Soai reaction
-Asymmetric autocatalysis with amplification of ee-

Literature seminar

2017/08/19

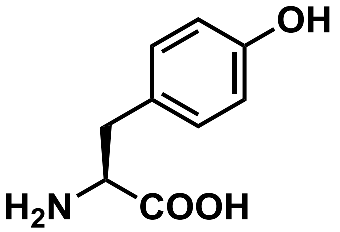
Takashi Ishiyama(M2)

Contents

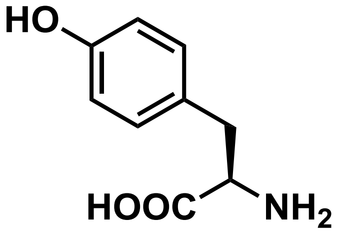
1. Introduction
2. Discovery of soai reaction
3. Application of soai reaction
(Various chiral sources and origin of homochirality)
4. Mechanism of soai reaction

Homochirality

Amino acid

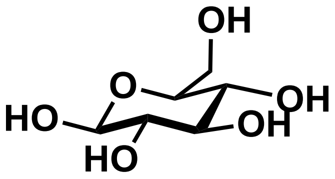


L-Tyrosine

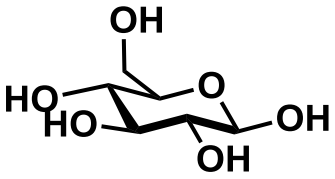


D-Tyrosine

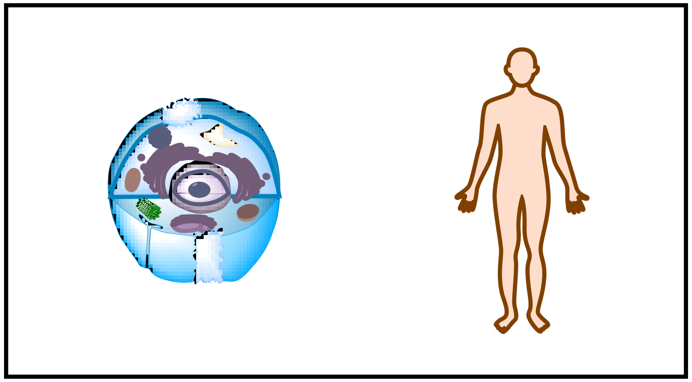
Sugar



L-Glucose

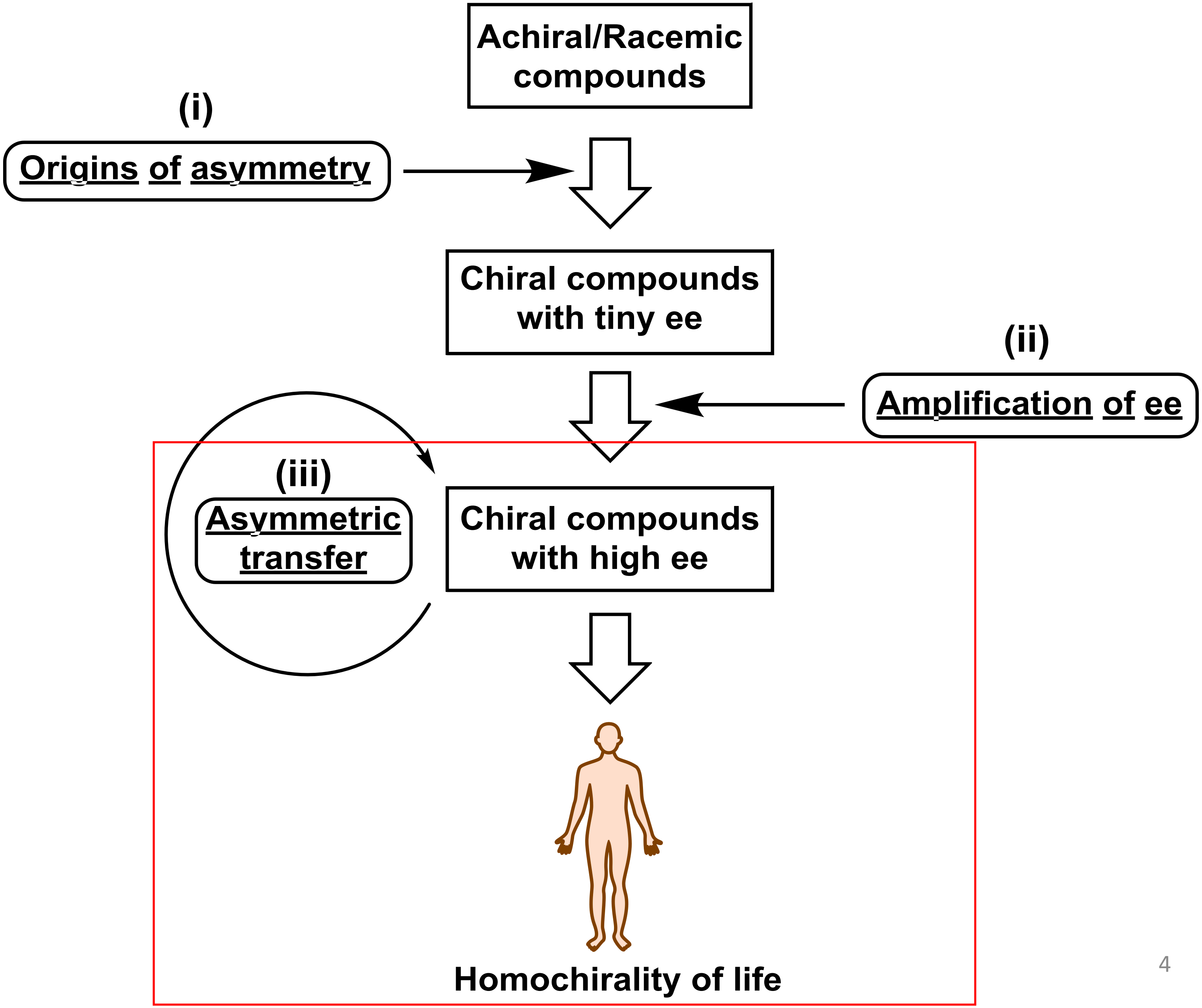


D-Glucose



All organism is composed of one enantiomer : *Homochirality of life*

What is origin of homochirality?



Achiral/Racemic compounds

(i)

Origins of asymmetry

Chiral compounds with tiny ee

(ii)

Amplification of ee

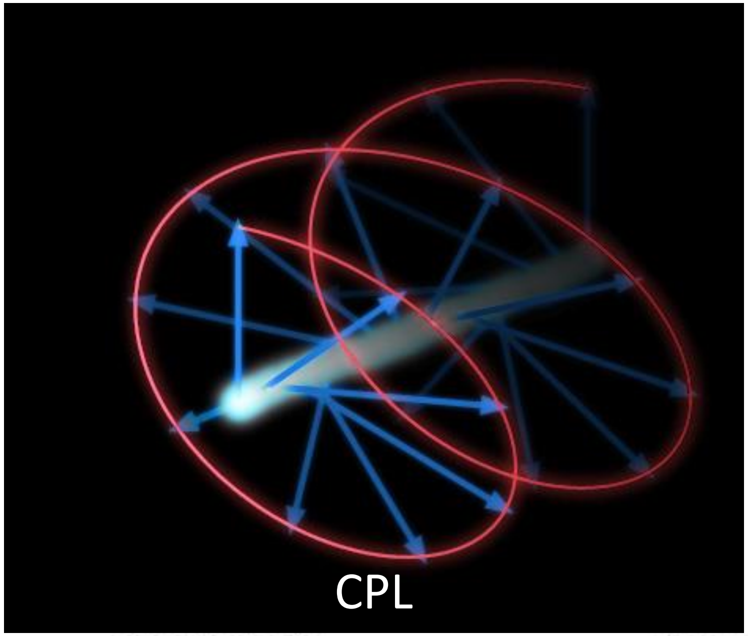
(iii)

Asymmetric transfer

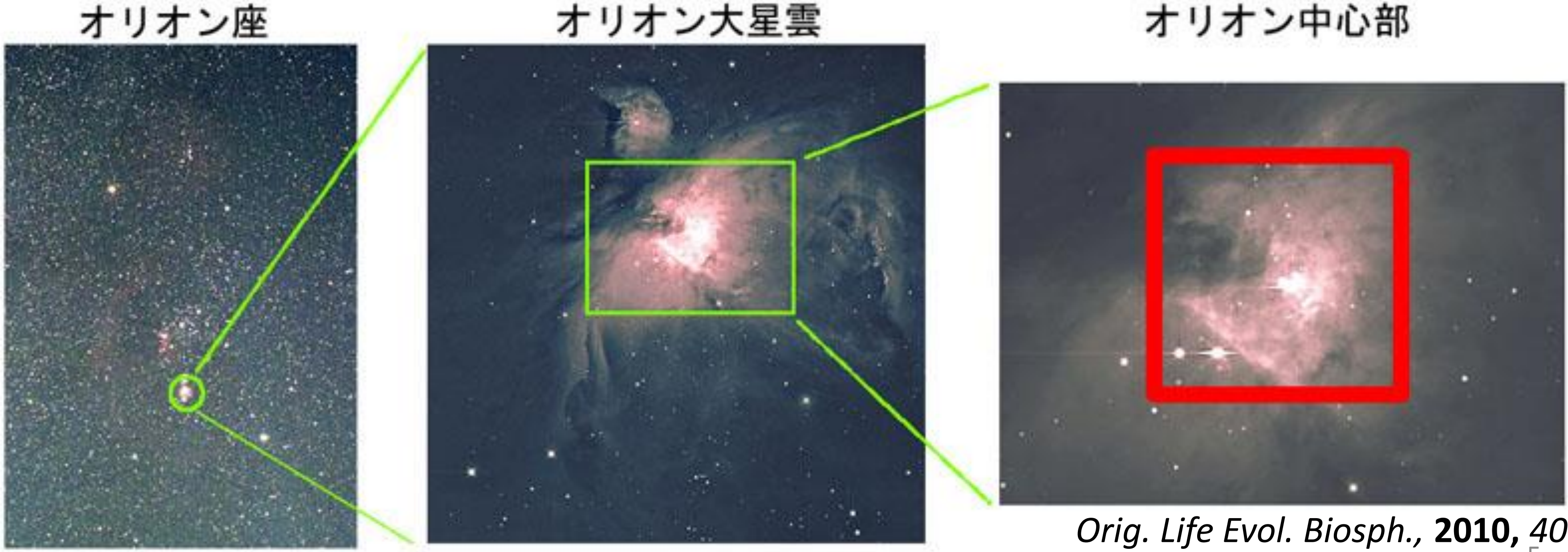
Chiral compounds with high ee

Homochirality of life

Origin of asymmetry(Circular polarized light)



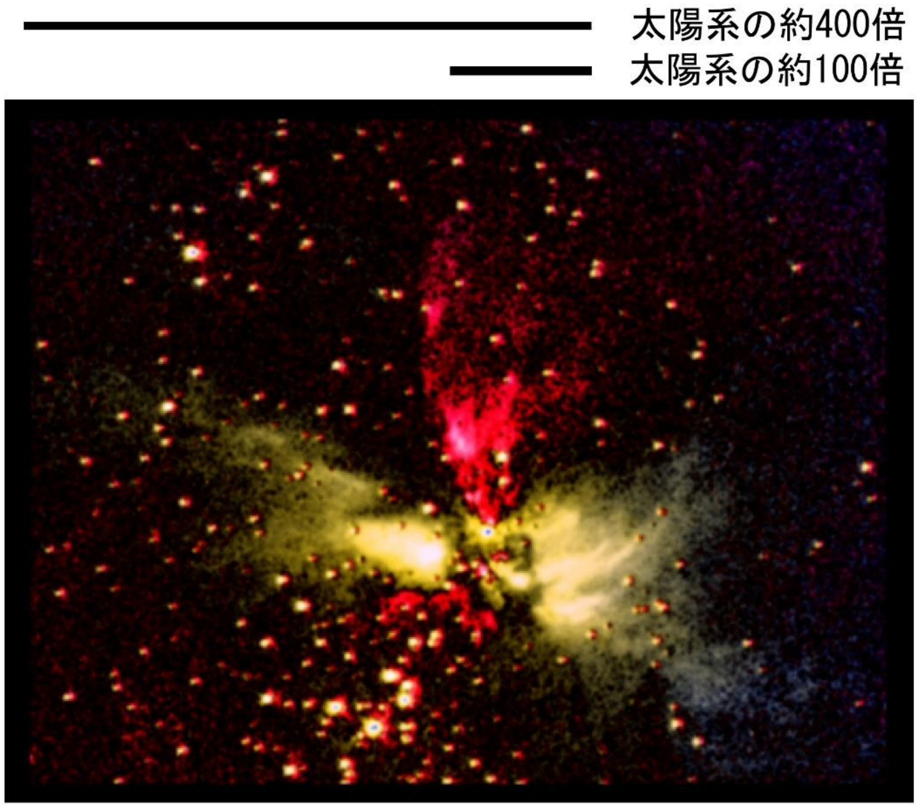
Circularly polarized light is proposed as one of the origins of chirality.

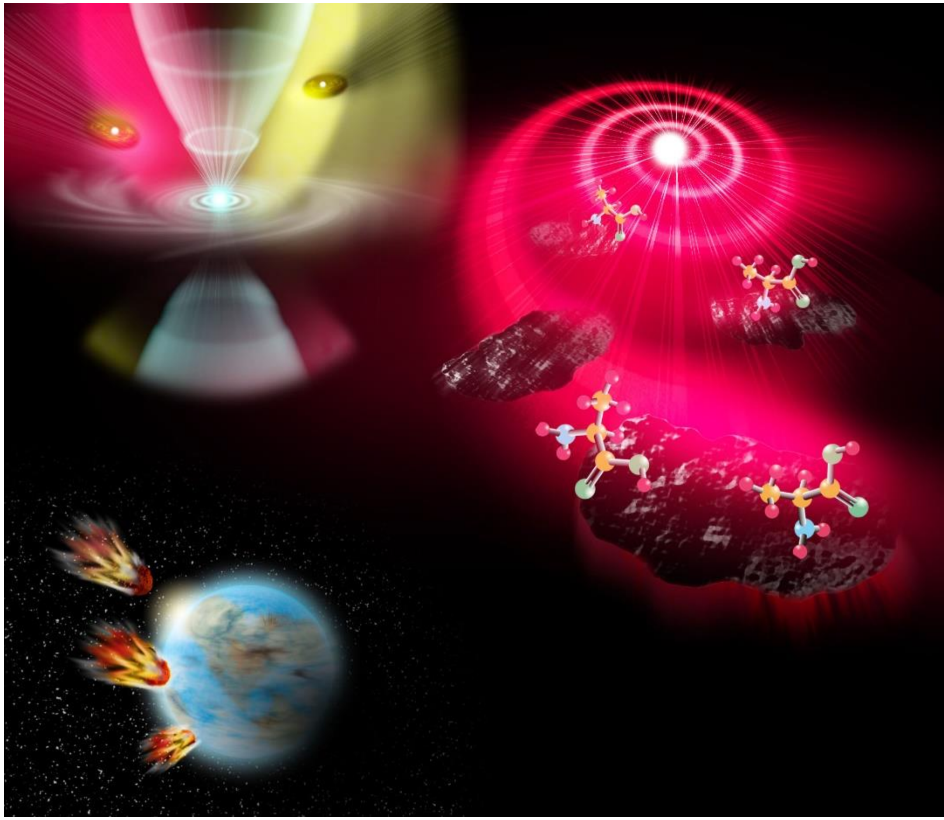


Orig. Life Evol. Biosph., **2010,** *40*, 335.

https://www.nao.ac.jp/releaselist/archive/20100406/index_j.html

Origin of asymmetry(Circular polarized light)





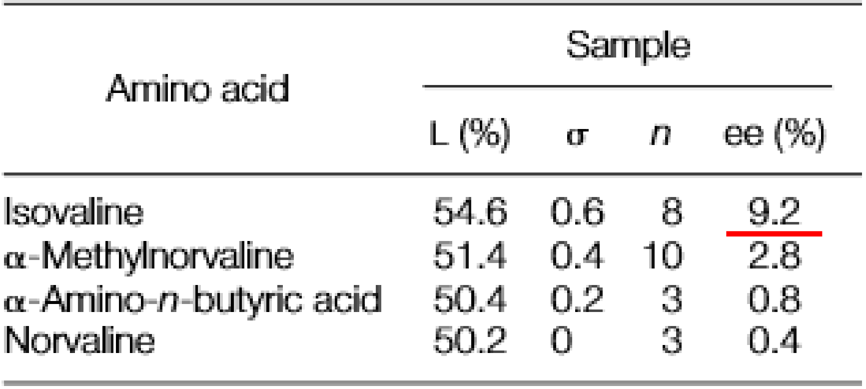
Infrared observation result of circularly polarized light of Orion great nebula

Red… ↻
Yellow… ↺

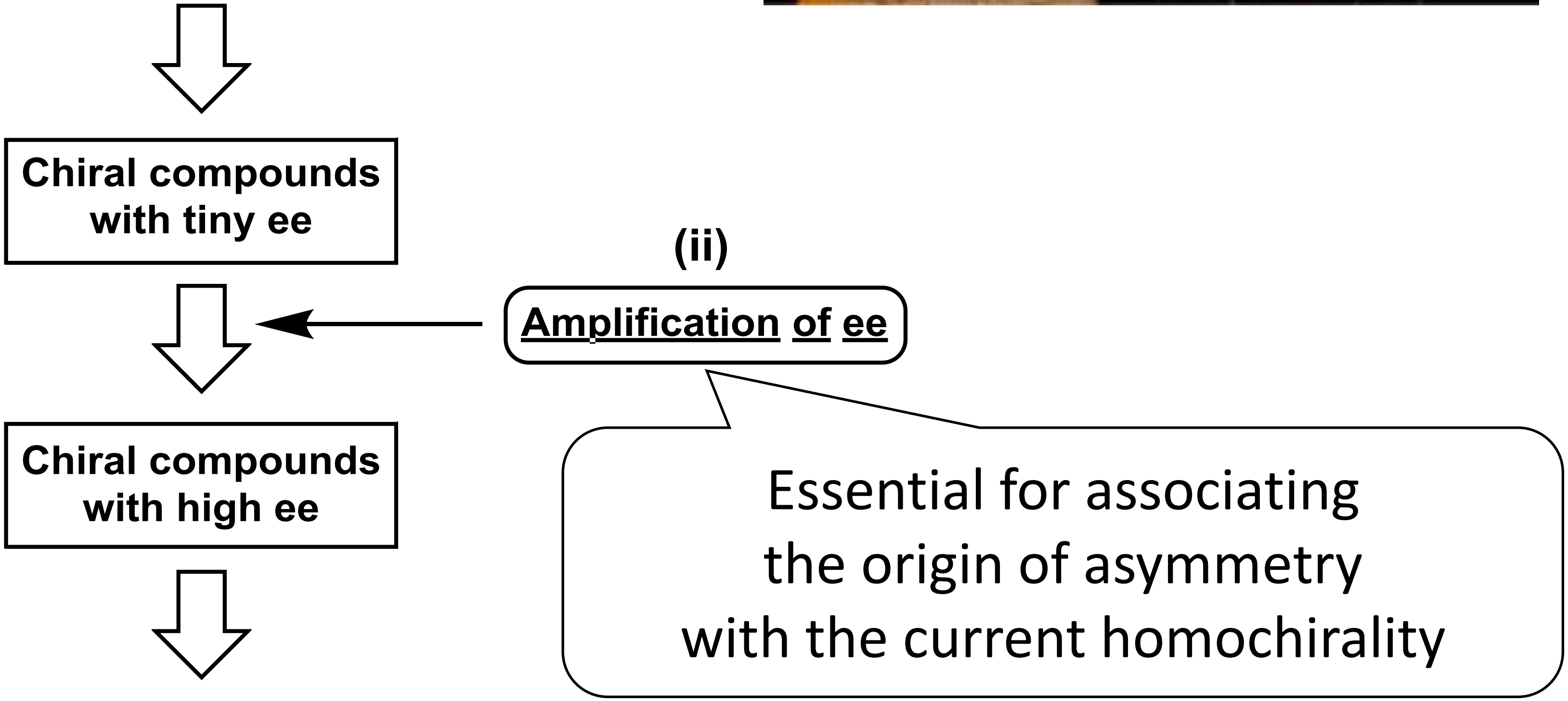
① Solar system formed in large mass star formation area.
② The primitive solar system was irradiated with circularly polarized light in one direction.
③ Amino acids were biased towards L-type and later introduced by meteorites onto the earth.

The theory that circular polarization is the origin of chirality

Origin of asymmetry(Circular polarized light)



Amino acid	Sample			
	L (%)	σ	*n*	ee (%)
Isovaline	54.6	0.6	8	9.2
α-Methylnorvaline	51.4	0.4	10	2.8
α-Amino-*n*-butyric acid	50.4	0.2	3	0.8
Norvaline	50.2	0	3	0.4



Chiral compounds with tiny ee

(ii)

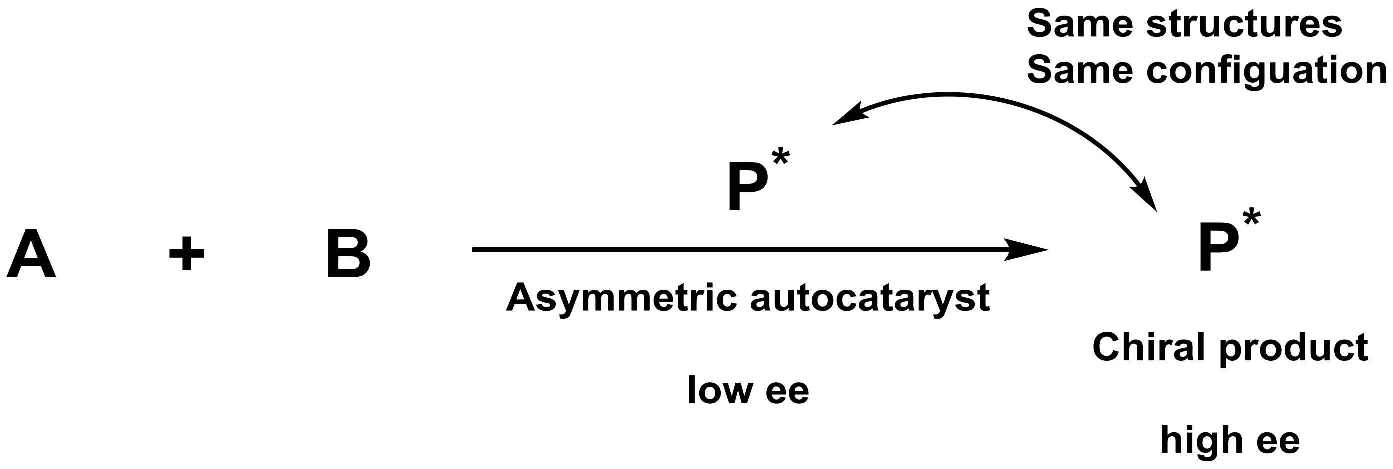
Amplification of ee

Chiral compounds with high ee

Essential for associating the origin of asymmetry with the current homochirality

J. R. Cronin, et al., *Science,* **1997,** *275,* 951.

Asymmetric autocatalysis with amplification of ee



Same structures
Same configuation

$A + B \xrightarrow[\text{Asymmetric autocataryst}]{P^*} P^*$

low ee

Chiral product

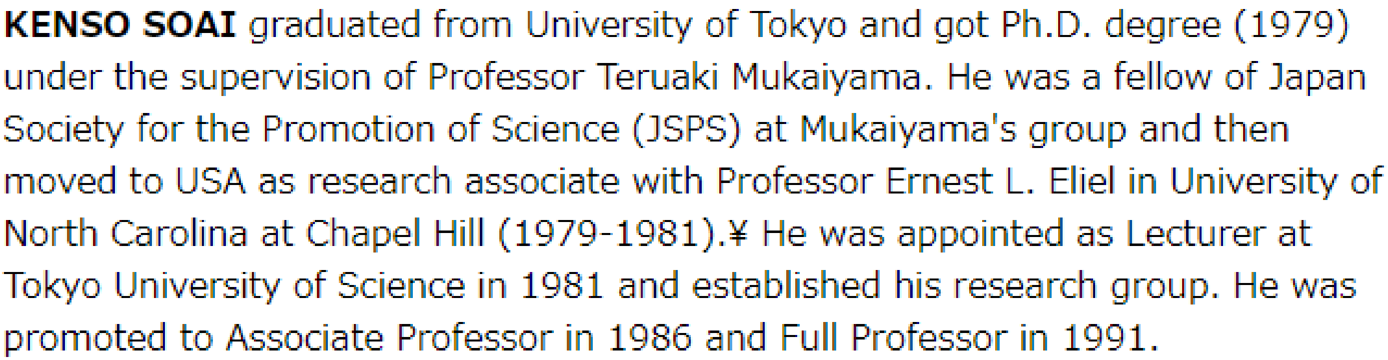
high ee

High reaction rate, theoretically infinite growth rate

Self-multiplication of chiral compounds resembles self-propagation of life.
→This reaction is related to the origin of homochirality???
(Suggested by frank in 1953)

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

Prof. Kenso Soai



KENSO SOAI graduated from University of Tokyo and got Ph.D. degree (1979) under the supervision of Professor Teruaki Mukaiyama. He was a fellow of Japan Society for the Promotion of Science (JSPS) at Mukaiyama's group and then moved to USA as research associate with Professor Ernest L. Eliel in University of North Carolina at Chapel Hill (1979-1981).¥ He was appointed as Lecturer at Tokyo University of Science in 1981 and established his research group. He was promoted to Associate Professor in 1986 and Full Professor in 1991.

His recent research

(1)Asymmetric autocatalysis (Asymmetric automultiplication, Self-replication of chiral compounds)

(2) Asymmetric autocatalysis with amplification of enantiomeric excess

(3) Origins of chirality, origins of chirality of biomolecules

(4) Dendritic chiral catalyst

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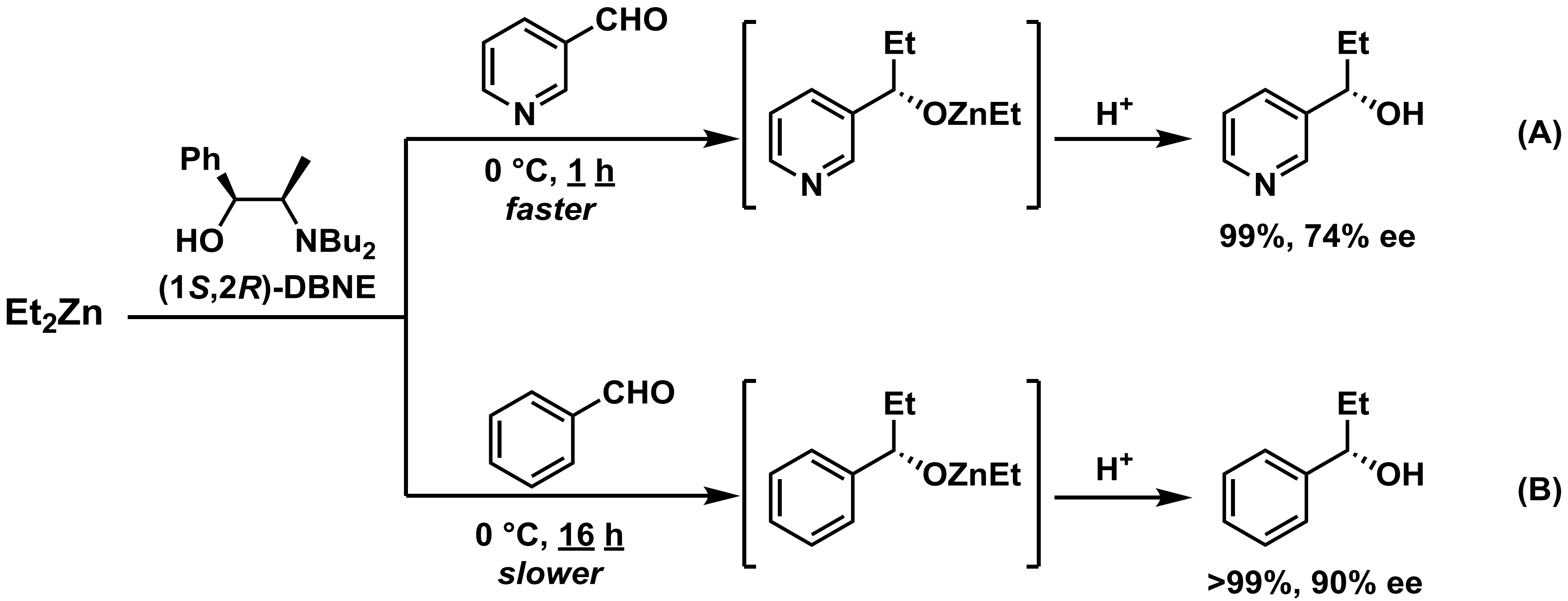
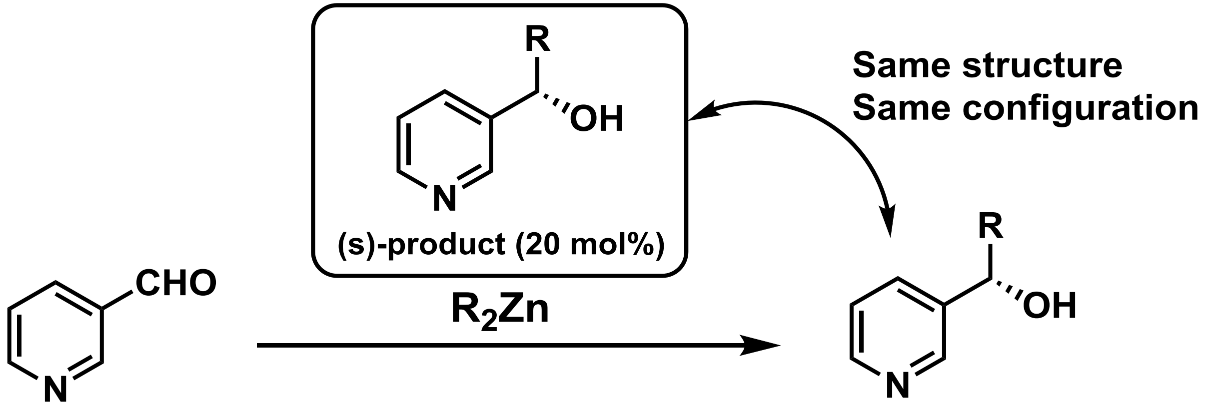
Asymmetric alkylation of aldehydes



Reaction rate (A)>(B) …→ Product of (A) accelerates this reaction?

K. Soai, S. Hori, S. Niwa, *Heterocycles,* **1989,** *29,* 2065.
K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem.,* **1991,** *56,* 4264.

First asymmetric autocatalytic reaction

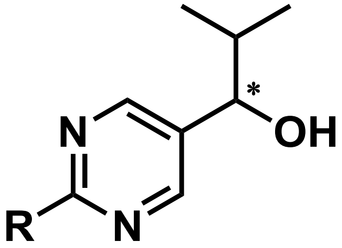


Asymmetric autocatalysis

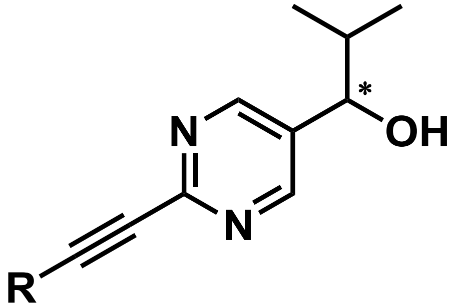
R	catalyst ee	yield	Product ee
Me	42%	——	7%
Et	56%	66%	14%
iPr	86%	67%	35%
Bu	47%	——	6%

K. Soai, S. Niwa, S. Hori, *J. Chem. Soc., Chem. Commun.,* **1990,** 982.

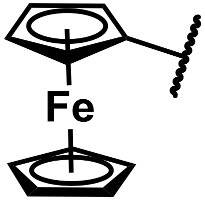
Other substrates for asymmetric autocatalytic reaction



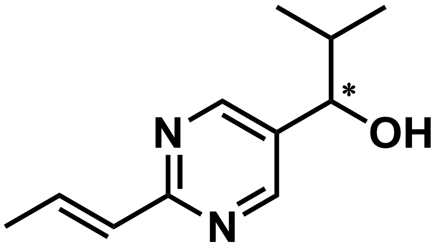
R = H (90% ee)
Me (98% ee)



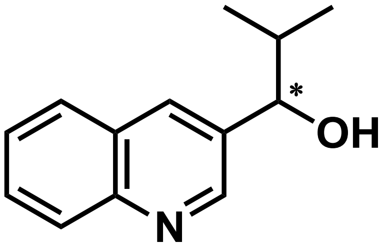
R = n-Bu
TMS
TBS (up to > 99.5% ee)
TIPS
Ph



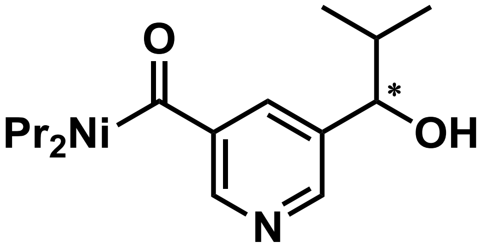
(up to > 99% ee)



R = tBu (up to 99% ee)
TMS (up to 71% ee)



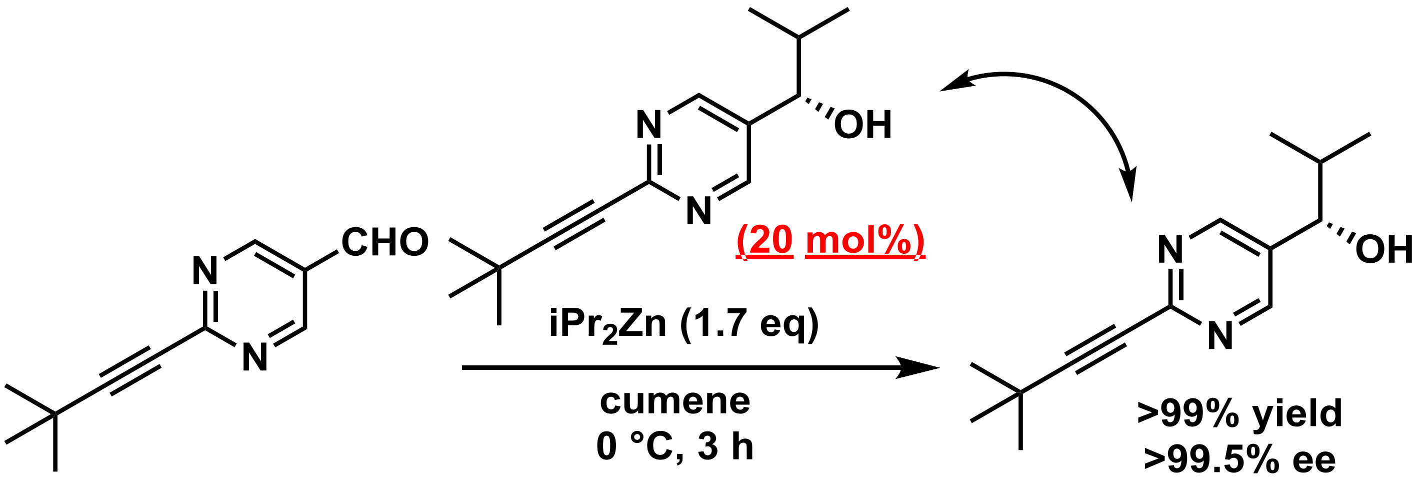
(up to 88% ee)



(up to 88% ee)

K. Soai, *et al. J. Fluorine Chem.*, **2010,** *131,* 525.

The most effective asymmetric autocatalyst

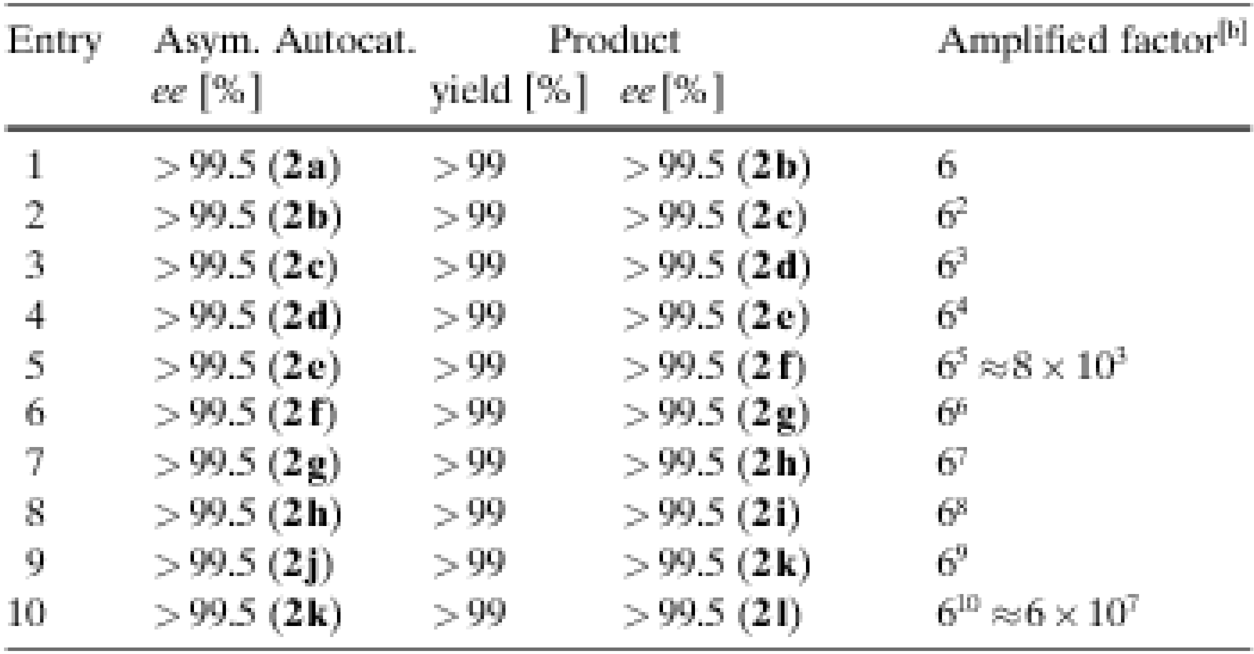


(20 mol%)

iPr_2Zn (1.7 eq)

cumene
0 °C, 3 h

>99% yield
>99.5% ee

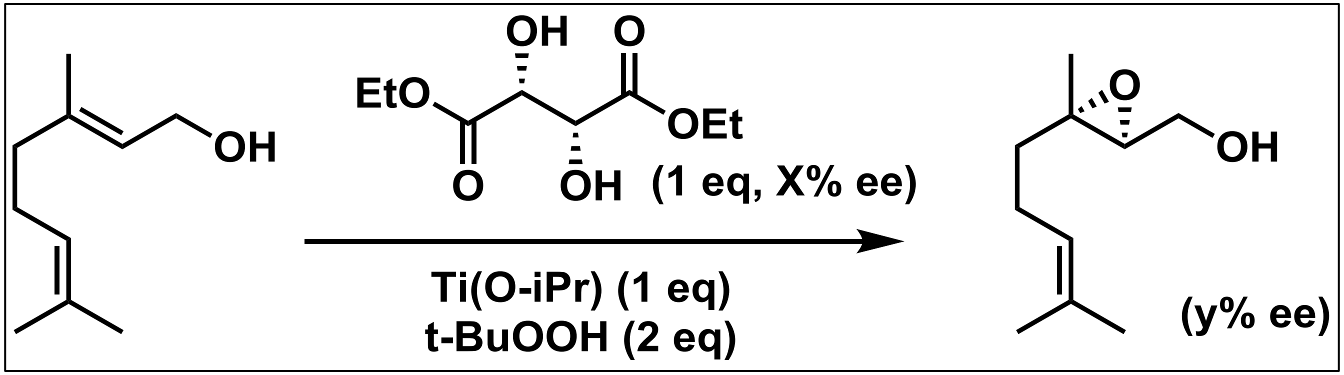


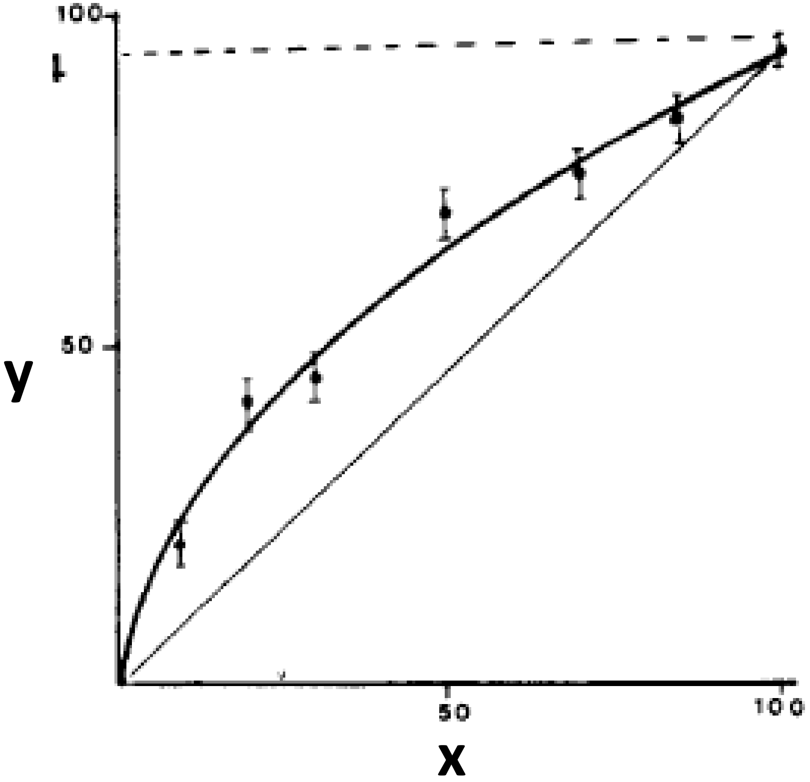
Entry	Asym. Autocat. *ee* [%]	Product yield [%]	Product *ee* [%]	Amplified factor[b]
1	> 99.5 (**2a**)	> 99	> 99.5 (**2b**)	6
2	> 99.5 (**2b**)	> 99	> 99.5 (**2c**)	6^2
3	> 99.5 (**2c**)	> 99	> 99.5 (**2d**)	6^3
4	> 99.5 (**2d**)	> 99	> 99.5 (**2e**)	6^4
5	> 99.5 (**2e**)	> 99	> 99.5 (**2f**)	$6^5 \approx 8 \times 10^3$
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**)	$6^{10} \approx 6 \times 10^7$

K. Soai, *et al. Angew. Chem., Int. Ed.*, **1999,** *38*, 659.

Asymmetric amplification

- First example of Asymmetric amplification





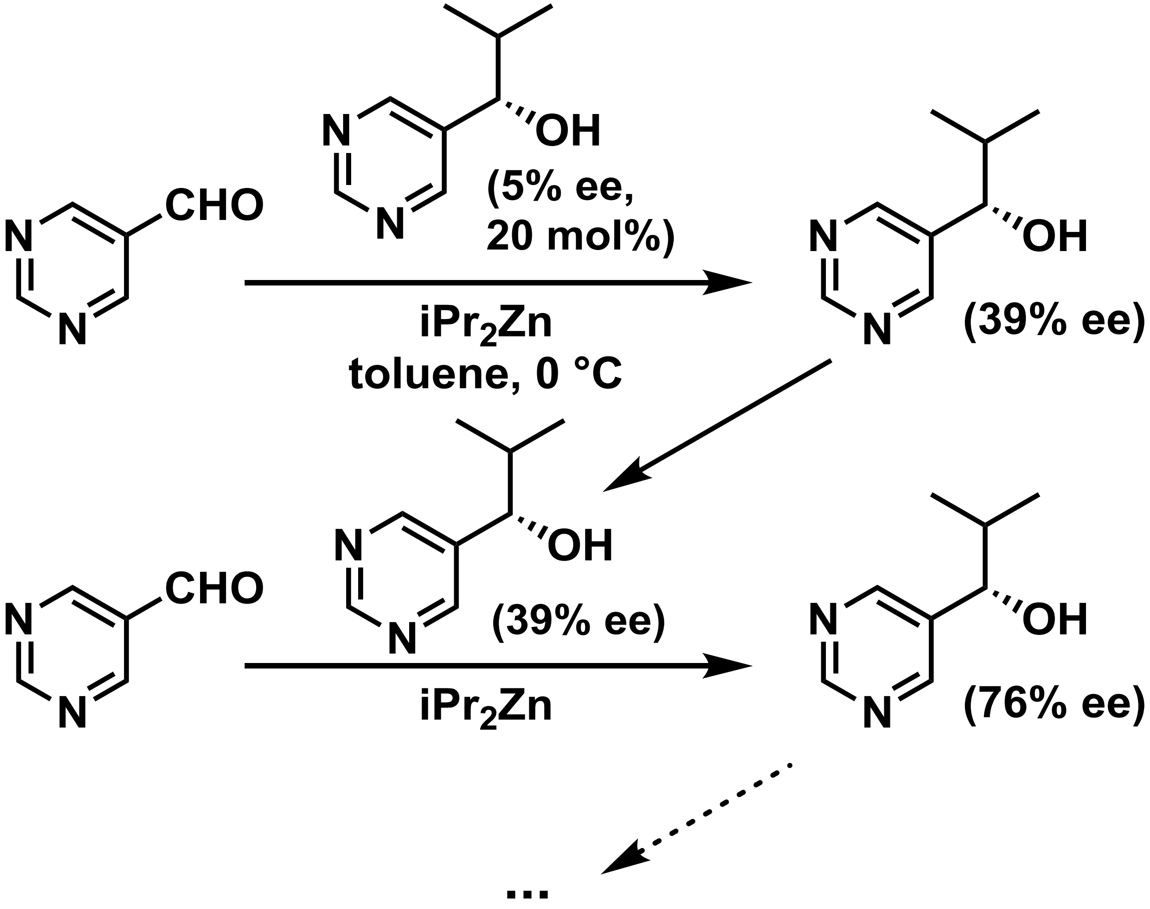
ee of Diethyl tartrate

∧

ee of product epoxide

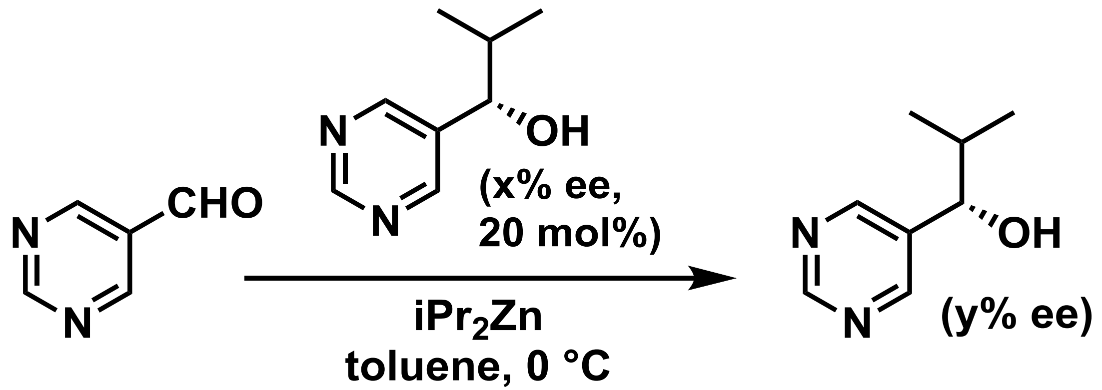
H. B. Kagan, *et al. J. Am. Chem. Soc.* **1986,** *108,* 2353.

Asymmetric autocatalyst and Asymmetric amplification

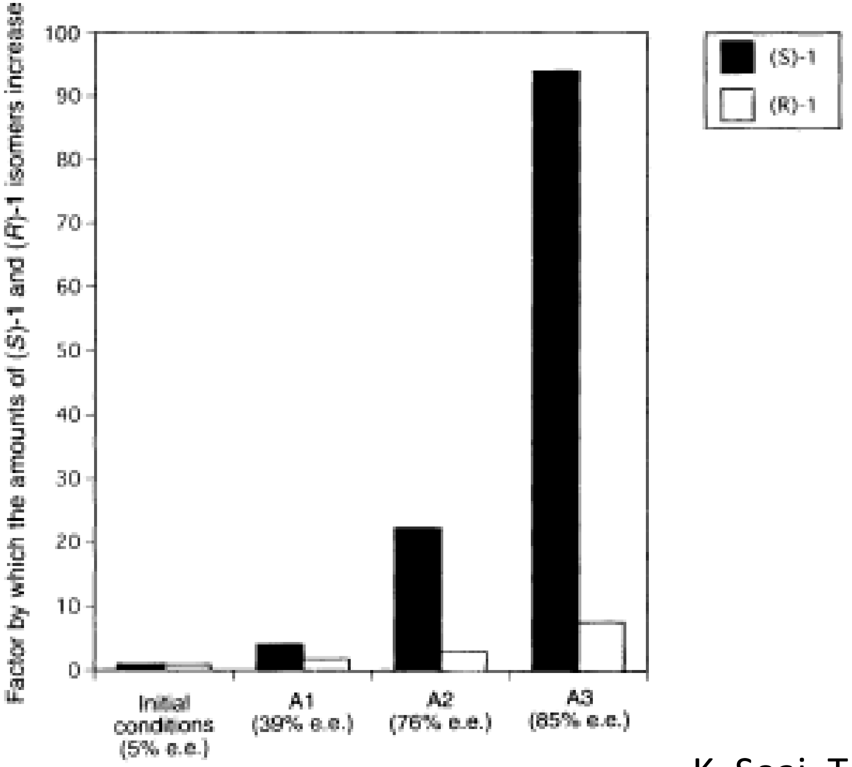


K. Soai, T. Shubata, H. Morioka, K. Choji, *Nature,* **1995,** *378,* 767.

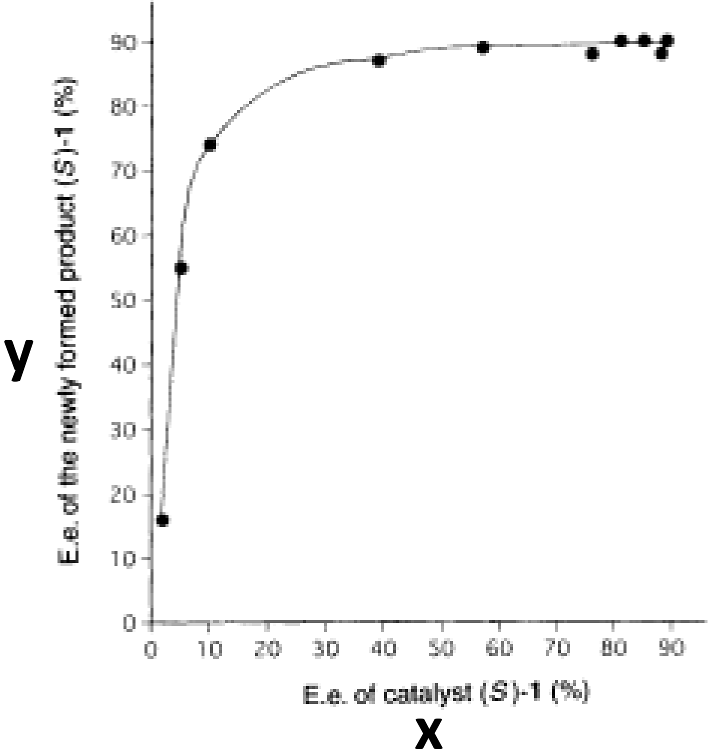
Asymmetric autocatalyst and Asymmetric amplification



Amplification of ee

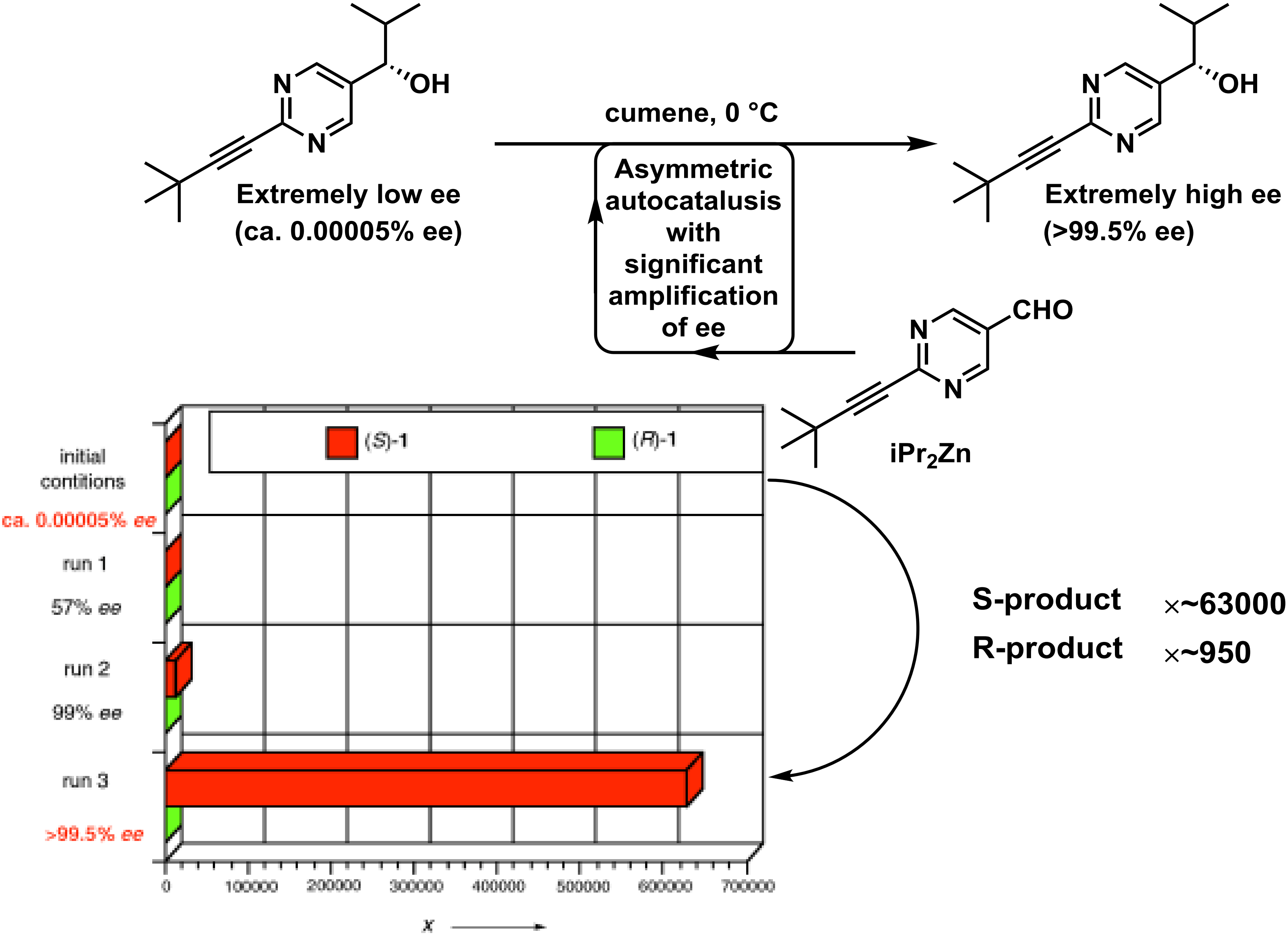


Relationship between catalyst and product ee



K. Soai, T. Shubata, H. Morioka, K. Choji, *Nature,* **1995,** *378,* 767.

The most effective asymmetric autocatalyst



Extremely low ee
(ca. 0.00005% ee)

cumene, 0 °C

Asymmetric autocatalusis with significant amplification of ee

Extremely high ee
(>99.5% ee)

iPr_2Zn

S-product ×~630000

R-product ×~950

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

Summary 1

- Soai Reaction is the only example of asymmetric autocatalytic reactions with elevated enantiomeric excess.
- Compounds with almost 100% ee can be obtained from low ee compounds.

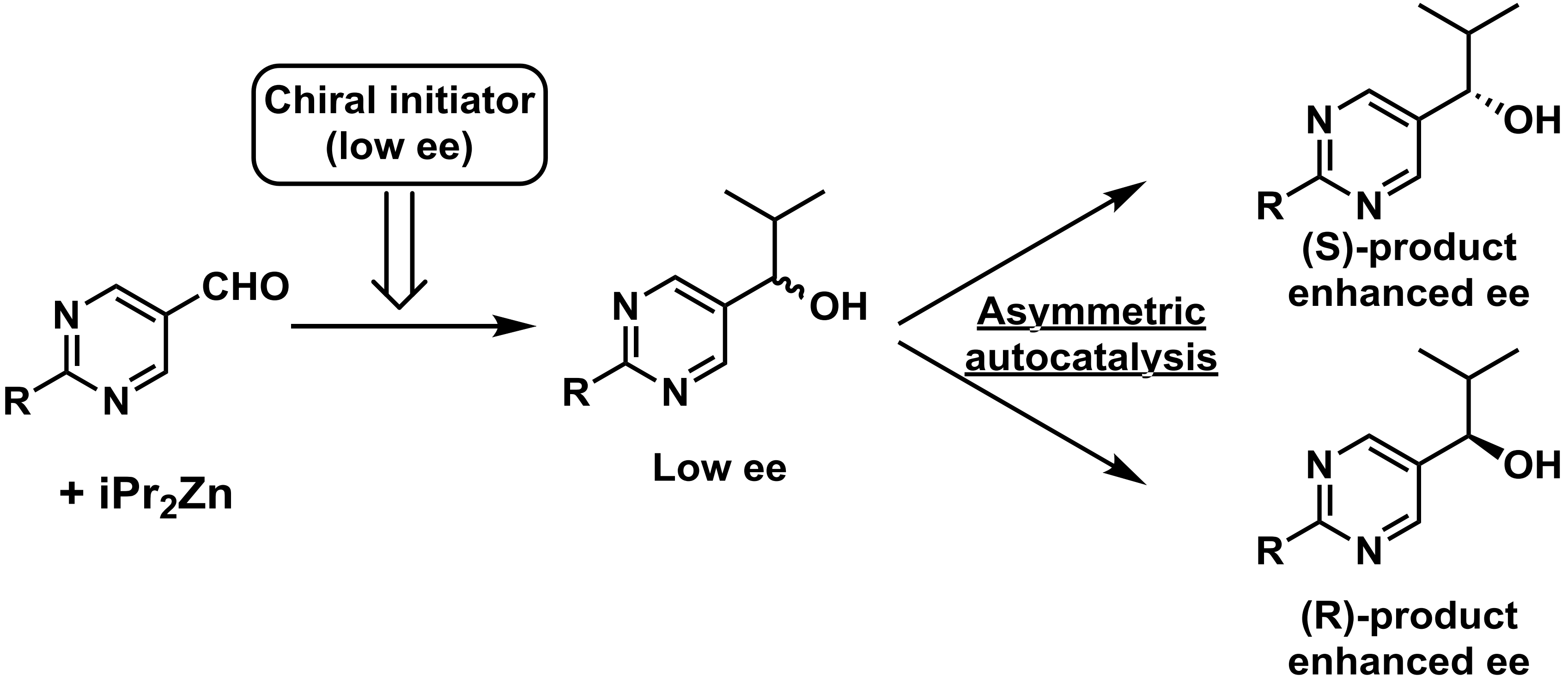
Contents

1. Introduction
2. Discovery of soai reaction
3. Application of soai reaction

(Various chiral sources and origin of homochirality)

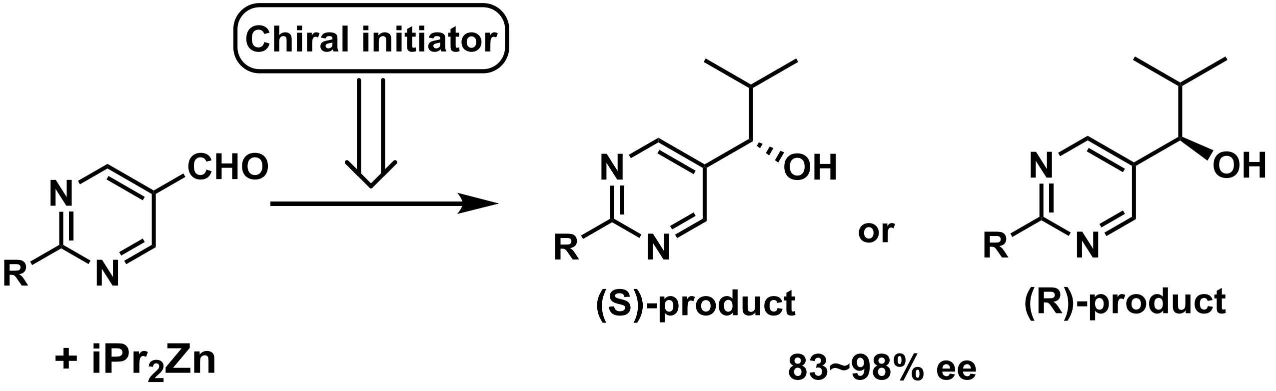
4. Mechanism of soai reaction

Association of high ee with the origin of asymmetry



- Establishing a model process where the origin of asymmetry has led to homochirality
- Finding new asymmetric origins

Various Chiral initiators



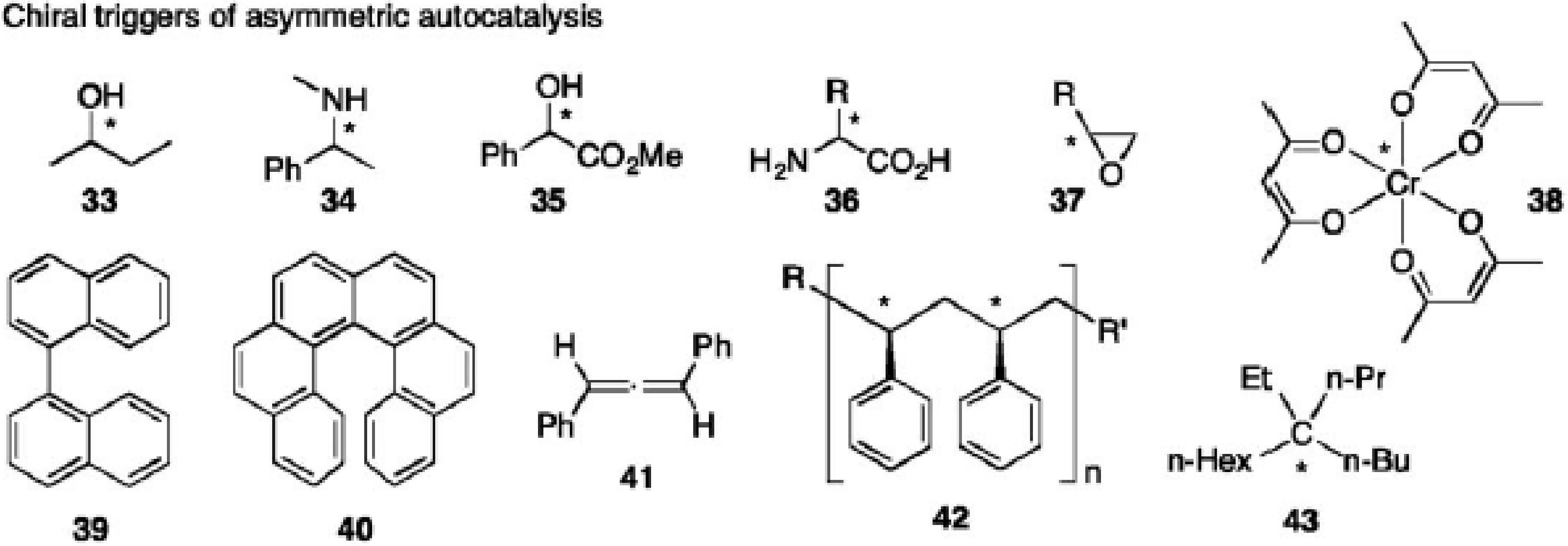


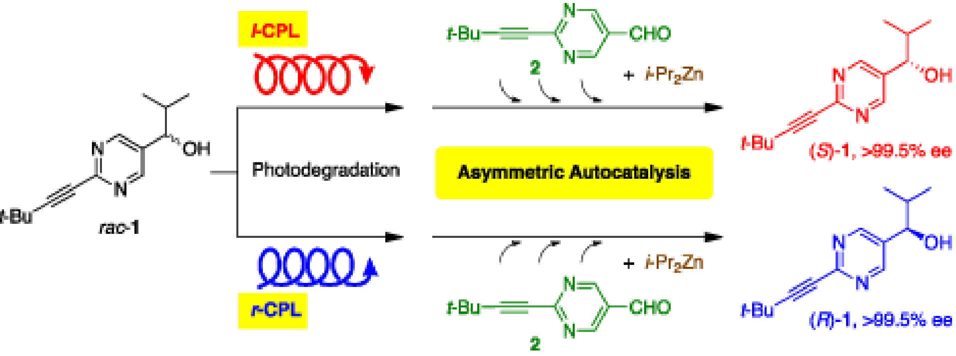
Fig. 14. Asymmetric autocatalysis initiated by chiral compounds.

Various chiral compounds induce chiral amplification.

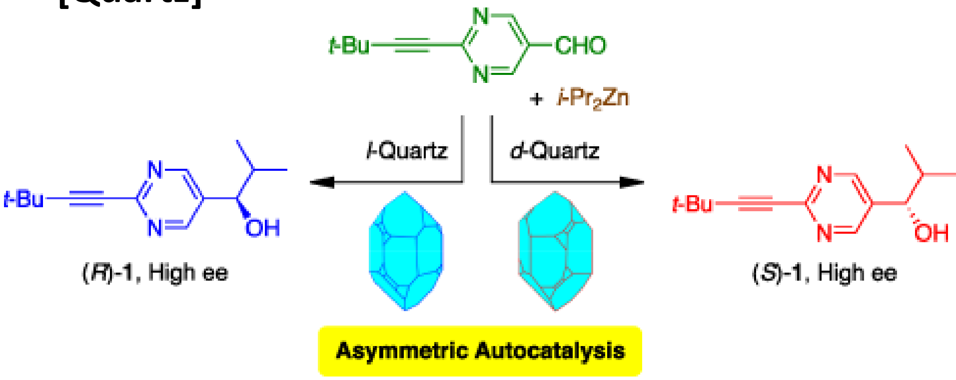
K. Soai, *et al. J. Fluorine Chem.,* **2010,** *131,* 525.

Various Chiral initiators(origin of chiral?)

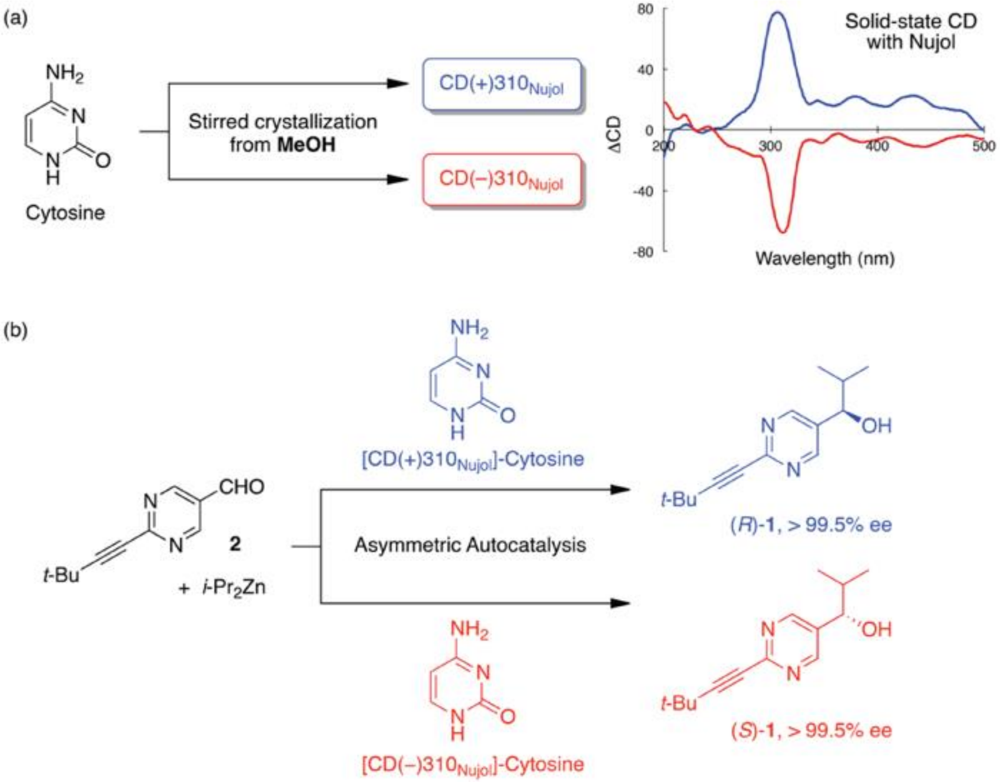
[Circularly polarized light]



[Quartz]



[Chiral organic crystal]

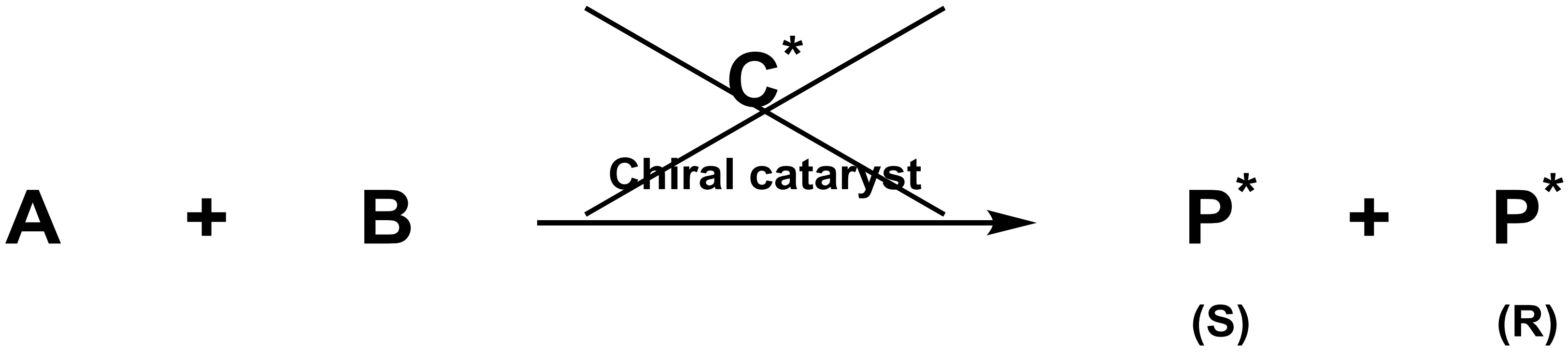


Candidate for origin of chiral
↓
>99.5% ee products

Indicating that
they can be the origin of chiral

K. Soai, *et al. Chem. Rec.*, **2014,** *14, 70.*

Spontaneous absolute asymmetric synthesis



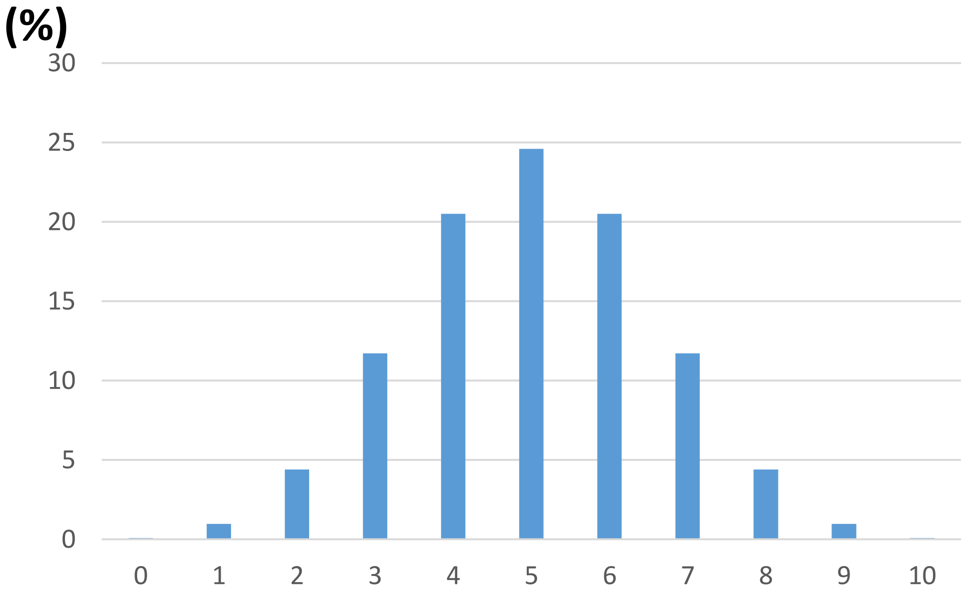
$$A + B \xrightarrow{\cancel{C^* \text{ Chiral cataryst}}} \underset{(S)}{P^*} + \underset{(R)}{P^*}$$

1 : 1

Racemic

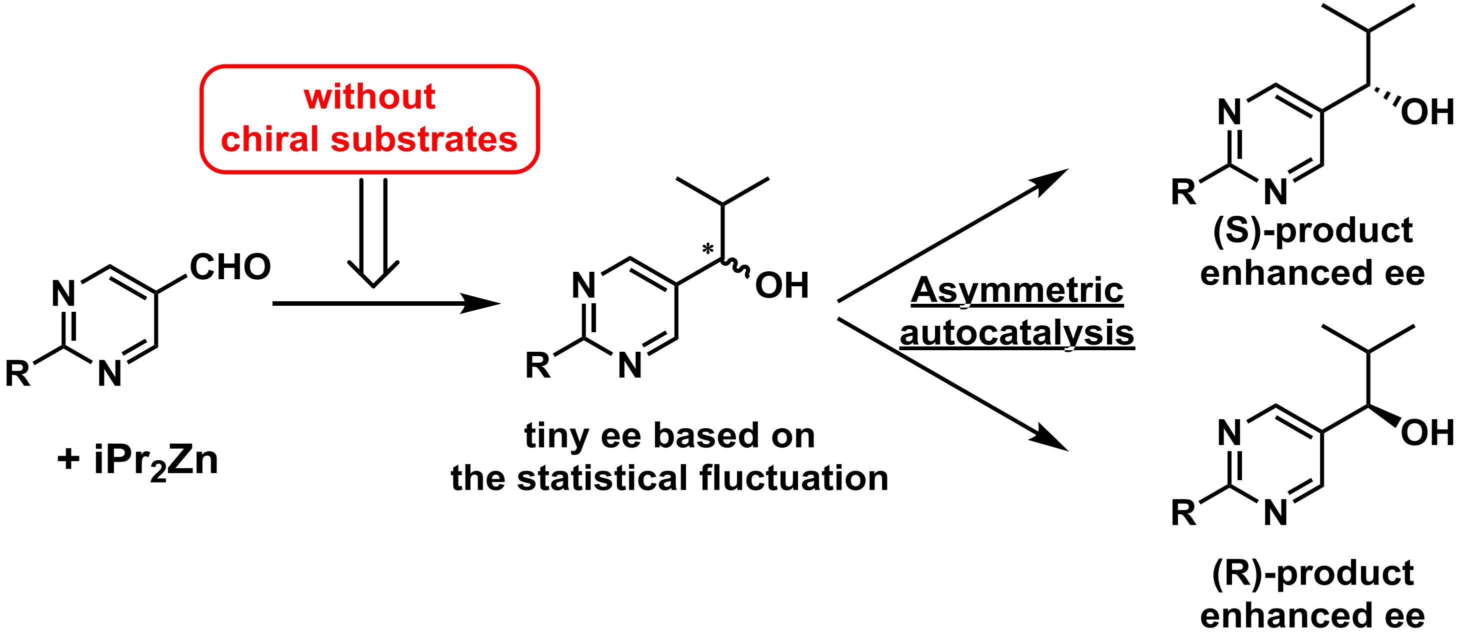
But…

Coin toss (×10)



Enantiomeric excess by statistical fluctuation (undetectable)

Spontaneous absolute asymmetric synthesis



without chiral substrates

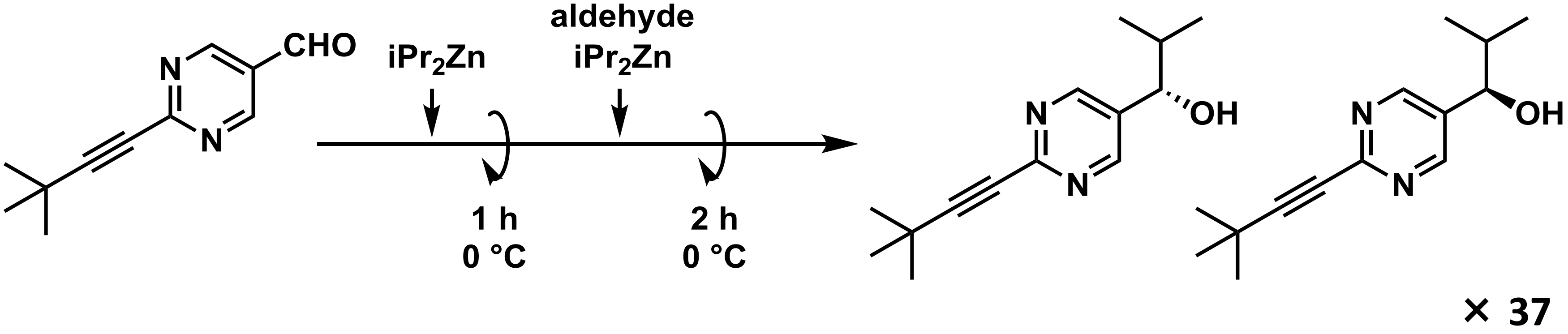
+ iPr$_2$Zn

tiny ee based on the statistical fluctuation

Asymmetric autocatalysis

(S)-product enhanced ee

(R)-product enhanced ee



K. Soai, *et al. Atetrahedron: Asymmetry.*, **2003,** *14,* 185.

Result (table)

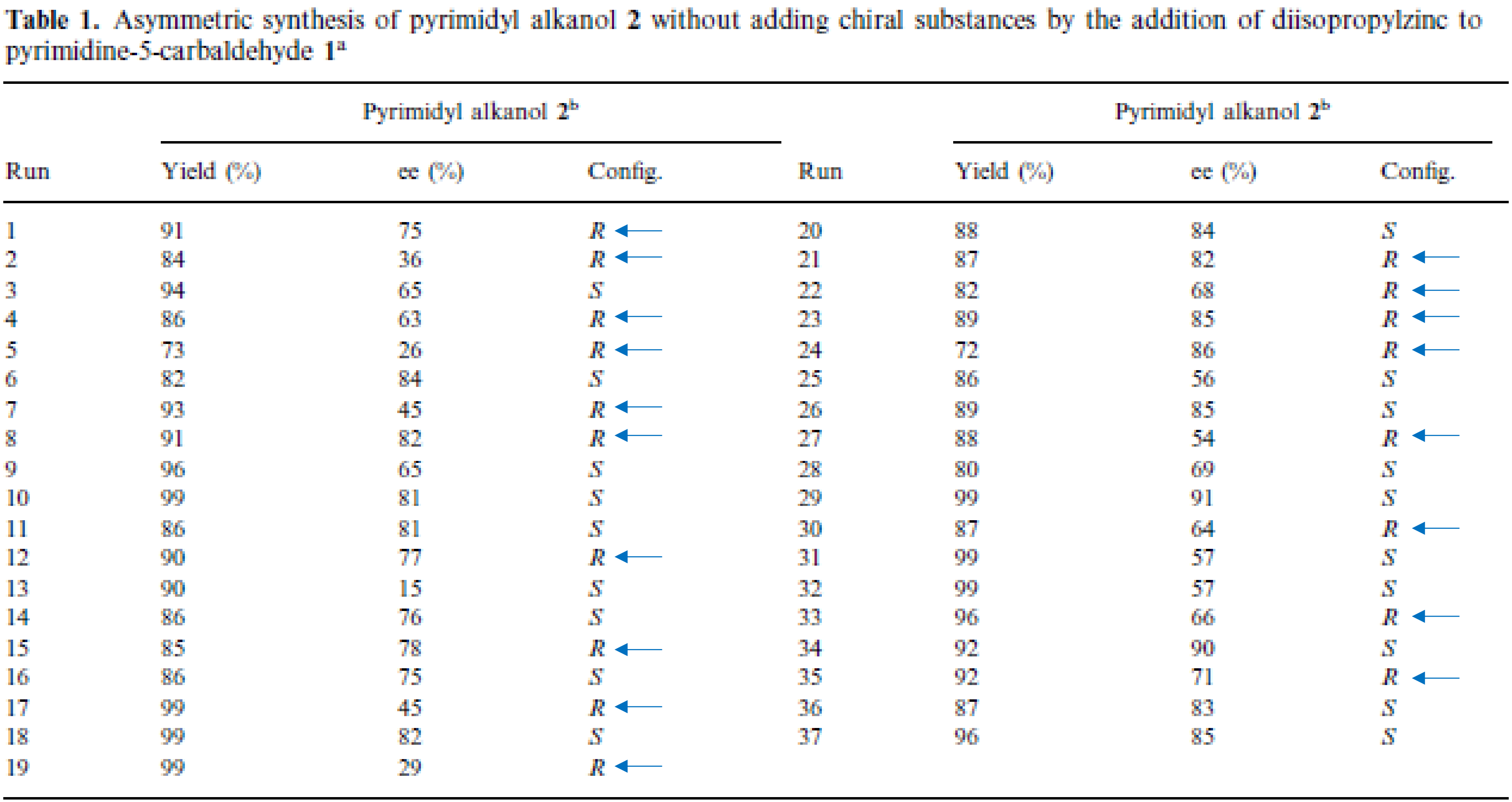


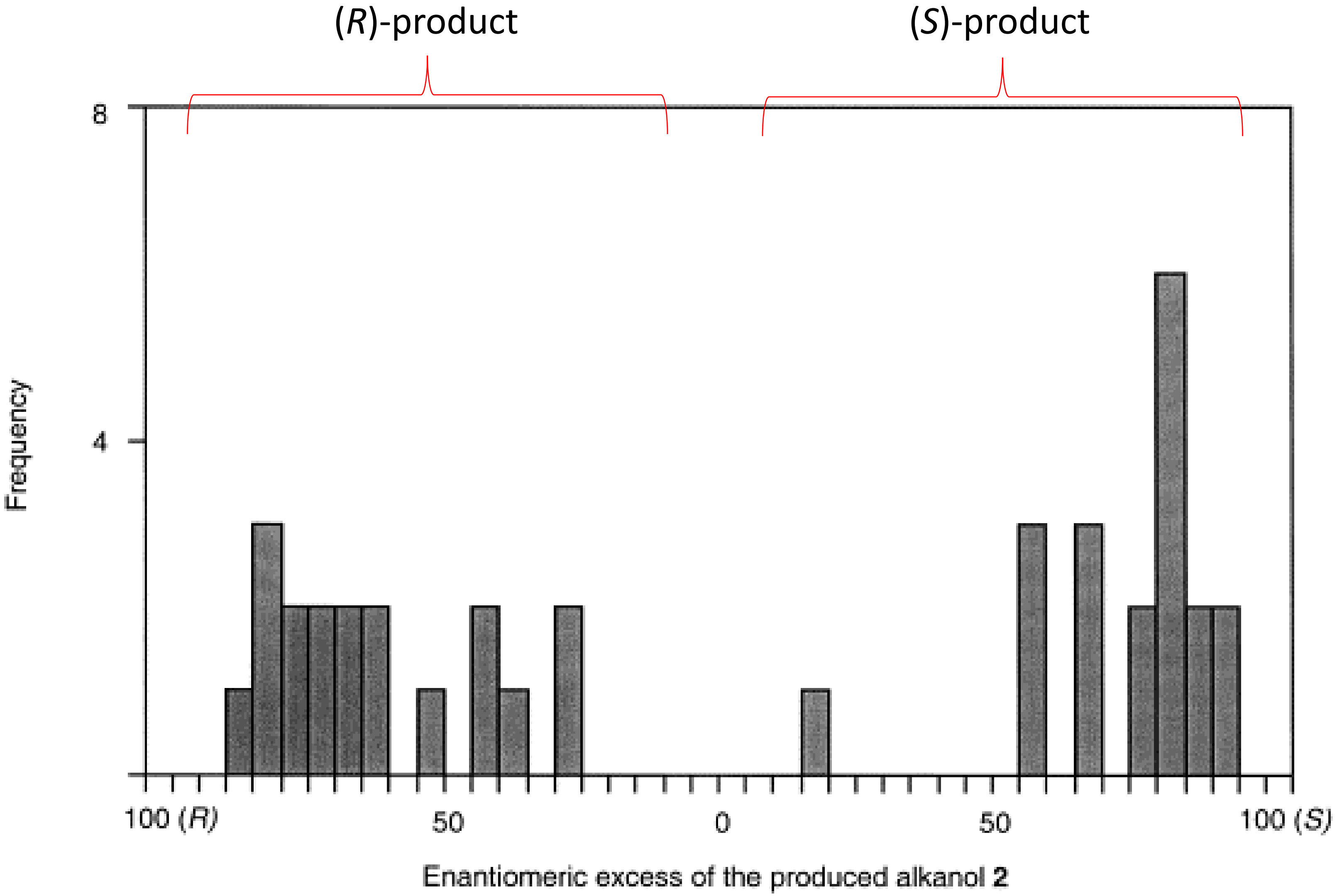
Table 1. Asymmetric synthesis of pyrimidyl alkanol **2** without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde **1**[a]

	Pyrimidyl alkanol **2**[b]				Pyrimidyl alkanol **2**[b]		
Run	Yield (%)	ee (%)	Config.	Run	Yield (%)	ee (%)	Config.
1	91	75	*R* ←	20	88	84	*S*
2	84	36	*R* ←	21	87	82	*R* ←
3	94	65	*S*	22	82	68	*R* ←
4	86	63	*R* ←	23	89	85	*R* ←
5	73	26	*R* ←	24	72	86	*R* ←
6	82	84	*S*	25	86	56	*S*
7	93	45	*R* ←	26	89	85	*S*
8	91	82	*R* ←	27	88	54	*R* ←
9	96	65	*S*	28	80	69	*S*
10	99	81	*S*	29	99	91	*S*
11	86	81	*S*	30	87	64	*R* ←
12	90	77	*R* ←	31	99	57	*S*
13	90	15	*S*	32	99	57	*S*
14	86	76	*S*	33	96	66	*R* ←
15	85	78	*R* ←	34	92	90	*S*
16	86	75	*S*	35	92	71	*R* ←
17	99	45	*R* ←	36	87	83	*S*
18	99	82	*S*	37	96	85	*S*
19	99	29	*R* ←				

(*S*)-product × 19, (R)-product × 18

K. Soai, *et al. Atetrahedron: Asymmetry.*, **2003,** *14,* 185.

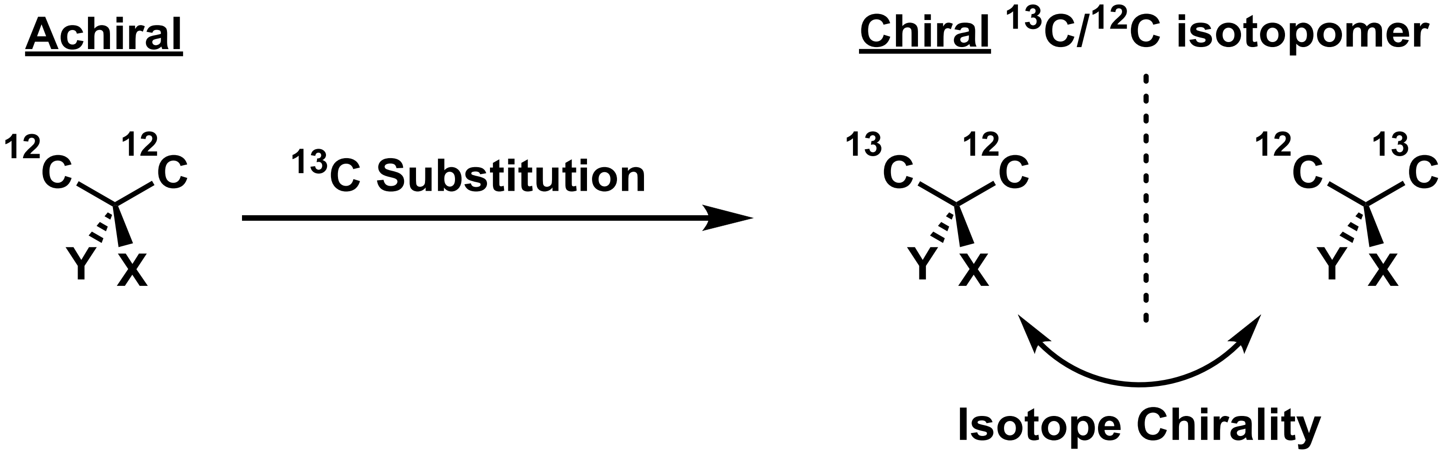
Result (graph)



The only example that achieved spontaneous asymmetric synthesis

K. Soai, *et al. Tetrahedron: Asymmetry.*, **2003,** *14,* 185.

Chirality by isotope replacement



Achiral

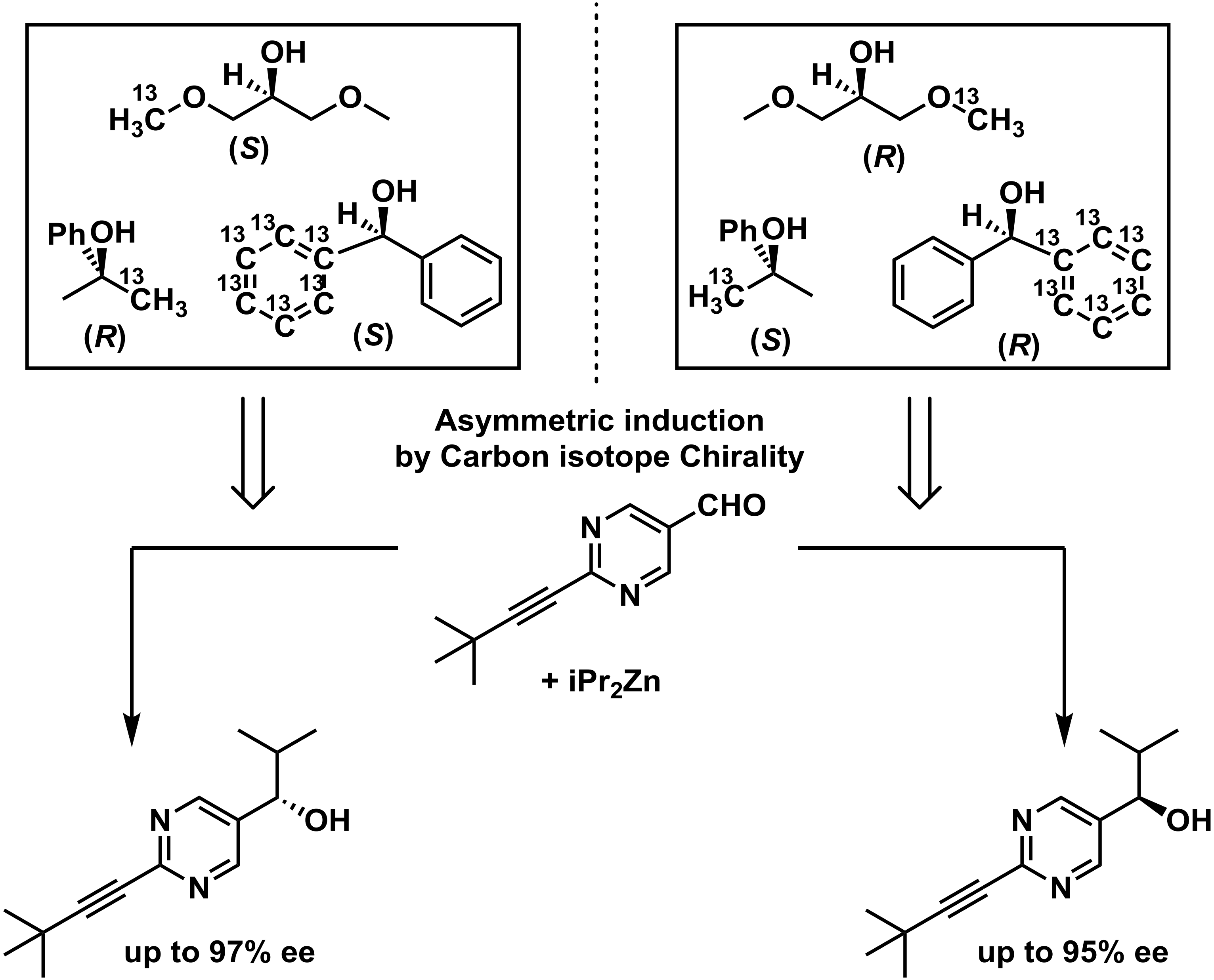
^{13}C Substitution

Chiral ^{13}C/^{12}C isotopomer

Isotope Chirality

	Carbon-13	Carbon-12
Electron	6	6
Neutron	7	6
Proton	6	6
natural abundance	1.1%	98.9%

Asymmetric Autocatalysis triggered by C12/C13 Chirality



Asymmetric induction
by Carbon isotope Chirality

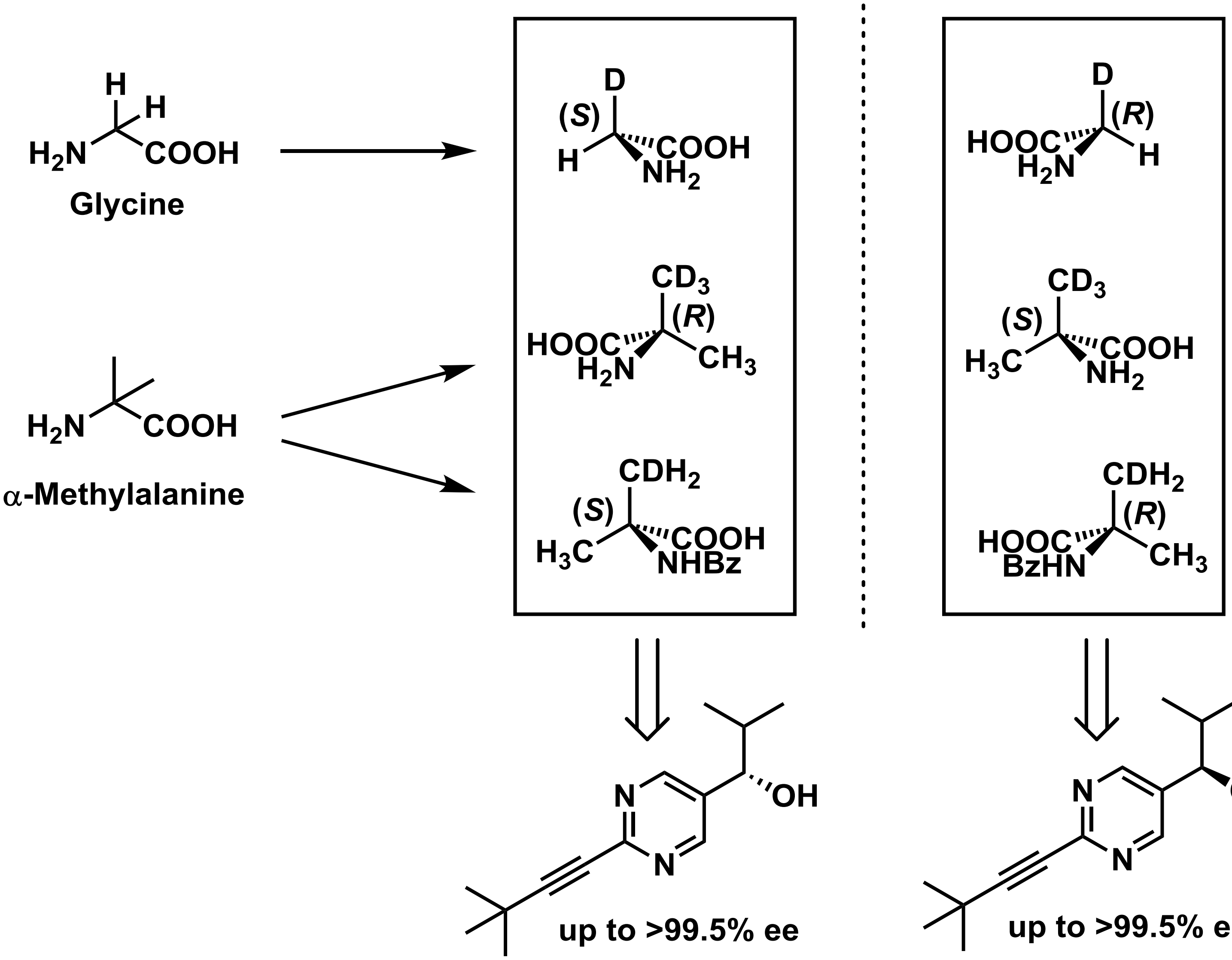
+ iPr_2Zn

up to 97% ee

up to 95% ee

K. Soai, *et al. Science,* **2009,** *324,* 109.

Asymmetric Autocatalysis triggered by H/D Chirality



K. Soai, *et al. Chem. Commun.*, **2009,** *4396*.

K. Soai, *et al. Chem. Lett.*, **2011,** *40,* 324.

Asymmetric Autocatalysis triggered by H/D Chirality

meteorite

Extraction

•

Analysis

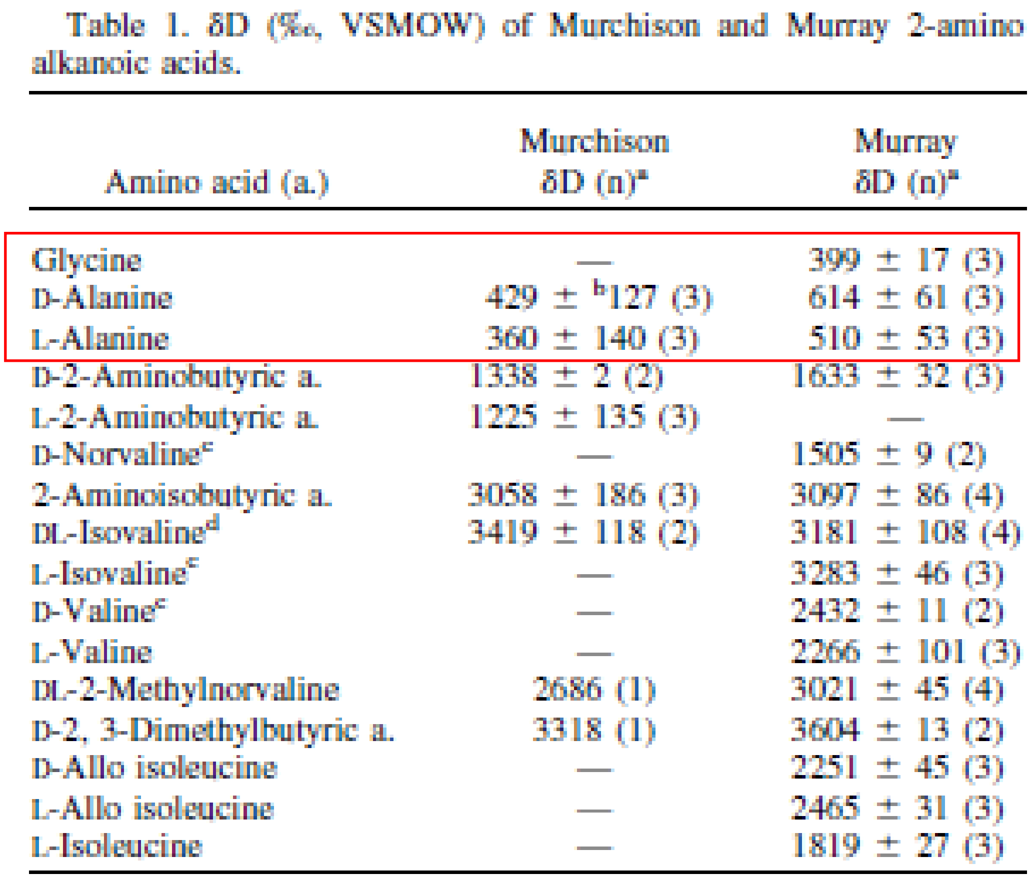


Table 1. δD (‰, VSMOW) of Murchison and Murray 2-amino alkanoic acids.

Amino acid (a.)	Murchison δD (n)[a]	Murray δD (n)[a]
Glycine	—	399 ± 17 (3)
D-Alanine	429 ± [b]127 (3)	614 ± 61 (3)
L-Alanine	360 ± 140 (3)	510 ± 53 (3)
D-2-Aminobutyric a.	1338 ± 2 (2)	1633 ± 32 (3)
L-2-Aminobutyric a.	1225 ± 135 (3)	—
D-Norvaline[c]	—	1505 ± 9 (2)
2-Aminoisobutyric a.	3058 ± 186 (3)	3097 ± 86 (4)
DL-Isovaline[d]	3419 ± 118 (2)	3181 ± 108 (4)
L-Isovaline[c]	—	3283 ± 46 (3)
D-Valine[c]	—	2432 ± 11 (2)
L-Valine	—	2266 ± 101 (3)
DL-2-Methylnorvaline	2686 (1)	3021 ± 45 (4)
D-2, 3-Dimethylbutyric a.	3318 (1)	3604 ± 13 (2)
D-Allo isoleucine	—	2251 ± 45 (3)
L-Allo isoleucine	—	2465 ± 31 (3)
L-Isoleucine	—	1819 ± 27 (3)

Amino acids in the meteorite contain a lot of deuterium.
A new theory that the origin of homochirality is chirality by deuterium substitution?

S. Pizzarello, *et al. GeoChim. Cosmochim. Acta,* **2005,** *69,* 599.

Summary 2

- From very small asymmetric bias induced by asymmetric environment, almost chiral molecules can be obtained.
- Association between asymmetric origin and homochirality
- Presentation of new asymmetric origin candidates

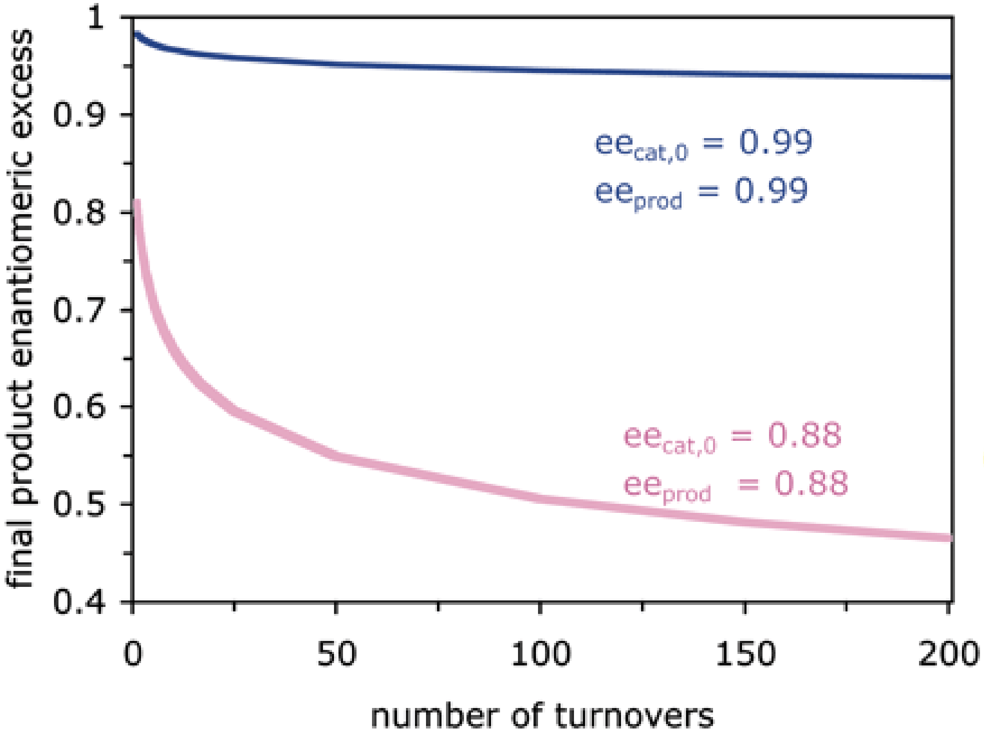
Contents

1. Introduction
2. Discovery of soai reaction
3. Application of soai reaction

(Various chiral sources and origin of homochirality)

4. Mechanism of soai reaction

Autocatalysis Alone



$$ee_{prod} = ee_0 \cdot ee_{cat}. \qquad [1]$$

catalyst is only a tiny fraction less than perfect ($ee_0 < 1$).

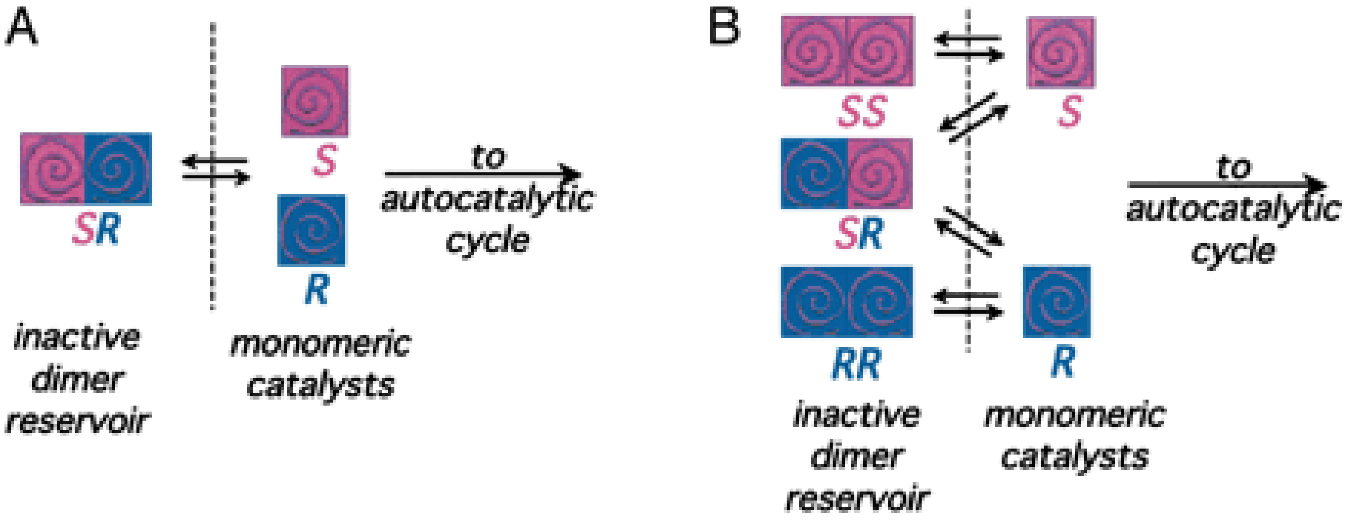
$$ee_{prod,f} = ee_{cat,0} \cdot (TON + 1)^{(ee_0 - 1)}.$$

$$< ee_{cat,0} \qquad [2]$$

Autocatalysis alone is not enough.
Need something to amplify ee of products.

D. G. Blackmond*, Proc. Nat. Acad. Sci. USA* **2004,** *101,* 5732.

Autocatalysis Plus Inhibition



[S]=80, [R]=20,

→ **[SR]=10, [S]=70, [R]=10**

↓ **70S** ↓ **10R**

→ **Amplification of ee!**

[S]=160, [R]=40, $\frac{[SR]^2}{[SS][RR]} = 4$

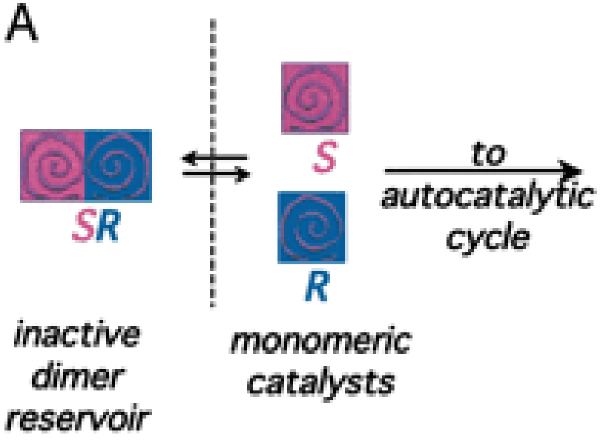
→ **[SR]=16, [SS]=32, [RR]=2**
[S]=80, [R]=20

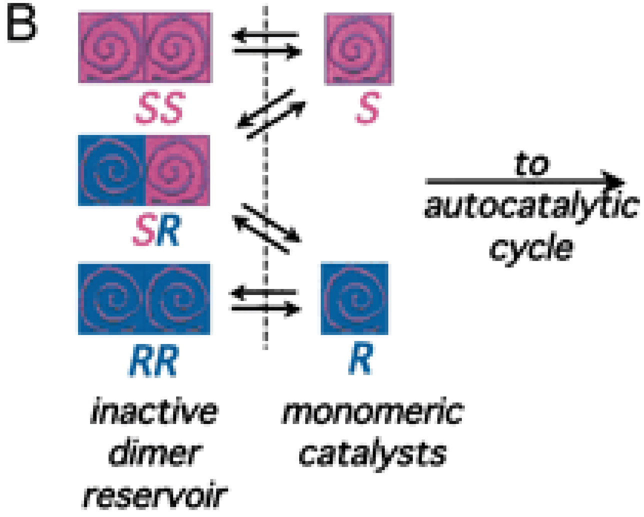
↓ **80S** ↓ **20R**

→ **No amplification of ee...**

F. C. Frank, *Biochim. Biophys. Acta,* **1953,** *11,* 459.
D. G. Blackmond, *Proc. Nat. Acad. Sci. USA* **2004,** *101,* 5732.

Autocatalysis Plus Inhibition





[S]=80, [R]=20,

$\longrightarrow$ **[SR]=10, [S]=70, [R]=10**

$\downarrow$ $\downarrow$

70S 10R

$\longrightarrow$ **Amplification of ee!**

[S]=160, [R]=40, $\frac{[SR]^2}{[SS][RR]} \geq 4$

$\longrightarrow$ **[SR]=20, [SS]=32, [RR]=2**
[S]=72, [R]=12

$\downarrow$ $\downarrow$

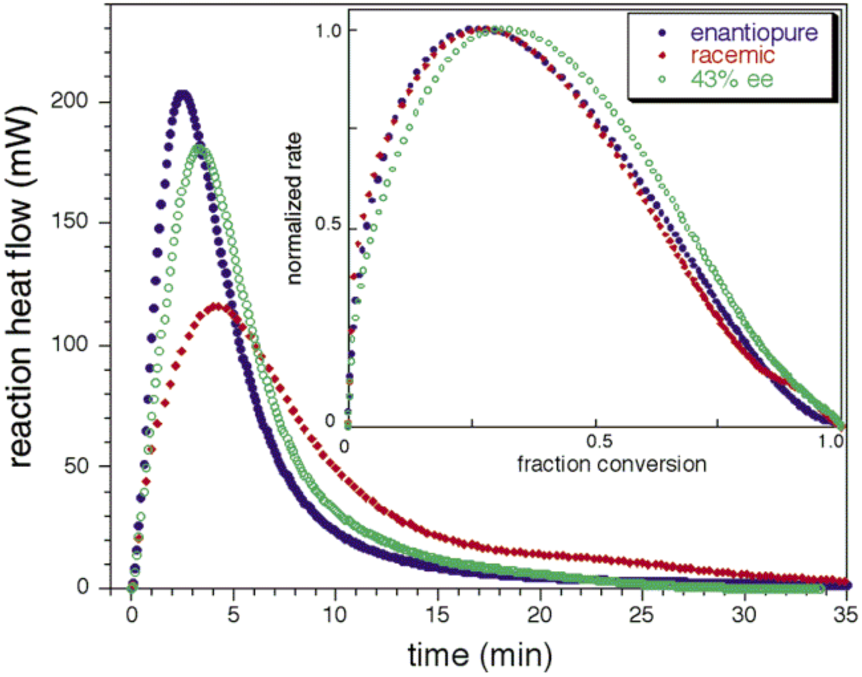
72S 12R

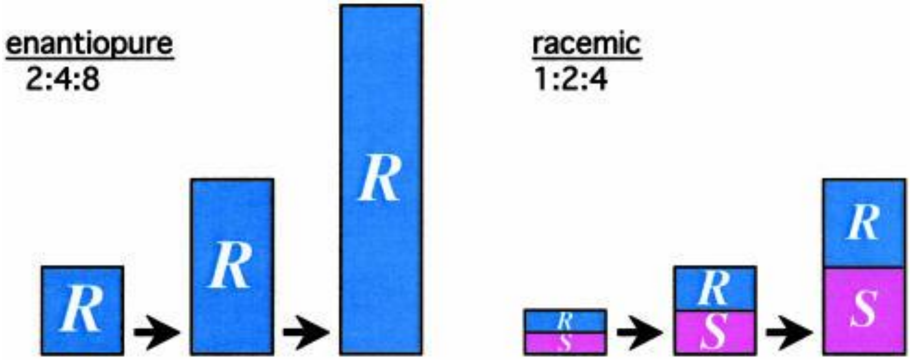
$\longrightarrow$ **Amplification of ee!**

Asymmetric amplification is achieved when the equilibria governing dimer formation are biased toward formation of *SR*.

F. C. Frank, *Biochim. Biophys. Acta,* **1953,** *11,* 459.
D. G. Blackmond, *Proc. Nat. Acad. Sci. USA* **2004,** *101,* 5732.

A Paradox Emerges





Initial rate for a racemic catalyst was observed to be approximately one-half that of an enantiopure catalyst.

$$K= \frac{[SR]^2}{[SS][RR]} = 4$$

→ **No amplification of ee**

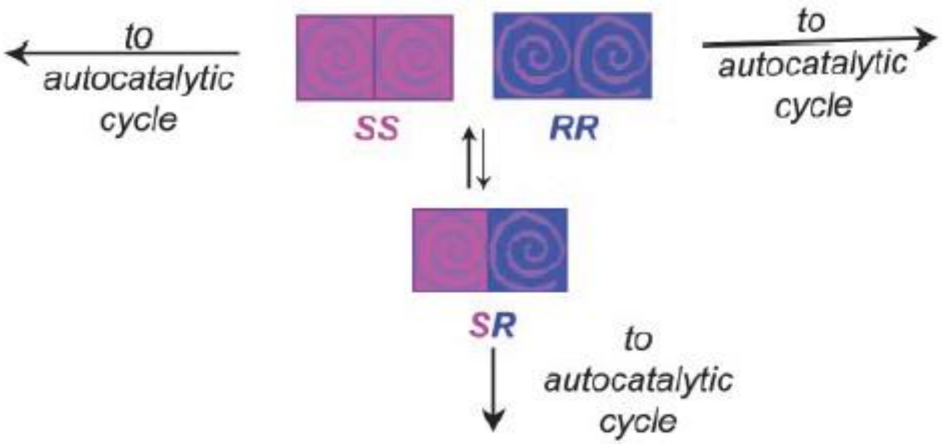
↕ **paradox**

Amplification of ee by soai reaction

How to describe compatibility between nonselective formation of the heterochiral and homochiral dimers and ee amplification in a compatible manner?

D. G. Blackmond, *Proc. Nat. Acad. Sci. USA* **2004,** *101,* 5732.

Catalyst is not monomer



Scheme 3. ML$_2$ model for autocatalysis. The monomeric *R* and *S* enantiomers form homochiral (*RR* and *SS*) and heterochiral (*SR*) dimers that themselves serve as the active catalysts in the autocatalytic reaction.

[S]=80, [R]=20, $\frac{[SR]^2}{[SS][RR]} = 4$ **SS+RR** $\rightleftharpoons$ **2SR**

$\longrightarrow$ **[SR]=16, [SS]=32, [RR]=2**

$\downarrow$ $\downarrow$

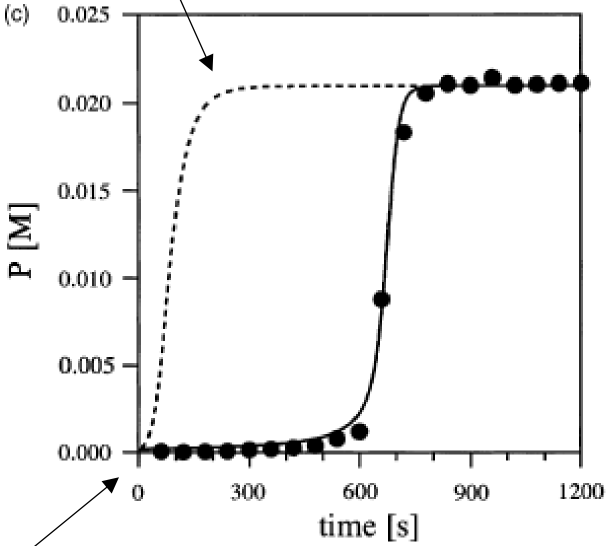
32S **2R** $\longrightarrow$ **Amplification of ee**

If the homochiral catalyst is more active than the heterochiral catalyst, we can explain the amplification of ee

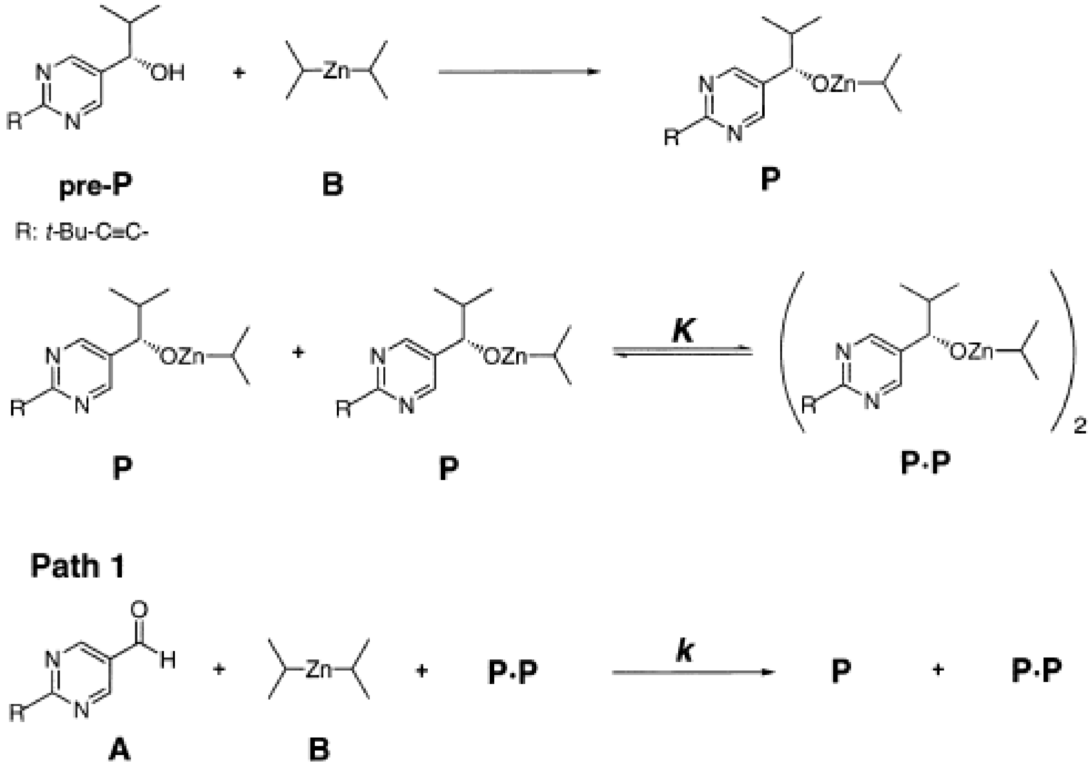
D. G. Blackmond*, Proc. Nat. Acad. Sci. USA* **2004,** *101,* 5732.

reaction rate analysis

Broken curve…
simulation assuming the first-order autocatalytic reaction



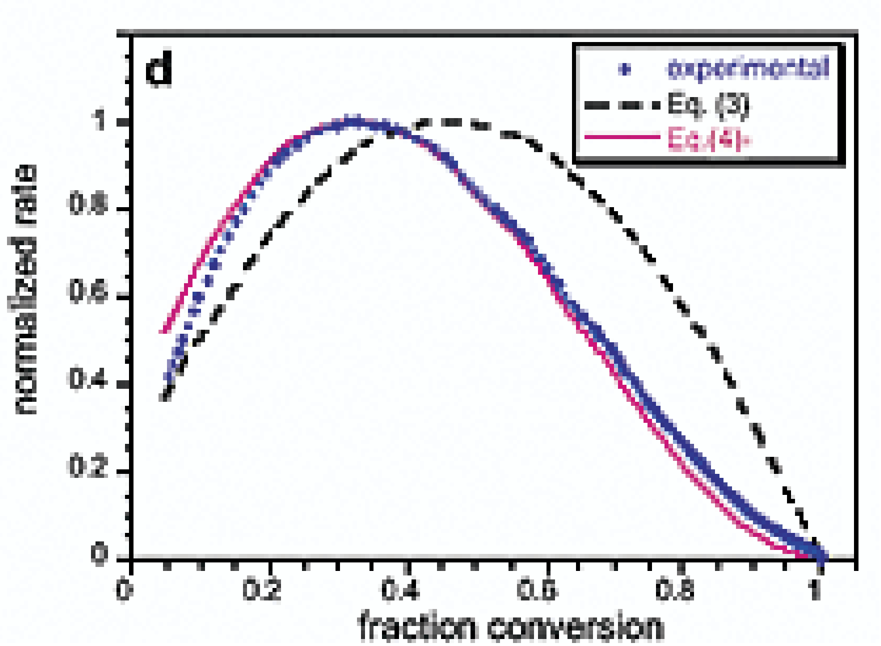
Start : 1 mol%

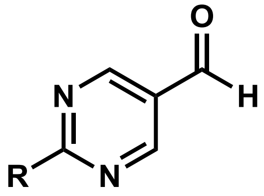


The active species of the reaction is not a monomer.

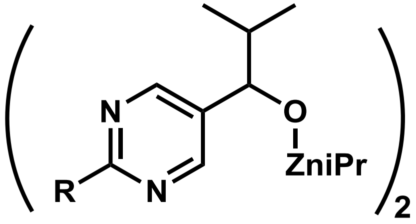
K. Soai, *et al. Tetrahedron: Asymmetry,* **2001,** *12,* 1965.

Tetrameric transition state?





1

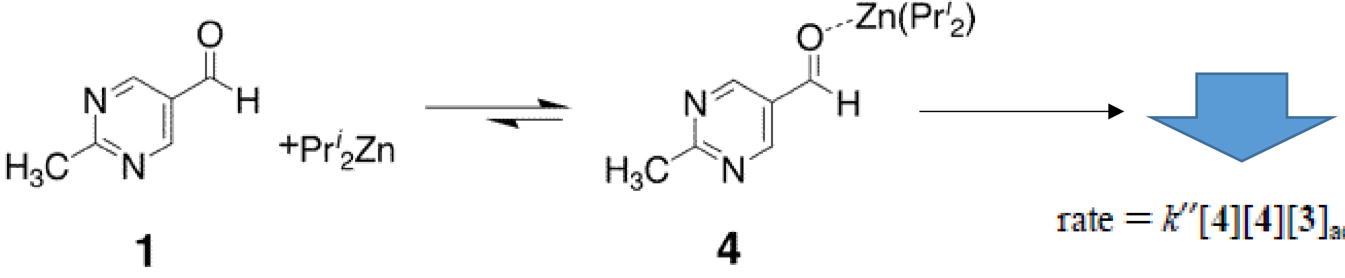


3

$$[3]_{\text{active}} = ([3_{RR}] + [3_{SS}]) \quad K_{\text{eq}} = 4 = \frac{[3_{RS}]^2}{[3_{RR}][3_{RR}]} \qquad (2)$$

$$\text{rate} = k[\mathbf{1}][\text{Pr}^i_2\text{Zn}][3]_{\text{active}} \qquad (3)$$

$$\text{rate} = k'[\mathbf{1}][\mathbf{1}][3]_{\text{active}} \qquad (4)$$

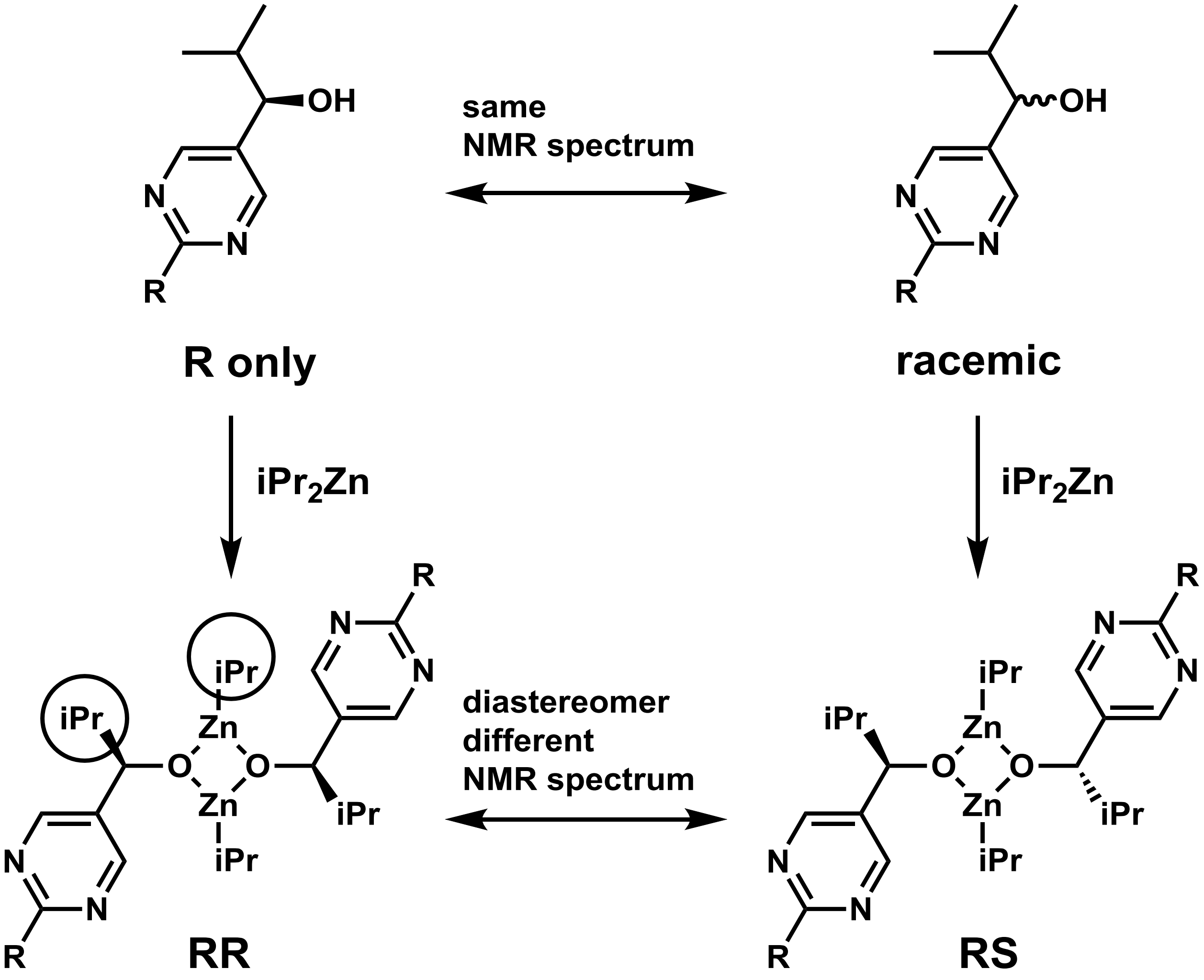


$$\text{rate} = k''[4][4][3]_{\text{active}} \qquad (7)$$

This result showed that Dimer of alkoxide reacts with two aldehyde.

F. G. Buono, D. G. Blackmond, *J. Am. Chem. Soc.*, **2003,** *125,* 8978.

NMR study of dimer catalyst



same
NMR spectrum

R only

racemic

iPr_2Zn

iPr_2Zn

diastereomer
different
NMR spectrum

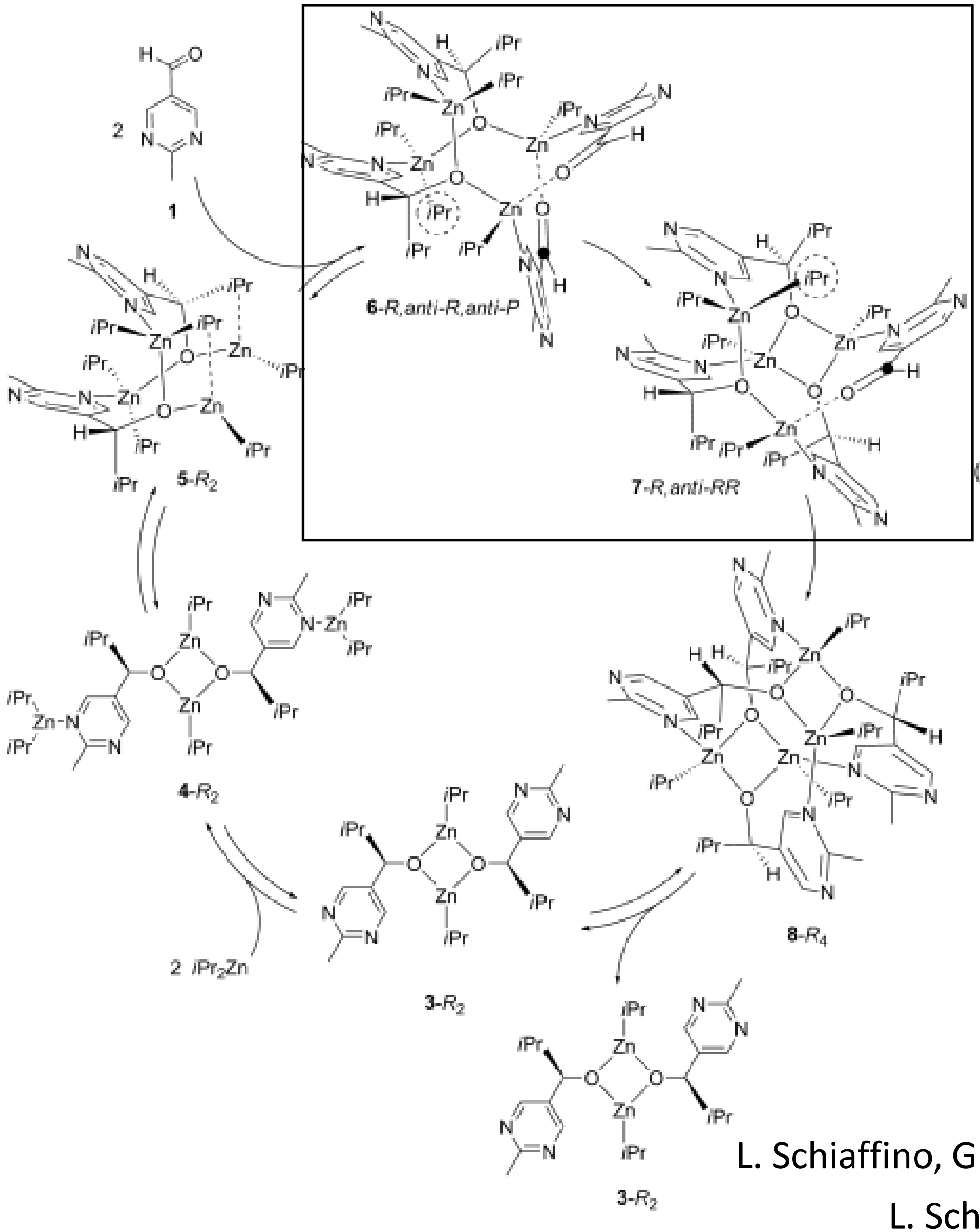
RR

RS

Dimer of the product was observed by NMR.

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

DFT study of soai reaction



$$\begin{aligned}
R_2 + 2\,Z &\rightleftharpoons (R_2Z_2)^{I} \\
(R_2Z_2)^{I} &\rightleftharpoons (R_2Z_2)^{II} \\
(R_2Z_2)^{II} + 2\,A &\rightleftharpoons R_2Z_2A_2 \\
R_2Z_2A_2 &\xrightarrow{slow} R_3ZA \\
R_3ZA &\longrightarrow R_4 \\
R_4 &\rightleftharpoons 2\,R_2
\end{aligned}$$

$$\begin{aligned}
S_2 + 2\,Z &\rightleftharpoons (S_2Z_2)^{I} \\
(S_2Z_2)^{I} &\rightleftharpoons (S_2Z_2)^{II} \\
(S_2Z_2)^{II} + 2\,A &\rightleftharpoons S_2Z_2A_2 \\
S_2Z_2A_2 &\xrightarrow{slow} S_3ZA \\
S_3ZA &\longrightarrow S_4 \\
S_4 &\rightleftharpoons 2\,S_2
\end{aligned}$$

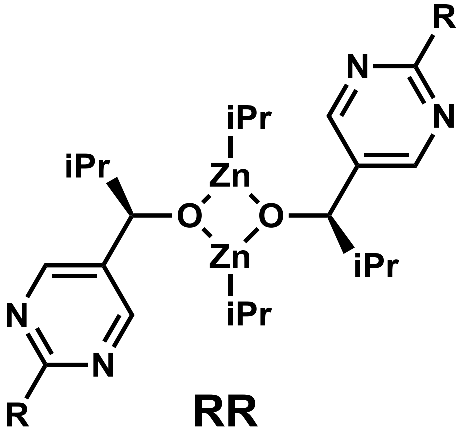
$$\begin{aligned}
R_2 + S_2 &\rightleftharpoons 2\,RS \\
(R_2Z_2)^{I} + (S_2Z_2)^{I} &\rightleftharpoons 2\,(RSZ_2)^{I} \\
(R_2Z_2)^{II} + (S_2Z_2)^{II} &\rightleftharpoons 2\,(RSZ_2)^{II}
\end{aligned}$$

L. Schiaffino, G. Ercolani, *Angew. Chem. Int. Ed.*, **2008,** *47,* 6832.

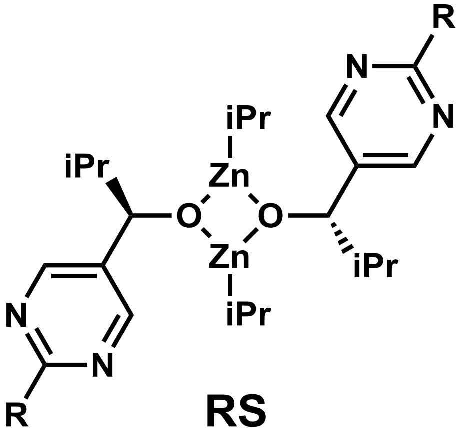
L. Schiaffino, G. Ercolani, *Chem. Eur. J.*, **2010,** *16,* 3156.

Problem of the simple dimer model

1. The homochiral dimers are the only catalytically active species.
2. The reaction rate is first-order in the homochiral dimers.
3. The homochiral dimers reproduce themselves with 100 % enantioselectivity.
4. There is a fast metathesis equilibrium between homo- and heterodimer which is only dictated by statistics.



RR



RS

$$A + RR \xrightarrow{k} 3/2\ RR$$

$$A + SS \xrightarrow{k} 3/2\ SS$$

$$RR + SS \xrightleftharpoons{K = 4} 2\ RS$$

L. Schiaffino, G. Ercolani, *ChemPhysChem,* **2009,** *10,* 2508.

Problem of the simple dimer model

$$ee = -\frac{1}{\alpha} + \sqrt{1 + \frac{1}{\alpha^2}}$$

$$\alpha = \left(\frac{A_{conv}}{C_0} + 1\right)\frac{2ee_0}{1 - ee_0^2}$$

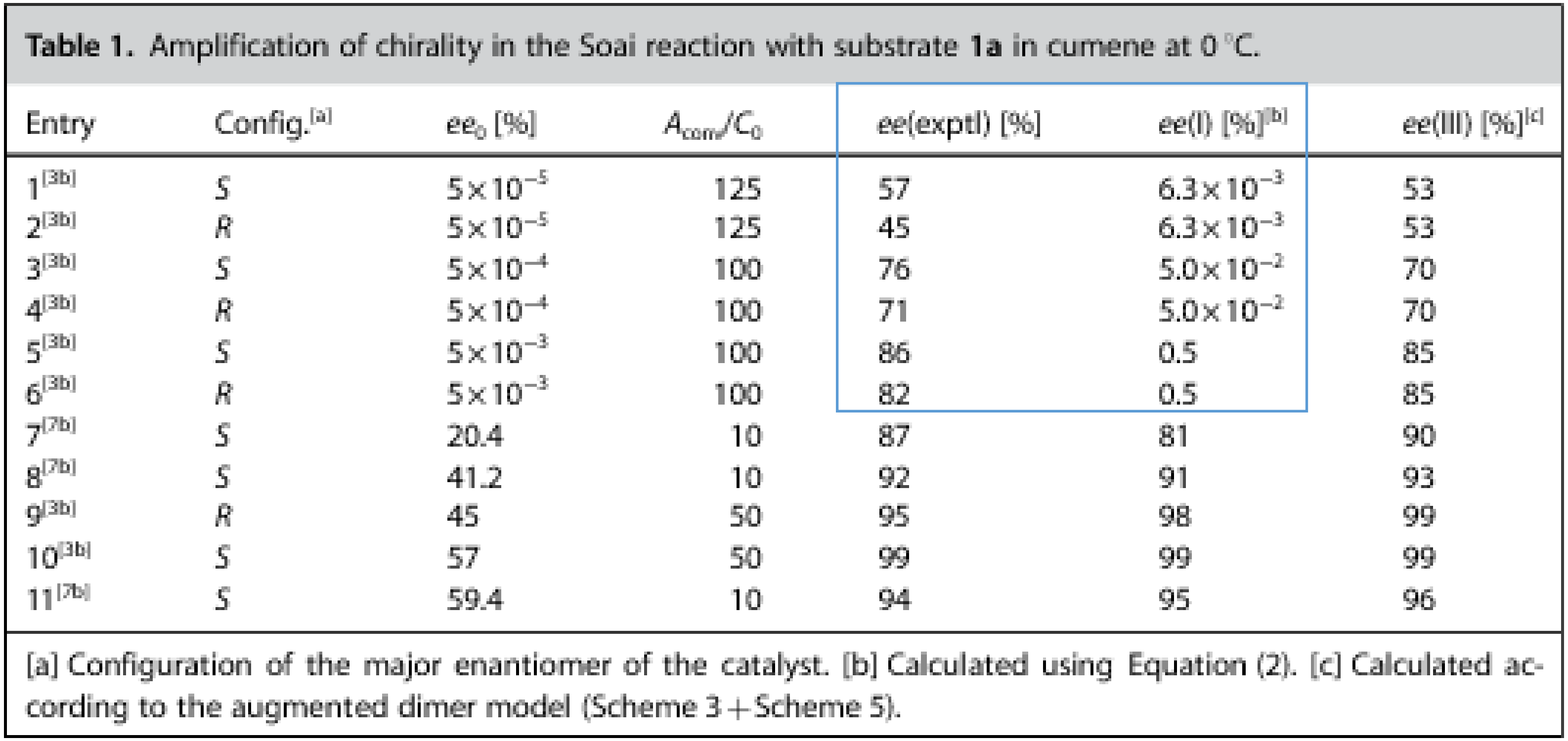


Table 1. Amplification of chirality in the Soai reaction with substrate **1a** in cumene at 0 °C.

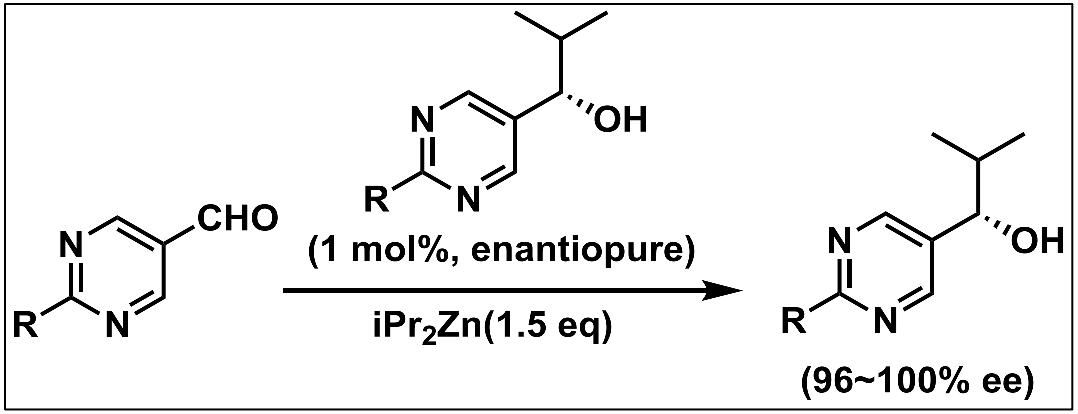
Entry	Config.[a]	ee_0 [%]	A_{conv}/C_0	ee(exptl) [%]	ee(I) [%][b]	ee(III) [%][c]
1[3b]	*S*	5×10^{-5}	125	57	6.3×10^{-3}	53
2[3b]	*R*	5×10^{-5}	125	45	6.3×10^{-3}	53
3[3b]	*S*	5×10^{-4}	100	76	5.0×10^{-2}	70
4[3b]	*R*	5×10^{-4}	100	71	5.0×10^{-2}	70
5[3b]	*S*	5×10^{-3}	100	86	0.5	85
6[3b]	*R*	5×10^{-3}	100	82	0.5	85
7[7b]	*S*	20.4	10	87	81	90
8[7b]	*S*	41.2	10	92	91	93
9[3b]	*R*	45	50	95	98	99
10[3b]	*S*	57	50	99	99	99
11[7b]	*S*	59.4	10	94	95	96

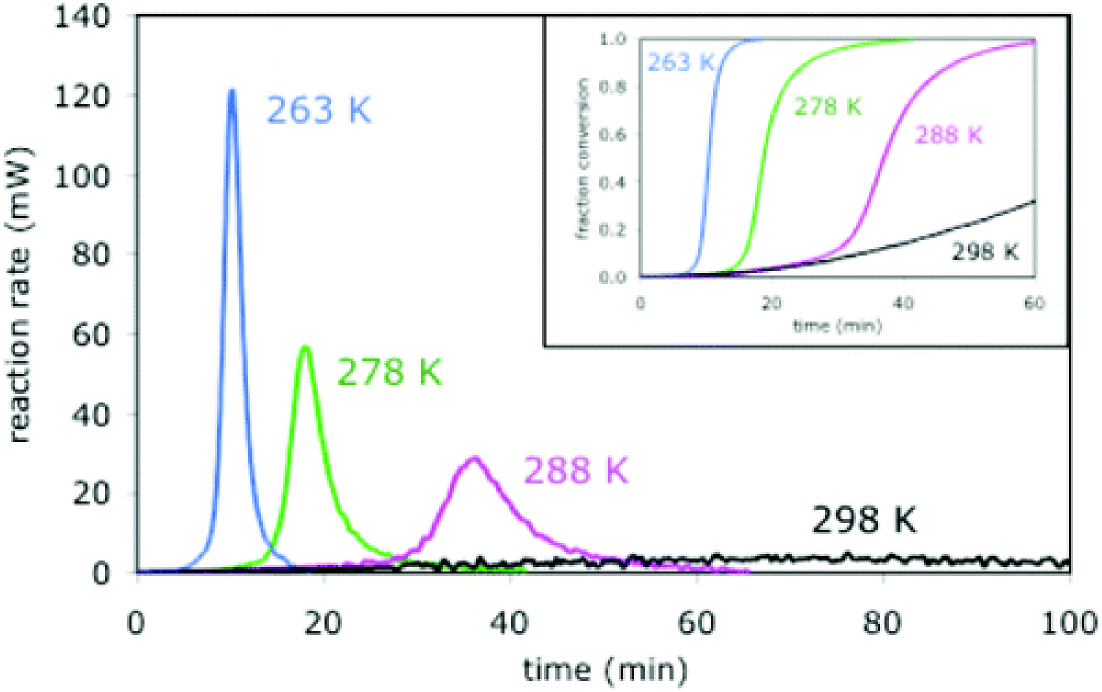
[a] Configuration of the major enantiomer of the catalyst. [b] Calculated using Equation (2). [c] Calculated according to the augmented dimer model (Scheme 3 + Scheme 5).

This simple dimer model is unsuitable to explain the amplification of chirality observed in the case of 1a at 0 °C.

L. Schiaffino, G. Ercolani, *ChemPhysChem*, **2009,** *10,* 2508.

Inverce temperature dependence on reaction rate





in situ formation of an active oligomeric catalyst−substrate complex?

It becomes increasingly stabilized as the temperature decreases.

D. G. Blackmond, *et al. J. Am. Chem. Soc.,* **2010,** *132,* 15104.

Detailed analysis by 2D-NMR

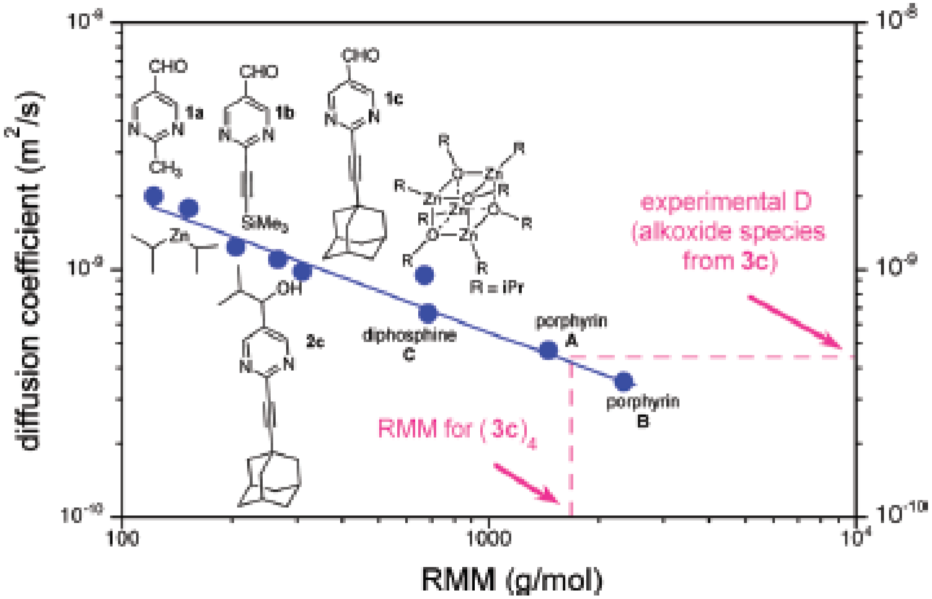
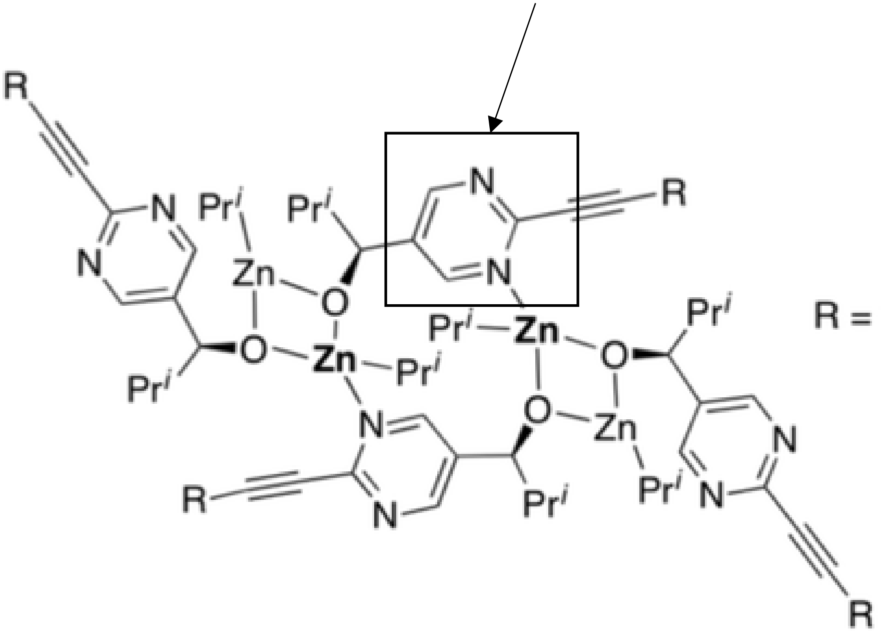


Figure 8. Diffusion coefficients as a function of RMM from ^{1}H DOSY experiments at 298 K for **1a**, **1b**, **1c**, **2c**, *i*-Pr_2Zn, (*i*-PrZnO*i*-Pr)$_4$,[14a] two reference porphyrins, and a reference diphosphine.[10,14]

Rotationally restricted pyrimidine rings

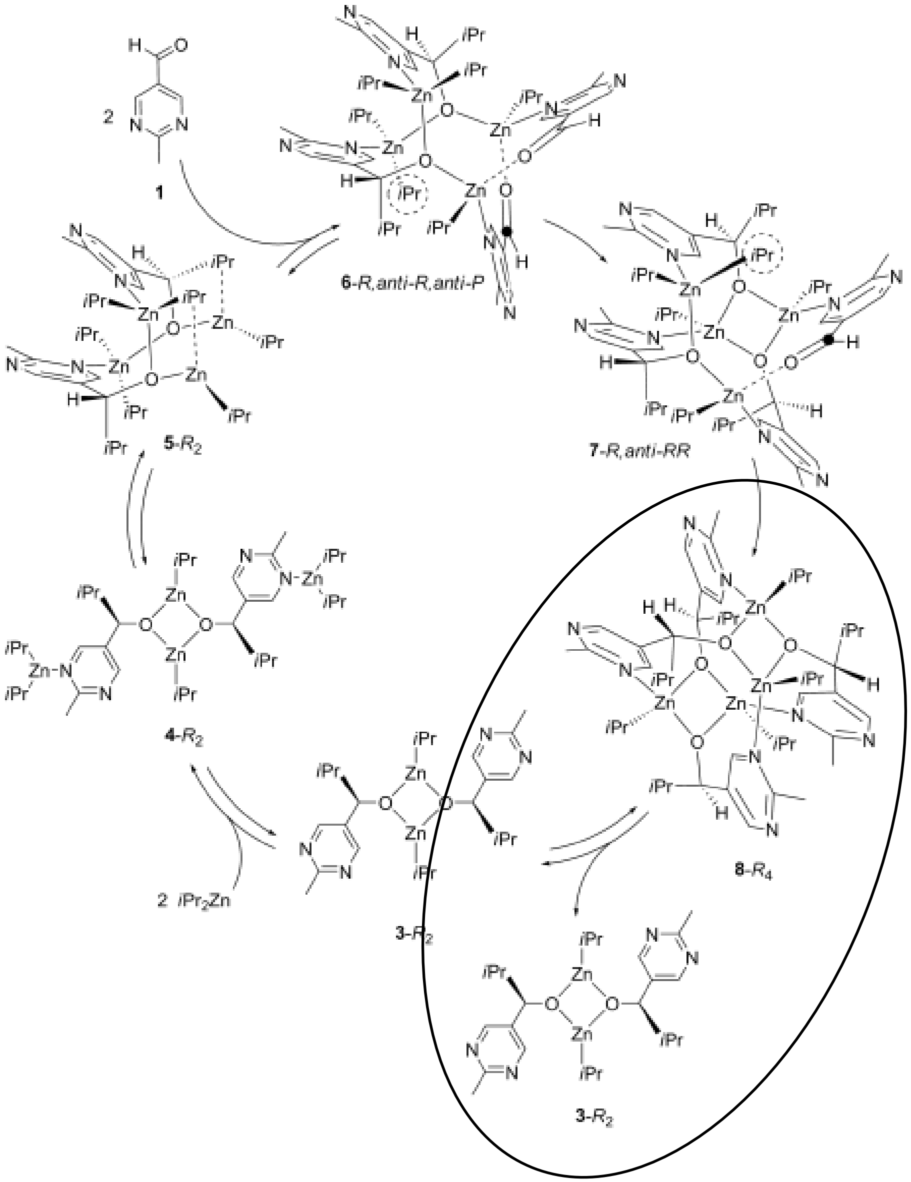


Proposed Structure for Homochiral Tetramer (**3c**)$_4$

Formation of tetramers at low temperature was observed by NMR studies.
Aggregation is maintained at ambient temperature.

D. G. Blackmond, *et al. J. Am. Chem. Soc.*, **2010,** *132,* 15104.

Problem of Schiaffino and Ercolani's model?



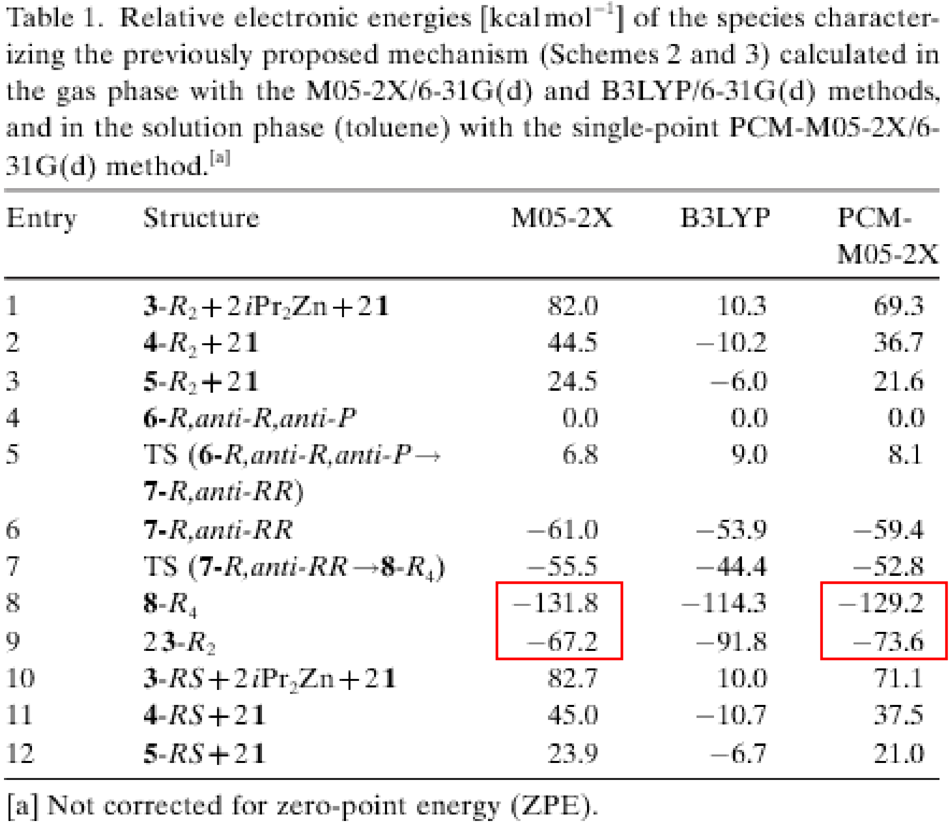


Table 1. Relative electronic energies [kcal mol^{-1}] of the species characterizing the previously proposed mechanism (Schemes 2 and 3) calculated in the gas phase with the M05-2X/6-31G(d) and B3LYP/6-31G(d) methods, and in the solution phase (toluene) with the single-point PCM-M05-2X/6-31G(d) method.[a]

Entry	Structure	M05-2X	B3LYP	PCM-M05-2X
1	**3**-*R*$_2$+2*i*Pr$_2$Zn+2**1**	82.0	10.3	69.3
2	**4**-*R*$_2$+2**1**	44.5	−10.2	36.7
3	**5**-*R*$_2$+2**1**	24.5	−6.0	21.6
4	**6**-*R*,*anti*-*R*,*anti*-*P*	0.0	0.0	0.0
5	TS (**6**-*R*,*anti*-*R*,*anti*-*P*→ **7**-*R*,*anti*-*RR*)	6.8	9.0	8.1
6	**7**-*R*,*anti*-*RR*	−61.0	−53.9	−59.4
7	TS (**7**-*R*,*anti*-*RR*→**8**-*R*$_4$)	−55.5	−44.4	−52.8
8	**8**-*R*$_4$	−131.8	−114.3	−129.2
9	2 **3**-*R*$_2$	−67.2	−91.8	−73.6
10	**3**-*RS*+2*i*Pr$_2$Zn+2**1**	82.7	10.0	71.1
11	**4**-*RS*+2**1**	45.0	−10.7	37.5
12	**5**-*RS*+2**1**	23.9	−6.7	21.0

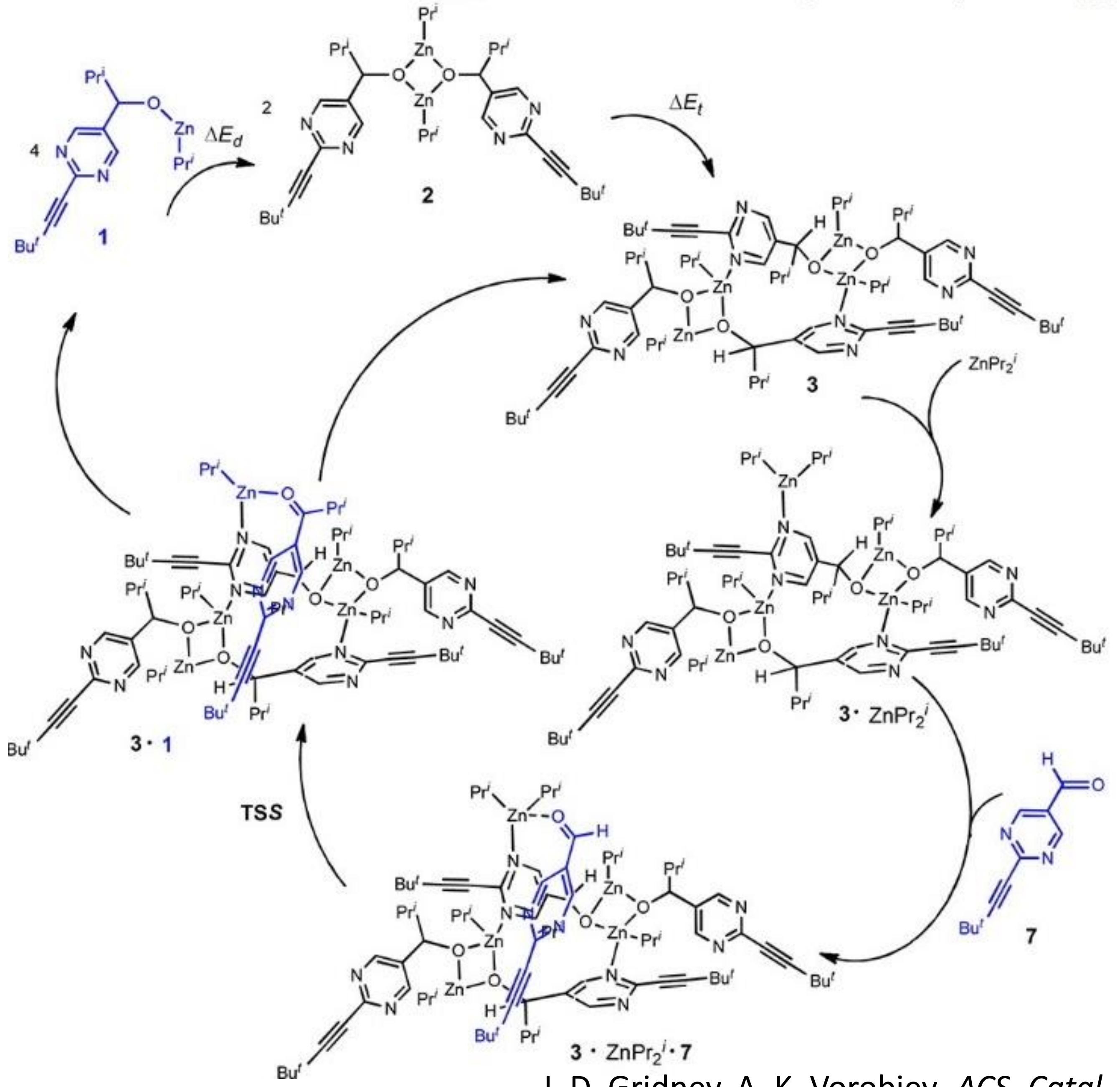
[a] Not corrected for zero-point energy (ZPE).

Large energy is required for the dissociation of the tetrameric product into two molecules of the dimeric catalyst.
Recovery of the catalyst from the product is virtually impossible?

L. Schiaffino, G. Ercolani, *Chem. Eur. J.*, **2010,** *16*, 3156.

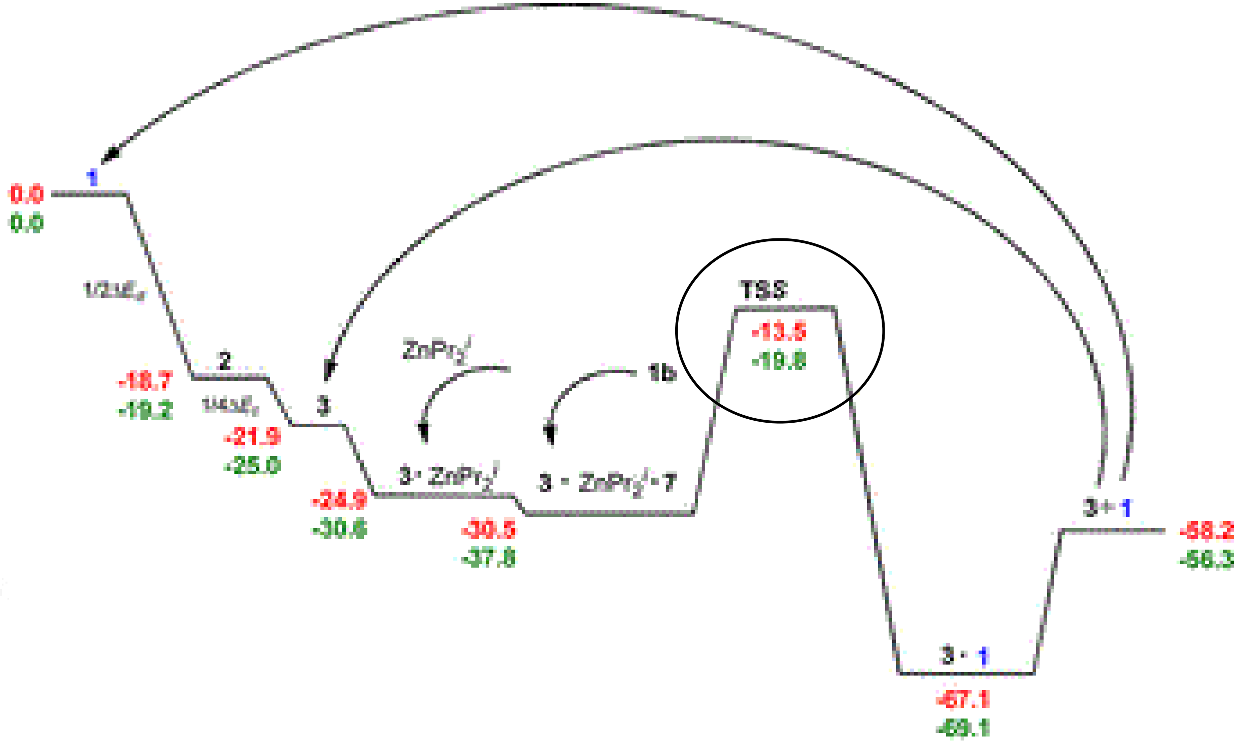
I. D. Gridnev, A. K. Vorobiev, *ACS. Catal.*, **2012,** *2,* 2137.

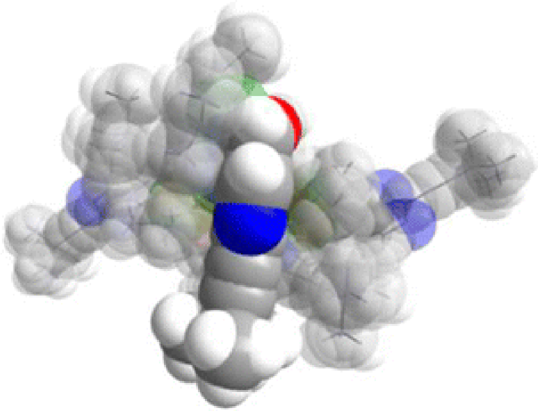
Computation of the catalytic cycle with the Homochiral tetramer

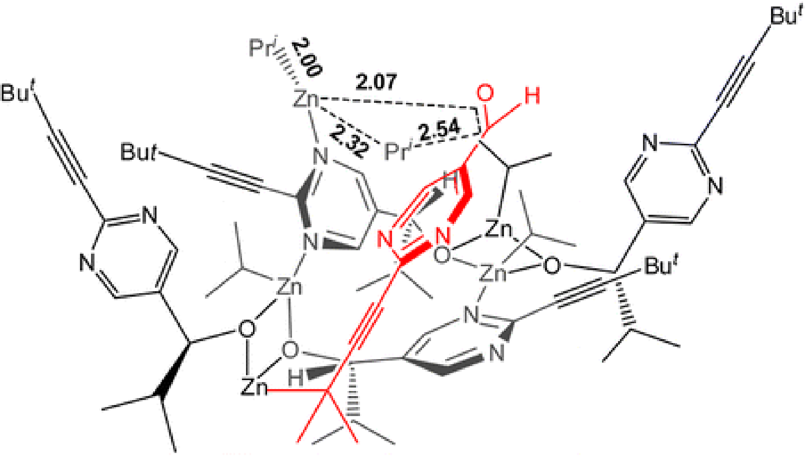


I. D. Gridnev, A. K. Vorobiev*, ACS. Catal.,* **2012,** *2,* 2137.

Transition state of this model

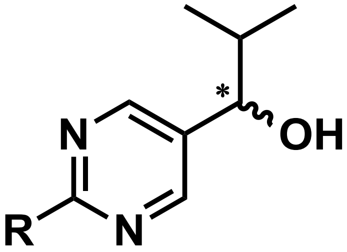




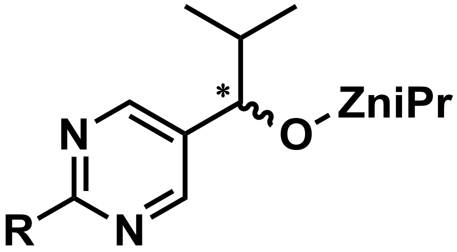


- Substrate molecule has a suitable shape complementarity to the cavity of **3**·$ZnPr_2^i$.
- Bu^t–C≡C– substituent of the pyrimidyl ring serves as a structural anchor leading to a well-defined substrate orientation.
- Formation of the product with the same handedness as the tetrameric catalyst

X-ray analysis of asymmetric autocatalyst



2



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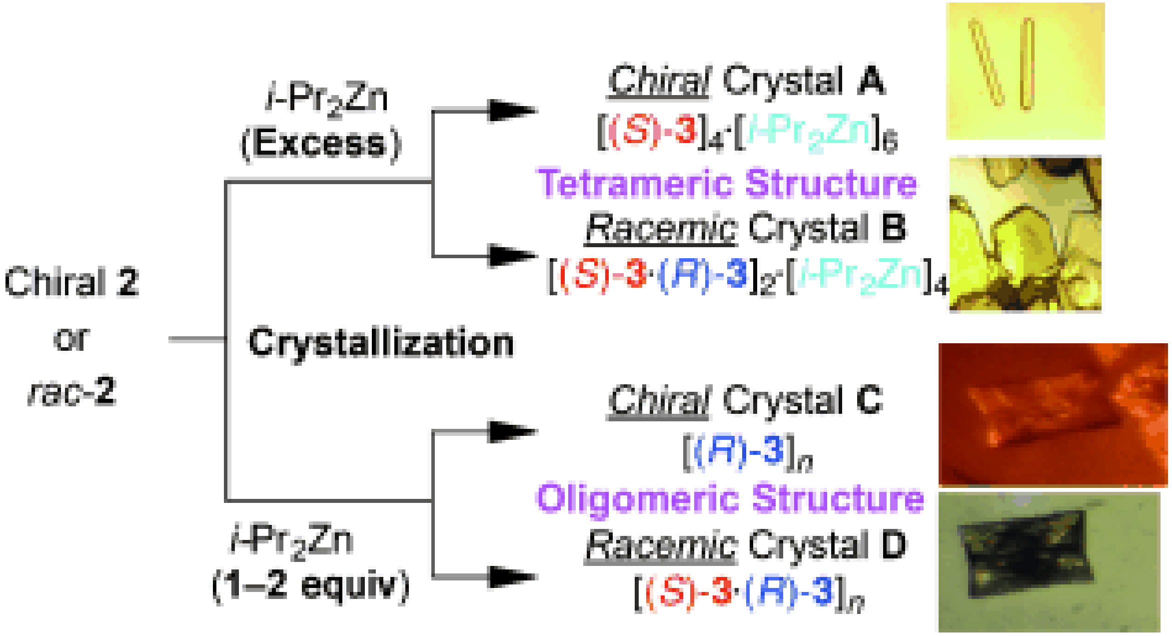
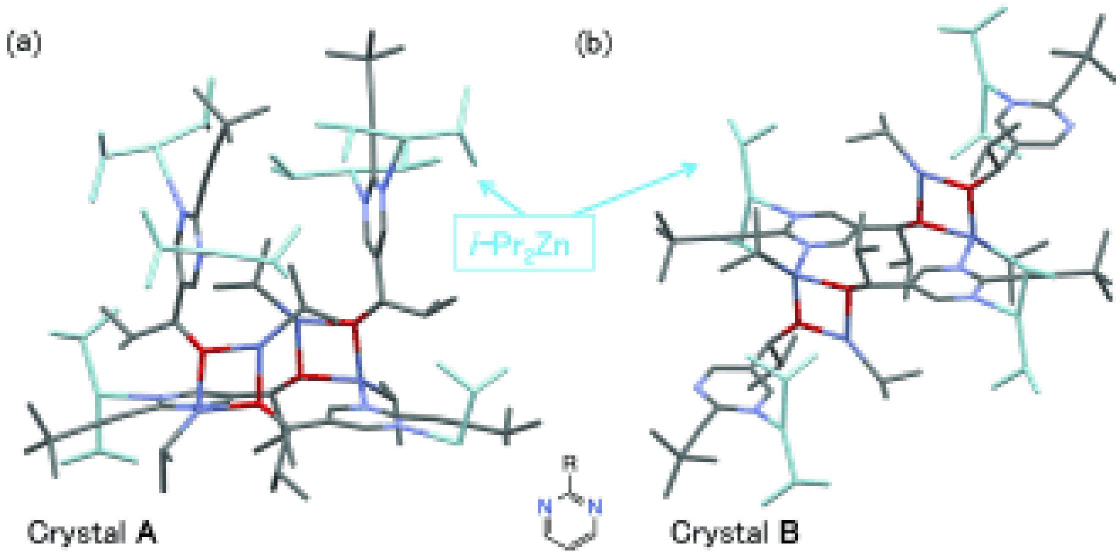
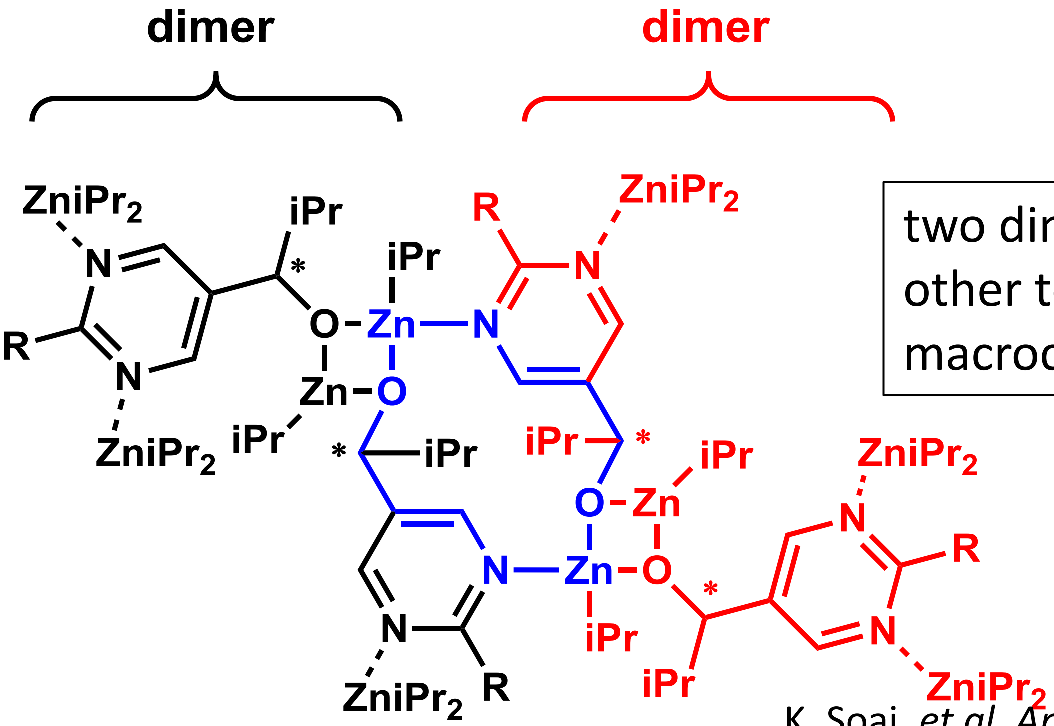


Obtained four kinds of single crystals

K. Soai, *et al. Angew. Chem. Int. Ed.*, **2015,** *54,* 15218.

Tetramer structures(crystal A/B)



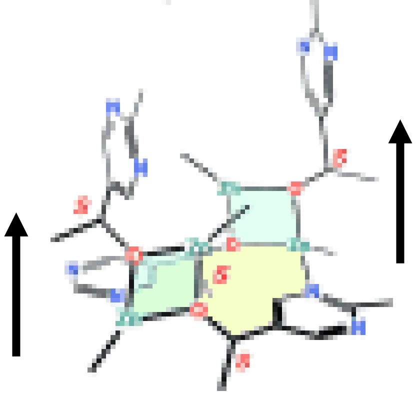


two dimers coordinate to each other to form a 12-membered macrocycle

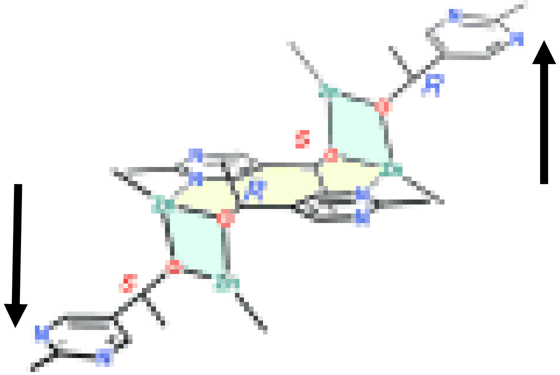
K. Soai, *et al. Angew. Chem. Int. Ed.*, **2015,** *54,* 15218.

Tetramer structures(crystal A/B)

Crystal A
$[(S)\text{-}3]_4\cdot[i\text{-}Pr_2Zn]_6$
Enantiopure Tetramer



Crystal B
$[(S)\text{-}3\cdot(R)\text{-}3]_2\cdot[i\text{-}Pr_2Zn]_4$
Racemic Tetramer

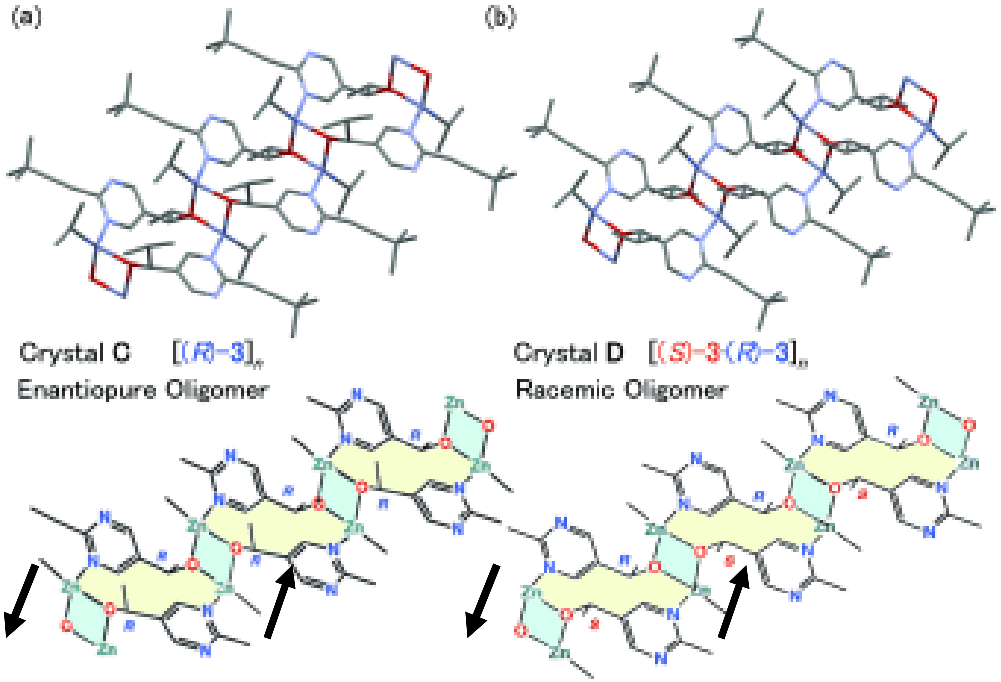


	tetramer A	**tetramer B**
two Zn_2O_2 ring	**same side**	**opposite side**
Zn-N distance	**2.26 Å**	**2.20 Å**
stability	×	○

- Difference of conformation around the 12-membered macrocycles seems to be important.
- Unsaturated Zn should have higher catalytic activity.

K. Soai, *et al. Angew. Chem. Int. Ed.*, **2015,** *54,* 15218.

Oligomeric structures(crystal C/D)



Crystal C $[(R)\text{-}3]_n$
Enantiopure Oligomer

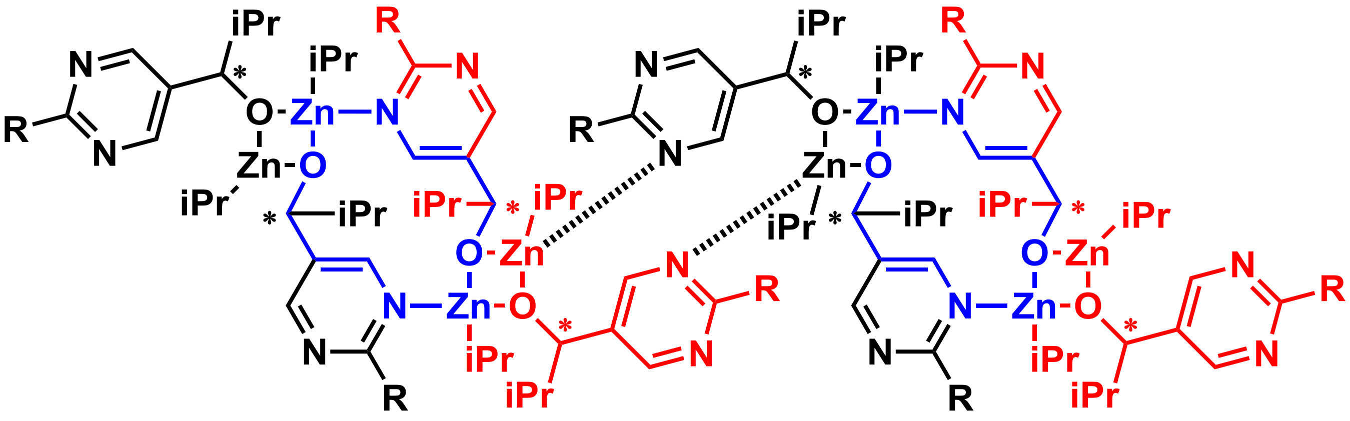
Crystal D $[(S)\text{-}3\cdot(R)\text{-}3]_n$
Racemic Oligomer

- No coordinative diisopropylzinc

→N in the pyrimidine ring forms anoter 12-membered macrocycles.

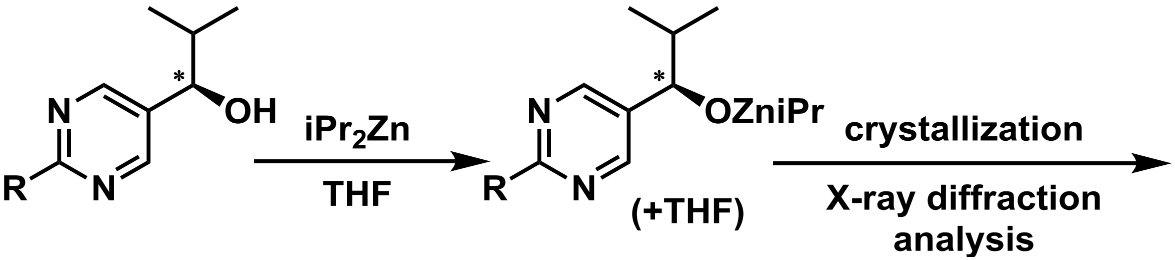
→oligomeric structure

- Both oligomer structure have similar conformation.



K. Soai, *et al. Angew. Chem. Int. Ed.*, **2015,** *54,* 15218.

Change of crystal structure due to THF

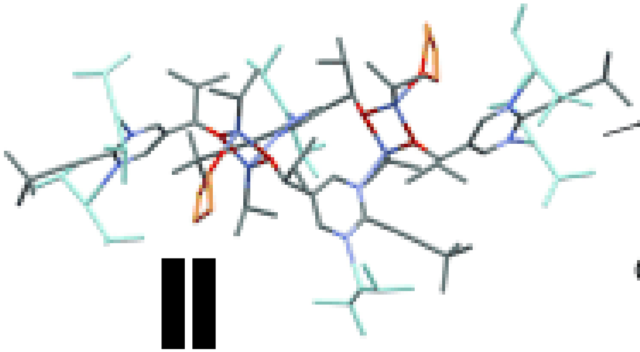


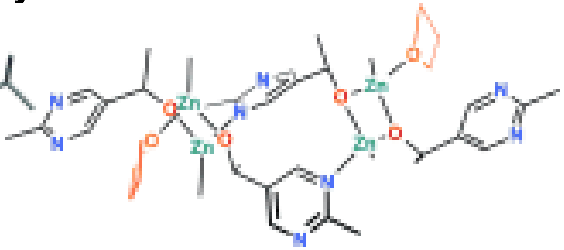
Crystal V $[(R)\text{-}3]_4 \cdot [i\text{-}Pr_2Zn]_6 \cdot THF_2$

Monoclinic, $P2_1$

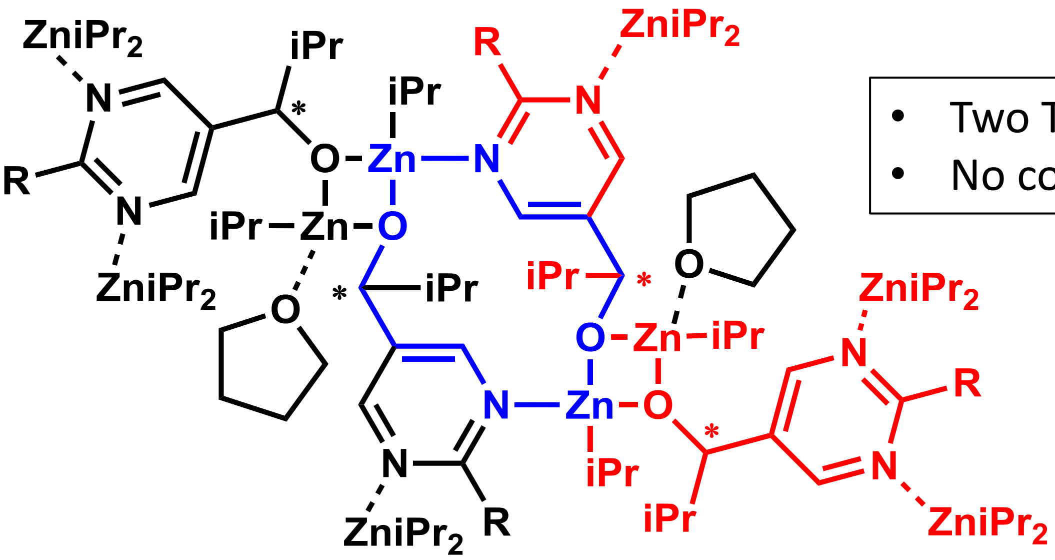
$a = 11.45$, $b = 25.919$, $c = 22.70$, $\beta = 103.4°$

$Z = 2$, $R_1 = 3.40\%$





Crystal E $[(R)\text{-}3]_4 \cdot [i\text{-}Pr_2Zn]_6 \cdot [THF]_2$



- Two THF in the tetramer structure
- No coordinatively unsaturated Zn atoms

→ **Inactivation**
unsaturated Zn atoms are important?

Summary 3

- Several groups examined mechanism of soai reaction based on kinetic experiments, reaction modeling, NMR, and DFT calculations.
- Asymmetric amplification of this reaction occurs because the alkoxide of the product forms a multimer and the homochiral catalyst is more active than the heterochiral catalyst.
- In particular, the tetramer has a structure that is significantly different between chiral and racemic. →key to asymmetric amplification?

Today's summary

- Prof. Soai showed that molecules of nearly pure chirality can be obtained from various asymmetric sources and gave great insight to unresolved problems of homochirality and the origin of life.
- Although the mechanism of the asymmetric self reaction reaction has not yet been elucidated, useful clues are being obtained.