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)
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:

\[ \text{ee}_{\text{prod}} = \text{ee}_{\text{max}} \times \text{ee}_{\text{cat}} \]

\( \text{ee}_{\text{max}} \) 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 product > ee catalyst
- Called negative nonlinear effect (-NLE) if ee product < ee catalyst
These effects can be quite large.

![Chemical Reaction Diagram]

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 ML$_2$ 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 ML$_2$

The following equilibrium is established:

\[
\begin{align*}
M + L_R + L_S & \rightarrow ML_{R L_R}^{x} + ML_{S L_S}^{y} + ML_{R L_S}^{z} \\
\end{align*}
\]

\[
\begin{align*}
\text{diastereomers} \\
\text{enantiomers} \\
\end{align*}
\]

\[
\begin{align*}
\text{R-product (ee$_{\text{max}}$)} & \rightarrow \text{S-product (-ee$_{\text{max}}$)} & \rightarrow \text{racemic product} \\
\end{align*}
\]

\[
x, y \text{ and } z \text{ are mol}\% \\
K = z^2/xy
\]

\[
ee_{\text{prod}} = ee_{\text{max}} * ee_{\text{cat}} \frac{1 + \beta}{1 + g\beta}
\]

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

\[
g = \frac{k_{RS}}{k_{RR}}
\]

Important points:
\[
\beta \text{ describes relative stability of homo and hetero chiral catalyst (but K is more useful)} \\
g \text{ describes relative reactivity of homo and hetero chiral catalyst} \\
\beta \text{ and } x, y, z \text{ depend on ee$_{\text{cat}}$ and } K \\
The origin of nonlinearity is g. The reactivity of the meso catalyst \textit{must} be different to see a NLE, i.e. \( g < 1 \) (+NLE) or \( g > 1 \) (-NLE)
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 $K = 1000$
$ee_{\text{max}} = 95$
$g = \frac{k_{\text{SR}}}{k_{\text{RR}}} = 0.35$
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
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

Homochiral dimer
(less stable)

Heterochiral dimer
(more stable)

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

Noyori, JACS, 1998, 9800
Reservoir model in glyoxylate ene reactions

\[
\text{Ph} = \text{H} \quad \text{CO}_2\text{CH}_3 \rightarrow \quad \frac{\text{(iPrO)}_2\text{TiX}_2}{\text{BINOL}} \rightarrow \quad \text{Ph} \quad \text{H} \quad \text{CO}_2\text{CH}_3 \\
\text{OH} \quad \text{CO}_2\text{CH}_3
\]

(R)-BINOL

Mikami, Tet. 1992, 5671
Equilibrium between active monomer and inactive dimer. Minor enantiomer is sequestered.

\[ \text{[(R)-BINOL)TiX}_2 \]  
\[ \text{[((R)-BINOL)TiX}_2]_2 \]  
\[ \text{[(S)-BINOL)TiX}_2 \]  

35 times more stable than homochiral dimer
Structural basis for dimer stability with (BINOL)TiX₂

Calculated structures for [(BINOL)₂TiCl₂]₂
Model 3
Transition-state dimers

\[
\begin{align*}
\text{Product ee} & \\
\text{Catalyst ee} &
\end{align*}
\]

Jacobsen, JACS, 1996, 10924
Recall bimetallic mechanism:

For $\text{ee} < 100\%$, 4 possible transition states:

- $(R,R)$-$\text{CrN}_3 + (R,R)$-$\text{Cr(Epox)} \rightarrow +X\% \text{ ee}$
- $(R,R)$-$\text{CrN}_3 + (S,S)$-$\text{Cr(Epox)} \rightarrow 0\% \text{ ee}$
- $(S,S)$-$\text{CrN}_3 + (R,R)$-$\text{Cr(Epox)} \rightarrow -X\% \text{ ee}$
- $(S,S)$-$\text{CrN}_3 + (S,S)$-$\text{Cr(Epox)}$

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

\[
\frac{\frac{d[(+)-\text{product}]}{dt}}{\frac{d[(-)-\text{product}]}{dt}} = \frac{[0.85]^2}{[0.15]^2} = 32.1 \quad \Rightarrow \quad 94\% \text{ ee!}
\]

Note $k_{\text{cat}}$, [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

\[
\text{Additives:} \\
\begin{align*}
\text{TMP} & \quad \text{AOD} \\
\text{PAA} &
\end{align*}
\]

Kobayashi, TL, 1994, 6325
Paying the piper: Kinetic repercussions of NLE’s

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

Blackmond, Accts, 2000, 402
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.
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

\[
\text{S.M.} \quad \text{Catalyst (100% ee)} \quad \text{Product (99.9%) + catalyst (100%) = total (99.95%)}
\]

\[
\text{repeat} \quad \text{99.85% ee} \quad \text{repeat} \quad \text{repeat} \quad \text{repeat} \quad \text{racemic}
\]

If autocatalysis is coupled to a positive nonlinear effect, can see increasing rate and increasing ee
Pyrimidine carboxaldehyde/R$_2$Zn 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

Soai, JACS, 2005, 3274
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:

\[
\begin{align*}
R + S & \rightarrow R, R & \rightarrow R, S & \rightarrow S, S & \rightarrow S, \text{product} \\
& \rightarrow \underset{K = 4}{R, S} & \text{no reaction} & \text{S, product} & \text{product of 94\% ee}
\end{align*}
\]

Predicted ratio for 70\% ee R:

- R-Product 72
- no reaction 26
- S-product 2.3

Both requirements for asymmetric amplification fulfilled: - autocatalytic - +NLE
Thermodynamic control of asymmetric amplification in amino acid catalysis

Martin Klussmann¹, Hiroshi Iwamura¹†, Suju P. Mathew¹, David H. Wells Jr†, Urvish Pandya¹, Alan Armstrong² & Donna G. Blackmond¹,²

Nature, 2006, 441, 621
See also Hayashi, ACIEE, 2006, 4593