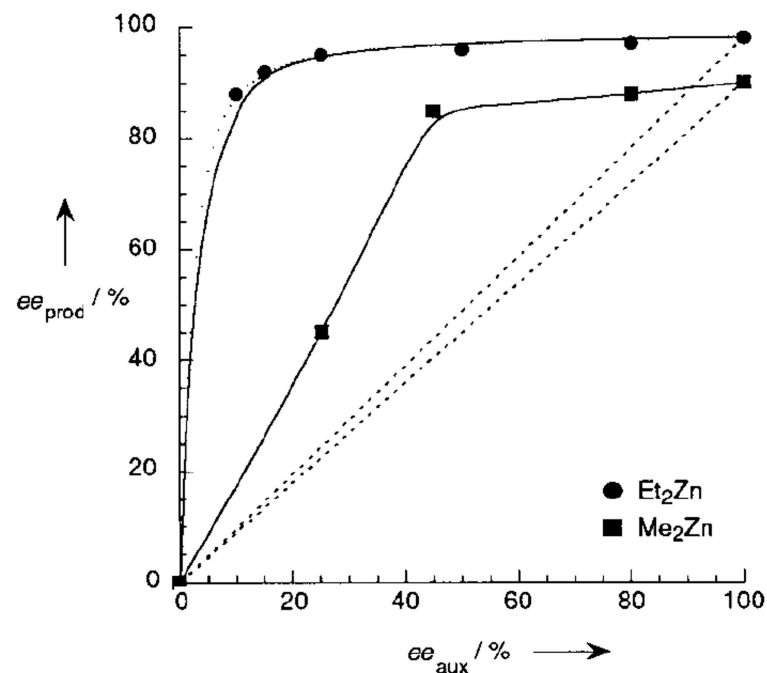
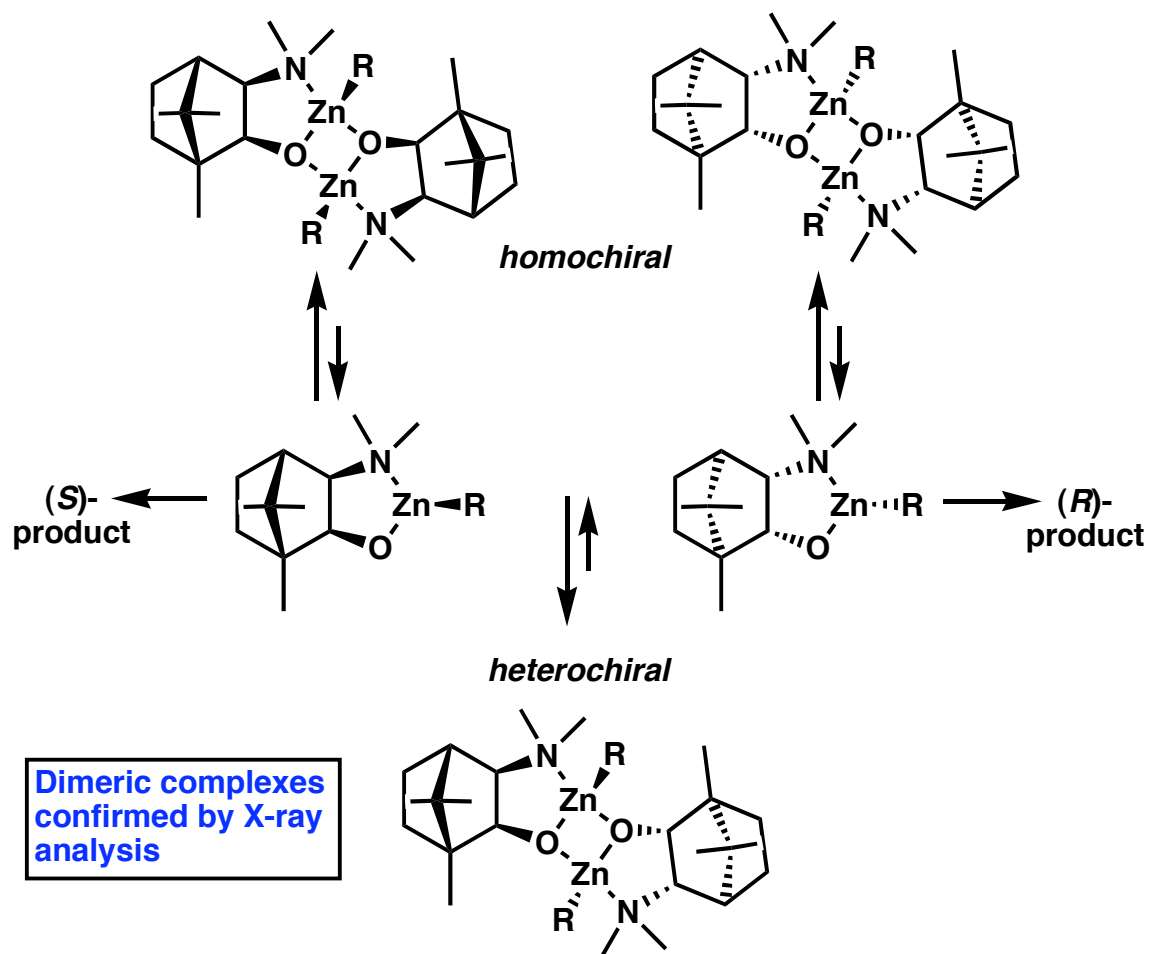
Henri Kagan
J. Am. Chem. Soc. **1984**, *106*, 8188-8193.

Mechanistic Study of Organozinc Complexes



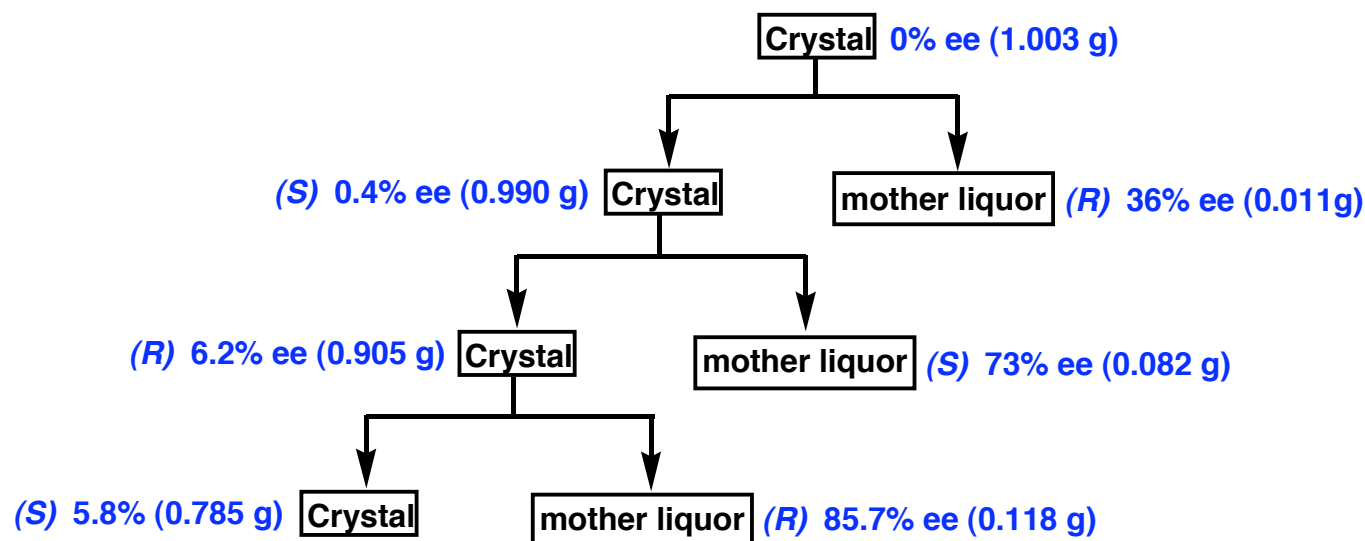
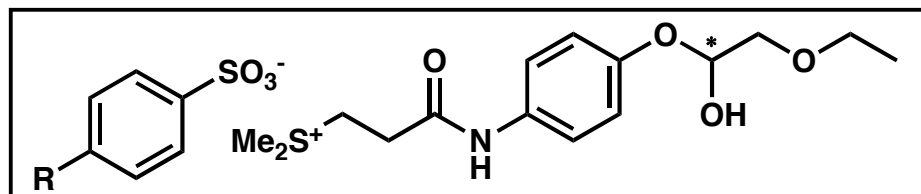
R. Noyori
J. Am. Chem. Soc. **1989**, *111*, 4028-4036.

$K = 5000$
 $g = 0.01$



Spontaneous Crystallization-Induced Resolution

Crystal growth takes advantage of statistical fluctuations



This can only occur if the racemate is a conglomerate in the solid state.

Mechanistic proposal deals with heterochiral chain structure preferred in crystals and homochiral chain structure preferred in solution.

R.-Y. Qian, G. D. Botsaris (Mechanistic Theory)
Chem. Eng. Sci. **1997**, *52*, 3429-3440.

R. Tamura, H. Takahashi, K. Hirotsu, Y. Nakajima, T. Ushio, F. Toda
Angew. Chem. Int. Ed. **1998**, *37*, 2876-2878.

M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios
Chem. Commun. **2000**, 887-892.

What About Absolute Asymmetric Synthesis?

Absolute asymmetric synthesis is the formation of enantiomerically enriched products from achiral precursors without the intervention of chiral chemical reagents or catalysts

K. Mislow

Collect. Czech. Chem. Commun. **2003**, 68, 849-864.



The statistical probability of flipping a fair coin 100 times and having exactly 50 heads and 50 tails is only 8%.

**Chemists unwittingly effect direct asymmetric syntheses!
In practice, it is unavoidable on statistical grounds alone.**

Mills' concept of "statistical dissymmetry":

$$k = 0.6743 / \sqrt{N}$$

k: enantiomeric excess "degree of statistical dissymmetry"

N: total number of molecules in the sample

kN: statistical average of enantiomeric molecules in excess
(1/2 the samples will contain more than this!)

To put this in perspective:

N = 10^{20} molecules (~1 mmol)

k = 6.7×10^{-11}

kN: 6.7×10^9 molecules

Some questions to ponder...

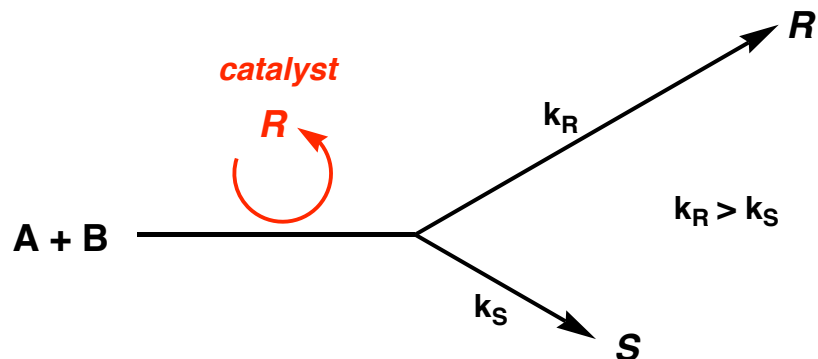
Is a man with one hair still bald?

Can a sample with an uneven number of molecules be racemic?

Is it impossible to make an enantiopure product with achiral reagents?

Asymmetric Autocatalysis Takes Advantage of Minute Differences!

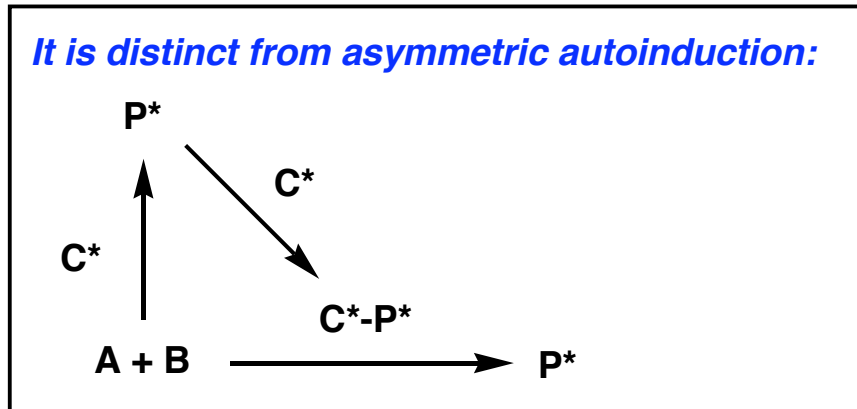
Is it the Answer to Absolute Asymmetric Synthesis?



If positive non-linear effects occur, amplification of ee is possible! However, there must be an additional inhibition mechanism.

The product can be recycled to further amplify the ee.

It is distinct from asymmetric autoinduction:



Why Autocatalysis Alone Is Not Sufficient To Amplify Enantiomeric Excess

It's Not Enough Says Blackmond!

recall:

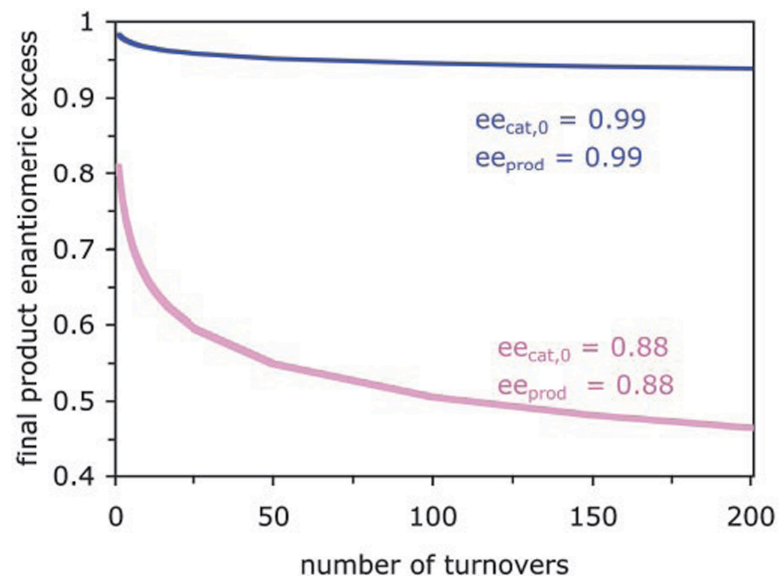
$$ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}}$$

ee_{prod} Final ee of the product

ee_0 ee_{prod} obtained using enantiopure auxilliary ($ee_{\text{aux}} = 1$)

ee_{aux} Catalyst or auxilliary ee

If the catalyst is not perfect ($ee_0 < 1$), the product ee will be less than catalyst ee and the lower ee products will be serving as catalysts in future reactions!



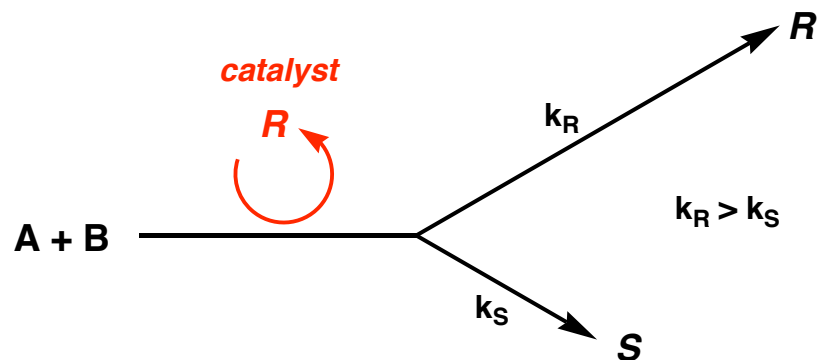
$$ee_{\text{prod}} = ee_{\text{aux},0} \cdot (\text{TON} + 1)^{(ee_0 - 1)}$$

A Simple Asymmetric Autocatalytic Reaction

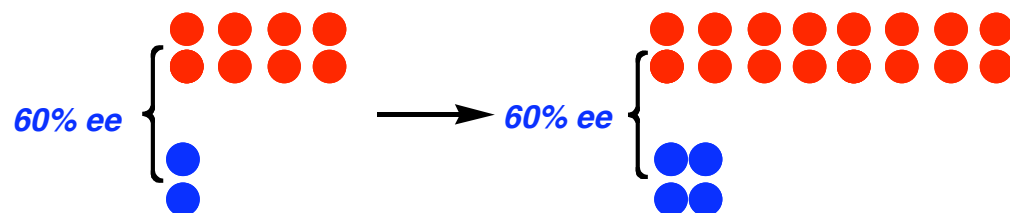
Donna Blackmond
Proc. Nat. Acad. Sci. **2004**, 101, 5732-5736.

Asymmetric Autocatalysis

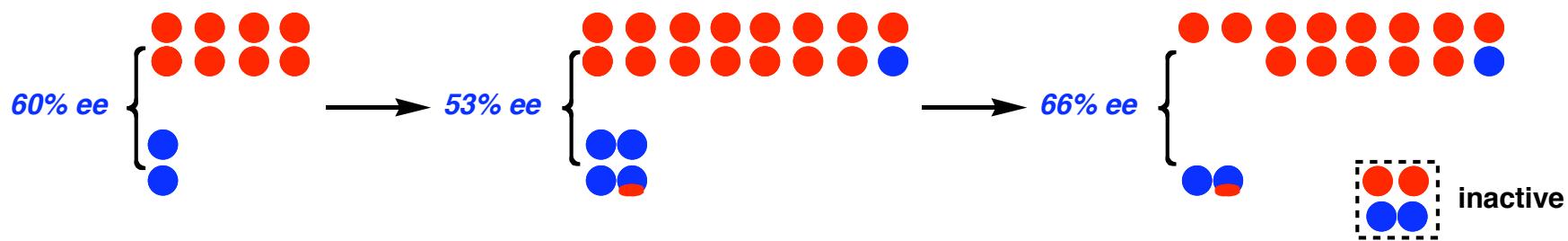
A Simplified Look



For a "perfect catalyst"



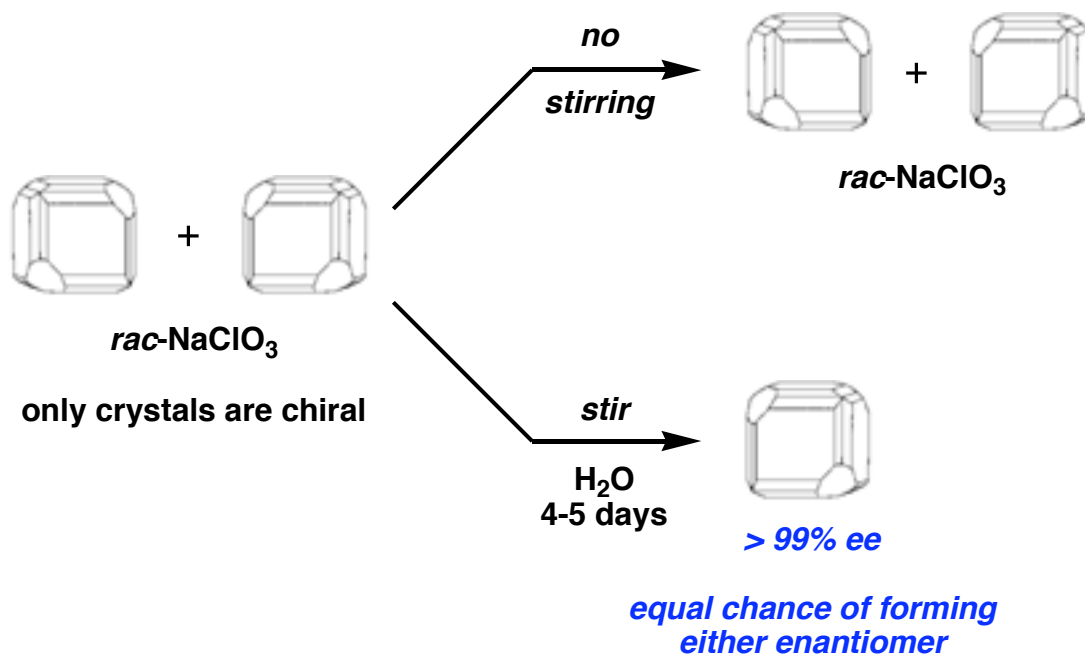
For an "imperfect catalyst"



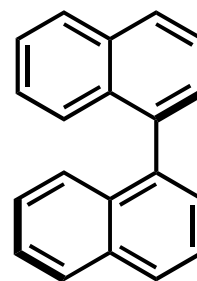
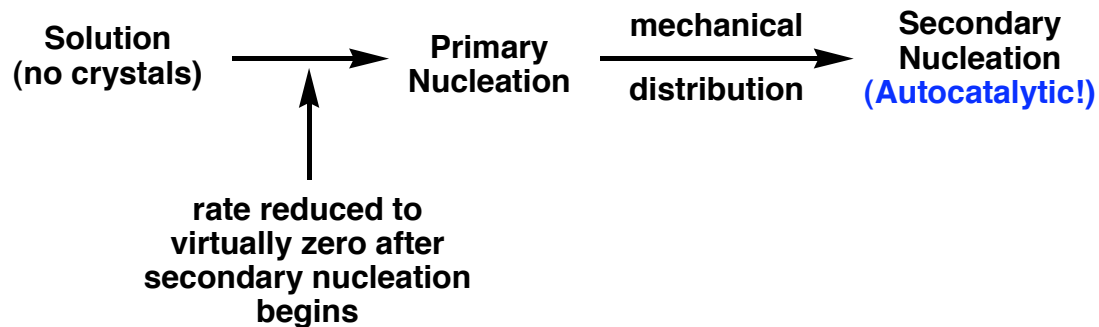
asymmetric amplification!

Spontaneous Crystallization-Induced Resolution

Autocatalytic Secondary Nucleation



How Does This Work? (not well understood)



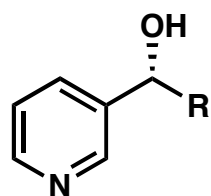
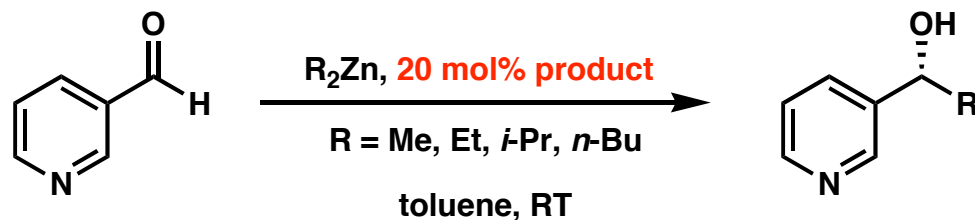
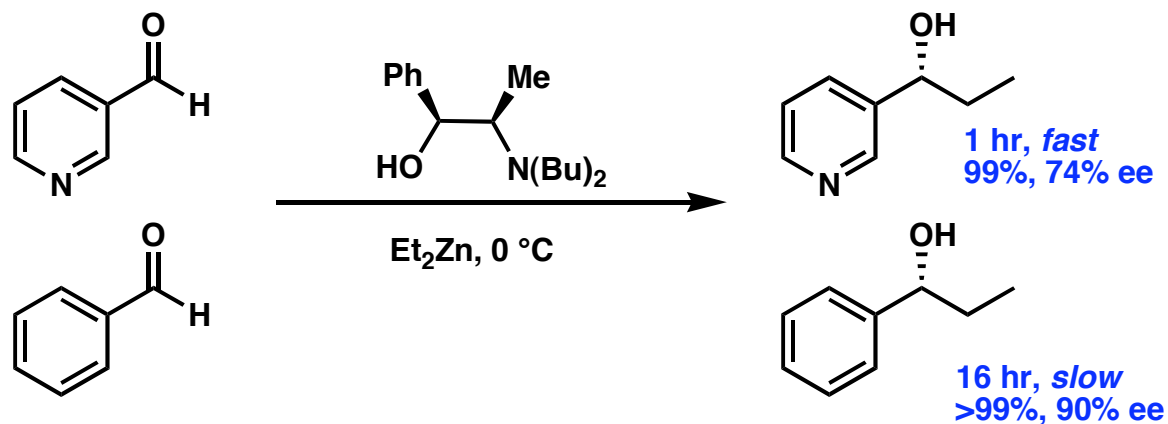
A similar phenomenon is observed with 1,1'-binaphthyl melts - **up to 80% ee!**

D. K. Kondepudi, J. Laudadio, K. Asakura
J. Am. Chem. Soc. **1999**, 121, 1448-1451.

D. K. Kondepudi, R. J. Kaufman, N. Singh
Science **1990**, 250, 975-976.

The First Asymmetric Autocatalyst Using an Organic Molecule!

A Humble Beginning



When 20 mol% added ($\text{R} = i\text{-Pr}$):

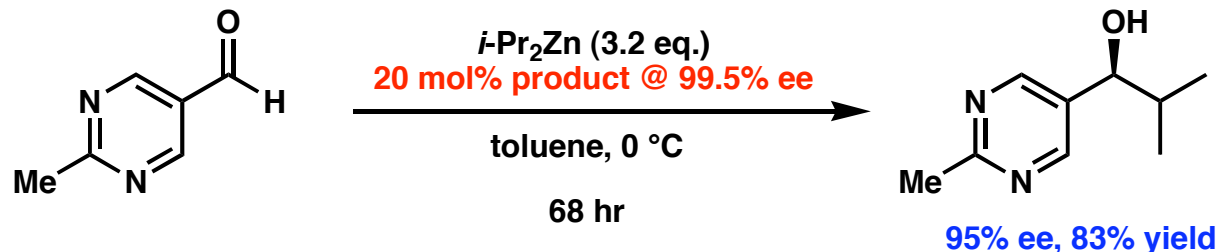
86% ee catalyst \rightarrow 35% ee product, 67% yield
with retention of configuration

Similar effects were observed for the other alkyl zinc reagents.

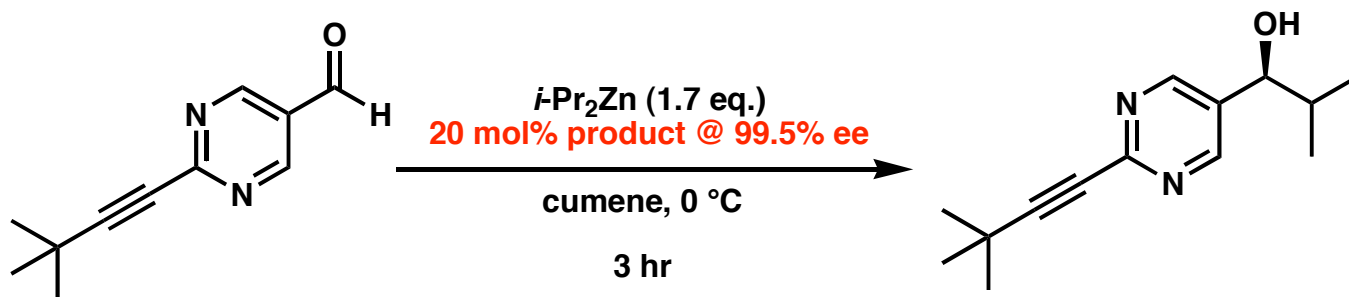
K. Soai
J. Chem. Soc. Chem. Comm. **1990**, 982-983.

Highly Enantioselective Asymmetric Autocatalysis

Chiral Pyrimidylalkanols



enhancement effect could be due to reduced rotational conformers



>99.5% ee, >99% yield

"practically perfect" -
product could be used in 10 consecutive
reactions as a catalyst with no loss in ee.

6 fold amplification/run = approx. 10^7 amplifications!!

- alkyne provides moderate electron withdrawing effect
- larger steric hindrance

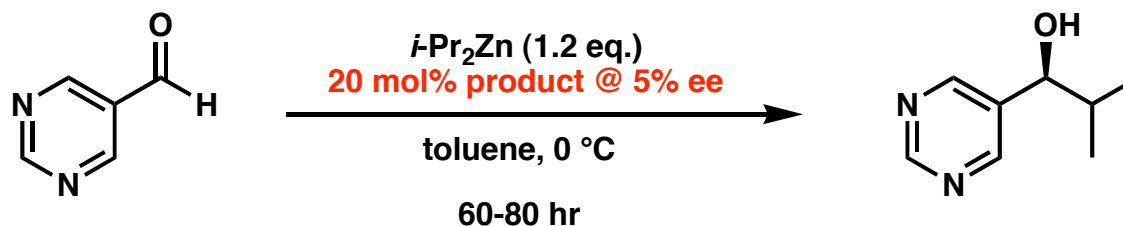
K. Soai

J. Am. Chem. Soc. **1996**, *118*, 471-472.

Angew. Chem. Int. Ed. **1999**, *38*, 659-661.

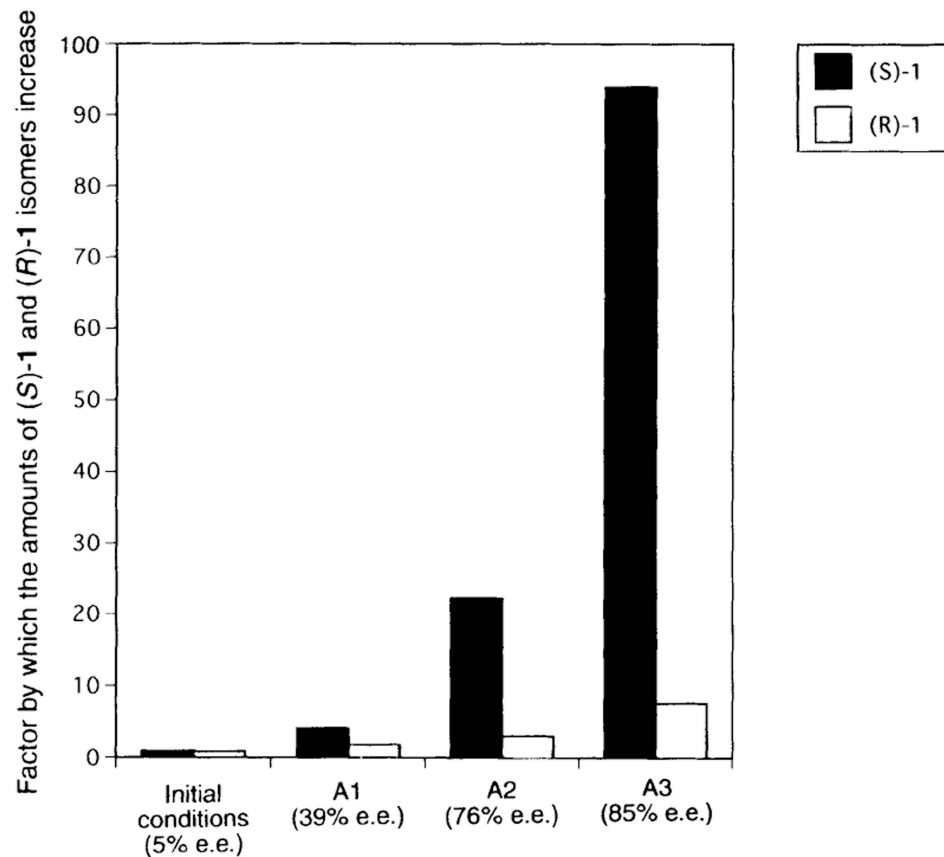
Asymmetric Autocatalysis *with* Amplification!

An Outstanding Achievement



The reaction products (yields ~ 60-80%) were used as a catalyst in the consecutive reaction.

Even 2% ee was successfully carried to 88% ee after only 4 trials.

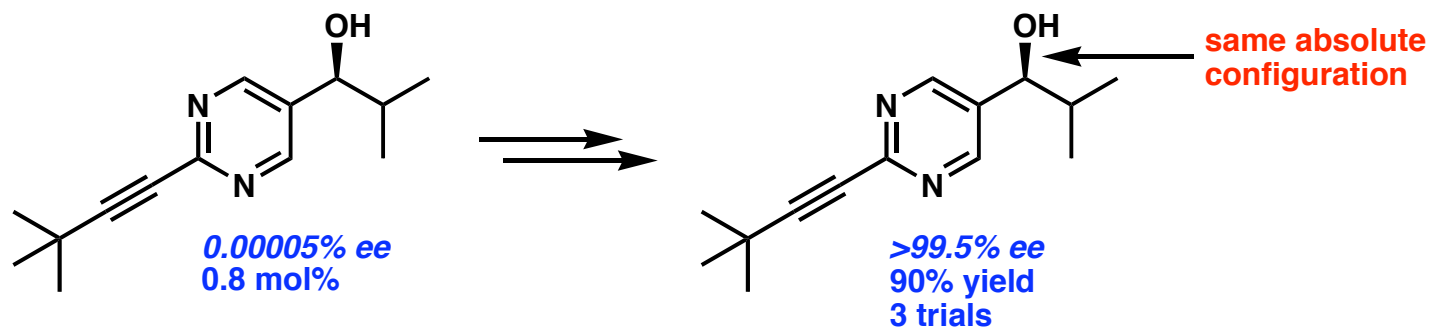
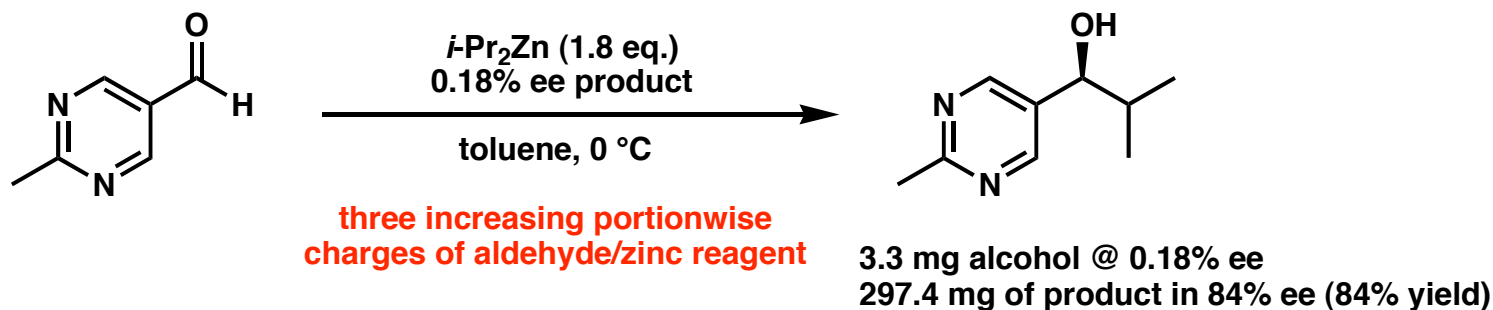


Note: *racemic* catalyst does not exhibit detectable levels of enantioselectivity.

K. Soai
Nature **1995**, 378, 767-768.

Asymmetric Autocatalysis *with Amplification!*

Now, in One Pot!



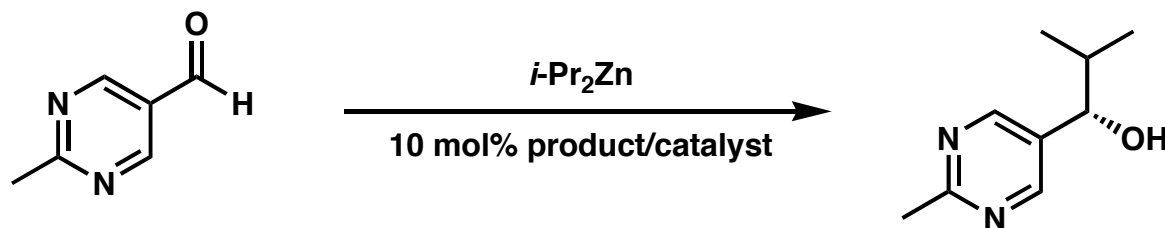
Chiral initiators (in as little as 1-2% ee and 2 mol% loading) can also be used, such as NaClO_3 , leucine, valine, helicenes, and quartz with excellent results.

K. Soai

Tetrahedron Asymm. **1997**, 8, 1717-1719.
Angew. Chem. Int. Ed. **2003**, 43, 315-317.

The Problem with Unspecific Mutual Antagonism

Detailed Mechanistic Studies

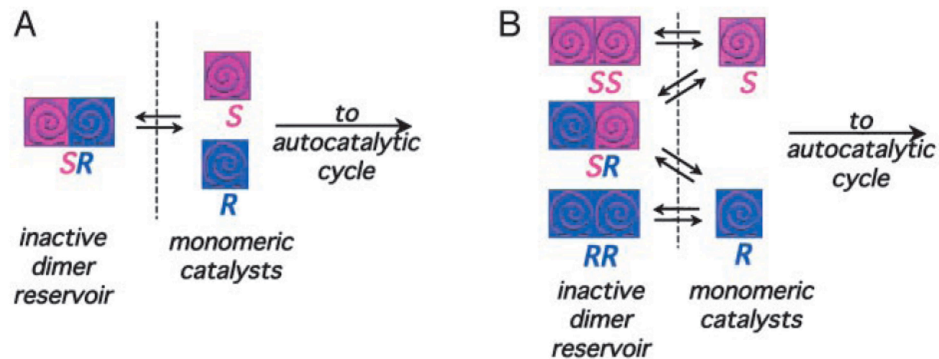


Any imbalance in ee is only preserved, but not amplified unless there is a preference for the heterodimer.

This microcalorimetry rate data fits with the unspecific mutual antagonism model as shown.

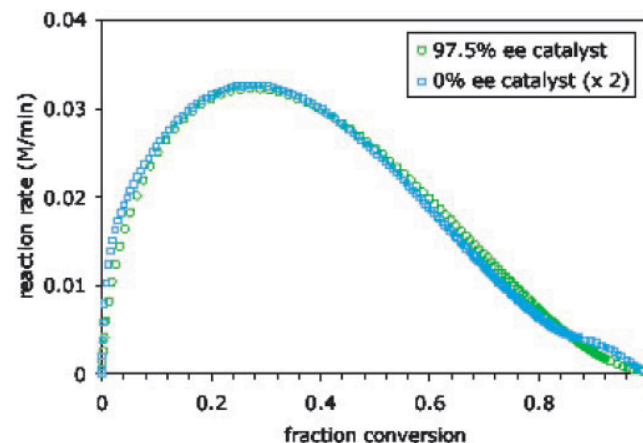
Racemic rate should lag behind the enantiopure (due to heterodimer) to cause an amplification in ee.

This data suggests no amplification in ee, but that is not true!



A: Specific Mutual Antagonism (1:1)

B: Unspecific Mutual Antagonism (Statistical)

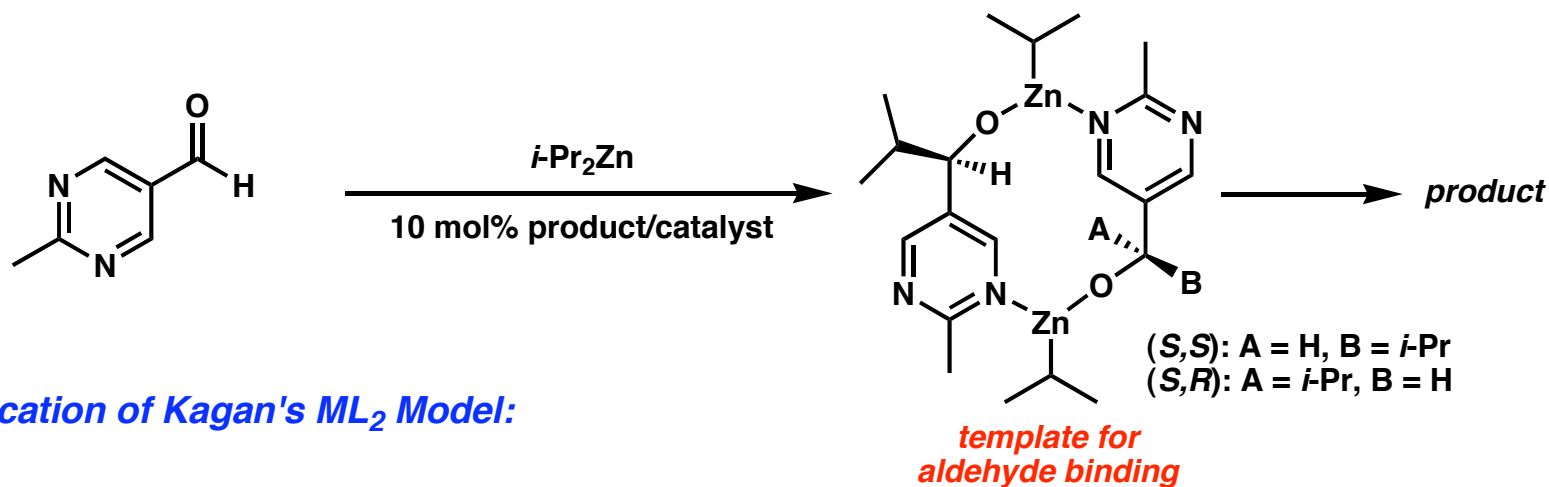


Donna Blackmond

J. Am. Chem. Soc. **2001**, 123, 10103-10104.

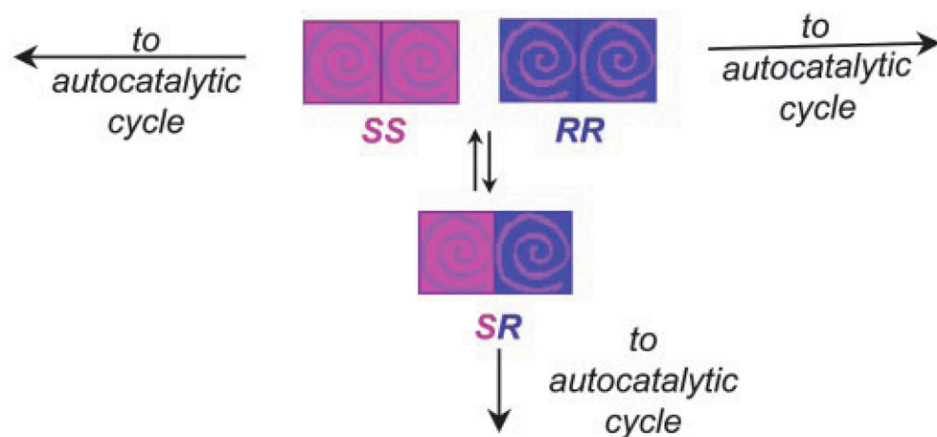
The Solution: Dimers Are the Catalysts

Paradox Resolved



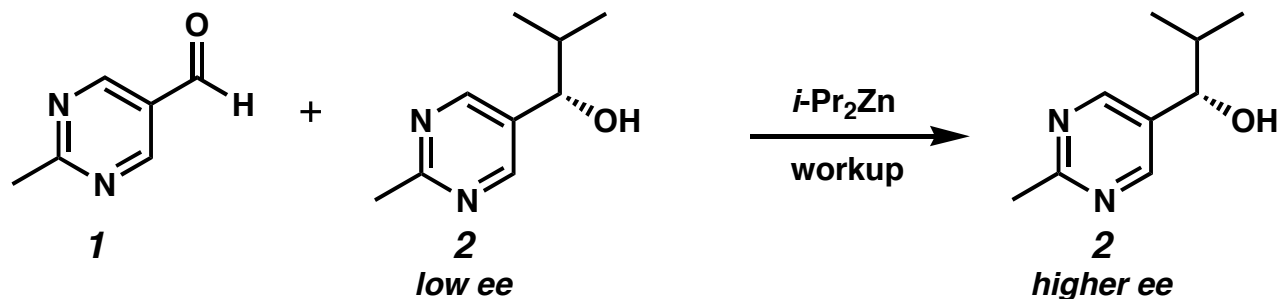
Modification of Kagan's ML_2 Model:

- This hybrid dimer model explains the rate data perfectly.
- All we need to assume for the amplification of ee is that the homochiral dimers are superior to the heterochiral dimers as catalysts.



Additional Mechanistic Evidence

Kinetics from Blackmond



Initial Kinetics:

$$\text{rate} = k \cdot [1][i\text{-Pr}_2\text{Zn}][3]_{\text{active}}$$

$$[3]_{\text{active}} = ([3]_{\text{RR}} + [3]_{\text{SS}})$$

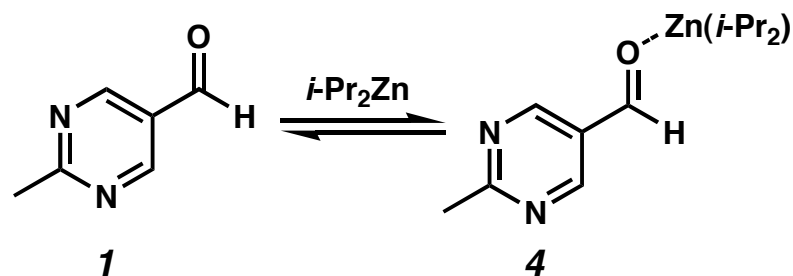
$K_{\text{eq}} = 4$ (statistical mixture of dimers);
RS dimer inactive

Refinements:

$$\text{rate} = k' \cdot [1]^2[3]_{\text{active}}$$

Gives an excellent fit when $[i\text{-PrZn}_2] \neq [1]$

How is the removal of $i\text{-PrZn}_2$ rationalized?



$$\text{rate} = k'' \cdot [4]^2[3]_{\text{active}}$$

Suggests a *tetrameric* transition state as opposed to the *trimeric* transition state implied by initial kinetics.

Donna Blackmond

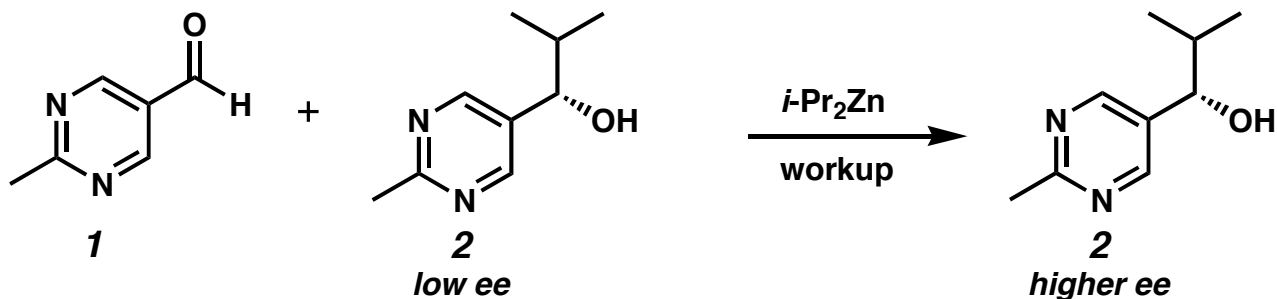
J. Am. Chem. Soc. **2001**, 123, 10103-10104.

J. Am. Chem. Soc. **2003**, 125, 8978-8979.

Proc. Nat. Sci. Acad. **2004**, 101, 5732-5736.

Additional Mechanistic Evidence

Final Thoughts



Additional Observations:

- Selective precipitation of the SR complex may play a role in the asymmetric amplification.
- Higher-order catalyst species may be imagined, and there is some kinetic evidence to suggest a trimeric or tetrameric complex for the transition state.
- Solvent choice plays an important role in this reaction, although it is not completely understood.

Implications:

- The fact that the *SR* is less active than the homochiral dimers (*SS* or *SR*) is just a stroke of luck.
- Statistics, and one such stroke of luck, are all that is required for a homochiral world to exist.
- The exact details of the transition state are not known.

Donna Blackmond

J. Am. Chem. Soc. **2001**, 123, 10103-10104.

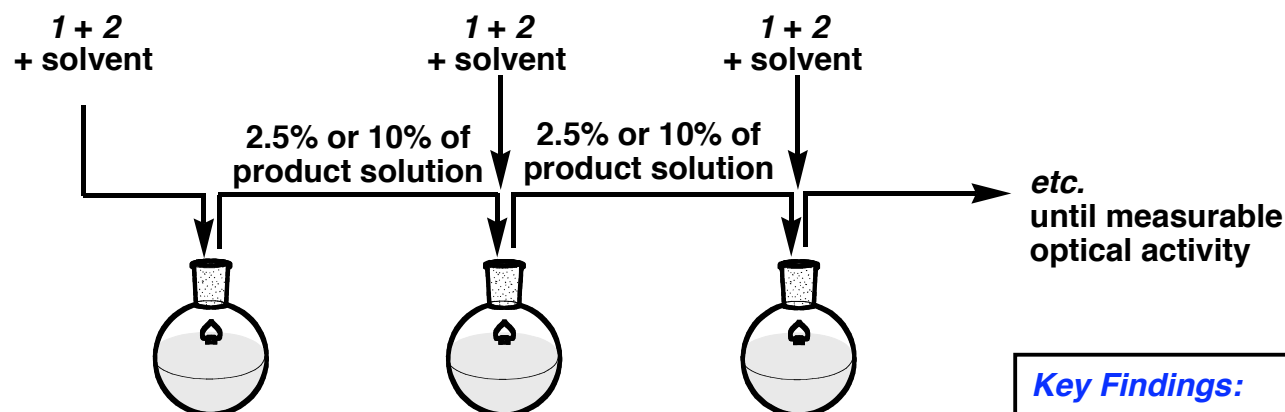
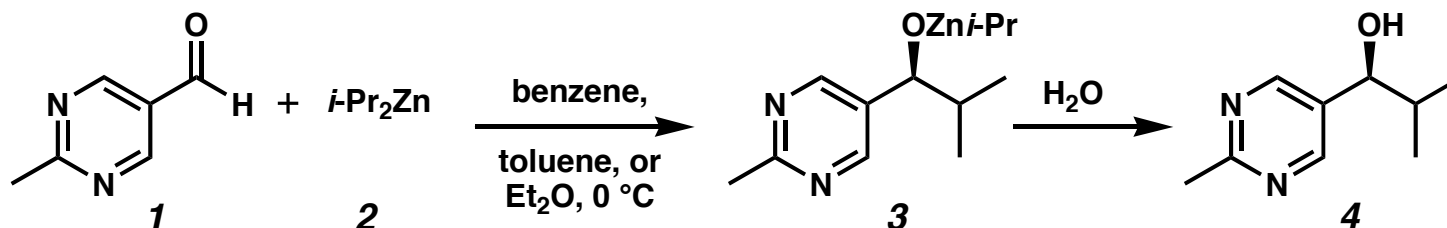
J. Am. Chem. Soc. **2003**, 125, 8978-8979.

Angew. Chem. Int. Ed. **2004**, 43, 2099-2103.

Proc. Nat. Sci. Acad. **2004**, 101, 5732-5736.

Just a Few Molecules Can Control the Enantiomeric Outcome

Is This Really Absolute Asymmetric Synthesis?



- Serial dilutions of 4 were prepared and used as a catalyst.
- Spiking with theoretical 10^{-16} M of 4 (~60,000 molecules/mL) gave the same enantiomer as the initial catalyst.
- Spiking with a theoretical 10^{-22} M of 4 (~0.06 molecules/mL) gave a random distribution.

Key Findings:

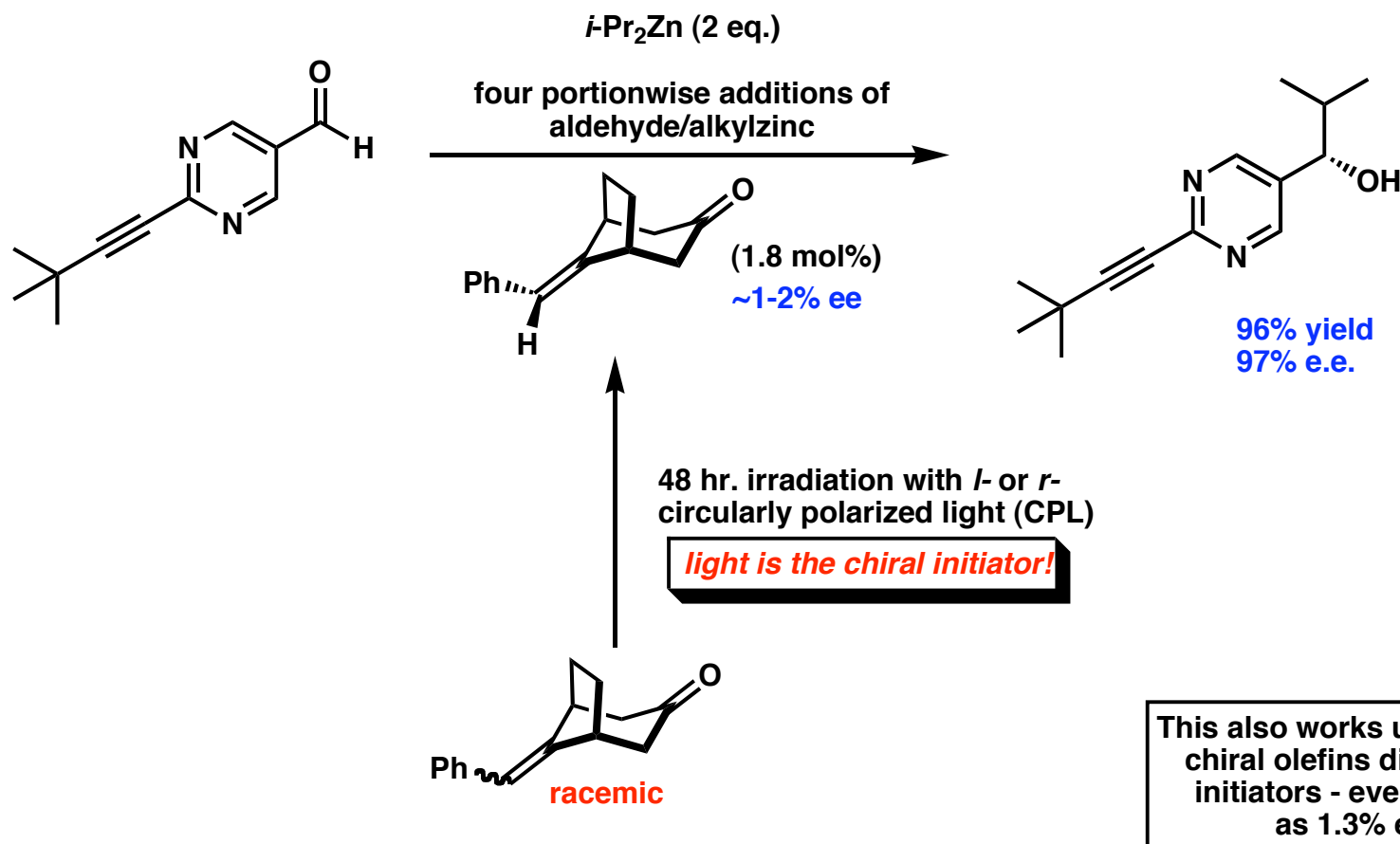
- Out of 48 trials, each one produced optically active material.
- But, there was an apparent nonrandom distribution of enantiomers.
- "Purity is a matter of degree" -- is it possible to perform experiments without trace optically active additives?

D. Singleton

J. Am. Chem. Soc. **2002**, *124*, 10010-10011.
Org. Lett. **2003**, *5*, 4337-4339.

The Soai Reaction Using Circularly Polarized Light (CPL)

The Photoequilibrium of Chiral Olefins



First example of such low ee values being associated with a highly enantioenriched compound with a stereogenic center.

These results are completely reproducible (*l*-CPL always gives the *S*-product, *r*-CPL always gives the *R*-product)

Kenso Soai
Angew. Chem. Int. Ed. **2004**, 43, 4490-4492.

Reflecting on Recent Developments

Mislow's Interpretation

- The possibility that at least a few of Singleton's trials were not triggered chiral impurities exists.
- Soai's claim of the initial small imbalance of enantiomers in racemic mixtures seems plausible, but it is just a conjecture.
- If an ee as tiny as $10^{-5}\%$ is sufficient to initiate the amplification, then smaller ee's are certainly capable in principle of initiating the process as well.

"...It is all but certain that the Soai reaction is capable of producing optically active compounds by an absolute asymmetric synthesis...It is a remarkable achievement."

Kurt Mislow

Collect. Czech. Chem. Commun. **2003**, 68, 849-864.

Asymmetric Amplification and Autocatalysis

Conclusion

- For asymmetric amplification or depletion to occur, there must be a diastereomeric *RS* complex which has different thermodynamic and/or kinetic (reactivity) properties than the *SS/RR* complexes.
- For asymmetric autocatalysis to occur with amplification, there must be an inhibition process associated with the opposite enantiomer.

Overall Benefits:

1. No need to use a different catalyst
2. Chiral product automultiplies exponentially (efficient)
3. Autocatalysts do not deteriorate (always being regenerated)
4. No need to purify catalyst away from product

and...it provides a demonstration of spontaneous asymmetric synthesis!