

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 stereinduction
- 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.

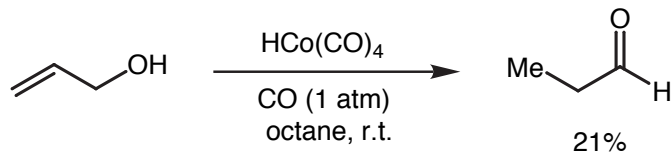
Allylic Rearrangement

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

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

Allylic Alcohols: Early Discoveries

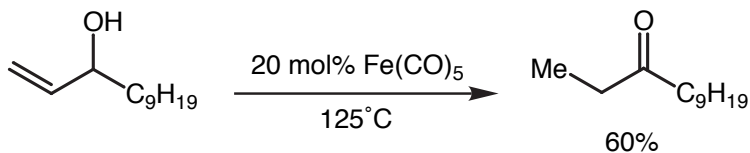
Metal Hydrides (Goetz, R., Orchin, M. *JACS*, **1963**, 1549.)



Observed during hydroformylation

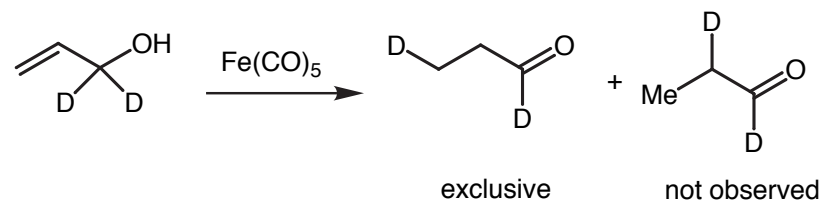
Substrate	Yield (%)
	3.7
	3

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

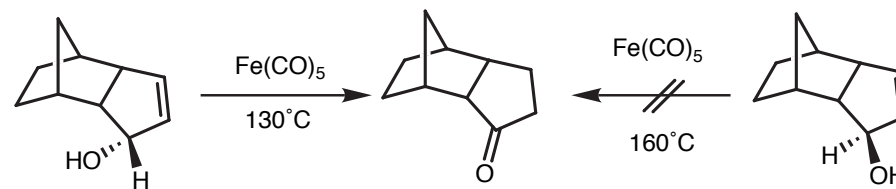


Substrate	Yield
	75
	80
	20

Deuterium Labelling Studies

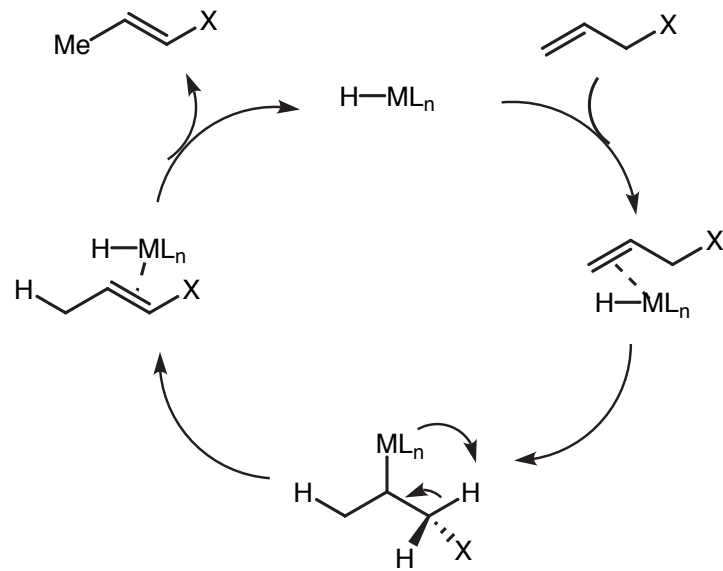


Supra-facial 1,3 H Migration

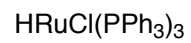
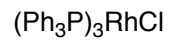
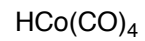


General Mechanism

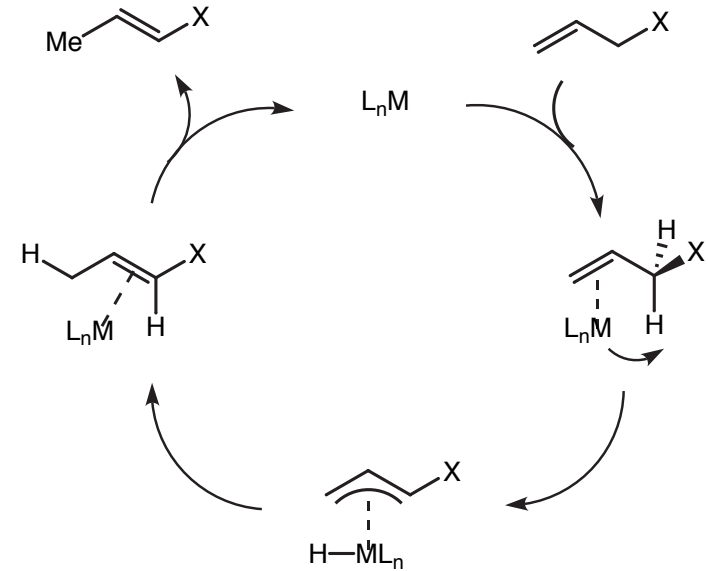
Hydride Addition-Elimination



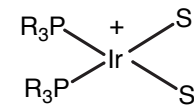
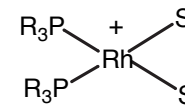
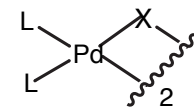
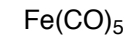
Common Catalysts



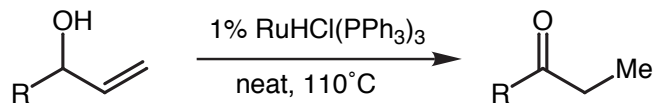
π -Allyl Metal & 1,3 H Shift

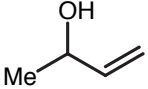
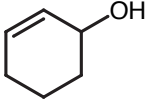
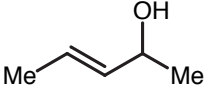
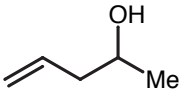
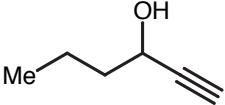



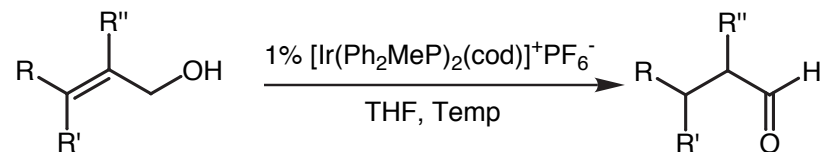
Common Catalysts


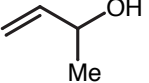
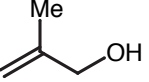
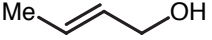
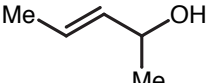
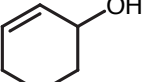
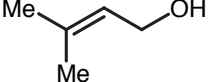
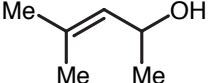


Early Ru and Ir catalysts



Alcohol	Yield (%)
	91
	81
	90
	79
	0
	0



Alcohol	Temp (°C)	Conversion (%)
	20	100
	20	100
	20	100
	65	99
	65	98
	65	9
	65	12
	65	0

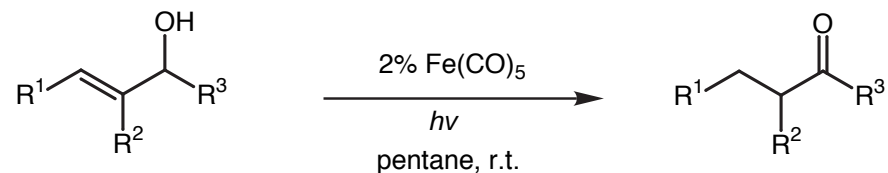
Limitations:

- 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.

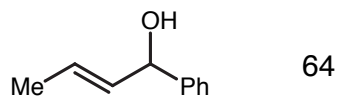
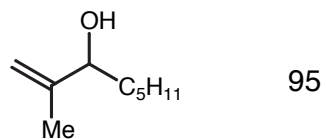
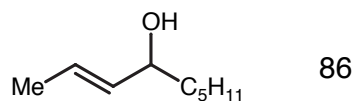
Baudry, D., Ephritikhine, M., Felkin, H. *Nouv. J. Chim.*, **1978**, 355.

Fe(CO)₅ Revisited: Light Activation



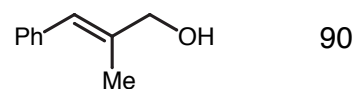
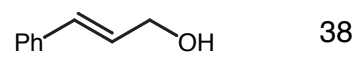
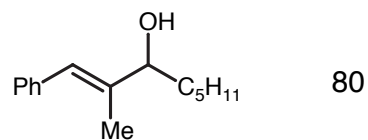
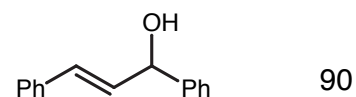
Hindered Aliphatic

<i>Substrate</i>	<i>Yield (%)</i>
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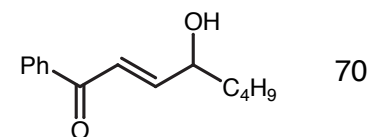
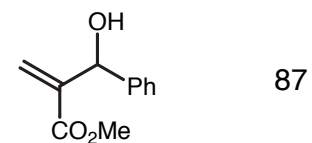
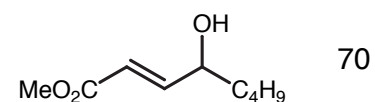
Cinnamyl derivatives

<i>Substrate</i>	<i>Yield (%)</i>
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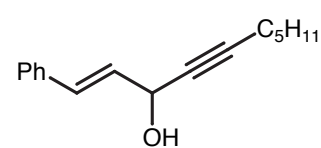
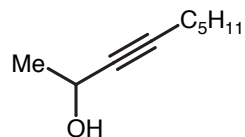
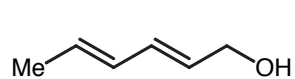


Carbonyls

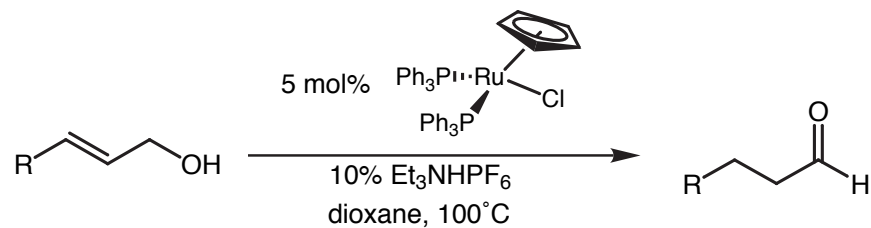
<i>Substrate</i>	<i>Yield (%)</i>
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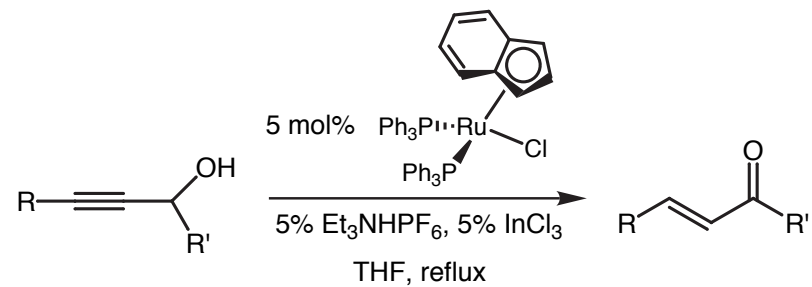
Poor Substrates (no reaction)



A Milder Catalyst: Ruthenium



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

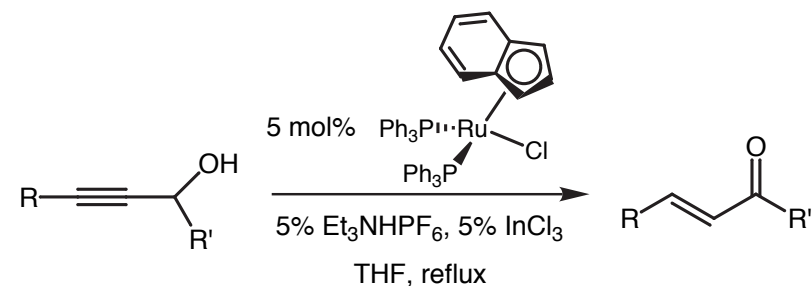
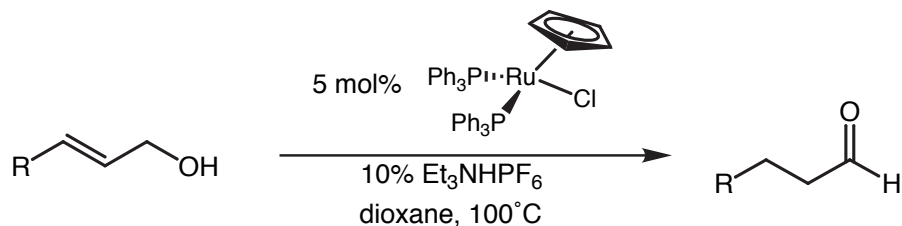


Substrates	Yield (%)
	88
	80
	86
	87
	83
	86
R = $\text{C}_{10}\text{H}_{21}$	
	83
R = C_4H_9	

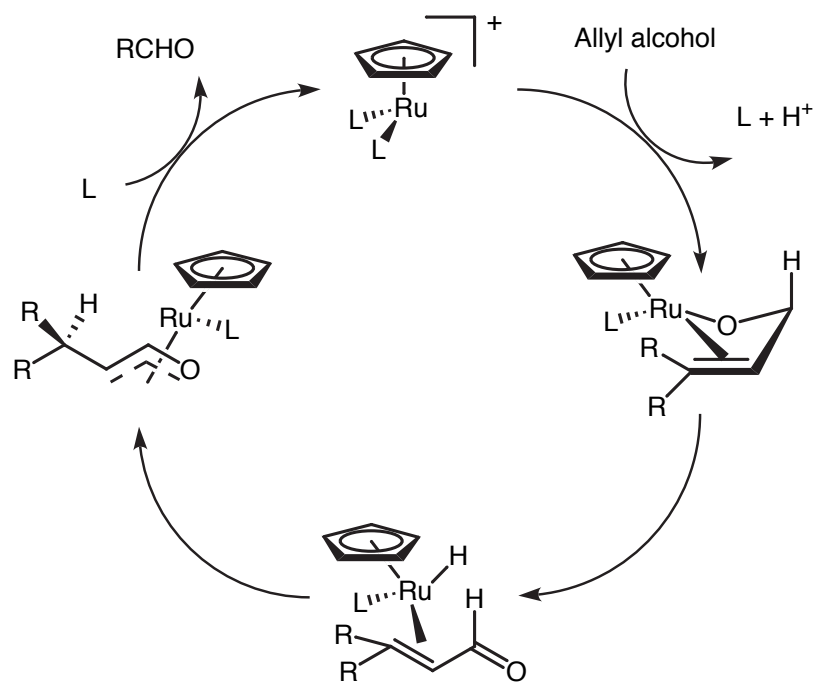
Only free allylic & propargylic alcohols isomerize!

Trost, B.M. *JACS*, **1993**, 207 & **1995**, 9586

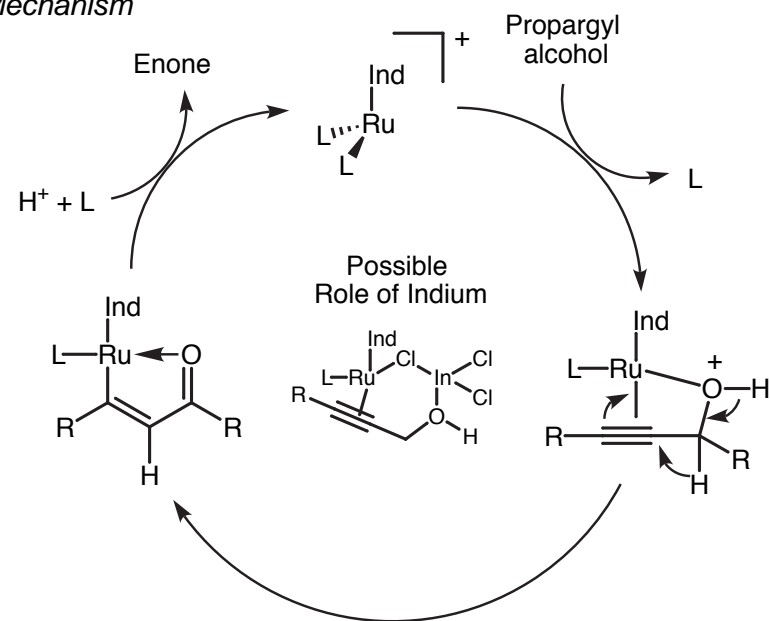
Ru Catalyzed Isomerization: Proposed Mechanism



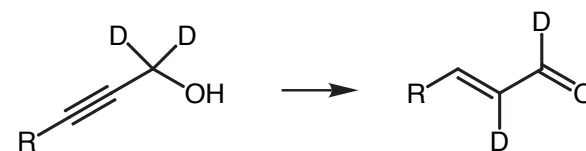
Mechanism



Mechanism



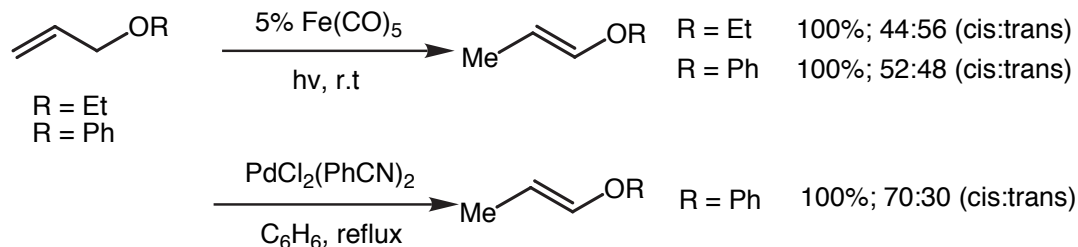
Evidence



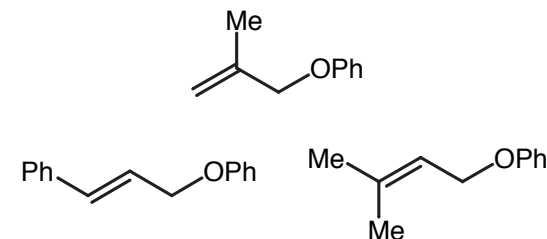
- Beta elimination requires opening of a coordination site (olefin, L, or Cp)
- Trost states that loss of olefin, oxygen, or PPh_3 is unlikely - hence, Cp slippage is required.

Allylic Ethers: E vs Z isomers

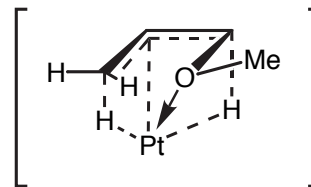
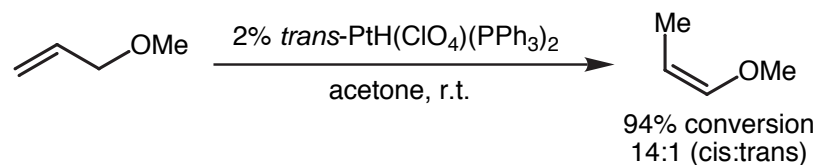
Early Examples



Poor substrates (no reaction)

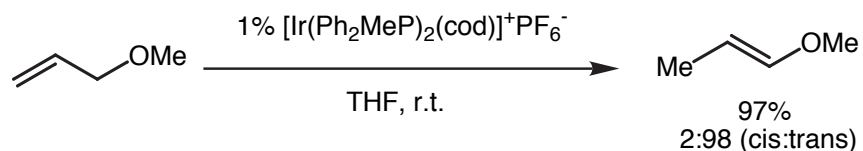


Stereospecific Cis Isomers

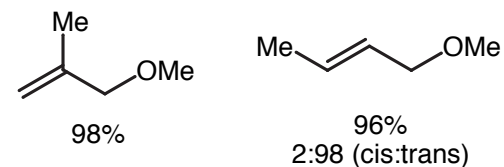


High cis selectivity due to possible platinum oxygen chelate

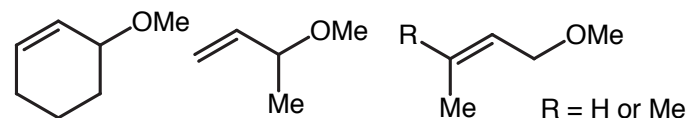
Stereospecific Trans Isomers



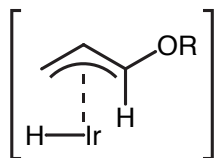
Good Substrates



Poor substrates (no reaction)



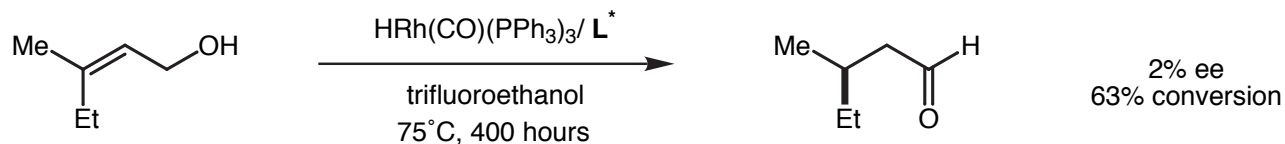
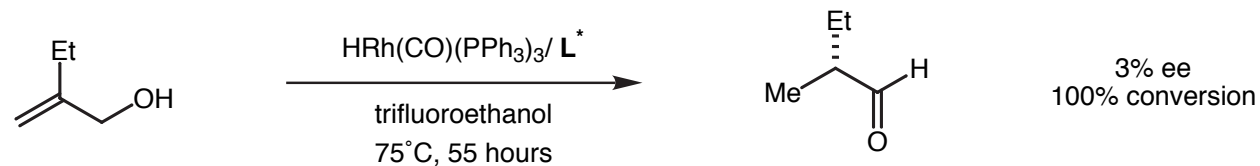
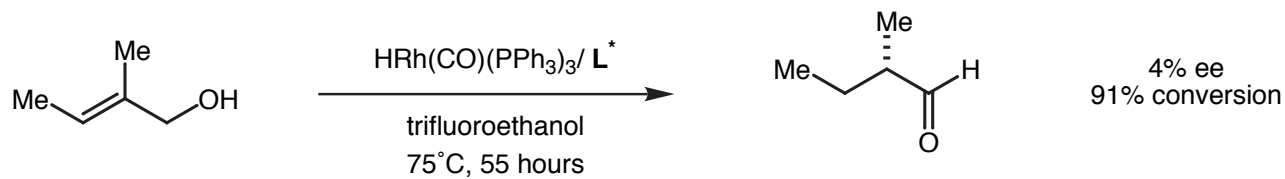
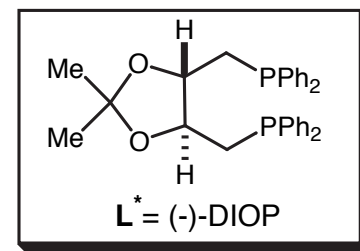
Model for High Trans Selectivity



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

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

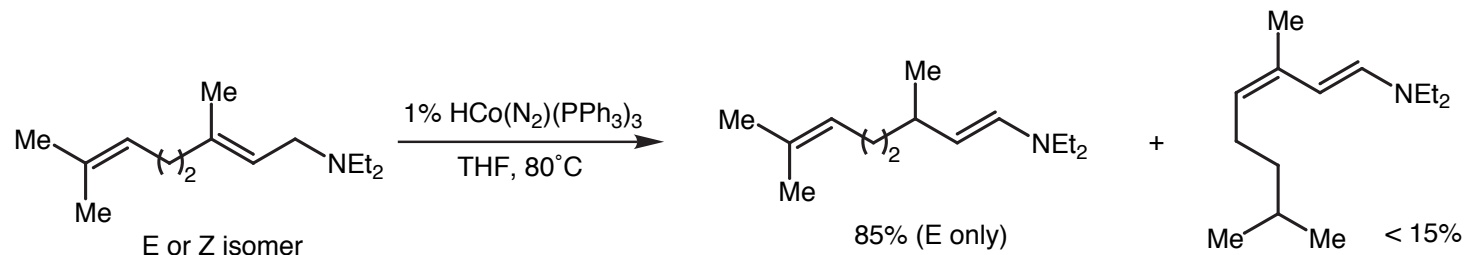
"Asymmetric" Isomerization: Earliest Report



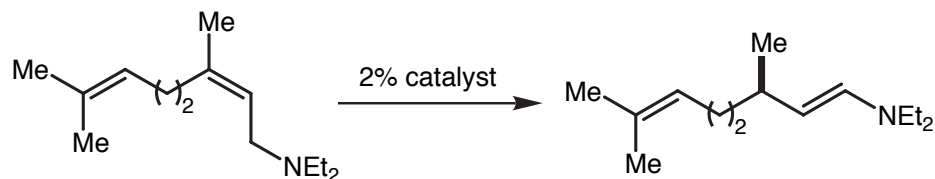
Enantiomeric excess determined by optical rotation.

Isomerization of Allyl Amines: Early Studies (Otsuka)

Early Discoveries

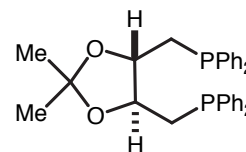
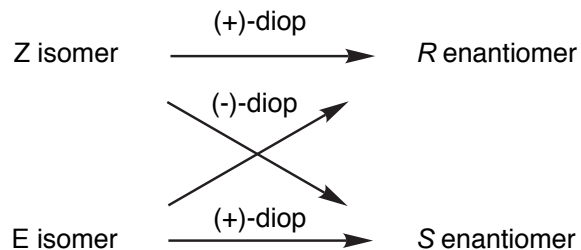


Asymmetric Version

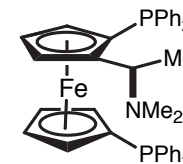


Catalyst mixture	Yield (%)	ee (%)
Co(acac) ₂ , (-)-Ph ₂ P-menthyl, DIBAL-H	16	7
Co(acac) ₂ , (+)-BINAP, DIBAL-H	15	20
Co(acac) ₂ , (+)-DIOP, DIBAL-H	39	32
Co(acac) ₂ , (S,R)-BPPFA, DIBAL-H	10	10

Correlation



DIOP



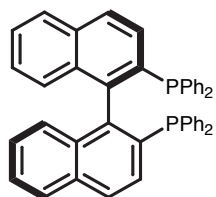
BPPFA

Allyl alcohols failed to isomerize.

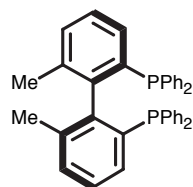
Development of an Asymmetric Catalyst

Metal choice: Rhodium (more stable, tetracoordinated complex)

Good Ligands

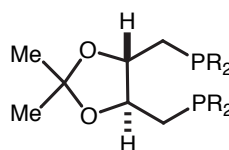


BINAP

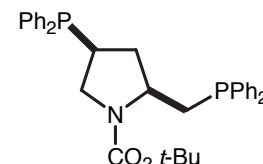


BIPHEMP

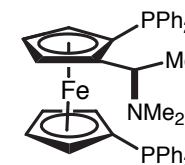
Poor Ligands



DIOP
(low ee%)
due to flexible conformation

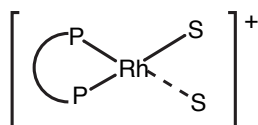


BPPM
(low ee%)



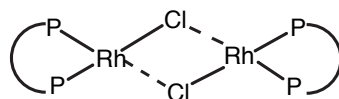
BPPFA
(no rxn)

Metal complex



cationic

vs.

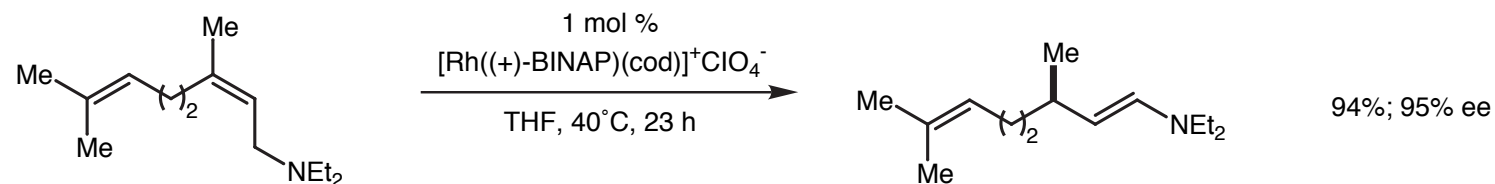
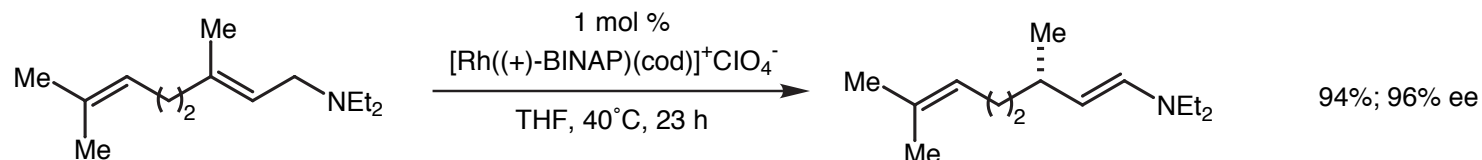


neutral

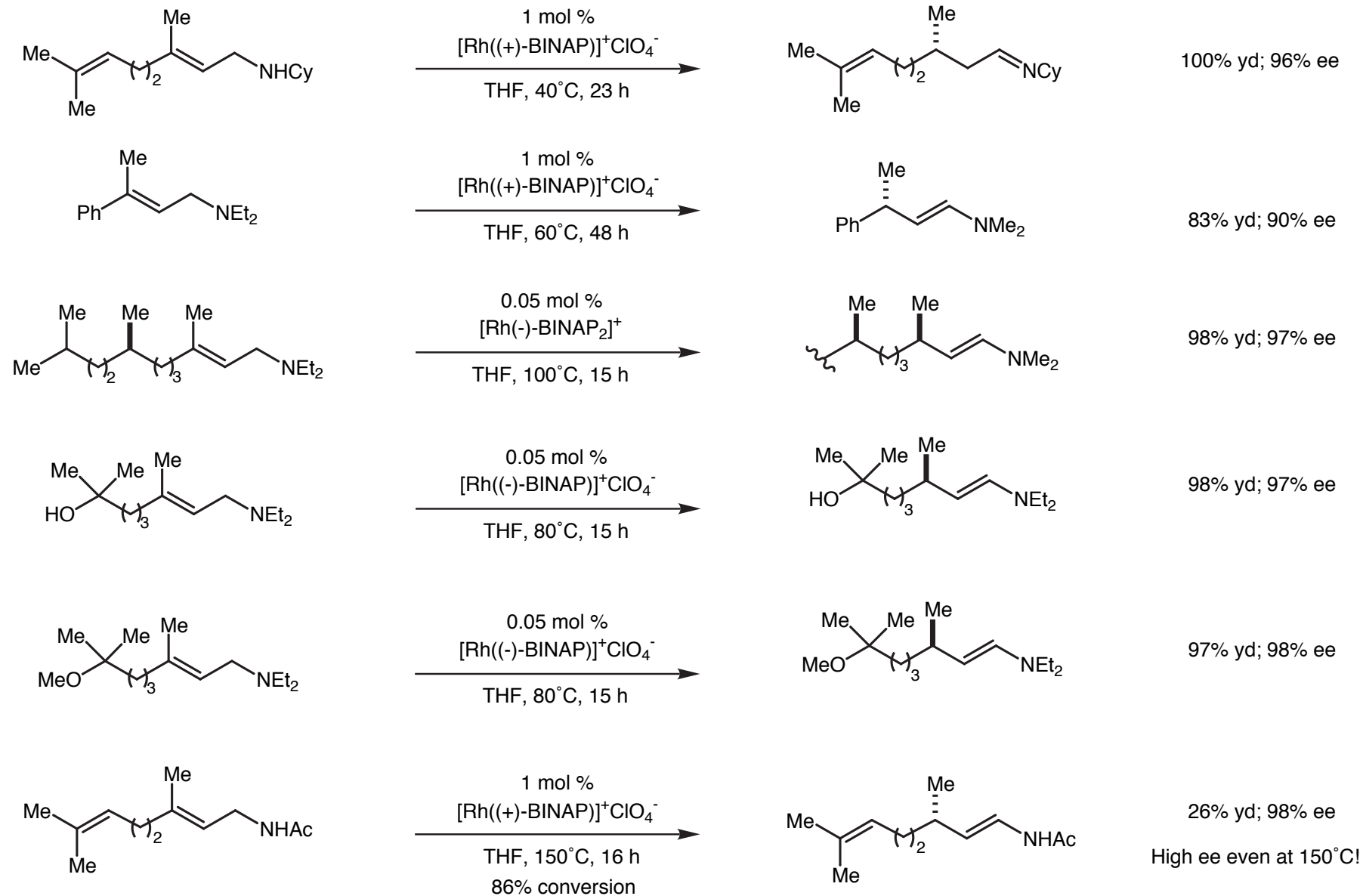
Additives:

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

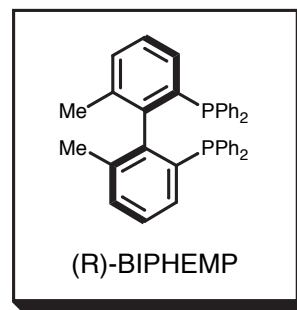
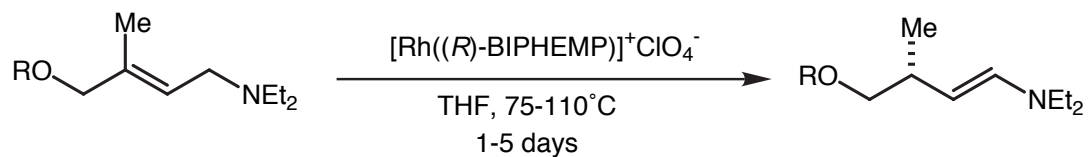
Most Efficient Catalyst System



Substrate Scope (Otsuka, Tani)

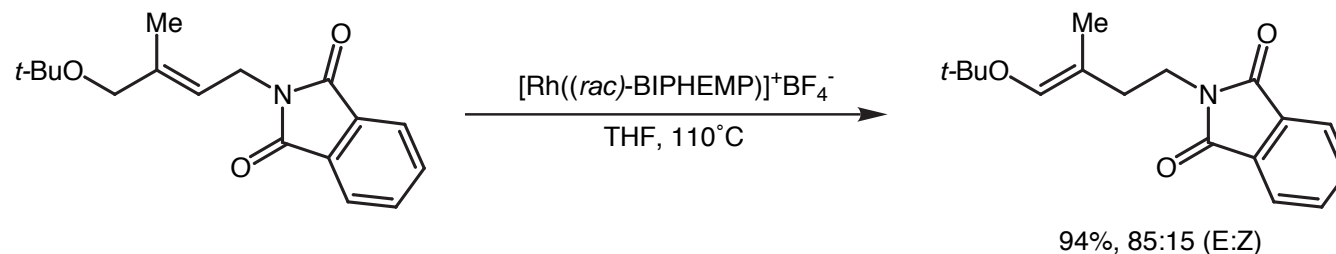


Selective Isomerization Towards Nitrogen



R	Yield (%)	ee (%)	R	Yield (%)	ee (%)
	73	99		19	96
	60	94		30	70
	50	96		34	90

Exception



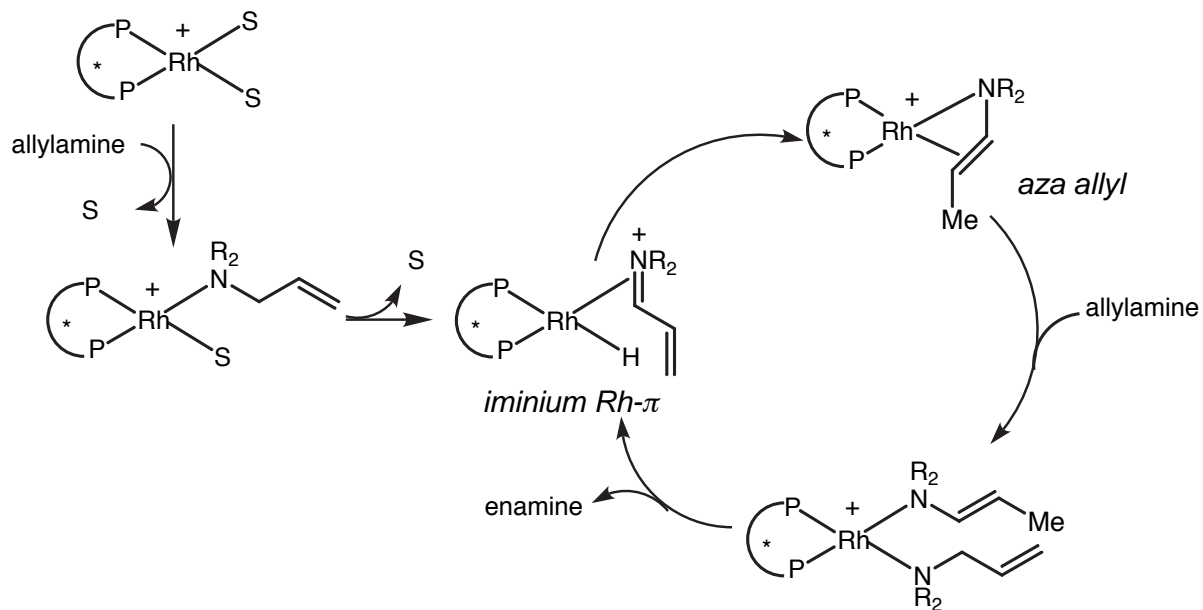
Unreactive Substrates



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

Mechanism & Stereoinduction

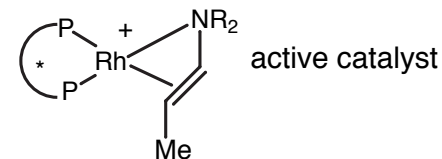
Nitrogen-Triggered Mechanism



Evidence:

- Et₃N exchange with solvent in Rh complex observed by ³¹P NMR

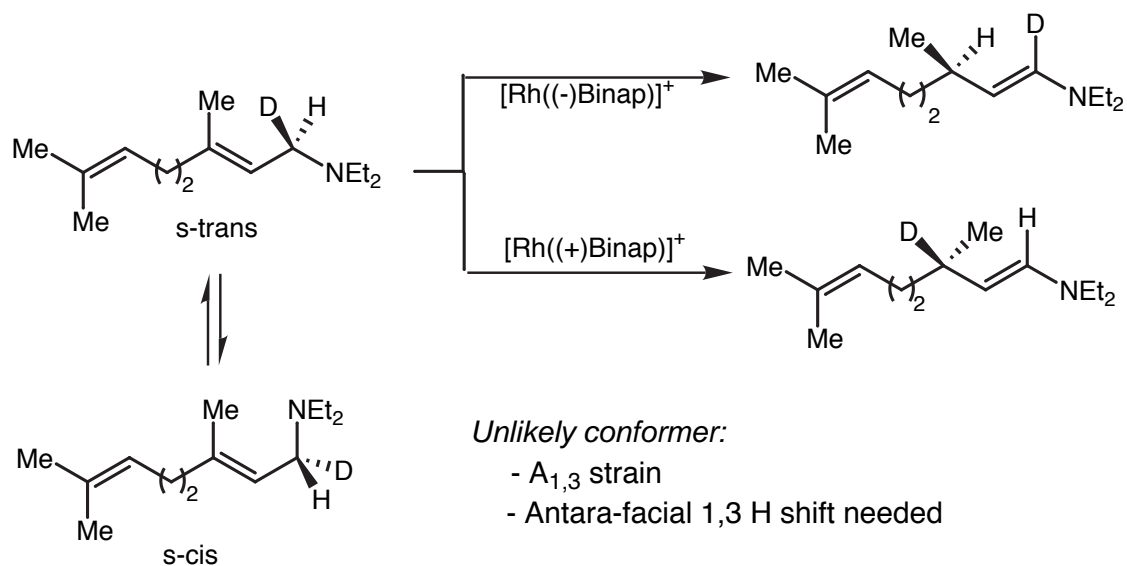
- Isolation of Rh-enamine complex



- 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



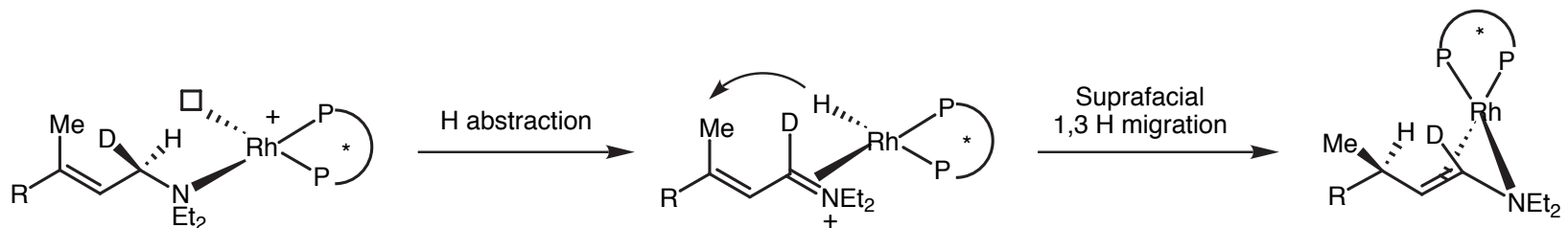
- Supra-facial 1,3 H shift

- No kinetic isotope effect observed

Mechanism & Stereoinduction II

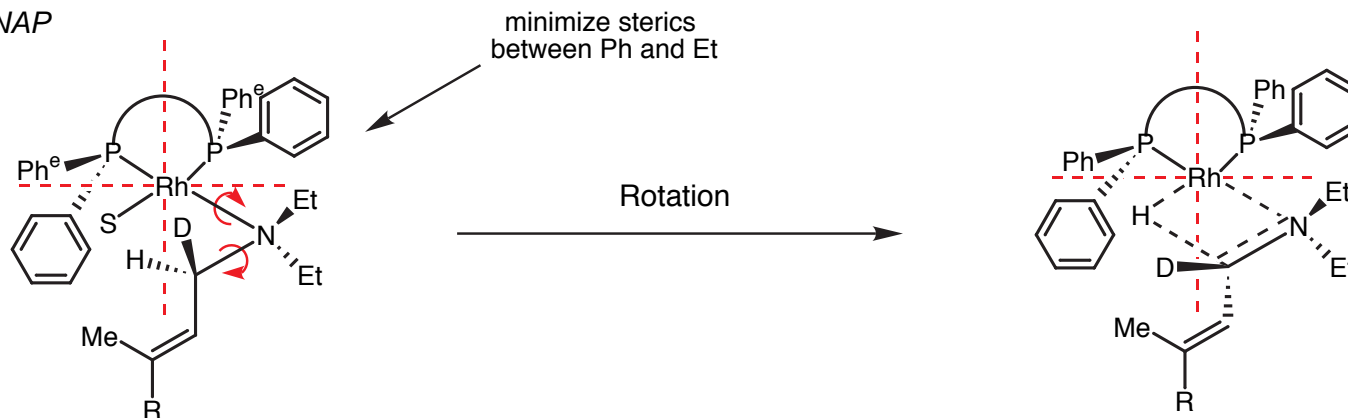
Model based on the following assumptions:

- Chiral Rh complexes recognize enantiotopic C₁ protons
- S-trans conformer is more stable relative to s-cis conformer



Chirality of BINAP determines conformation of allylamine

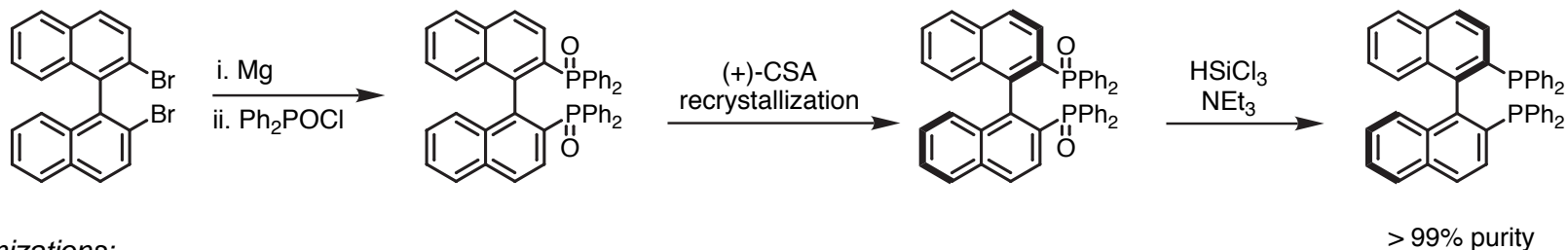
With Rh-(-)-BINAP



Ph^e = edge on Ph group

From Laboratory to Industry

Synthesis of Enantiomerically Pure BINAP (Takasago Perfumery Industry)

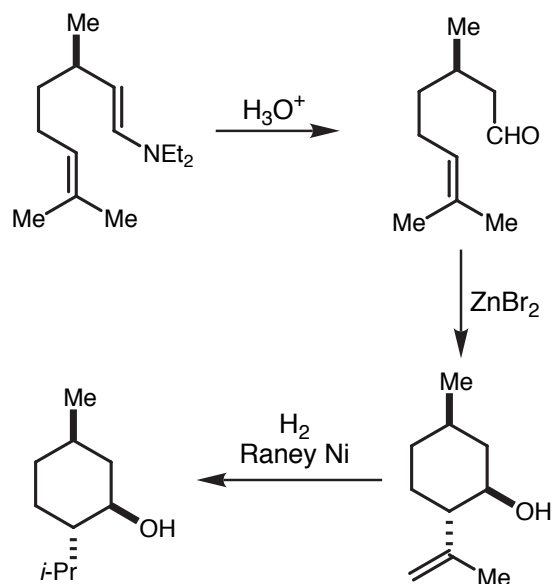


Optimizations:

- 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 $[\text{Rh}(\rho\text{-ToIBINAP})_2]^+$

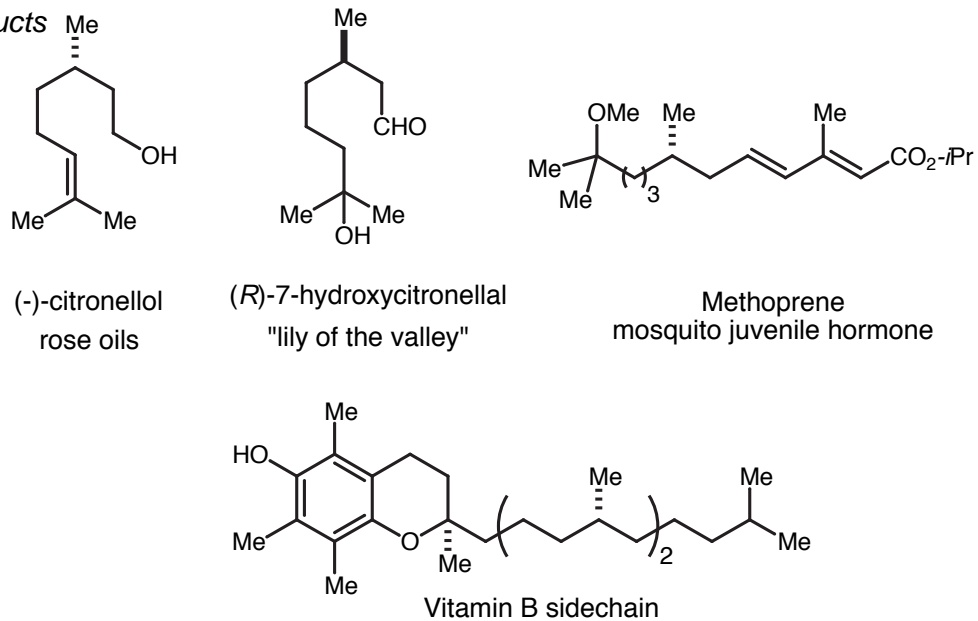
TN: > 8000

Commercial Synthesis of (-) Menthol



> 4500 tons/yr.
14 lab to industry 3/14/02 5:29 PM

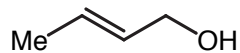
Other Natural Products



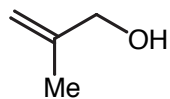
Otsuka, S., Tani, K. *Synthesis*, **1991**, 665.

Allylic Alcohol Isomerization

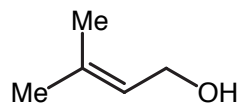
Simple Substrates



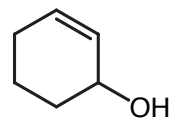
Conversions: 87%



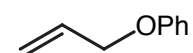
99%



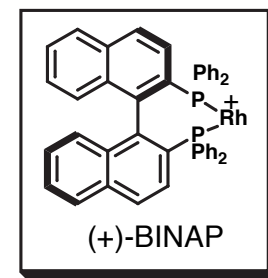
88%



82%

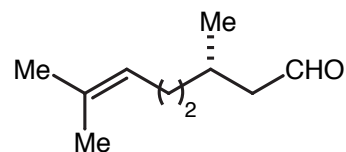
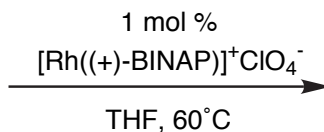
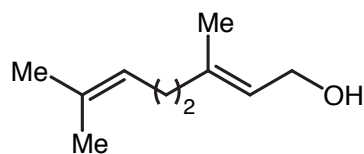


97%
87:13 (E:Z)

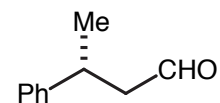
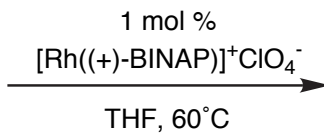
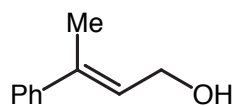


Yields are lower due to Rh(I) promoted decarbonylation of aldehydes.

Asymmetric Catalysis

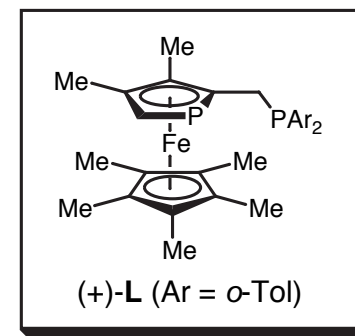
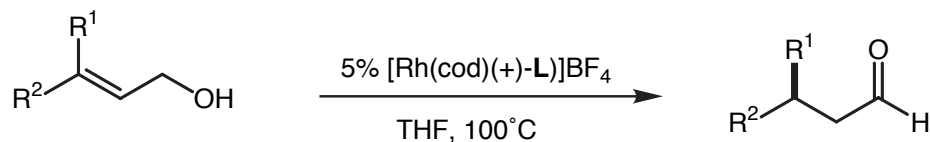


70% yd, 37% ee



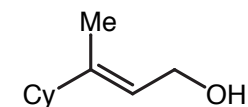
47% yd, 53% ee

Enantioselective Allylic Alcohol Isomerization



<i>E</i> Allylic Alcohols	Yield (%)	ee (%)	<i>Z</i> Allylic Alcohols	Yield (%)	ee (%)
	91	75		80	59
	96	76		78	57
	98	92		82	82
	90	91		90	90
	86	92		83	77
				83	85

Non-Aromatic Substrate



Z isomer: 87% yd, 88% ee

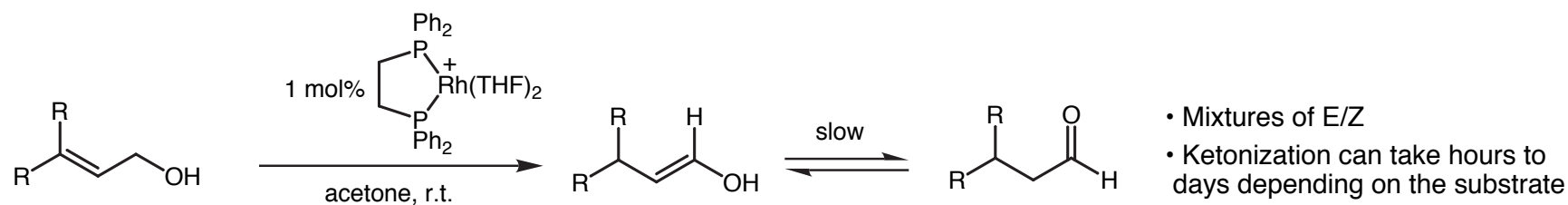
E isomer: 94% yd, 74% ee

- 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.

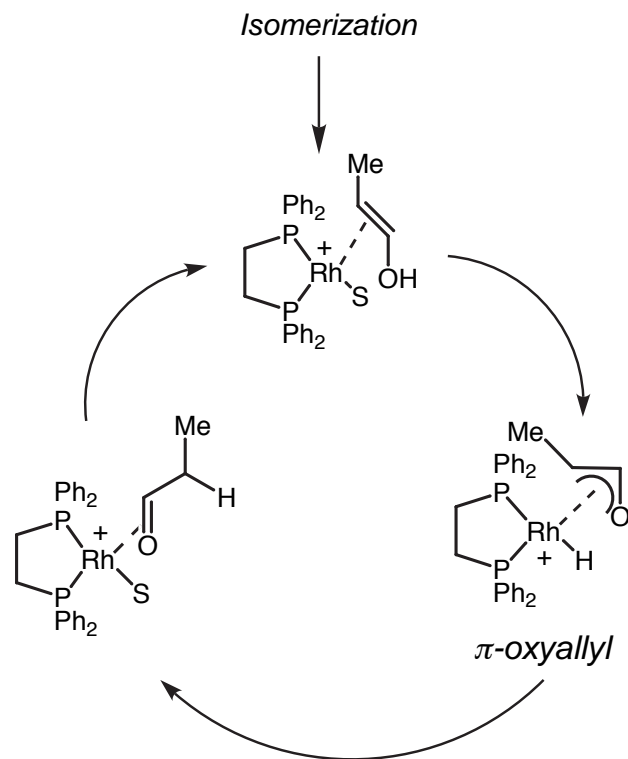
Fu, G.C. *et al*, JACS, **2000**, 9870.

Fu, G.C. *et al*, JOC, **2001**, 8177.

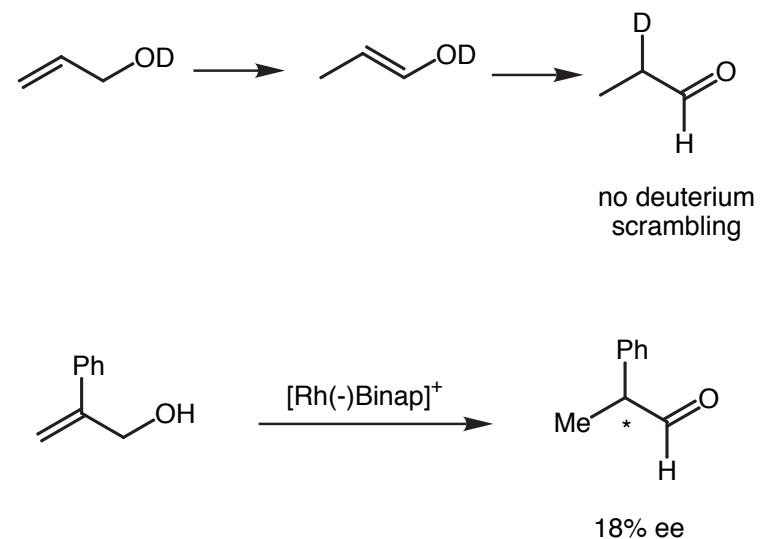
Generation of Simple Enols: Rh catalysts (Bosnich)



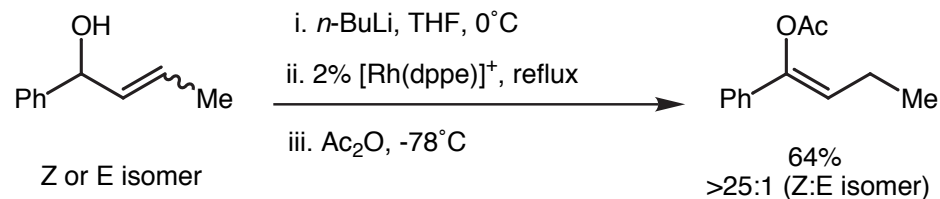
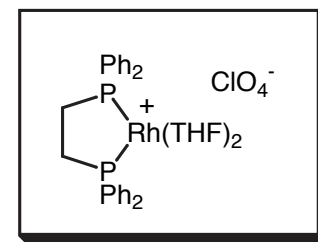
Rh Mediated Ketonization



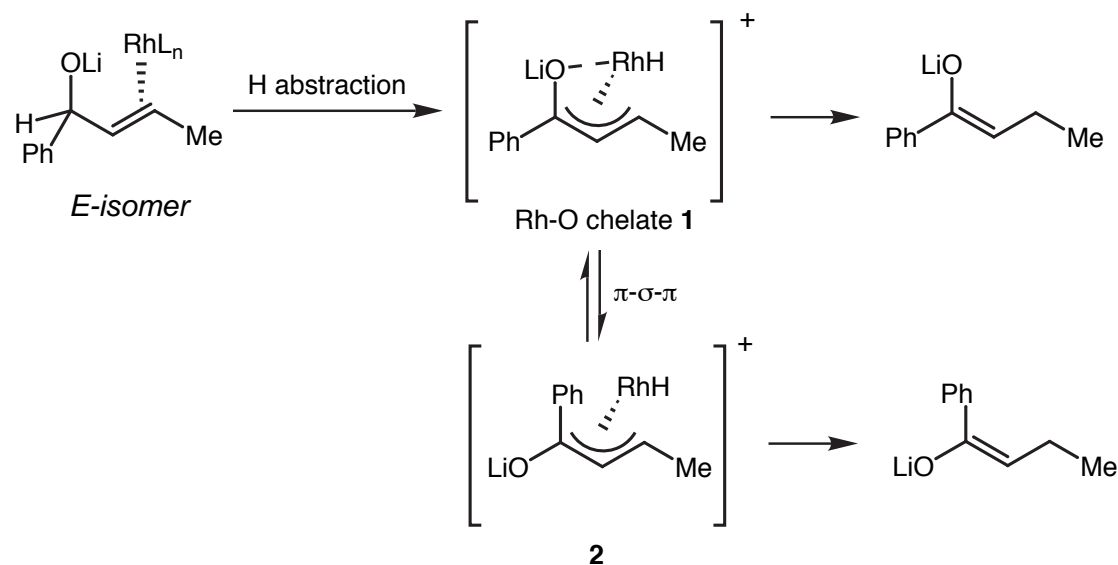
Evidence



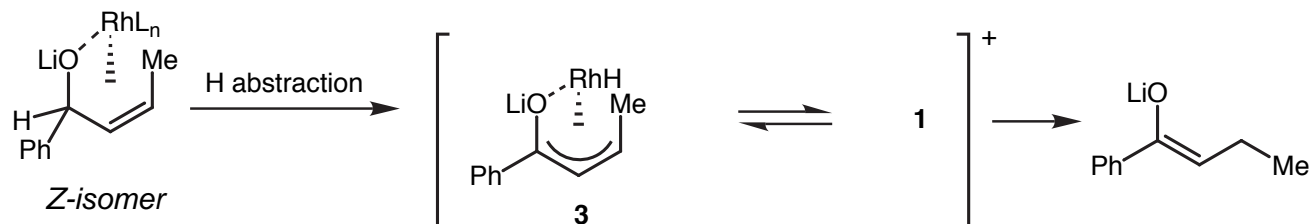
An Approach to Enolate Anions (Motherwell)



Stereocontrol



- 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)
- (Ph₃P)₃RhCl also effective as a catalyst



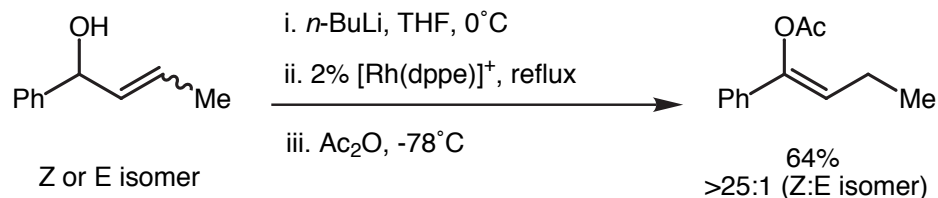
- Slightly longer isomerization times required for Z allylic alcohol - sterics or equilibration?

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

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

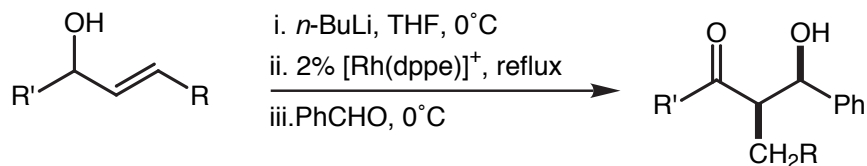
Enolization & Aldol (Motherwell)

Enolate Geometry

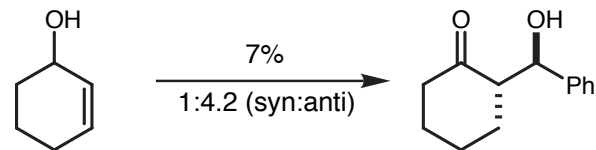
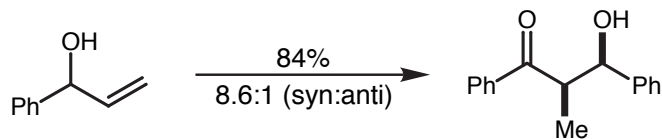
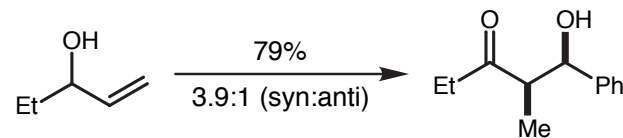
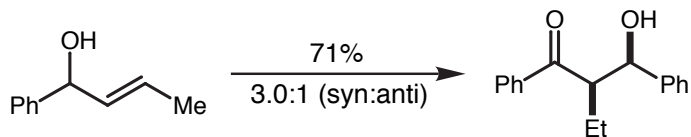


Substrate	Product	Yield (%) & E/Z selectivity
		70 1:3 (Z:E)
		78 1:10 (Z:E)
		41 1:2.8 (Z:E)
	---	no rxn

Isomerization-Aldol Processes

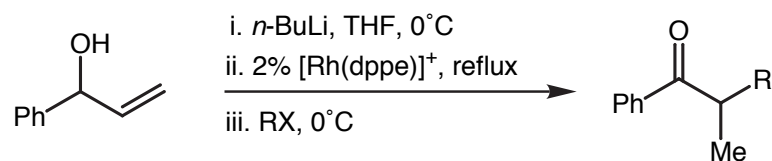


- Benchmark: 98% pure Z Li enolate gives 7.3:1 (syn:anti) product
- Erosion in diastereoselectivity
 - retro aldol vs unselective enolization from competitive ketonization of Rh-enolate complex
- Cyclohexenol precludes cisoid Rh-oxygen intermediate - implications in transition state?



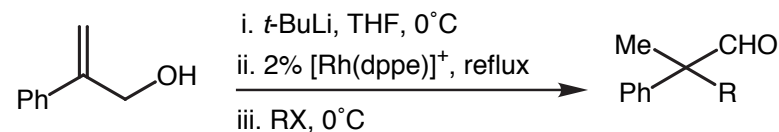
Enolate Alkylations (Motherwell)

Alkylations



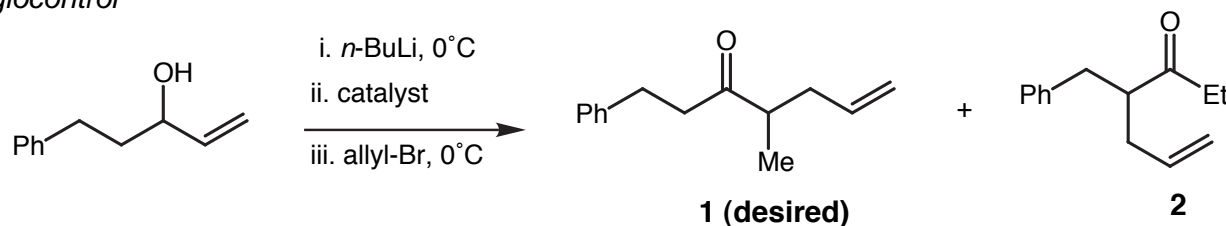
Electrophile RX	yield (%)
allyl bromide	82
benzyl bromide	75
methyl iodide	62
<i>n</i> -Bu iodide	60

Aldehyde enolates

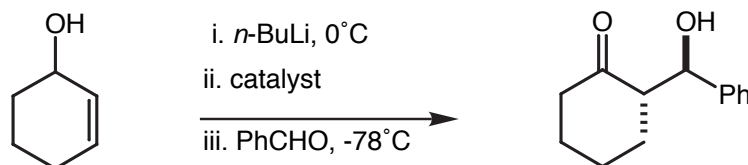


Electrophile RX	yield (%)
allyl bromide	72
benzyl bromide	74

Regiocontrol

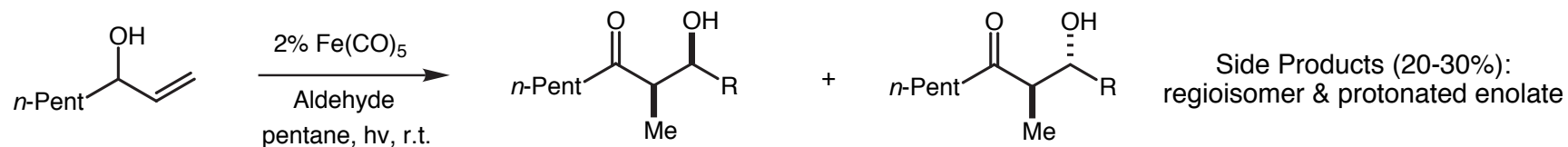


catalyst	yield (%)	1:2
[Rh(dppe)] ⁺	79	1:1.2
(Cy ₃ P) ₂ NiCl ₂ [*]	78	15:1



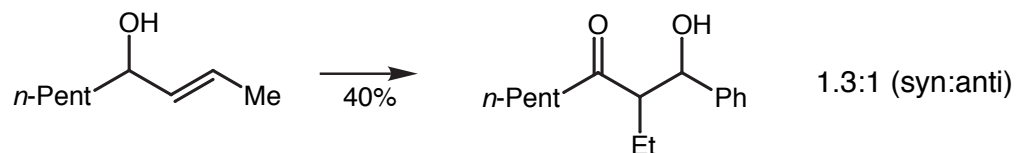
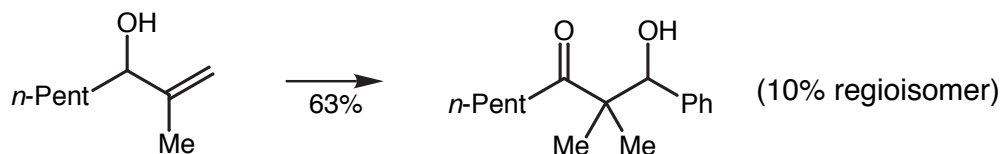
catalyst	yield (%)	syn:anti
[Rh(dppe)] ⁺	7	1:4.2
(Cy ₃ P) ₂ NiCl ₂ [*]	64	1:4.2

Isomerization/Aldol: $\text{Fe}(\text{CO})_5$ (Gree)

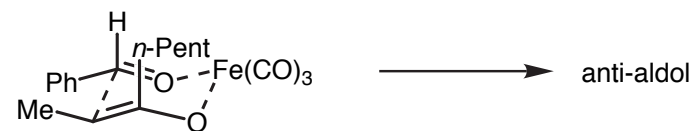
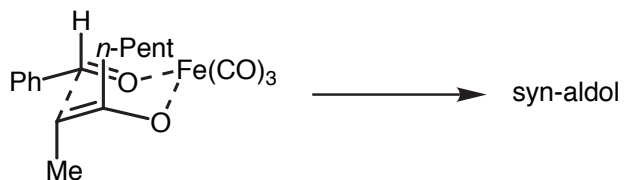


Aldehyde	Yield (%)	Syn:Anti
PhCHO	66	3:1
HCOH (anh.)	62	--
MeCHO	65	3:1
PhCH ₂ CHO	65	2.6:1
(<i>i</i> -Pr) ₂ CCHO	48	2.2:1

Other substrates

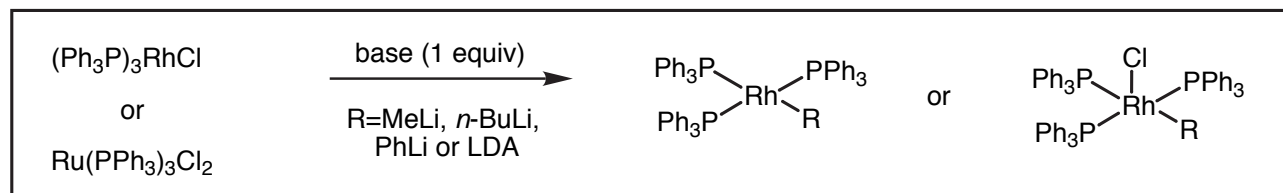


Cyclic Chair Transition State?

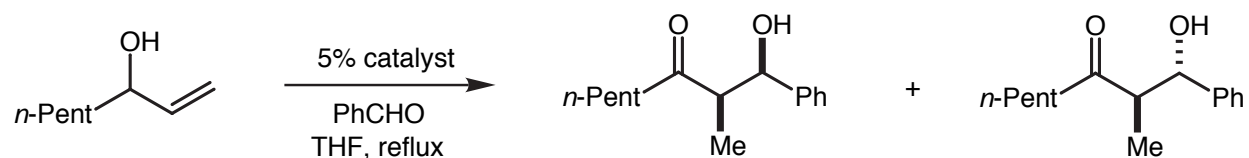


Improvements on Regioselectivity (Gree)

In situ generation of catalyst:



Tandem Enolization/Aldol



$(\text{Ph}_3\text{P})_3\text{RhCl}$

base	yield (%)	syn:anti
MeLi	56	39:61
<i>n</i> -BuLi	54	40:60
PhLi	63	37:63

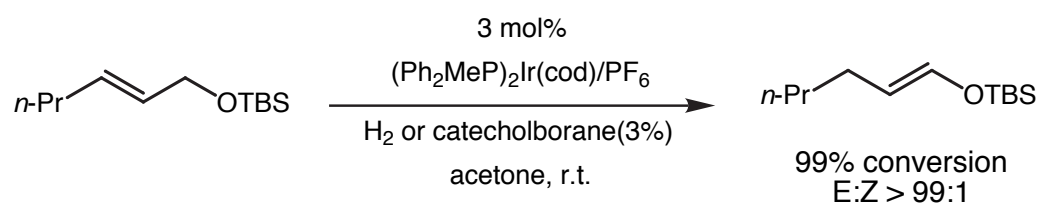
$\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$

base	yield (%)	syn:anti
MeLi	73	51:49
<i>n</i> -BuLi	62	55:45
PhLi	75	55:45

Advantages:

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

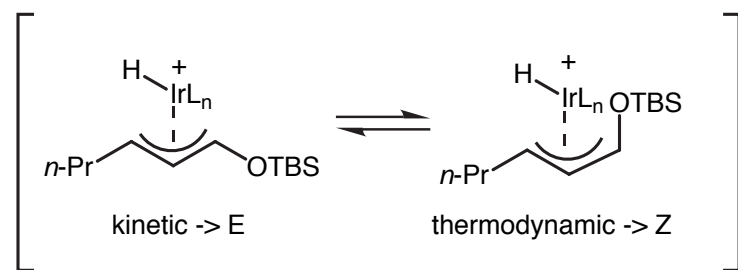
Stereoselective Silyl Enol Ether Formation (Miyaura)



NMR Study: (CH_2Cl_2 :acetone (50:1), 0°C)

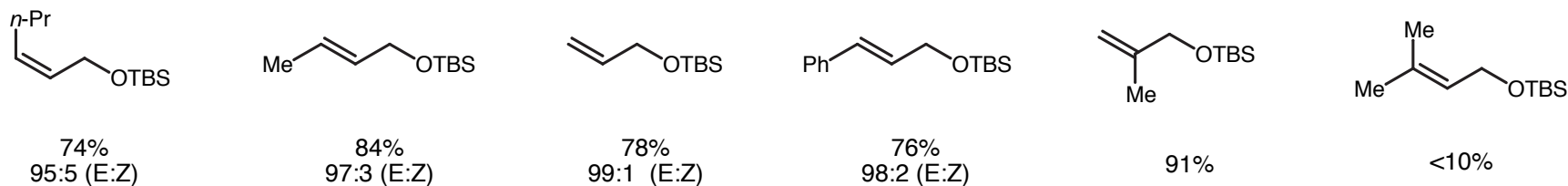
time (min)	conversion (%)	E:Z
5	61	98:2
60	>99	85:15
360	>99	38:63

Authors proposed that E selectivity is kinetically driven:

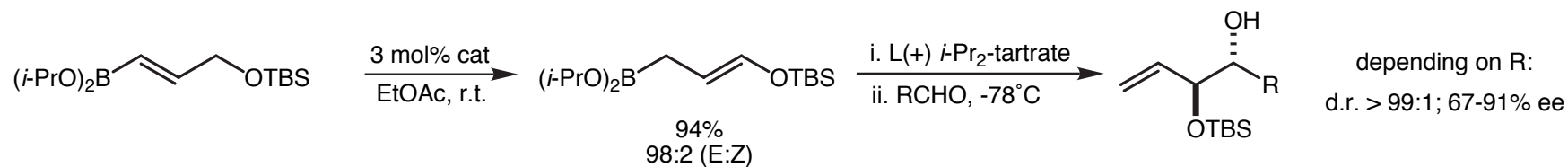


- Acetone - best solvent (fast isomerization, no product equilibration)
- Treating pure E or Z enol silanes with Ir catalyst in CH_2Cl_2 /acetone leads to a thermodynamic ratio.
- Unfortunately, cannot equilibrate all the way to give only Z enol silanes.

Substrate Scope

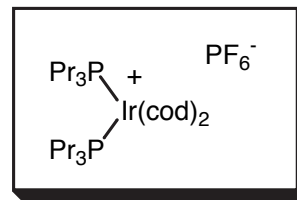


Chiral Allyl Boronates

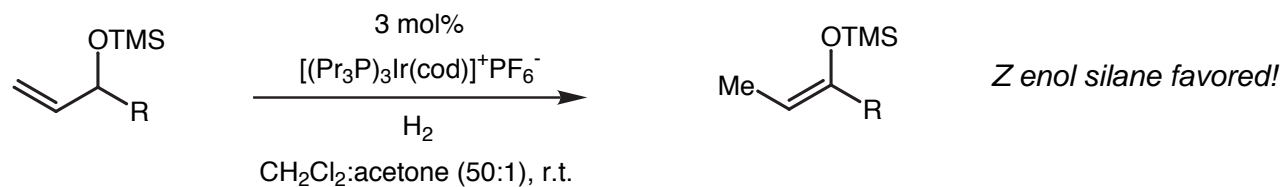


Miyaura, N. JOC, **1999**, 296.
Miyaura, N. *OrgMet.*, **1999**, 413.

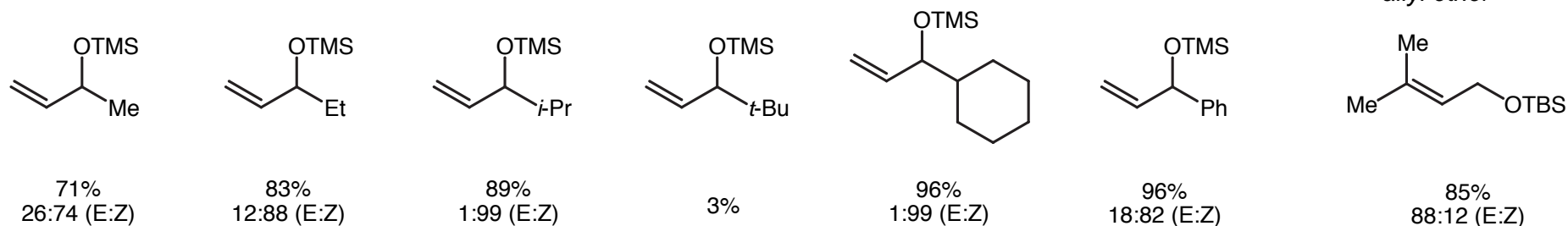
Secondary Enol Silanes (Miyaura)



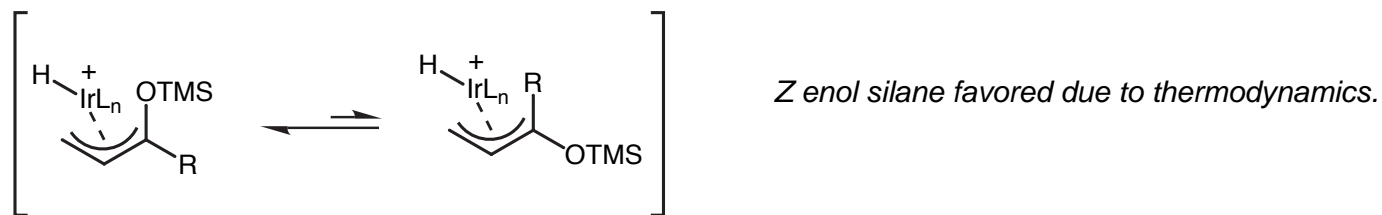
A More Active Catalyst



Substrate Scope

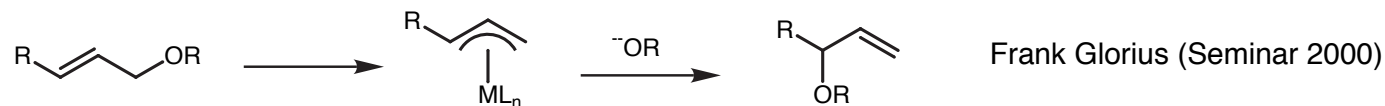


Stereocontrol

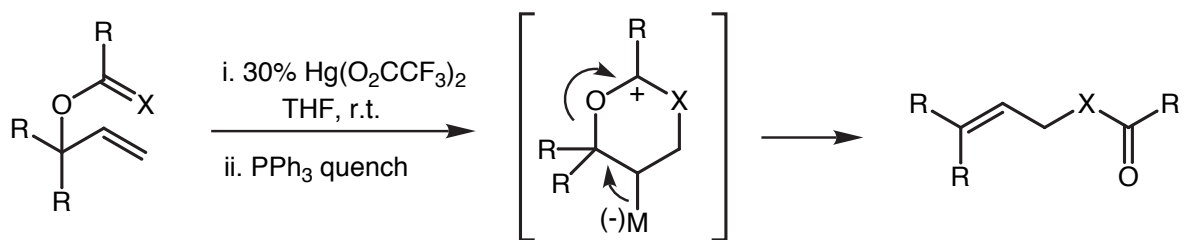


Allylic Rearrangements (Hg salts-Overman)

Rearrangements involving π -allyl complexes (not covered)



Mercuric Salts (Overman)



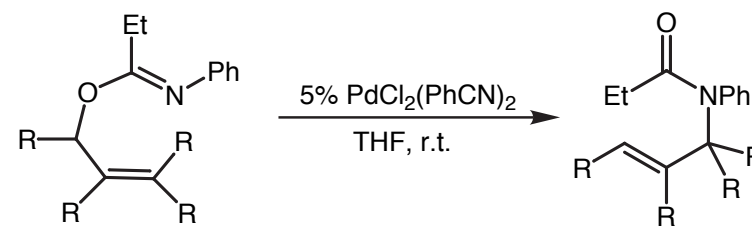
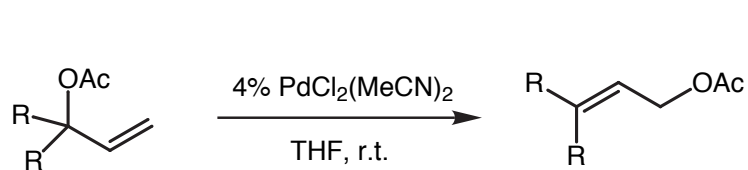
"Contra-thermodynamic" Cases

Substrate	Yield (%)	Terminal: starting material
	95	
	92	
	70	
	98	
	96	
<i>n</i> -Pr-CH=CH-CH2-OC(=O)NMe2	80	95:5
Ph-CH=CH-CH2-OC(=O)NMe2	86	71:29
Alkyl-CH=CH-CH2-OC(=O)NMe2 Me	61	15:85
Excess Hg salts and PPh ₃ are needed to overcome thermodynamic preference.		
<i>n</i> -Pr-CH=CH-CH2-O-C(=S)NMe2	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

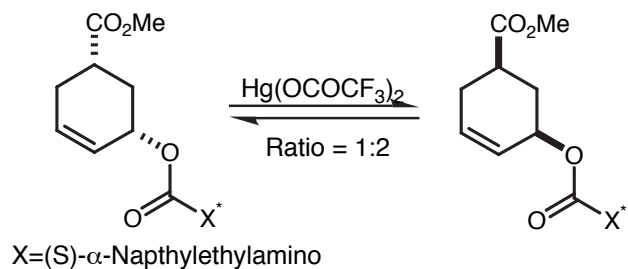


Substrate	Yield (%)
	88 78:22 (E:Z)
	96% 89:11 (E:Z) rxn at 70°C
	93
	96
	74
	18
	no rxn
	no rxn

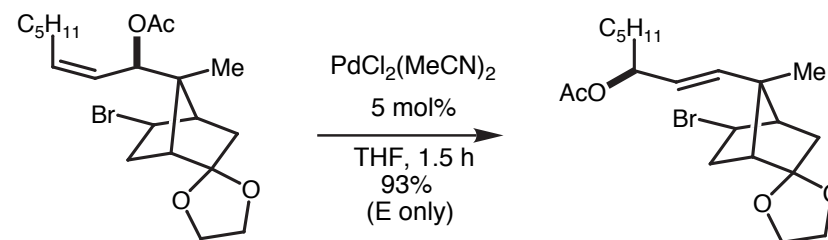
Substrate	Yield (%)
	79
	74
	90
	75
	68

Allylic Rearrangement: Chirality Transfer

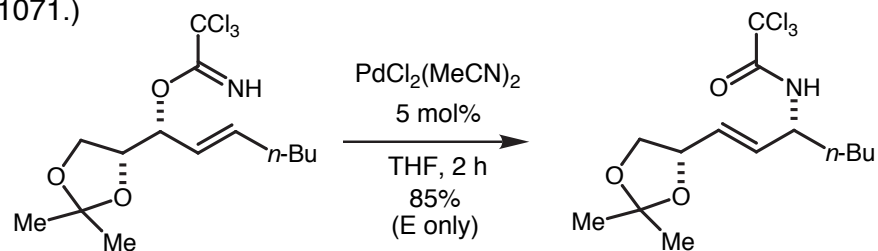
Trost (CC, 1978, 436.)



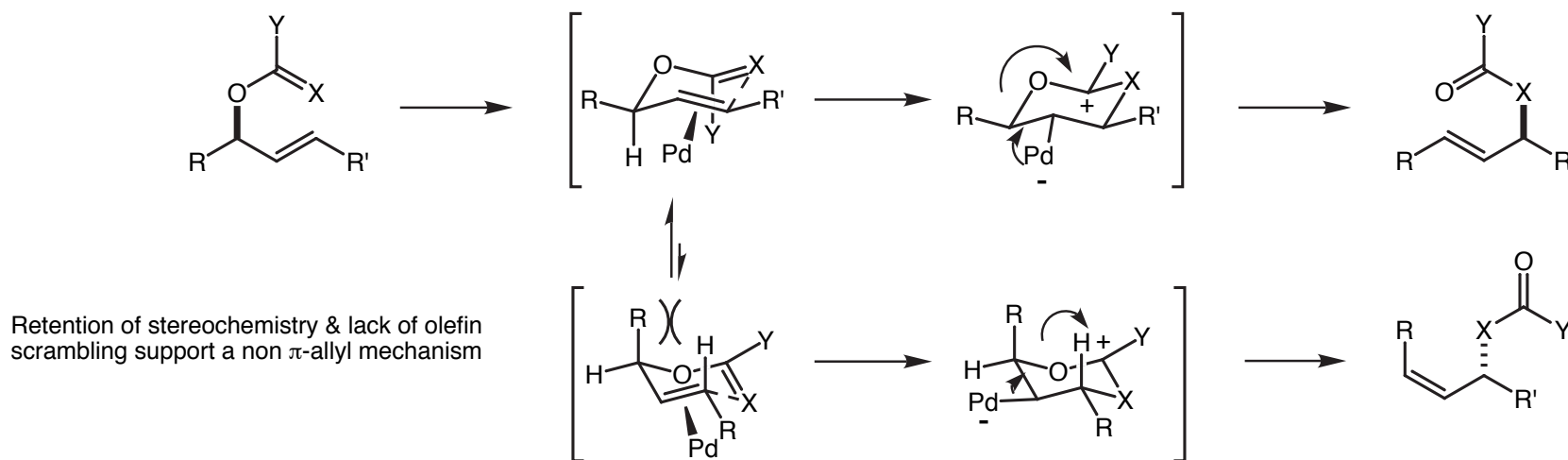
Grieco (JACS, 1980, 7587.)



Meetz (Tet., 1992, 1071.)

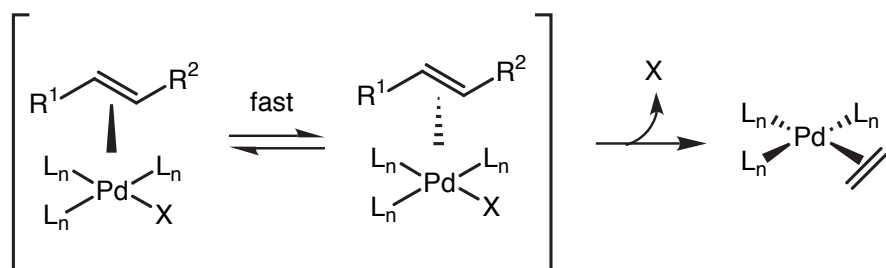
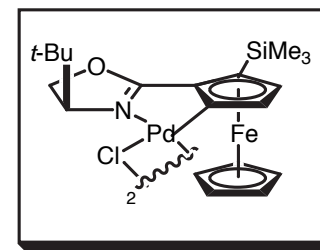
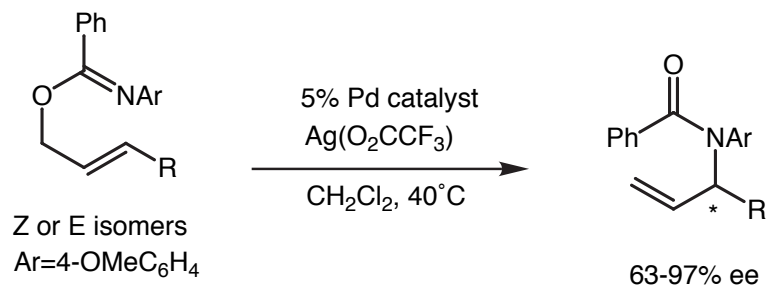


Cyclization-Induced Rearrangement (Overman)

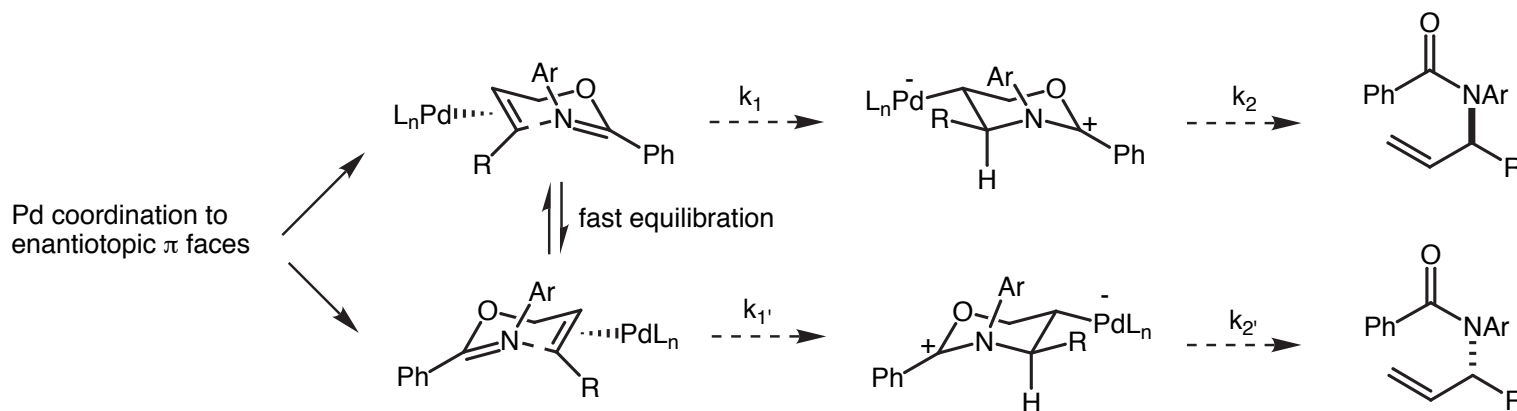


Overman, L.E. *ACIEE*, 1984, 579.

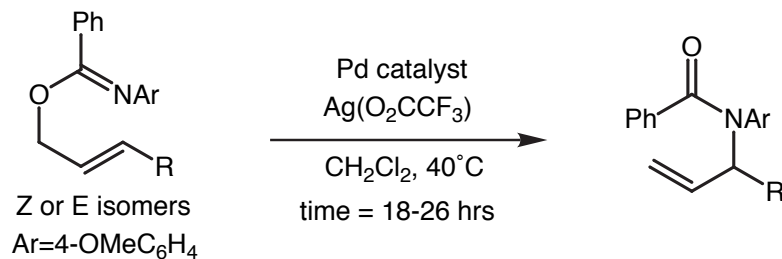
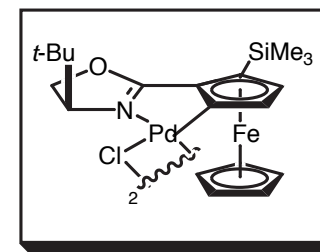
Enantioselective Rearrangement: Allylic Imidates



- Initial steps are likely: association, pseudo-rotation, dissociation
- Coordination of Pd to π -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



Substrate Scope and Other Ligands



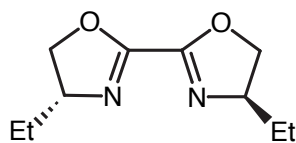
Z Isomers

R	Yield (%)	ee (%)
Me	96	75 (R)
<i>n</i> -Pr	83	91 (R)
<i>i</i> -Bu	90	97 (R)
<i>i</i> -Pr	59	86 (R)
Bn	85	88 (R)
Ph	11	77 (R)

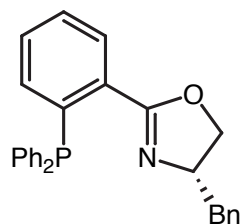
E Isomers

R	Yield (%)	ee (%)
<i>n</i> -Pr	93	83 (S)
<i>i</i> -Bu	97	84 (S)
Ph	59	63 (S)

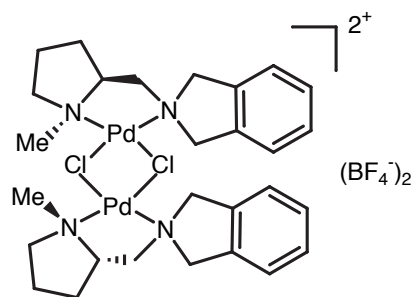
Earlier Catalyst Systems



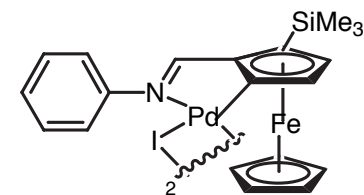
62% yield
10% ee
(Hayashi)



41% yield
76% ee
(Hayashi)



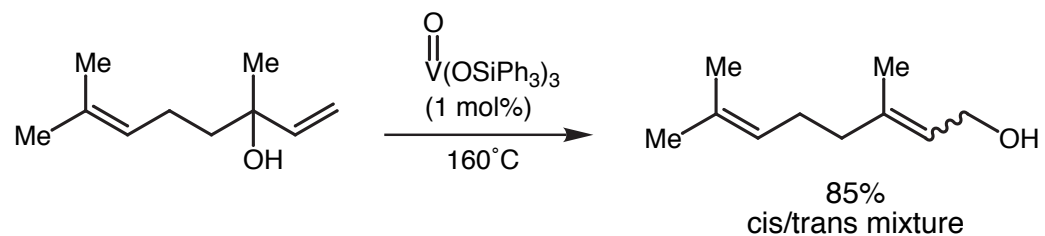
69% yield
55% ee
(Overman)



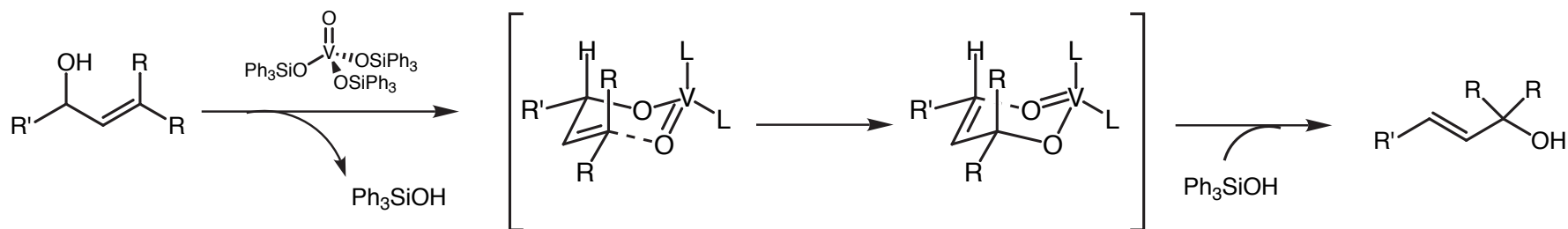
91% yield
49% ee
(Overman)

Allylic Rearrangements with Oxo Metals

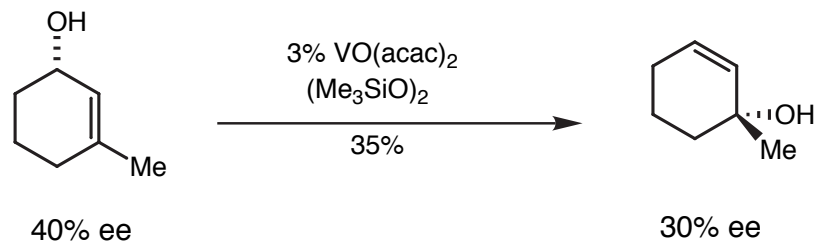
Earliest Example



Charbardes' Proposal



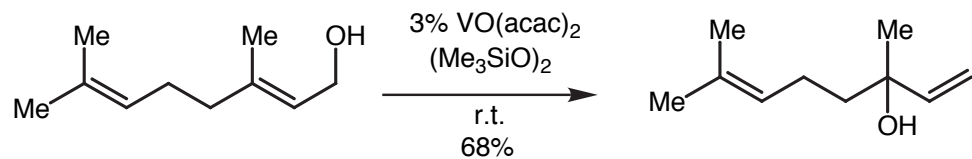
Chirality Transfer



Chabardes, P. *Tet.*, **1977**, 1775.

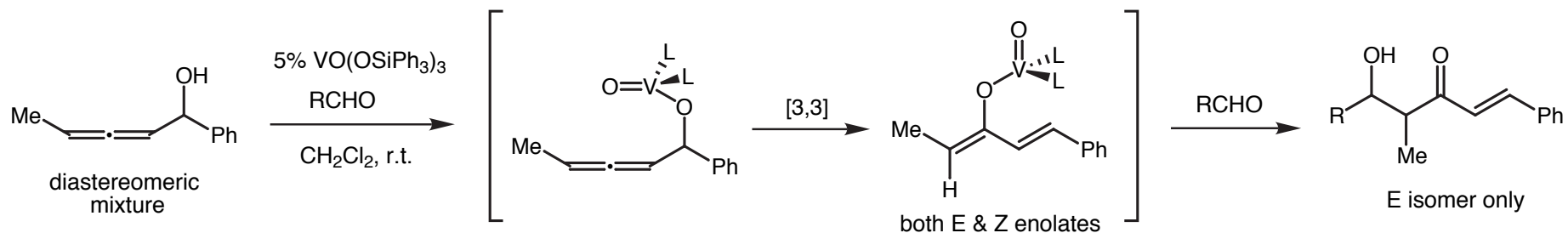
Takai, K. *Bull. Chem. Soc. Jpn.*, **1985**, 844.

Vanadate Catalysts (Takai)

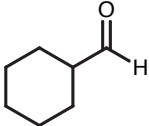
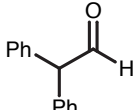
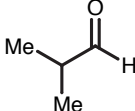
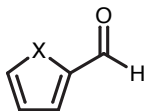
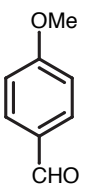


Substrate	Product	Starting Material (%)	Product (%)
		0	97 E only
		0	85
		20	53
		41	35
		0	70 E only

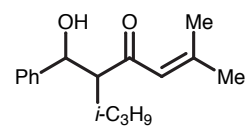
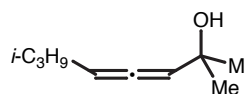
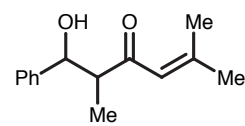
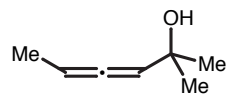
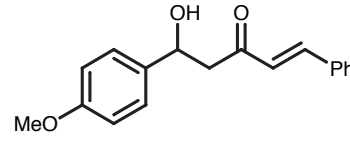
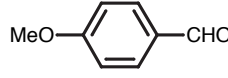
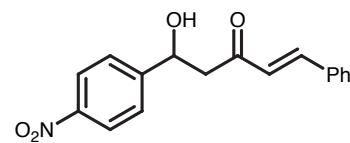
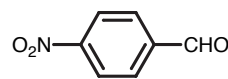
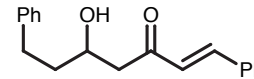
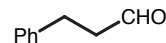
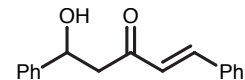
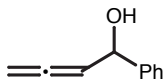
Allenic Alcohol Isomerizations (Trost)



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

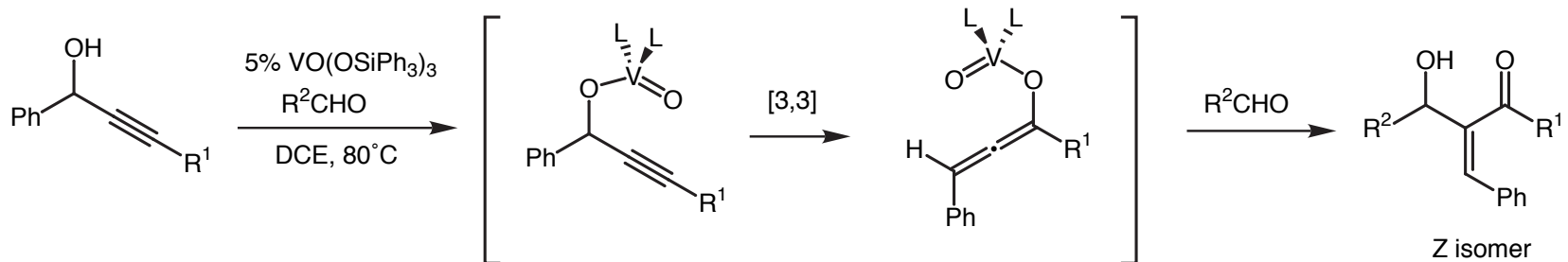


Other Allenes	Aldehyde	Product	Yield(%)
	PhCHO		85
II			70
II			83
II			64
	PhCHO		86
	PhCHO		57



• Diastereomerically pure allenol gave similar syn:anti ratios

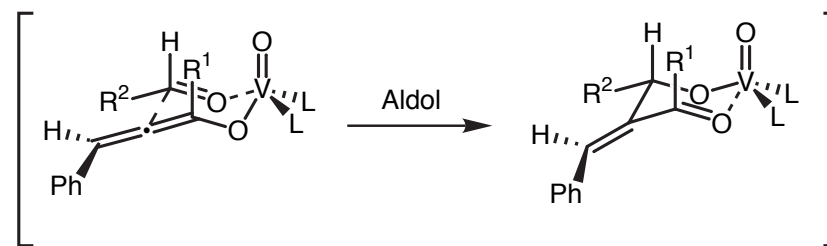
Propargyl Alcohol Isomerizations (Trost)



Propargyl Alcohol (R ¹)	Aldehyde (R ²)	Yield (%)	Z:E
<i>n</i> -Bu	PhCHO	94	91:9
<i>t</i> -Bu	PhCHO	95	98:2
Ph	PhCHO	73	88:12
CH ₂ OTBS	PhCHO	42	only Z

<i>n</i> -Bu		77	only Z
<i>n</i> -Bu		92	only Z
<i>n</i> -Bu	<i>n</i> -PrCHO	55	89:11
<i>n</i> -Bu	chex-CHO	58	96:4

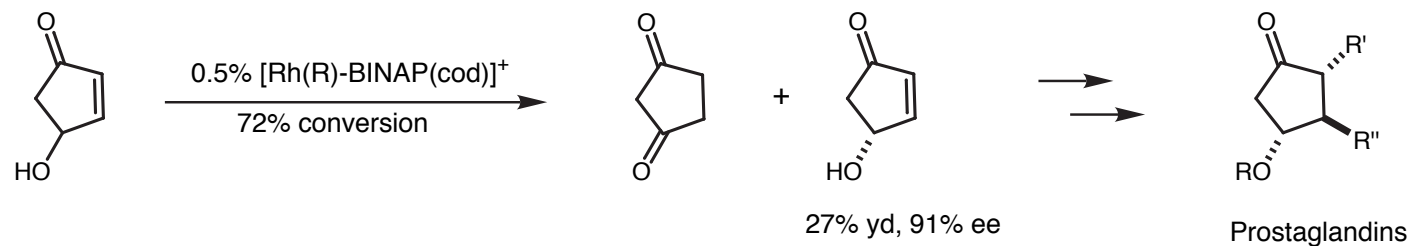
Chair Transition State Model



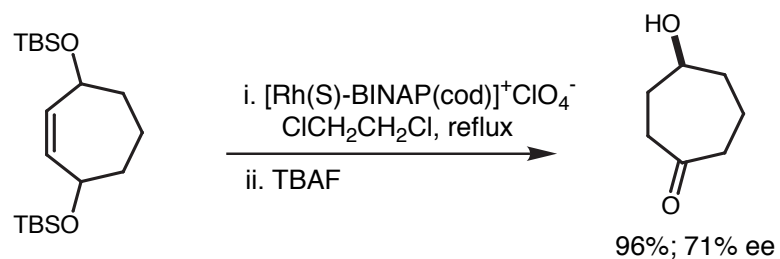
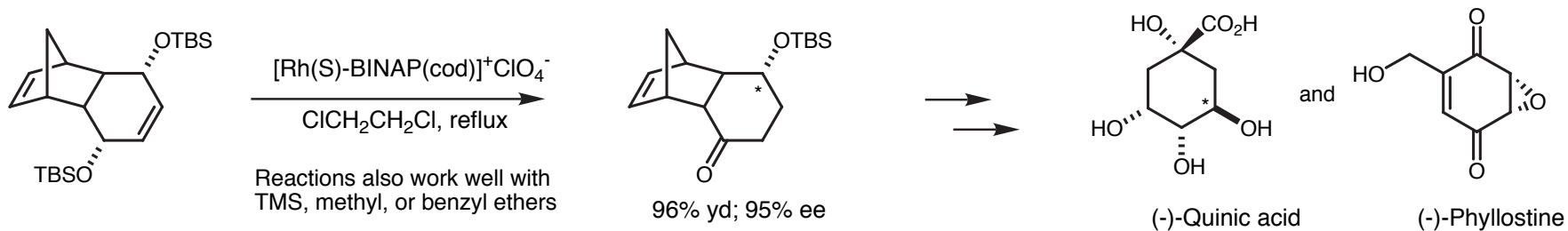
Aldehyde approach from opposite face of Ph explains high selectivity for Z isomer.

Desymmetrizations

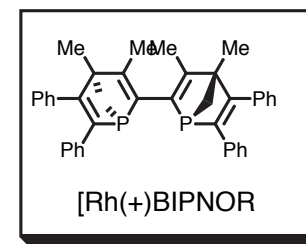
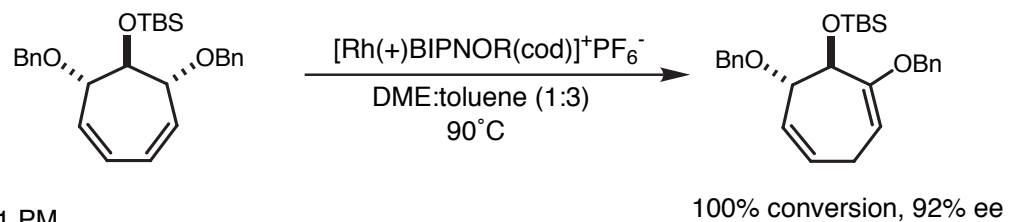
Noyori, R. *TL*, **1987**, 4719.



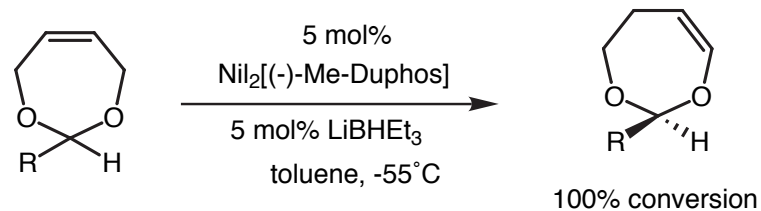
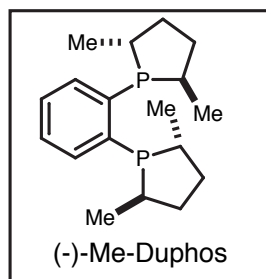
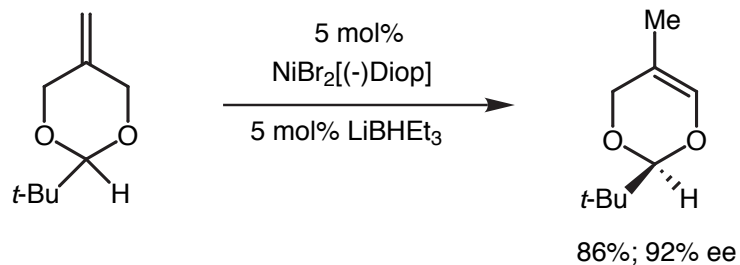
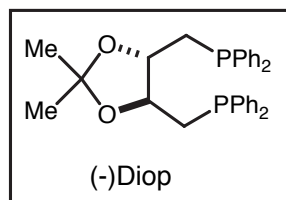
Ogasawara, K., *ACIEE*, **1995**, 2287.



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

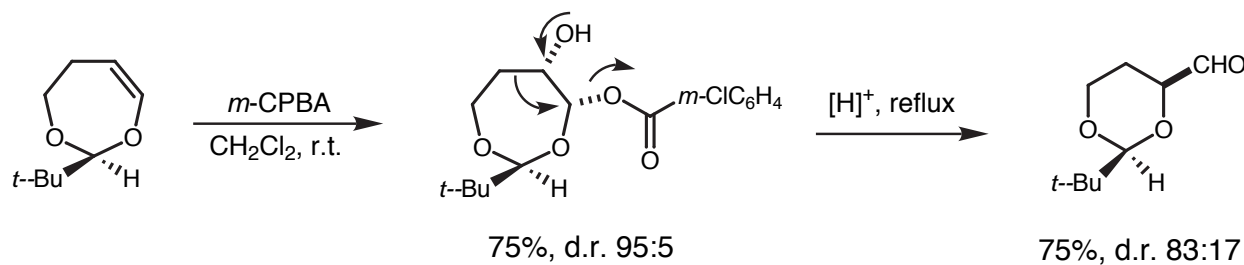


Desymmetrization of Cyclic Allylic Acetals (Frauenrath)



R	ee (%)
<i>t</i> -Bu	98
<i>i</i> -Pr	90
<i>n</i> -Bu	90

Synthetic Use:

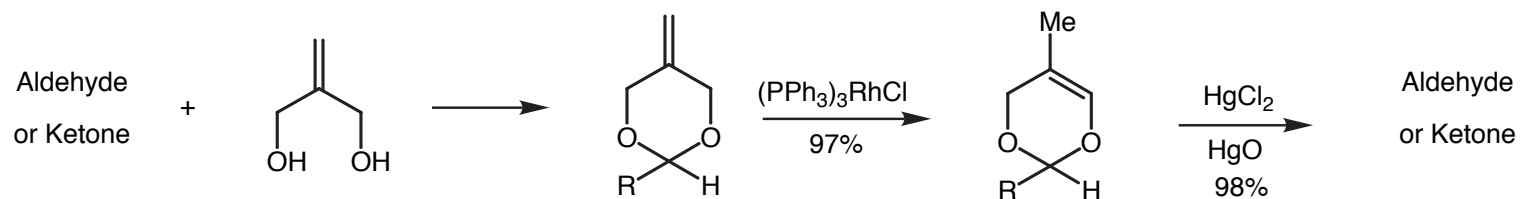


Frauenrath, H. *et al. Tet. Asym.*, **1998**, 1103

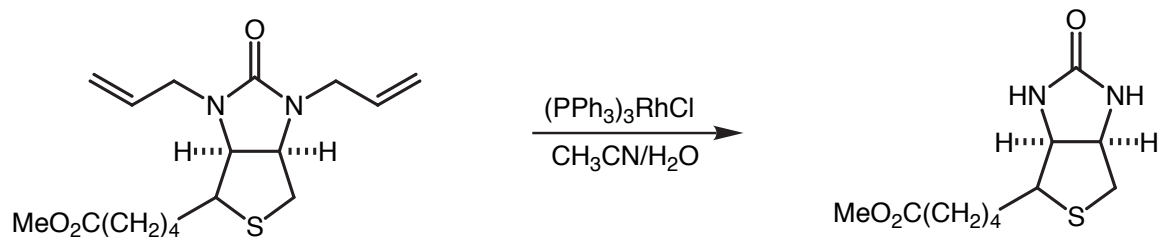
Frauenrath, H. *et al. ACIEE*, **2001**, 177

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.)

