

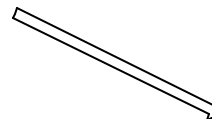
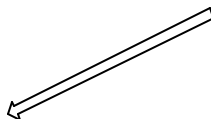
**ASYMMETRIC AMPLIFICATION AND PROPAGATION OF
CHIRALITY IN CHEMICAL SYSTEMS**

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CREATION AND PROPAGATION OF CHIRALITY IN CHEMICAL SYSTEMS



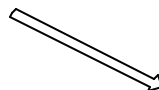
AUGMENTATION OF ee

AUGMENTATION OF THE AMOUNT



AUGMENTATION OF THE AMOUNT

AUGMENTATION OF ee



LARGE AMOUNT, ~100% ee

OUTLINE



NON-LINEAR EFFECTS



ASYMMETRIC AMPLIFICATION



HOMOCHIRALITY IN CHEMICAL SYSTEMS



HOMOCHIRALITY IN BIOLOGICAL SYSTEM



CONCLUSION

NON-ENANTIOPURE AUXILIARIES IN ASYMMETRIC SYNTHESIS



Behaviour of a mixture of **(R)-** and **(S)-**catalysts (or reagents) of $ee_{\text{aux}} = \frac{(\text{R-cat}) - (\text{S-cat})}{(\text{R-cat}) + (\text{S-cat})} ?$

Assuming independence of systems ① and ②, one calculates the relative amounts of P_R and P_S coming by the two routes, without considering a particular kinetic scheme. The enantiomeric excess of the final product (ee_{prod}) is then obtained :

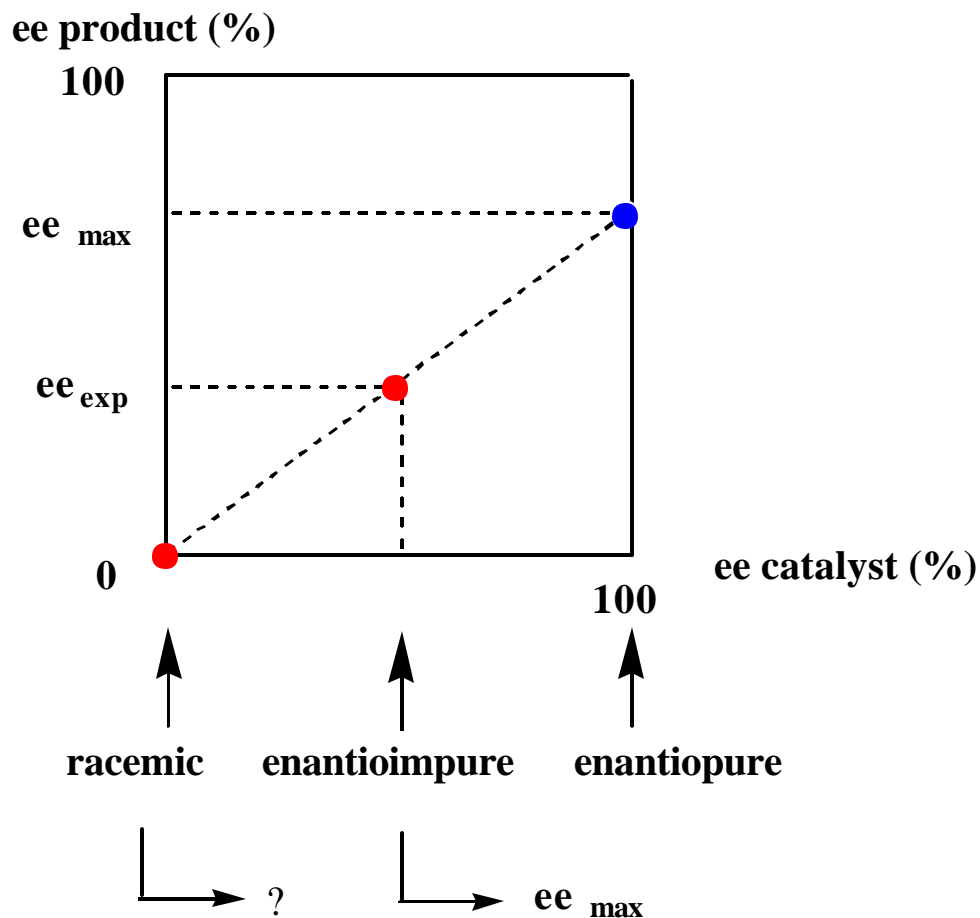
$$ee_{\text{prod}} = ee_{\max} ee_{\text{aux}}$$

There is proportionality between ee of the product and ee of the auxiliary, allowing to calculate ee_{\max} when using an enantioimpure auxiliary.

ENANTIOIMPURE CATALYSTS

The enantiomeric excess of the product is, *in principle*, proportional to the enantiomeric excess of the chiral auxiliary in the catalyst.

Consequencies:



ENANTIOMERIC EXCESS FOR PRODUCTS IN ASYMMETRIC SYNTHESISES WITH NON ENANTIOSELECTIVE CHIRAL AUXILIARIES

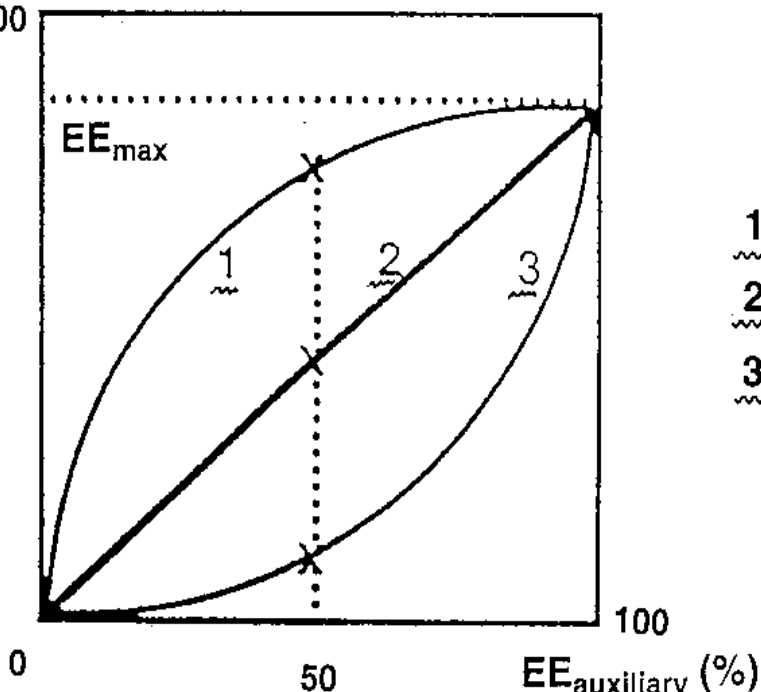
Law of proportionality:

If a chiral auxiliary 100% ee \longrightarrow product EE_{max}
 then a chiral auxiliary 50% ee will give a product of $EE_{prod} = 50\% EE_{max}$

It was discovered that the linear correlation $EE_{prod} = EE_{max} \times EE_{aux}$ was not always

follow

$E_{product}$ (%)



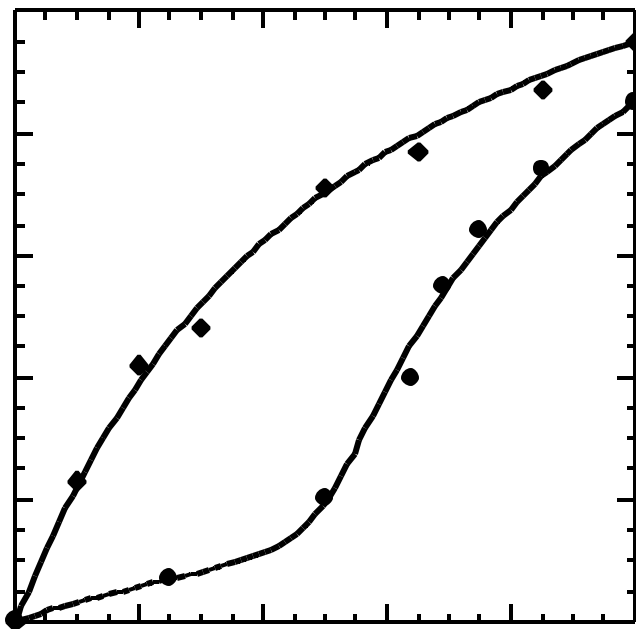
Puchot, Samuel, Dunach, Agami, Kagan

J. Am. Chem. Soc., 1986, 104, 2353.

1 : positive nonlinear effect ((+)- NLE, asymmetric amplification)

2 : linear correlation

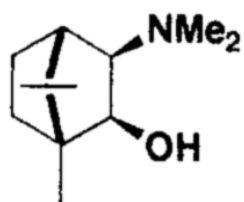
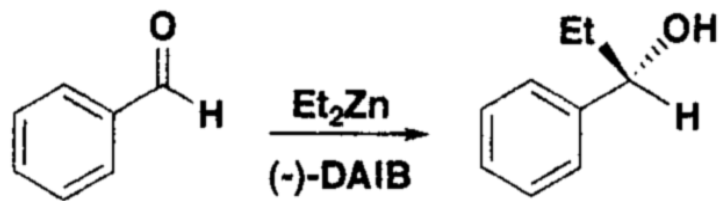
3 : negative nonlinear effect ((-)- NLE, asymmetric depletion)



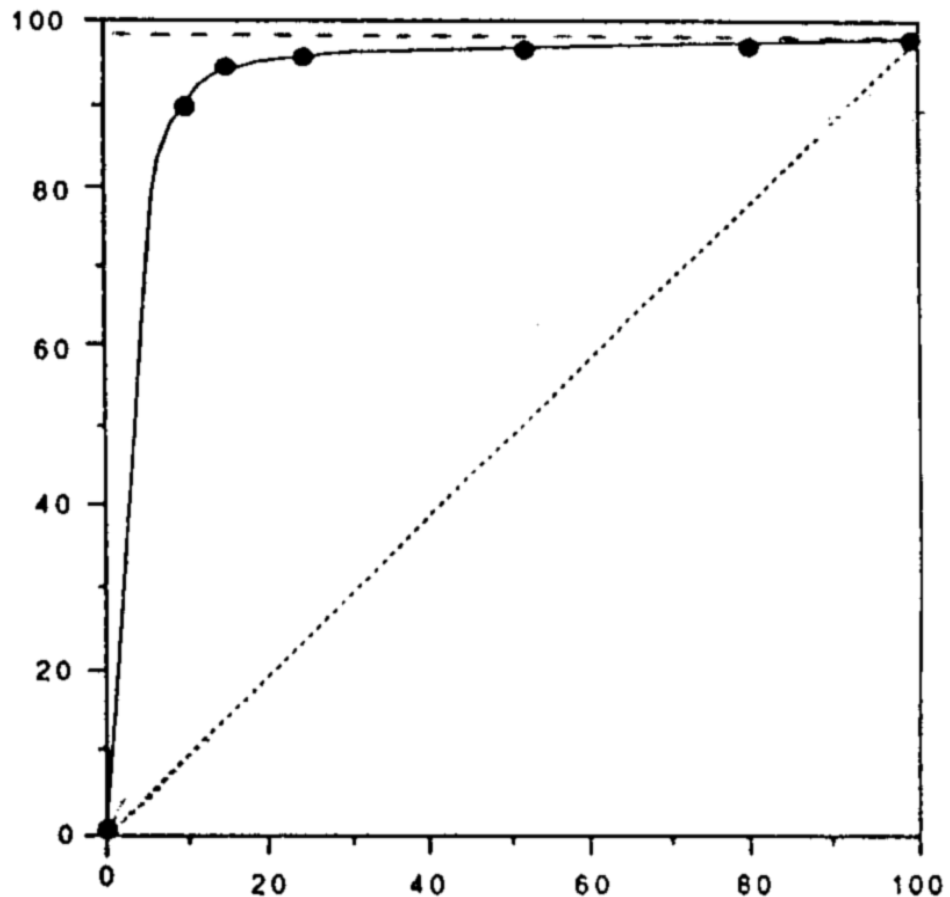
A : Sharpless asymmetric epoxidation of geraniol

B: Asymmetric sulfoxidation by *t*-BuOOH / Ti(O-*i*Pr)₄ / DET / H₂O (1 : 1 : 1 : 2)

C. Puchot, O.Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan,
J. Am. Chem. Soc., **1986**, *108*, 2353



(-)-DAIB



R. Noyori et al., *J. Am. Chem. Soc.*, 1989

**NECESSARY CONDITIONS (BUT NOT ALWAYS SUFFICIENT)
FOR OBSERVING A NONLINEAR EFFECT IN CATALYSIS**

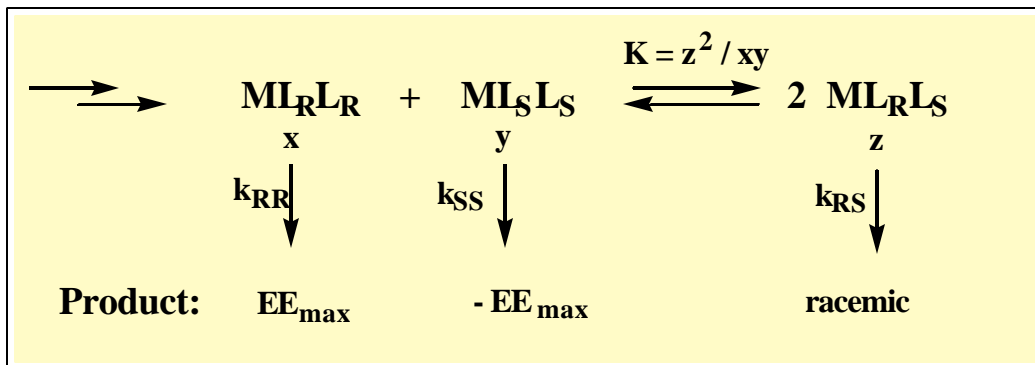
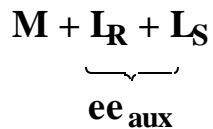
The chiral auxiliary L^* must be included in species (**catalytically active or not**)
which involve several molecules of L^* .

Then, when L^* is not enantiopure, there is the possibility of formation of new
species, diastereomeric of the former one, giving rise to new properties
to the system.

D. Guillaneux, S. H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.*, 1994, 116, 9430-9439

2-ligand catalyst

ML_2 , $(ML)_2$ or $(L)_2$



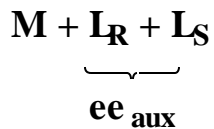
$$EE_{product} = EE_{max} ee_{aux} \frac{1 + b}{1 + gb}$$

$$g = k_{RS} / k_{RR}, b = z / (x+y)$$

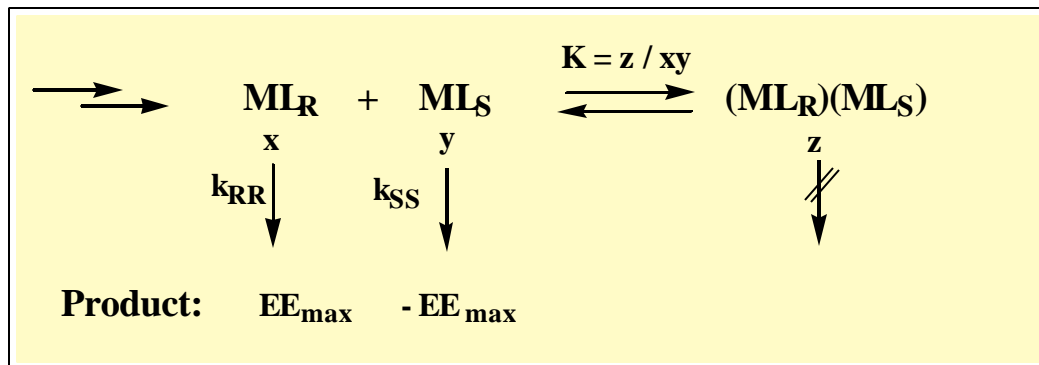
$g = 1$ or $b = 0 \rightarrow$ Linear

$g > 1 \rightarrow$ (-)-NLE $g < 1 \rightarrow$ (+)-NLE

1-ligand catalyst with partial dimerization



(+)-NLE

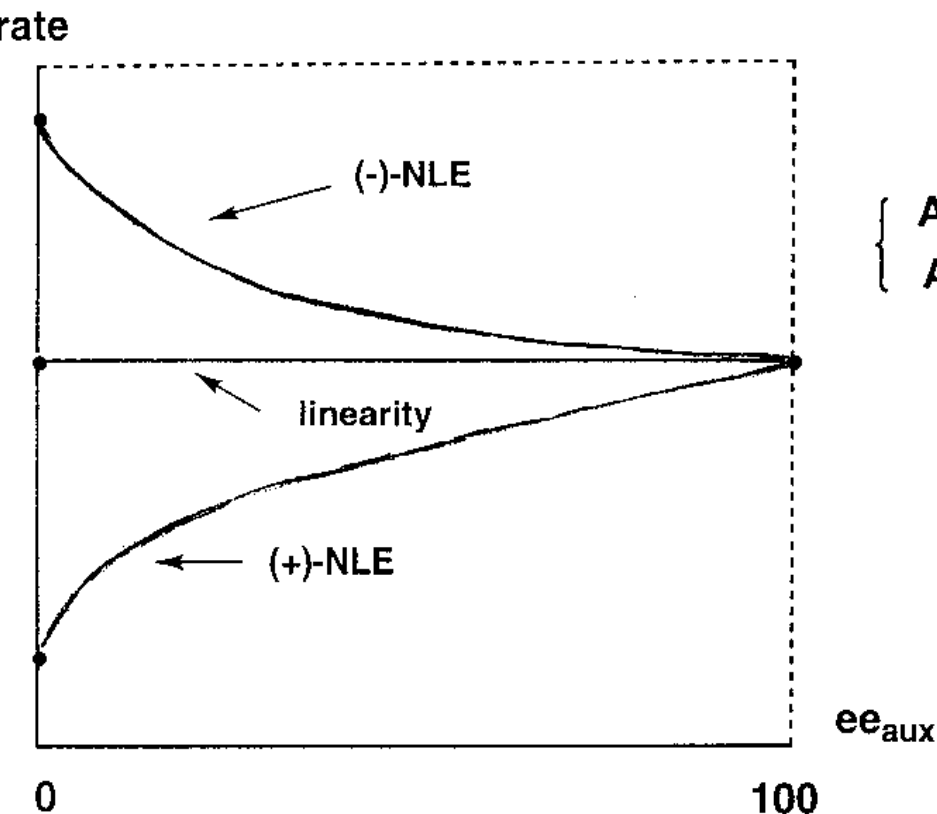


"reservoir" effect by removal of racemic ligand

REACTION RATES

Nonlinear effects will change the reactivity of the catalyst. The rate will depend of the enantiomeric excess of the catalyst.

Linearity: rate is independent of the enantiomeric excess of the catalysis



$$d[\text{Product}] / dt = k [\text{Cat}_{total}] [\text{Substrate}]$$

- Asymmetric amplification \rightarrow rate decrease for low ee'
- Asymmetric depletion \rightarrow rate increase for low ee'

ML₂ model:

D. Blackmond

J. Am. Chem. Soc., 1997, 119, 12934-12939

PRACTICAL AND FUNDAMENTAL ASPECTS

- **Asymmetric amplification in enantioselective catalysis**

 - Comparison of amplifications**

 - Reaction rates**

 - Usefulness in synthesis**

 - Autocatalysis**

 - Diastereomeric catalysts**

- **Asymmetric depletion**

- **Asymmetric amplification in kinetic resolution**

- **Asymmetric amplification for chiral reagents**

- **Nonlinear effects as a mechanistic tool**

Practical consequences of non-linear effects in asymmetric synthesis
H. B. Kagan, *Adv. Synth. Catal.*, 2001, 343, 227-233.

ORIGIN OF HOMOCHIRALITY IN LIVING SYSTEMS

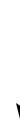
Prebiotic chemistry



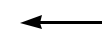
Racemic biomolecules



Slight enrichment ($R \approx S$)



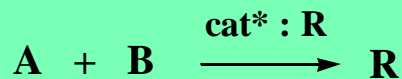
Asymmetric autocatalysis ($n R$)



Amplification of ee ($R \gg S$)

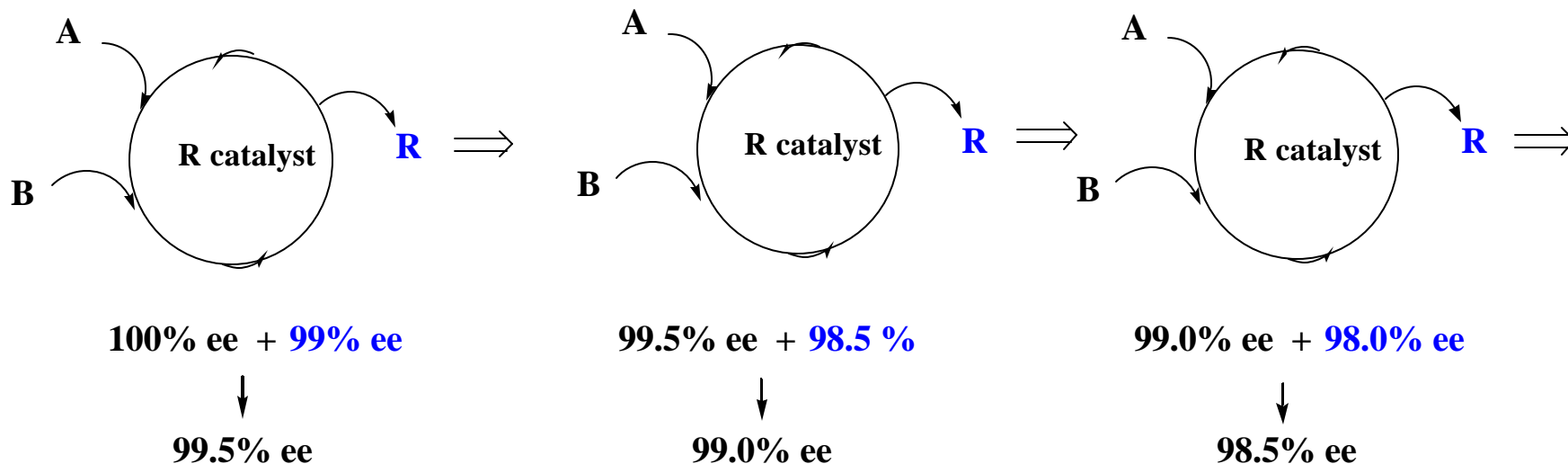
Mills, Wald , Calvin, Frank...

non-linear effects and asymmetric autocatalysis



100% ee

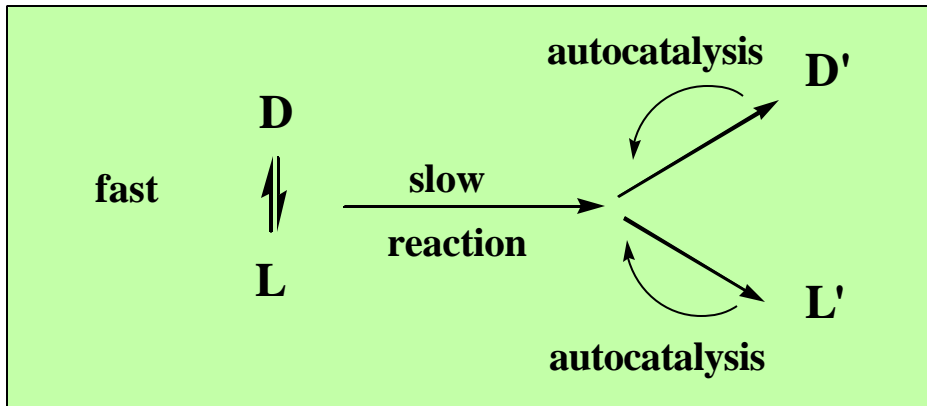
If the catalyst gives 99% ee



A way to overcome the slow ee erosion:
to combine asymmetric autocatalysis and (+)-NLE (asymmetric ampli

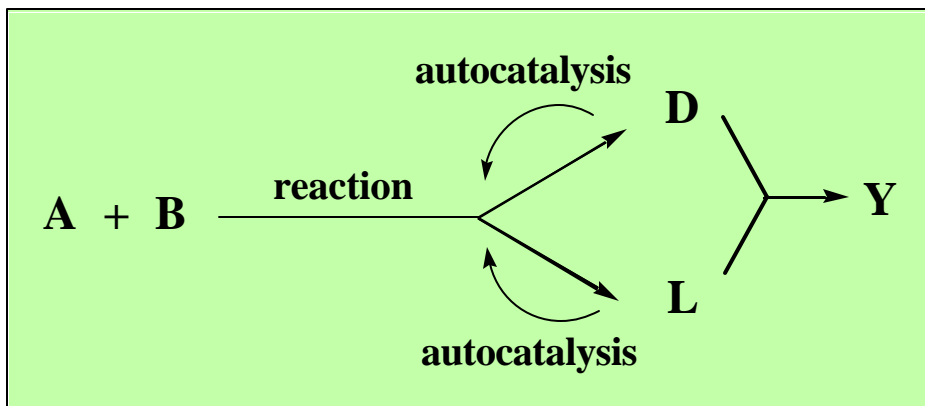
ASYMMETRIC AUTOCATALYSIS

Model of Calvin (1969)



the initial enantiomeric excess
is propagated by a fast autocatalysis

Model of Frank (1953)



D is catalyst of its own formation
and is a poison of its L enantiomer

A RANDOM STATISTICAL PHENOMENON AT THE MOLECULAR LEVEL

(ENANTIOSELECTIVE REACTIONS, SELECTION FROM A RACEMIC MIXTURE

Hypothesis : **events R or S have the same probability**

The simple statistic rules : for **n events** the two enantiomers are in the quantities

$$\frac{n + n^{1/2}}{2} \quad \text{and} \quad \frac{n - n^{1/2}}{2} \quad \text{with an excess of } n^{1/2} \text{ in one configuration}$$

$$n = 1000 \quad ee(\%) = 1.6, \text{ excess : } 32$$

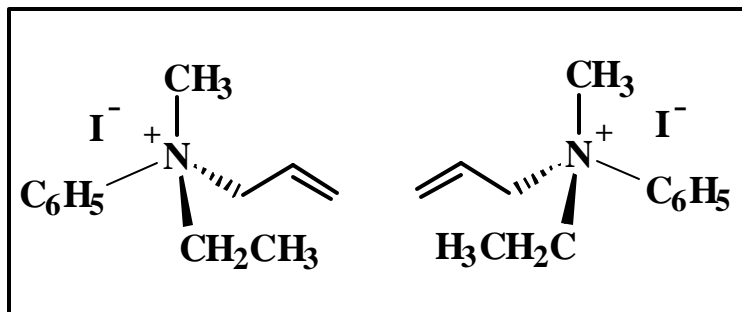
$$n = 10000 \quad ee(\%) = 0.5, \text{ excess : } 100$$

$$n = 10^6 \quad ee(\%) = 10^{-3}, \text{ excess : } 600$$

$$n = 10^9 \quad ee(\%) = 10^{-5}, \text{ excess : } 3300$$

J. S. Siegel, *Chirality*, 1998, 10, 24 and references quoted therein

SPONTANEOUS TRANSFORMATION OF A RACEMIC MIXTURE INTO A SINGLE ENANTIOMER



Racemic mixture

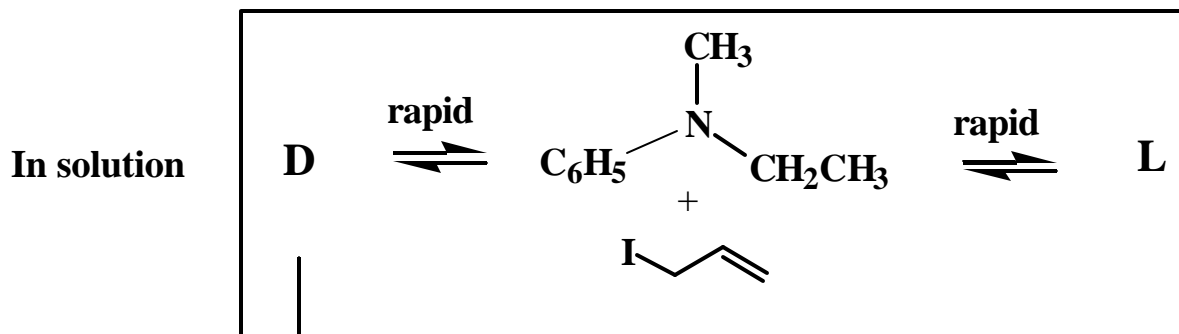
N is stereochemically stable

dissolution in warm
chloroform

slow crystallization

filtration

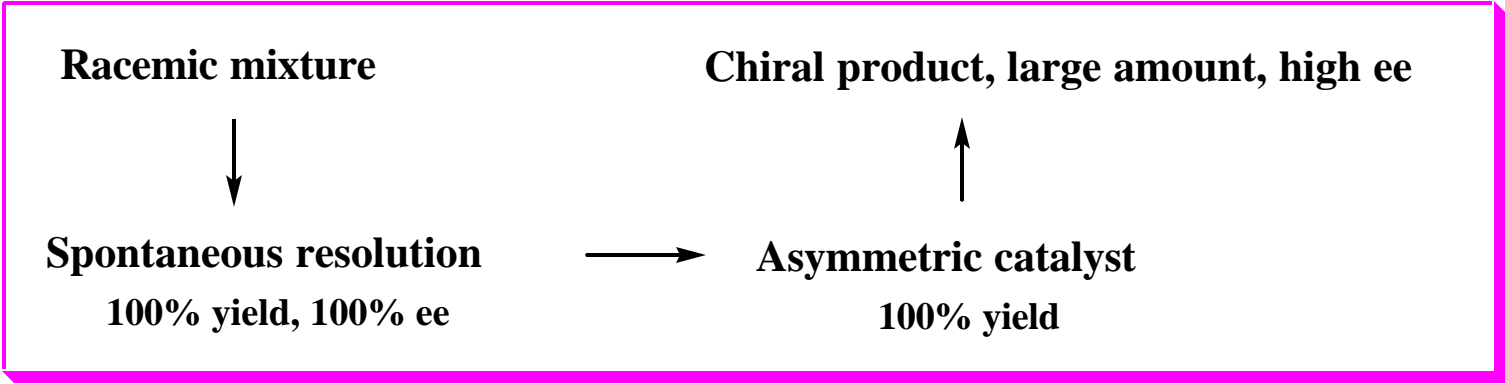
crystals recovered
in good yield
optically active
(measure in water)



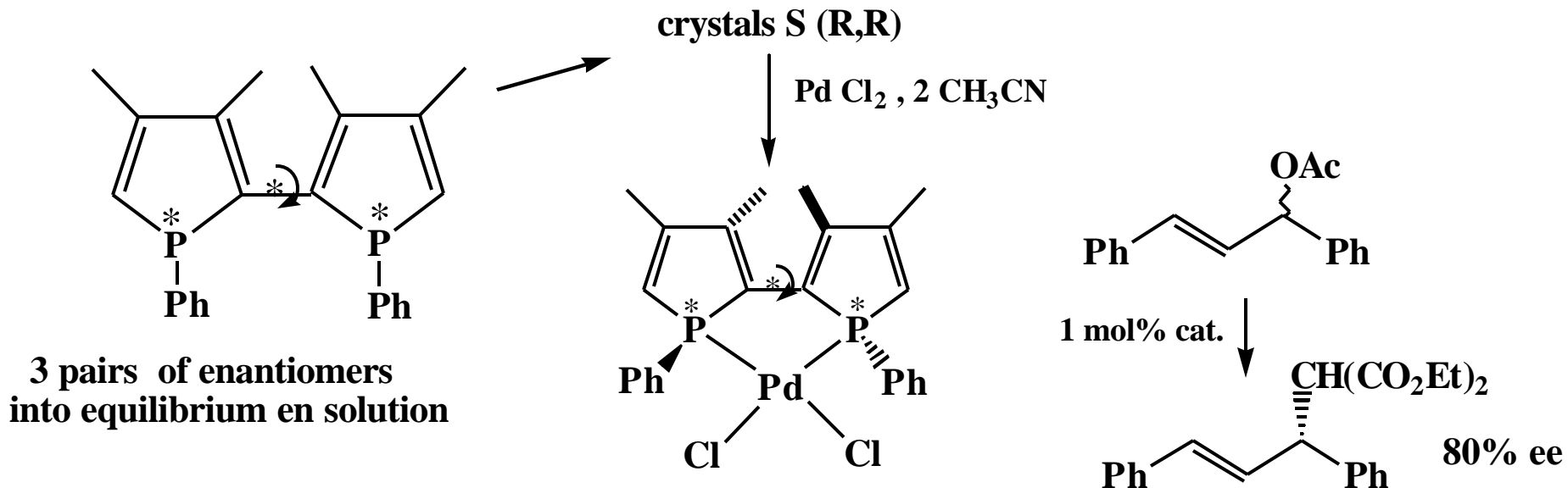
slow

crystals D D D D

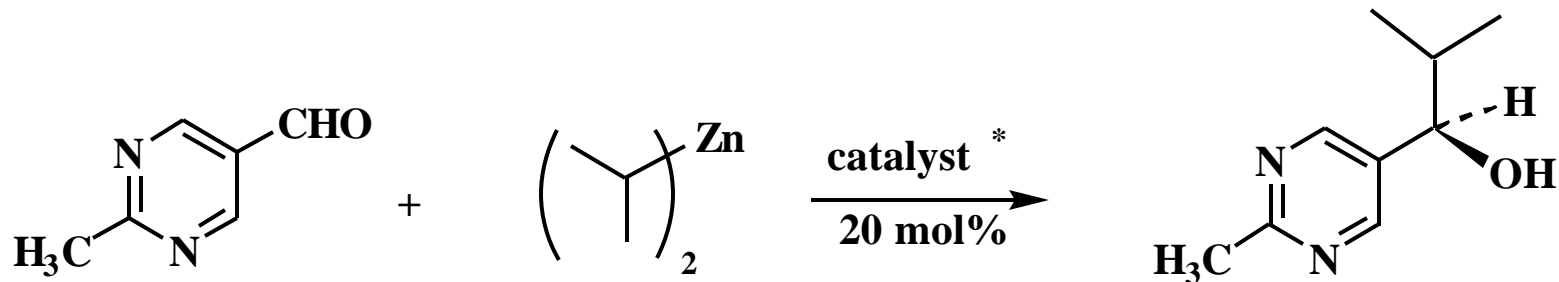
Havinga (1954)



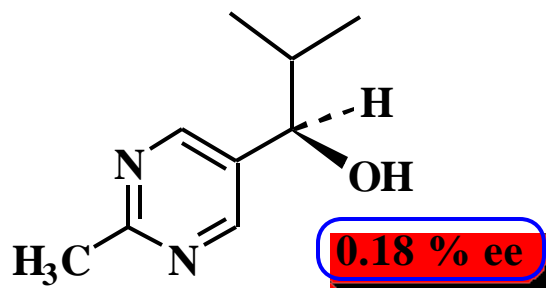
O. Tissot, M. Gouygou, F. Dallemer, J.-C. Daran, G. A. Balavoine
Angew. Chem. Int. Ed. , 2001, 40, 1076.



THE SOAI AUTOCATALYTIC SYSTEM

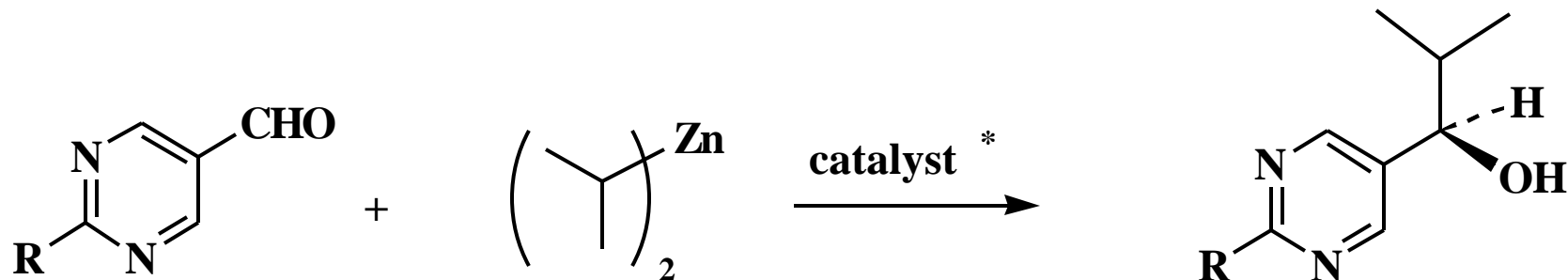


catalyst* :



3 mg 0.18% ee \longrightarrow 323 mg 83.9% ee

SOME DEVELOPMENTS



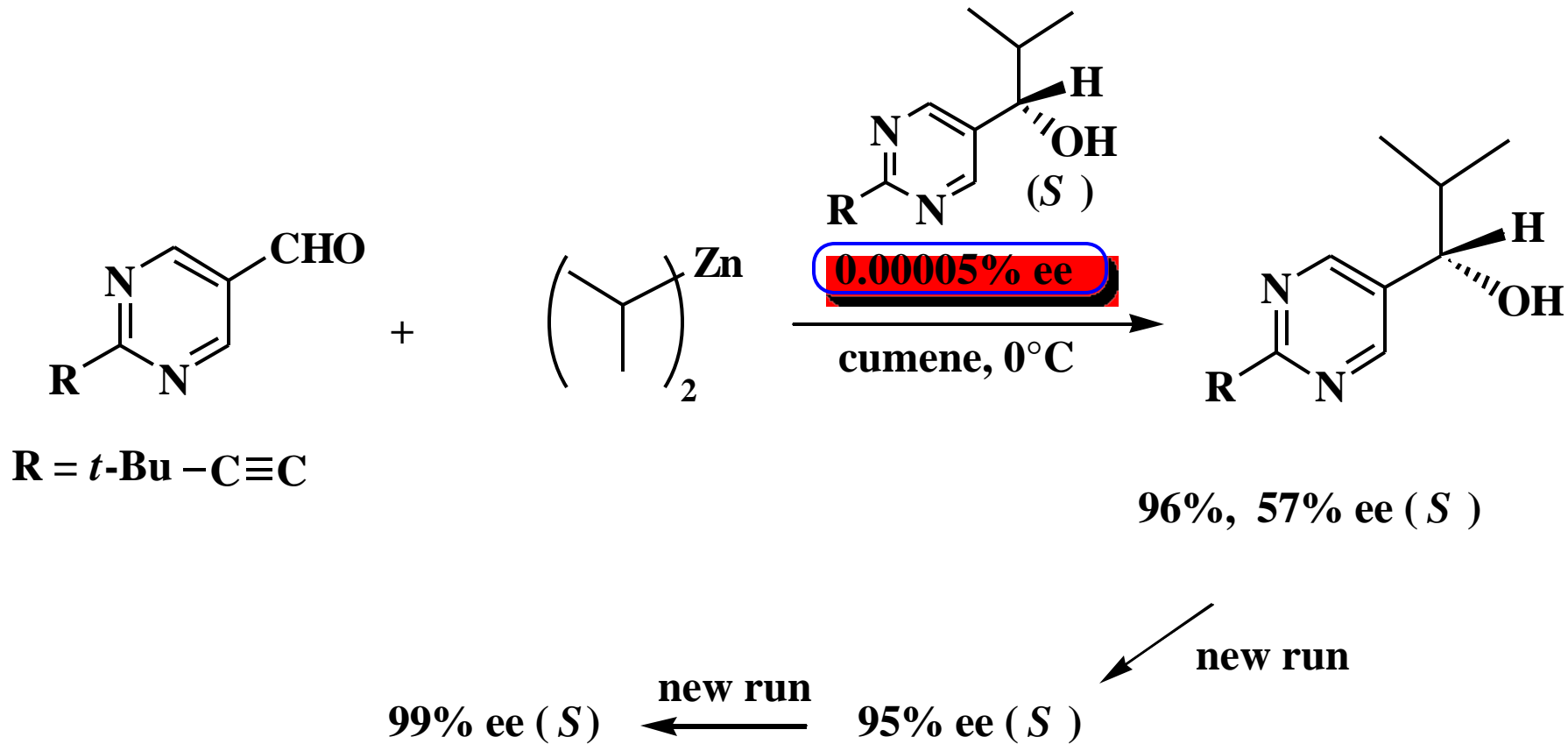
Many enantioenriched compounds can play control the steric course of the reaction

Application

To assign an absolute configuration to a product of weak ee and in small amount: alcohols, hydrocarbons, helicenes, quartz, etc

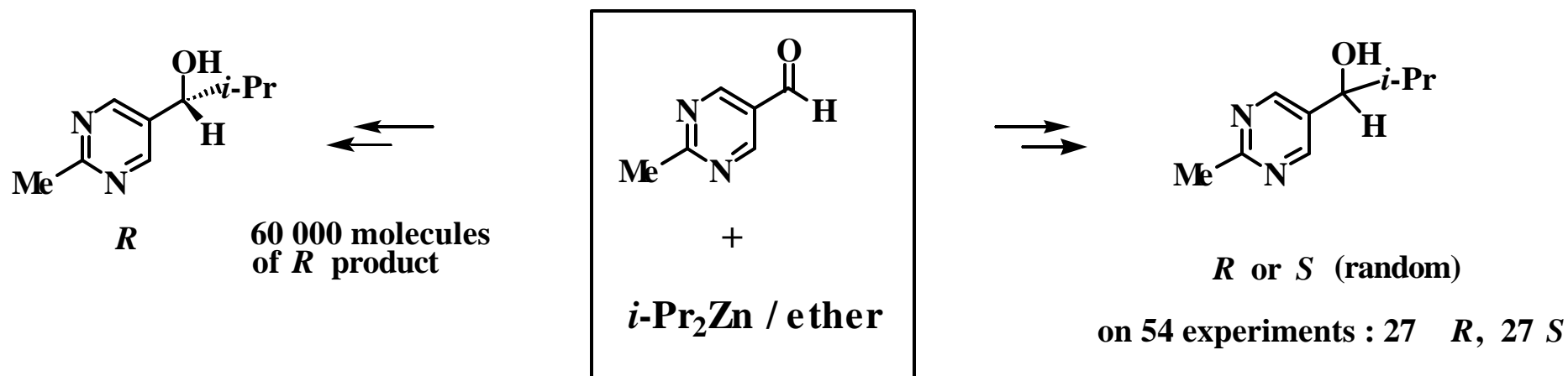
K. Soai et al, *J. Am. Chem. Soc.* , 1999, 121, 11235.

What happens in absence of chiral compounds ?



K. Soai et al, *Angew. Chem. Int. Ed.* , 2003, 42, 315.

Control of product configuration by a tiny amount of enantiopure product



1 mL 10^{-16} M (*R*)
= 60 000 molecules

no control of configuration at
 10^{-22} M (*R*)

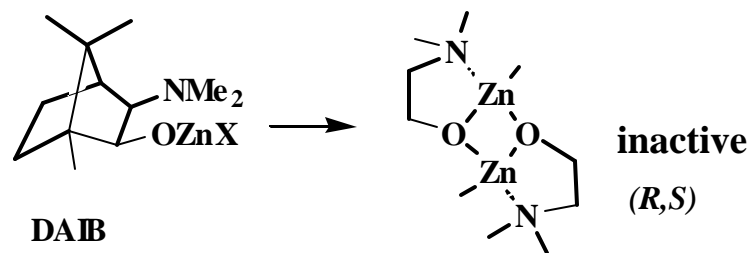
D. A. Singleton, L.K. Vo *Organic Lett.* , 2003, 5, 4337

Some mechanistic studies on the Soai reaction

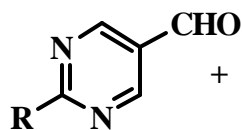
D. Blackmond et al, *J. Am. Chem. Soc.* , 2001, *123*, 10103 ; *J. Am. Chem. Soc.* , 2003, *125*, 8978

J. M. Brown et al, *Angew. Chem. Int. Ed.* , 2004, *43*, 4884

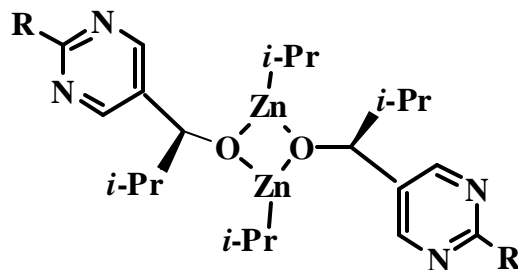
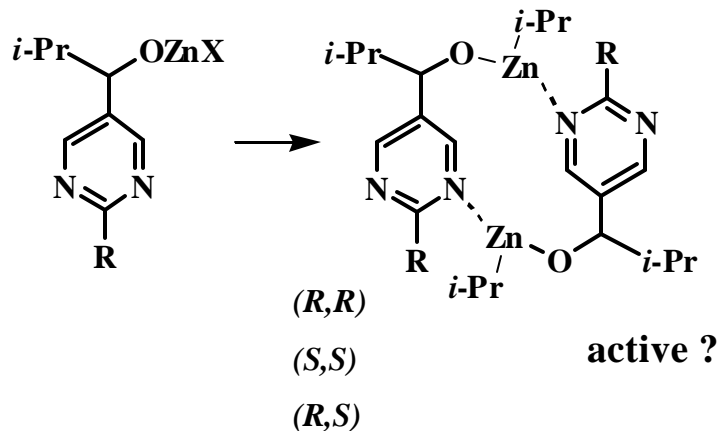
Noyori: catalyst from a β -aminoalcohol



Soai: catalyst from a rigid γ -aminoalcohol



+ $(i\text{-Pr})_2\text{Zn}$

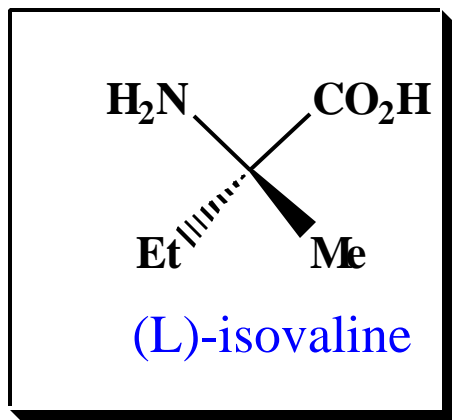


$(i\text{-Pr})_2\text{Zn}$ active ?

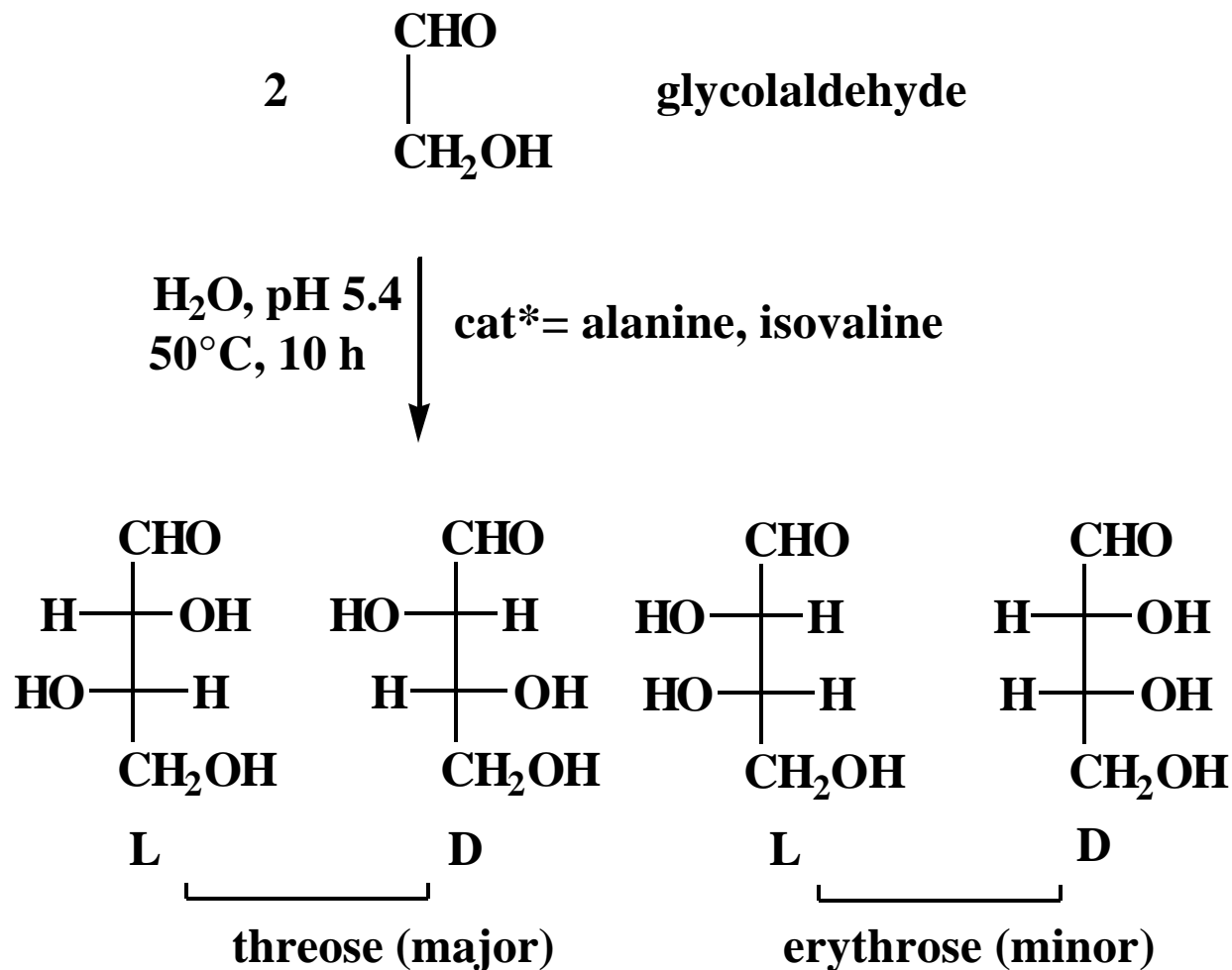


PREBIOTIC AMINO ACIDS ASYMMETRIC CATALYSTS

S. Pizzarello, A. L. Weber *Science*, 2004, 303, 1151

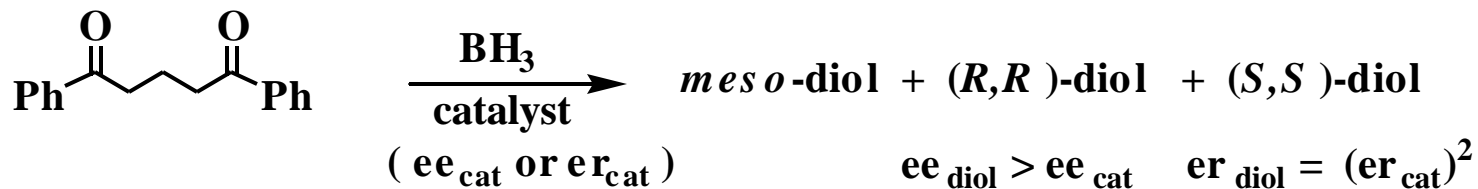


found in meteorites
with 15% ee

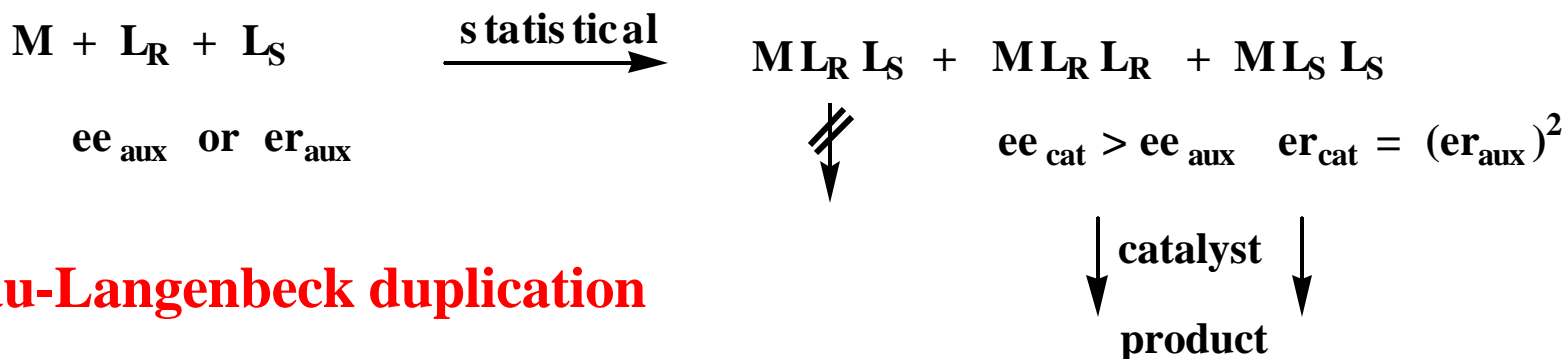


AS YMMETRIC AMPLIFICATION OF ee IN DIFFERENT PROCESSES (APPARENTLY UNRELATED)

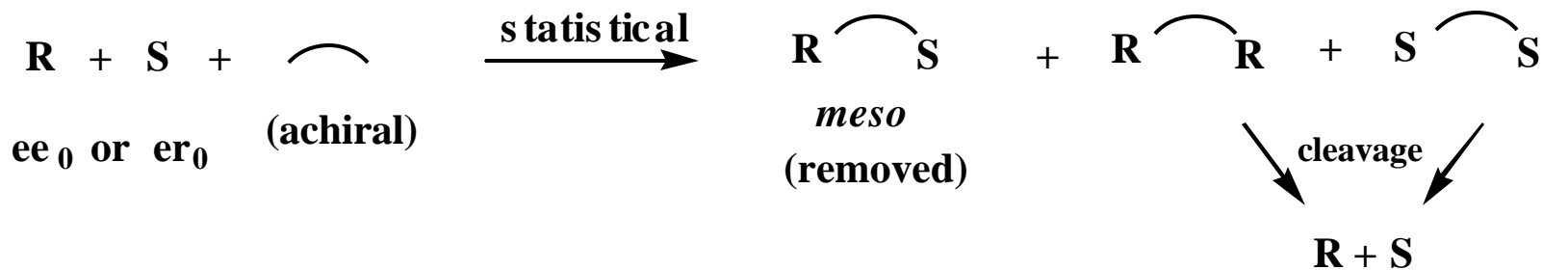
Double asymmetric reactions



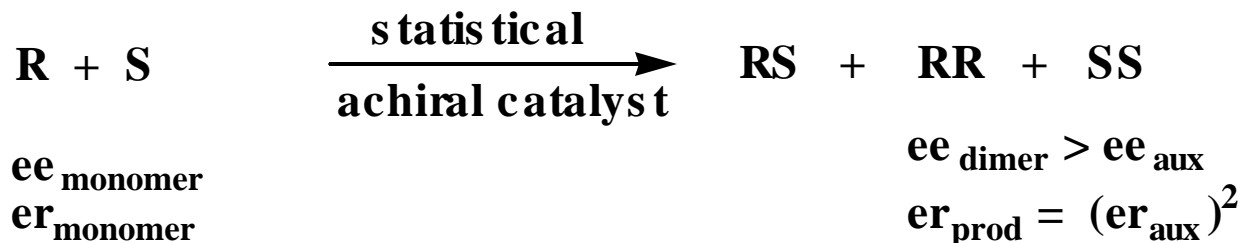
Non-linear effects



Horeau-Langenbeck duplication



Polymerization



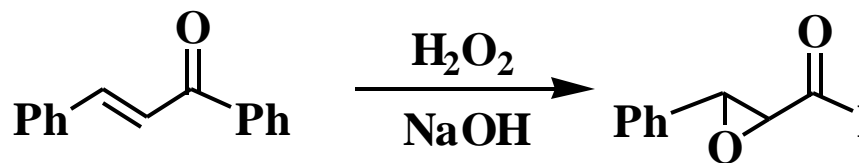
Chiral-Columna epoxidation



100% ee

5% ee

43% ee (er = 2.5)

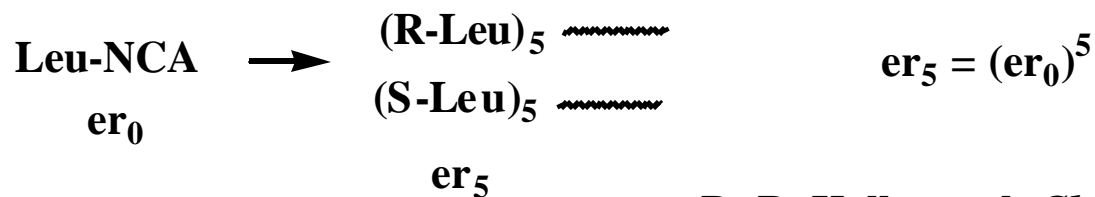


96% ee

26% ee

92% ee (er = 15)

Single catalytic site: 5 *homo*-Leu residues at N-end of polymer



D. R. Kelly et al. *Chem. Commun.*, 2004, 2021.

	ee ↘	ee →	ee ↗
n ↗		asymmetric catalysis	
n →			
n ↘			

← **(+)-non-linear effects.
asymmetric autocatalysis.**

← **asymmetric transformation
(cryst.).**

← **resolution (spontaneous, kinetic).
Horeau-Langenbeck duplication.
multiple asymmetric syntheses.**

CONCLUSION

Chemical systems

Many processes are known to afford an enantiopure compound from a achiral or racemic starting material (use of crystallization).

Only few processes are known giving a product of high ee in large amount in homogeneous conditions.

Living systems

Many hypotheses on the origin, amplification and propagation of optical activity. Not much is established.

S. ZHAO

S. ZHANG

D. GUILLANEUX

C. GIRARD

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D. FENWICK

O. SAMUEL

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