Nonlinear Effects in Enantioselective Catalysis

A MacMillan Group Meeting

Presented by Jake Wiener

28 May 2003

I. Introduction
   A. Overview of concept
   B. Theoretical models
   C. Early examples
II. Catalytic systems involving nonlinear effects
III. Conclusions and future directions of the field

Relevant reviews:

Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2297.

Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.

Kagan, H. B. *Synlett* **2001**, 888.

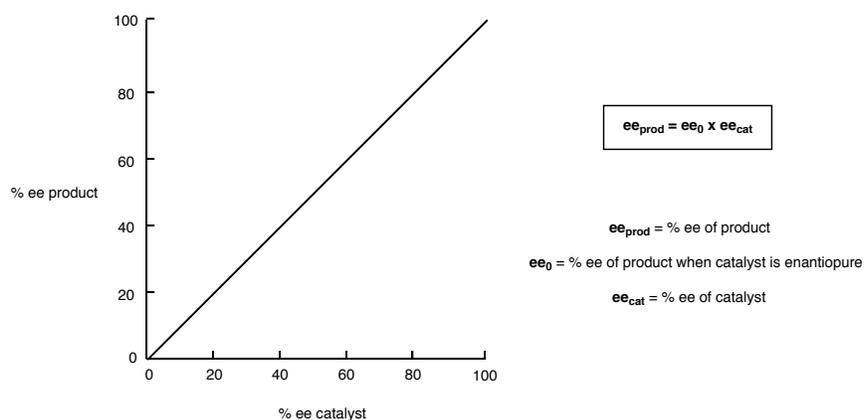Noyori, R. *Angew. Chem. Int. Ed.* **1991**, *30*, 49.

Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211.

Mathematical treatment:

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

## Ideal Enantioselective Catalysis: Linear Relationship

■ Linear Relationship: % ee of catalyst correlates linearly with % ee of products

$$ee_{prod} = ee_0 \times ee_{cat}$$

ee_{prod} = % ee of product

ee_0 = % ee of product when catalyst is enantiopure

ee_{cat} = % ee of catalyst

■ Deviations from linearity, known as nonlinear effects, are possible

Nonlinear Effects: Enantiopurity of Products Can Deviate from Linearity

■ Nonlinear relationship: % ee of products can be higher or lower than predicted by % ee of catalyst
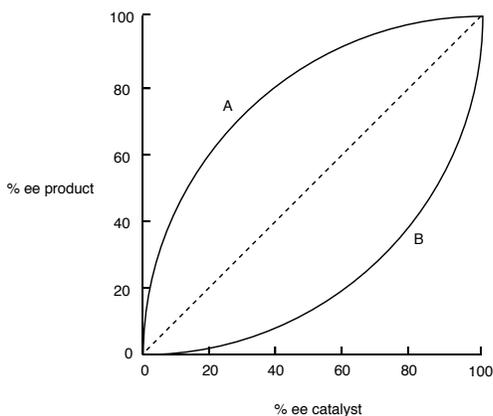
$$ee_{prod} = ee_0 \times ee_{cat} \times \text{correction factor}$$

ee_{prod} = % ee of product

ee_0 = % ee of product when catalyst is enantiopure

ee_{cat} = % ee of catalyst

content of correction factor depends on nature of model

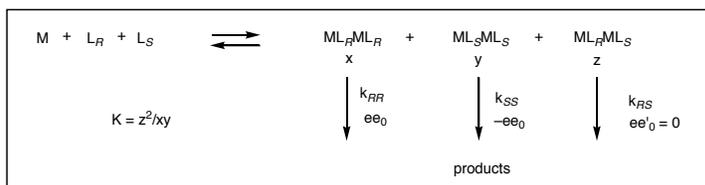■ Kagan has developed several mathematical models describing these phenomena

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Modelling of Nonlinear Effects: Kagan's (ML)$_2$ System

■ Model based on a system with a fast ligand exchange at a metal center bearing two chiral ligands

Complexes are in fast interconversion during their formation

The two ligands are L_R and L_S The metal is denoted as M

$$M + L_R + L_S \rightleftharpoons \underset{x}{ML_RML_R} + \underset{y}{ML_SML_S} + \underset{z}{ML_RML_S}$$

$K = z^2/xy$

$$\begin{array}{ccc} \downarrow k_{RR} & \downarrow k_{SS} & \downarrow k_{RS} \\ ee_0 & -ee_0 & ee'_0 = 0 \end{array}$$

products

Heterochiral *(meso)* catalyst (ML$_R$ML$_S$) generates racemic product   Homochiral catalysts afford enantiomeric product

$$ee_{prod} = ee_0 \times ee_{cat} \times \frac{1 + \beta}{1 + g\beta}$$

β = relative amounts of complexes = $\dfrac{n_{meso}}{n_{chiral}}$

g = relative reactivities of complexes = $\dfrac{k_{RS}}{k_{RR}}$

■ How does this model make sense in the context of observed data?

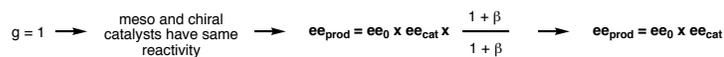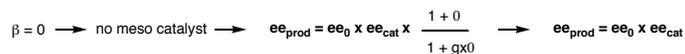## Kagan's $(ML)_2$ System: Understanding the Model

Limiting cases demonstrate prescience of $(ML)_2$ model

$$ee_{prod} = ee_0 \times ee_{cat} \times \frac{1 + \beta}{1 + g\beta}$$

g = relative reactivities of complexes = $\dfrac{k_{meso}}{k_{chiral}}$

β = relative amounts of complexes = $\dfrac{n_{meso}}{n_{chiral}}$

■ Model returns to linearity when $\beta = 0$ or $g = 1$

$\beta = 0 \longrightarrow$ no meso catalyst $\longrightarrow$ $ee_{prod} = ee_0 \times ee_{cat} \times \dfrac{1 + 0}{1 + g \times 0}$ $\longrightarrow$ $ee_{prod} = ee_0 \times ee_{cat}$

$g = 1 \longrightarrow$ meso and chiral catalysts have same reactivity $\longrightarrow$ $ee_{prod} = ee_0 \times ee_{cat} \times \dfrac{1 + \beta}{1 + \beta}$ $\longrightarrow$ $ee_{prod} = ee_0 \times ee_{cat}$

■ $g < 1$: (+)-NLE

meso complex is less reactive

$\dfrac{1 + \beta}{1 + g\beta} > 1 \implies$ ee_{prod} is greater than any given ee_{cat}

■ $g > 1$: (−)-NLE

meso complex is more reactive

$\dfrac{1 + \beta}{1 + g\beta} < 1 \implies$ ee_{prod} is smaller than any given ee_{cat}

■ Qualitative understanding: *meso* complex binds some racemate, enriching ee of active catalyst

■ Actual calculation of curves only possible after further mathematical elaboration

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Early Observation of NLE: Sharpless Epoxidation of Geraniol

■ Kagan and Agami investigate the Sharpless epoxidation, uncovering a (+)-NLE


(R,R)-(+)-DET =
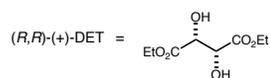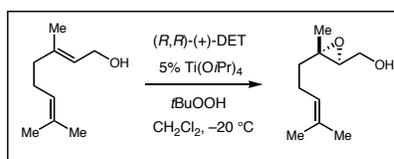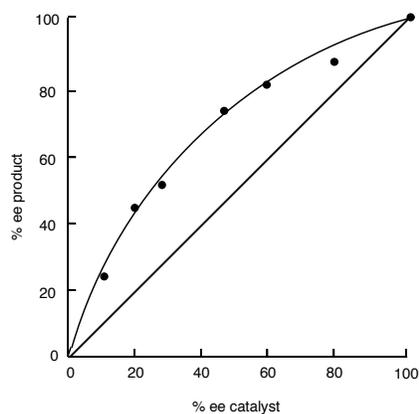
Involvement of less reactive dimeric meso complex and more reactive dimeric chiral catalyst in $(ML)_2$ model can explain the NLE, and is consistent with the Sharpless mechanism implicating two DET's in active catalyst

Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113.

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

Early Observation of NLE: Kagan's Asymmetric Sulfide Oxidation

■ Kagan and Agami report a (–)-NLE not adequately described by any ML_2 models
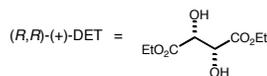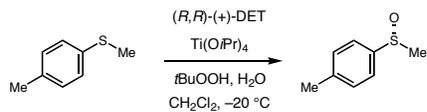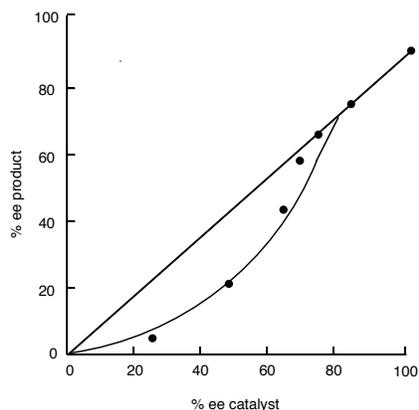

(–)-NLE until 70% ee of catalyst achieved, then linear

⇓

Not readily explained by $(ML)_2$. Rather, $(ML)_4$, involving dimeric Ti complex with 4 DET's is proposed

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

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

Early Observation of NLE: Hajos–Wiechert, et al. Reaction

■ Kagan and Agami report a (–)-NLE not adequately described by any ML_2 models
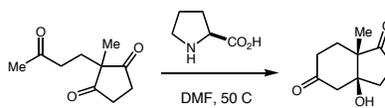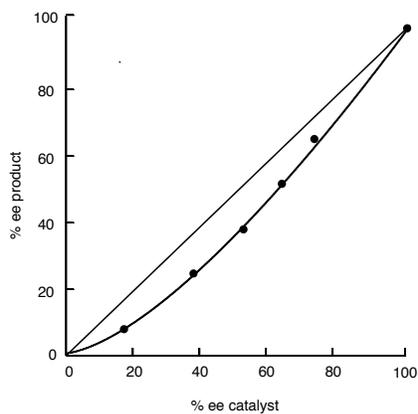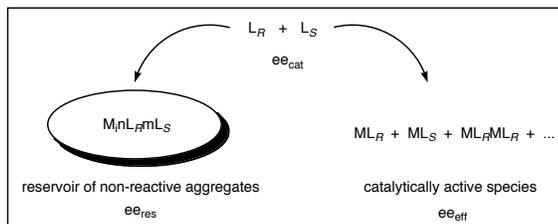

Search for NLE began when reaction was observed to be second order in proline

⇓

Agami: Reaction proceeds via formation of chiral enamine, followed by complexation with a second proline

⇓

Not readily explained by $(ML)_2$, though NLE clearly present

Agami, C. *Bull. Soc. Chim. Fr.* **1988**, 499.

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

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

Modelling of Nonlinear Effects: Kagan's Reservoir Effect

Formation of nonreactive catalyst aggregates can also explain observed NLE's

$$L_R \ + \ L_S$$
$$ee_{cat}$$

$$M_i nL_R mL_S$$

$$ML_R \ + \ ML_S \ + \ ML_R ML_R \ + \ ...$$

reservoir of non-reactive aggregates
$$ee_{res}$$

catalytically active species
$$ee_{eff}$$

■ Assume $ee_{res} \neq ee_{cat}$. The ee of catalyst involved in the reaction (ee_{eff}) will be effectively different.

α = fraction of ligand engaged in nonreactive aggregation, with % ee = ee_{res}

Assume one mole of chiral ligand with % ee = ee_{cat}

$$\Longrightarrow \quad ee_{eff} \ = \ \frac{ee_{cat} - \alpha ee_{res}}{1 - \alpha}$$

■ Example of the reservoir effect increasing the effective catalyst %ee

A catalyst of 60% ee in which 30% of material is stored in non-reactive racemic aggregates.

$$\left.\begin{array}{l} ee_{cat} = 60\% \\ \alpha = 0.3 \\ ee_{res} = 0\% \end{array}\right\} \Longrightarrow \quad ee_{eff} \ = \ \frac{60\% - 0.3(0)}{1 - 0.3} \ = \ 86\% \ ee$$

■ How do the ML_2 and reservoir models compare and can they operate in tandem?
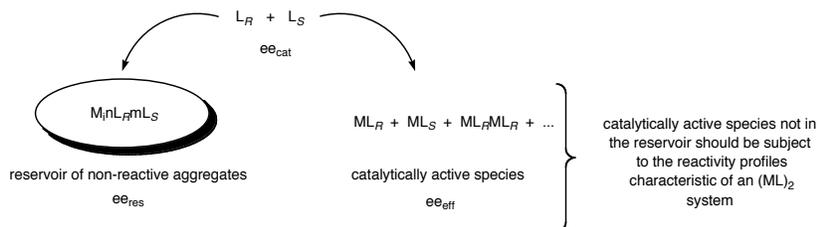

Modelling of Nonlinear Effects: (ML)$_2$ and Reservoir Systems

Most NLE data can be fit to either the (ML)$_2$ or reservoir models

■ A simple way to store a racemate is as a thermodynamically stable and kinetically inactive meso dimer

This model is the same as an (ML)$_2$ model in which $g = \dfrac{k_{meso}}{k_{chiral}} = 0 \quad \Longrightarrow \quad$ many data will fit both models

■ (ML)$_2$ and reservoir models can be thought of as operating cooperatively

$$L_R \ + \ L_S$$
$$ee_{cat}$$

$$M_i nL_R mL_S$$

$$ML_R \ + \ ML_S \ + \ ML_R ML_R \ + \ ...$$

reservoir of non-reactive aggregates
$$ee_{res}$$

catalytically active species
$$ee_{eff}$$

catalytically active species not in the reservoir should be subject to the reactivity profiles characteristic of an (ML)$_2$ system
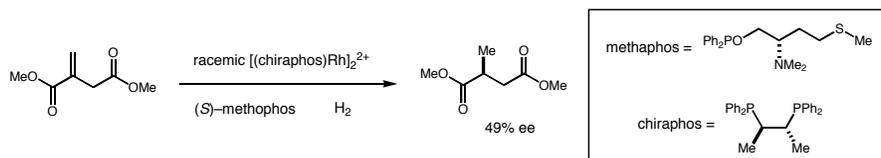
How does this cooperation become manifest?

(ML)$_2$ and Reservoir Effects Cooperate: Enantioselective Catalytic Hydrogenation

Chiral poisoning results in non-reactive aggregate formation and a positive NLE

■ Doping of racemic catalyst results in enantioselective hydrogenation

catalyst	%ee
racemic [(chiraphos)Rh]$_2$$^{2+}$	0
(S)–methophos	< 2

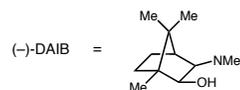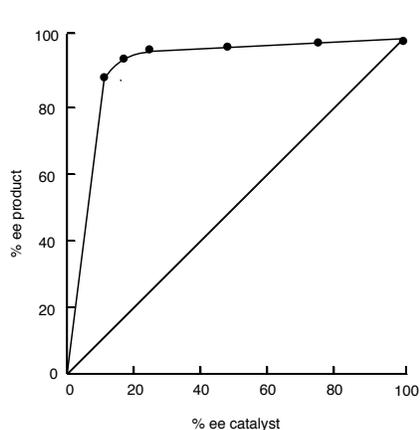$\Longrightarrow$ chiral additive does not catalyze enantioselective reaction

■ Rationale:

(S)–methophos selectively binds [(S,S)–chiraphosRh]$^+$ in an unreactive aggregate.

This binding leaves behind unequal amounts of [(S,S)–chiraphosRh]$^+$ and [(R,R)–chiraphosRh]$^+$, allowing a positive NLE to develop via an (ML)$_2$–type pathway

Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804.

Addition of Organozincs to Aldehydes: Noyori Elucidates Nonlinear Effect

■ Noyori reports a dramatic (+)-NLE in the addition of Et$_2$Zn to benzaldehyde; (ML)$_2$ or reservoir Apply

Reservoir
ee$_0$ = 98%
ee$_{res}$ = 0%
α = 0.88

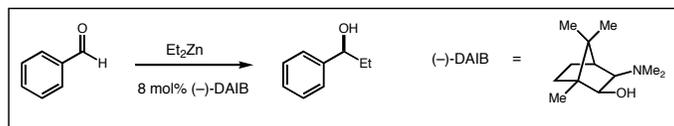| (ML)$_2$ |
|---|
| ee$_0$ = 98% |
| $g = \dfrac{k_{RS}}{k_{RR}} = 0.01$ |
| $K = \dfrac{(n_{RS})^2}{n_{RR} n_{RS}} = 5000$ |

What are the origins of this astounding (+)-NLE?

Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
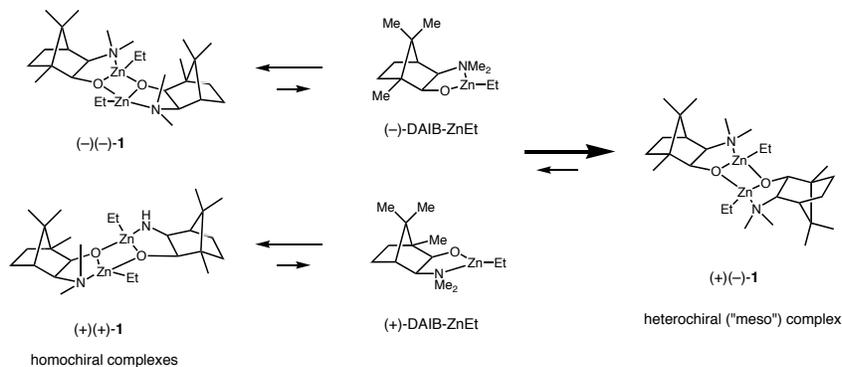
Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800.

First report of NLE in organozinc addition: Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.

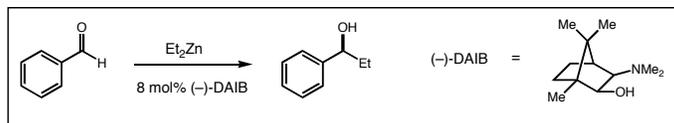## Origins of the Dramatic (+)-NLE in Noyori's Diethyl Zinc Addition

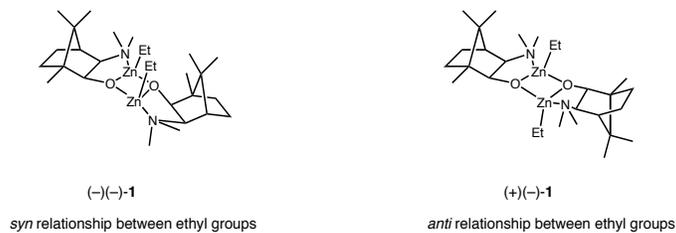■ Organometallic catalyst dimerizes to homochiral (very reactive) and meso (very stable) complexes

(−)(−)-**1**

(−)-DAIB-ZnEt

(+)(+)-**1**

(+)-DAIB-ZnEt

homochiral complexes

(+)(−)-**1**

heterochiral ("meso") complex

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

Noyori's Diethyl Zinc Addition: Differential Stability of Dimeric Complexes

Heterochiral complex is much more stable than the homochiral complex under reaction conditions

■ X-ray diffraction shows conformational differences between dimeric complexes

(−)(−)-**1**

syn relationship between ethyl groups

(+)(−)-**1**
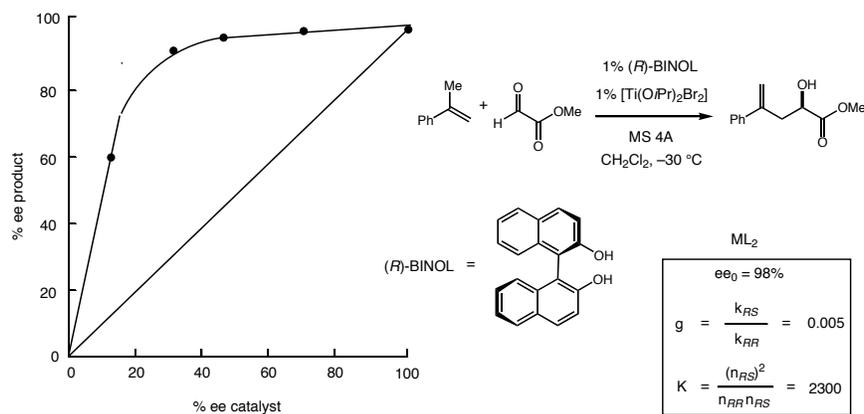
anti relationship between ethyl groups

Kagan: *"The effect of diverting the minor enantiomer from the reaction mixture will be a net increase in the ee value of the active catalyst, thus generating this strong (+)-NLE."*

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

Glyoxylate–Ene Reaction: Mikami Demonstrates Pronounced Nonlinear Effect

■ Mikami's data can be fit to an $(ML)_2$ model involving inactive heterochiral species

1% (R)-BINOL
1% [Ti(OiPr)$_2$Br$_2$]
MS 4A
CH$_2$Cl$_2$, –30 °C

(R)-BINOL =

ML_2

$ee_0 = 98\%$

$$g = \frac{k_{RS}}{k_{RR}} = 0.005$$

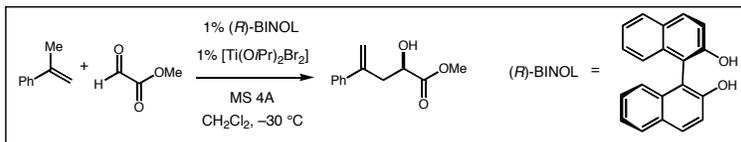$$K = \frac{(n_{RS})^2}{n_{RR}\,n_{RS}} = 2300$$

Studies of the catalyst in solution shed light on nonlinear effect

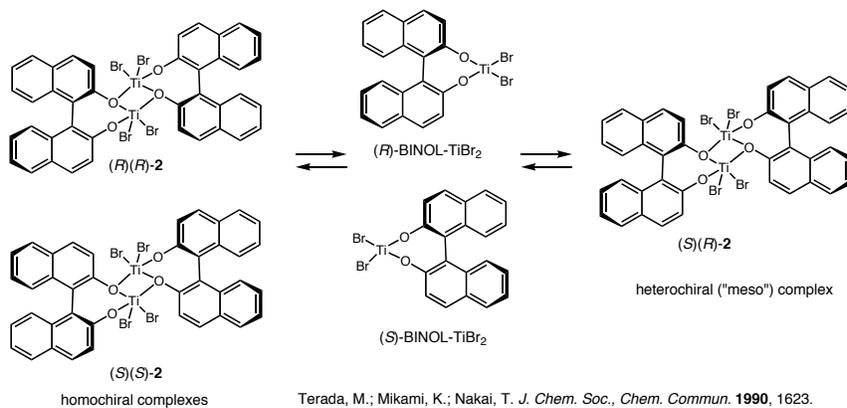Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623.

Mikami, T.; Terada, M. *Tetrahedron* **1992**, *48*, 5671.

Mikami, K.; terada, M.; Narisawa, S.; Nakai, T. *Synlett*, **1992**, 255.

## Glyoxylate–Ene Reaction: Dimeric Complexes Implicated in Mechanism

1% (R)-BINOL
1% [Ti(OiPr)$_2$Br$_2$]
MS 4A
CH$_2$Cl$_2$, –30 °C

(R)-BINOL =

■ Organometallic catalyst dimerizes to homochiral (very reactive) and meso (very stable) complexes

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

(R)-BINOL-TiBr$_2$

(S)(R)-**2**

heterochiral ("meso") complex

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

(S)-BINOL-TiBr$_2$

homochiral complexes

Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623.

Glyoxylate–Ene Reaction: Differential Stability of Dimeric Complexes

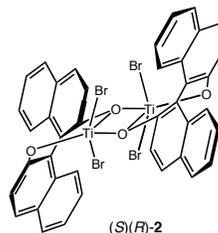*Heterochiral complex is much more stable than the homochiral complex under reaction conditions*
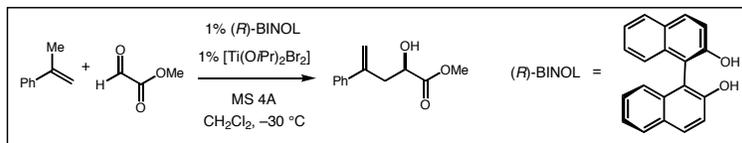
■ Proposed dimer structures rationalize contrasting reactivity of complexes

(*R*)(*R*)-**2**
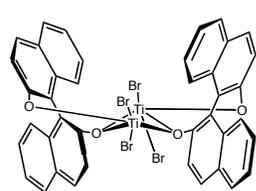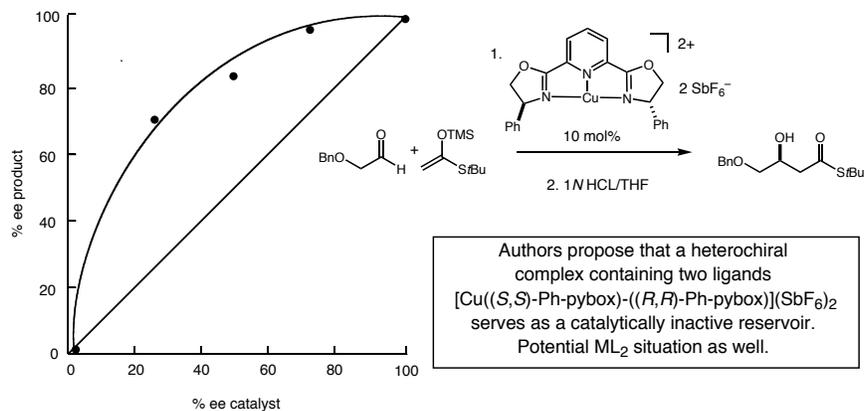
binapthyl moeities are *syn*-periplanar

(*S*)(*R*)-**2**

binapthyl moeities are *anti*-periplanar

Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623.

Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.

Mukaiyama Aldol Reaction: Evans Finds Strong Nonlinear Effect with Cu(Ph-pybox)

*NLE was investigated in an effort to better understand catalyst operation*

Authors propose that a heterochiral complex containing two ligands [Cu((*S*,*S*)-Ph-pybox)-((*R*,*R*)-Ph-pybox)](SbF$_6$)$_2$ serves as a catalytically inactive reservoir. Potential ML$_2$ situation as well.

Pre-generated heterochiral complex was insoluble, catalytically inactive

Addition of (R,R)-Ph-pybox to [Cu((S,S)-Ph-pybox)](SbF$_6$)$_2$ resulted in precipitation of solid

X-ray crystal structures and PM3 calculations rationalize stability of heterochiral complex

Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

Hetero Diels-Alder: Inanaga Reports First ML$_3$ System

Extreme positive nonlinear effect using chiral ytterbium catalyst
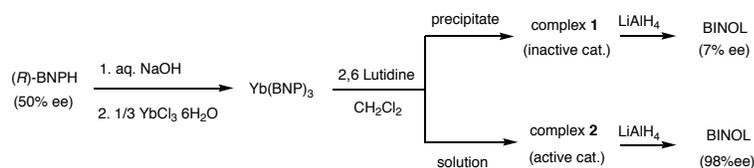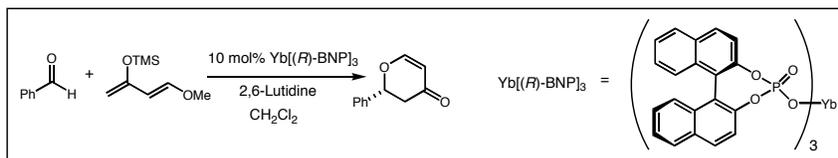

Yb[(R)-BNP]$_3$ =
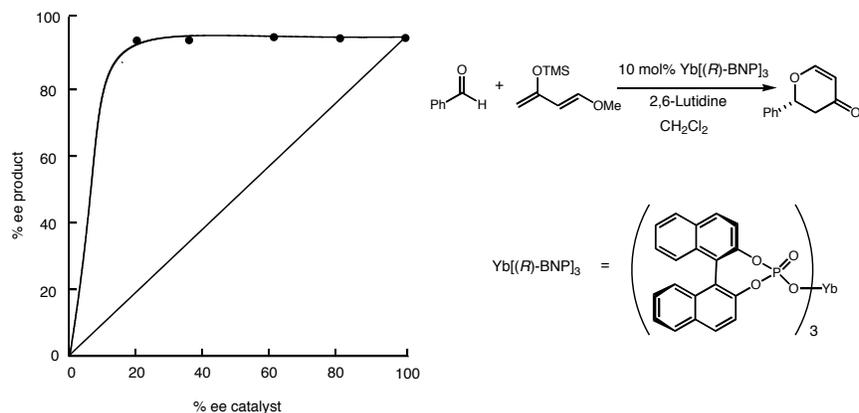
A series of experiments provides mechanistic evidence to support ML$_3$

Furuno, H.; hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49.

Theoretical treatment of ML$_3$ systems: Kagan, H. B. et al. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

Hetero Diels-Alder: Activity and Optical Purity of Various Complexes

Yb[(R)-BNP]$_3$ =

(R)-BNPH (50% ee) → 1. aq. NaOH / 2. 1/3 YbCl$_3$ 6H$_2$O → Yb(BNP)$_3$ → 2,6 Lutidine / CH$_2$Cl$_2$ →

precipitate → complex **1** (inactive cat.) → LiAlH$_4$ → BINOL (7% ee)

solution → complex **2** (active cat.) → LiAlH$_4$ → BINOL (98%ee)

■ Conlusions from these experiments:

   Active catalyst **2** is composed entirely of enantiopure ligands

    Inactive catalyst **1** is almost a 1:1 mixture of enantiomers

■ Yet, authors can not rule out the potential stereogenicity of the metal center

■ Separate experiments show the components of the inactive complexes to be highly stable

Furuno, H.; hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2*, 49.

## Hetero Diels-Alder: Proposed ML₃ Nonlinear Effect

$NaL_R > NaL_S$
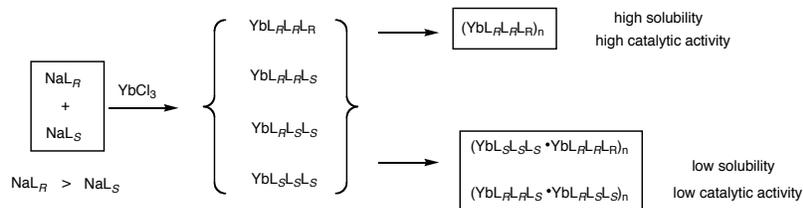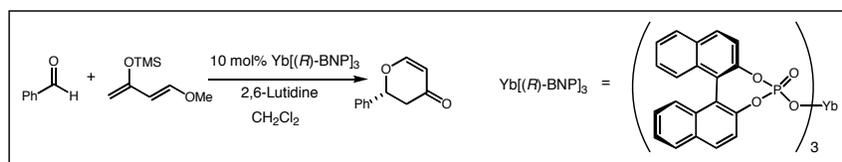
Since the active species is enantiopure and the inactive species are 1:1 *R:S,* the inactive species must involve sequestering in heterochiral pairs

Furuno, H.; Hanamoto, T.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2,* 49.

Nonlinear Effect in Organocatalytic Conjugate Addition
Complicated effect using proline as catalyst

NLE highly affected by choice of additive
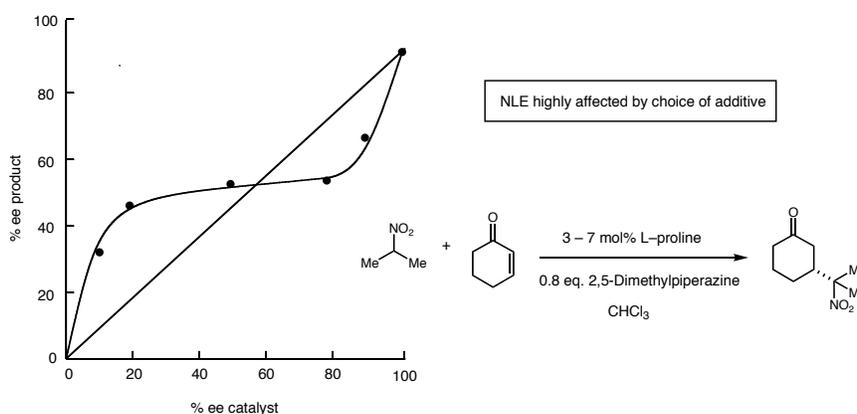
Hanessian: *"While it is not possible to derive clear mechanistic conclusions in a complex system that comprises a catalyst and an additive, in addition to the nitroalkane and the enone, the results are reminiscent of ML_x systems where NLE curves show a similar trend."*

Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2,* 2975.

Nonlinear Effects in Enantioselective Catalysis: Conclusions and Future Directions

■ Conclusions:

   NLE's are found throughout the literature of enantioselective catalysis

   NLE's are common across different metals and ligand classes, and are important in organocatalysis as well

   NLE's are highly dependent on solvent, temperature, concentration, additives

   NLE's are often investigated in an effort to explain mechanistic findings such as reaction rate order

   NLE's are often investigated to gain insight into the mechanism of a reaction, including the nature of the active catalyst

■ Future directions of the field:

   NLE's will continue to help explain poorly understood enantioselective catalytic processes

   Complicated NLE's will be uncovered and better modelled to help understand complex catalytic systems

   Predicting NLE's is at present a near-impossible task – future work will seek rationally to design catalyst systems that will take advantage of NLE's

   Enantiomer–selective activation/deactivation of racemic catalysts is a relatively recent development and remains largely unexplored – chances for rational design in this area, related to NLE and largely growing out of NLE studies, are high (see Mikami, K., et al. *Acc. Chem Res.* **2000**, *33*, 391.)