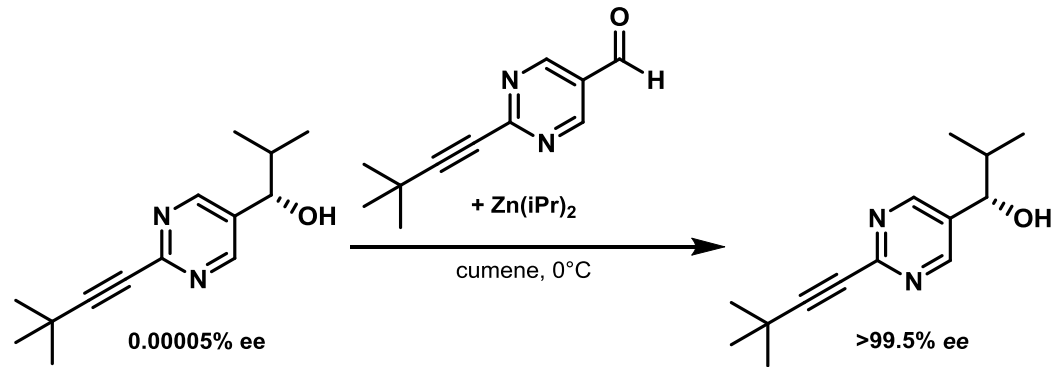


Chiral Amplification



Literature Talk
Fabian Schneider
Konstanz, 18.10.2017

Overview

- 1) Motivation
- 2) The nonlinear Effect in asymmetric catalysis
 - First encounters
 - Basic principles
 - Formalization and models
 - Synthetic use
 - Further examples
- 3) Asymmetric autocatalysis
 - The Frank model
 - The Soai reaction
 - The NLE vs autocatalysis
 - Absolute asymmetric catalysis via CPL
 - Spontaneous asymmetric catalysis
- 4) Conclusions and Summary

Further reviews:

Angew. Chem., Int. Ed. **1998**, *37*, 2922-2959 - NLE basic principles

Adv. Synth. Catal. **2001**, *343*, 227-233 - NLE basic principles

Angew. Chem., Int. Ed. **2009**, *48*, 456-494 – NLE, many examples

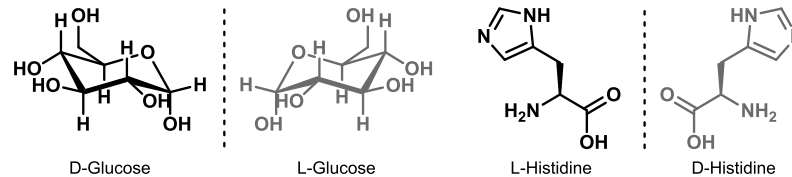
Chem. Rev. **2003**, *103*, 3369-3400 - NLE and autocatalysis, many examples

Proc. Natl. Acad. Sci. U. S. A. **2004**, *101*, 5732-5736 - autocatalysis and the origin of homochirality

Chem. Soc. Rev. **2002**, *31*, 211-222 - brief overview NLE and autocatalysis

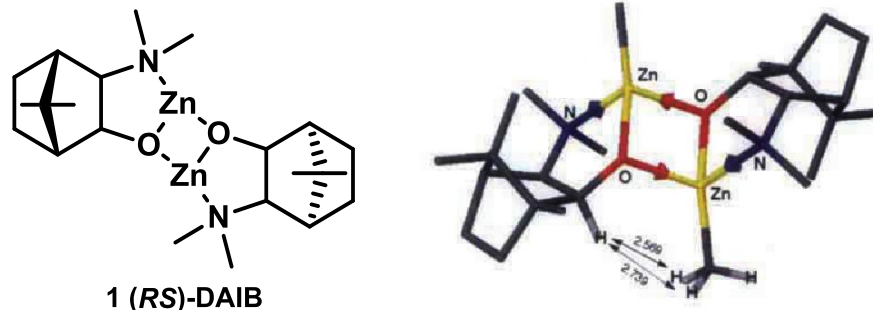
Acc. Chem. Res. **2000**, *33*, 382-390 - focus on autocatalysis

Motivation



- 1 The origin of homochirality in nature is one of the central questions concerning the origin of life. This issue can be divided into two aspects:
- 1) Existence of an 'mirror symmetry' breaking event, leading to a bias in enantiomeric ratio
 - 2) Amplification this (small) bias towards homochirality

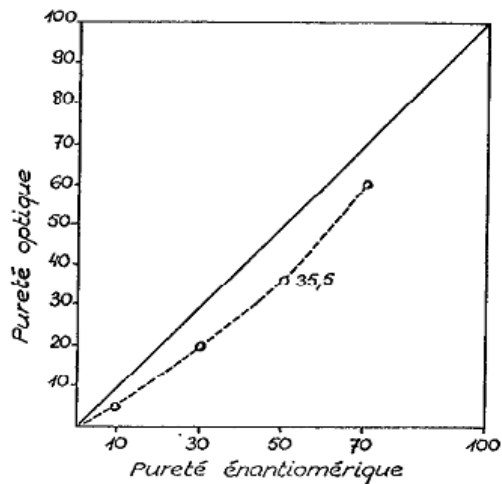
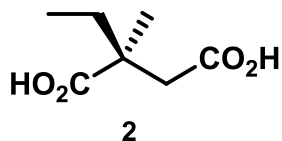
Existing approaches for the mirror symmetry breaking event (CPL, asymmetry in electroweak interaction, specific surface processes on crystals) can only produce small enantiomeric excess (< 2%). Thus an amplification mechanism must take place to obtain homochirality.



- 2 Synthetic use to enhance the enantiomeric excess of a product obtained from a reaction with an auxiliary/catalyst with low ee.

Proc. Natl. Acad. Sci. U. S. A. **2004**, 101, 5732-5736
Physical Review **1956**, 102, 290-291
Physical Review **1957**, 105, 1413-1415
Angew. Chem., Int. Ed. **1999**, 38, 3418-3438
Naturwissenschaften **1929**, 17, 227-228
Chemistry – A European Journal **1996**, 2, 1173-1181

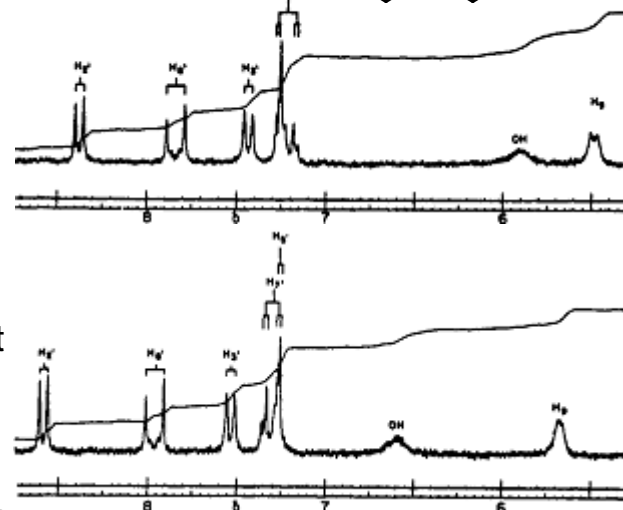
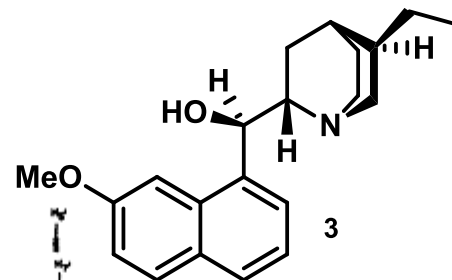
The nonlinear effect (NLE) in asymmetric catalysis – first encounters



Tetrahedron Lett. **1969**, 10, 3121-3124

Studies by Horeau show a nonlinear relationship between ee and specific rotation $[\alpha]_D$

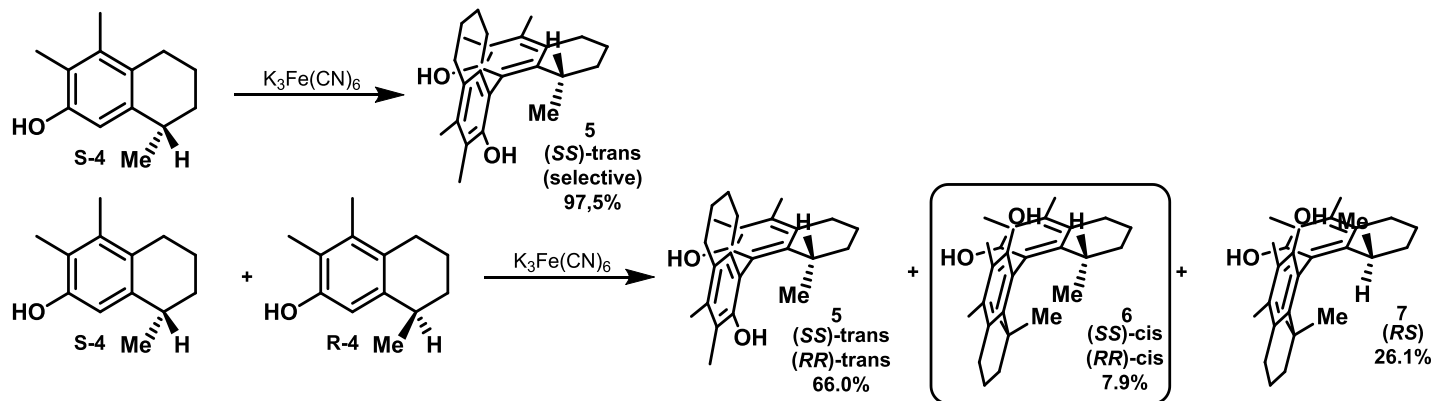
Early nmr studies of dihydroquinine found different spectra for enantiopure (-)-dihydroquinine and racemic dihydroquinine. At very low concentrations, the spectra become identical.



J. Am. Chem. Soc. **1969**, 91, 1871-1872

Early studies found in specific cases unexpected differences in the behavior of enantiopure (or enantioenriched) and racemic samples of substance, even in a nonchiral environment. Those can be sufficiently explained by a noncovalent dimerisation (n-merisation) of a molecule, e.g. by hydrogen bonds, whereas the combination with a molecule of specific configuration (same or opposite) is preferred (,diastereomeric solute-solute interactions').

The nonlinear effect (NLE) in asymmetric catalysis – first encounters

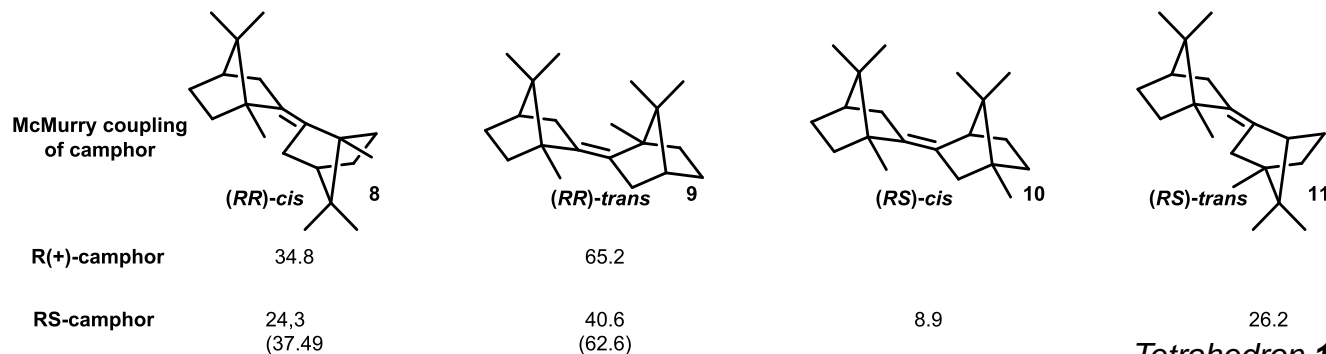


J. Am. Chem. Soc. **1976**, *98*, 3372-3373

In Feringa's argumentation molecules of a given enantiomer have different chemical surroundings in either a racemate or an enantiopure solution. Since the previous examples indicate that nonbonding interactions can occur, that are specific for combinations of either same or opposite enantiomers. Feringa estimates differences in the transition state energies.

$$\Delta G_R^\ddagger - \Delta G_{RS}^\ddagger \approx 20 - 5000 \text{ cal/mole}$$

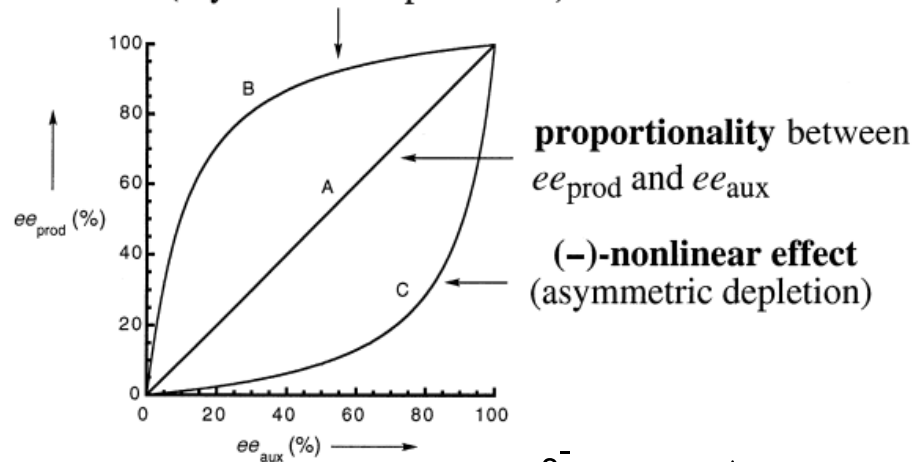
Feringa proposes that this may influence the outcome of certain reactions in terms of selectivity. Noteworthy, he predicts systems of a ML_2 type as later investigated by Kagan and Noyori.



Tetrahedron **1976**, *32*, 2831-2834

The NLE: basic principles and requirements

(+)-nonlinear effect
(asymmetric amplification)



In general, an proportionality between the ee of an auxiliary and product is expected, following

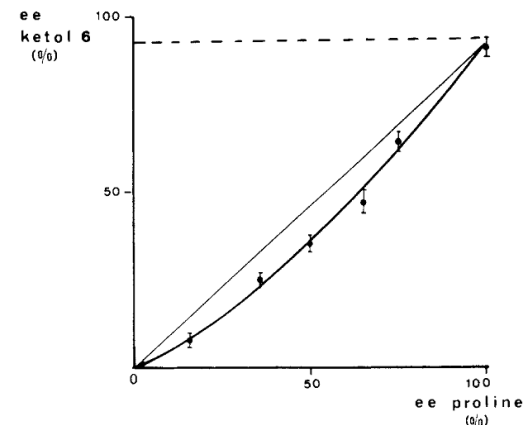
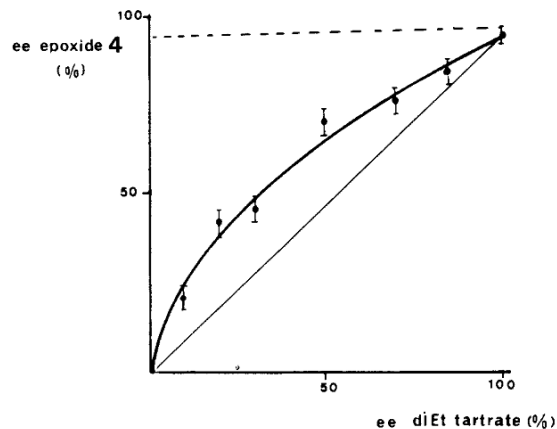
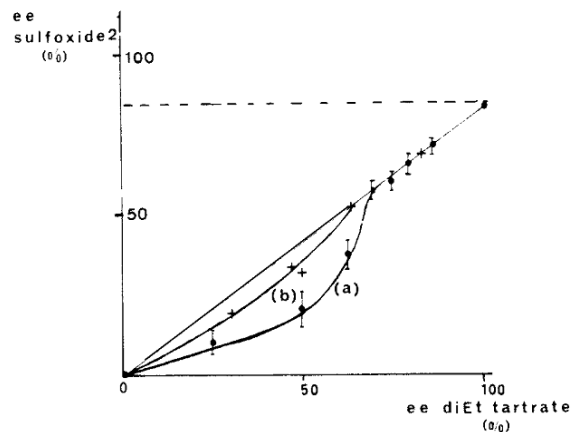
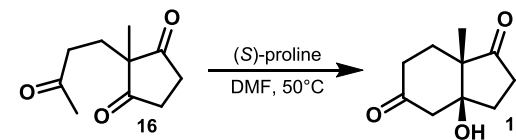
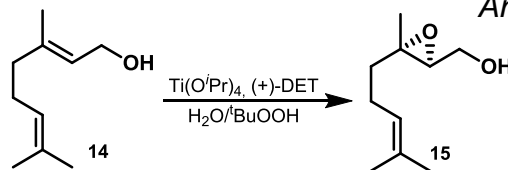
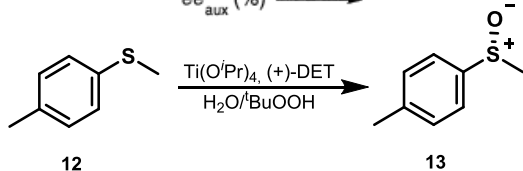
$$ee_{max} = \left(\frac{ee_{prod}}{ee_{aux}} \right) \times 100$$

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

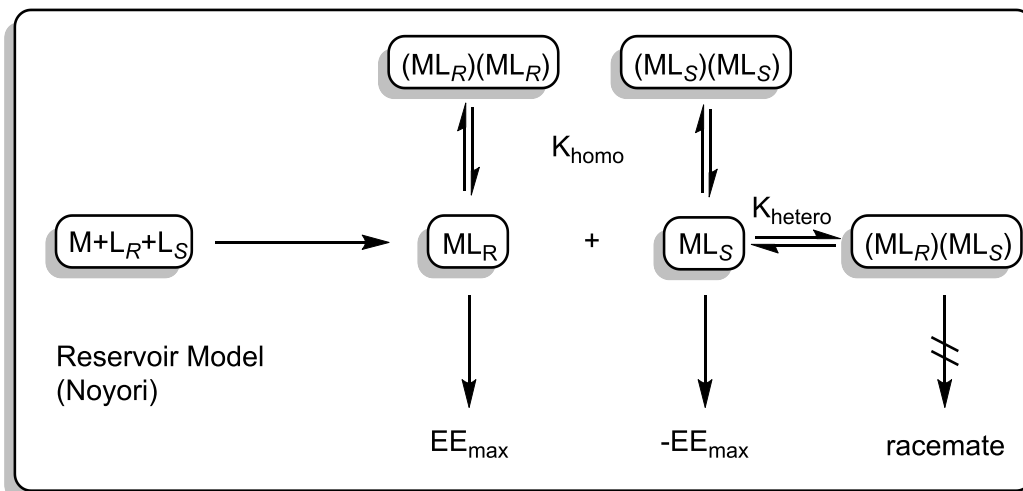
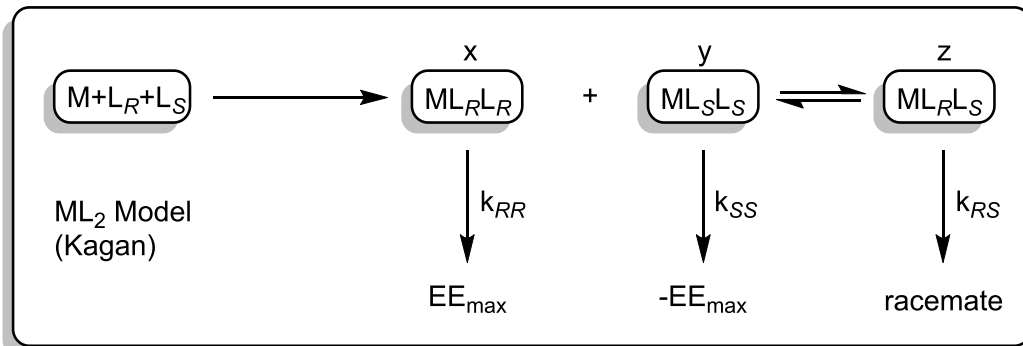
Kagan and coworkers first published several examples in which a deviation of this principle is observed in form of a nonlinear relationship and coined the term nonlinear effect (NLE).

J. Am. Chem. Soc. **1986**, *108*, 2353-2357

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



NLE – basic principles and requirements



In Kagan's ML₂ model the ee can be expressed as

$$ee_{prod} = (ee_{max} ee_{aux}) \frac{1 + \beta}{1 + g\beta}$$

whereas β describes the relative concentrations of homo- and heterochiral complexes.

$$\beta = \frac{z}{x + y}$$

The factor g describes the relative catalysis activity of the homo- and heterochiral complexes.

$$g = \frac{k_{RS}}{k_{RR}}$$

For $g < 1$ a (+)-NLE, for $g > 1$ a (-)-NLE is obtained.

An important consequence of the reservoir model is that amplification only occurs if

$$K_{hetero} > 2K_{homo}$$

Kagan

J. Am. Chem. Soc. **1986**, 108, 2353-2357

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

Adv. Synth. Catal. **2001**, 343, 227-233

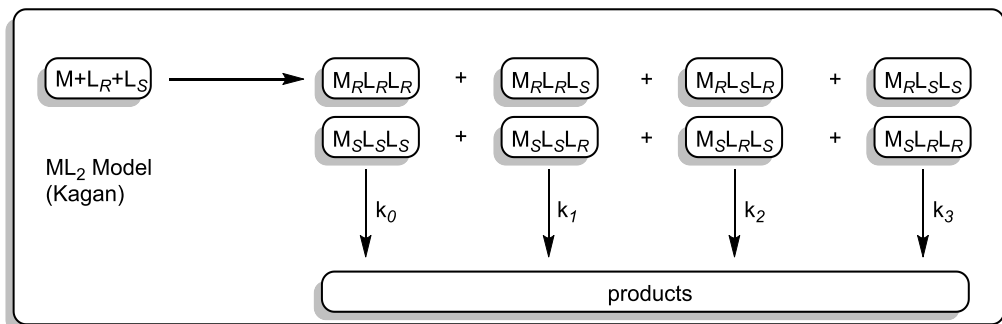
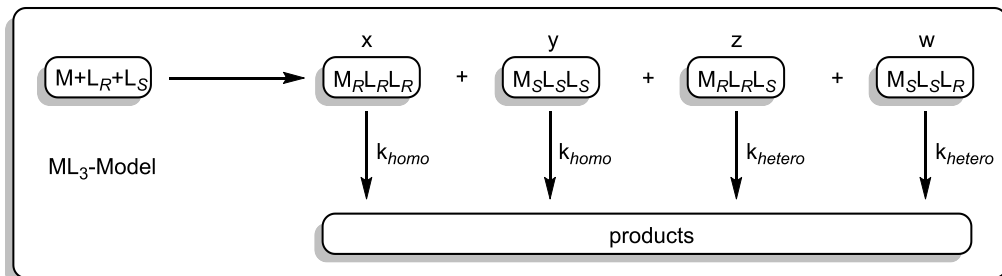
Angew. Chem., Int. Ed. **2009**, 48, 456-494

Noyori

J. Am. Chem. Soc. **1995**, 117, 4832-4842.

J. Am. Chem. Soc. **1998**, 120, 9800-9809.

The NLE – quantification and formalization: other scenarios



More complex relationships are obtained for complexes bearing 3 or 4 ligand. Further introduction of a chirality center at the metal/ a chiral-at-metal scenario might be considered.

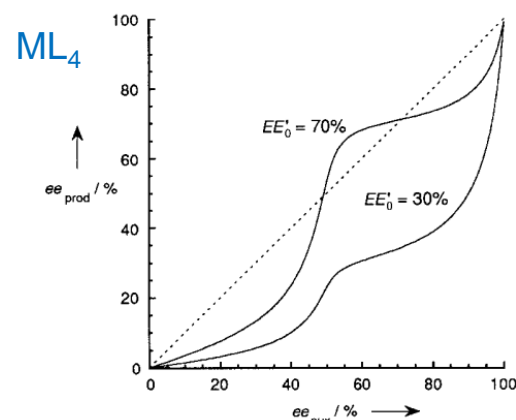
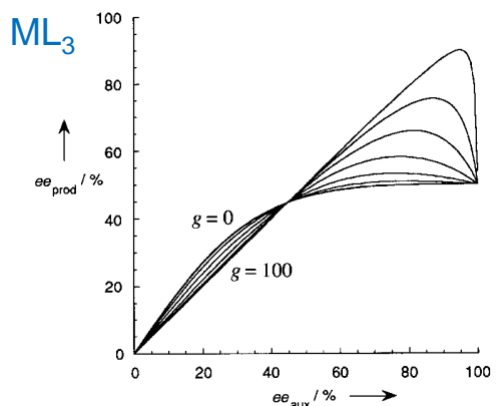
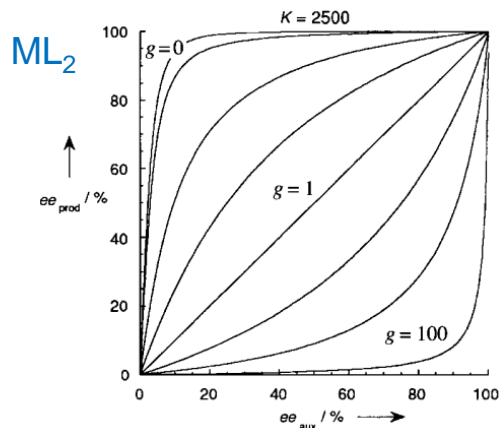
A special case represent reactions where the products themselves interact with the catalyst (e.g. In case of asymmetric autocatalysis), since the ee of the catalyst/ auxiliary does not remain constant.

ML_n systems:

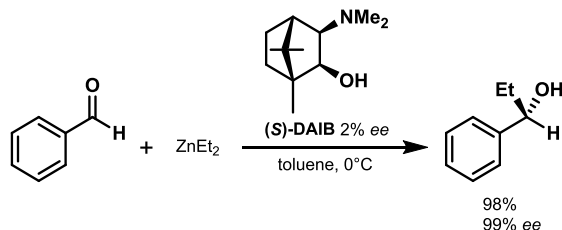
Angew. Chem., Int. Ed. **1998**, 37, 2922-2959

Adjustment for autocatalysis

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

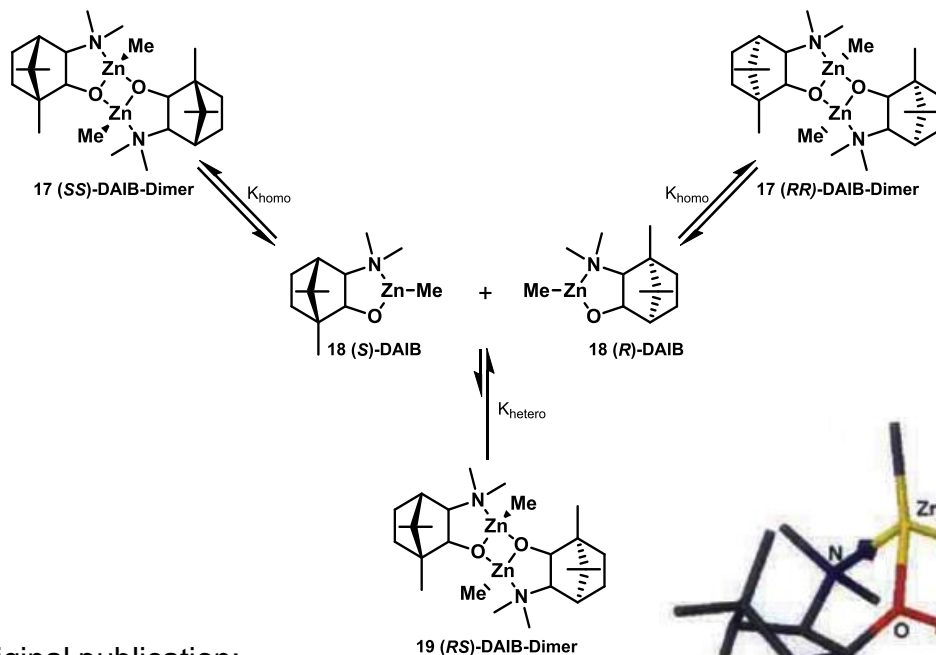


The NLE: a case study

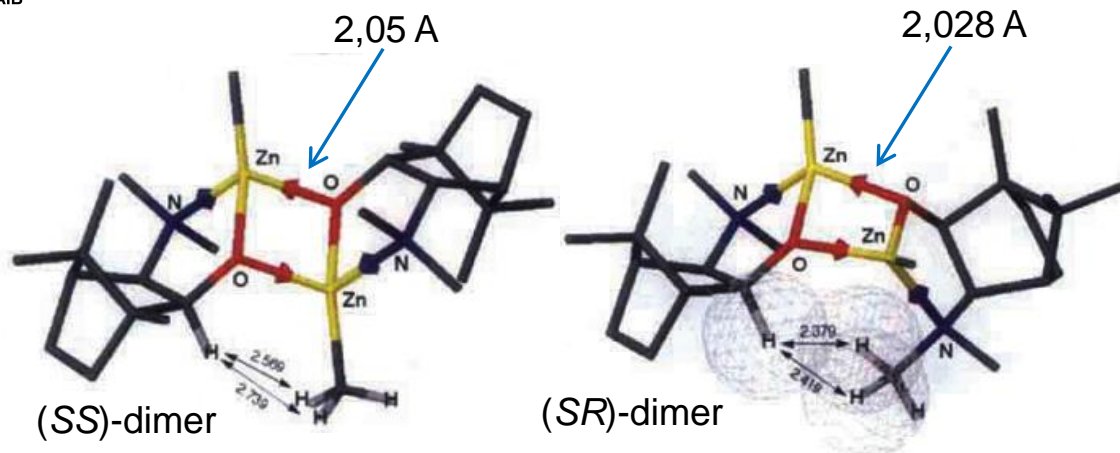


Initial findings:

(+)-NLE, with amplification from 2% ee (auxiliary) to 99% ee (product)



Mechanistic studies by Noyori found $K_{\text{homo}} = (3.0 \pm 1.0) \times 10^{-2} \text{ M}$ and $K_{\text{hetero}} = 1 \times 10^{-5} \text{ M}$. Effectively, only 3% of the heterochiral dimer are dissociated at a given time, while the homochiral dimer is found 60% dissociated. Only the monomer species is catalytically active.



Original publication:

J. Am. Chem. Soc. **1986**, 108, 6071-6072

Mechanism:

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

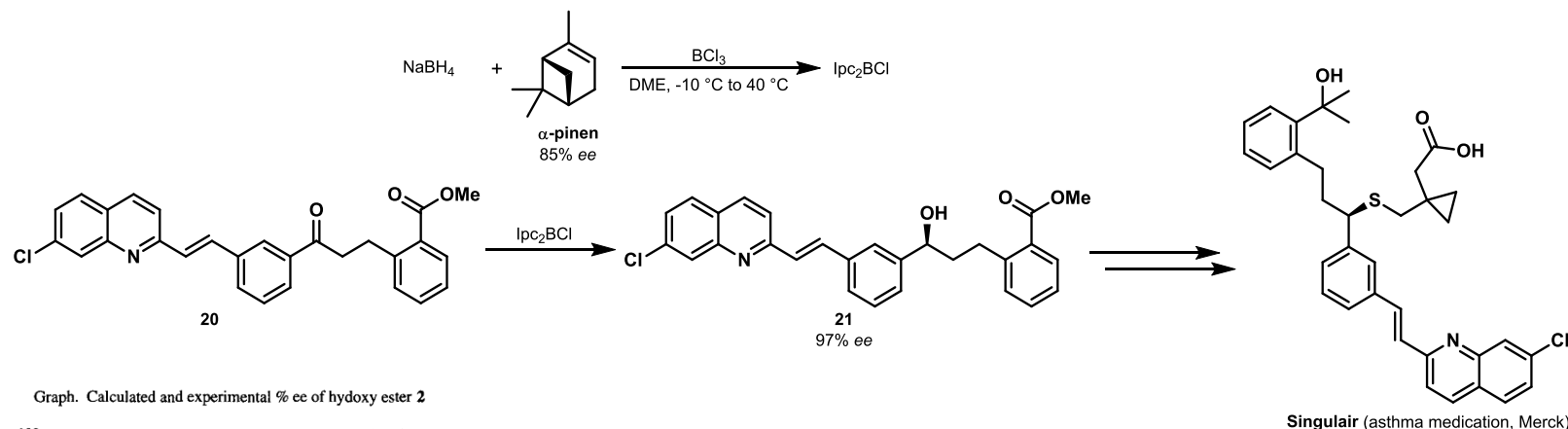
J. Am. Chem. Soc. **1995**, 117, 4832-4842

Chem. Eur. J. **1996**, 2, 1173-1181

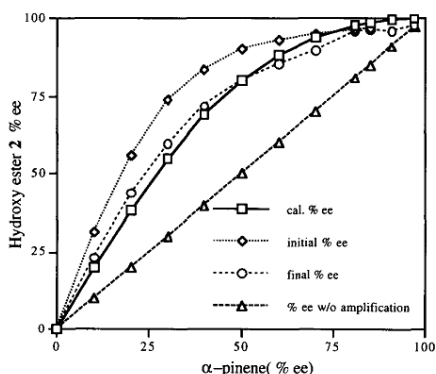
J. Am. Chem. Soc. **1998**, 120, 9800-9809

Both dimers were crystallized, analysis of the crystal structure and further calorimetry experiments confirm the differences in stability

The NLE: a case study



Graph. Calculated and experimental % ee of hydroxy ester 2



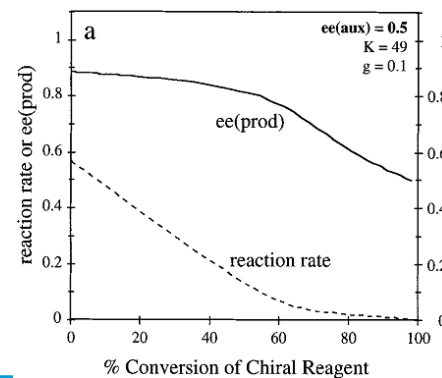
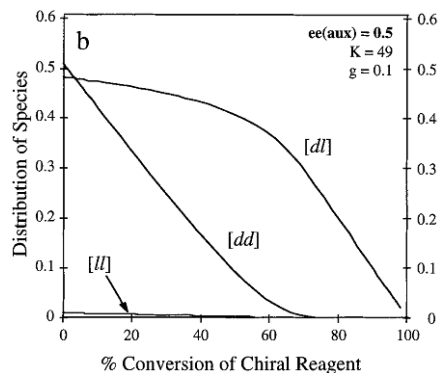
Initially Merck chemists suspected a ML_2 type model with a nonreactive (+)-isomer ($g=0$). This is in accordance with the final ees, but cannot account for the dependence of the ees with the conversion.

Tetrahedron Lett.
1997, 38, 2641-2644
J. Am. Chem. Soc.
1998, 120, 13349-13353

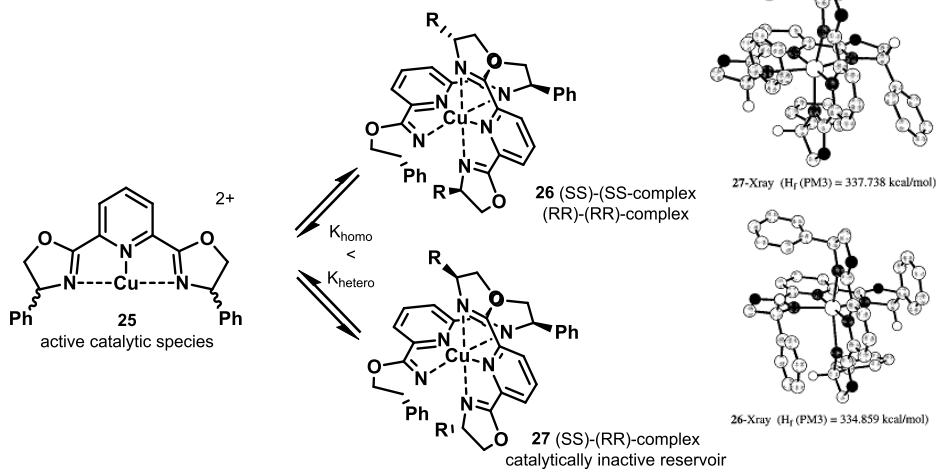
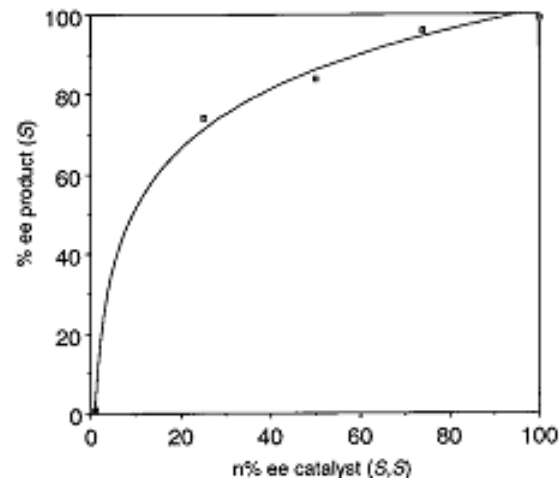
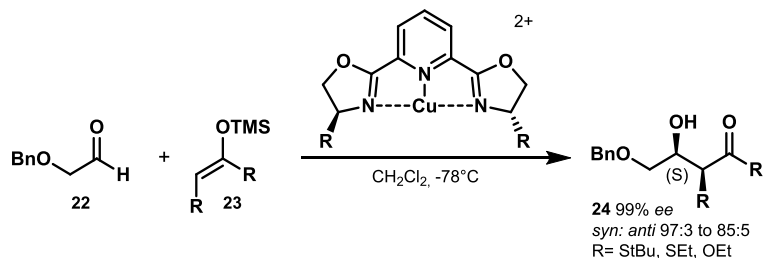
Deviations from the ML_2 model:

- 1) Ligand exchange is not fast on reaction scale
- 2) Species are consumed upon reaction

A modified ML_2 model by Blackmond accounts for these factors. With $K=49$ and $g=0.1$ a good fit of the experimental data is obtained. Note that the slower reaction rate of the heterochiral (+)-species causes also an increase in its relative concentration, causing decay of the enantioselectivity.

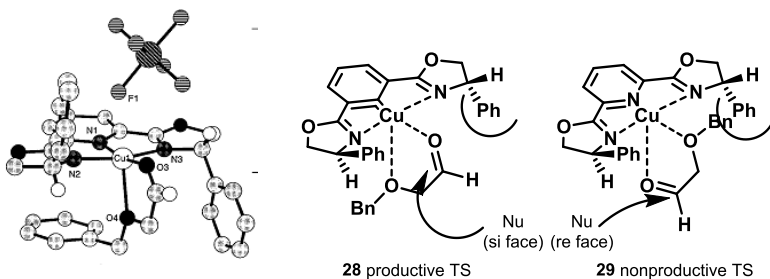


The NLE: expanding the scope



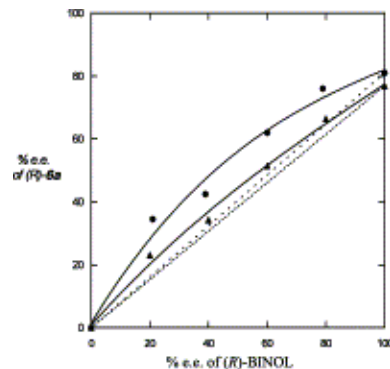
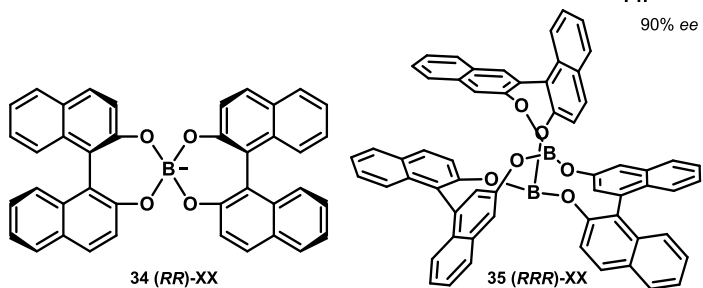
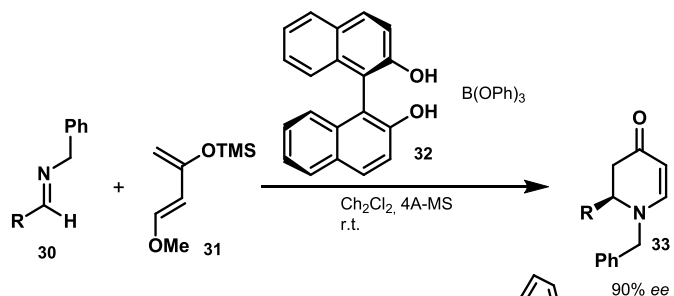
Evans and coworkers report a strong (+) NLE in a Cu catalyzed asymmetric Mukayama aldol reaction. The data fits a ML_2 model with $g=0$.

The stereochemical outcome is explained by steric shielding of one side of the carbonyl by the phenyl group. An alternative orientation of the carbonyl group on the other hand in the axial position gives weaker coordination, thus activation, leading to a nonproductive TS.



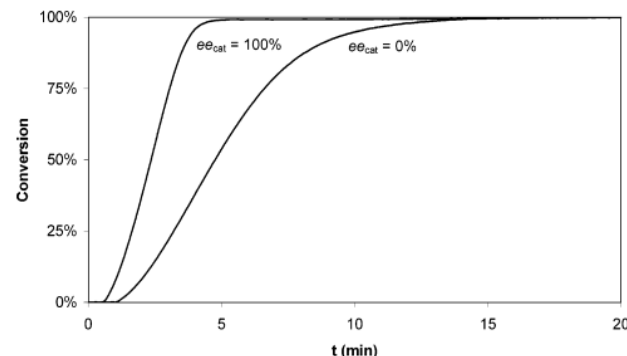
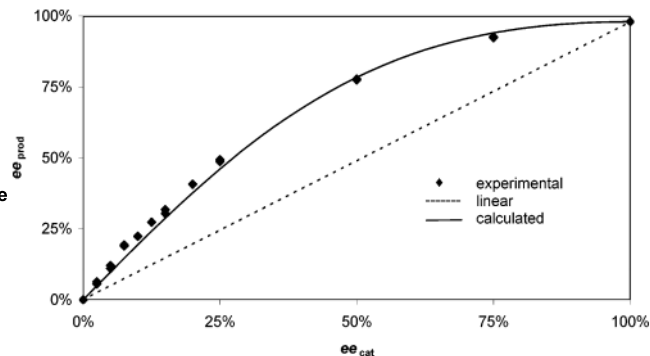
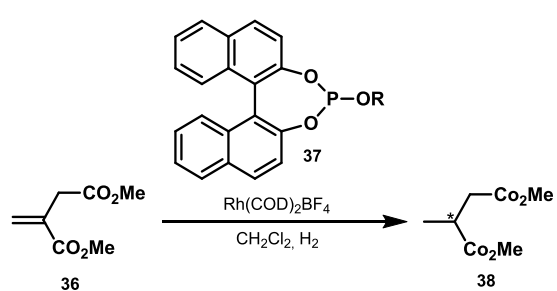
J. Am. Chem. Soc. **1999**, 121, 669-685

The NLE: expanding the scope



An appearance of a (+)-NLE upon usage of scalemic binole and $B(OPh)_3$ in 2:1 ratio implies a homochiral (RR) or (RRR) complex as active catalytic species. This is also an example that the appearance of a NLE can be used to probe reaction mechanisms.

Tetrahedron: Asymmetry **2003**, 14, 1965-1968.



A (+)-NLE was reported for Rh-catalysed hydrogenation using binol ligands. The data fitted a ML_2 model with $K=4$, $g=0$. Note that this example also illustrates that the price for a strong (+)-NLE with an auxiliary with poor ee a decrease in reaction rate is.

J. Am. Chem. Soc. **2005**, 127, 10305-10313

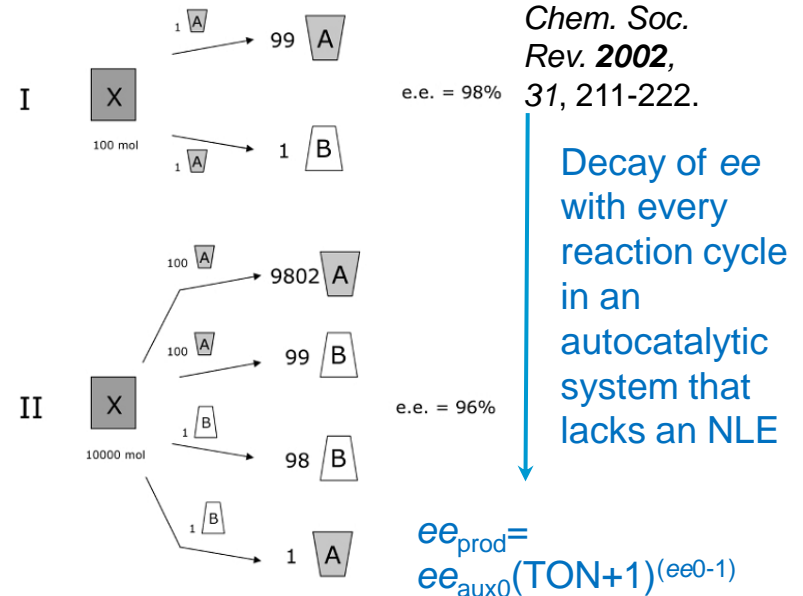
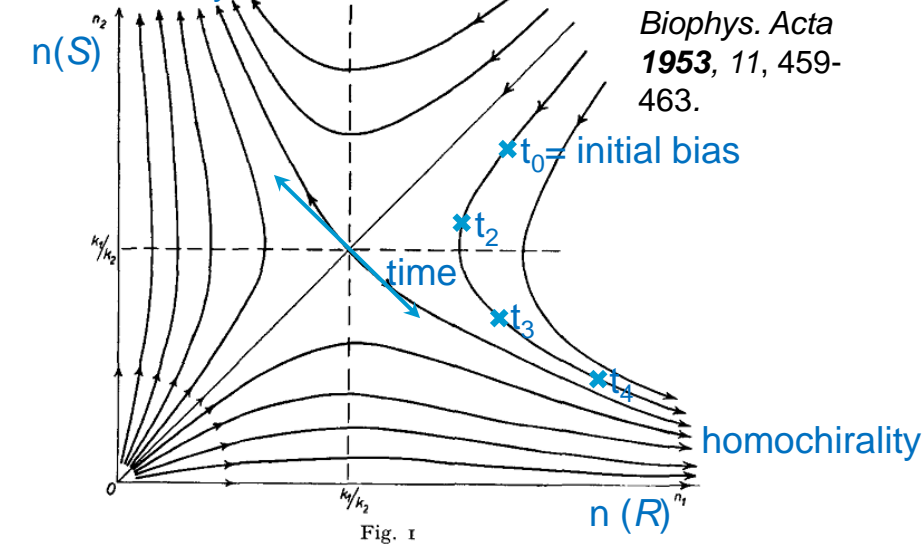
Autocatalysis and the origin of homochirality: the Frank model

By a 'simple mathematical demonstration' Frank's model shows that systems that inherit a set of specific prerequisites will be driven towards homochirality starting from a small bias in the enantiomeric ratio.

Those prerequisites are:

- 1) 'Selfreplication' - i.e. **asymmetric autocatalysis**
- 2) 'Antagonistic principle' – suppression of the activity of the minor enantiomer i.e. **a NLE**

homochirality



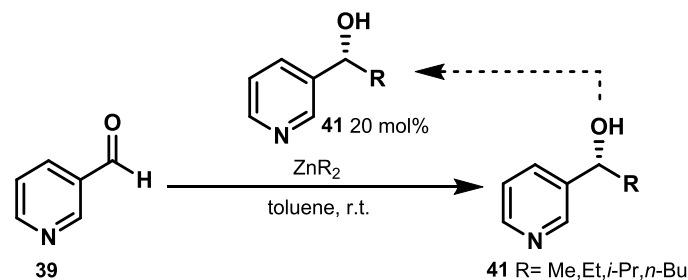
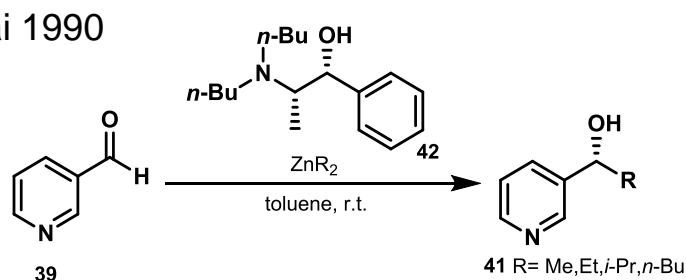
Further implications:

A system that inherits asymmetric autocatalysis, but not antagonistic effects tends towards a decay of the enantiomeric excess and eventually racemization. This is a consequence of imperfect stereo induction ($ee_0 < 1$).

'The main conclusion established is that spontaneous synthesis is a natural property of life, which may be present in simpler autocatalytic systems. A laboratory demonstration may not be impossible'

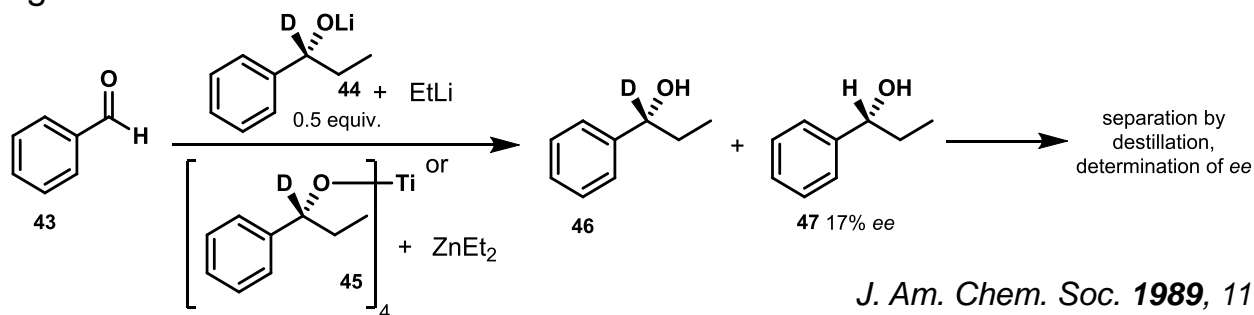
First example of an autocatalysis system: The Soai reaction (I) and its limitations

Soai 1990



Chem. Soc., Chem. Commun. **1990**, 982-983

Alberts, Wynberg 1989

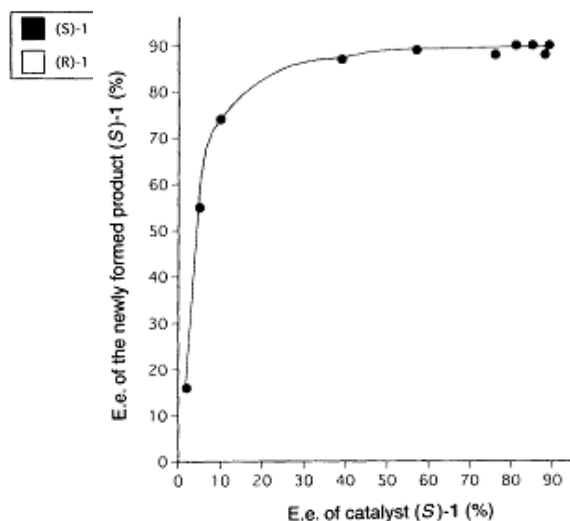
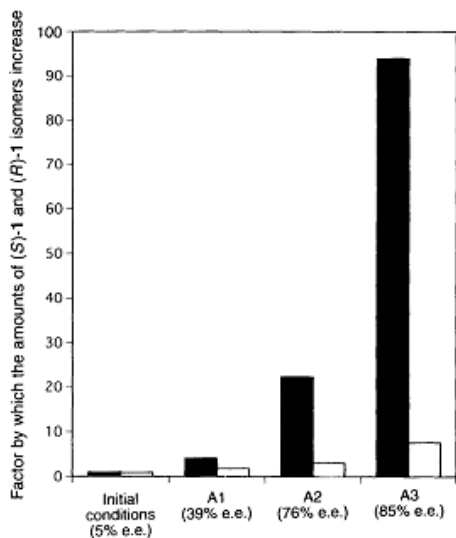
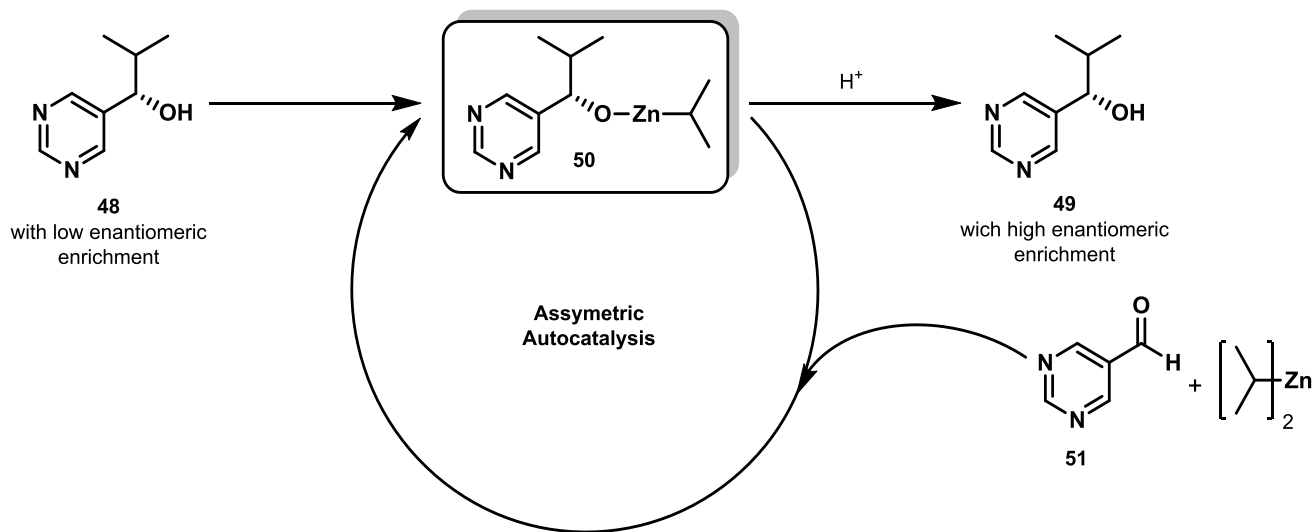


J. Am. Chem. Soc. **1989**, 111, 7265-7266
J. Chem. Soc., Chem. Commun. **1990**, 453-454

Alberts, Wynberg demonstrated 1989 the concept of enantioselective autoinduction for the alkylation of benzaldehyde. Soai published 1990 a similar system that exemplified enantioselective autocatalysis for the first time in literature.

However, the enantiomeric excess of these systems decreases with reaction cycle, thus representing not an autocatalytic system in the sense of the Frank model. An 'antagonistic principle' is missing.

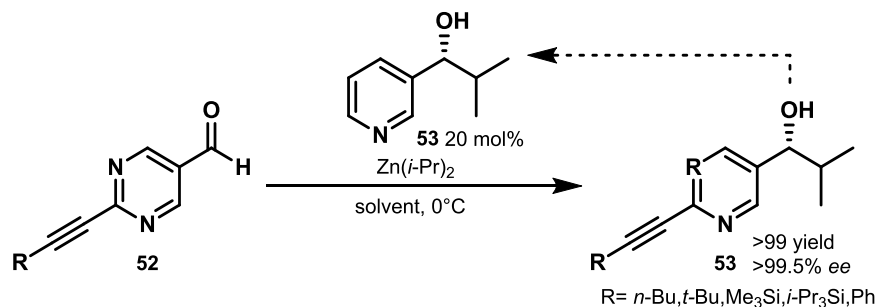
First example of an Frank type autocatalysis: The Soai reaction (II)



The Soai represents the only literature known example of a 'real' asymmetric autocatalysis as described by the Frank model. The enantiomeric excess increases with every reaction cycle.

Nature **1995**, 378, 767-768

Autocatalysis: engineering the Soai reaction



Eintrag	X	Lösungsmittel	asym. Autokat.	neu gebildetes	
			und Produkt	Produkt	
			ee [%]	Ausb. [%]	ee [%]
1	2.2	Toluol ^[a]	99.3 (<i>S</i>)	98	99.1 (<i>S</i>)
2	2.2	Cumol ^[a]	99.4 (<i>S</i>)	98	99.3 (<i>S</i>)
3	2.2	<i>tert</i> -Butylbenzol ^[a]	99.3 (<i>S</i>)	99	99.1 (<i>S</i>)
4	2.2	Cumol ^[b]	>99.5 (<i>S</i>)	99	>99.5 (<i>S</i>)
5	1.7	Cumol ^[b]	>99.5 (<i>S</i>)	>99	>99.5 (<i>S</i>)
6	1.7	Cumol ^[b]	>99.5 (<i>R</i>)	>99	>99.5 (<i>R</i>)

Runde	asym. Autokat.	Produkt		Verstärkungsfaktor ^[b]
	ee [%]	Ausb. [%]	ee [%]	
1	>99.5 (2a)	>99	>99.5 (2b)	6
2	>99.5 (2b)	>99	>99.5 (2c)	6 ²
3	>99.5 (2c)	>99	>99.5 (2d)	6 ³
4	>99.5 (2d)	>99	>99.5 (2e)	6 ⁴
5	>99.5 (2e)	>99	>99.5 (2f)	6 ⁵ $\approx 8 \times 10^3$
6	>99.5 (2f)	>99	>99.5 (2g)	6 ⁶
7	>99.5 (2g)	>99	>99.5 (2h)	6 ⁷
8	>99.5 (2h)	>99	>99.5 (2i)	6 ⁸
9	>99.5 (2j)	>99	>99.5 (2k)	6 ⁹
10	>99.5 (2k)	>99	>99.5 (2l)	6 ¹⁰ $\approx 6 \times 10^7$

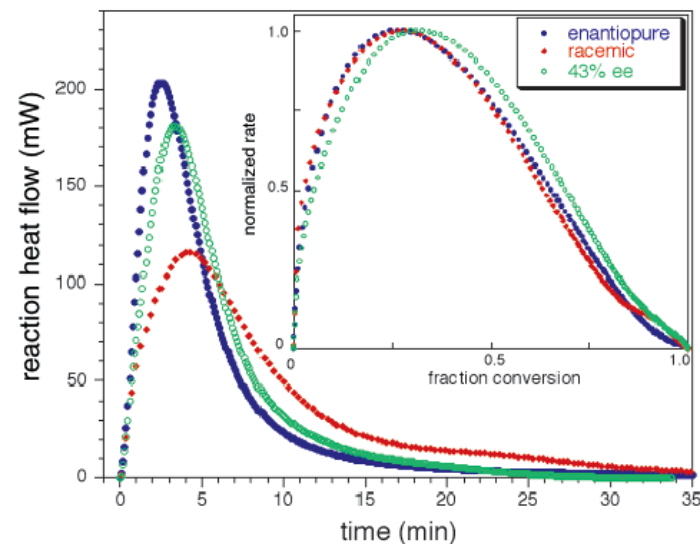
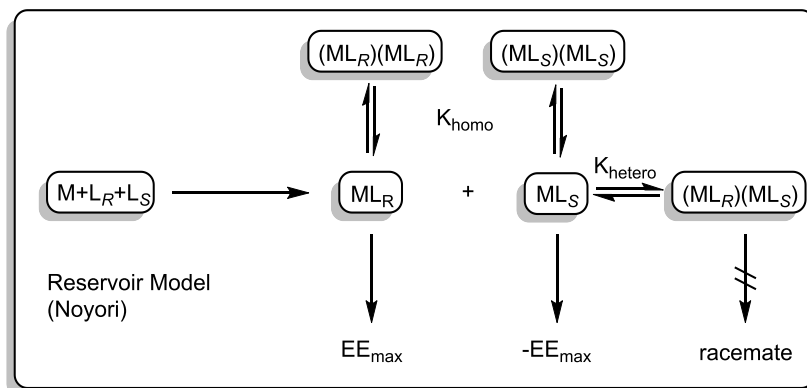
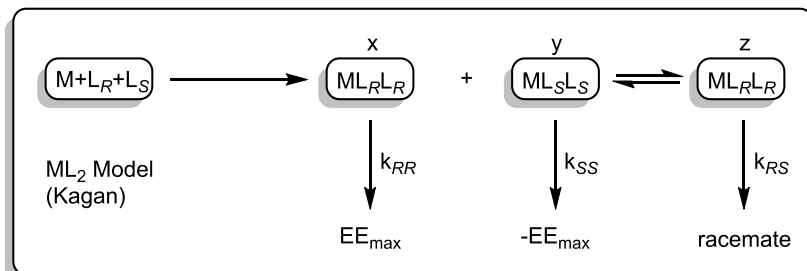
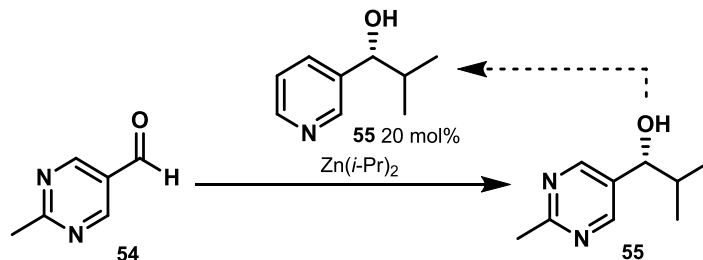
The enantiomeric excess of a given asymmetric reaction depends on the difference of the free energies of the Gibbs free energy of the (*R*)- and (*S*)-transition states.

$$\frac{n_R}{n_S} = \frac{k_1}{k_2} = e^{\frac{-\Delta\Delta G^\ddagger}{RT}}$$

thus really high ee values are increasingly difficult to reach. In light of this, the improved Soai reaction represents a remarkable example.

Angew. Chem. **1999**, *111*, 746-748

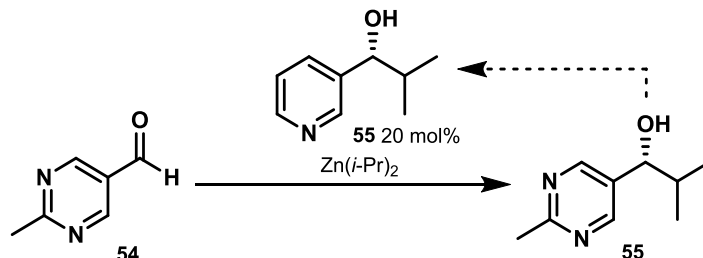
What makes the Soai reaction (II) a ,real' Frank type autocatalysis?



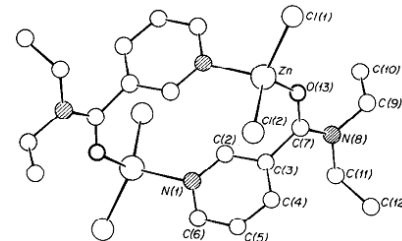
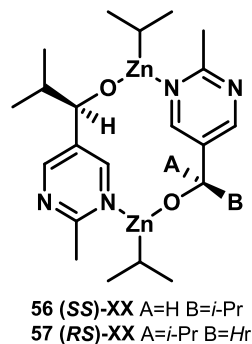
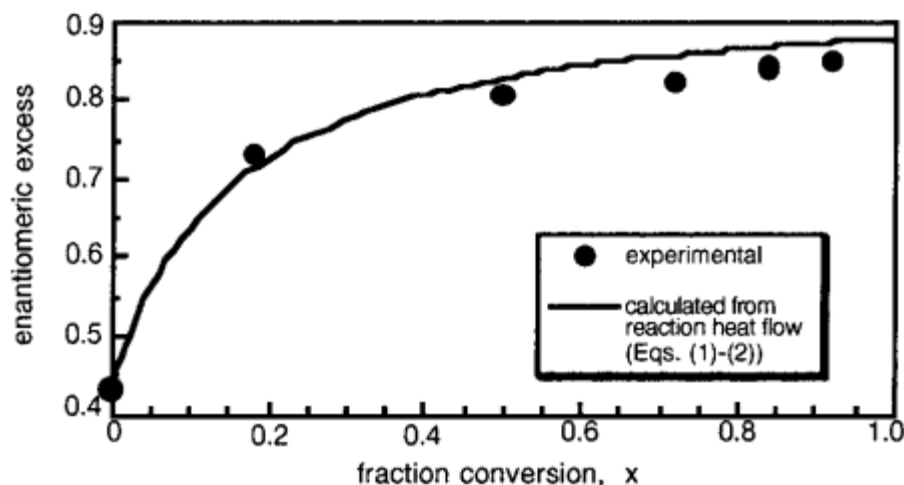
Normalized rates in case of enantiopure and racemic reaction are proportional, a reservoir model (Noyori) would lead to $K_{hetero}=2K_{homo}$. This is inconsistent with this model.

J. Am. Chem. Soc. **2001**, *123*, 10103-10104
Proc. Natl. Acad. Sci. U. S. A. **2004**, *101*, 5732-5736

What makes the Soai reaction (II) a ,real' Frank type autocatalysis?



If Kagan's ML_2 model is modified to account for the shifting auxiliary ee and concentration the kinetic data can be reasonably fitted.

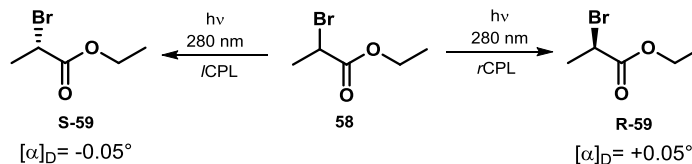


This lead Blackmond to the implication that the active catalyst is a dimer. Crystal structures of similar structures are reported.

J. Am. Chem. Soc. **2001**, 123, 10103-10104
Proc. Natl. Acad. Sci. U. S. A. **2004**, 101, 5732-5736
Inorg. Chim. Acta **1984**, 84, 41-50.

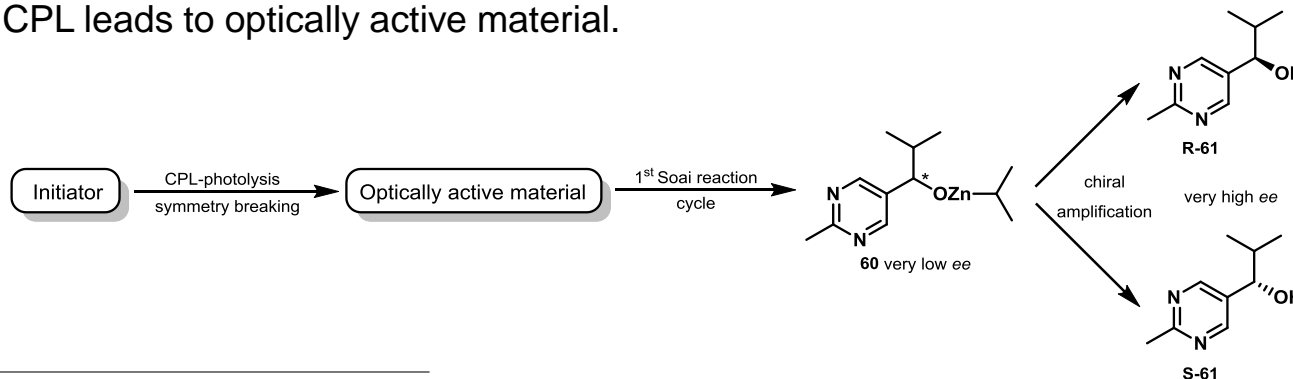
Autocatalysis and CPL: absolute asymmetric synthesis

Kuhn 1929



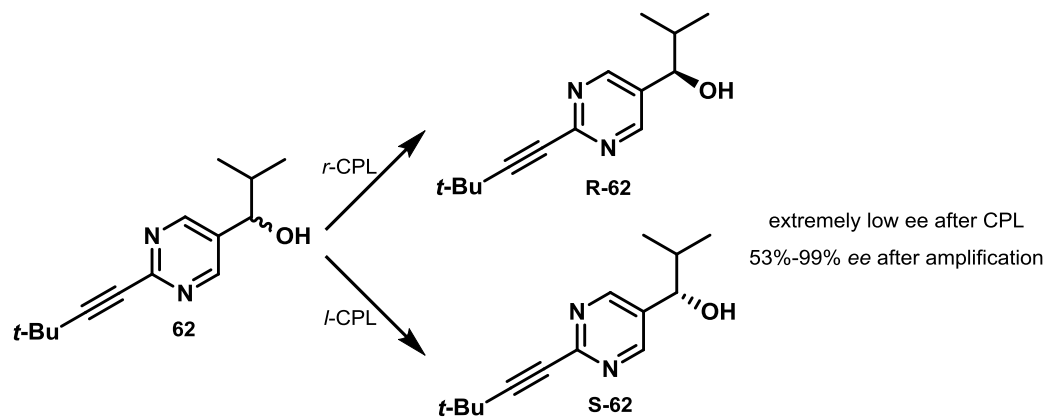
As a consequence of different absorption of light of *l*-CPL and *r*-CPL for an given enantiomer, photolysis of a racemate with CPL leads to optically active material.

Soai 1998

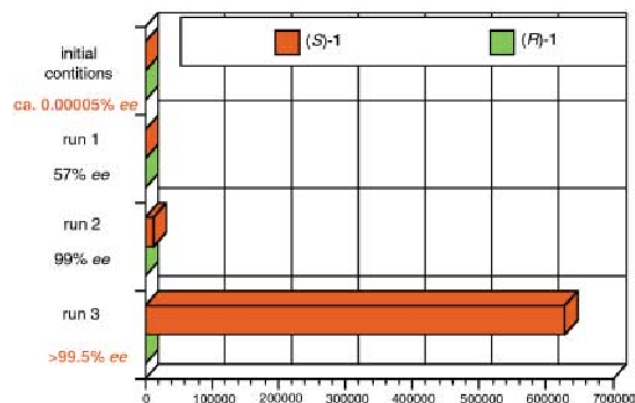
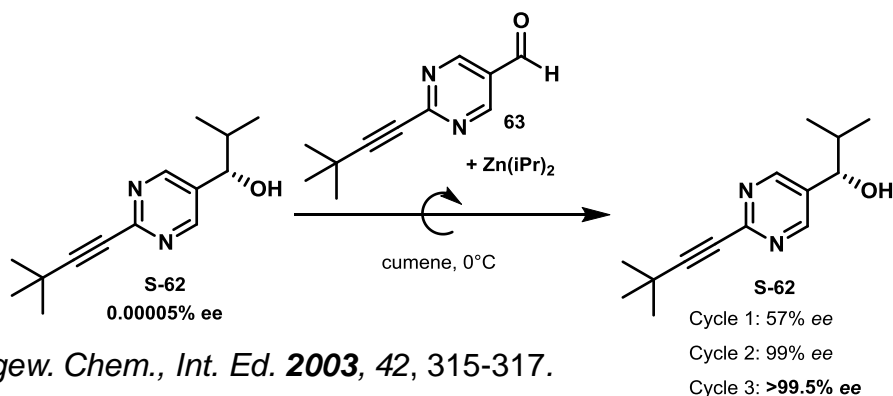


entry ^a	chiral initiator		pyrimidyl alkanol 2	
	structure	ee / %	structure	ee. / %
1		ca. 0.1 (S)		68 (R)
2		ca. 0.1 (R)		70 (S)
3		ca. 0.05 (S)		54 (R) ^b
4		ca. 0.05 (R)		38 (S) ^c
5		ca. 0.1 (S)		76 (R)
6		ca. 0.1 (R)		73 (S)
7		ca. 0.1 (S)		79 (R)
8		ca. 0.1 (R)		85 (S)
9		ca. 0.1 (S)		73 (S)
10		ca. 0.1 (R)		76 (R)

Alternatively certain olefins or (racemic) alkyl-substituted pyrimidyl alcohols themselves can be used



Autocatalysis: can statistical fluctuations lead to spontaneous absolute asymmetric synthesis?

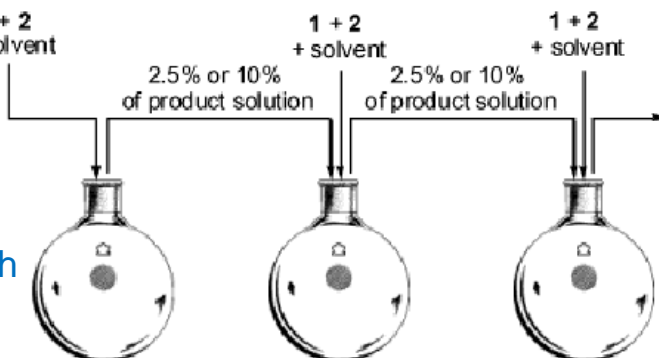


As demonstrated by Soai, even very small ees in the range of 10^{-5} can be easily amplified to macroscopically accessible optical activity. This may not yet represent the limit.

Statistically, a racemate of n molecules should still exhibit a random bias for one enantiomer by $n^{1/2}$, so for 1 Mole $n \approx 10^{23}$ and $n^{1/2} \approx 10^{11}$ which leads to $ee \approx 10^{-12}$. For a nanomole one would obtain $ee \approx 10^{-7}$...

achiral starting material

chiral product with statistical bias



etc. until measurable optical activity

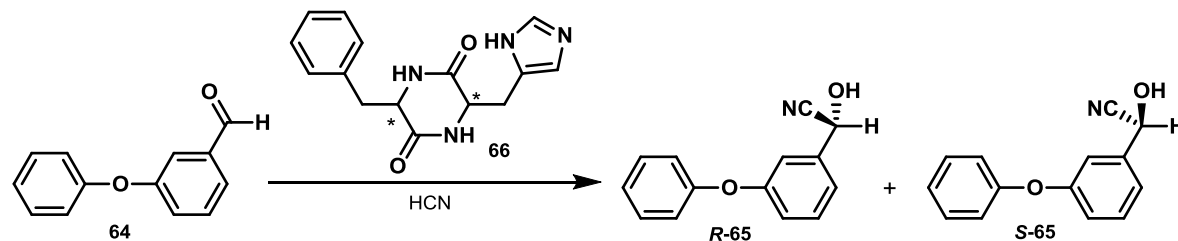
macroscopic, detectable optical activity

replicative asymmetric amplification

J. Am. Chem. Soc. **2002**, 124, 10010-10011.
Tetrahedron: Asymmetry **2003**, 14, 185-188.
Org. Lett. **2003**, 5, 4337-4339.

After overcoming initial issues caused by chiral contamination (indicated by a distribution of enantiomers that varies significantly from unity), the groups of Soai (2002) and Singleton (2003) could demonstrate an spontaneous asymmetric catalysis. The even probability of an (*R*) or (*S*) detection event indicates that chiral impurities as origin of the chirality are unlikely.

Autocatalysis and organocatalysis



J. Org. Chem. **1991**, *56*, 6740-6741.

Table I. Effect of the Initial Presence of (*S*)-2 or (*R*)-2 on the Enantioselective Addition of Hydrogen Cyanide to 3-Phenoxybenzaldehyde (1) Catalyzed by (*R,R*)-3^a

method ^a	time (h)	conversion of 1 ^{b,c} (%)	optical purity of (<i>S</i>)-2 ^{c,d} (% ee)
A	0.5	21	34.4
	1	39	66.2
	2	92	91.6
	4	94	92.0
B	0.5	59 (55)	95.4 (95.8)
	1	81 (79)	96.0 (96.4)
	2	93 (92)	96.4 (96.8)
	4	95 (95)	96.2 (96.6)
C	0.5	24 (17)	25.1 (34.8)
	1	43 (38)	54.0 (66.2)
	2	93 (92)	77.8 (92.2)
	4	95 (95)	78.0 (92.4)

Table II. Effect of the Optical Purity of the (*R,R*)-3 Catalyst on the Enantioselective Autoinduction^a

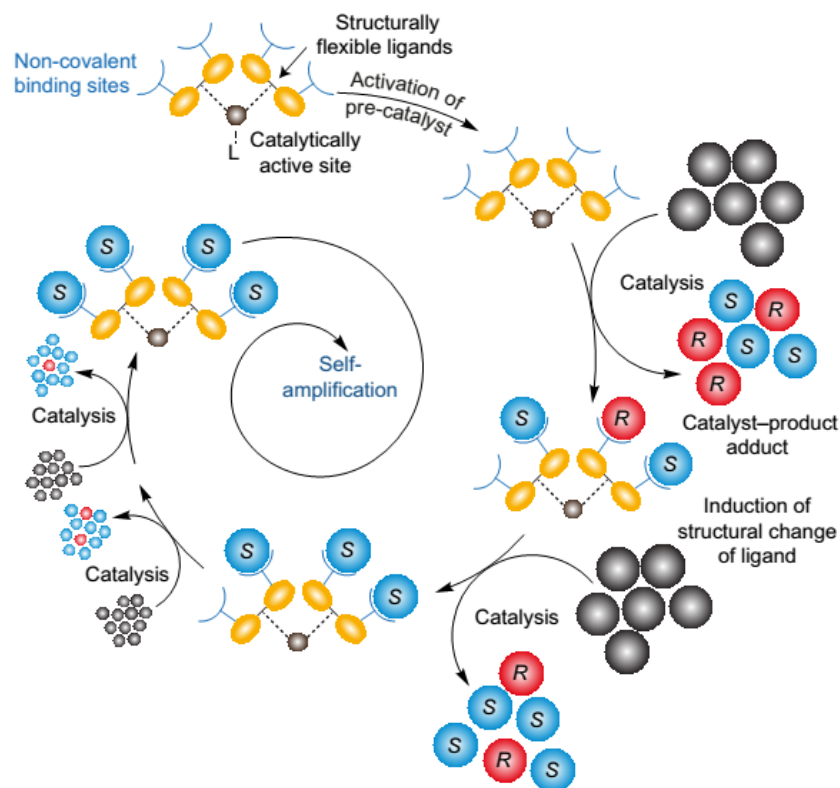
entry	optical purity of (<i>R,R</i>)-3 ^b (% ee)	conversion of 1 ^c (%)	optical purity of 2 (% ee) (configuration) ^{d,e}	method ^a
1	100	94	92.0 (<i>S</i>)	A
2	84.6	89	80.0 (<i>S</i>)	A
3	79.4	89	76.2 (<i>S</i>)	A
4	66.8	81	64.6 (<i>S</i>)	A
5	40.0	62	37.2 (<i>S</i>)	A
6	12.2	27	11.0 (<i>S</i>)	A
7	100	95	96.2 (<i>S</i>)	B
8	84.6	96	94.8 (<i>S</i>)	B
9	79.4	96	96.8 (<i>S</i>) ^f	B
10	66.8	89	96.0 (<i>S</i>)	B
11	40.0	90	90.2 (<i>S</i>)	B
12	12.2	79	86.6 (<i>S</i>)	B
13	12.2	68	39.6 (<i>R</i>)	C
14	2.0	4	3.4 (<i>S</i>)	A
15	2.0	43	81.6 (<i>S</i>)	B
16	2.0	39	74.0 (<i>R</i>)	C
17	no catalyst	no reaction		B
18	no catalyst	no reaction		C

When attempting organocatalysis via a phenylalanine-histidine adduct, a dependence of the ee on conversion was noticed, indicating autocatalysis. When enantiomerically enriched product was added, the stereoselection of the product outweighed the amino acid catalyst. This indicates that also non-metal complex systems should be actually possible.

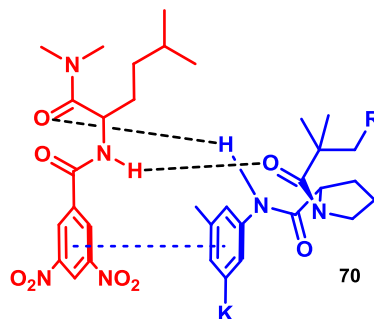
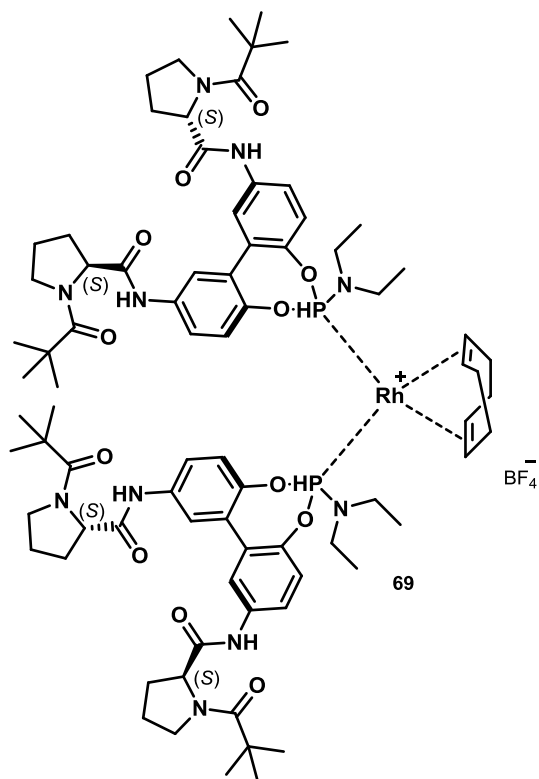
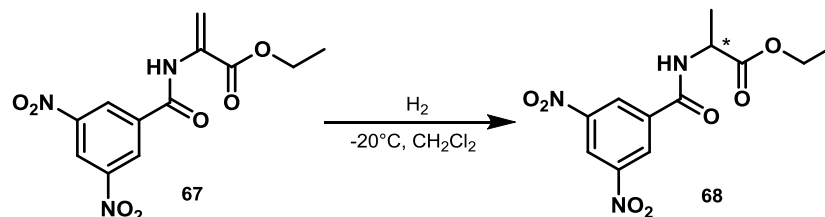
Rational design of a novel autocatalysis system

General idea:

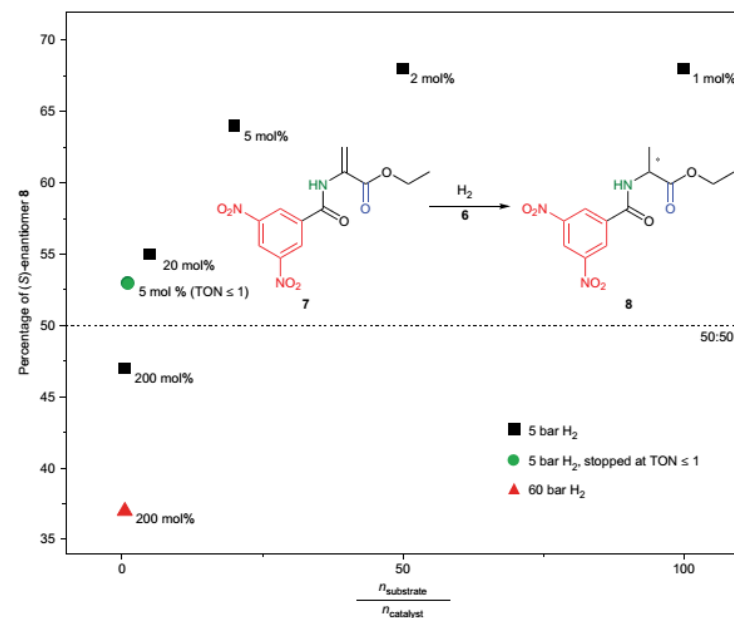
- 1) The catalyst inherits a **flexible ligand with weak stereoreduction**
- 2) By this induction, a **small ee is generated** in the first turnover cycles
- 3) The product binds noncovalent to the flexible ligand, leading to changes in the ligand system, **changing stereoreduction**
- 4) **Asymmetric autocatalysis**



Rational design of a novel autocatalysis system



Recognition of the substrate by N-pivaloylproline-3,5-dimethylanilide
– 3,5-dinitrobenzoylleucine dimethylamide complex



At high catalyst loading the stereoinduction of the catalyst dominates the outcome, at low catalyst loadings, the induction by autocatalysis, with opposite selectivity dominates.

Nat Chem **2017**, *9*, 179-187

Summary and conclusions

- Racemates and enantiopure substance may show different behavior even in achiral environments
- The reason for this is formation of diastereomeric hetero- and homochiral dimers (n-mers) with different behavior/ properties
- One consequence are NLEs in catalysis, if the prerequisites for this are met
- The NLE may amplify or decrease the ee that can be obtained by a scalemic auxiliary
- Models for different NLE scenarios
- Frank Model concerning the origin of homochirality
- Prerequisites of autocatalysis
- The Soai reaction and its implications
- Absolute and spontaneous asymmetric catalysis (?)