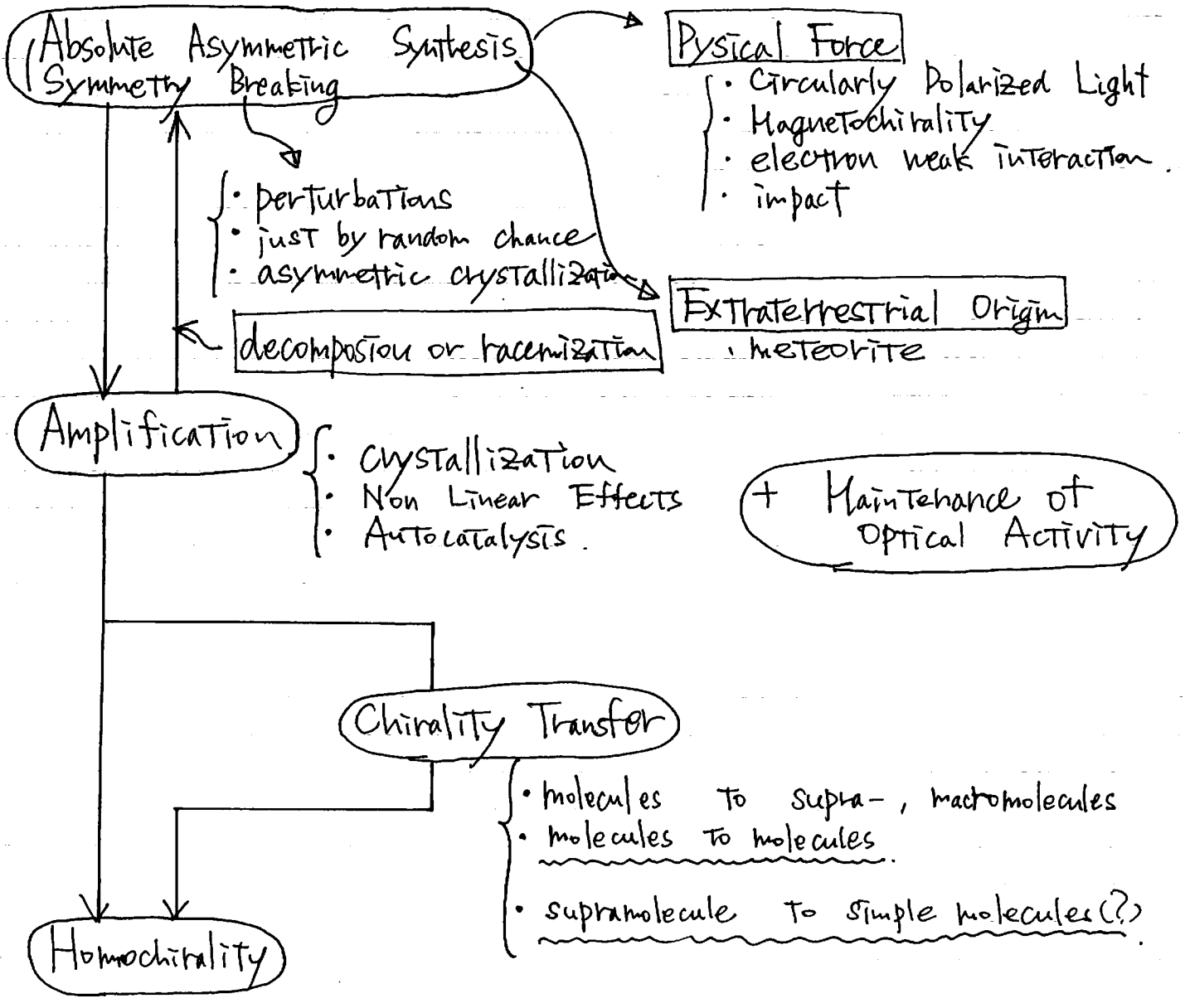
Literature Seminar 104 7/28 Wed.

Ryo Takita (D2)

▶ Another Aspect of the Origin of Homochirality

Review etc.)
e.g.
- B. L. Feringa Angew. Chem., Int. Ed. 1999, 38, 3418.
  - ↳ Vijay's literature seminar (03/10/29)
- Chem. Commun. 2000, 887.
- PNAS, 2004, 101, 5732. etc.



- Usual misunderstanding
  - "Racemates are made of exactly equal amounts of enantiomers."

$$\longrightarrow \left(\frac{n}{2} + \sqrt{n}\right) : \left(\frac{n}{2} - \sqrt{n}\right) \quad (n \to \infty \; ; \longrightarrow 50:50)$$

- laboratory vs nature ; lab is closed system (in the flask)
  nature is open system.

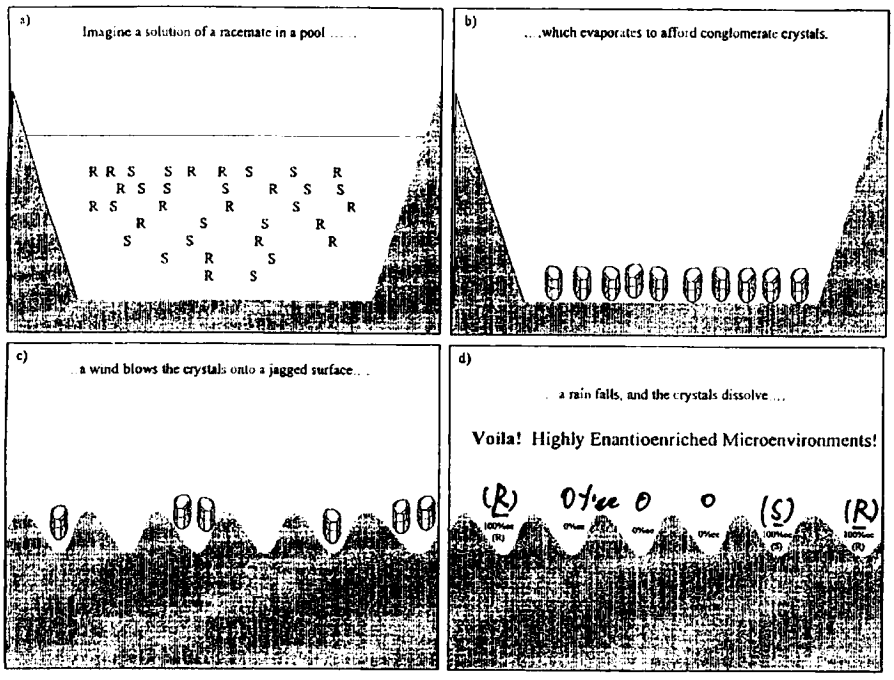
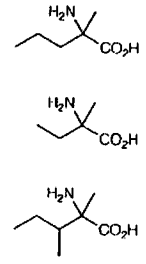


Fig. 2. Abiotic generation of highly enantioenriched microenvironments by stochastic sorting of conglomerate crystals.
(Chirality, 2001, 13, 425.)

ex). Science, 1997, 275, 951.



Scheme 1 Enantiomeric excesses of α-ramified amino acids of ex terrestrial origin found in the Murchison meteorite.

(impacted in Australia in 1969.)

— anyway, only one scenario would not be true.

< Contents >

① theory of autocatalysis

② Autocatalytic Secondary Nucleation

③ Asymmetric Autocatalysis
- Soai's reaction
- others

④ Chirality Transfer
- molecules To molecules
- supramolecules To simple molecules

① theory of autocatalysis

Frank's model (Biochim. Biophys. Acta., 1953, 11, 459.)

"The initial production of life is rare event."

‖

if the production of living molecules is an infrequent processes, compaired with the rate of multiplication of living molecules, the whole earth is likely to be extensively populated with the progeny of the first before another appears.

→ "mutual antagonism".

the key — an "anticatalyst" in self-replicating systems.

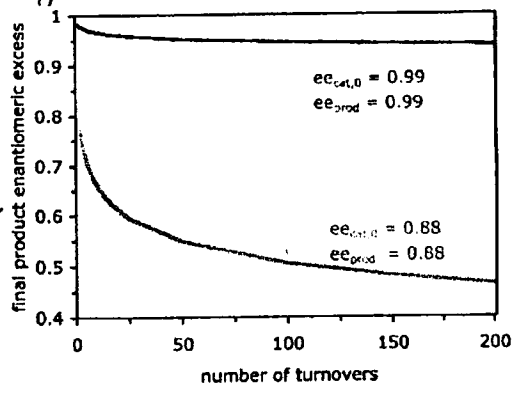
without anticatalyst ; autocatalysis alone

$ee_{prod.} = ee_0 \cdot ee_{cat}$

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

(PNAS, 2004, 101, 5732.)

* pure autocatalitic self-replication would lead inexorably to a racemic world.



when the enantiomers n_1, n_2

$$\frac{dn_1}{dt} = (k_1 - k_2 n_2)\, n_1 \qquad (1)$$

$$\frac{dn_2}{dt} = (k_1 - k_2 n_1)\, n_2 \qquad (2)$$

"anticatalyst".

where $k_1, k_2 > 0$

Subtracting we have

$$d(n_1 - n_2)/dt = k_1(n_1 - n_2) \qquad (3)$$

and hence,

$$(n_1 - n_2) = (n_{01} - n_{02})\, e^{k_1 t} \qquad (4)$$

Combining (4) and (7)

$$n_1/n_2 = (n_{01}/n_{02}) \exp.\, [k_2\,(n_{01} - n_{02})(e^{k_1 t} - 1)] \qquad (8)$$

→ the ratio increases.

where n_{01}, n_{02} are initial values: *i.e.* the excess of one over the other increases exponentially; whereas the total, $(n_1 + n_2)$, governed by the differential equation

$$d(n_1 + n_2)/dt = k_1(n_1 + n_2) - z\, k_2\, n_1\, n_2 \qquad 5)$$

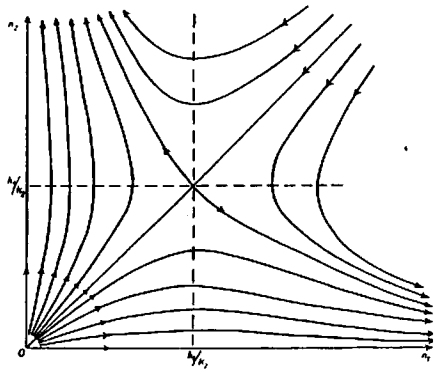
has a slower relative rate of increase.

Eliminating dt from (1) and (2) we have

$$\frac{dn_1}{dn_2} = \frac{(k_1 - k_2 n_2)n_1}{(k_1 - k_2 n_1)n_2} \qquad (6)$$

and hence

$$n_1/n_2 = (n_{01}/n_{02}) \exp.\, [k_2\,(n_1 - n_2 - n_{01} + n_{02})/k_1] \qquad (7)$$



cf)

Scheme 1

$S + T \rightleftharpoons X_L$

$S + T \rightleftharpoons X_D$

$S + T + X_L \rightleftharpoons 2X_L$

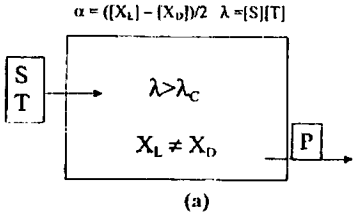
$S + T + X_D \rightleftharpoons 2X_D$

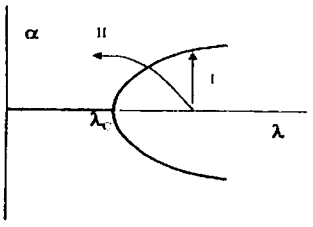
$X_L \rightleftharpoons X_D$

$X_L + X_D \rightleftharpoons P$

$\alpha = ([X_L] - [X_D])/2$

$\lambda = [S][T]$





$$\frac{d\alpha}{dt} = -A\alpha^3 + B(\lambda - \lambda_C)\alpha \qquad (1)$$

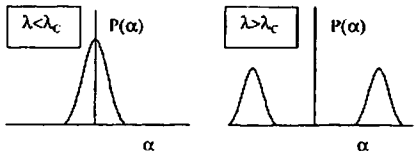


FIGURE 1. Spontaneous chiral symmetry breaking in nonequilibrium chemical systems. (a) Open flow systems. (b) Bifurcation of asymmetric states. I and II indicate the trajectories in open and closed systems, respectively. (c) Probability distributions associated with stochastic

Just Extention of Frank's model by Kondepudi.

② Autocatalytic Secondary Nucleation

Chiral Symmetry Breaking in Sodium Chlorate Crystallization

DILIP K. KONDEPUDI,* REBECCA J. KAUFMAN, NOLINI SINGH

Science, 1990, 250, 975.
Acc. Chem. Res. 2001, 34, 946. etc. Cf. Vijayls report (03.029)

· unstirred solution,
a statistically equal number of (d)- or (l)-crystals are obtained (from supersaturated solution) (unstirred)
(Kipping and Pope JCS. Trans. 1898, 73, 606.)

⇓

in stirred solution. → (stirred)

the resulting crystals are almost all l- or almost all d- in every crystallization.

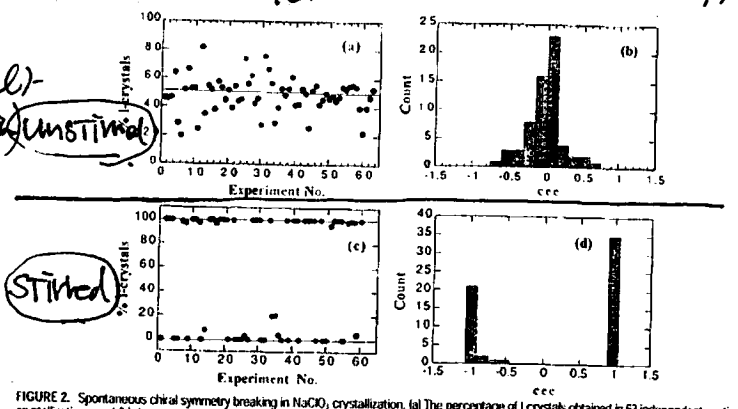


FIGURE 2. Spontaneous chiral symmetry breaking in $NaClO_3$ crystallization. (a) The percentage of l crystals obtained in 63 independent unstirred crystallizations and (b) the corresponding histogram of crystal enantiomeric excess (cee) = $(N_l - N_d)/(N_l + N_d)$. (c) The percentage of l crystals obtained in 60 independent stirred crystallizations and (d) the corresponding histogram of cee.

<process> not fully understood

primary nuclei → "secondary nuclei" from the surface (or the vicinity) of an existing crystal. (primary nuclei)

$\left(\left(\frac{n}{2}+n^{1/2}\right):\left(\frac{n}{2}-n^{1/2}\right)\right)$ not always 50:50 (= d:l)

* stirring would suppress the slow process of primary nucleation, thereby favoring the formation of secondary crystals with the same homochirality.

· this phenomenon also occurs in the crystallization of $NaBrO_3$.

· chirally selective nucleation of $NaClO_3$ occurs near the surface of $NaBrO_3$ crystal. (Phys. Rev. Lett. 2000, 84, 4405.)

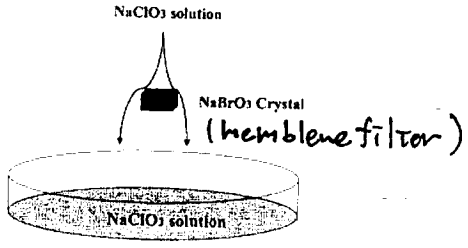
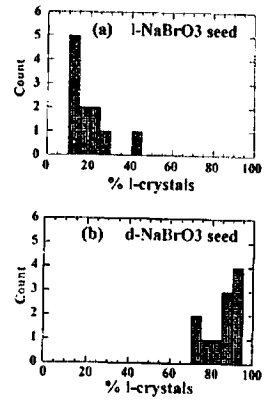


FIG. 1. Chirally selective crystallization of $NaClO_3$ using seeds of $NaBrO_3$ crystals

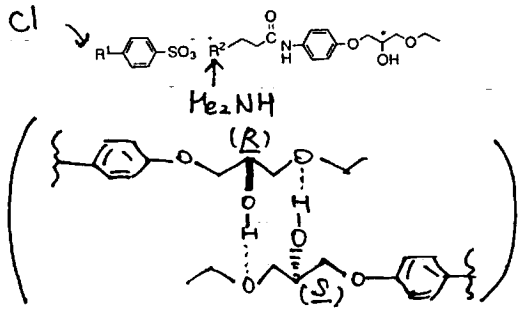
FIGURE 3. Secondary nucleation due to fluid flow over seed crystals. Note that $NaBrO_3$ and $NaClO_3$ crystals with enantiomerically similar structure have opposite optical rotations. (a) The distribution of percent levorotatory crystals obtained by flow of $NaClO_3$ solution on l-$NaBrO_3$ crystals. (b) The distribution of percent levorotatory crystals obtained by flow of $NaClO_3$ solution on d-$NaBrO_3$ crystals.



· no solid-solid collision or contact was involved.

Cf. **Unusual Disordered Crystal Structure of a Racemate Exhibiting a Novel Enantiomeric Resolution: Preferential Enrichment****

Rui Tamura,* Hiroki Takahashi, Ken Hirotsu,* Yoshitaka Nakajima, Takanori Ushio, and Fumio Toda



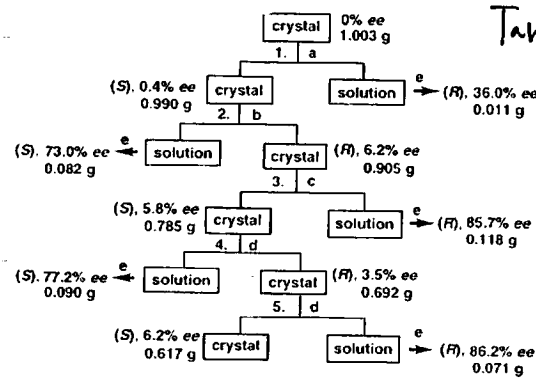
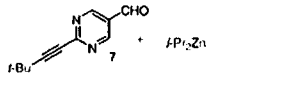


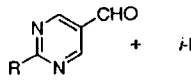
Figure 1. Preferential enrichment of NC. The crystals were dissolved in EtOH by heating. The saturated solution was cooled to 25 °C, stirred until crystallization began, and then allowed to stand for the stated period of time.

Tamura et al.
Angew. Chem. Int. Ed. 1998, 37, 2876.
"anti-resolution" of heterochiral clusters of Serine
JACS, 2004, 126, 4110.

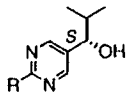
③ Asymmetric Autocatalysis — Soai's reaction

ex.)

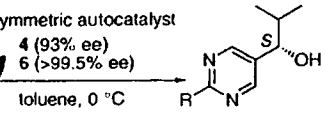




3 (R=H)
5 (R=Me)

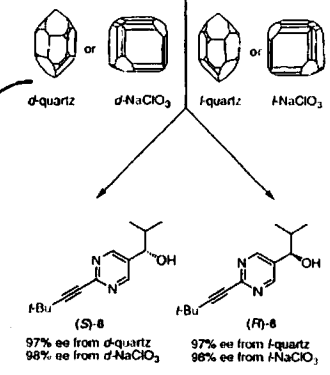


Asymmetric autocatalyst
4 (93% ee)
6 (>99.5% ee)



4 (R=H) 93.3% ee
6 (Me) 98.2% ee

ref)
Nature, 1995, 378, 767.
JACS, 1998, 120, 12157.
Angew. Chem, Int. Ed. 1999, 38, 659.
2003, 42, 315.
Bull. Chem. Soc. Jpn. 2004, 77, 1063.
etc.



Scheme 6.

or other chiral organic compounds (even with low ee)

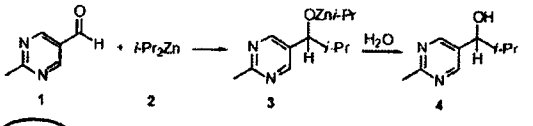
* using low ee - autocatalyst, after several cycles, pyrimidyl alkanols were obtained with high ee.

See also; JACS, 2001, 123, 10103, JACS, 2003, 125, 8978
Adv. Synth. Catal. 2002, 344, 156, Angew. 2004, 43, 2679

Enantioselective Synthesis without Discrete Optically Active Additives

Daniel A. Singleton* and Loan K. Vo

JACS, 2002, 124, 10010.
(see also: Nature, 2002, 419, 346.
PNAS, 2004, 101, 5732.)



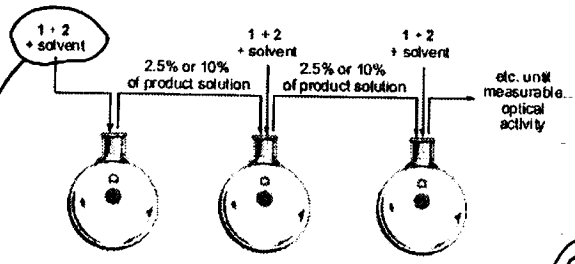


Figure 1. Process for replicative asymmetric amplification.

* Spontaneous achiral symmetry breaking occurs completely in homogeneous solution.

(0.1 M, 0°C)

pair → side-by-side rxn.

Table 1. Results from Trials of Replicative Asymmetric Amplification without Discrete Optically Active Additives

trial[a]	% ee[b]	trial[a]	% ee[b]	trial[a]	% ee[b]
1[c]	16 S^k	17[g,l,u]	65 S^m	33[e,s,u]	21 S^l *
2[c,l]	11 S^k, 78 S^l	18[g,t,u]	70 S^m	34[e,s,u]	81 R^l
3[c,d]	18 S^k	19[g,i,r,u]	85 S^l	35[e,h,u]	29 S^l
4[c,d]	16 S^k	20[g,i,r,u]	86 S^l	36[e,h,u]	29 S^l
5[c,e,j]	32 S^l	21[g,h,t]	48 S^l	37[g,i,h,r,u]	18 S^l, 54 S^m
6[c,f,j]	22 S^l	22[g,h,i]	52 S^l	38[g,i,u]	11 S^l, 42 S^m
7[c,f,h,j]	30 R^m	23[g,h,i,u]	48 S^l	39[g,i,u]	5 S^k, 48 S^l
8[c,e,h,j,t,u]	80 S^n	24[g,t,u]	37 S^l	40[g,i,u,v]	3 S^k, 43 S^l
9[c,e,j,t,u]	75 S^n	25[g,h,i]	32 S^l	41[e,i,u]	18 S^n, 48 S^o
10[c,h,u]	26 R^l	26[s]	21 R^l	42[e,s,u]	8 S^m, 32 S^n
11[t,u]	54 S^l	27[e,s]	67 S^m	43[e,h,u]	4 S^p, 18 S^q
12[e,h,u]	22 R^l *	28[e,j,s,u]	25 R^l	44[e,i,u]	22 S^p, 45 S^q
13[e,u]	23 R^l	29[e,j,s,u]	32 S^l	45[e,i,u]	5 S^n, 21 S^o
14[e,h]	48 R^m *	30[e,j,s,u]	26 R^l	46[e,i,u]	4 S^n, 24 S^o
15[e,i]	21 S^n, 70 S^o	31[e,j,s,u]	18 S^l	47[e,h,i,u]	8 S^n, 26 S^o
16[e,i]	13 S^l	32[e,s,t]	34 R^l	48[e,i,u]	13 S^n, 21 S^o

[a] The trials employed the procedure of Figure 1, transferring 10% of the product solution at each generation unless otherwise noted. [b] Determined by NMR using $Eu(hfc)_3$. [c] Toluene solvent, reagent grade or purified as noted. [d] Solvent distilled from P_2O_5. [e] Solvent distilled from Na/benzophenone. [f] Solvent treated with H_2SO_4 followed by distillation. [g] Solvent purified by repeated crystallization. [h] New batch of solvent, relative to previous otherwise identical trials. [i] Benzene solvent, reagent grade or purified as noted. [j] Reaction in Teflon flask. [k] After second generation. [l] After third generation. [m] After fourth generation. [n] After fifth generation. [o] After sixth generation. [p] After seventh generation. [q] After eighth generation. [r] Transferring 2.5% of the product solution at each generation. [s] Ethyl ether solvent, reagent grade or purified as noted. [t] Reaction used a Teflon septum. [u] The pairs of trials 8/9, 12/13, 17/18, 19/20, 23/24, 28/29, 30/31, 33/34, 35/36, 37/38, 39/40, 41/42, 43/44, 45/46, and 47/48 were carried out side-by-side using identical reagents. [v] Absence of light.

ex)
- When 10 mol% of 4 (0.00003% ee) was added to the initial reaction, 4 was obtained in 71% ee by the end of the fourth generation.

For
- the first nanomole ($n = 6 \times 10^{14}$) of "racemic" product from uncatalyzed process, there will by random chance be an average of 2×10^7 molecules ($n^{1/2}$) excess of one enantiomer (0.000004 % ee).

- the products were formed in imbalanced proportions. (≤ - favorable)
- in 12 out of 15 pairs of side-by-side trials, the same enantiomer was formed with ~ the same ee.

⇒ optically active impurities (but unclear, probably in solvent.)

· the addition of 5 ppm of (-) or (+)-menthol → 25% ee R and 4% ee S after third generation

10 ppm of (D) or (L)-Fmoc-phenylalanine → 42% ee S and 39% ee R after third generation

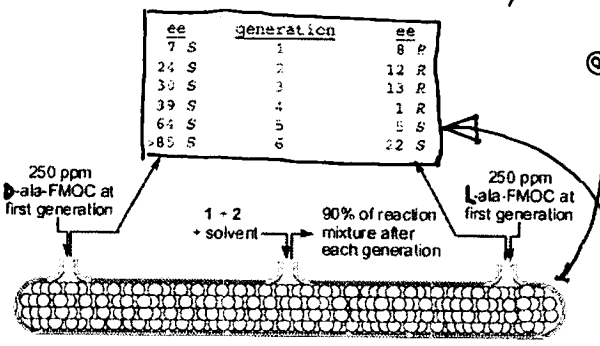


Figure 2. Competition between enantiomers in asymmetric autocatalysis.

@ the model for localized areas.
filled with glass beads to elongate the path length between ends
(experimental details are not mentioned.).

the ee at left end by chance grows faster, and diffusional mixing is ultimately unavoidable.

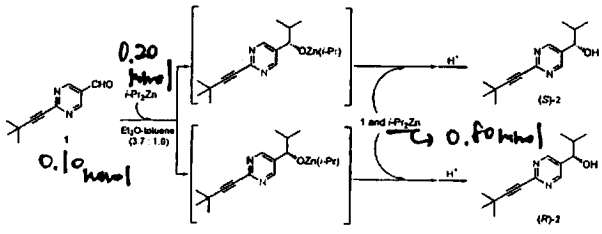
↓

by 6th generation, S-product predominated throughout the tube.

cf. Tetrahedron: Asymmetry 2003, 14, 185.

Asymmetric synthesis of pyrimidyl alkanol without adding chiral substances by the addition of diisopropylzinc to pyrimidine-5-carbaldehyde in conjunction with asymmetric autocatalysis

Kenso Soai,*[a] Itaru Sato,[a] Takanori Shibata,[a] Soichiro Komiya,[a] Masanobu Hayashi,[a] Yohei Matsueda,[a] Hikaru Imamura,[a] Tadakatsu Hayase,[a] Hiroshi Morioka,[a] Hayami Tabira,[a] Jun Yamamoto[a] and Yasunori Kowata[b]



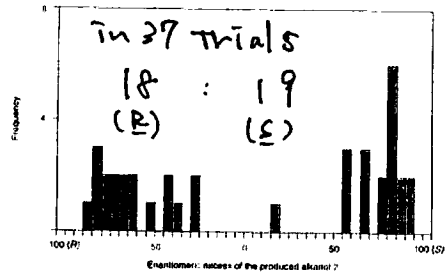


Figure 1. Histogram of the absolute configuration and the enantiomeric excess of pyrimidyl alkanol 2.

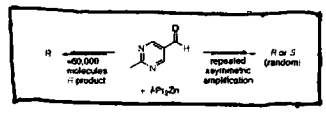
Using ethereal solvents is crucial for stochastic behavior.

Singleton also obtained similar results (stochastic behavior) as Soai's case.

cf.) OL 2003, 5, 4337.

A Few Molecules Can Control the Enantiomeric Outcome. Evidence Supporting Absolute Asymmetric Synthesis Using the Soai Asymmetric Autocatalysis

Daniel A. Singleton* and Loan K. Vo



— anyway, these reports showed on the origin of biological homochirality a mechanism for asymmetric amplification

+

for maintenance of optical activity despite decomposition and racemization

+

for dispersal of optical activity from localized areas

+

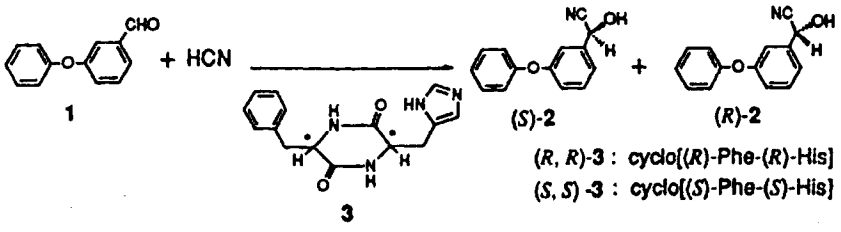
@ by which one enantiomer can take over in areas where the opposite enantiomer is in excess.

Other Salient Examples.

Enantioselective Autoinduction in the Asymmetric Hydrocyanation of 3-Phenoxybenzaldehyde Catalyzed by Cyclo[(*R*)-phenylalanyl-(*R*)-histidyl] JOC, 1991, 56, 6740.

Hidenori Danda,* Hiroyuki Nishikawa, and Ken Otaka

Scheme I



(R.R)-3-(S)-2 should be the active chiral catalyst. ⟹

in Toluene, racemic 2 + (R.R)-3

↓

gel formation.

dilution ↓

(R.R)-3 + 93.3 : 6.7 of (S)- and (R)-2

as a catalyst ; (S)-2 in 97% ee.

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

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

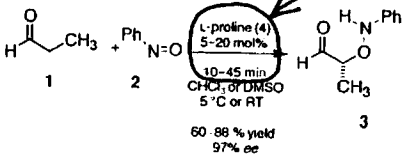
[a] Method A: (*R*,*R*)-3:1:HCN = 1.1:50:99 mmol; toluene (40 mL), 5 °C. Method B: As method A, except that (*S*)-2 of 92.0 % ee (4.4 mmol) was present initially. Method C: As method A, except that (*R*)-2 of 84.9 % ee (4.4 mmol) was present initially. [b] Determined by HPLC (Ultron ES-OVM). [c] Determined by HPLC (LiChrosorb SI-60). No byproducts were observed by HPLC. [d] Determined by HPLC (Sumipax OA-4100). [e] For the absolute configurations of (*R*)-2 and (*S*)-2 see: Tanaka, K.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. [f] $[\alpha]^{25}_{D}$ −17.5° (*c* 0.80, benzene).

Asymmetric Amplification

Amplification of Enantiomeric Excess in a Proline-Mediated Reaction**

*Suju P. Mathew, Hiroshi Iwamura, and Donna G. Blackmond**

Angew. Chem. Int. Ed. 2004, 43, 3317.



Compared with other proline-catalyzed reactions, much higher reactivity

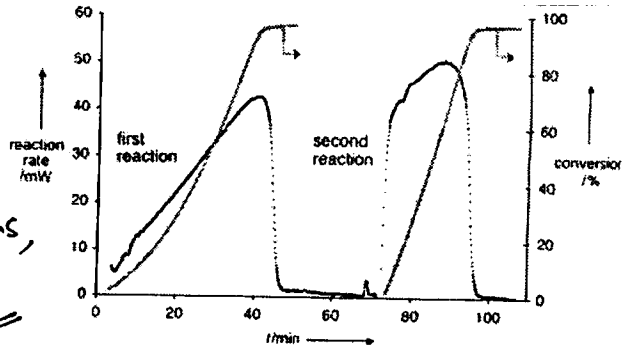


Figure 1. Reaction rate (filled black circles, corresponding to the left axis) and percent conversion (shaded grey line, corresponding to the right axis) versus time for a one-pot, two-consecutive-reaction sequence of the reaction shown in Equation (1) ($CHCl_3$ solvent, 278 K). Initial concentrations of aldehyde 1 and L-proline 4 were 2.07 and 0.07 M, respectively. First reaction: 0.26 M PhNO; second reaction: 0.24 M PhNO.

* the reaction rate lose steadily throughout the course of the reaction.

⇓

- ✗ Substrate inhibition ✗→ the rate of second reaction (as high as that at the end of the first
- ✗ autocatalysis ✗→ no heat flow of the addition of product to fresh reagents
- autoinductive reaction → plausible

Amplification

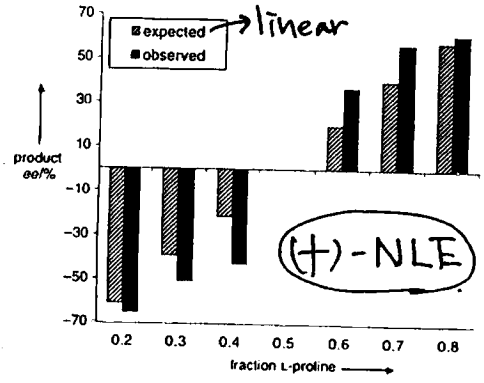


Figure 2. Final enantiomeric excess of the product as a function of the fraction of L-proline in the reaction shown in Equation (1) carried out using mixtures of D- and L-proline. Initial concentrations of aldehyde 1, nitrosobenzene 2, and total (L + D)-proline 4 were 2.07, 0.7, and 0.07 M, respectively ($CHCl_3$ solvent, 278 K). Conversions were greater than 90%.

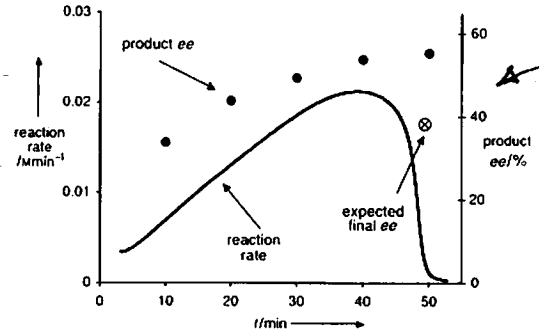
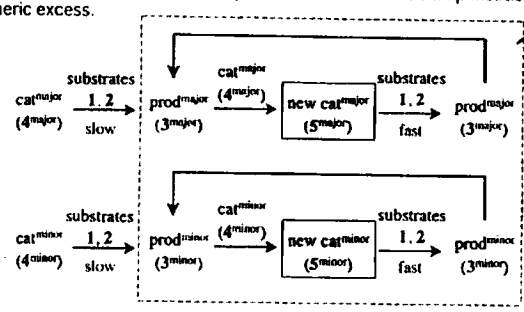


Figure 3. Reaction rate and enantiomeric excess of the product of the reaction of Scheme 1 carried out with a mixture of L- and D-proline with 40% *ee* (L). Reaction conditions: 278 K, total proline concentration (L + D): 0.071 M, nitrosobenzene: 0.70 M, propionaldehyde: 1.95 M.

ee rose over the course of the reaction

Scheme 1. General mechanism for the product-induced kinetic amplification of enantiomeric excess.

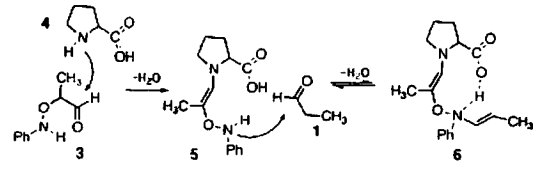


kinetic process

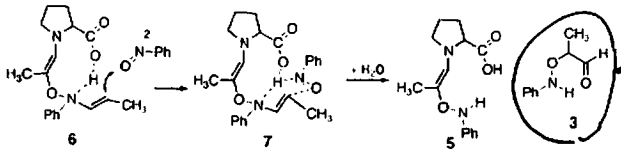
⇓

the ee of 3 will rise until the formation of new catalyst 5 has reached equilibrium, after which the ee value will slowly erode back to the linear relationship.

(lower concentrations of proline → milder asymmetric amplification)



5 : multifunctional
- active nitrogen nucleophile (α effect)
- carboxylic acid moiety



3 might also attack aldehyde (→ oligomer) but not autocatalytic → the lack of a Brønsted acid function.

Scheme 2. Proposed mechanism for product induction in the reaction shown in [Eq. (1)].

- In contrast to Soai's reaction, this represents a purely organic autoinductive reaction.
- In an open system (nature), not a closed system (in reaction vials in the lab), the chemical propagation mechanism in Scheme 1 would permit enantiomeric excess to continue to rise.

④ Chirality Transfer

· molecules to molecules

Prebiotic Amino Acids as Asymmetric Catalysts

Sandra Pizzarello[1] and Arthur L. Weber[2]

Science, 2004, 303, 1151.

in Triethylammonium acetate buffer (pH 5.4 at 50°C)

in water

Table S1. Percent D-enantiomeric excess (ee) of tetrose sugars synthesized from glycolaldehyde in the presence of amino acid catalysts.

Catalyst (ee%)	D-Threose ee% (n)[1]	D-Erythrose ee% (n)
DL-Ala[1]	0.5 ± 0.7 (13)	0.3 ± 1.3 (8)
L-Ala (100)	6.9 ± 0.4 (14)	-5.4 ± 0.6 (10)
D-Ala[a] (100)	-7.1 ± 0.7 (11)	4.3 ± 0.9 (12)
S-Iva[1] (100)	10.6 ± 0.3 (14)	-4.8 ± 0.6 (11)
R-Iva (100)	-10.7 ± 1.2 (11)	4.8 ± 0.9 (8)
R-Iva (75)	-7.9 ± 0.2 (12)	4.0 ± 0.8 (6)
R-Iva (50)	-6.1 ± 0.2 (9)	3.9 ± 1.3 (5)
R-Iva (25)	-3.5 ± 0.3 (7)	0.2 ± 1.3 (5)
R-Iva (10)	-1.4 ± 0.5 (11)	0.8 ± 0.7 (8)
R-Iva (5)	-0.7 ± 0.3 (11)	0.1 ± 0.5 (7)
L-Pro[1] (100)	None synthesized	None synthesized

[1](n) = number of statistical sample da... [1]Alanine. [1]Isovaline. [1]Proline.
[a] Reaction time three hours.

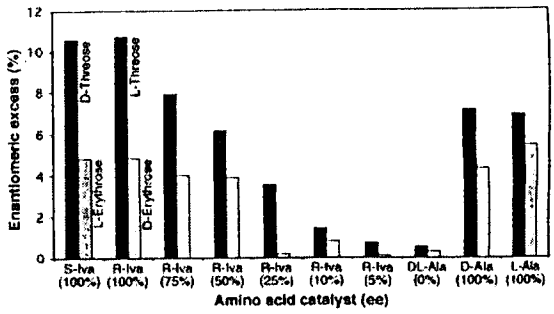
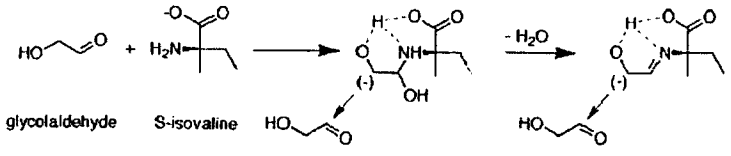


Fig. 1. Effect of amino acid catalyst ee on the asymmetric synthesis of threose and erythrose from glycolaldehyde. S-ivaline is equivalent to L-2-amino 2-methyl butyric acid.

Figure S2. A possible pathway for the asymmetric aldose condensation of glycolaldehyde in the presence of enantiomerically pure S-isovaline catalyst. Chiral carbons are marked by asterisks.



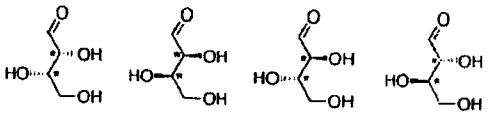
· Proline did not catalyze the reaction.

· isovaline — unnatural amino acid

found in meteorites with ee up to 15%

extraterrestrial asymmetry provided the initial induction toward homochirality

asymmetric induction at C-2



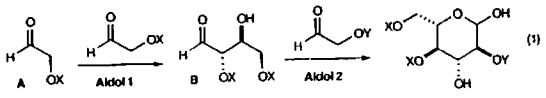
cf.) Angew. Chem. Int. Ed. 2004, 43, 2152.

Aldehyde Coupling Reactions

Enantioselective Organocatalytic Direct Aldol Reactions of α-Oxyaldehydes: Step One in a Two-Step Synthesis of Carbohydrates**

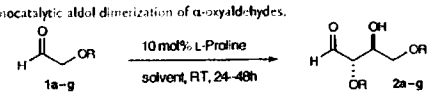
*Alan B. Northrup, Ian K. Mangion, Frank Hettche, and David W. C. MacMillan**

Two-Step Carbohydrate Synthesis: Iterative Aldehyde Aldol



Aldol 1 requires α-oxyaldehyde A (reagent) is reactive in aldol union
Aldol 1 requires α-oxyaldehyde B (product) is nonreactive in aldol union

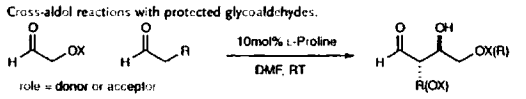
Table 1: Organocatalytic aldol dimerization of α-oxyaldehydes.



Entry	Product	Solvent	Yield [%]	*anti*:*syn*	*ee* [%][a,b]
1	OAc	DMF	0	–	–
2	OBn	DMF	73	4:1	98
3	OPMB	DMF	64	4:1	97
4	OMOM	DMF	42	4:1	96
5	OTBDPS	DMF/dioxane	61	9:1	96[c]
6	OTIPS	DMSO	92	4:1	95
7	OTBS	dioxane	62	3:1	88[a,b]

[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral HPLC. [c] Using 20 mol% catalyst. Bn = benzyl, PMB = *para*-methoxybenzyl, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl.

Table 2: Cross-aldol reactions with protected glycoaldehydes.



Entry	Aldehyde α-alkyl	Aldehyde OX	Product	Yield [%]	*anti*:*syn*	*ee* [%][a,b]
1		OTIPS acceptor		75	4:1	99
2	donor	OTBDPS acceptor		84	5:1	99[c]
3		OTIPS acceptor		54	4:1	99
4	donor	OBn acceptor		64	4:1	94
5		OTIPS donor		43	8:1	99
6	acceptor	OBn donor		33	7:1	96

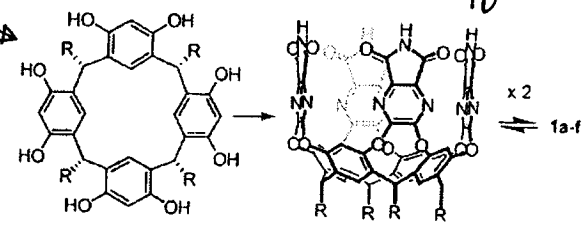
[a] Absolute and relative stereochemistry assigned by chemical correlation. [b] Determined by chiral HPLC. [c] Determined by Mosher ester analysis.

a cylindrical capsule

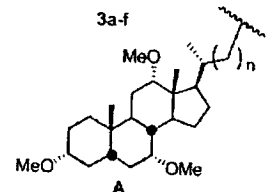
original report

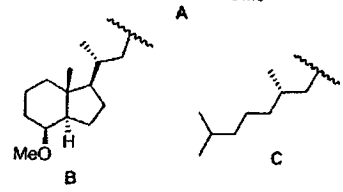
Nature, 1998, 394, 764.

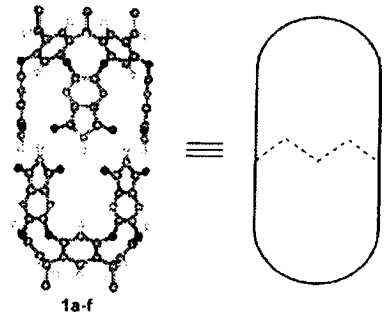
1D



2a: R = $C_{11}H_{23}$
2b: R = A, n = 1
2c: R = A, n = 2
2d: R = A, n = 3
2e: R = B
2f: R = C





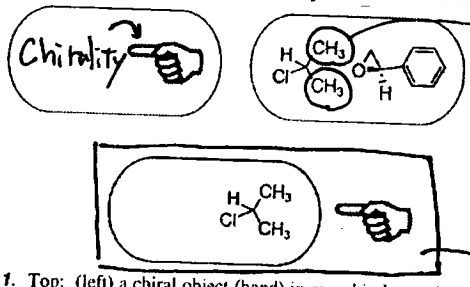


- Supramolecules to simple molecules.

☆ Rebek, Jr. et al. JACS, 2004, 126, 6216.

Steric and Magnetic Asymmetry Distinguished by Encapsulation

Toru Amaya and Julius Rebek, Jr.*



diastereotopic methyl groups were observed in its NMR spectrum. (JACS, 2003, 125, 6239.)

this time

remote effect?

Figure 1. Top: (left) a chiral object (hand) in an achiral container leaves a chiral space; (right) the methyl groups of isopropyl chloride are diastereotopic in the coencapsulation complex with styrene oxide. Bottom: can a chiral center outside the capsule affect the behavior of the methyl groups of isopropyl chloride?

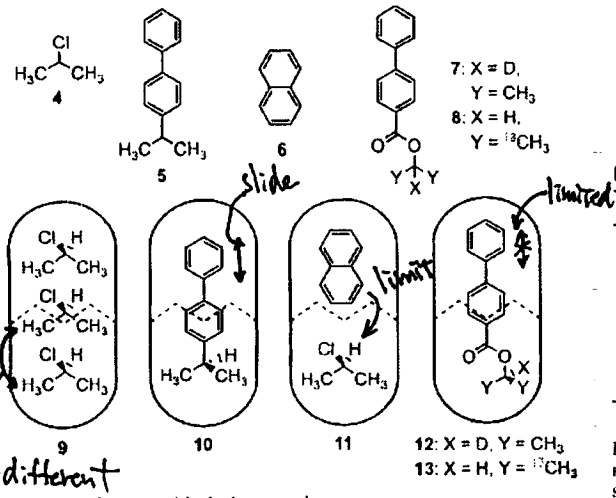


Figure 3. Guests and inclusion complexes.

Table 1. Δδ between Diastereotopic Methyl Groups of Encapsulated Species[a]

	complex	9	10	11	12	13
	PC[b]	53%	45%	47%	50%	50%
	Δδ between diastereotopic methyl groups [Hz]					
host	1b	0	5.9	16.1	13.2	13.8[c]
	1c	0	0	0	4.4	0[c]
	1d	0	0	0	0	
	1e	<2	7.3	19.1	14.7	16.1[c]
	1f	0	0	6.6	5.9	8.0[c]

[a] Capsule: 1 mM, guest: excess, mesitylene-d_{12}: 0.6 mL, 300 K, 600 MHz. [b] PC was calculated on the basis of the volumes which were minimized with the program Hyperchem 7.0, Hypercube Inc., 2002, at semiempirical PM3 level and calculated with WebLab Viewer Pro 4.0 by Molecular Simulation, Inc. [c] ^{13}C NMR (Apt) experiment (150 MHz).

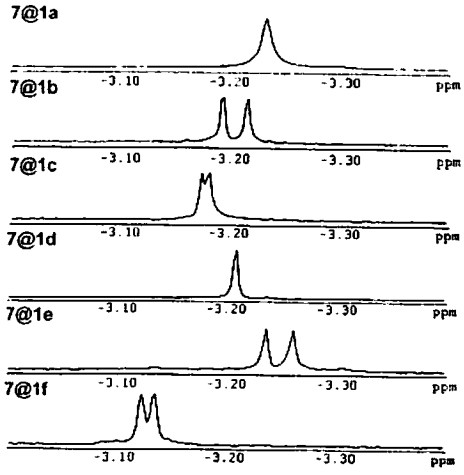


Figure 4. Upfield region of the ^1H NMR spectra (600 MHz, 300 K) of encapsulation complexes of 1a–f (1 mM) in mesitylene-d_{12} (0.6 mL) and the guest 7 (1.5 μL).

- None of the guests in 1d showed any evidence of the anisotropy of its exterior asymmetric centers. Nor did any capsules containing only 4.

↓

} distance between asymmetric centers, the mobility of the guests.

- no direct contact between the guests and asymmetric centers

☆ Raymond, Bergman et al

Supramolecular Chemistry

Selective C–H Bond Activation by a Supramolecular Host–Guest Assembly**

Angew. Chem. Int. Ed. 2004, 43, 963.

Dennis H. Leung, Dorothea Fiedler, Robert G. Bergman, and Kenneth N. Raymond**

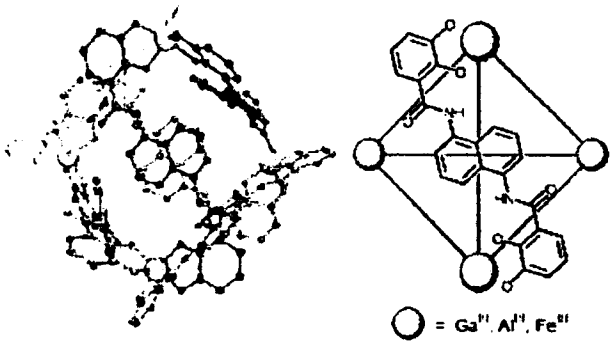
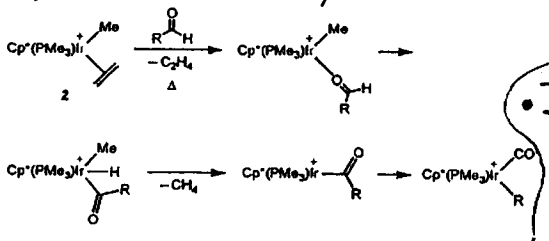


Figure 1. Left: view down the twofold axis of the crystal structure of the tetrahedral supramolecular $[M_4L_6]^{12-}$ host which can encapsulate monocationic guest molecules. Ligands are colored for differentiation. Right: schematic representation showing the structure of one of the six identical ligands that span the edges of the tetrahedral host.

supramolecular encapsulations and reactivity studies of organometallic complexes

- $[M_4L_6]^{12-}$ stoichiometry ($M = Ga^{3+}, Al^{3+}, Fe^{3+}$; L = bis(bidentate) catecholamide
- homochiral Δ,Δ,Δ,Δ- or Λ,Λ,Λ,Λ- clusters (with Δ or Λ configuration at each metal center) racemic
- highly negative(12-) — soluble in polar solvents, such as water
- hydrophobic cavity inside — encapulation of hydrophobic monocations.

Angw. Chem. Int. Ed 1998, 37, 1840. ibid. 2000, 39, 1239. JACS, 1998, 120, 8003. Inorg. Chem. 2004, 43, 846, etc.



Scheme 1. Mechanism of C–H bond activation with aldehydes.

- C-H activation catalyzed by Ir-complex $[Cp^*(PMe_3)Ir(Me)OTf]$ 1

- Is it possible to encapsule the Ir-complex 1 ?
- possible to realize C-H activation in the cavity ?
- selectivity ?

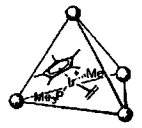
encapsuled

$[Cp^*(PMe_3)Ir(Me)(C_2H_4)][OTf] + [Na_4(NMe_4)_7][NMe_4 \subset Ga_4L_6]$

2

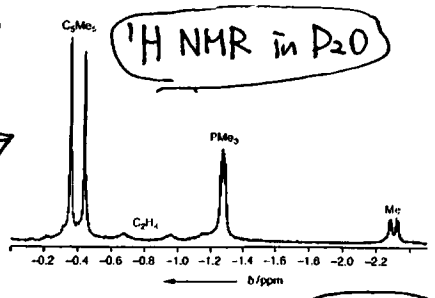
$\longrightarrow [Na_3(NMe_4)_8][Cp^*(PMe_3)Ir(Me)(C_2H_4) \subset Ga_4L_6]$

3a

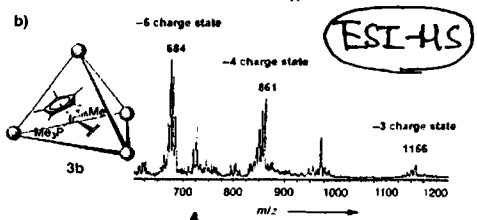


Two-diastereomeric host-guest assemblies

e.g.) Cp* protons are shifted upfield from a single peak at δ = 1.96 ppm for the unbound species to Two signals at δ = −0.35, and −0.44 ppm.



^{1}H NMR in D_2O



ESI-MS

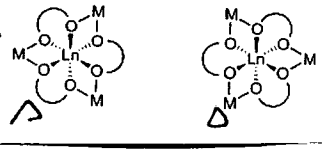
$2 + Na_{12}[Ga_4L_6] \longrightarrow Na_{11}[Cp^*(PMe_3)Ir(Me)(C_2H_4) \subset Ga_4L_6]$

3b

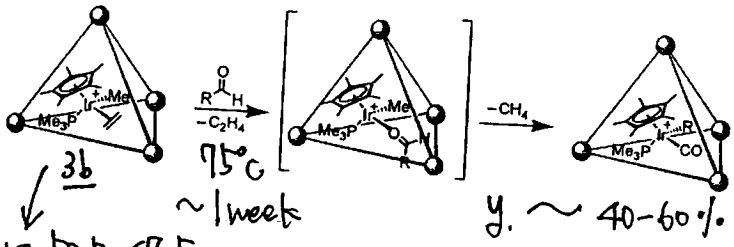
Cf.)

Chart 2. Possible Configurations of $M_3[Ln(binol)_3]$-Type (LnMB) Complexes

from (S)-BINOL



$[Cp^*(PMe_3)Ir(Me)(C_2H_4)][OTf]$ (2) + RCHO $\xrightarrow[75°C]{H_2O}$ $[Cp^*(PMe_3)Ir(R)(CO)][OTf]$ + $C_2H_4\uparrow$ + $CH_4\uparrow$



3b

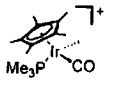
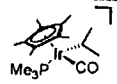
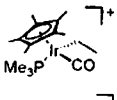
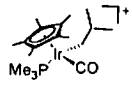
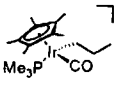
75°C ~1 week

y. ~ 40-60%

dr 52.5:47.5

$Na_{12}[Ga_4L_6]$ + $[Cp^*(PMe_3)Ir(R)(CO)][OTf]$ ← 75°C

· for 4, 5, 6, some diastereoselectivity was observed.

	Substrate	Guest product[a]	d.r.		Substrate	Guest product[a]	d.r.
4			60:40	9			55:45
5			65:35	10			58:42
6			70:30	11		n. r.	n/a
7		n. r.	n/a	12		n. r.	n/a
8		n. r.	n/a				

[a] n. r. = no reaction.

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- 4 (0.5eq) + 5 (0.5eq) + 2 (unencapsuled Ir-complex) $\xrightarrow{75°C}$ 1:1 ratio (from 4 or 5)
- 4 + 5 + 3b $\longrightarrow$ only one complex from 4 + 5 (unreacted)