Asymmetric Amplification

\[
\text{Reaction: } \text{Ar}-\text{CH} = \text{CH} \rightarrow \text{Ar}-\text{CH} = \text{CH} \text{OH}
\]

\[\text{i-Pr}_2\text{Zn} \text{ (2 eq.)} \rightarrow 96\% \text{ yield, } 95\% \text{ e.e.}\]

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:

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

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
How Do Chemists Prepare Enantioenriched Compounds?

Typically accomplished using a chiral reagent or catalyst

**Quinone Diels-Alder:**

![Quinone Diels-Alder Reaction Scheme]

**Crystallization-Induced Dynamic Kinetic Resolution:**

![Crystallization-Induced Dynamic Kinetic Resolution Scheme]

**E. J. Corey**


**Bristol-Myers Squibb Process Group**

**Case Study: Merck Process Development of Singulair**

![Chemical Structures and Reactions]

- Reaction with 1.0 eq. of BCI to yield a product with 98% ee.
- Reaction with 1.8 eq. of lpc₂BCl to yield a product with 70% ee (85:15).
- Racemic mixture with 72:2:26 for 95% ee, predicted as 72:2 or 94% ee.
- 52% conversion achieved.

**Merck Process**

**Donna Blackmond (Detailed Kinetics)**
Non-Linear Effects (NLE) and How They Can Arise

\[ ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}} \]

- \( ee_{\text{prod}} \): Final ee of the product
- \( ee_0 \): \( ee_{\text{prod}} \) obtained using enantiopure auxiliary (\( ee_{\text{aux}} = 1 \))
- \( ee_{\text{aux}} \): 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.

(+)-nonlinear effect
(asymmetric amplification)

proportionality between \( ee_{\text{prod}} \) and \( ee_{\text{aux}} \)

(−)-nonlinear effect
(asymmetric depletion)

First studied in 1986 by Kagan.

Henri Kagan
Models for Asymmetric Nonlinear Effects

**Noyori’s Model:**

\[
\begin{align*}
\text{Reactant} & \quad \begin{array}{c} 1/2 \text{SS} \quad 1/2 \text{RR} \\
\text{Catalytic Cycle} & \quad \text{S} + \text{R} \quad \text{Catalytic Cycle} \\
\text{Product (S)} & \quad \text{SR} \quad \text{Product (R)}
\end{array} \\
\end{align*}
\]

Amplification if: \( K_{\text{Hetero}} > 2K_{\text{Homo}} \)

R. Noyori

**Kagan's ML₂ Model:**

\[
\begin{align*}
\text{M} + \text{L}_R + \text{L}_S & \quad \xrightarrow{\text{ee}_{\text{aux}}} \quad \text{ML}_S\text{L}_S + \text{ML}_R\text{L}_R \\
\text{Product (S)} & \quad \text{Product (R)} \quad \text{Product (Racemic)}
\end{align*}
\]

\[\text{ee}_{\text{prod}} = \text{ee}_0 \cdot \text{ee}_{\text{aux}} \cdot (1 + \beta)/(1 + g\beta)\]

**ee** <sub>prod</sub> Final ee of the product
**ee** <sub>0</sub> \( \text{ee}_{\text{prod}} \) obtained using enantiopure auxilliary (\( \text{ee}_{\text{aux}} = 1 \))
**g** \( k_{\text{SR}}/k_{\text{RR}} \) 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
Models for Asymmetric Nonlinear Effects

Kagan's ML₂ Model:

\[ ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}} \cdot \frac{(1 + \beta)}{(1 + g\beta)} \]

- \( ee_{\text{prod}} \) Final ee of the product
- \( ee_0 \) ee_{\text{prod}} obtained using enantiopure auxilliary (\( ee_{\text{aux}} = 1 \))
- \( g \) \( k_{SR}/k_{RR} \) or relative activities of hetero and homo complexes
- \( \beta \) \( z/(x + y) \) 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:

\[
\begin{align*}
\text{Me} & \quad \quad \text{S} & \quad \quad \text{Me} \\
\text{Me} & \quad \quad \text{S} & \quad \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
(R,R)\text{-}(+)\text{-DET} & \quad \quad \text{Ti(Oi-Pr)}_4 \\
\text{t-BuOOH, H}_2\text{O} & \quad \quad \text{CH}_2\text{Cl}_2, -20 \, ^\circ\text{C}
\end{align*}
\]

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

Henri Kagan

Mechanistic Study of Organozinc Complexes

R. Noyori

\[
\text{Et}_2\text{Zn} \quad \text{toluene} \quad 8 \text{ mol\%}, 15\% \text{ ee} \quad \text{92\% yield, 95\% ee}
\]

Dimeric complexes confirmed by X-ray analysis
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)

R. Tamura, H. Takahashi, K. Hirotsu, Y. Nakajima, T. Ushio, F. Toda

M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios
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

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 dissymetry":

\[ k = \frac{0.6743}{\sqrt{N}} \]

\( k \): 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)

\[ k = 6.7 \times 10^{-11} \]

\( kN \): 6.7 x 10^8 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:*

\[ A + B \rightarrow C^* \]
\[ C^* \rightarrow P^* \]
\[ P^* \rightarrow C^* \]
\[ k_R > k_S \]
Why Autocatalysis Alone Is Not Sufficient To Amplify Enantiomeric Excess

*It’s Not Enough Says Blackmond!*

**recall:**

\[ ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}} \]

- \( ee_{\text{prod}} \): Final ee of the product
- \( ee_0 \): \( ee_{\text{prod}} \) obtained using enantiopure auxilliary (\( ee_{\text{aux}} = 1 \))
- \( ee_{\text{aux}} \): 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!*

---

**A Simple Asymmetric Autocatalytic Reaction**

---

**Donna Blackmond**

Asymmetric Autocatalysis

A Simplified Look

For a "perfect catalyst"

60% ee → 60% ee

For an "imperfect catalyst"

60% ee → 53% ee → 66% ee

asymmetric amplification!
Spontaneous Crystallization-Induced Resolution

**Autocatalytic Secondary Nucleation**

- **no stirring**
  - +
  - **rac-NaClO₃**

- **stir**
  - **H₂O**
  - 4-5 days
  - > 99% ee

only crystals are chiral

equal chance of forming either enantiomer

---

**How Does This Work?**

*(not well understood)*

- **Solution** (no crystals) → **Primary Nucleation** → mechanical distribution → **Secondary Nucleation (Autocatalytic!)*

rate reduced to virtually zero after secondary nucleation begins

---

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

D. K. Kondepudi, J. Laudadio, K. Asakura

D. K. Kondepudi, R. J. Kaufman, N. Singh
*Science* 1990, 250, 975-976.
The First Asymmetric Autocatalyst Using an Organic Molecule!

*A Humble Beginning*

\[ \text{PhMe} \xrightarrow{\text{Et}_2\text{Zn}, 0 \degree \text{C}} \text{O} \rightarrow \text{PhP}_{\text{Me}} \]

1 hr, fast
99%, 74% ee

16 hr, slow
>99%, 90% ee

When 20 mol% added (R = i-Pr):
86% ee catalyst → 35% ee product, 67% yield with retention of configuration

Similar effects were observed for the other alkyl zinc reagents.

K. Soai
Highly Enantioselective Asymmetric Autocatalysis

*Chiral Pyrimidylalkanols*

\[
\text{Me} \quad \text{H} \\
\text{N} \quad \text{N} \\
\text{C} \quad \text{O} \\
\text{Me} \quad \text{N} \\
\text{C} \quad \text{H}
\]

\[
i\text{-Pr}_2\text{Zn} \text{ (3.2 eq.)} \\
20 \text{ mol\% product @ 99.5\% ee} \\
toluene, 0 \degree \text{C} \\
68 \text{ hr}
\]

\[
\text{Me} \quad \text{H} \\
\text{N} \quad \text{N} \\
\text{C} \quad \text{O} \\
\text{Me} \quad \text{N} \\
\text{C} \quad \text{H}
\]

95\% ee, 83\% yield

Enhancement effect could be due to reduced rotational conformers

\[
\text{Me} \quad \text{H} \\
\text{N} \quad \text{N} \\
\text{C} \quad \text{O} \\
\text{Me} \quad \text{N} \\
\text{C} \quad \text{H}
\]

\[
i\text{-Pr}_2\text{Zn} \text{ (1.7 eq.)} \\
20 \text{ mol\% product @ 99.5\% ee} \\
cumene, 0 \degree \text{C} \\
3 \text{ hr}
\]

>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
Asymmetric Autocatalysis with Amplification!

An Outstanding Achievement

\[
\text{Reaction: } \text{I-Pr}_2\text{Zn (1.2 eq.)} \\
20 \text{ mol\% product @ 5\% ee} \\
toluene, 0 \, ^\circ\text{C} \\
60-80 \text{ hr}
\]

The reaction products (yields \(\sim 60-80\%\)) 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

Asymmetric Autocatalysis with Amplification!

Now, in One Pot!

\[
\text{N} = \text{N} - \text{H} \xrightarrow{i-\text{Pr}_2\text{Zn (1.8 eq.)}} \text{N} = \text{N} - \text{OH}
\]

toluene, 0 °C

three increasing portionwise charges of aldehyde/zinc reagent

3.3 mg alcohol @ 0.18% ee
297.4 mg of product in 84% ee (84% yield)

Chiral initiators (in as little as 1-2% ee and 2 mol% loading) can also be used, such as NaClO₃, leucine, valine, helicenes, and quartz with excellent results.

K. Soai
The Problem with Unspecific Mutual Antagonism

**Detailed Mechanistic Studies**

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
& \quad i-\text{Pr}_2\text{Zn} \\
\text{10 mol\% product/catalyst} & \quad \Rightarrow \\
& \quad \text{N} \quad \text{O} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

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
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.

Donna Blackmond

Additional Mechanistic Evidence

Kinetics from Blackmond

**Initial Kinetics:**

rate = $k \cdot [1][i-Pr_2Zn][3]_{active}$

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

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

**Refinements:**

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

Gives an excellent fit when $[i-PrZn_2] \neq [1]$

**How is the removal of $i$-PrZn$_2$ rationalized?**

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

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

Donna Blackmond


**Additional Mechanistic Evidence**

**Final Thoughts**

![Chemical reaction diagram]

**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**


Just a Few Molecules Can Control the Enantiomeric Outcome

*Is This Really Absolute Asymmetric Synthesis?*

\[ \text{N} \text{N} \text{H} + i\text{-Pr}_2\text{Zn} \rightarrow \text{OZn}i\text{-Pr} \rightarrow \text{OH} \]

1 + 2 + solvent

2.5% or 10% of product solution

1 + 2 + solvent

2.5% or 10% of product solution

etc.

until measurable optical activity

---

**Key Findings:**

- 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.

D. Singleton


The Soai Reaction Using Circularly Polarized Light (CPL)

The Photoequilibrium of Chiral Olefins

\[ \text{i-Pr}_2 \text{Zn (2 eq.)} \]

four portionwise additions of aldehyde/alkylzinc

\[
\begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\]

(1.8 mol%)  

\~1-2\% ee

\[
\begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\]

96\% yield  

97\% e.e.

48 hr. irradiation with \textit{i-} or \textit{r-} circularly polarized light (CPL)

\textbf{light is the chiral initiator!}

\[
\begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\]

\textbf{This also works using other chiral olefins directly as initiators - even as low as 1.3\% ee!}

\[
\begin{array}{c}
\text{Ph} \\
\text{H}
\end{array}
\]

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

These results are completely reproducible (\textit{i-CPL always gives the S-product, r-CPL always gives the R-product})

Kenso Soai

\textit{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
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!