# *Transition Metal Catalyzed Olefin Isomerization of Allylic Systems*

Evans Group Seminar

March 15, 2002

Anna Chiu

## *Outline:*

*Introduction*

- Mechanism
- Simple allyl alcohol/ether isomerizations

*Asymmetric Catalysis*

- Development of an asymmetric catalyst for allyl amines
- A new mechanism and model for stereoinduction
- Asymmetric allyl alcohol isomerization

*Generation of Enolate Equivalents*

- Stereoselective isomerizations
- Tandem reactions

*Rearrangements*

- Hg & Pd catalyzed allylic rearrangements
- Oxo metal catalyzed rearrangements and tandem reactions

*Synthetic Applications*

## *Leading References:*

*General*

Davies, S.G. *Organotransition Metal Chemistry. Applications to Organic Synthesis;* Pergamon Press: Oxford, 1982; pp. 266-290.

*Enantioselective Allyl Amine Isomerization*

Otsuka, S., Tani, K. *Synthesis*, **1991,** 665.

Noyori, R., Takaya, H. *JACS*, **1990**, 4897.

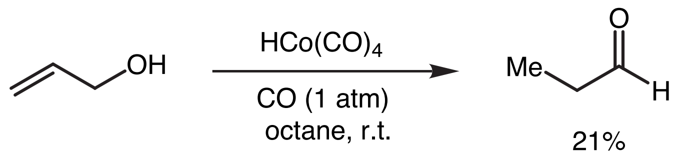
*Allylic Rearrangement*

Overman, L.E. *ACIEE,* **1984**, 579.

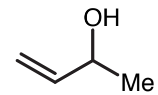
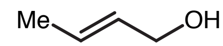
Overman, L.E., Hollis, T.K. *J. Organomet. Chem.,* **1999**, 290.

# *Allylic Alcohols: Early Discoveries*

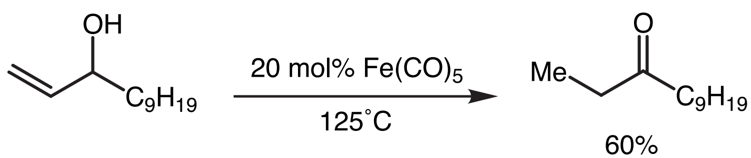
*Metal Hydrides* (Goetz,R., Orchin, M. *JACS*, **1963**, 1549.)

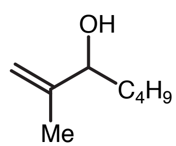
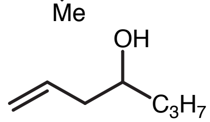
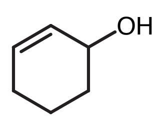



Observed during hydroformylation

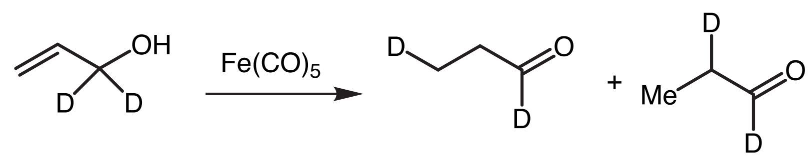
| *Substrate* | *Yield (%)* |
|---|---|
|  | 3.7 |
|  | 3 |

*Metal Carbonyls* (Damico, R., Logan,T.J. *JOC,* **1967**, 2356.)




| Substrate | Yield |
|---|---|
|  | 75 |
|  | 80 |
|  | 20 |

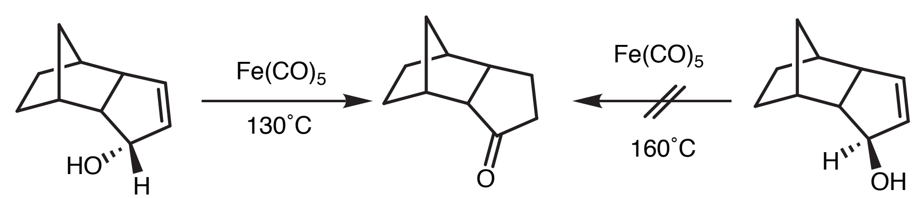
*Deuterium Labelling Studies*




exclusive

not observed

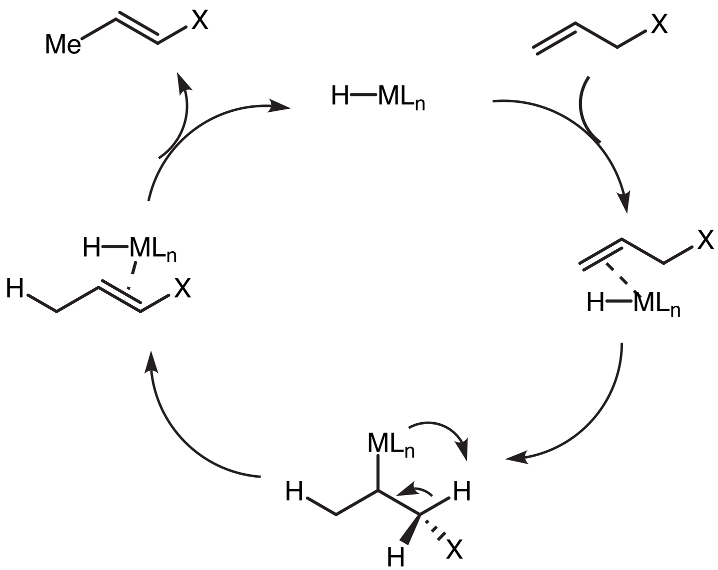
*Supra-facial 1,3 H Migration*




Rosenberg, J.L. *Chem. Comm*., **1968**, 97.

# *General Mechanism*

### *Hydride Addition-Elimination*



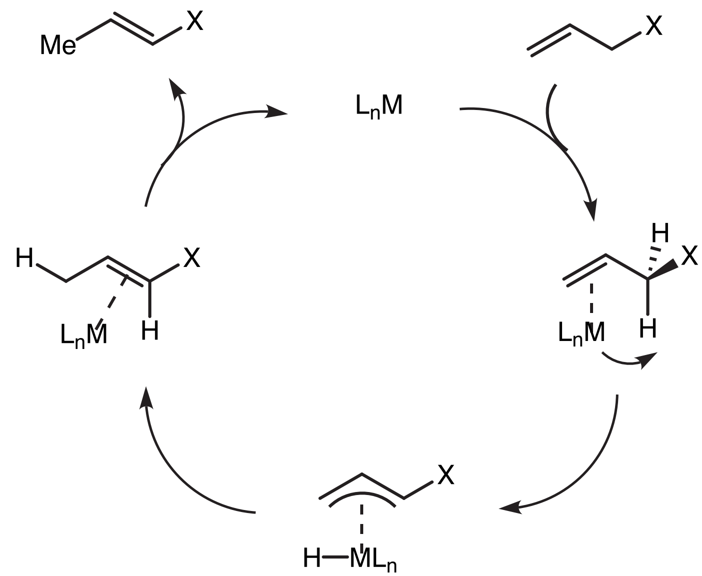
### *Common Catalysts*

$HCo(CO)_4$

$(Ph_3P)_3RhCl$

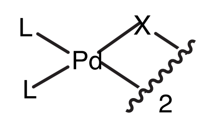
$HRuCl(PPh_3)_3$

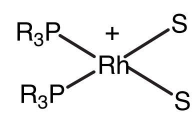
### *$\pi$-Allyl Metal & 1,3 H Shift*

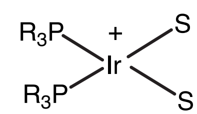


### *Common Catalysts*

$Fe(CO)_5$

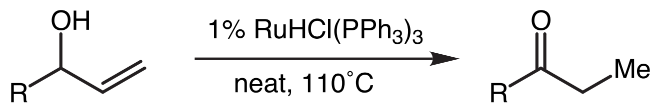


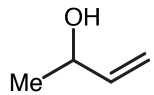
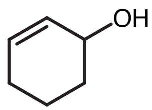
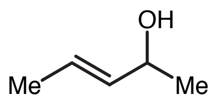
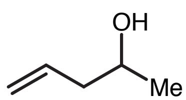
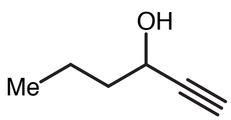
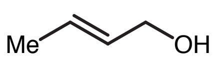




02 general mechanism  3/15/02  9:52 AM

# *Early Ru and Ir catalysts*

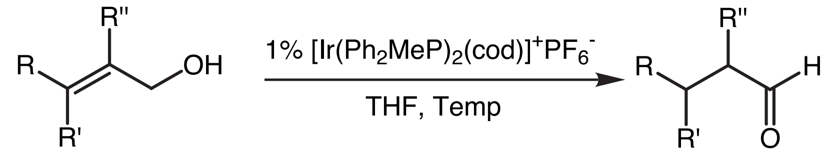


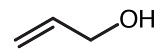
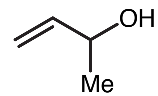
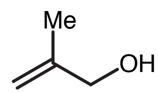
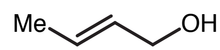
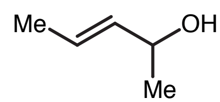
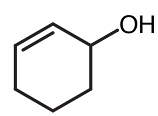
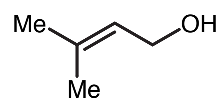
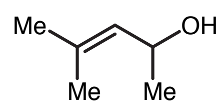

| *Alcohol* | *Yield (%)* |
|---|---|
|  | 91 |
|  | 81 |
|  | 90 |
|  | 79 |
|  | 0 |
|  | 0 |

*Limitations:*

- Air sensitive catalyst (immediate preparation and cannot be recycled)
- Not selective for allylic alcohols; other olefins also isomerize

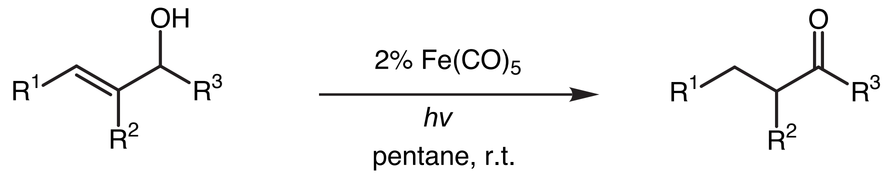
Sasson, Y., Rempel, G.L. *TL*, **1974**, 4133.



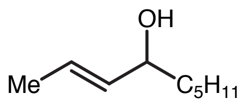
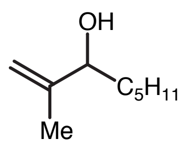
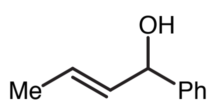

| *Alcohol* | *Temp (˚C)* | *Conversion (%)* |
|---|---|---|
|  | 20 | 100 |
|  | 20 | 100 |
|  | 20 | 100 |
|  | 65 | 99 |
|  | 65 | 98 |
|  | 65 | 9 |
|  | 65 | 12 |
|  | 65 | 0 |

Baudry,D., Ephritikhine,M., Felkin,H. *Nouv. J. Chim.,* **1978**, 355.

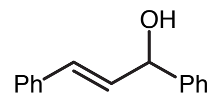
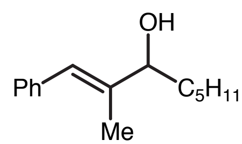
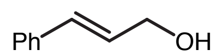
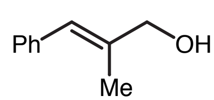
# *$Fe(CO)_5$ Revisited: Light Activation*



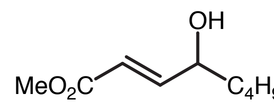
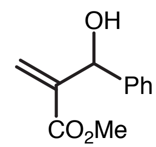
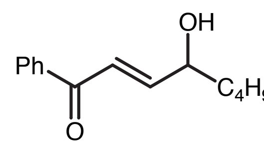

*Hindered Aliphatic*

| *Substrate* | *Yield (%)* |
|---|---|
|  | 86 |
|  | 95 |
|  | 64 |

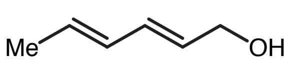
*Cinnamyl derivatives*

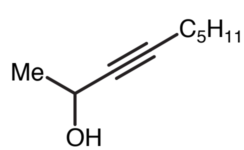
| *Substrate* | *Yield (%)* |
|---|---|
|  | 90 |
|  | 80 |
|  | 38 |
|  | 90 |

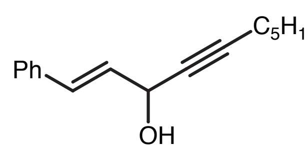
*Carbonyls*

| *Substrate* | *Yield (%)* |
|---|---|
|  | 70 |
|  | 87 |
|  | 70 |

*Poor Substrates (no reaction)*

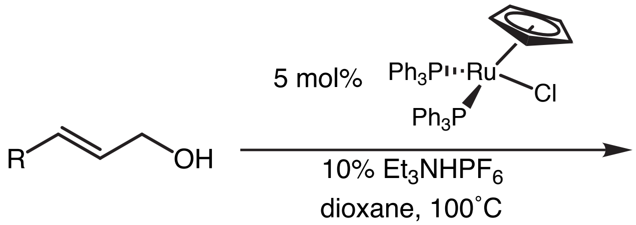


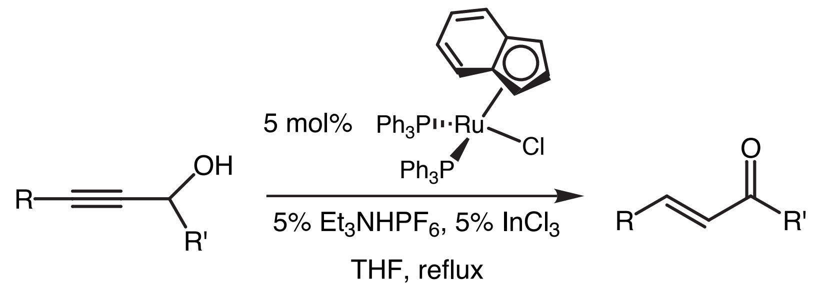



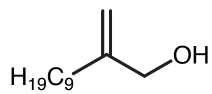
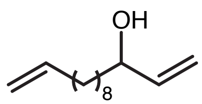
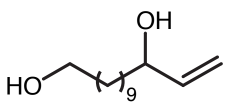
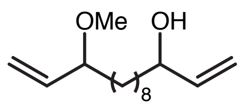
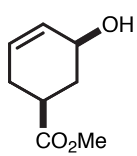
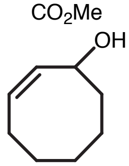
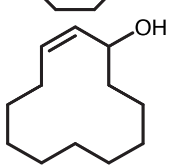



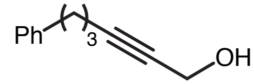
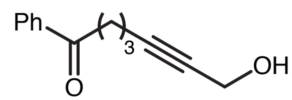
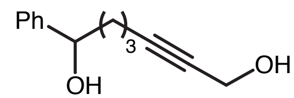
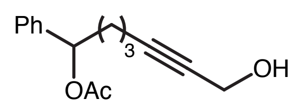
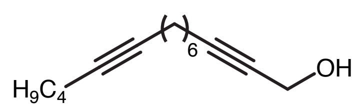
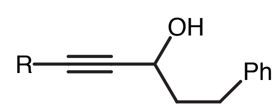
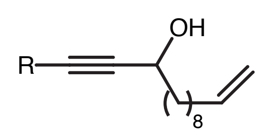

Gree, R. *Tet.*, **2001**, 2379.

# *A Milder Catalyst: Ruthenium*



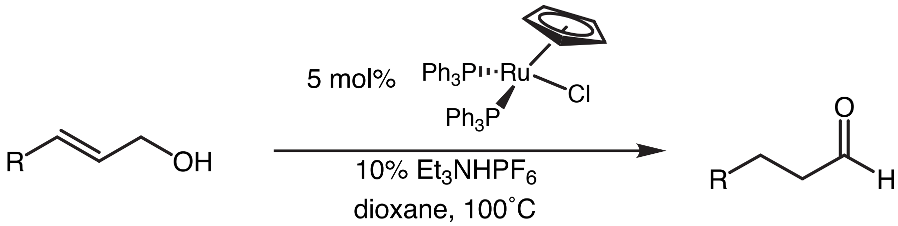

| *Substrates* | *Yield (%)* |
|---|---|
|  | 90 |
|  | 68 |
|  | 87 |
|  | 90 |
|  | 93 |
|  | 0 |
|  | 31 (47% w/ Indenyl) |
|  | 84 |

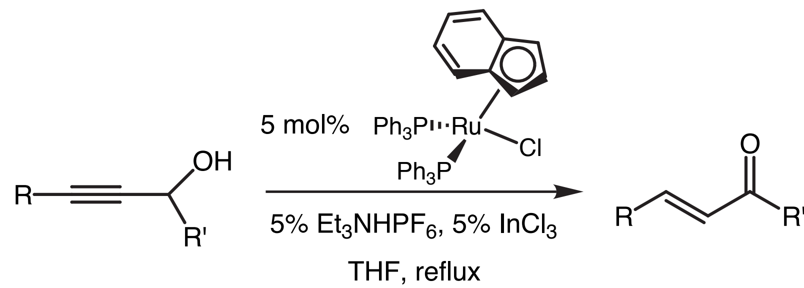
| *Substrates* | *Yield (%)* |
|---|---|
|  | 88 |
|  | 80 |
|  | 86 |
|  | 87 |
|  | 83 |
|  R = $C_{10}H_{21}$ | 86 |
|  R = $C_4H_9$ | 83 |

*Only free allylic & propargylic alcohols isomerize!*

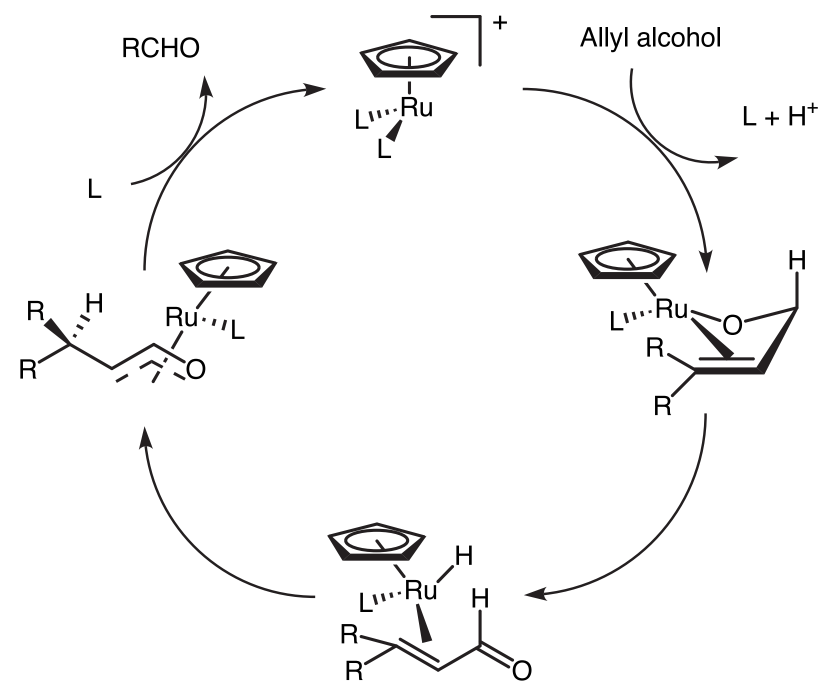
Trost, B.M. *JACS*, **1993**, 2027 & **1995**, 9586

# *Ru Catalyzed Isomerization: Proposed Mechanism*



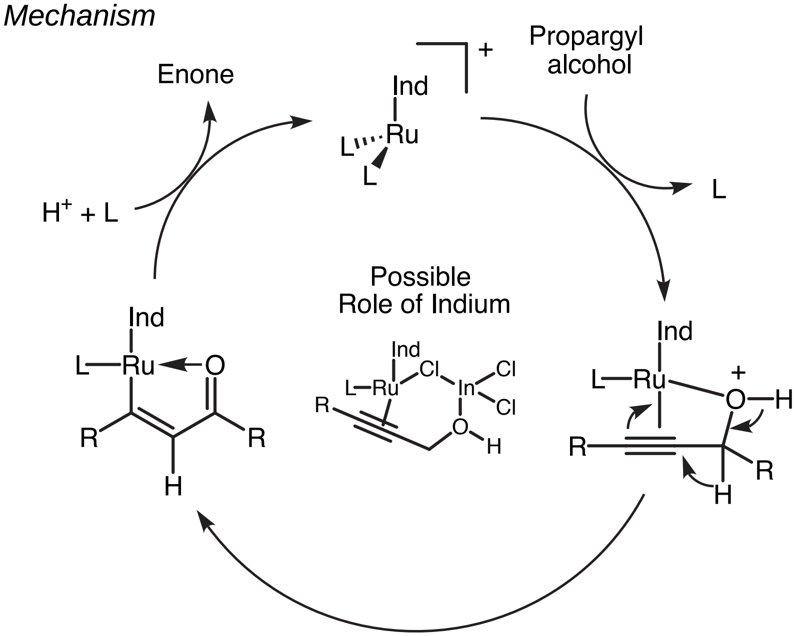




*Mechanism*

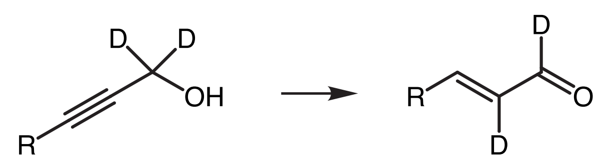



- Beta elimination requires opening of a coordination site (olefin, L, or Cp)
- Trost states that loss of olefin, oxygen, or $PPh_3$ is unlikely - hence, Cp slippage is required.

*Mechanism*



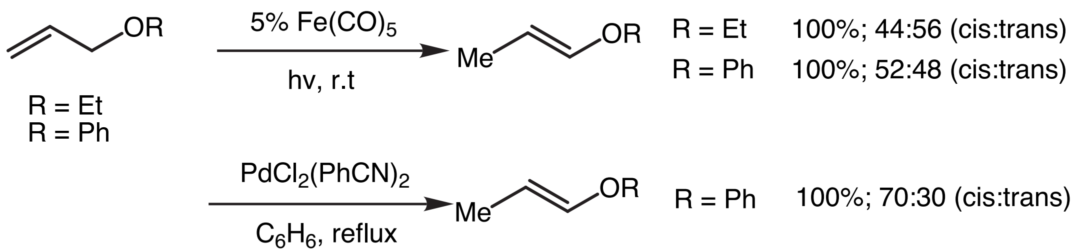

*Evidence*



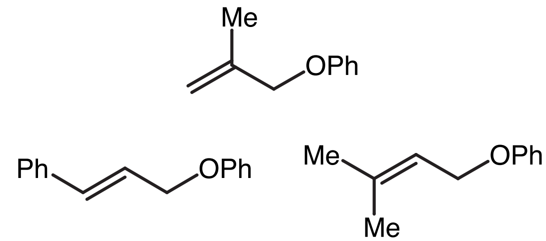

Trost, B.M. *JACS*, **1993**, 2027 & **1995**, 9586

# *Allylic Ethers: E vs Z isomers*

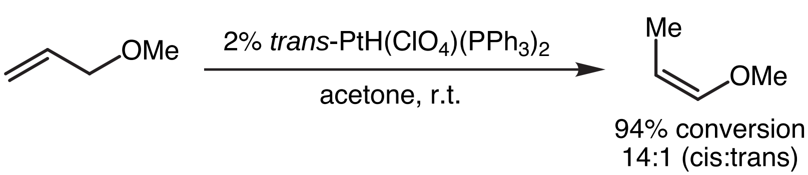
### *Early Examples*

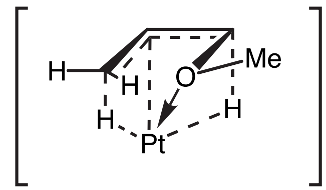



### *Poor substrates (no reaction)*



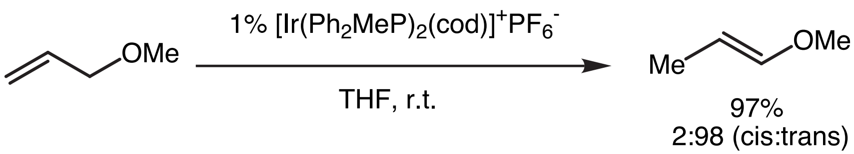

### *Stereospecific Cis Isomers*



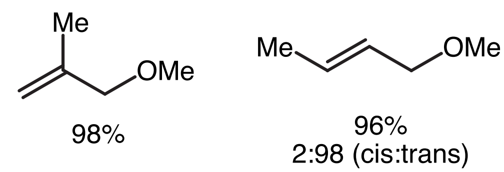




High cis selectivity due to possible platinum oxygen chelate

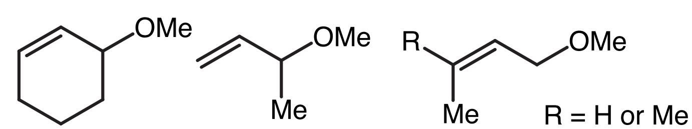
### *Stereospecific Trans Isomers*



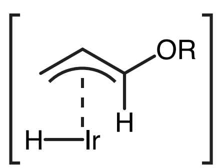

### *Good Substrates*




### *Poor substrates (no reaction)*




### *Model for High Trans Selectivtiy*

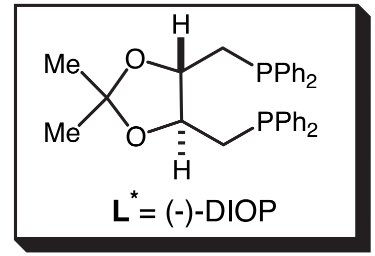


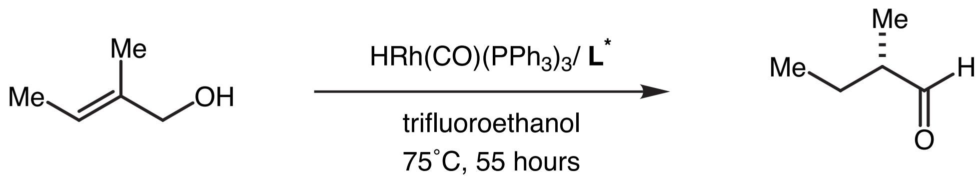


Clark, H.C. *Inorg. Chem.*, **1973**, 1566.

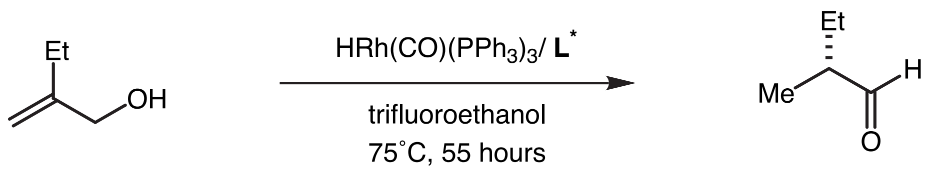
Baudry, D., Ephritikhine, M. *J.C.S. Chem. Comm.*, **1978**, 694.

# "Asymmetric" Isomerization: Earliest Report

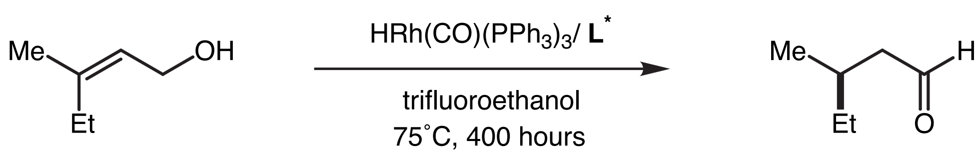



4% ee
91% conversion




3% ee
100% conversion



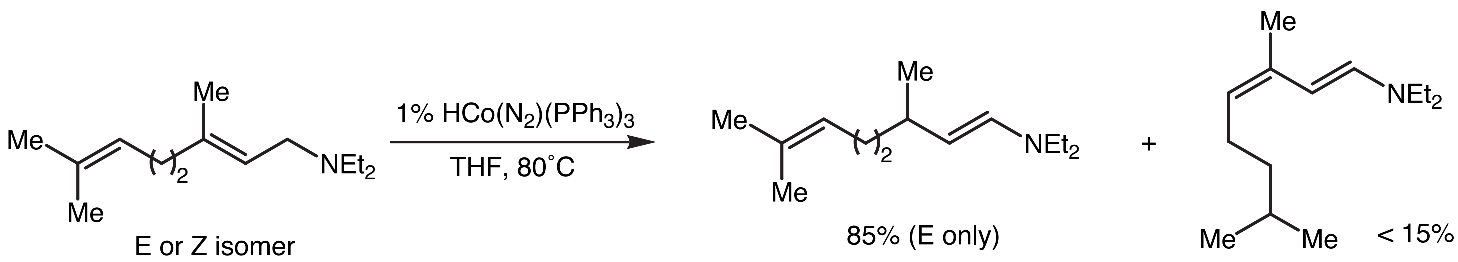

2% ee
63% conversion

Enantiomeric excess determined by optical rotation.

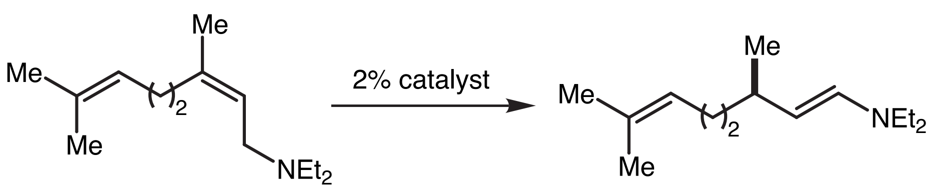
Botteghi, C, Giacomelli, G. *Gazz. Chim. Ital.* **1976**, 1131.

# *Isomerization of Allyl Amines: Early Studies (Otsuka)*

*Early Discoveries*

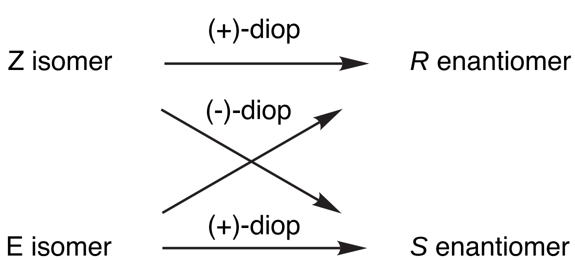


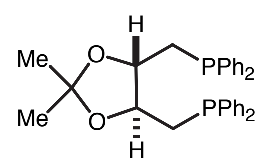

*Asymmetric Version*



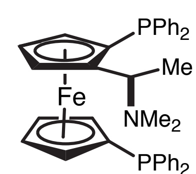

| *Catalyst mixture* | *Yield (%)* | *ee (%)* |
|---|---|---|
| $Co(acac)_2$, (-)-$Ph_2P$-menthyl, DIBAL-H | 16 | 7 |
| $Co(acac)_2$, (+)-BINAP, DIBAL-H | 15 | 20 |
| $Co(acac)_2$, (+)-DIOP, DIBAL-H | 39 | 32 |
| $Co(acac)_2$, (*S,R*)-BPPFA, DIBAL-H | 10 | 10 |

*Correlation*




DIOP




BPPFA

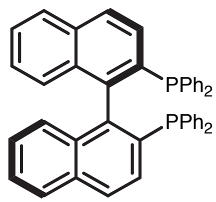
Allyl alcohols failed to isomerize.

Otsuka, S. *JACS*, **1978**, 3950.

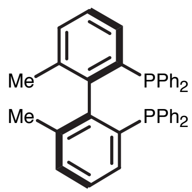
# Development of an Asymmetric Catalyst

*Metal choice: Rhodium (more stable, tetracoordinated complex)*

*Good Ligands*

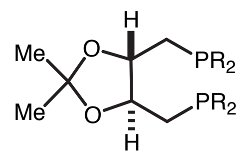


BINAP

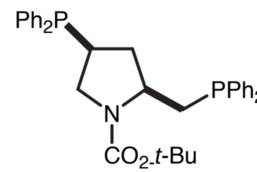


BIPHEMP

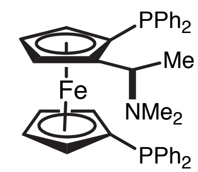
*Poor Ligands*



DIOP
(low ee%)
due to flexible conformation

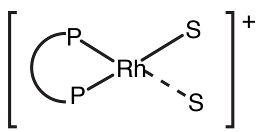


BPPM
(low ee%)



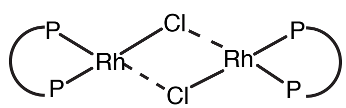
BPPFA
(no rxn)

*Metal complex*



cationic

vs.

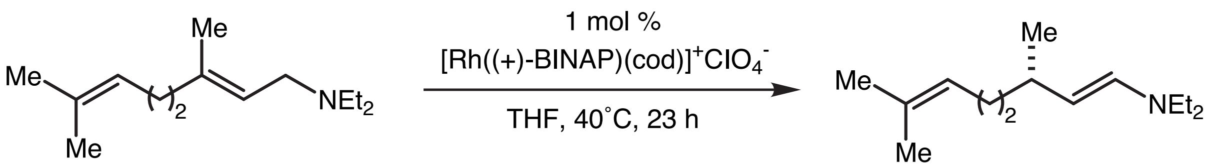


neutral

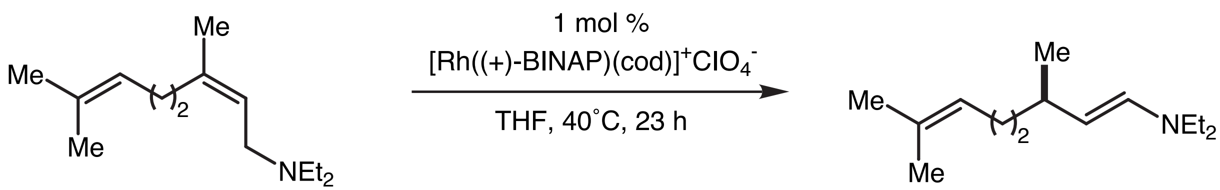
*Additives:*

Donor ligands such as amines,
COD, and diphosphines act as inhibitors.

*Most Efficient Catalyst System*




94%; 96% ee

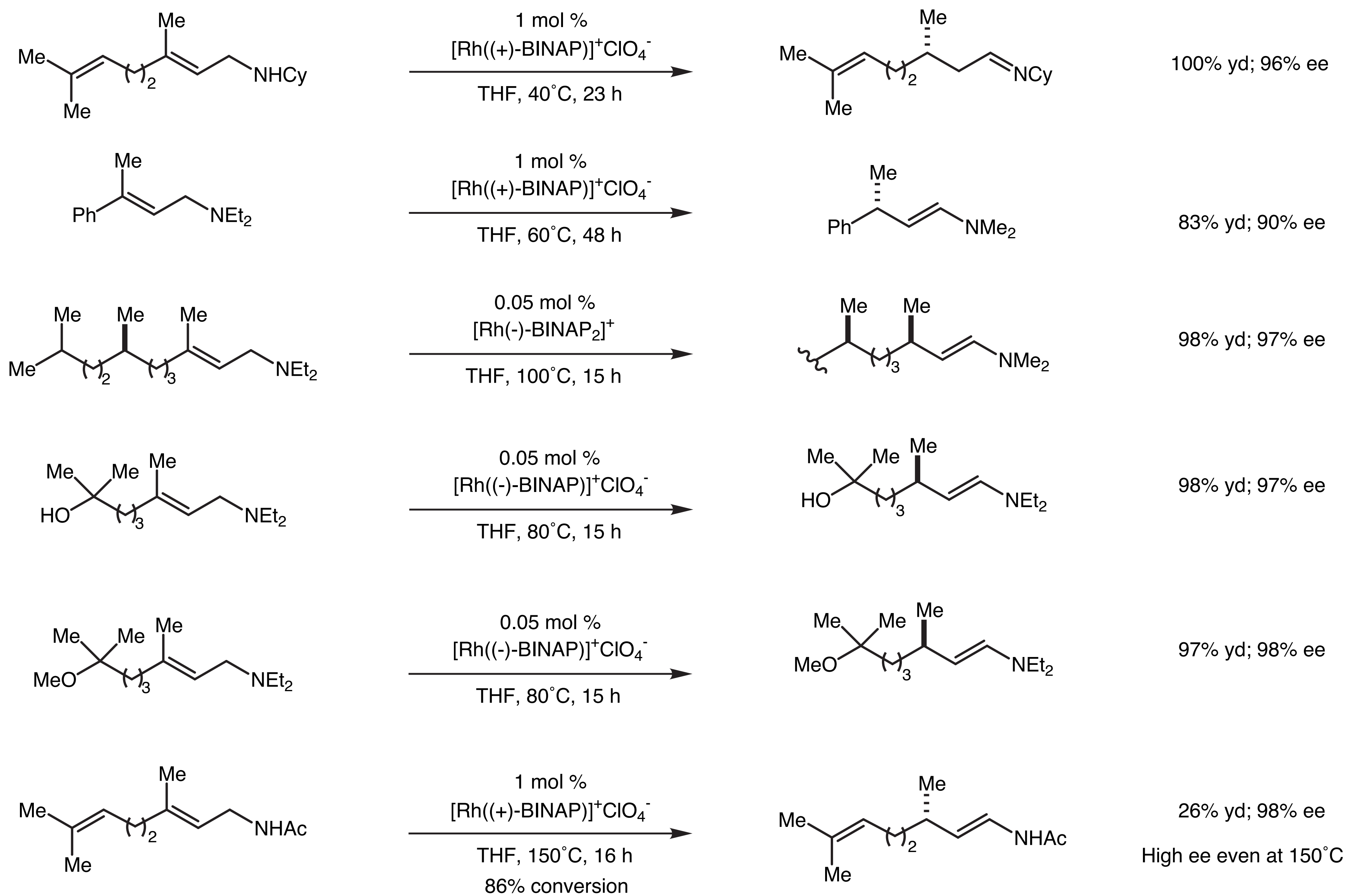



94%; 95% ee



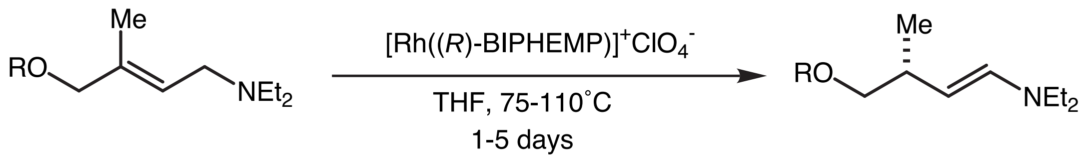
Otsuka, S., Tani, K. *JACS*, **1984**, 5208.

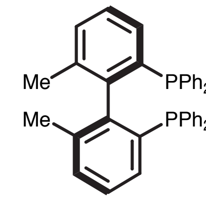
# *Substrate Scope (Otsuka, Tani)*



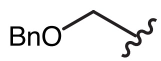
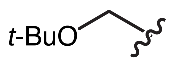
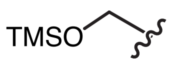

Otsuka, S., Tani, K. *Synthesis*, **1991**, 665.

# *Selective Isomerization Towards Nitrogen*

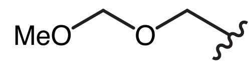
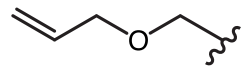
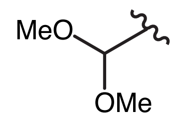



(R)-BIPHEMP

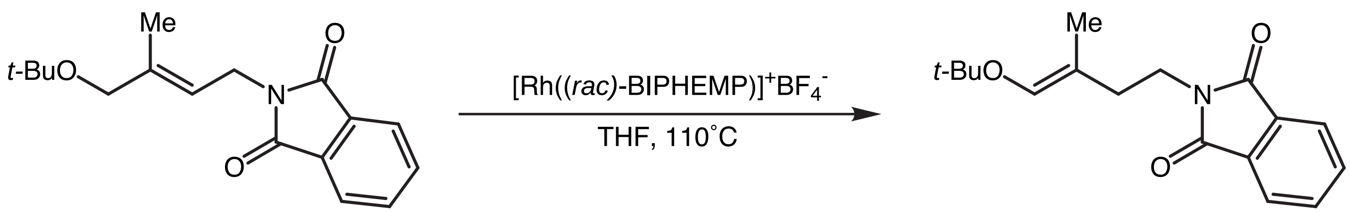
| *R* | *Yield (%)* | *ee (%)* |
|---|---|---|
|  | 73 | 99 |
|  | 60 | 94 |
|  | 50 | 96 |



| *R* | *Yield (%)* | *ee (%)* |
|---|---|---|
|  | 19 | 96 |
|  | 30 | 70 |
|  | 34 | 90 |

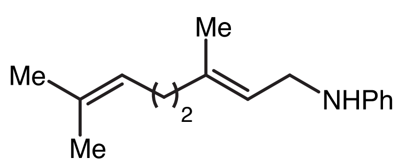


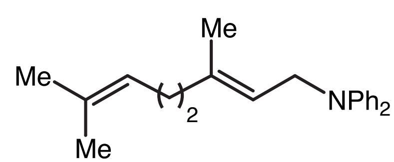
*Exception*




94%, 85:15 (E:Z)

*Unreactive Substrates*



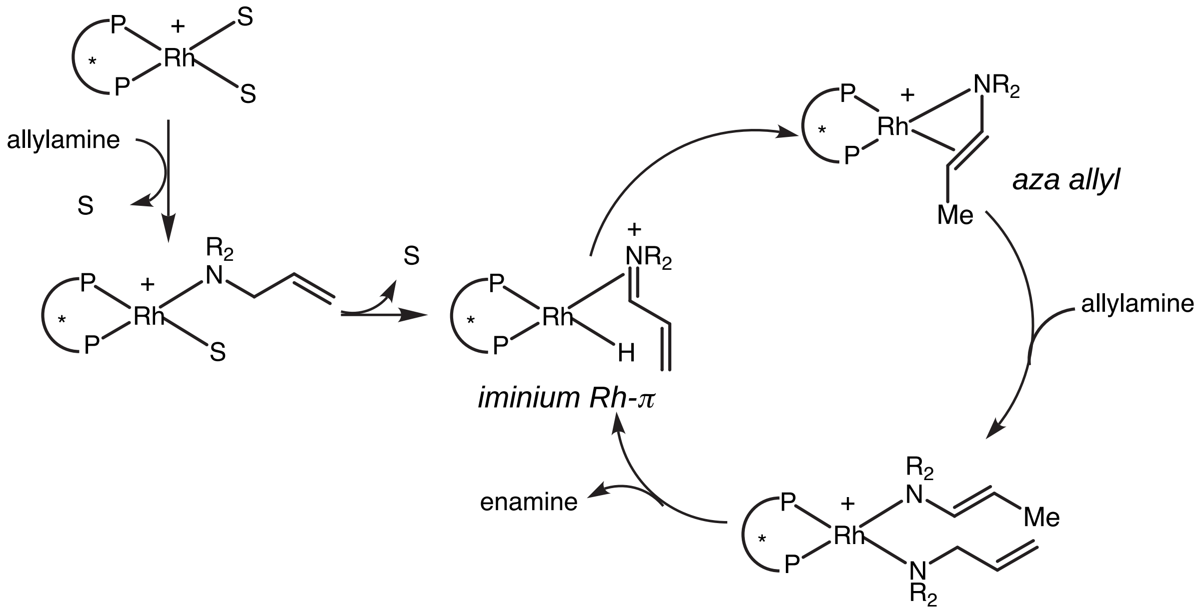





Akutagawa, S. *Compreh. Asym. Cat.*, Vol 2., Ch. 23.
Tani, K. *Pure & Appl. Chem.*, **1985**, 1845.

# *Mechanism & Stereoinduction*

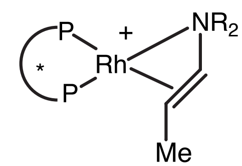
*Nitrogen-Triggered Mechanism*




*Evidence:*

- $Et_3N$ exchange with solvent in Rh complex observed by $^{31}P$ NMR

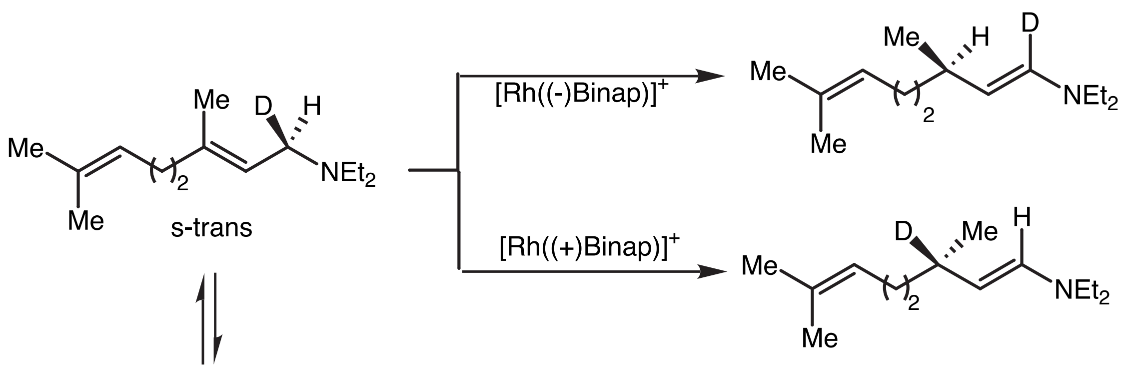
- Isolation of Rh-enamine complex

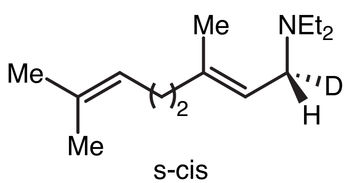


active catalyst

- π-allyl mechanism
  - No NMR evidence of Rh-olefin complex
  - Doesn't explain the need for nitrogen basicity
  - Rate not affected by presence of other olefins

*Stereoinduction*




*Unlikely conformer:*
- $A_{1,3}$ strain
- Antara-facial 1,3 H shift needed

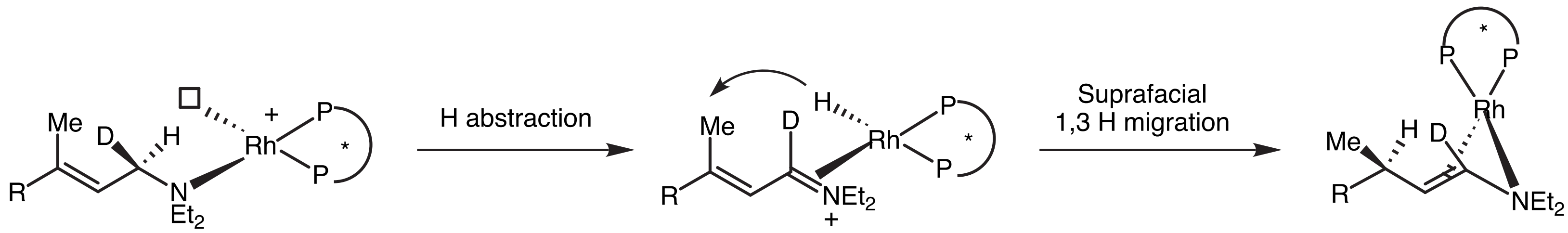
- Supra-facial 1,3 H shift
- No kinetic isotope effect observed

Noyori,R., Takaya, H. *JACS*, **1990**, 4897.

# *Mechanism & Stereoinduction II*

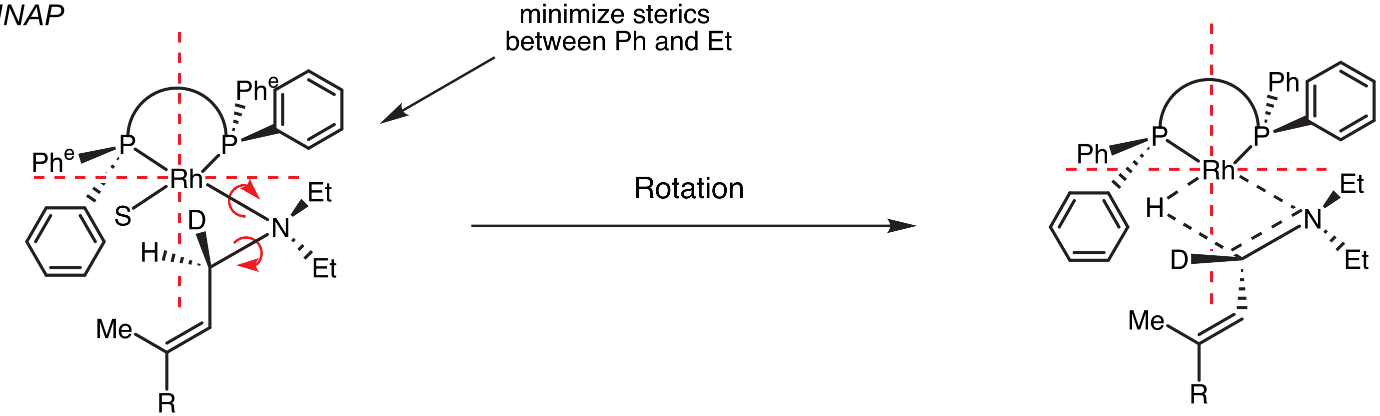
*Model based on the following assumptions:*

- Chiral Rh complexes recognize enantiotopic $C_1$ protons
- S-trans conformer is more stable relative to s-cis conformer




*Chirality of BINAP determines conformation of allylamine*

*With Rh-(-)-BINAP*



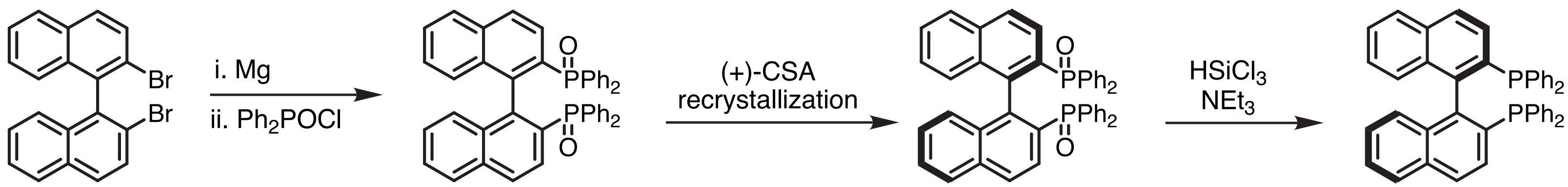

Ph$^e$ = edge on Ph group



Noyori,R., Takaya, H. JACS, **1990**, 4897.

# *From Laboratory to Industry*

## *Synthesis of Enantiomerically Pure BINAP (Takasago Perfumery Industry)*



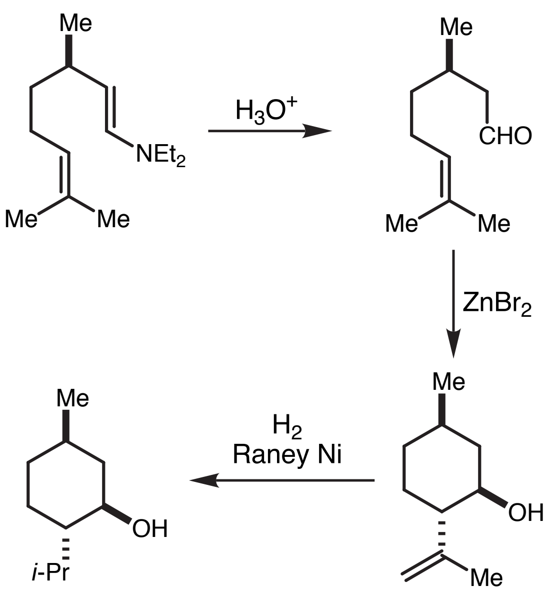

> 99% purity

### *Optimizations:*

- Geometrically pure E/Z isomers of starting allyl amines
- Stringent removal of moisture, air, and donor substances (ie. amines, enamines and olefin isomers)
- Development of a more thermally stable and soluble catalyst: chiral $[Rh(p\text{-TolBINAP})_2]^+$

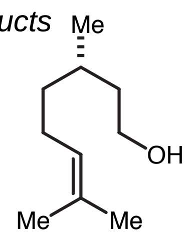
TN: > 8000

### *Commercial Synthesis of (-) Menthol*

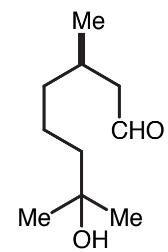



> 4500 tons/yr.

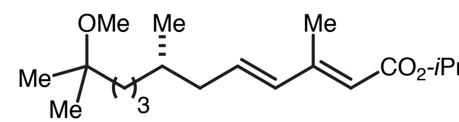
### *Other Natural Products*



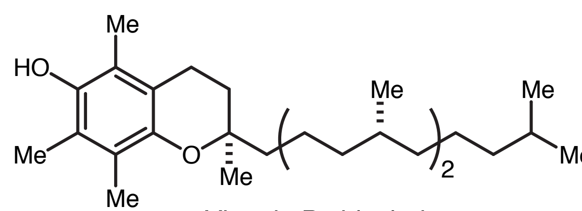

(-)-citronellol
rose oils




(*R*)-7-hydroxycitronellal
"lily of the valley"




Methoprene
mosquito juvenile hormone

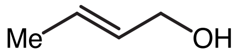


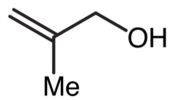

Vitamin B sidechain

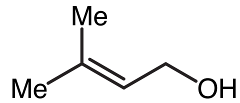
Otsuka, S., Tani, K. *Synthesis*, **1991,** 665.

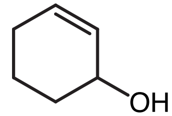
# *Allylic Alcohol Isomerization*

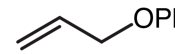
*Simple Substrates*

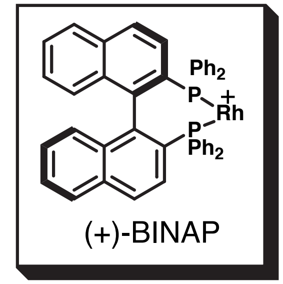


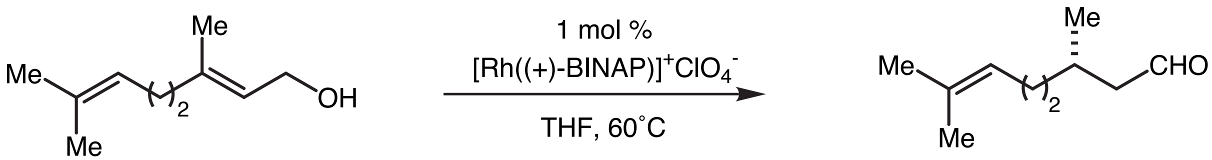




(+)-BINAP

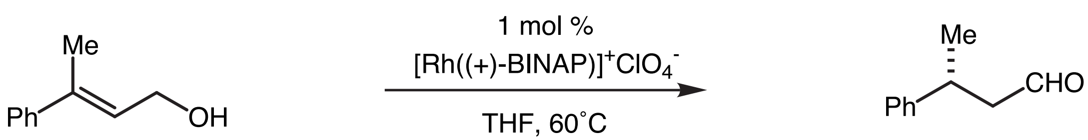
| | | | | | |
|---|---|---|---|---|---|
| *Conversions:* | 87% | 99% | 88% | 82% | 97%<br>87:13 (E:Z) |

*Yields are lower due to Rh(I) promoted decarbonylation of aldehydes.*

*Asymmetric Catalysis*




70% yd, 37% ee

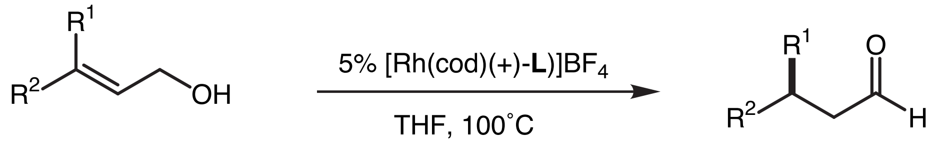


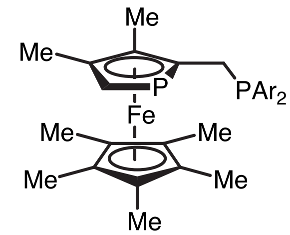

47% yd, 53% ee

15 allylic alcohols 3/15/02 10:17 AM

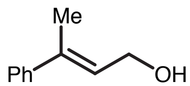
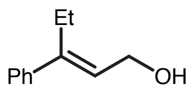
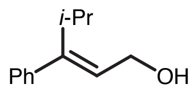
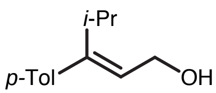
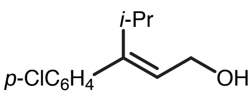
Tani, K. *Pure & Appl. Chem.*, **1985**, 1845.

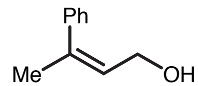
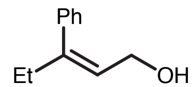
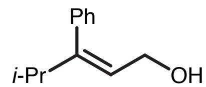
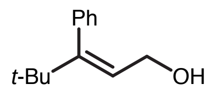
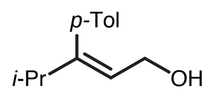
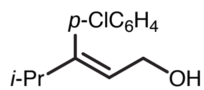
# *Enantioselective Allylic Alcohol Isomerization*



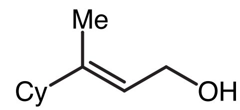



(+)-**L** (Ar = *o*-Tol)

| *E Allylic Alcohols* | *Yield (%)* | *ee (%)* |
|---|---|---|
|  | 91 | 75 |
|  | 96 | 76 |
|  | 98 | 92 |
|  | 90 | 91 |
|  | 86 | 92 |

| *Z Allylic Alcohols* | *Yield (%)* | *ee (%)* |
|---|---|---|
|  | 80 | 59 |
|  | 78 | 57 |
|  | 82 | 82 |
|  | 90 | 90 |
|  | 83 | 77 |
|  | 83 | 85 |

*Non-Aromatic Substrate*



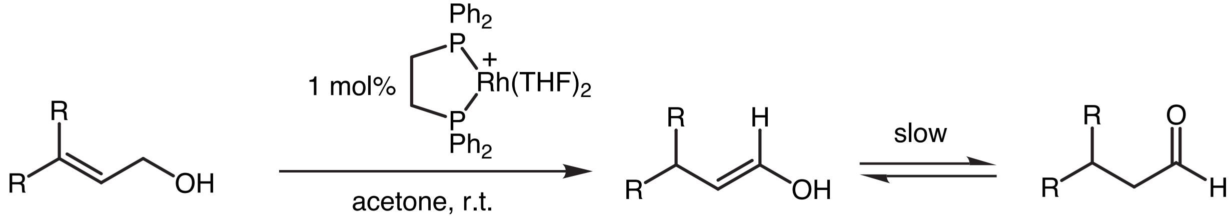
Z isomer: 87% yd, 88% ee

E isomer: 94% yd, 74% ee

- A similar mechanism (based on deuterium studies) to the Rh catalyzed isomerization of allylic amines was proposed involving Rh coordination to oxygen.
- No isomerization observed with allyl methyl ethers or homoallylic alcohols.
- Yield and enantioselectivity remain excellent at lower catalyst loading (1 mol%) and catalyst can be recycled.

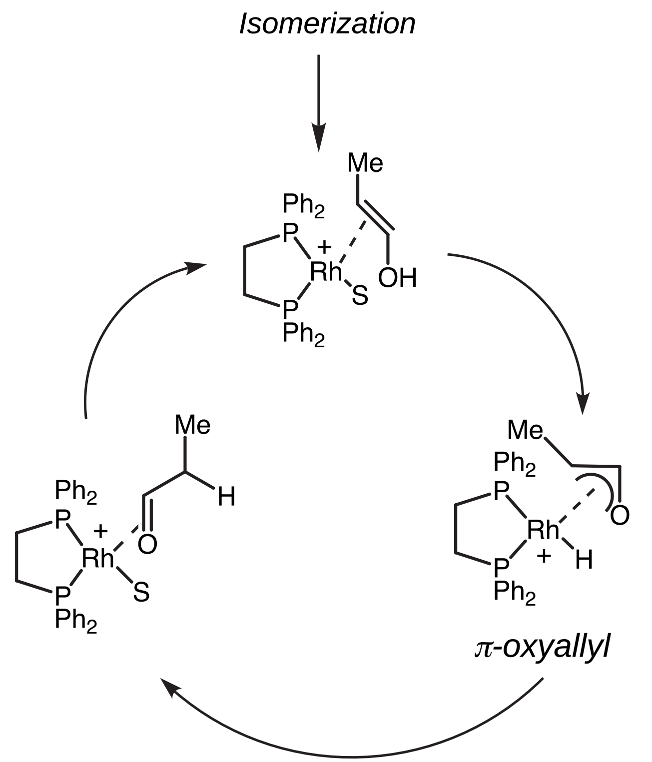

Fu, G.C. *et al*, *JACS,* **2000**, 9870.
Fu, G.C. *et al*, *JOC*, **2001**, 8177.

# *Generation of Simple Enols: Rh catalysts (Bosnich)*

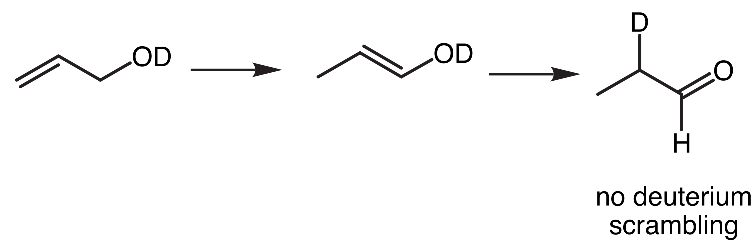


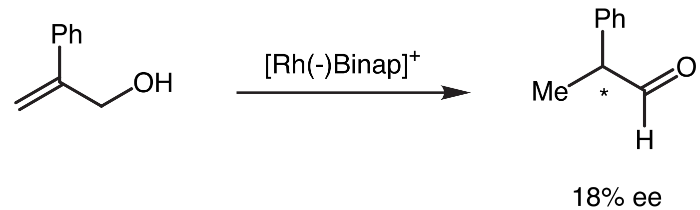

- Mixtures of E/Z
- Ketonization can take hours to days depending on the substrate

*Rh Mediated Ketonization*



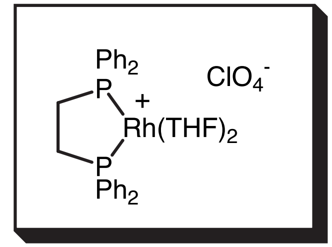

*Evidence*

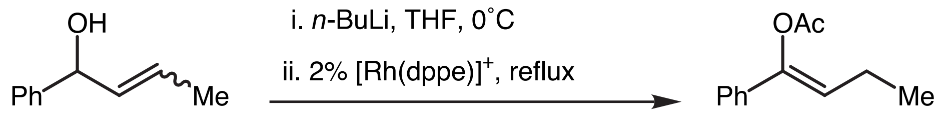



Bosnich, B. *JACS*, **1991**, 958

# *An Approach to Enolate Anions (Motherwell)*

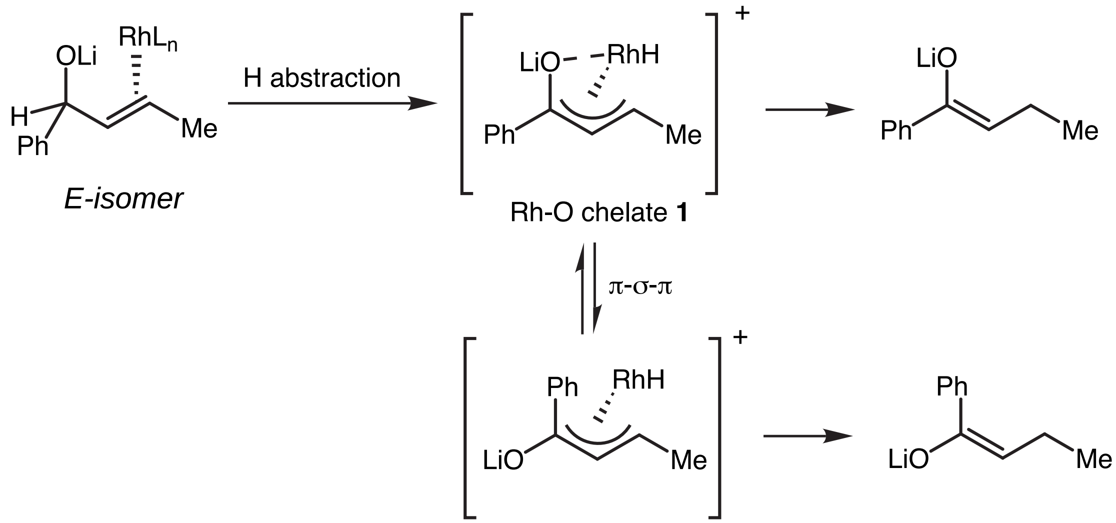



Z or E isomer

64%
>25:1 (Z:E isomer)

*Stereocontrol*

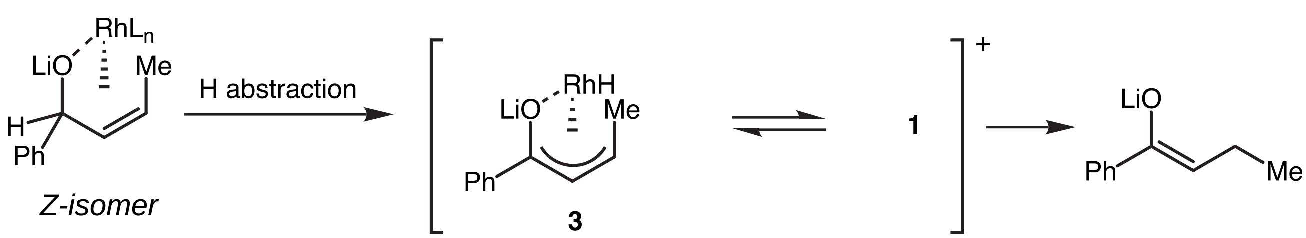



*E-isomer*

Rh-O chelate **1**

**2**

- Rh-oxygen chelate? Maybe/ maybe not...
- Z/E ratio was independent of additives such as TMEDA or 12-crown-4
- Data seems to indicate that enolate geometry is governed by thermodynamics (ie. equilibration of **1** & **2**)
- $(Ph_3P)_3RhCl$ also effective as a catalyst




*Z-isomer*

**3**

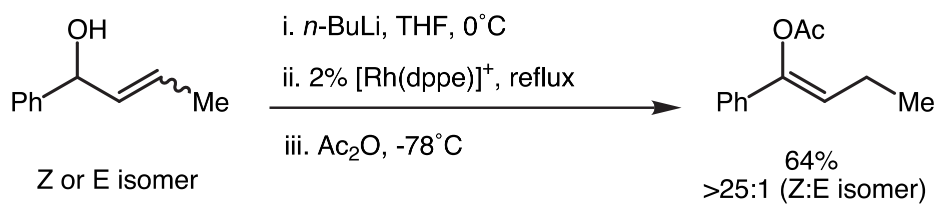
- Slightly longer isomerization times required for Z allylic alcohol - sterics or equilibration?

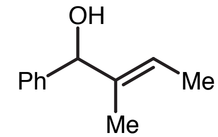
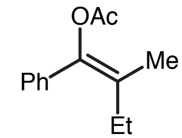
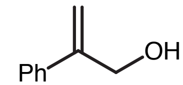
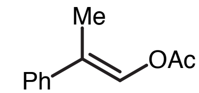
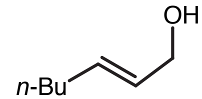
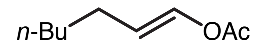
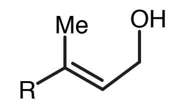

Motherwell, W.B. *et al. J. Chem. Soc. CC,* **1991**, 1399.

Motherwell, W.B. *et al. J.Chem.Soc., P.T. I,* **1999**, 979.

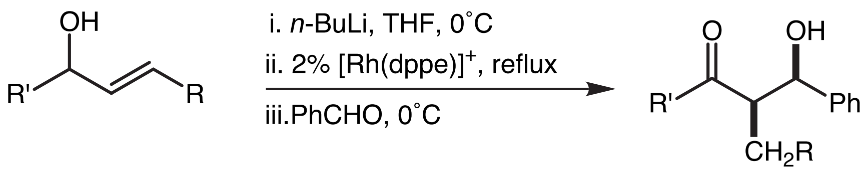
# *Enolization & Aldol (Motherwell)*

*Enolate Geometry*

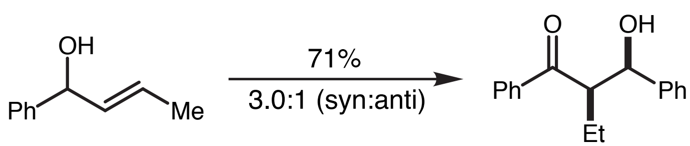


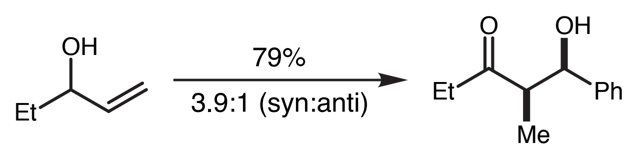

| *Substrate* | *Product* | *Yield (%) & E/Z selectivity* |
|---|---|---|
|  |  | 70<br>1:3 (Z:E) |
|  |  | 78<br>1:10 (Z:E) |
|  |  | 41<br>1:2.8 (Z:E) |
|  | - - - | no rxn |

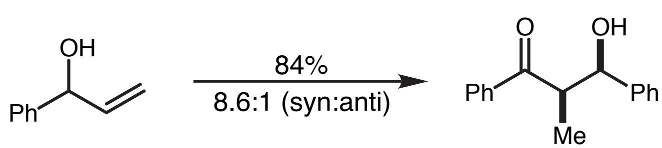
*Isomerization-Aldol Processes*

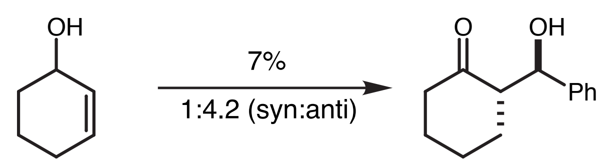



- Benchmark: 98% pure Z Li enolate gives 7.3:1 (syn:anti) product
- Erosion in diastereoselectivity
  - retro aldol vs unselective enolization from competitive ketonization of Rh-enolate complex
- Cyclohexenol precludes cisoid Rh-oxygen intermediate - implications in transition state?



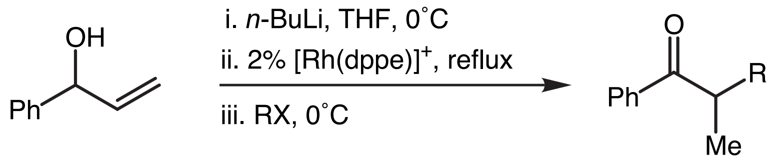




Motherwell, W.B. *et al. J.C.S., P.T. I,* **1999**, 979.

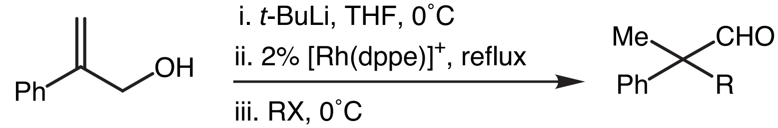
# *Enolate Alkylations (Motherwell)*

*Alkylations*



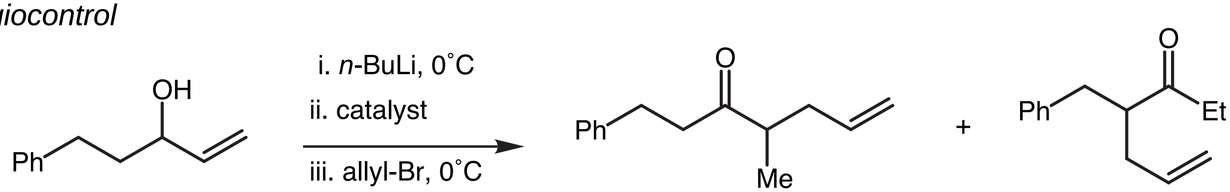

| *Electrophile RX* | *yield (%)* |
|---|---|
| allyl bromide | 82 |
| benzyl bromide | 75 |
| methyl iodide | 62 |
| *n*-Bu iodide | 60 |

*Aldehyde enolates*



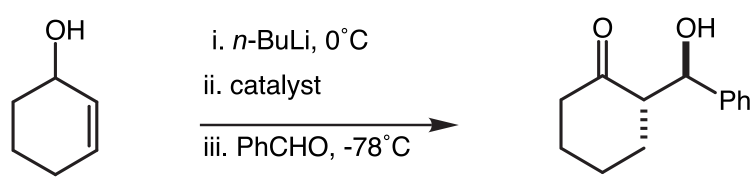

| *Electrophile RX* | *yield (%)* |
|---|---|
| allyl bromide | 72 |
| benzyl bromide | 74 |

*Regiocontrol*




**1 (desired)** **2**

| *catalyst* | *yield (%)* | ***1:2*** |
|---|---|---|
| $[Rh(dppe)]^+$ | 79 | 1:1.2 |
| $(Cy_3P)_2NiCl_2$* | 78 | 15:1 |

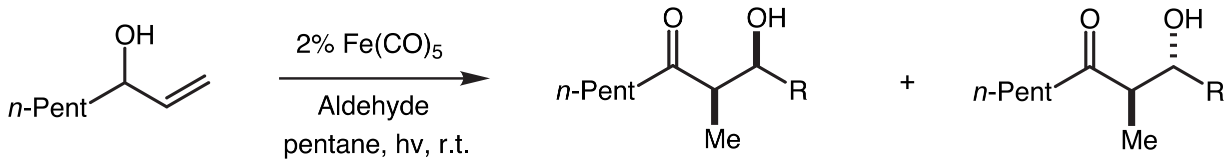



| *catalyst* | *yield (%)* | *syn:anti* |
|---|---|---|
| $[Rh(dppe)]^+$ | 7 | 1:4.2 |
| $(Cy_3P)_2NiCl_2$* | 64 | 1:4.2 |

*Ni hydride catalyst

Motherwell, W.B. *TL*, **1992**, 6187.

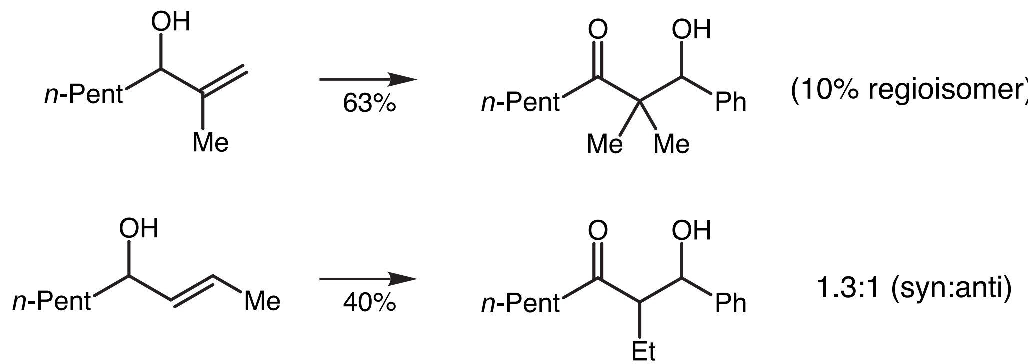
# *Isomerization/Aldol: $Fe(CO)_5$ (Gree)*




Side Products (20-30%):
regioisomer & protonated enolate

| *Aldehyde* | *Yield (%)* | *Syn:Anti* |
|---|---|---|
| PhCHO | 66 | 3:1 |
| HCOH (anh.) | 62 | -- |
| MeCHO | 65 | 3:1 |
| $PhCH_2CHO$ | 65 | 2.6:1 |
| (*i*-Pr)$_2$CCHO | 48 | 2.2:1 |

*Other substrates*

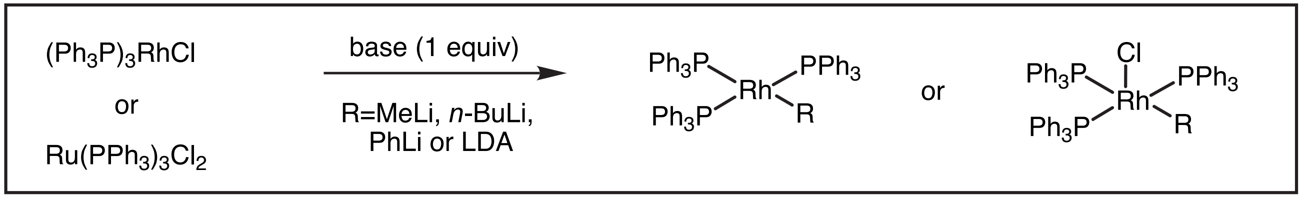



*Cyclic Chair Transition State?*

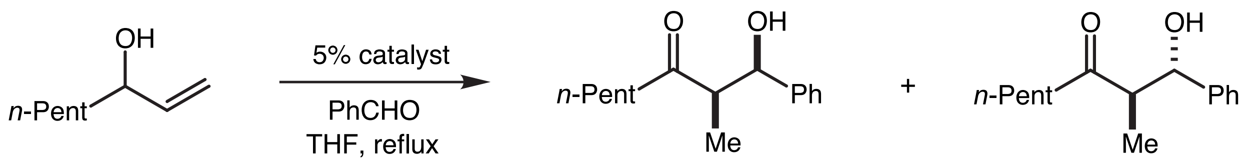

Gree, R. *TL*, **2001**, 395.
Gree, R. *TL*, **2001**, 3069.

# *Improvements on Regioselectivity (Gree)*

*In situ generation of catalyst:*




*Tandem Enolization/Aldol*




*$(Ph_3P)_3RhCl$*

| *base* | *yield (%)* | *syn:anti* |
|---|---|---|
| MeLi | 56 | 39:61 |
| *n*-BuLi | 54 | 40:60 |
| PhLi | 63 | 37:63 |

*$Ru(PPh_3)_3Cl_2$*

| *base* | *yield (%)* | *syn:anti* |
|---|---|---|
| MeLi | 73 | 51:49 |
| *n*-BuLi | 62 | 55:45 |
| PhLi | 75 | 55:45 |

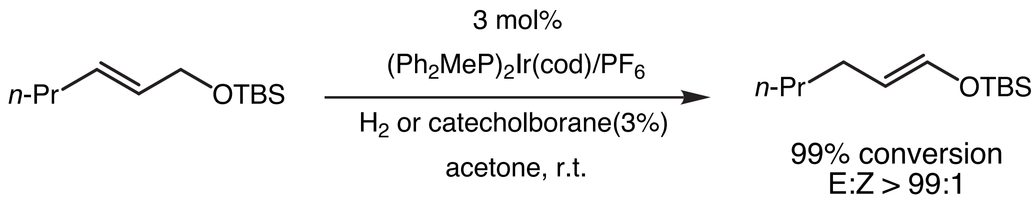
*Advantages:*

- No regioisomers formed
- Possible development of asymmetric catalysis
- Neutral rather than basic conditions



Gree, R. *TL*, **2001**, 3069.

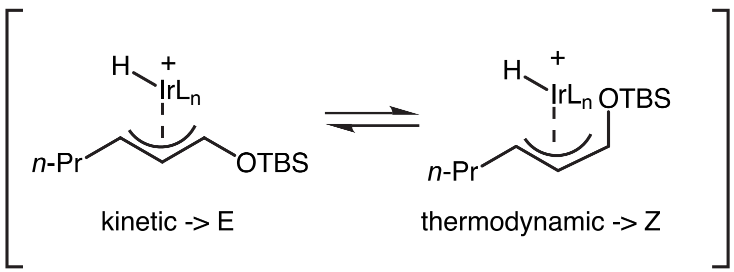
# *Stereoselective Silyl Enol Ether Formation (Miyaura)*




*NMR Study: ($CH_2Cl_2$:acetone (50:1), 0˚C)*

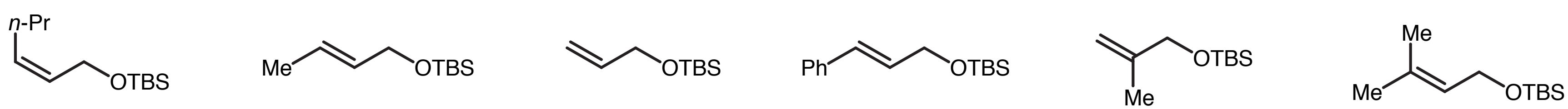
| *time (min)* | *conversion (%)* | *E:Z* |
|---|---|---|
| 5 | 61 | 98:2 |
| 60 | >99 | 85:15 |
| 360 | >99 | 38:63 |

*Authors proposed that E selectivity is kinetically driven:*



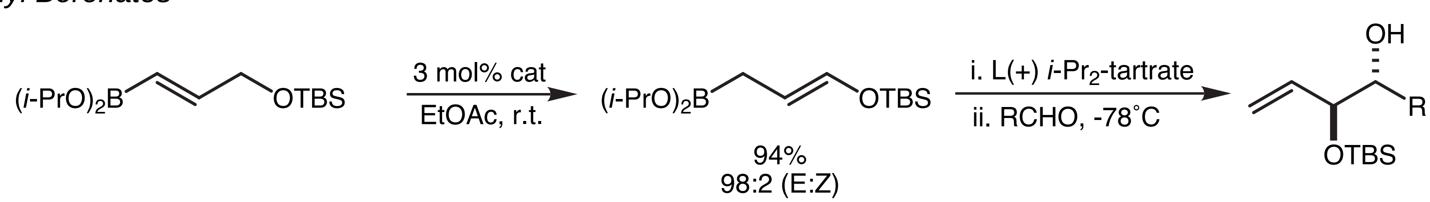

- Acetone - best solvent (fast isomerization, no product equilibration)
- Treating pure E or Z enol silanes with Ir catalyst in $CH_2Cl_2$/acetone leads to a thermodynamic ratio.
- Unfortunately, cannot equilibrate all the way to give only Z enol silanes.

*Substrate Scope*




| 74% 95:5 (E:Z) | 84% 97:3 (E:Z) | 78% 99:1 (E:Z) | 76% 98:2 (E:Z) | 91% | <10% |
|---|---|---|---|---|---|

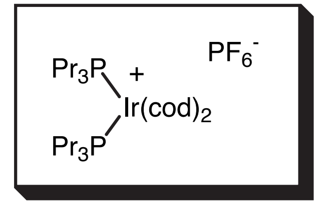
*Chiral Allyl Boronates*



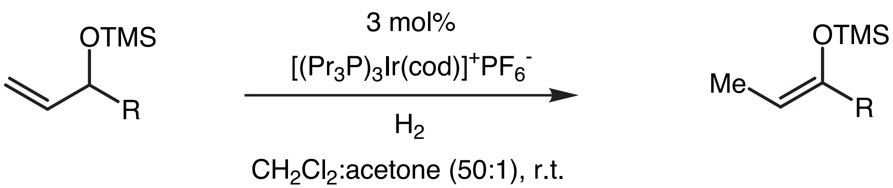

depending on R:
d.r. > 99:1; 67-91% ee


Miyaura, N. JOC, **1999**, 296.
Miyaura, N. *OrgMet.*, **1999**, 413.

# *Secondary Enol Silanes (Miyaura)*

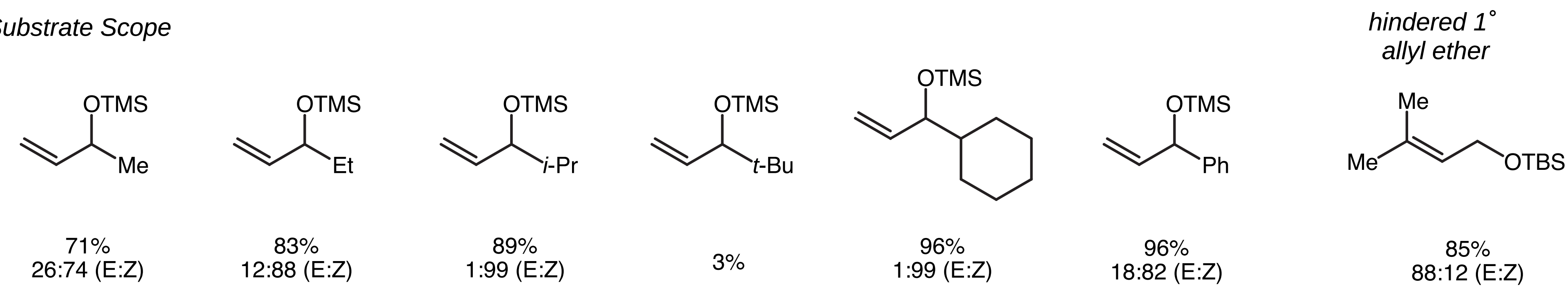



*A More Active Catalyst*

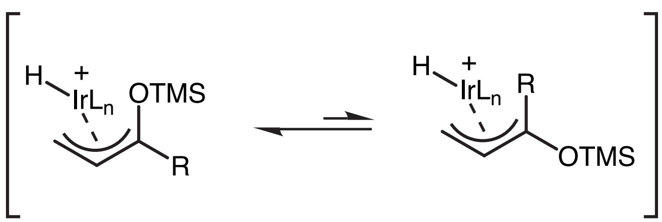



*Z enol silane favored!*

*Substrate Scope*




*Stereocontrol*

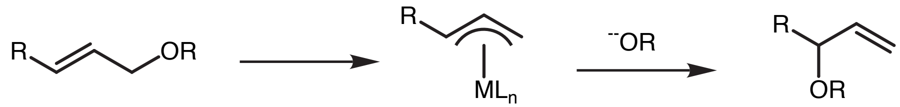



*Z enol silane favored due to thermodynamics.*

Miyaura, N. *Organometallics*, **1999**, 413.

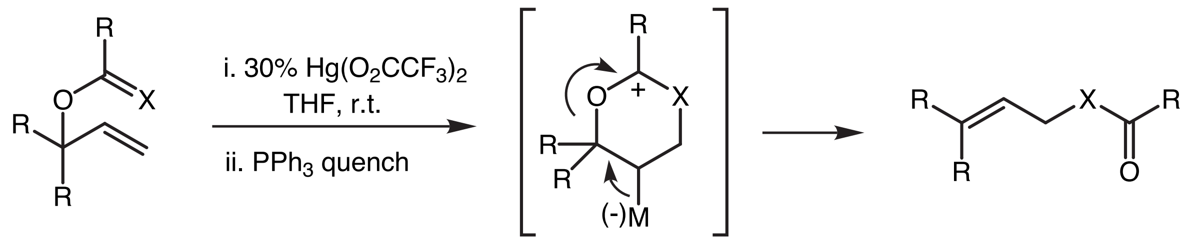
# Allylic Rearrangements (Hg salts-Overman)

*Rearrangements involving $\pi$-allyl complexes (not covered)*

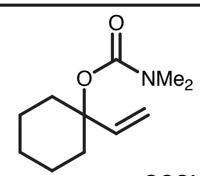
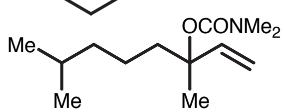
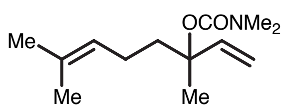
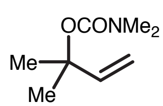
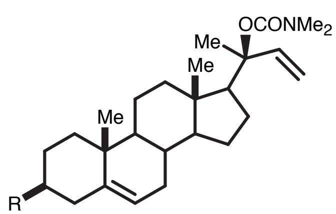


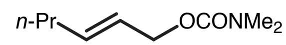
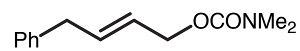
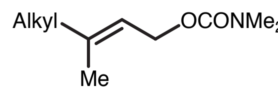

Frank Glorius (Seminar 2000)

*Mercuric Salts (Overman)*

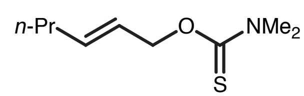
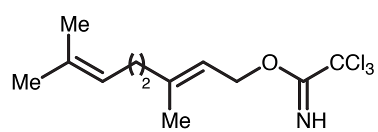



*"Contra-thermodynamic" Cases*

| *Substrate* | *Yield (%)* |
|---|---|
|  | 95 |
|  | 92 |
|  | 70 |
|  | 98 |
|  | 96 |

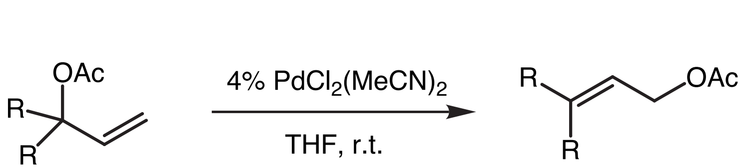
| *Substrate* | *Yield (%)* | *Terminal: starting material* |
|---|---|---|
|  | 80 | 95:5 |
|  | 86 | 71:29 |
|  | 61 | 15:85 |

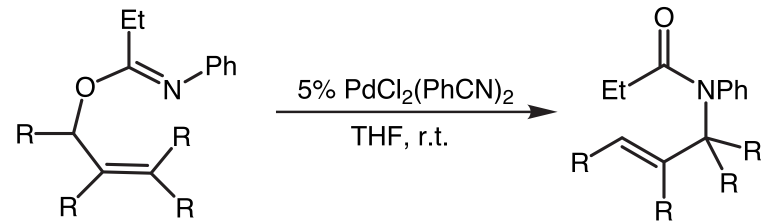
Excess Hg salts and $PPh_3$ are needed to overcome thermodynamic preference.

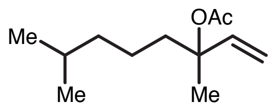
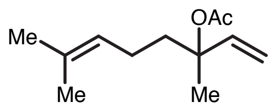
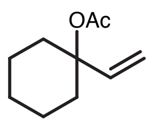
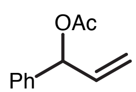
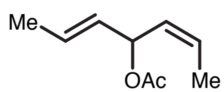
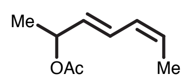
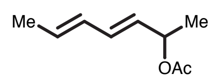
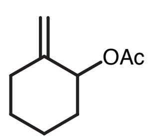
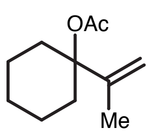
| | | |
|---|---|---|
|  | 52 | 100:0 |
|  | 79 | 100:0 |

Overman, L.E. *et al. JACS*, **1978**, 4822.
Review: Overman, L.E. *et al. ACIEE*, **1984**, 579.

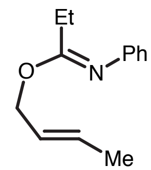
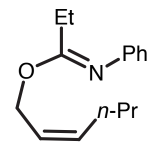
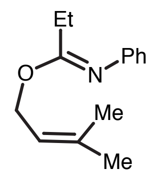
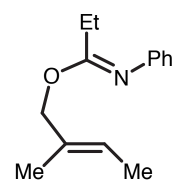
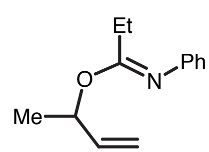
# *More Active Catalysts: Pd(II) salts*




| *Substrate* | *Yield (%)* |
|---|---|
|  | 88<br>78:22 (E:Z) |
|  | 96%<br>89:11 (E:Z)<br>rxn at 70˚C |
|  | 93 |
|  | 96 |
|  |  + <br>74 18 |
|  | no rxn |
|  | no rxn |

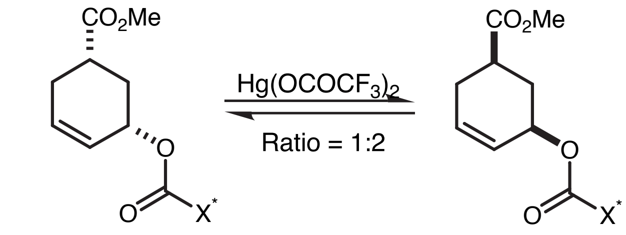
Overman, L.E. *et al. ACIEE*, **1984**, 579.

| *Substrate* | *Yield (%)* |
|---|---|
|  | 79 |
|  | 74 |
|  | 90 |
|  | 75 |
|  | 68 |

Metz, P. *Tet*, **1992**, 1071.

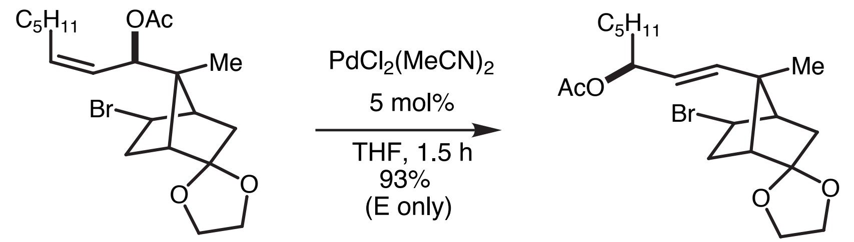
# *Allylic Rearrangement: Chirality Transfer*

*Trost* (*CC*, **1978**, 436.)

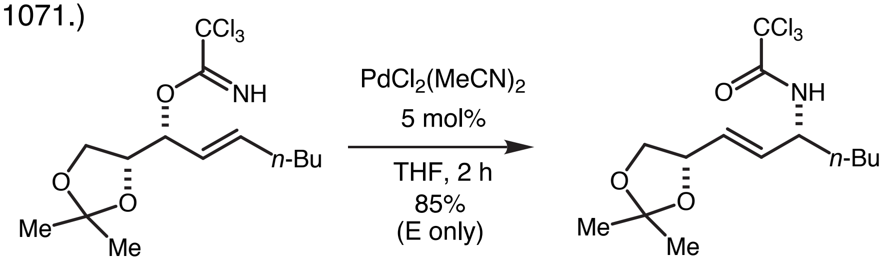



X=(S)-α-Napthylethylamino

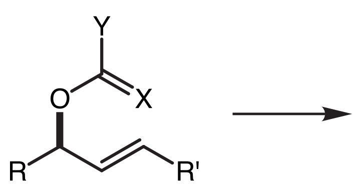
*Grieco* (*JACS*, **1980**, 7587.)

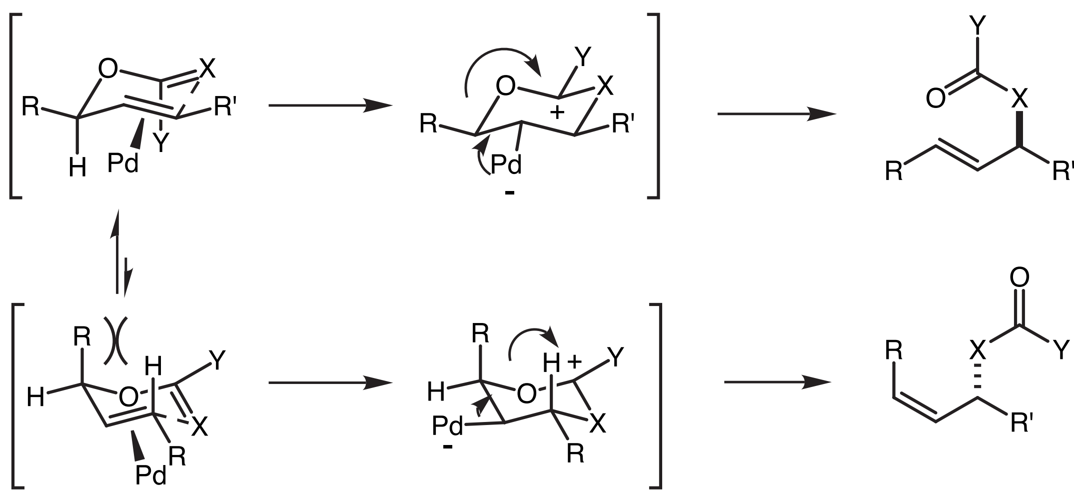



*Meetz* (*Tet.*, **1992,** 1071.)




*Cyclization-Induced Rearrangement (Overman)*

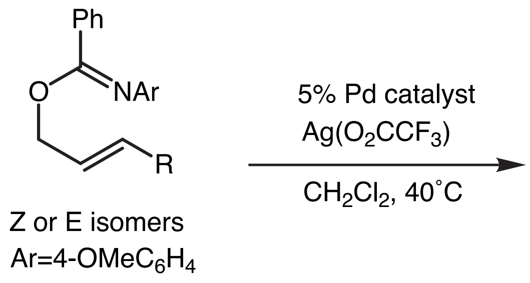


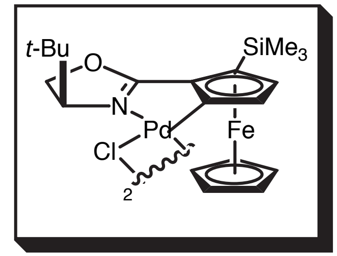



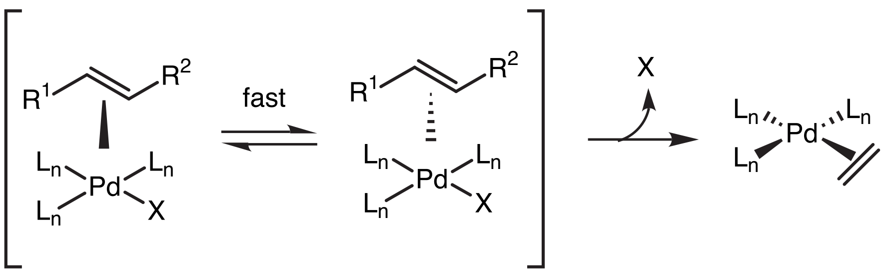

Retention of stereochemistry & lack of olefin scrambling support a non π-allyl mechanism

Overman, L.E. *ACIEE*, **1984**, 579.

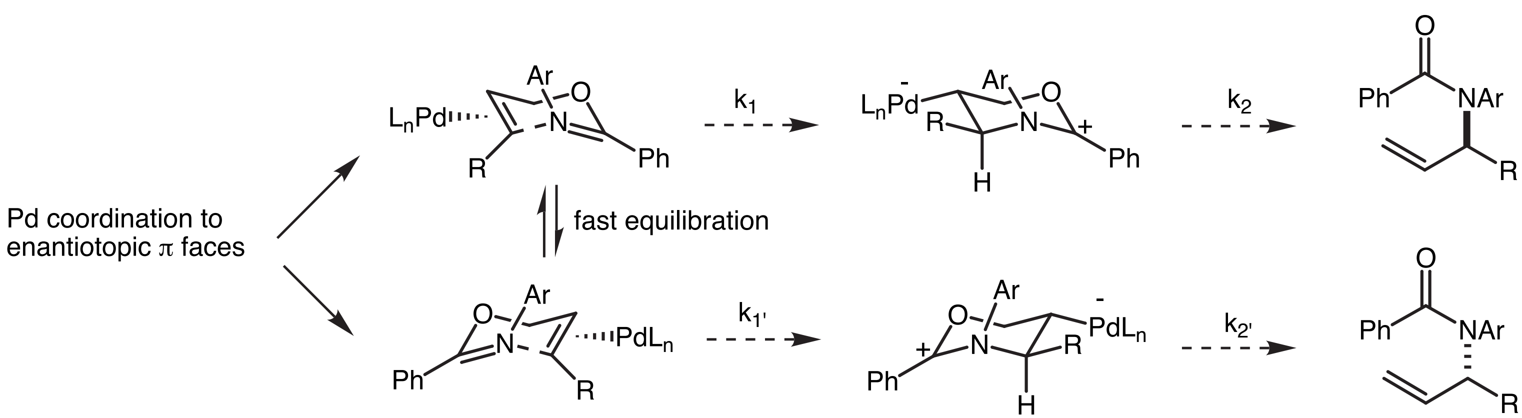
# *Enantioselective Rearrangement: Allylic Imidates*



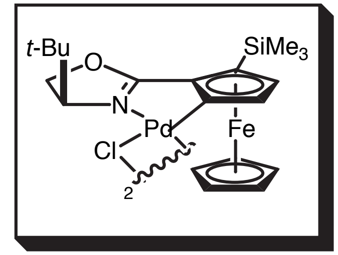



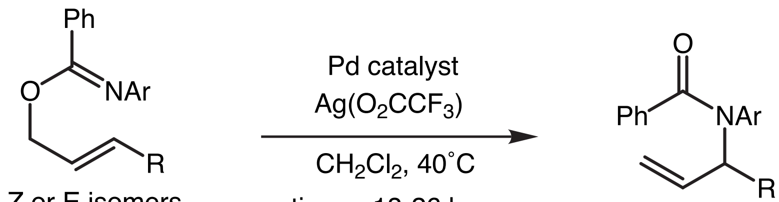

- Initial steps are likely: association, psuedo-rotation, dissociation
- Coordination of Pd to $\pi$-face of the olefin determines enantioselectivity; it is, however, not the rate determining step
- Possible rate determining steps that lead to observed enantioselectivity: cyclization or elimination




Overman, L *et al. J. Orgmet. Chem*., **1999**, 290.

# *Substrate Scope and Other Ligands*



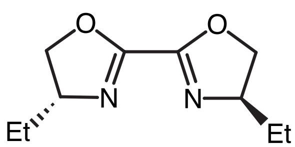




Z or E isomers
Ar=4-OMe$C_6H_4$

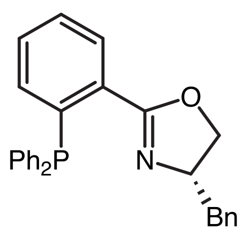
| *Z Isomers* | | |
|---|---|---|
| *R* | *Yield (%)* | *ee (%)* |
| Me | 96 | 75 (*R*) |
| *n*-Pr | 83 | 91 (*R*) |
| *i*-Bu | 90 | 97 (*R*) |
| *i*-Pr | 59 | 86 (*R*) |
| Bn | 85 | 88 (*R*) |
| Ph | 11 | 77 (*R*) |

| *E Isomers* | | |
|---|---|---|
| *R* | *Yield (%)* | *ee (%)* |
| *n*-Pr | 93 | 83 (*S*) |
| *i*-Bu | 97 | 84 (*S*) |
| Ph | 59 | 63 (*S*) |

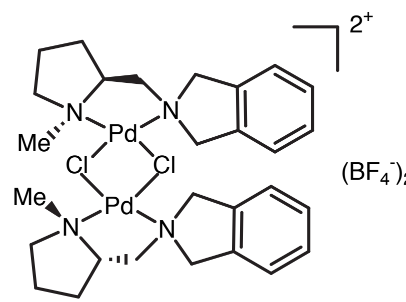
*Earlier Catalyst Systems*



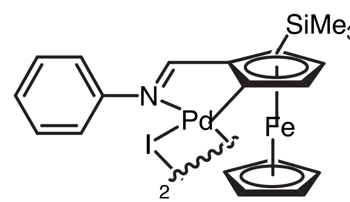

62% yield
10% ee
(Hayashi)




41% yield
76% ee
(Hayashi)




69% yield
55% ee
(Overman)



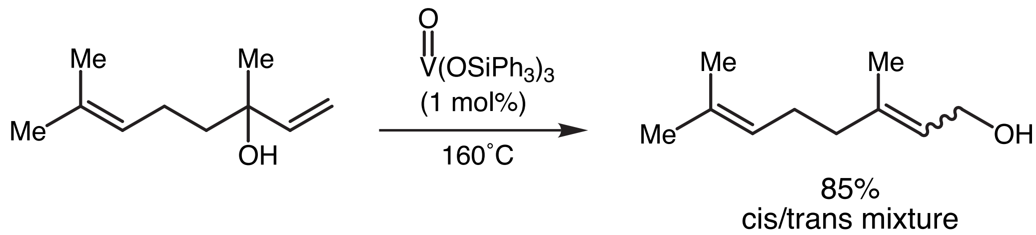

91% yield
49% ee
(Overman)

Yields/ee for R = *n*-Pr (E isomer)

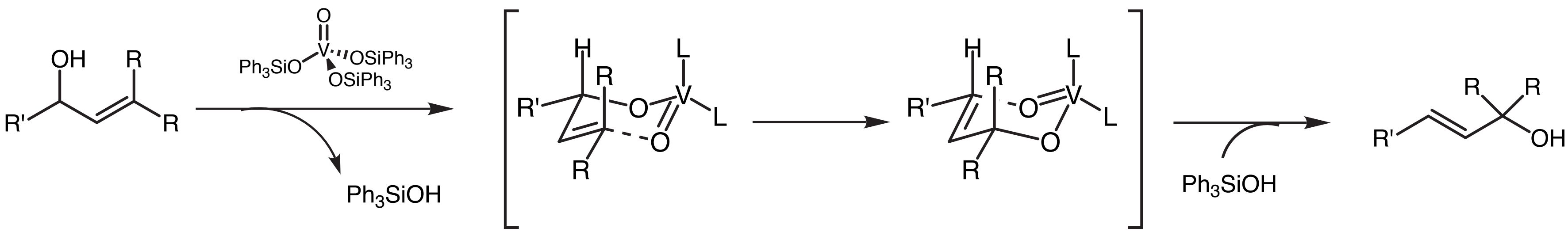
Overman, L. *J. Orgmet. Chem.*, **1999**, 290.

# *Allylic Rearrangements with Oxo Metals*

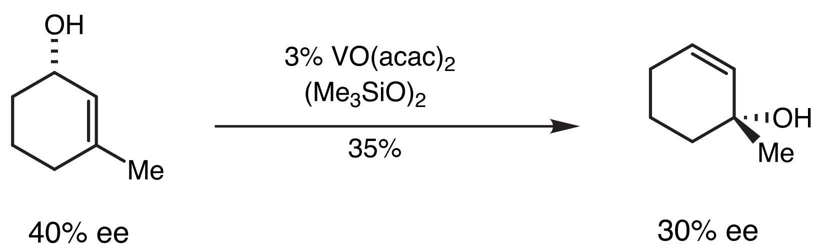
*Earliest Example*




*Charbardes' Proposal*

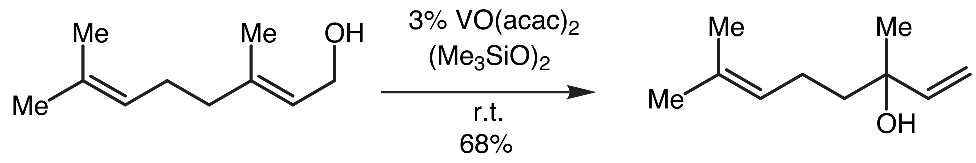


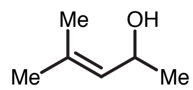
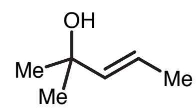
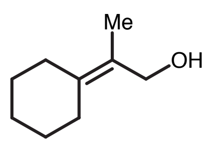
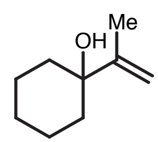
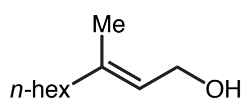
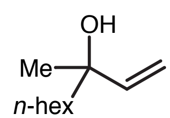
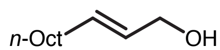
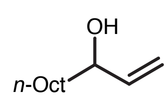
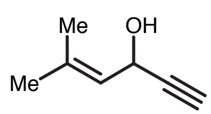
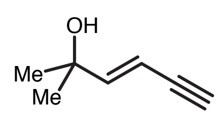

*Chirality Transfer*




Chabardes, P. *Tet.*, **1977**, 1775.
Takai, K. *Bull. Chem. Soc. Jpn.*, **1985**, 844.

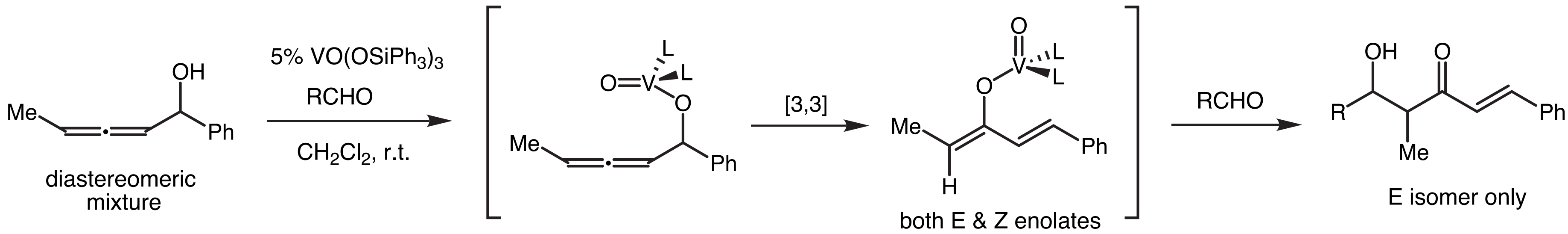
# *Vanadate Catalysts (Takai)*

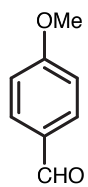
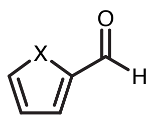
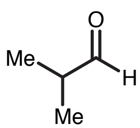
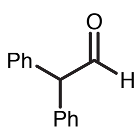
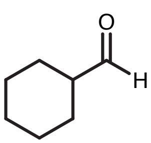


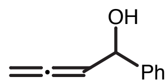
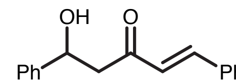
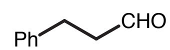
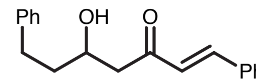
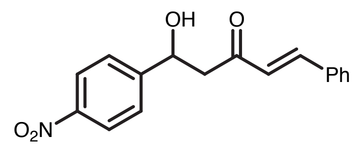
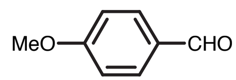
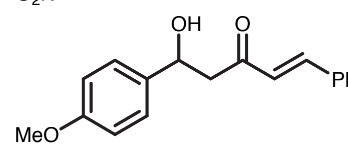
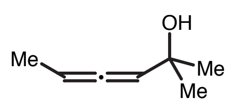
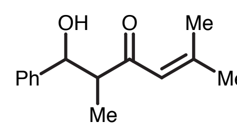
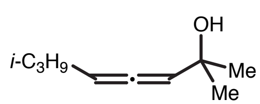
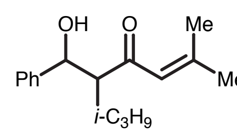

| *Substrate* | *Product* | *Starting Material (%)* | *Product (%)* |
|---|---|---|---|
|  |  | 0 | 97<br>E only |
|  |  | 0 | 85 |
|  |  | 20 | 53 |
|  |  | 41 | 35 |
|  |  | 0 | 70<br>E only |

Takai, K. *Bull. Chem. Soc. Jpn.*, **1985**, 844.

# *Allenic Alcohol Isomerizations (Trost)*



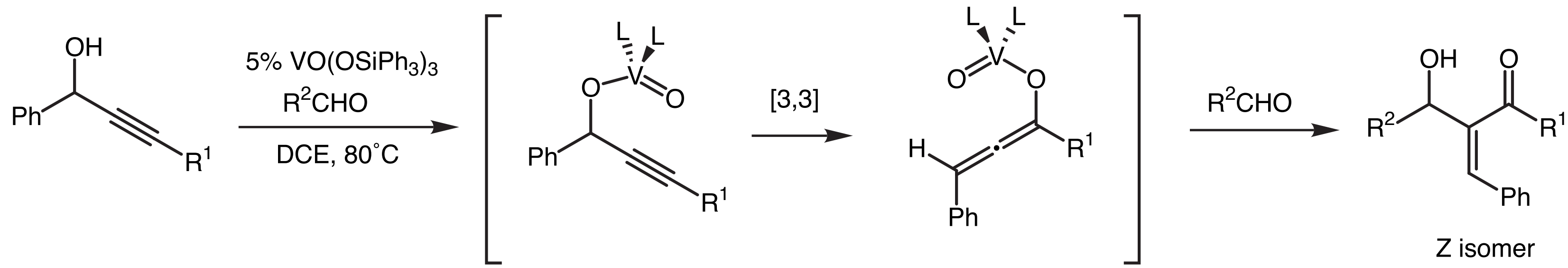

| *Aldehyde* | | *Yield(%)* | *Syn:Anti* |
|---|---|---|---|
| PhCHO | | 86 | 80:20 |
|  | | 83 | 42:58 |
|  | X=O | 88 | 67:33 |
| | X=S | 86 | 68:32 |
| | X=NBoc | 88 | 70:30 |
|  | | 79 | 78:22 |
|  | | 71 | 80:20 |
|  | | 61 | 66:33 |

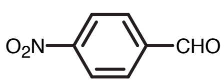
| *Other Allenes* | *Aldehyde* | *Product* | *Yield(%)* |
|---|---|---|---|
|  | PhCHO |  | 85 |
| " |  |  | 70 |
| " |  |  | 83 |
| " |  |  | 64 |
|  | PhCHO |  77:23 (syn:anti) | 86 |
|  | PhCHO |  88:12 (syn:anti) | 57 |

- Diastereomerically pure allenol gave similar syn:anti ratios

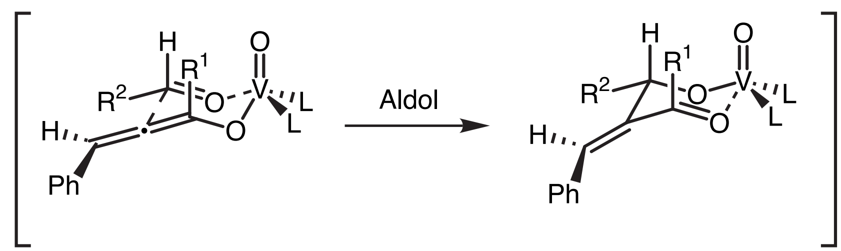
Trost, B.M. *et al. JACS* **2001**, 12736.

# *Propargyl Alcohol Isomerizations (Trost)*




| *Propargyl Alcohol ($R^1$)* | *Aldehyde ($R^2$)* | *Yield (%)* | *Z:E* |
|---|---|---|---|
| *n*-Bu | PhCHO | 94 | 91:9 |
| *t*-Bu | PhCHO | 95 | 98:2 |
| Ph | PhCHO | 73 | 88:12 |
| $CH_2OTBS$ | PhCHO | 42 | only Z |
| *n*-Bu |  | 77 | only Z |
| *n*-Bu |  | 92 | only Z |
| *n*-Bu | *n*-PrCHO | 55 | 89:11 |
| *n*-Bu | chex-CHO | 58 | 96:4 |

*Chair Transition State Model*



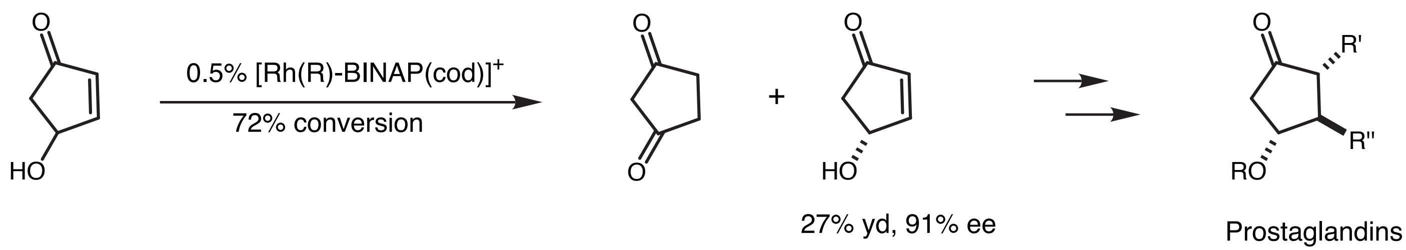

Aldehyde approach from opposite face of Ph explains high selectivity for Z isomer.



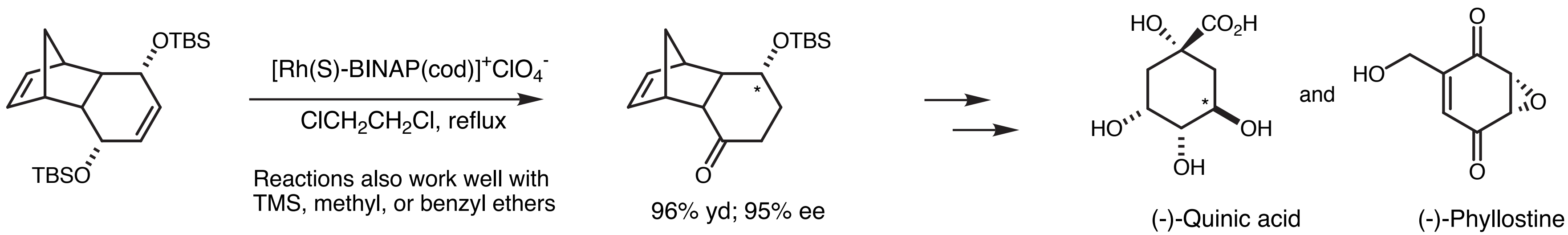
Trost, B.M. *JACS,* **2001**, 1230.

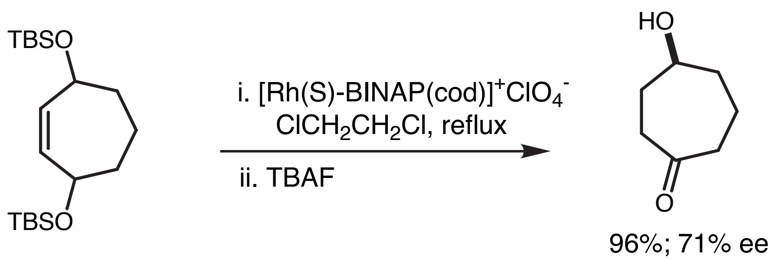
# *Desymmetrizations*

Noyori, R. *TL*, **1987**, 4719.

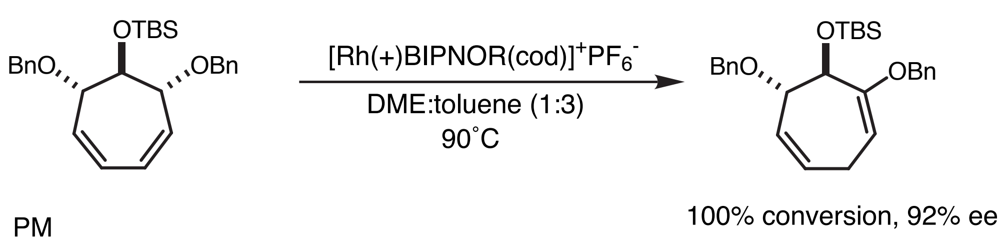


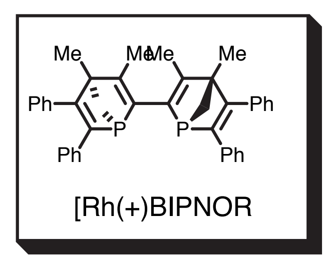

Ogasawara, K., *ACIEE,* **1995**, 2287.



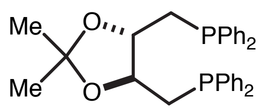




Mathey, F. *Tet*, **2000**, 101.

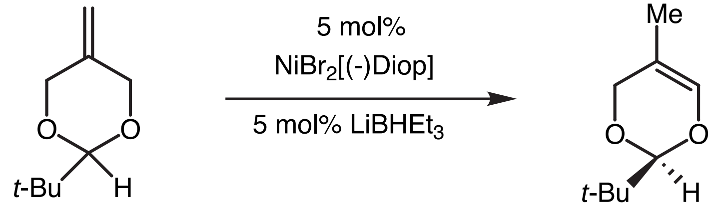


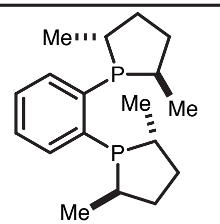
# *Desymmetrization of Cyclic Allylic Acetals (Frauenrath)*



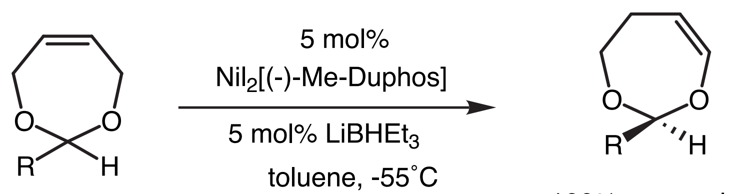

(-)Diop




86%; 92% ee



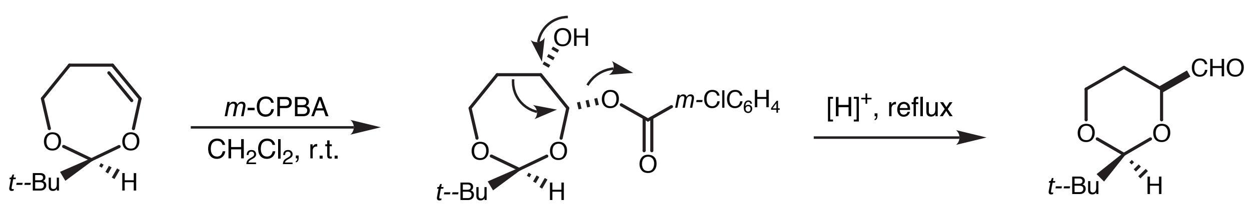

(-)-Me-Duphos




100% conversion

| R | *ee (%)* |
|---|---|
| *t*-Bu | 98 |
| *i*-Pr | 90 |
| *n*-Bu | 90 |

*Synthetic Use:*



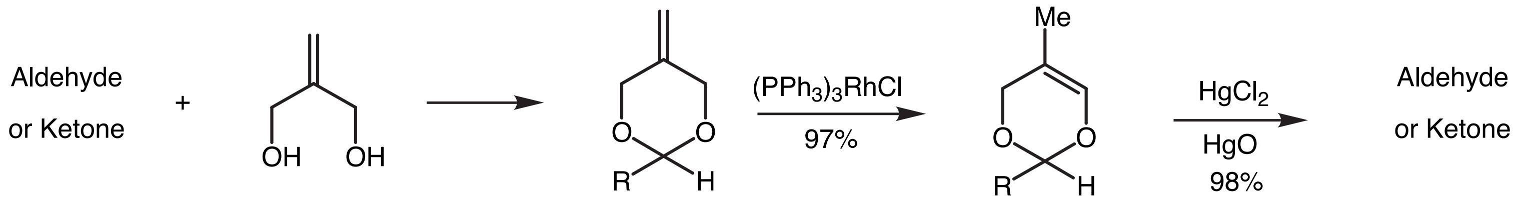

75%, d.r. 95:5

75%, d.r. 83:17

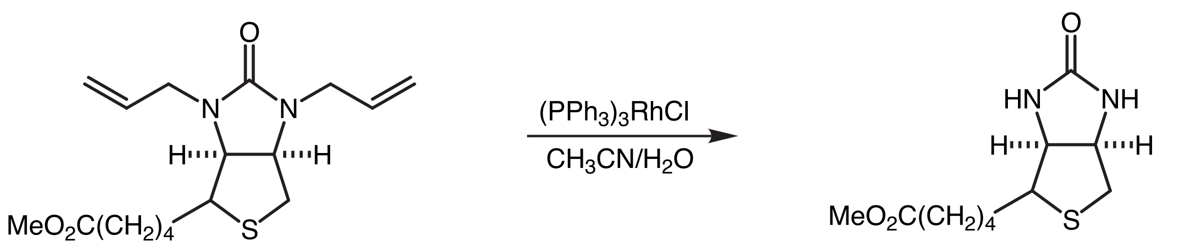
Frauenrath, H. *et al. Tet. Asym.*, **1998**, 1103
Frauenrath, H. *et al. ACIEE*, **2001**, 177

# *Allyl Protecting Groups*

*Protection of Aldehydes/Ketones* (*TL*, **1975**, 3775)




*Biotin Synthesis* (*J.C.S. P.T.II*, **1973**, 1954)




*Carbohydrates* (*J.C.S. P.T.I.*, **1980**, 738.)