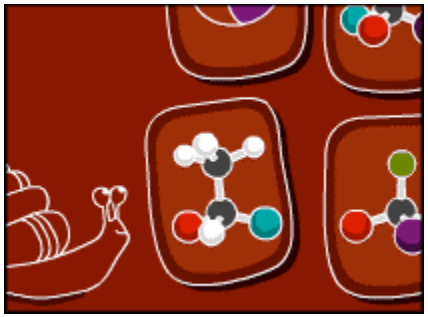
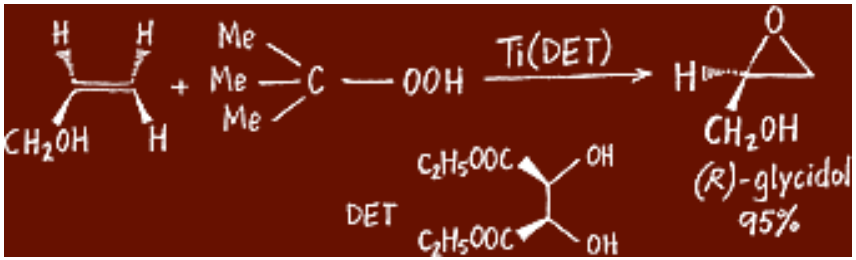




Nonlinear Effects (NLE) in Asymmetric Catalysis

by Tummanapalli Satyanarayana, Susan Abraham, and Henri B. Kagan*

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

Karla Bravo

Current Literature

02/14/2009

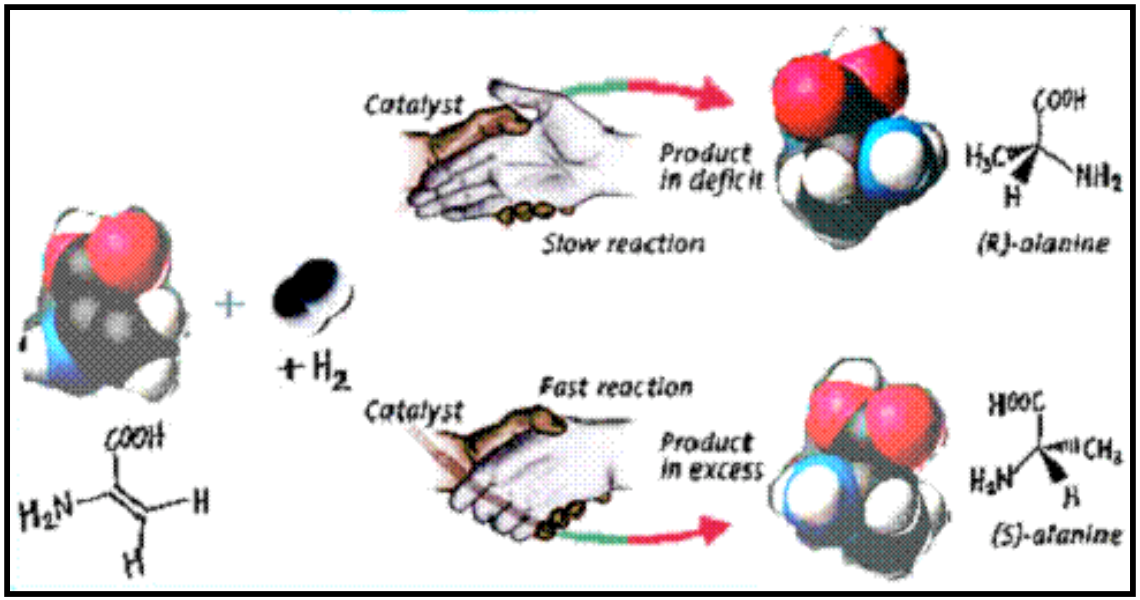
http://nobelprize.org/nobel_prizes/chemistry/laureates/2001/illpres/catalyst.html

How does a chiral molecule function in asymmetric catalysis?

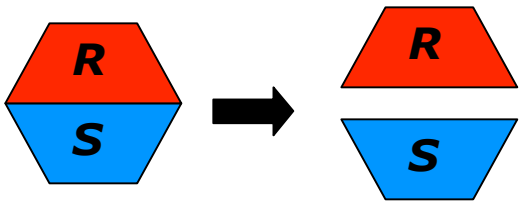
Research Labs & Industry Goals: Prepare drug candidates of defined configuration for biological tests.

Fact: The substances used as the starting point for these syntheses are in general *not* chiral.

Chemists approach: Use of **chiral auxiliaries (catalysts)** to control the production of the desired chiral product

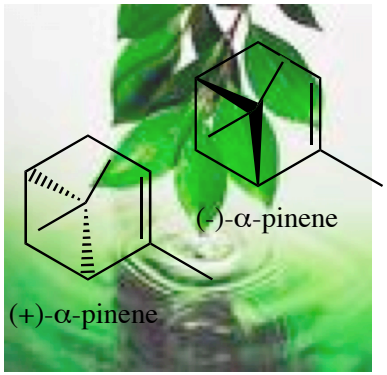


resolution of racemates ← chiral auxiliary → natural products



max. yield = 50%

often non enantiopure!!

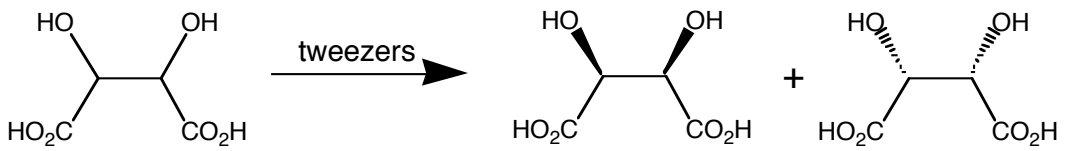


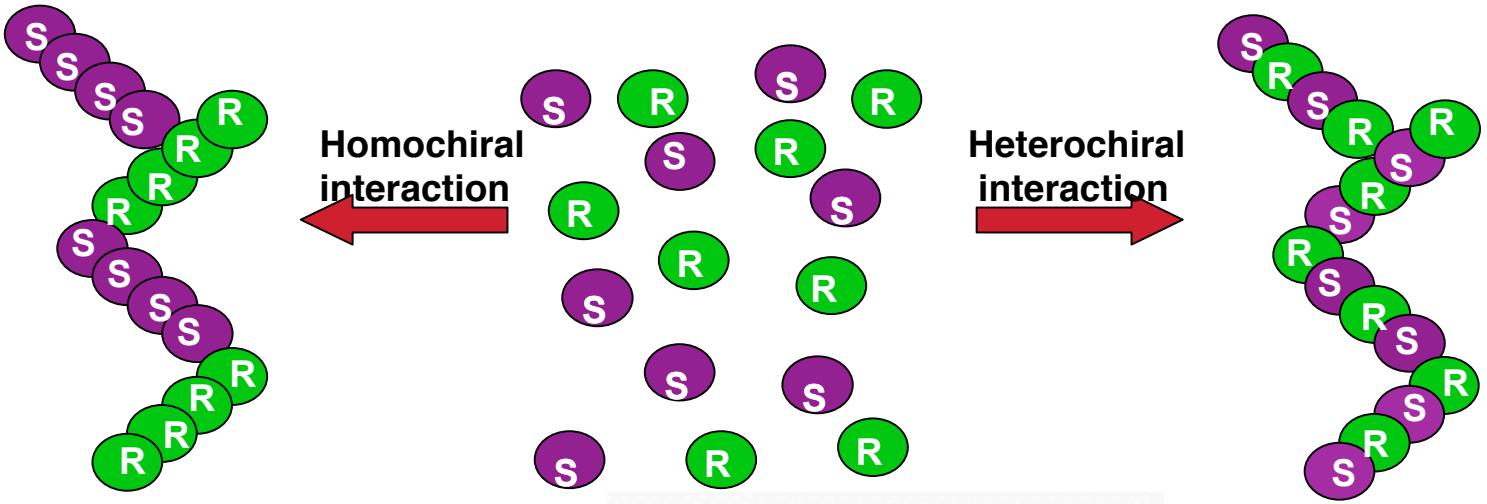
70-90% ee

http://www.nobel.se/chemistry/educational/poster/2001/catalyst.html

Self & nonself recognition of enantiomers at the molecular level: aggregation

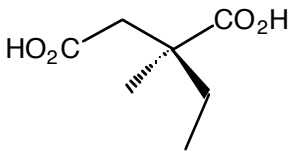
Solid state: Pasteur (1848)[1] & Noyori (2001)[2]



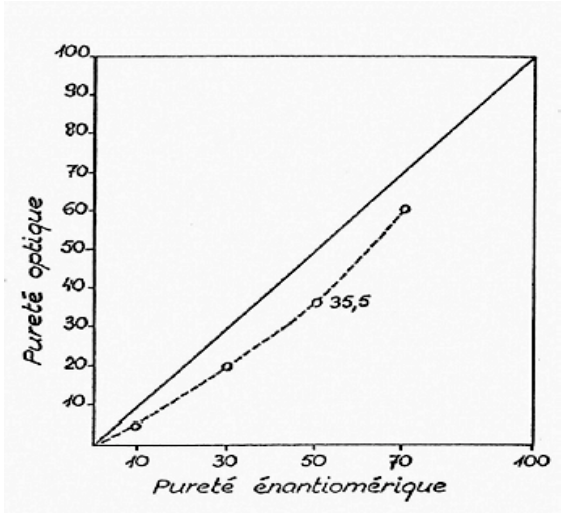


Solution: Houreau (1969)[3]

NLE in specific rotation



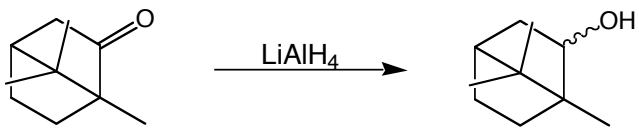
2-methyl-2-ethyl succinic acid



[1] Pasteur, L. *Ann. Chim. Phys.* **1848**, *24*, 442; [2]R. Noyori, S. Suga. *The Chemical Record* **2001**, *1*, 85; [3] A. Houreau, *Tetrahedron Lett.* **1969**, 3121.

Nonlinear effect in chemical reactions

Dependence of chemical reactivity on *ee* of starting material: **reactivity = f(ee_{SM})**

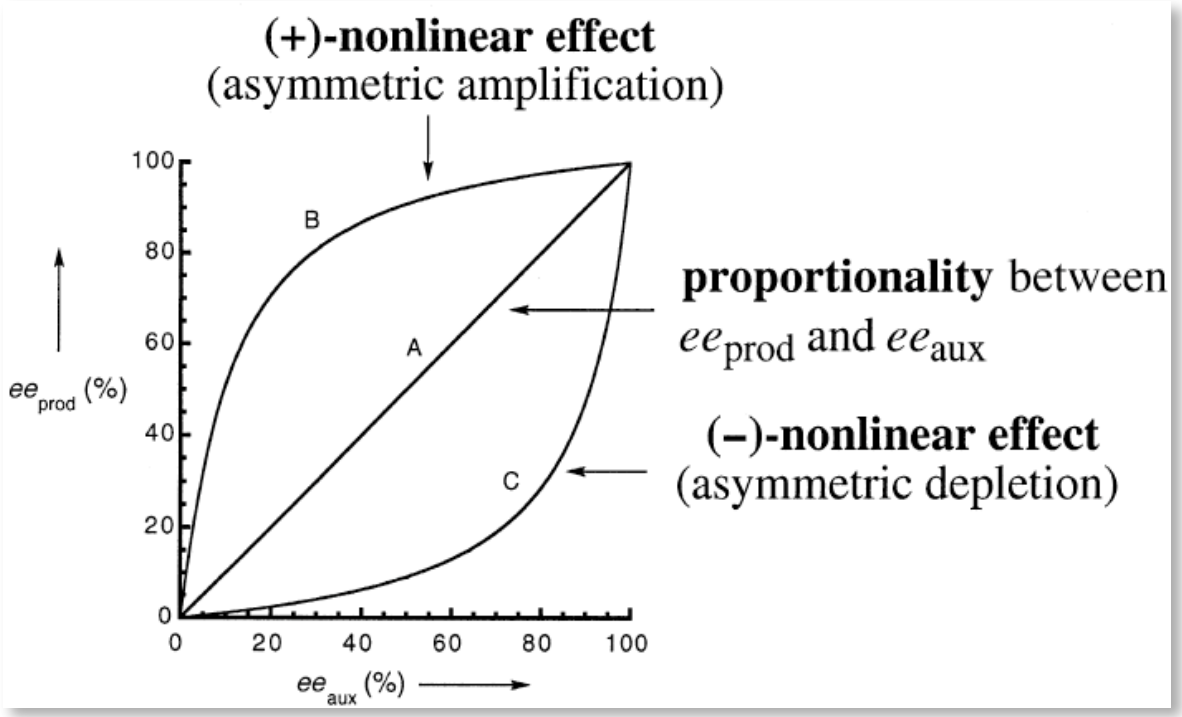


	Isoborneol (%)	Borneol (%)
d-(+)-camphor	90.2	9.8
dl-camphor	88.7	11.3

"When a chiral substance undergoes a reaction, the reaction rate and product ratio will depend, upon the enantiomeric excess present in the starting material" … Feringa et al. (1976) *Tetrahedron* **1976**, *32*, 2831.

Kagan (1986)[1]

ee_{aux} = f (asymmetric induction) ?



Linear relationship (Curve A) :

$$ee_{prod} = ee_o\ ee_{aux}$$

$ee_o = ee_{prod}$ *using auxiliary* $ee_{aux}=100$

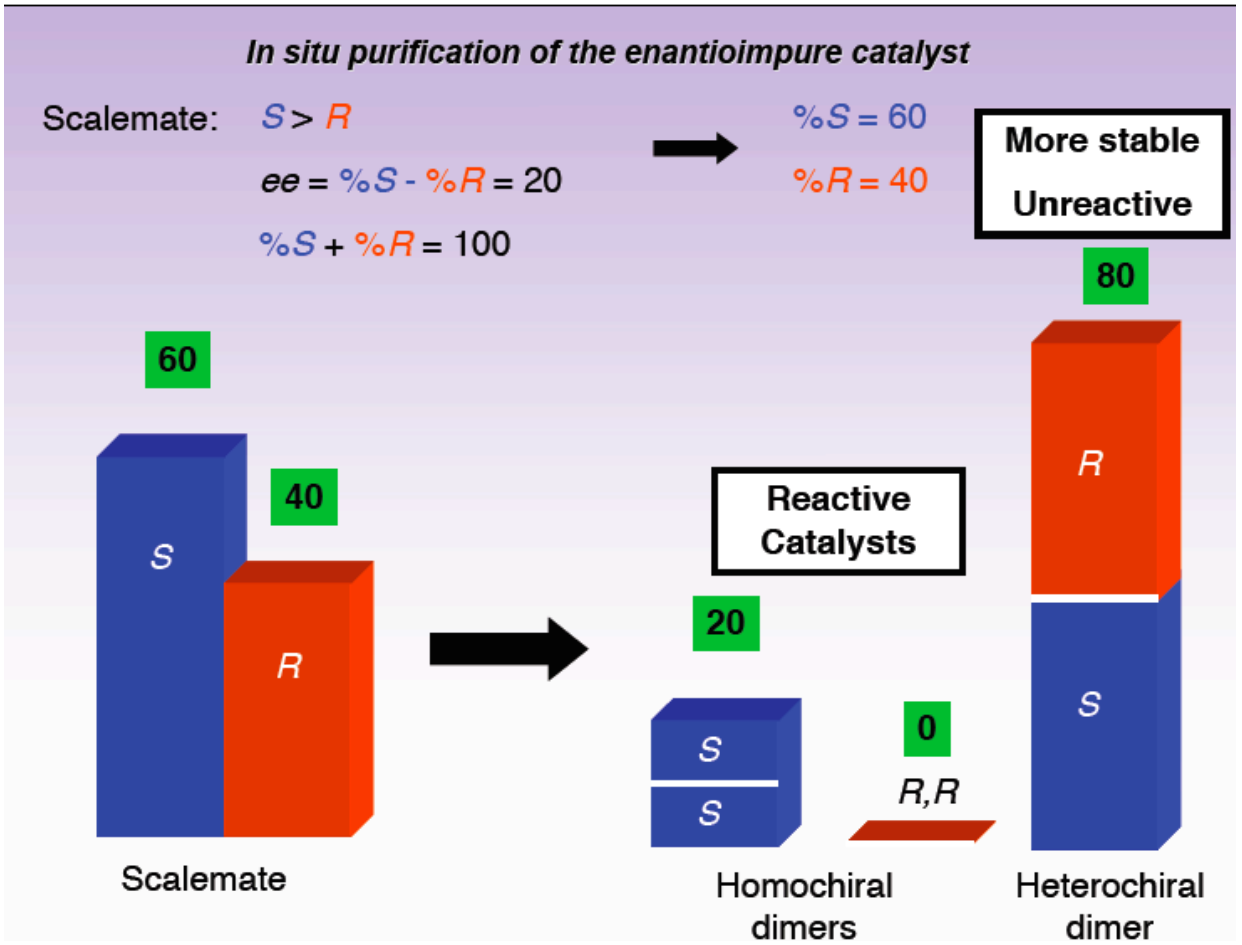
C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353

NLE in Asymmetric Catalysis *(title review)*

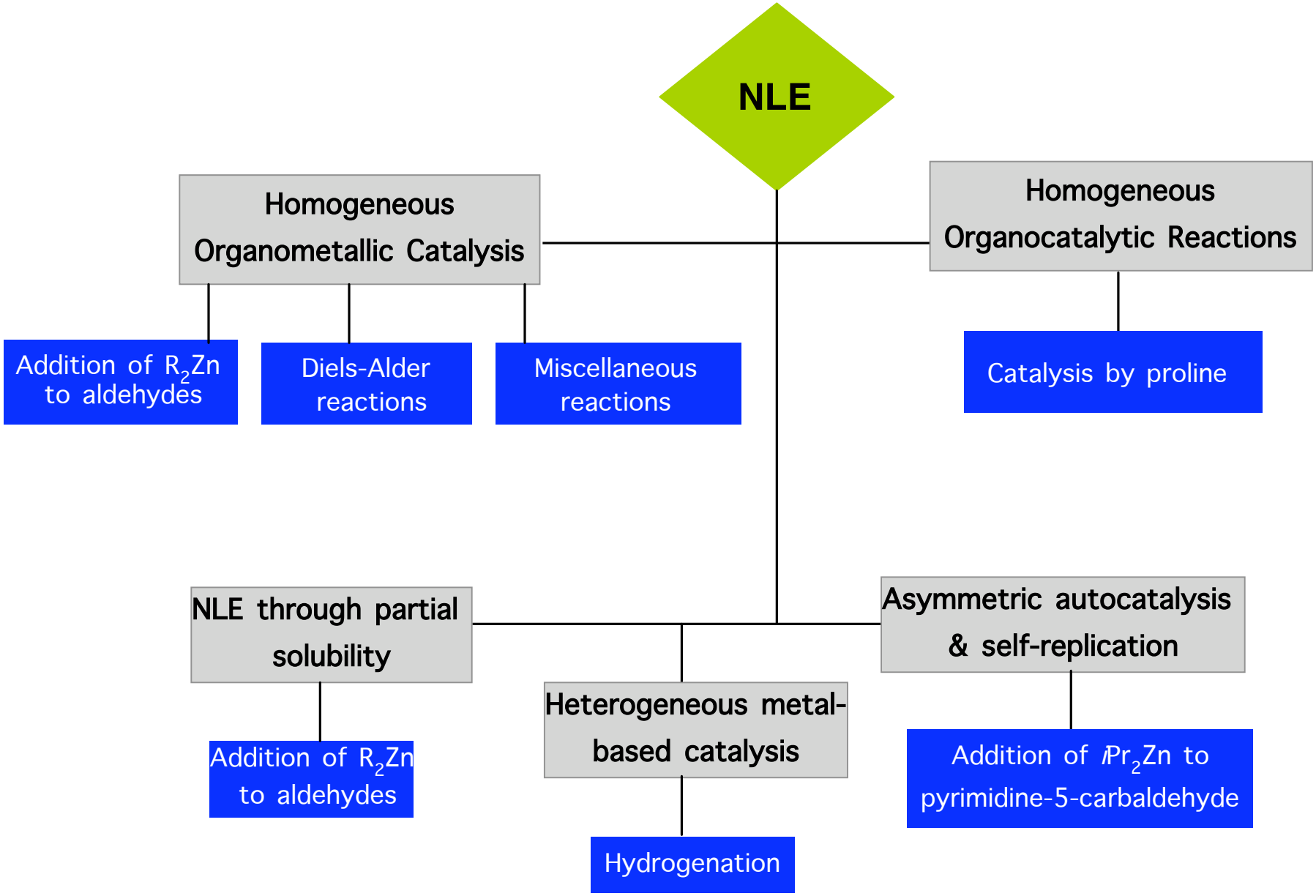
"When autoassociation or formation of multiligand catalysts occur, Eq 1 generally is no longer obeyed, because diastereomeric species may be produced which are impossible to generate from the enantiopure auxiliaries" …. ***from Angew. Chem. Int. Ed.* 2009, *48*, 456-494**

$$ee_{prod} = ee_o\ ee_{aux} \quad \textbf{(Eq 1)}$$

(+)-NLE

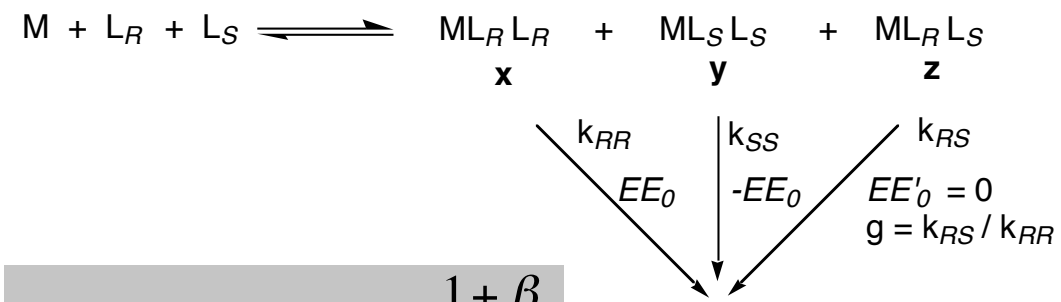


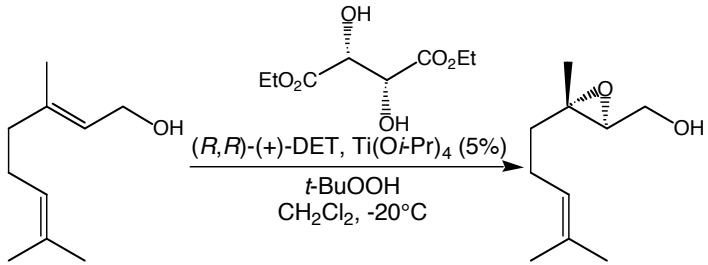
Impact of NLE studies on asymmetric catalysis



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

Theoretical models of NLE. (a) for ML_2 systems: Sharpless epoxidation of geraniol

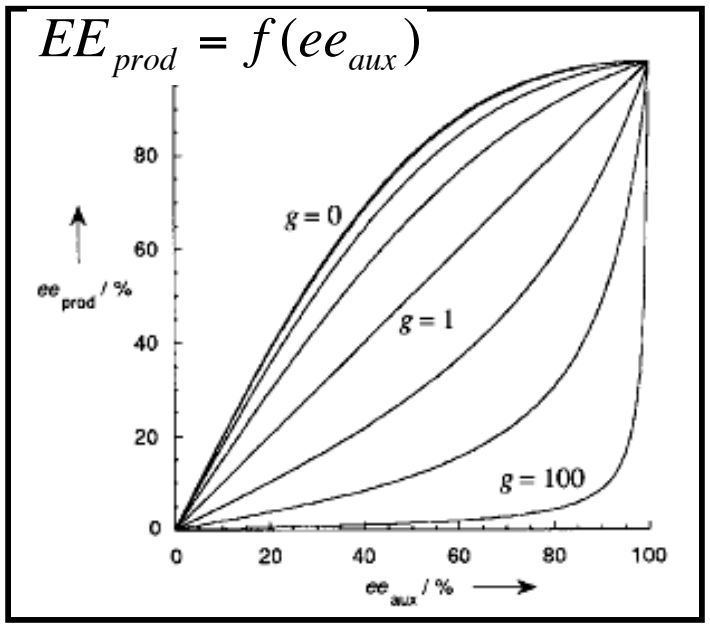


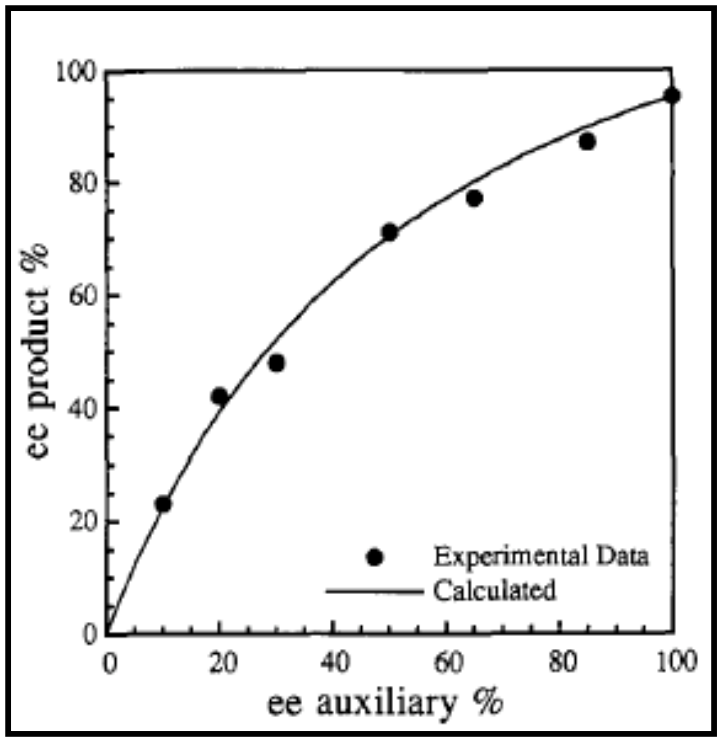


$$EE_{prod} = EE_o \bullet ee_{aux} \frac{1+\beta}{1+g\beta}$$

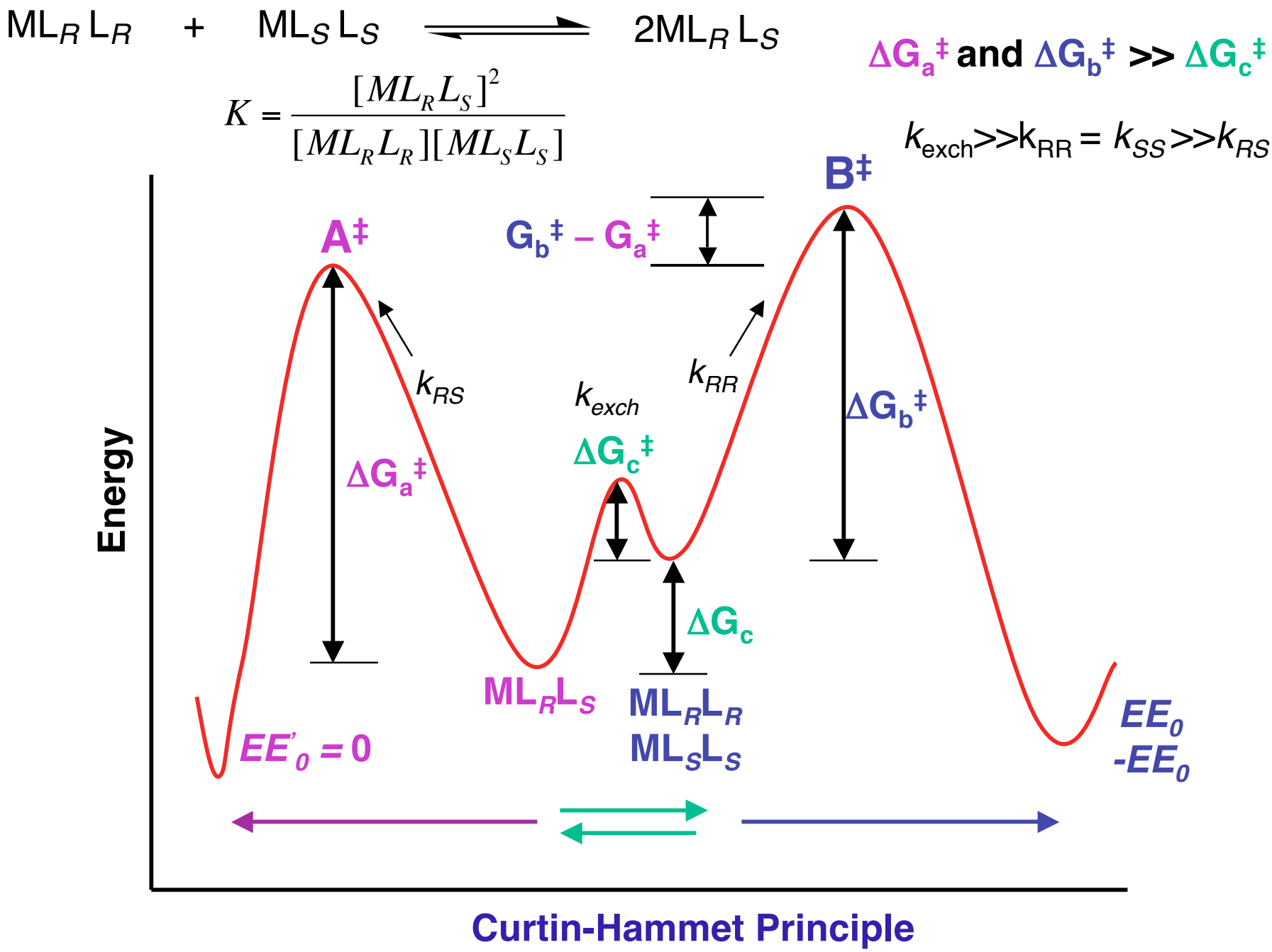
EEo = 95%, K = 1000, g = 0.35

$$\beta = \frac{z}{x+y} \qquad g = \frac{k_{RS}}{k_{RR}} \qquad \beta = f(K, ee_{aux})$$

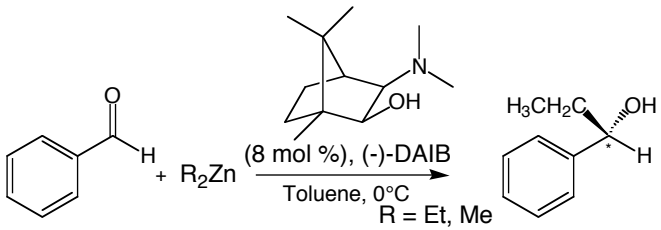




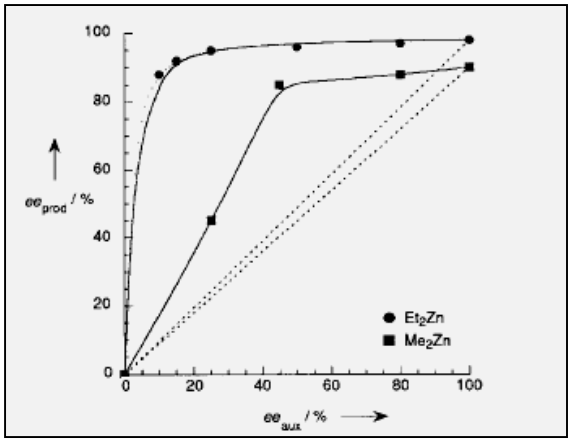
K. Katsuki; K. B. Sharpless. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
D. Guillaneux; S. Zhao; O. Samuel; D. Rainford; H. B. Kagan. *J. Am. Chem. Soc.* **1994**, *116*, 9430.


ML_R L_R + ML_S L_S ⇌ 2ML_R L_S
K = [ML_R L_S]^2 / [ML_R L_R][ML_S L_S]
ΔG_a‡ and ΔG_b‡ >> ΔG_c‡
k_exch>>k_RR = k_SS>>k_RS
A‡
B‡
G_b‡ – G_a‡
k_RS
k_exch
k_RR
ΔG_a‡
ΔG_c‡
ΔG_b‡
ΔG_c
Energy
ML_R L_S
ML_R L_R
ML_S L_S
EE'_0 = 0
EE_0
-EE_0
Curtin-Hammet Principle

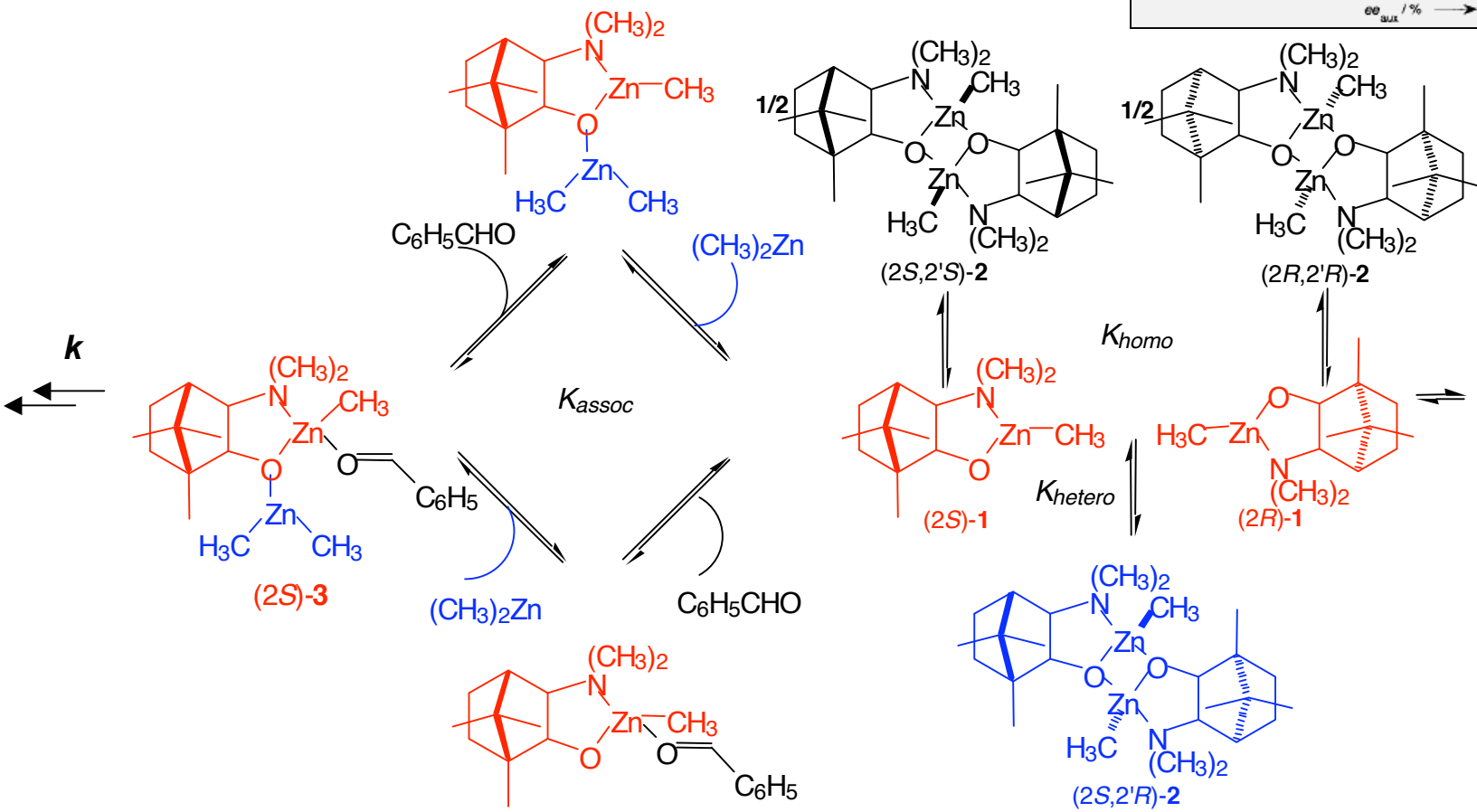
Theoretical models of NLE. (b)The Noyori model: Addition of R_2Zn to Benzaldehyde



L*	ee_{au} x	EE_{pro} d	Configuration
(-)-DAIB	100	98	***S***
(-)-DAIB	15	95	***S***

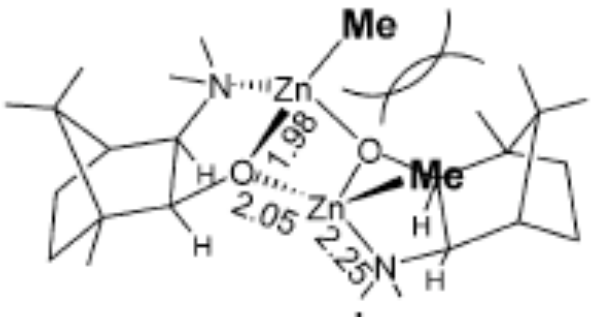


Model follows Curtin-Hammet Principle



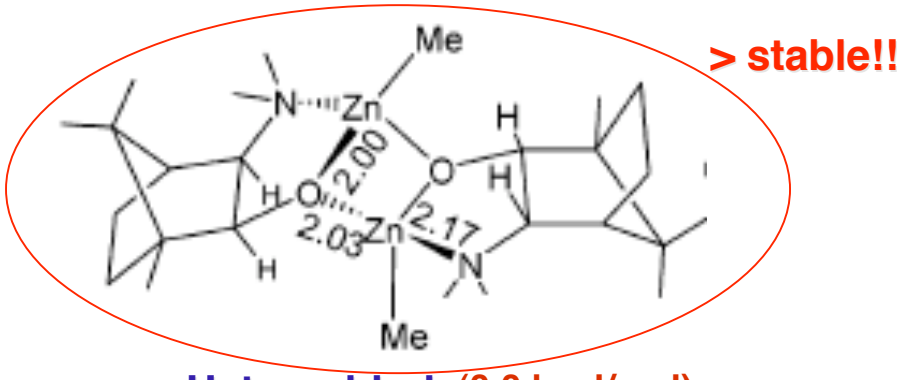
M. Kitamura; S. Okada; S.Suga; R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028.

Theoretical models of NLE (Cont…)



Homochiral (+ 3.1 kcal/mol)

$K_{homo} = (3.0 \pm 1.0) \times 10^{-2}$ M

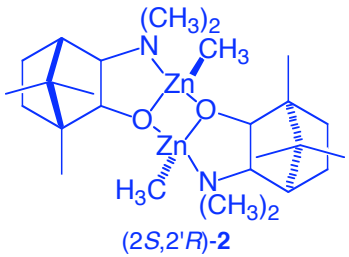


> stable!!

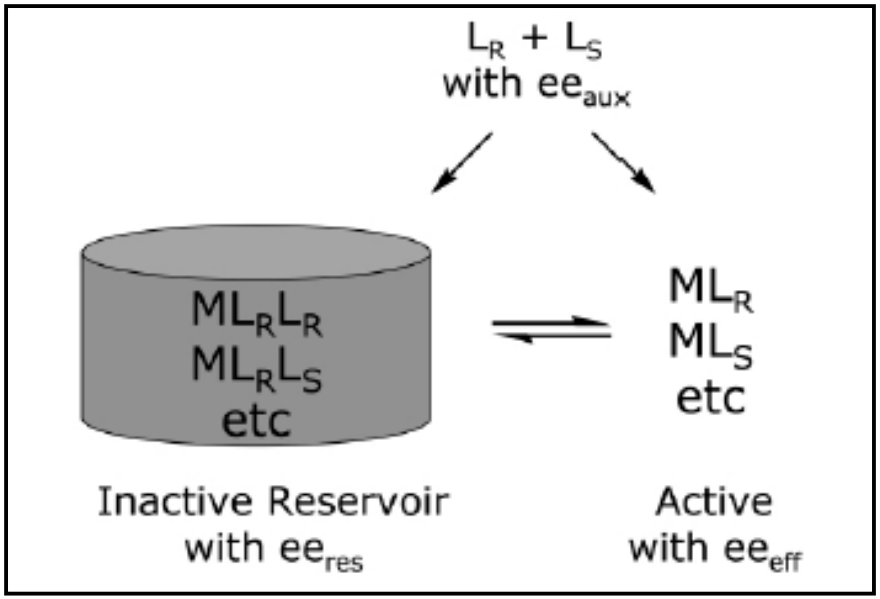
Heterochiral (0.0 kcal/mol)

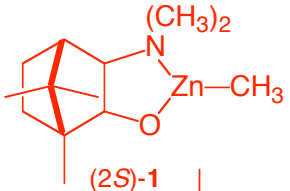
$K_{hetero} = 1 \times 10^{-5}$ M

(c) The reservoir effect: for the formation of various metal complexes, one being the active catalyst

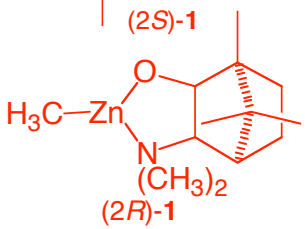


(2*S*,2'*R*)-**2**



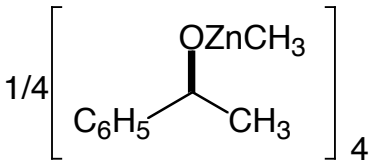


(2*S*)-**1**



(2*R*)-**1**

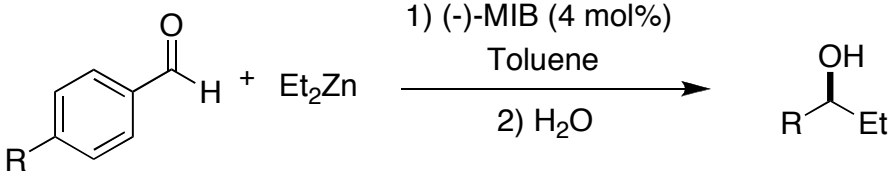
If [(2*S*)-1] >> [(2*R*)-1]

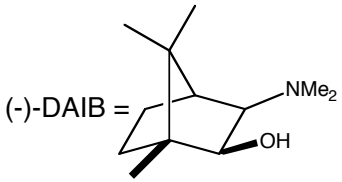


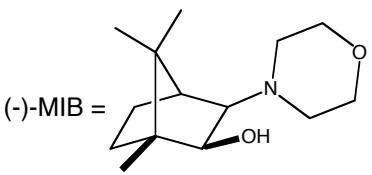
Product (*S*)-**5**

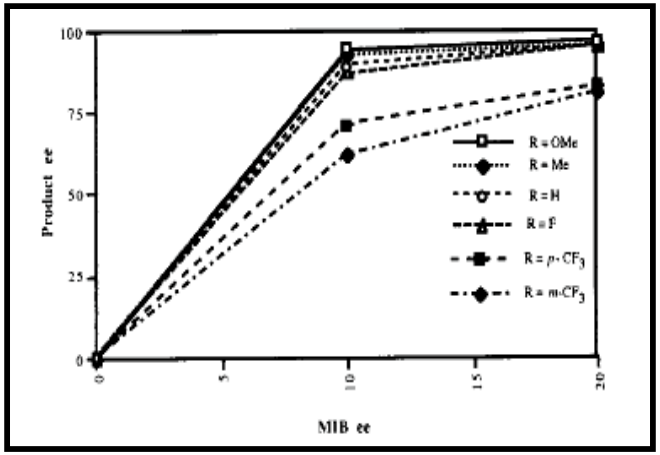
D. Guillaneux; S. Zhao; O. Samuel; D. Rainford; H. B. Kagan. *J. Am. Chem. Soc.* **1994**, *116*, 9430-9439.
M. Kitamura; M. Yamakawa; H. Oka; R. Noyori, *Chem. Eur. J.* **1996,** *2*, 1173.

Homogeneous Organometallic Cat.: Addition of R_2Zn to aldehydes (exception to the Noyori model)









***ee* of product vs *ee* of MIB for substituted benzaldehyde derivatives**

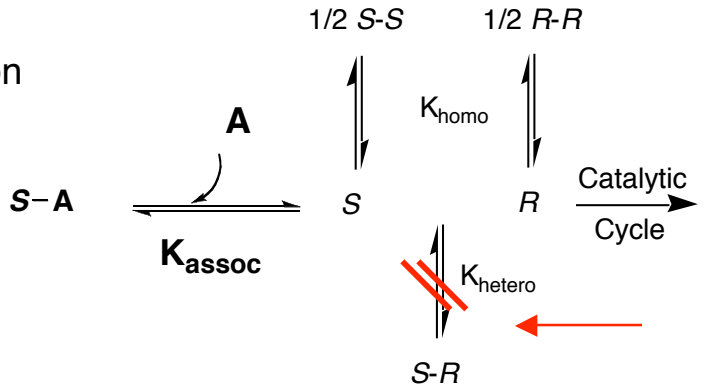
R	MIB 10% ee	MIB 20% ee	MIB 100% ee
OMe	94.5	96.9	98.4
Me	92.2	95.9	98.9
H	89.1	95.1	98.0
F	87.2	94.9	98.3
CF_3	71.3	82.6	97.3

Curtin-Hammet Principle is not obeyed with strongly binding electron-rich aldehydes!!

"The amount or total monomer available to be channeled into the catalytic cycle will depend of the strength of binding of substrate..."

Assumption: monomer/dimer equilibration after substrate binding is not so fast

Weak & Strong binding limits



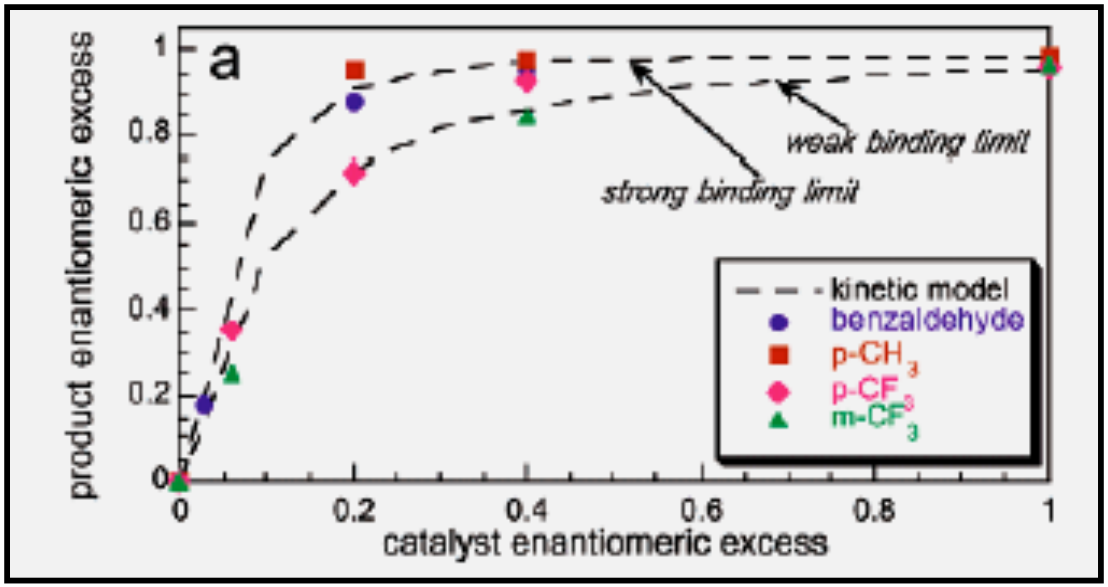
Strong binding limit
no reversibility
(slow equilibration)

Y. Chen; A. Costa; P. Walsh, *J. Am. Chem. Soc.* **2001**, *123*, 5378; F. Buono; P. Walsh; D. Blackmond, *J. Am. Chem. Soc.* **2002**, *124*, 13652.

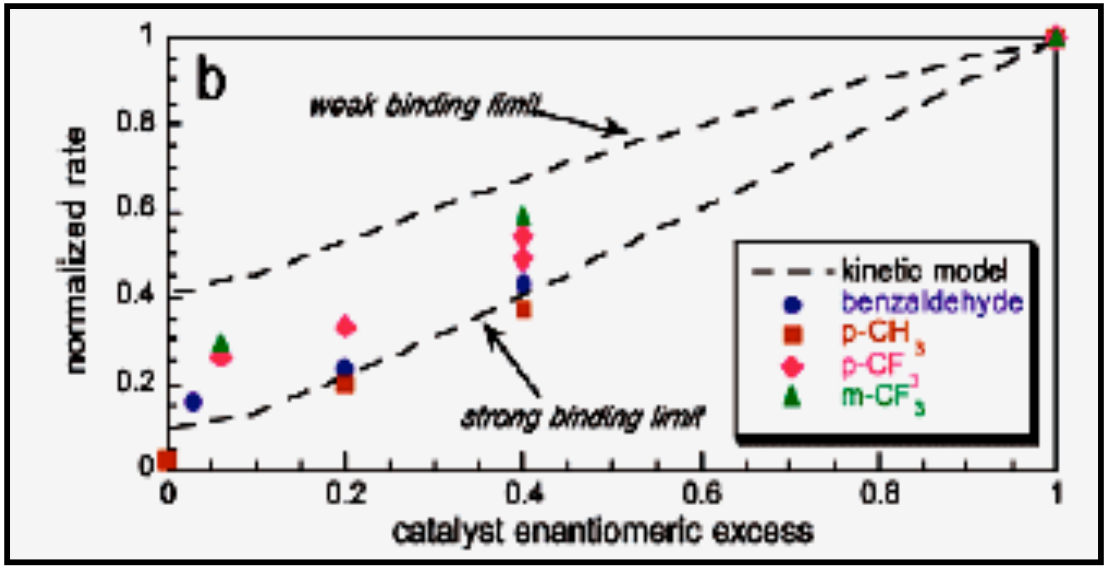
Homogeneous Organometallic Cat.: Addition of R_2Zn to aldehydes (exception to the Noyori model)

Validity of the Mathematical Treatment : calorimetric studies

"Catalyst composition may be a function of the substrate properties"



$K_{hetero} / K_{homo} = 30$

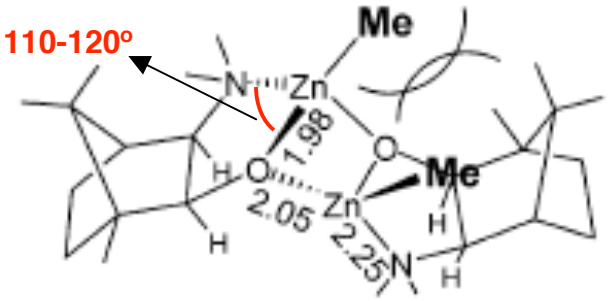


F. Buono; P. Walsh; D. Blackmond, *J. Am. Chem. Soc.* **2002**, *124*, 13652.

Homogeneous Organometallic Cat: Absence of NLE in R_2Zn addition to aldehydes by rational design

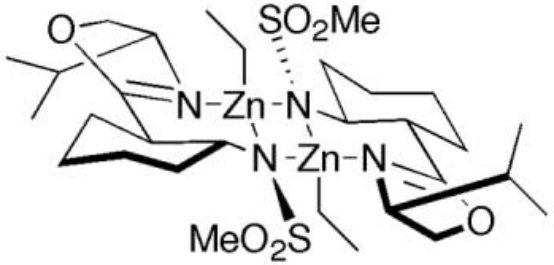
"The absence of an NLE is a good indication of the involvement of one ligand or chiral auxiliary in the catalytic cycle. However, this is not a proof, since linearity, for example, is possible with a ML2 system when g=1"…(title paper)

- Compression of the NZnN bond angle increases reactivity at Zn.
- Presence of Ms group on N precludes the 4-membered Zn_2N_2 ring.

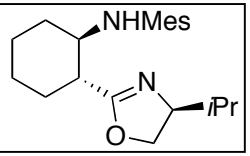


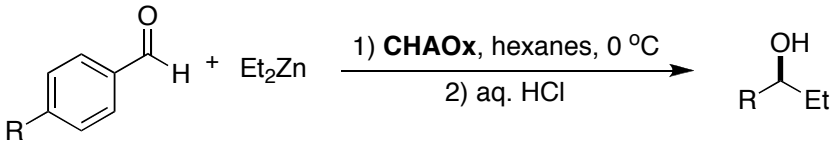
DAIB-Zn dimer

2 [**7**•ZnEt] ⇉ [(**7**•ZnEt)$_2$]



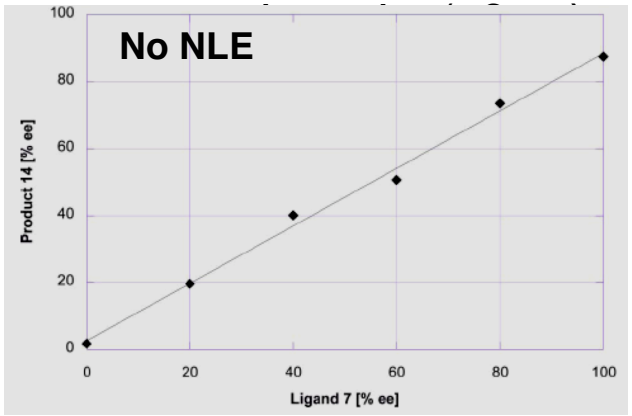
CHAOx =

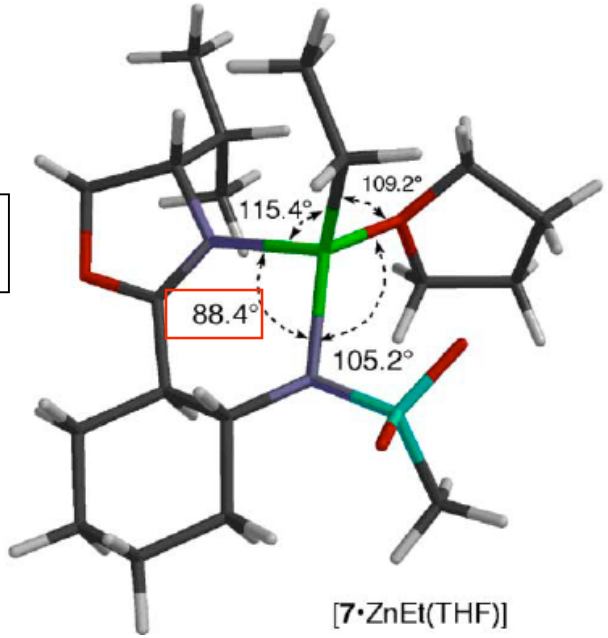




(**7**·ZnEt)$_2$ ⇌ **7**·ZnEt ➡

loadings 0.05 - 0.1 mol%
High turnover (1000 - 2000)





[**7**•ZnEt(THF)]

P. Wipf, J. G. Pierce, X. Wang, *Tetrahedron: Asymmetry* **2003**, *14*, 3605.

Homogeneous Organometallic Cat: Diels Alder & Hetero-Diels Alder reaction

"A scalemic organometallic catalyst can be prepared either directly from the scalemic ligand or by mixing two enantiopure catalysts. If there is an NLE in the first case and not in the second one, it is good evidence that the catalyst retains its integrity during the reaction."…(title paper)

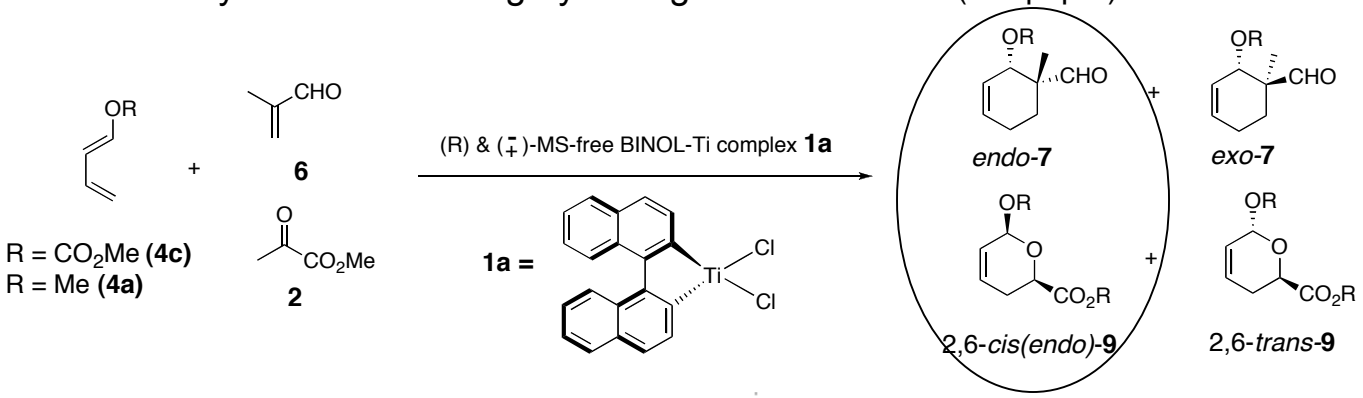
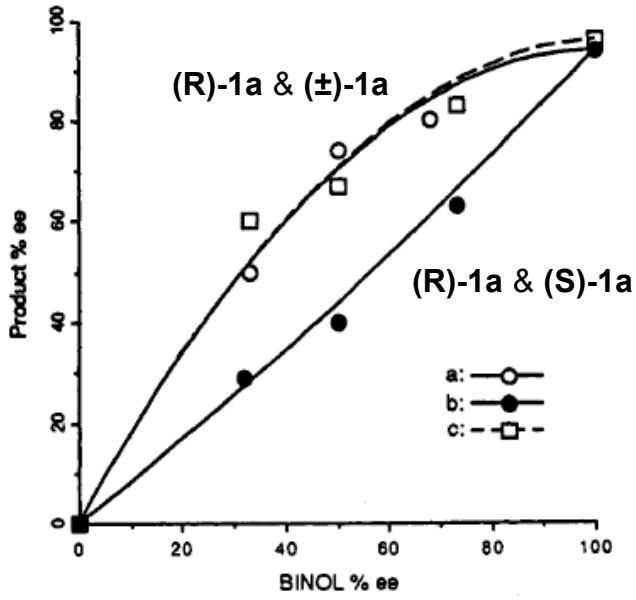


Table 3. Hetero-Diels–Alder Reaction Catalyzed by the Mixture of (*R*)- and (±)-MS-Free BINOL–Ti Complexes (**1a**)

4	dienophiles	1a (*x*% ee)	conditions	% yield	% *endo*	% ee[a]
4c	6	33	rt, 18 h	54	99	50
4c	6	50	rt, 18 h	50	99	74
4c	6	68	rt, 18 h	69	99	80
4c	6	100	rt, 18 h	63	99	94
4c	6	32[b]	rt, 18 h	42	98	29
4c	6	50[b]	rt, 18 h	62	99	40
4c	6	73[b]	rt, 18 h	51	98	63
4a	2	33	–30 °C, 1 h	43	72	60
4a	2	50	–30 °C, 1 h	50	77	67
4a	2	73	–30 °C, 1 h	60	86	83
4a	2	100	–30 °C, 1 h	78	88	96

[a] Refer to the major *endo*-isomer. [b] Catalyzed by the mixture of (*R*)- and (*S*)-MS-free BINOL–Ti complexes (**1a**).

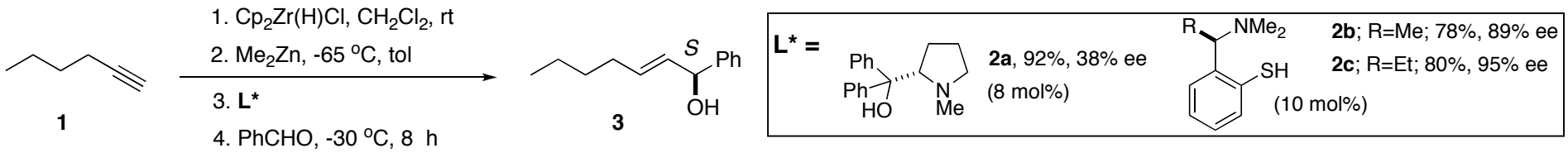


No M.S. ➡ (*R*)(*R*)-$\mathbf{1}_2$ + (*S*)(*S*)-$\mathbf{1}_2$ ⇌ (*R*)-**1** + (*S*)-**1** ⇌ (*R*)(*S*)-$\mathbf{1}_2$

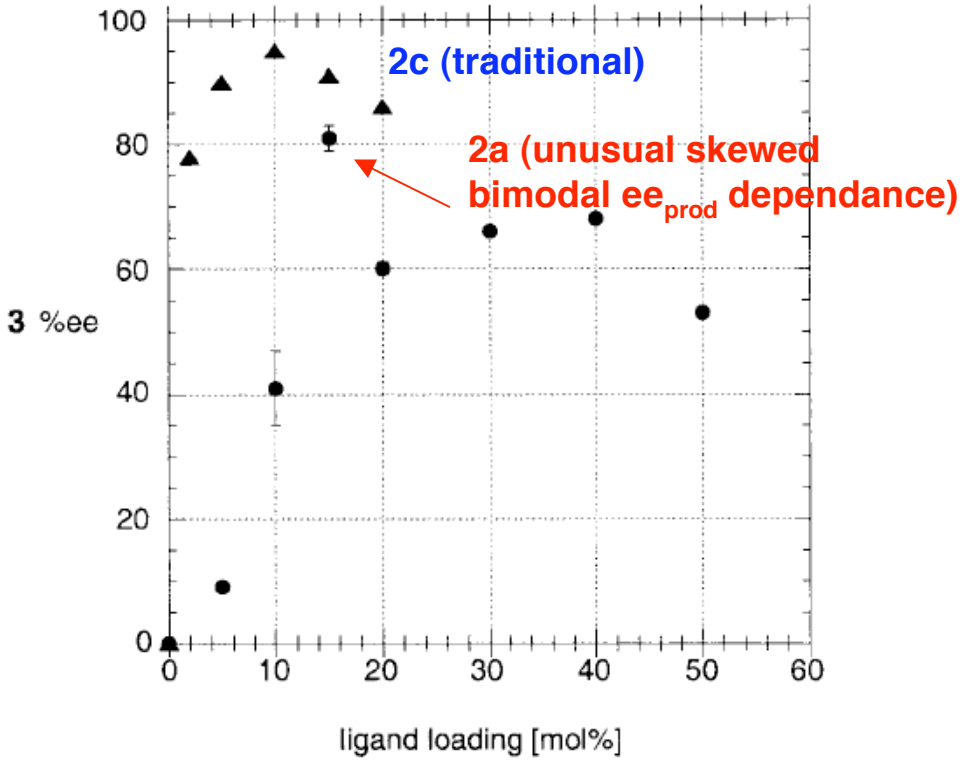
"no reservoir"

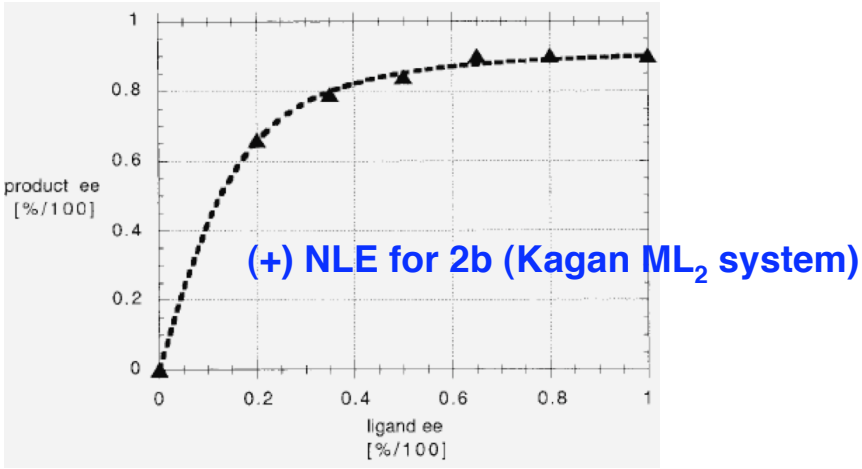
K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812.

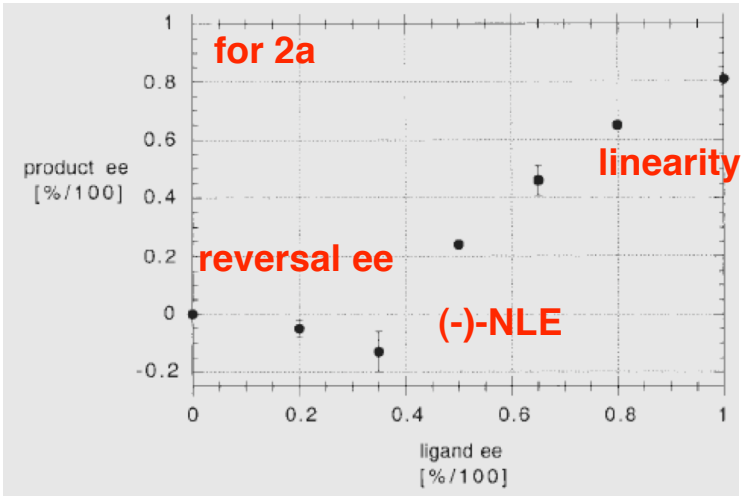
Homogeneous Organometallic Catalysis (Misc.) Alkenyl zirconocene/Zn addition to aldehydes



- Unusual NLE profile due to participation of monomeric and aggregated metal–ligand species in the catalysis.
- Rational for unusual NLE in **2a**: Lewis acid zirconocene species facilitate generation of tricoordinate Zn species



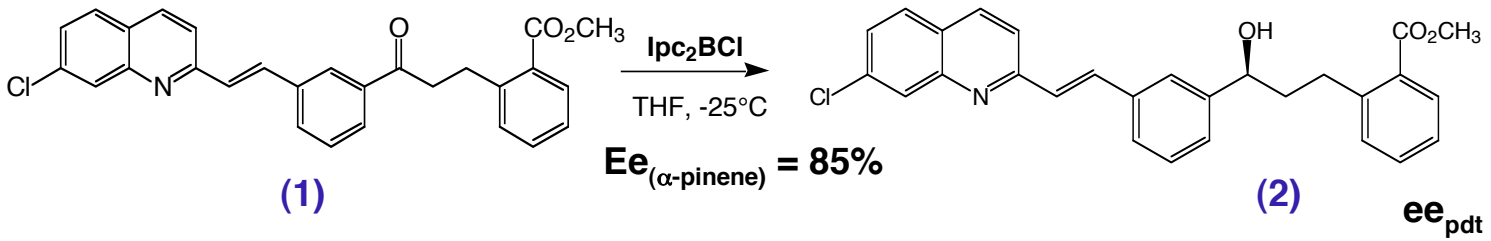




P. Wipf, N. Jayasuriya, S. Ribe, *Chirality* **2003**, *15*, 208.

Homogeneous Organometallic Cat. Misc. A practical exploitation of NLE in a stoichiometric reaction.[1]

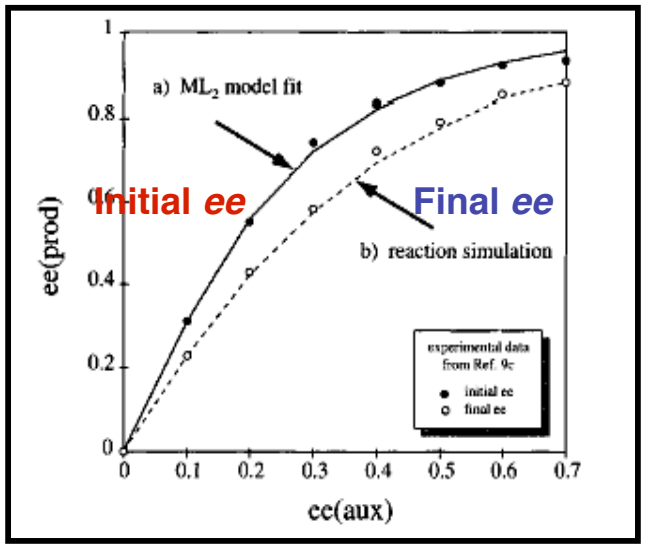
Preparation of an intermediate in the synthesis of a LTD_4 antagonist by Merck.



(1) $Ee_{(\alpha\text{-pinene})}$ = 85% (2) ee_{pdt} = 97%

Kinetic modeling approach applied to the Merck study.[2] (+)-NLE in Ipc_2BCl reduction of the ketone (1).

Relative concentrations or chiral auxilliary change over the course of the reaction → **Dynamic equilibrium**



Experimental and modeling results of NLE in the reduction of ketone **1** with 1 eq of Ipc_2BCl prepared from α-pinene.

Initial conditions

ML_2 Model: K = 49, g = 0.1

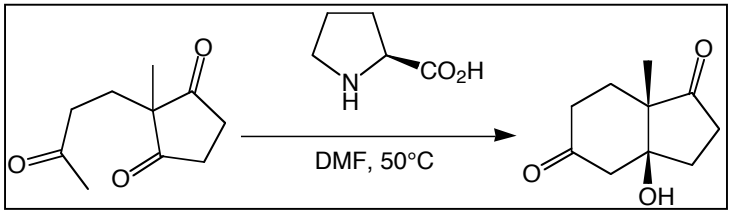
Final conditions:

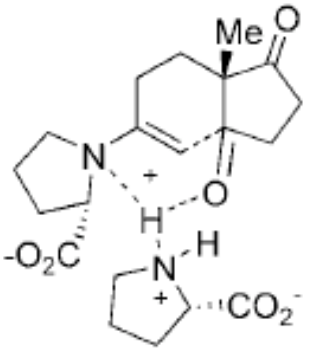
$$ee_{prod} = f(t)$$

[1] M. Zhao; A. O. King; R. Larsen; T. Verhoeven; P. Reider, *Tetrahedron Letters,* **1997**, *38,* 2641; [2] D. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402.

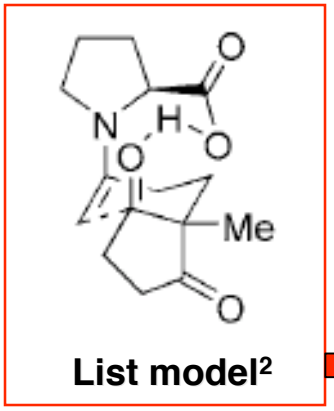
Homogeneous Organocatalytic Reactions: Catalysis by proline

- **Agami et al. (1985)[1]: (-)-NLE vs No NLE**

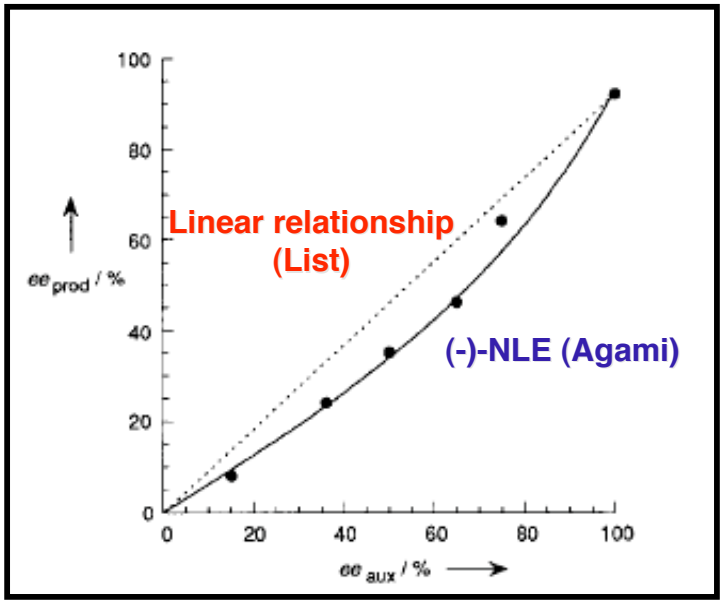




Agami model[1]

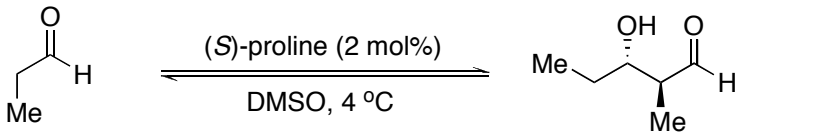


List model[2]



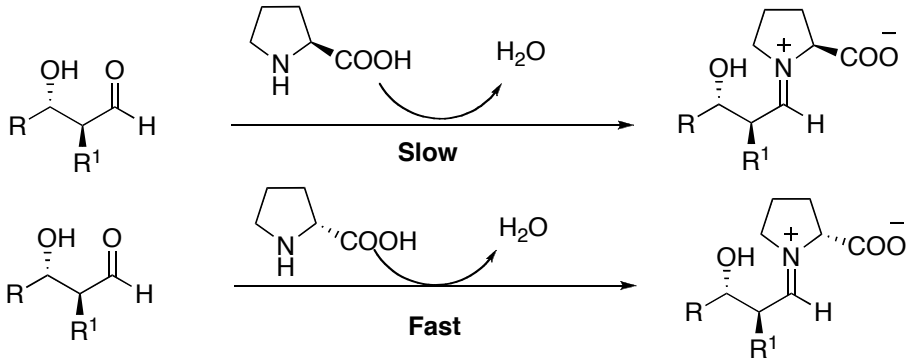
supported by kinetic studies, theoretical calculations!!

- **Córdova et al. (2006)[3]: (+)-NLE**



(68% yield, 4:1 d.r., 98% *ee*)

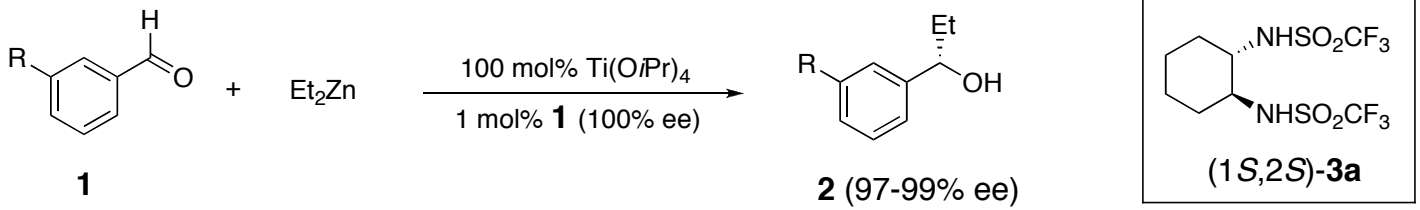
(+)-NLE source: kinetic resolution of the catalyst by the product



[1]C. Agami, C. Puchot. *J. et al. Chem. Soc. Chem. Commun.* **1985**, 441; [2] L. Hoang; S. Bahmanyar; K. Houk; B. List. *J. Am. Chem. Soc.* **2003**, *125*,16;
[3] A. Cordova, H. Sundn, Y. Xu, I. Ibrahem, W. Zou, M. Engqvist, *Chem. Eur. J.* **2006**, *12*, 5446.

NLE through partial solubility: Addition of R_2Zn to aldehydes

- **Ohno–Kobayashi (1989).**[1]



Ohno–Kobayashi.

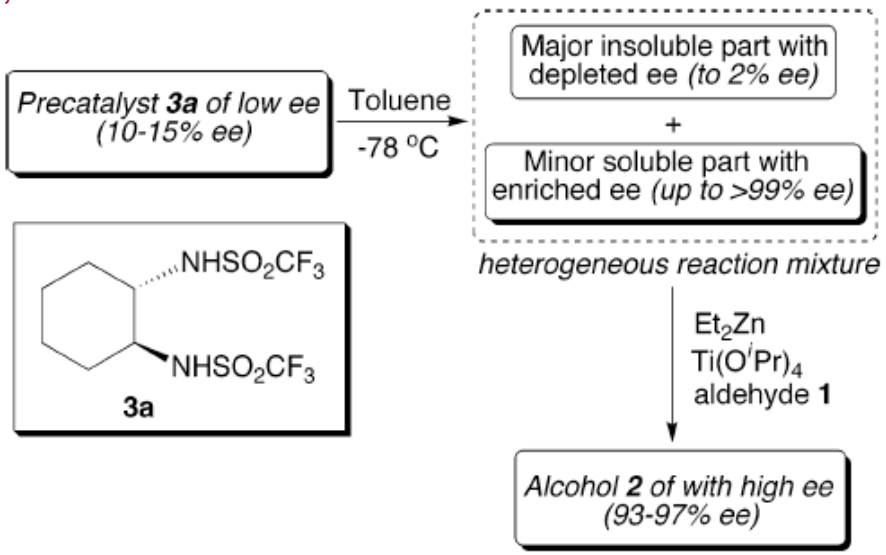
3a + $Ti(OiPr)_4$ (-40 °C) → **1** + R_2Zn (-78 °C)

Walsh[2] : No NLE

3a + R_2Zn (rt) → $Ti(OiPr)_4$ + **1** (-78 °C)

- **Kagan studies of Ohno–Kobayashi system.**[3,4]

"The partial solubility of non-enantiopure auxiliaries or complexes in the experimental conditions of the reaction may generate NLEs. The insoluble racemate compound usually acts as a reservoir of the racemic auxiliary, hence enhancing the *ee* value of the actual catalyst"… *(title paper)*



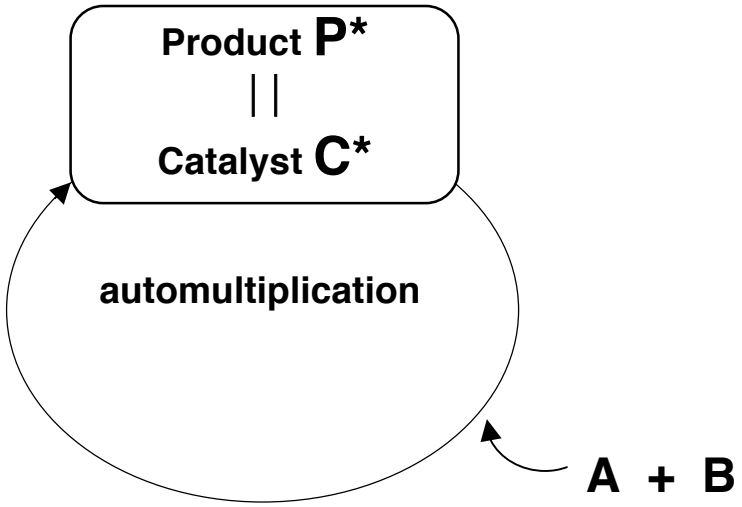
[1] H. Takahashi, T. Kawakita, M. Yoshioka, S. Kobayashi, M. Ohno, *Tetrahedron Lett.* **1989**, *30*, 7095; [2] S. Pritchett, D. H. Woodmansee, P. Gantzel, P. J. Walsh, *J. Am. Chem. Soc.* **1998**, *120*, 6423; [3] T. O. Luukas, D. R. Fenwick, H. B. Kagan, *C. R. Chim.* **2002**, *5*, 487; [4] T. Satyanarayana, B. Ferber, H. B. Kagan, *Org. Lett.* **2007**, *9*, 251.

Asymmetric Autocatalysis

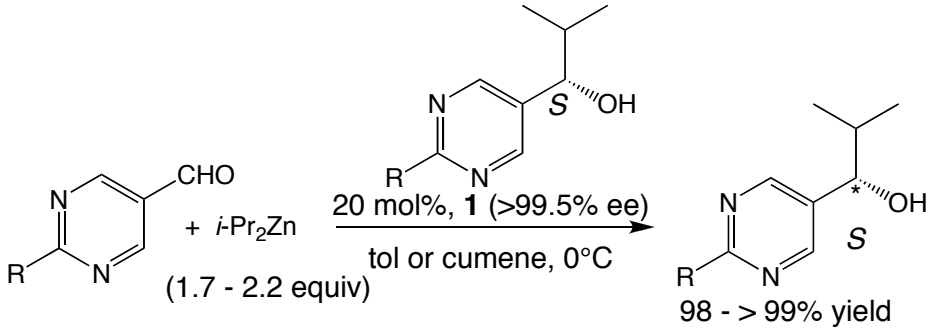
Enantioselective synthesis in which the chiral product acts as an asymmetric catalyst for its own production.

Advantage

Enantiomerically enriched product in each reaction can be used as asymmetric autocatalyst for the next run!!



The "close to perfect" asymmetric autocatalysis



1 & Pdt.

1a: R = H	93.3% ee	toluene
1b: R = Me	98.2% ee	
1c: R = t-Bu	99.3% ee	
1d: R = t-Bu	>99.5% ee (*S*)	cumene
1e: R =	>99.5% ee (*R*)	

Consecutive asymmetric autocatalysis

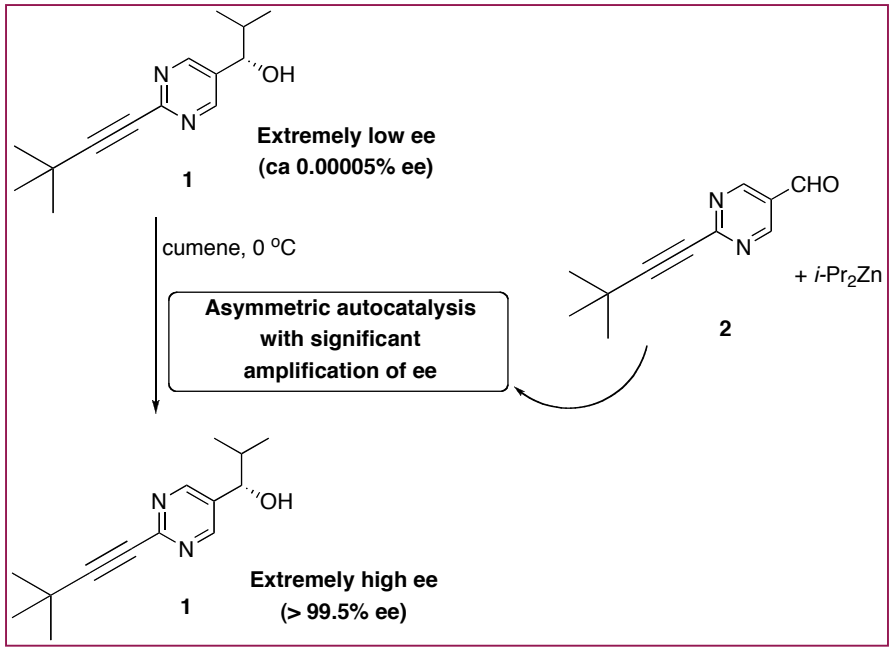
Run	Catalyst **1**	Pdt yield, % (% ee)	Amplified factor
1st	> 99.5 (1a)	> 99 (> 99.5) (1b)	6
2nd	> 99.5 (1b)	> 99 (> 99.5) (1c)	6^2
5th	> 99.5 (1e)	> 99 (> 99.5) (1f)	6^5
7th	> 99.5 (1g)	> 99 (> 99.5) (1h)	6^7
10th	> 99.5 (1k)	> 99 (> 99.5) (1l)	$6^{10} \sim 10^7$

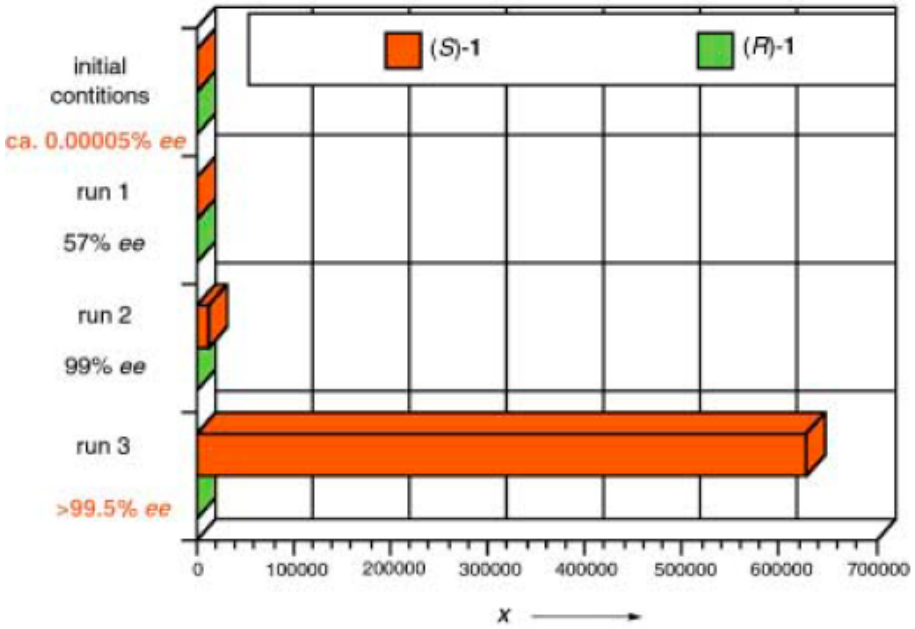
Unlimited!!

T. Shibata, S. Yonekubo, K. Soai, *Angew. Chem. Int. Ed.* **1999**, *38*, 659.
K. Soai; I. Sato, *Chirality* **2002**, 14, 548.

Asymmetric Autocatalysis (Cont..)

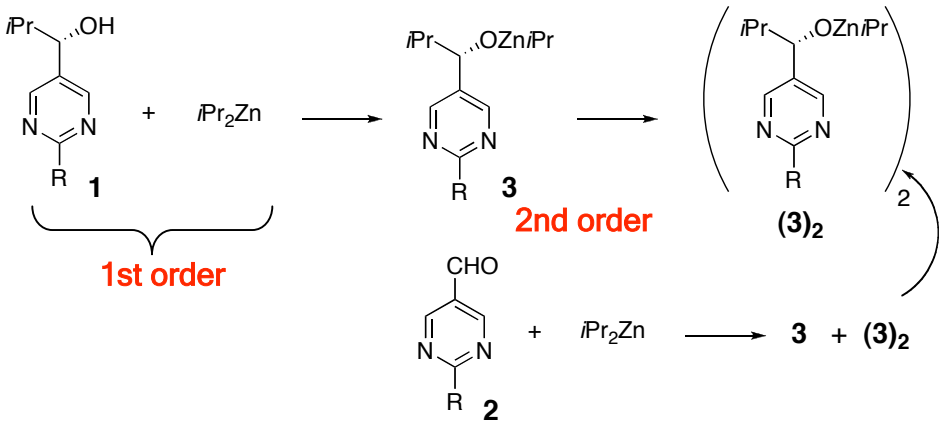
Amplification of Chirality from Extremely Low to Greater than 99.5% ee[1]

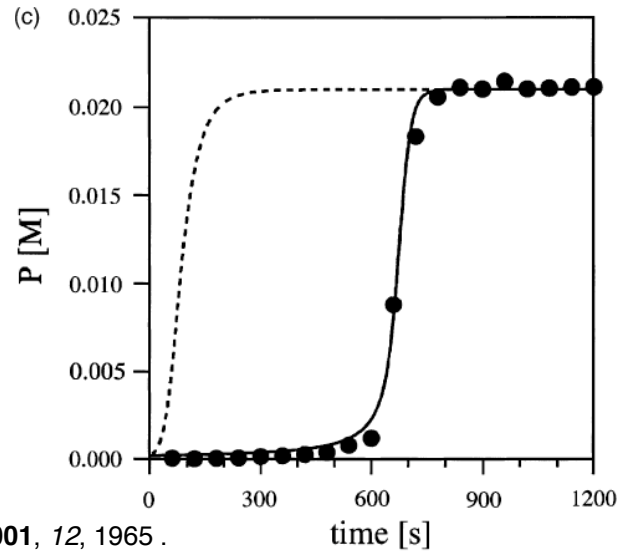




Increase in the amount of S and R isomers by the factor x during consecutive asymmetric autocatalyses.

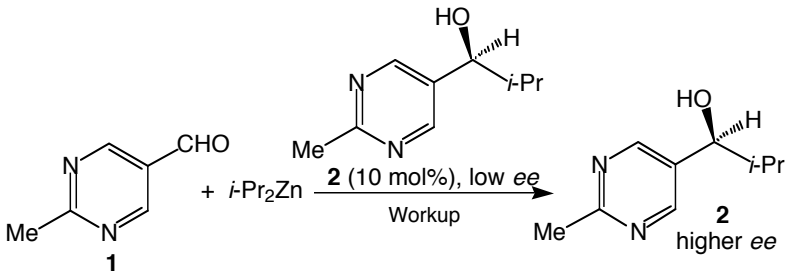
Mechanistic studies : HPLC kinetic analysis[2]

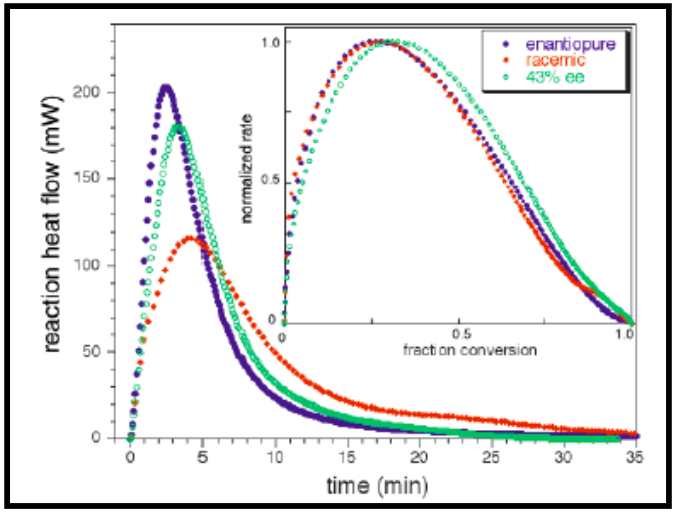




[1] K. Soai et al. *Angew. Chem. Int. Ed.* **2003**, *42*, 315; [2] K. Soai, et al. *Tetrahedron: Asymmetry* **2001**, *12*, 1965 .

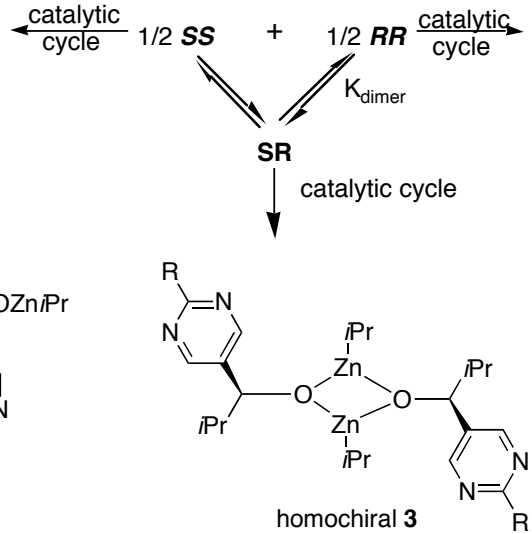
Asymmetric Autocatalysis (Cont..): Calorimetric study of reaction rate

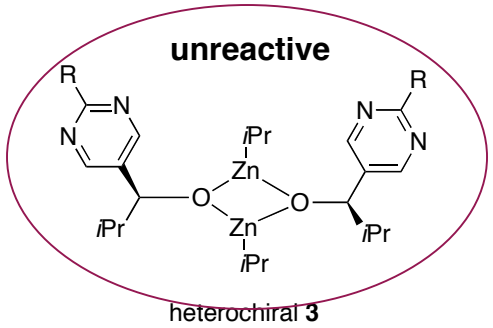




Reaction heat flow as a function of time, using catalyst **2** of different ee.
Inset: reaction rate normalized by the maximum value vs fraction conversion of **1**

Fit ML_2 model experimental data:

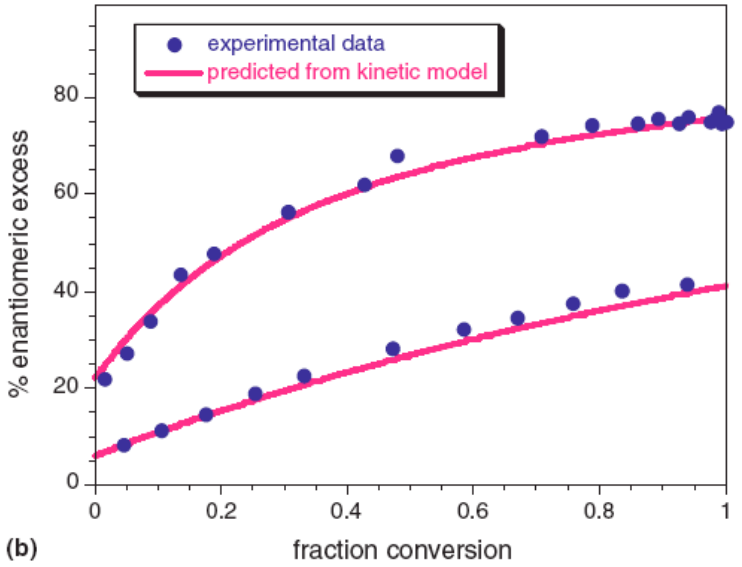




Statistical distribution of ligands:

K=4, g=0

✓ **NLE through partial solubility is also implicated**

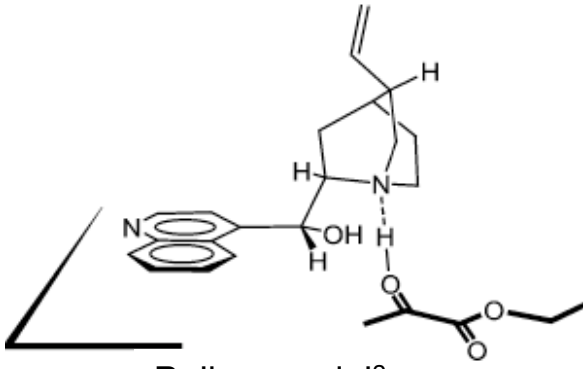


ee as a function of fraction conversion, **x**, using catalyst **2** with 22% & 6% cat. ee

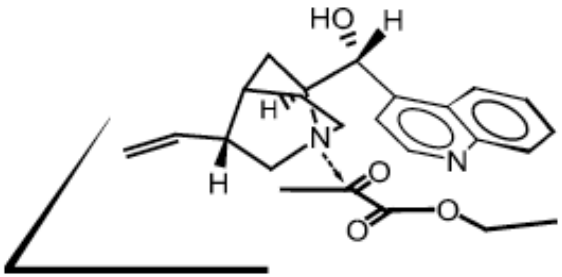
D. Blackmond; C. R. McMillan; S. Ramdeehul; A. Schorm; J. Brown, *J. Am. Chem. Soc.* **2001**, *123*, 10103.
D. G. Blackmond, Tetrahedron: Asymmetry **2006**, *17*, 584.

Heterogeneous Metal-Based Catalysis: Adsorption of chiral modifiers on the metal surface.[1]

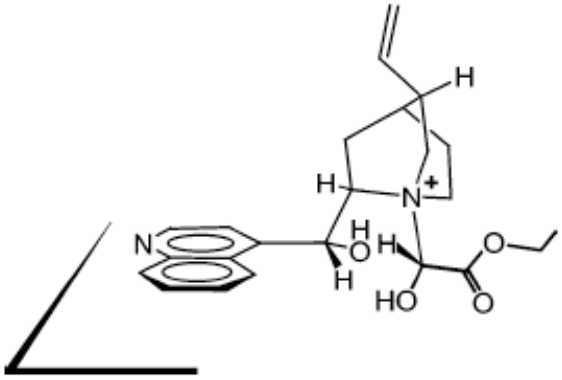
- Supported metal catalysts (Pd, Pt) modified by cinchona alkaloids provide high ee's in hydrogenation reactions.
- Experiments on NLE represent very useful tool to estimate *in situ* the efficiency of a chiral modifier.
- Absorption mode of substrate-modifier in the enantio-differentiating step is the most speculative step.



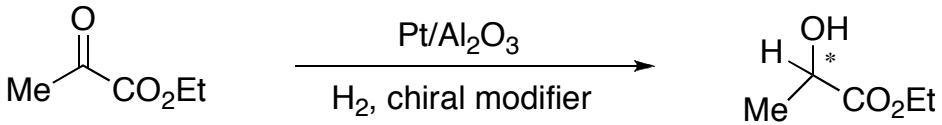
Baiker model[2]



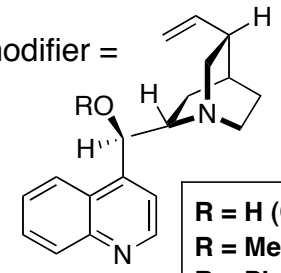
Margitfalvi model[3]



Sun model[4]

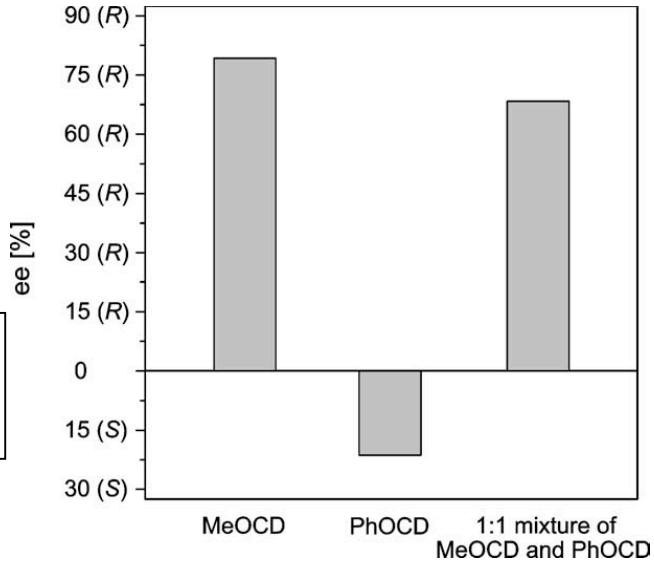


chiral modifier =



R = H (CD)
R = Me (MeOCD)
R = Ph (PhOCD)
R = TMS (TMSOCD)

ee_{calc} = 5%, but ee_{exp} = 68%, PhOCD adsorbs weaker on Pt, ∴ minor influence on enantioselection.

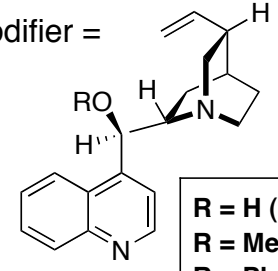


[1] S. Diezi, T. Mallata, A. Szabo, A. Baiker, *J. Catal.* **2004**, *228*, 162; [2] A. Baiker, *J. Mol. Catal. A* 163 (2000) 205; [3] J.L. Margitfalvi, E. Tfirst, J. Mol. Catal. A 139 (1999) 81; [4] G. Vayner, K.N. Houk, Y.-K. Sun, J. Am. Chem. Soc. 126 (2004) 199.

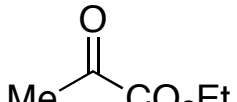
Heterogeneous Metal-Based Catalysis (Cont…)

Transient behavior of the hydrogenation of ethyl pyruvate over Pt/Al_2O_3 induced by addition of 1 M equiv. of ROCD or CD to the reaction mixture containing already a chiral modifier.

chiral modifier =

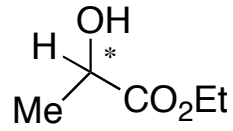


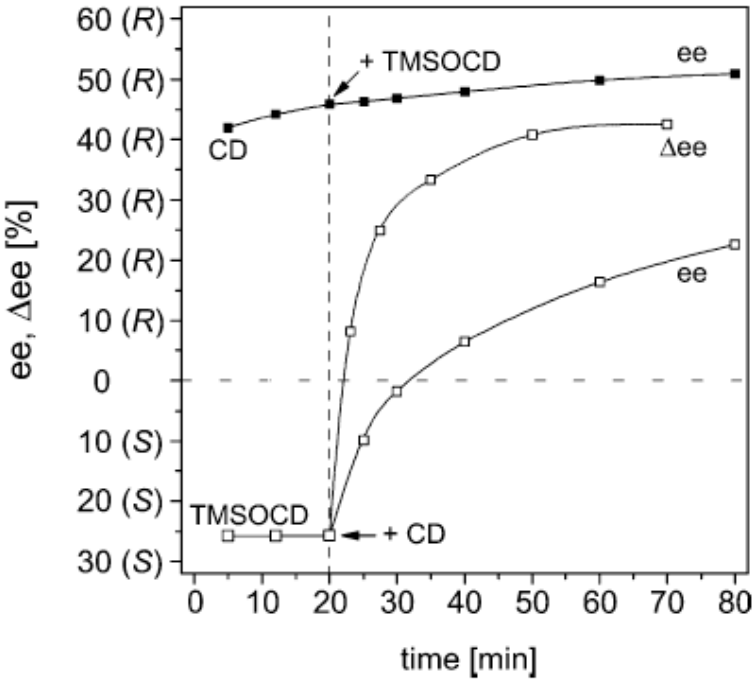
R = H (CD)
R = Me (MeOCD)
R = Ph (PhOCD)
R = TMS (TMSOCD)

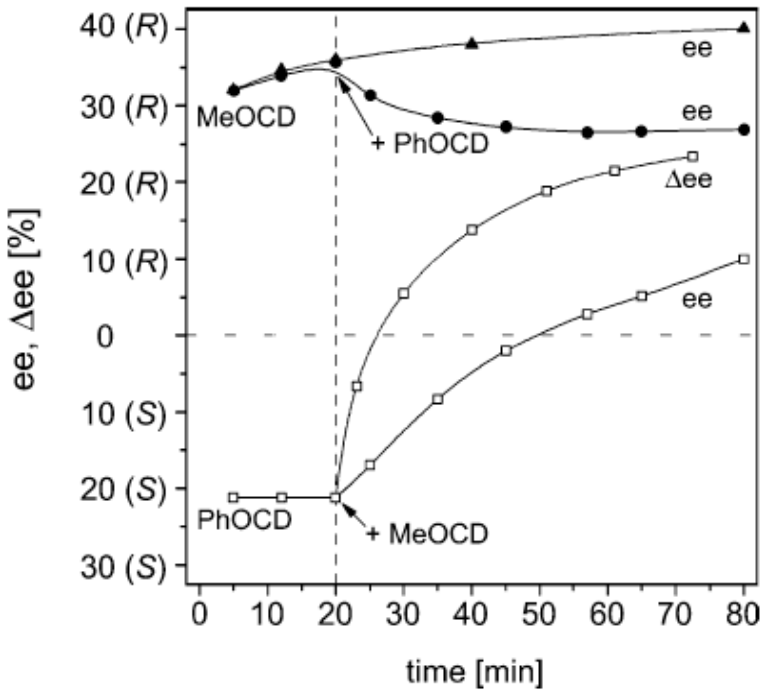


Pt/Al_2O_3

H_2, chiral modifier







Order of adsorption strength on Pt: CD > MeOCD > EtOCD > PhOCD ≈ TMSOCD.

S. Diezi, T. Mallata, A. Szabo, A. Baiker, *J. Catal.* **2004**, *228*, 162.

Conclusions

- NLE occurs when the relation between the *ee* value of the chiral catalyst or auxilliary and the *ee* value of the product deviates from linearity.

$$ee_{prod} = ee_{o}\, ee_{aux}$$

- NLEs can act as a probe to obtain information on the subtle mechanisms by which enantioselectivity is generated. The reaction rate dependence on ee's of the chiral auxilliary is also useful to consider.

- NLEs can be used to generate products with high *ee*'s from an enantiomerically impure, and more economical to prepare, chiral auxiliary or ligand.

- The concepts that form the foundations of non-linear effects may be extended to asymmetric autocatalysis, kinetic resolution and other nonlinear processes.

What is the correlation between NLE & enantiomer differentiation in the prebiotic age?