## DEVELOPMENT OF ASYMMETRIC SYNTHESIS

S. Masamune, C&EN, August 5, 1985

**First Generation, 1944–1980:**

Creation of a new asymmetric carbon induced by asymmetry in the substrate

**Second Generation:**

Local induction of desired configuration using chiral auxiliaries attached to the substrates

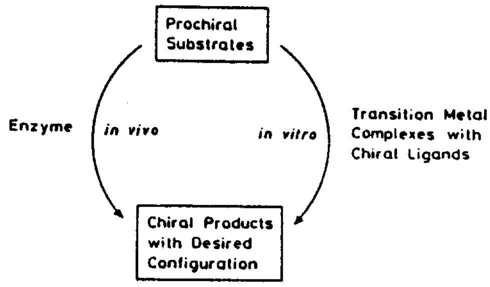
**Third Generation:**

Asymmetric synthesis by reagent control of induction

**Fourth Generation:**

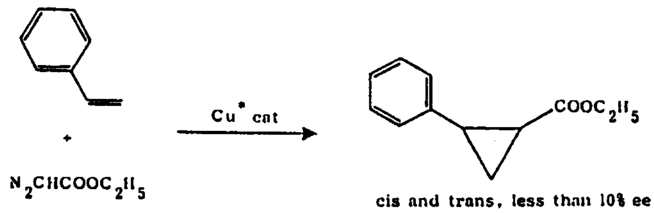
Asymmetric induction by chiral catalysts

## Production of Useful Optically Active Compounds

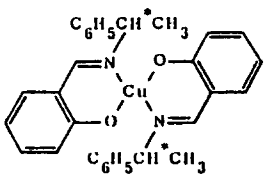



## ASYMMETRIC CARBENOID REACTION

Discovered in Kyoto in 1966




cis and trans, less than 10% ee




## TRANSITION METAL CATALYZED ASYMMETRIC REACTIONS IN HOMOGENEOUS PHASE

H. Nozaki, S. Moriuti, H. Takaya, and R. Noyori, Tetrahedron Lett., 5239 (1966).

Cyclopropanation of olefins by decomposition of diazoalkanes by a chiral Schiff base/Cu(II) catalyst

→ Synthesis of Chrysanthemic Acid and (S)-2,2-Dimethylcyclopropanecarboxylic Acid at Sumitomo Co.

W. S. Knowles and M. J. Sabacky, Chem. Commun., 1445 (1968).
L. Horner, H. Siegel, and H. Büthe, Angew. Chem., 80, 1034 (1968).

Hydrogenation of olefins by chiral phosphine/Rh(I) catalysts

→ L-DOPA Synthesis at Monsanto Co.

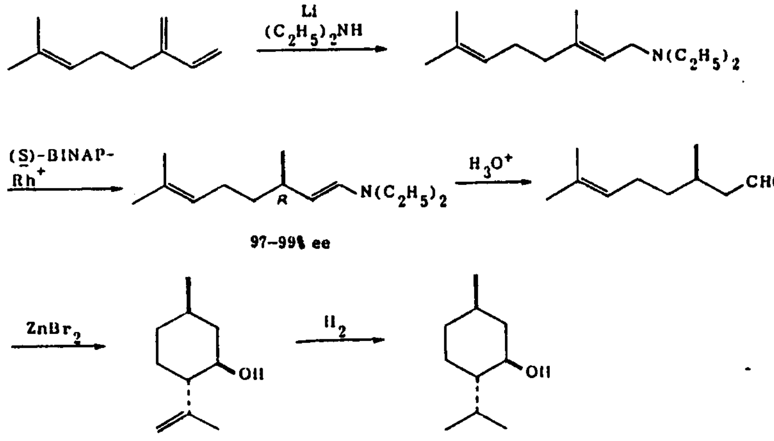
## INDUSTRIAL APPLICATION OF TRANSITION METAL CATALYZED ASYMMETRIC REACTIONS IN HOMOGENEOUS PHASE

| Compound | Key Reaction | Metal | Firm |
|---|---|---|---|
| L-DOPA | Olefin hydrogenation | Rh | Monsanto |
| Disparlure[a] | Allyl alcohol epoxidation | Ti | J. T. Baker<br>Shanghai Inst Organic Chem |
| (S)-Dimethylcyclopropanecarboxylic acid[b] | Olefin cyclopropanation | Cu | Sumitomo |
| Menthol | Allylamine isomerization | Rh | Takasago |

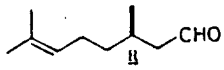
[a] Sex attractant of the gypsy moth

[b] Component of cilastatin, an inhibitor to dehydropeptidase-I

## TAKASAGO MENTHOL SYNTHESIS



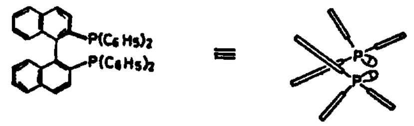
## SUPER-NATURAL CITRONELLAL




natural $[\alpha]_D^{25}$ +11.50° (neat)

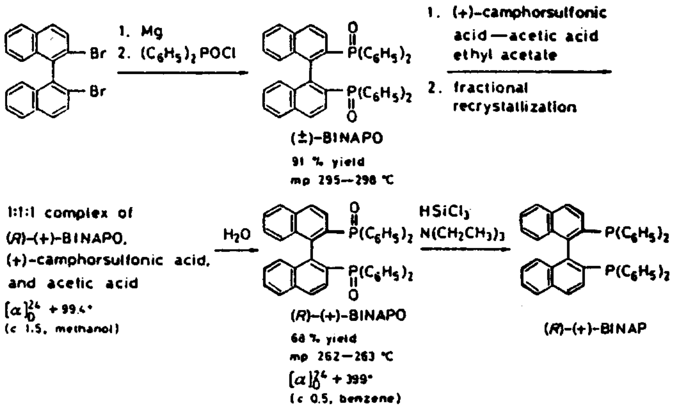
synthetic $[\alpha]_D^{25}$ +16.20° (neat)

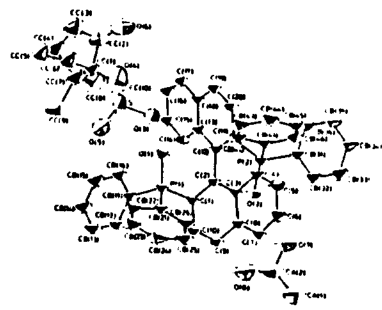
## 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, an Atropisomeric Bis(triaryl)phosphine




(*R*)-(+)-BINAP

## Practical Synthesis of Optically Pure BINAP



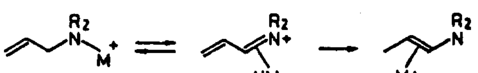
ORTEP drawing of the complex of (S)-(-)-BINAPO, (R)-(+)-camphorsulfonic acid, and acetic acid, showing atomic labeling.

## Double-Bond Migration

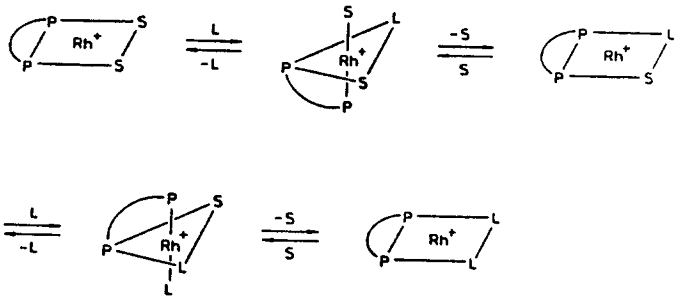
A. Addition/elimination of a metal hydride


B. π-Allyl mechanism


C. Nitrogen-triggered mechanism



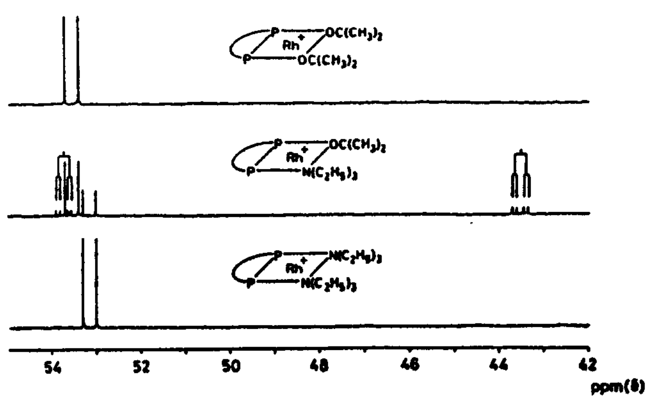

## Ligand Exchange of BINAP-Rh$^+$ Complexes



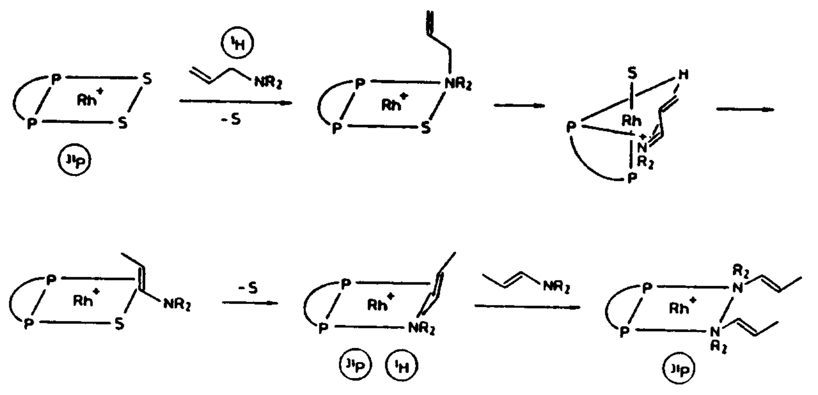

P-P = BINAP

S, L = acetone, THF, $N(C_2H_5)_3$, etc.

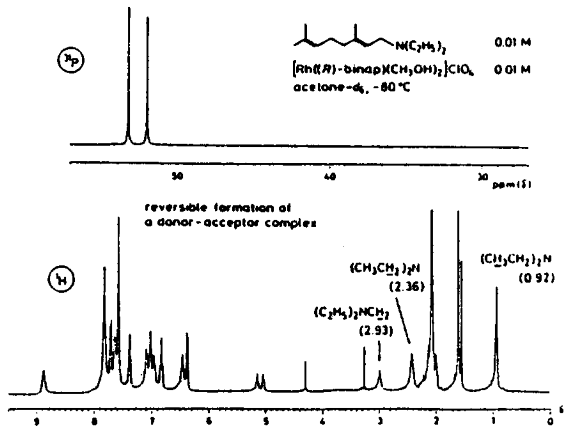
## $^{31}P$ NMR Spectra



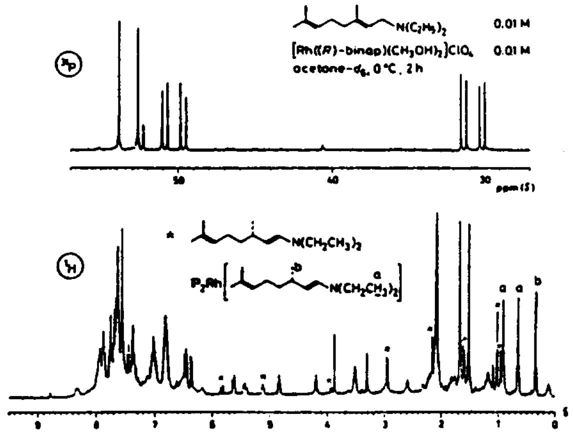
## Mechanism of the Stoichiometric Reaction



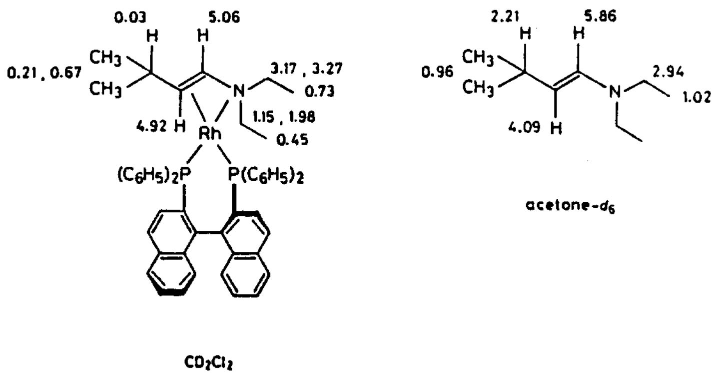

## NMR Spectra of a Mixture of the Geranylamine and BINAP-Rh Complex



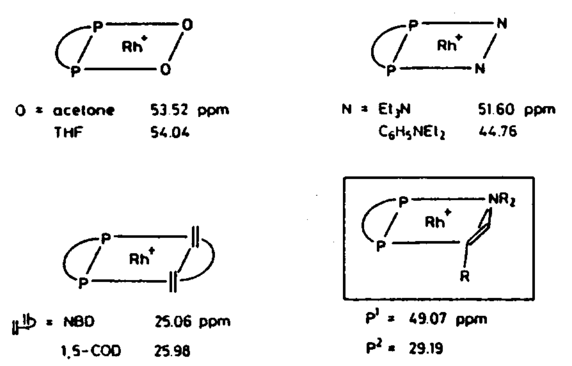

## NMR Spectra of a Mixture of the Geranylamine and BINAP-Rh Complex



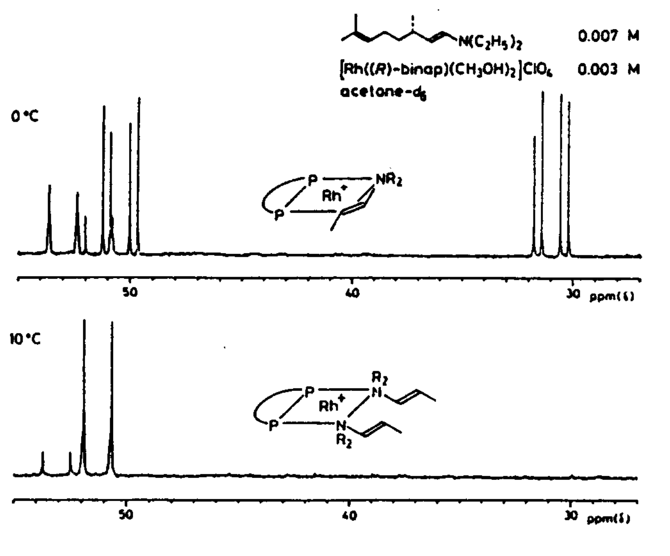

## $^1H$ NMR of the $\eta^3$-Enamine Complex



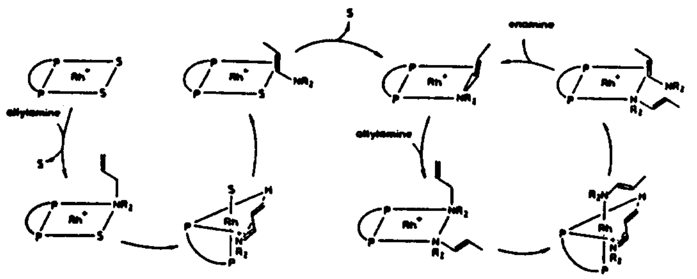

## $^{31}P$ Chemical Shifts



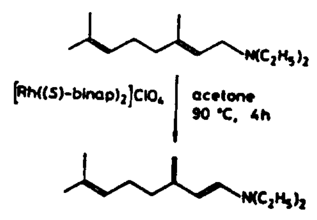

## $^{31}P$ NMR Spectra of a Mixture of the Enamine and Rh-BINAP Complex



Catalytic Cycle

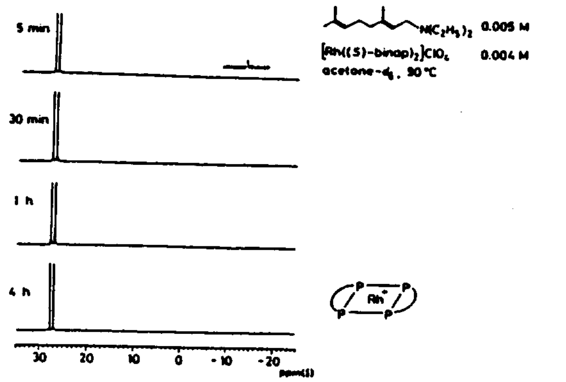



Asymmetric Isomerization Catalyzed by Bis-BINAP-Rh Complex

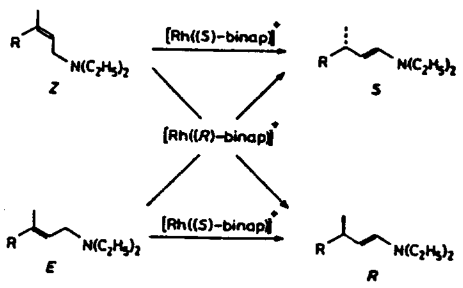



Tani, Otsuka, Akutagawa (1985)

[31]P NMR Spectra of a Mixture of the Geranylamine and Bis-BINAP-Rh Complex

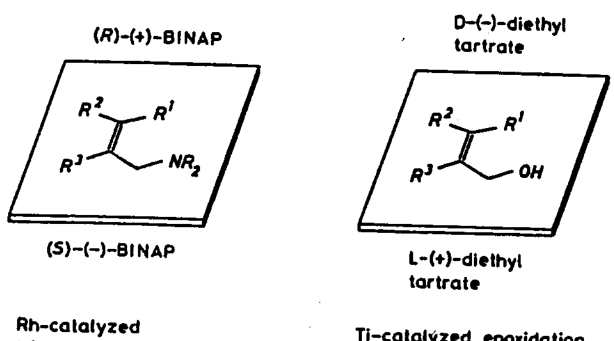



Asymmetric 1,3-Hydrogen Shift




R = $(CH_3)_2C{=}CHCH_2CH_2$, simple alkyl, $C_6H_5$, *etc.*

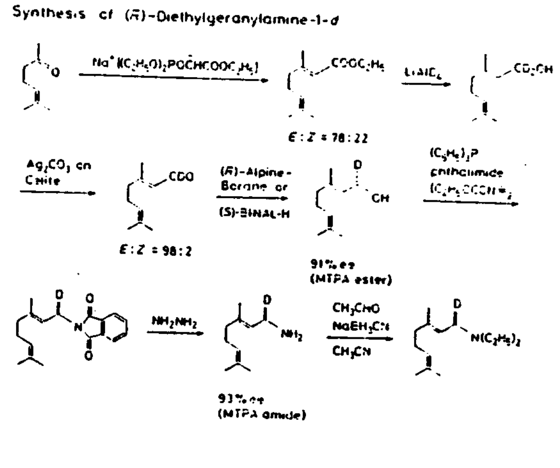
## Chiral Recognition Modes



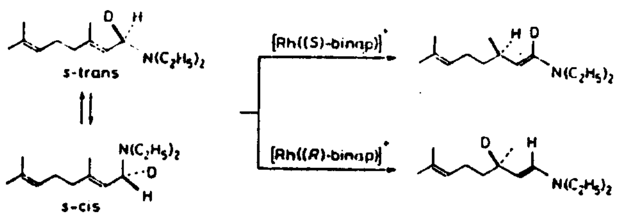

Rh-catalyzed 1,3-hydrogen transfer

Ti-catalyzed epoxidation with $t$-$C_4H_9OOH$ Sharpless (1980)

Synthesis of (R)-Diethylgeranylamine-1-d



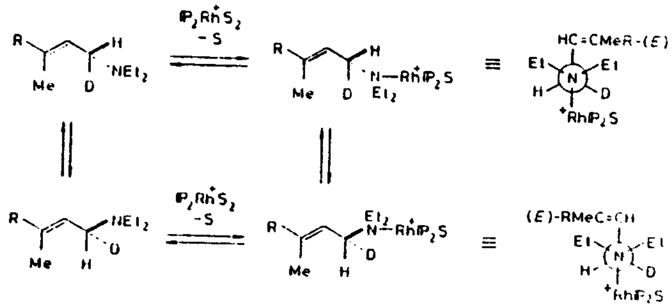
## Enantioselective 1,3-Hydrogen Transfer




canonical conformations

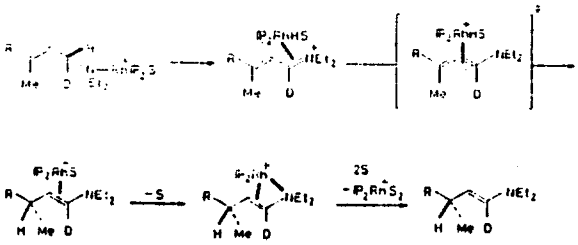
In THF, 2.5—5 % $Rh^{+}$-BINAP, 40 °C, 24 h.

## Formation of the N-Complex *via* Associative Mechanism

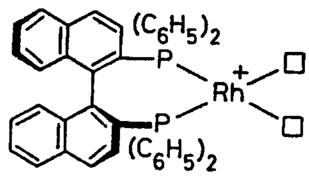


R = $(CH_3)_2C{=}CHCH_2CH_2$
$P_2$ = (S)-BINAP
S = solvent, substrate, or product

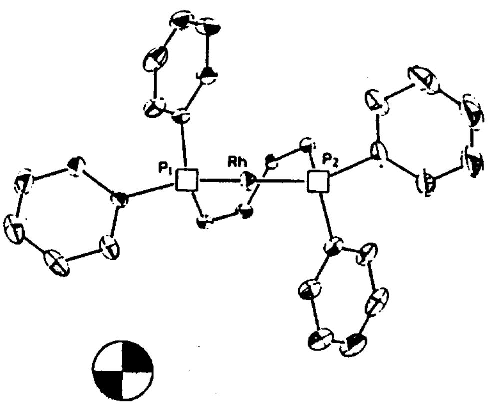
### Suprafacial Pathway *via* the N-Complex



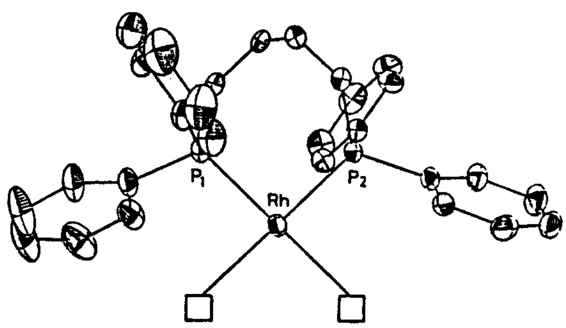
R = $(CH_3)_2C{=}CHCH_2CH_2$
$P_2$ = (S)-BINAP
S = solvent, substrate, or product



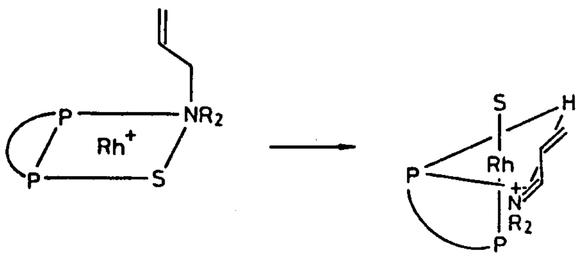
## Origin of the Chiral Recognition



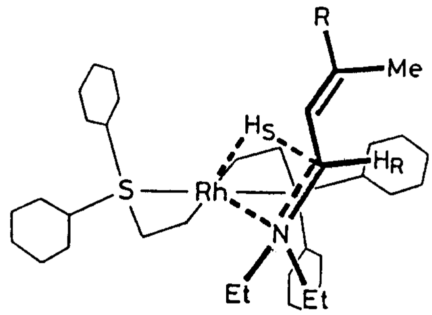

## Origin of the Chiral Recognition



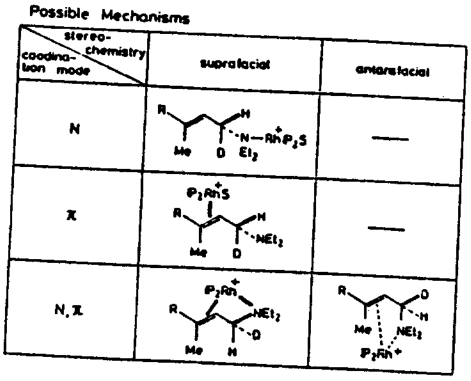
## Stereo-Determining Step



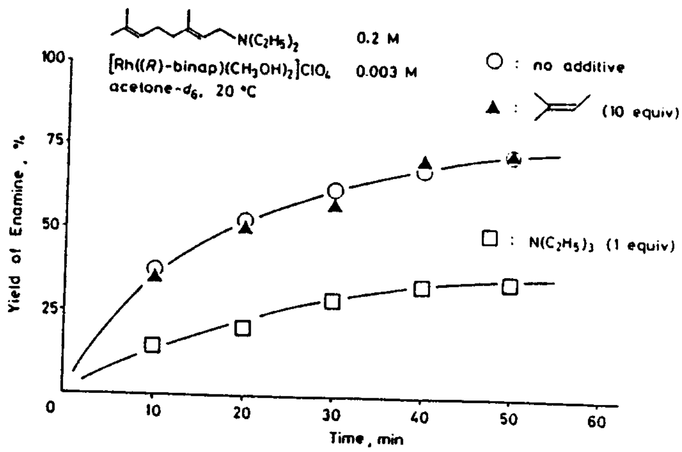

## Transition State



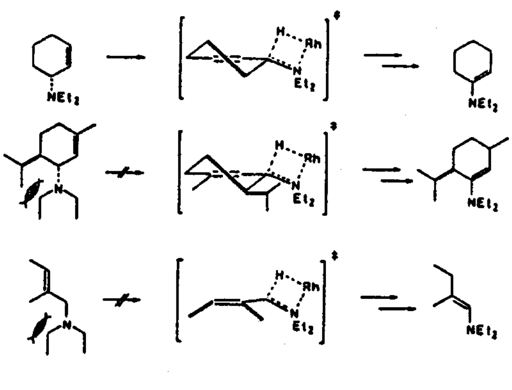

Possible Mechanisms




Effects of Added Olefins and Amines




Retardation by Alkyl Substituents




**FACTORS CONTROLLING ENANTIOSELECTIVITY**

| | |
|---|---|
| Steric bulkiness | Electronic properties |
| Heteroatom functionalities | Hydrocarbon backbone |
| $C_1$ chirality (nonsymmetrical) | $C_2$ chirality (symmetrical) |
| Molecular rigidity | Molecular pliancy |

COLLABORATORS


Nagoya University
Dr. M. Kitamura
Dr. T. Sato
Mr. Yi Hsiao
Mr. S. Inoue
Miss M. Ohta
Mr. M. Osada
Mr. T. Souchi

Osaka University
Prof. S. Otsuka
Dr. K. Tani
Dr. T. Yamagata

Institute for Molecular Science
Prof. H. Takaya
Prof. A. Miyashita
Dr. K. Koyano
Dr. K. Mashima
Dr. T. Ohta
Dr. A. Yasuda

Prof. T. Ito
Dr. K. Toriumi

Takasago Perfumery Co.
Dr. S. Akutagawa
Dr. H. Kumobayashi
Dr. T. Taketomi
Dr. M. Yagi