

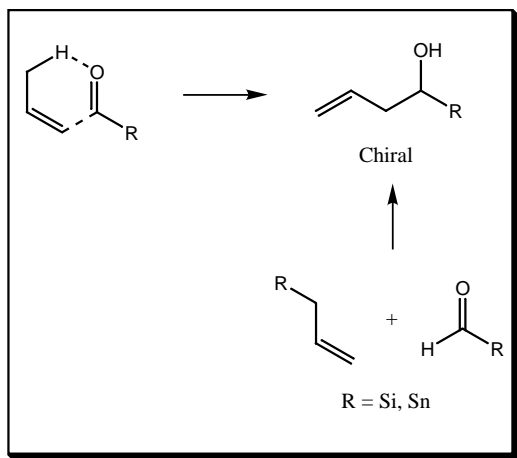
# **Asymmetric Ene Reaction**

**Evans Group Seminar**

by  
Steven Tregay

December 12, 1997

## Seminar Topics



### History:

Alder, *Ber.*, **1943**, 76, 27.  
Alder, *Ann.*, **1962**, 651, 141.

Covered in this Seminar:

Asymmetric Ene  
(Metallo-Ene not covered)

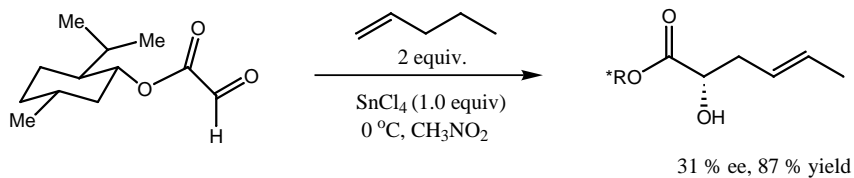
Chiral Auxiliaries

Catalytic/Promoted

### Reviews:

Snider in *Comprehensive Organic Chemistry*, **1991**, vol 2, 527.  
Mikami, *Chem. Rev.* **1992**, 92, 1021.  
Mikami, *Advances in Asymmetric Synthesis*, **1995**, 1.  
Bolm, *ACIEE*, **1995**, 34, 1717.  
Mikami, *Advances in Catalytic Processes*, **1995**, 1, 123.  
Mikami, *Pure & Applied Chem.*, **1996**, 68, 639.

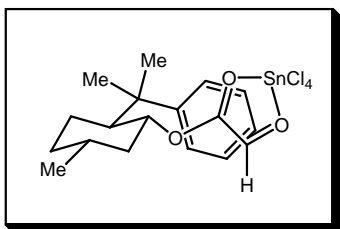
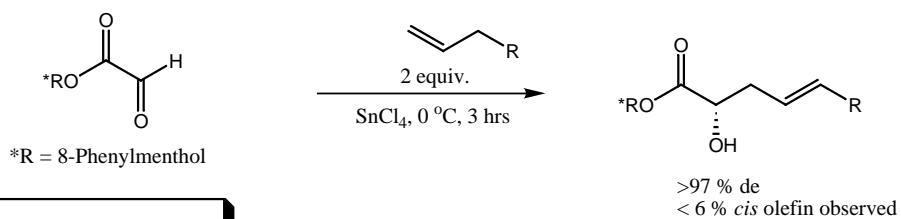
### Early Work on Chiral Glyoxylates



Thermal reaction (160 °C) gave no induction

Achmatzowicz, *JOC*, **1972**, 37, 964.

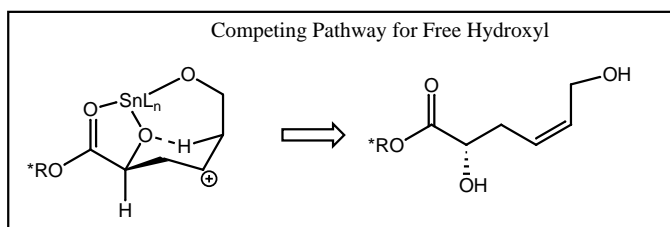
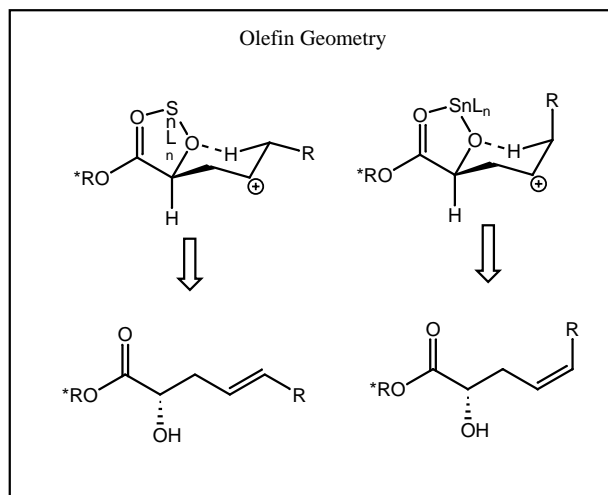
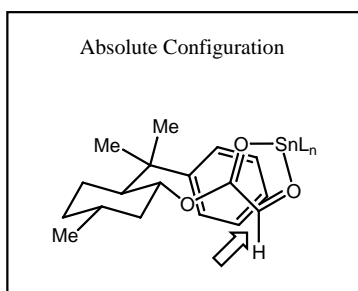
### Ene reactions of 8-Phenylmenthol Glyoxylate Ester



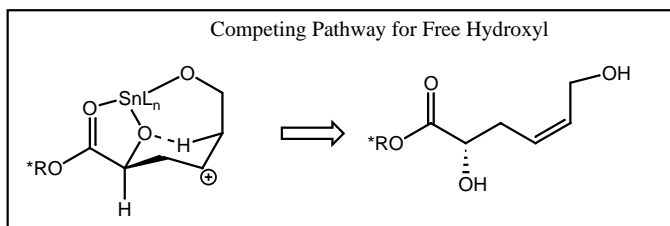
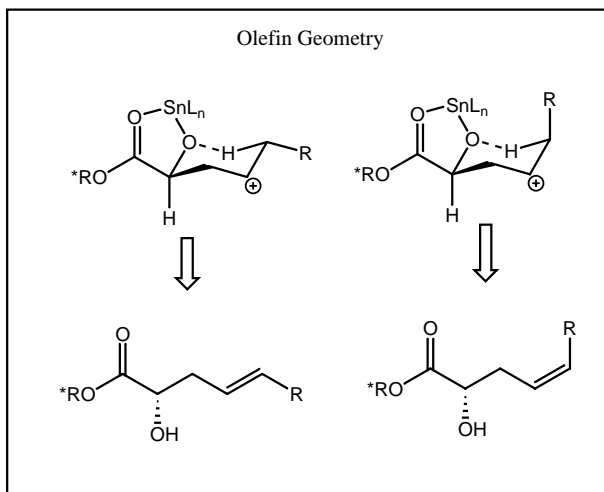
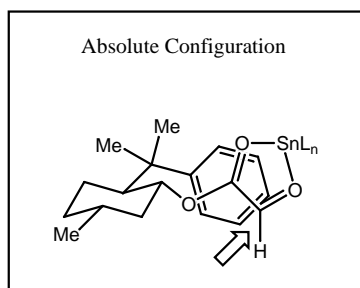
Alkene	Product	Yield
		99 %
		92 %
		R=H 100 % (2:1 <i>cis</i> : <i>trans</i> ) R=OAc 59 % R=Bn 99 % R=TBS 89 %

Whitesell, JCS CC, **1982**, 989.  
Whitesell, Tetrahedron, **1986**, 42, 2993.

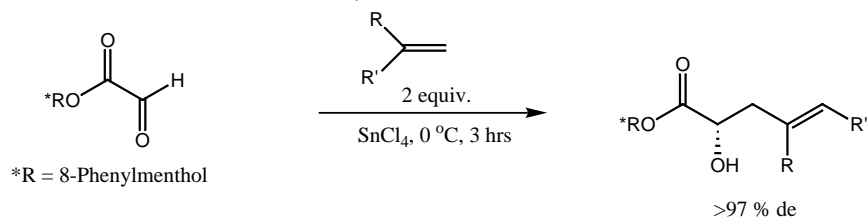
### Mechanism for 1-Substituted Olefins



### Mechanism for 1-Substituted Olefins



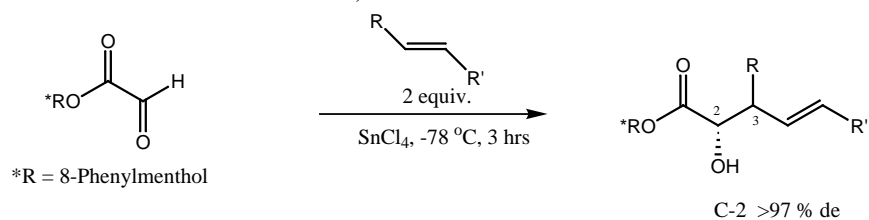
### 1,1 Disubstituted Olefins



Alkene	Product	Yield
		94 %
		84%
		R=H "Dominant product"
		R=OAc 42 %
		24 % trans olefin
		20 % cis olefin

Whitesell, JCS CC, **1982**, 989.  
Whitesell, Tetrahedron, **1986**, 42, 2993.

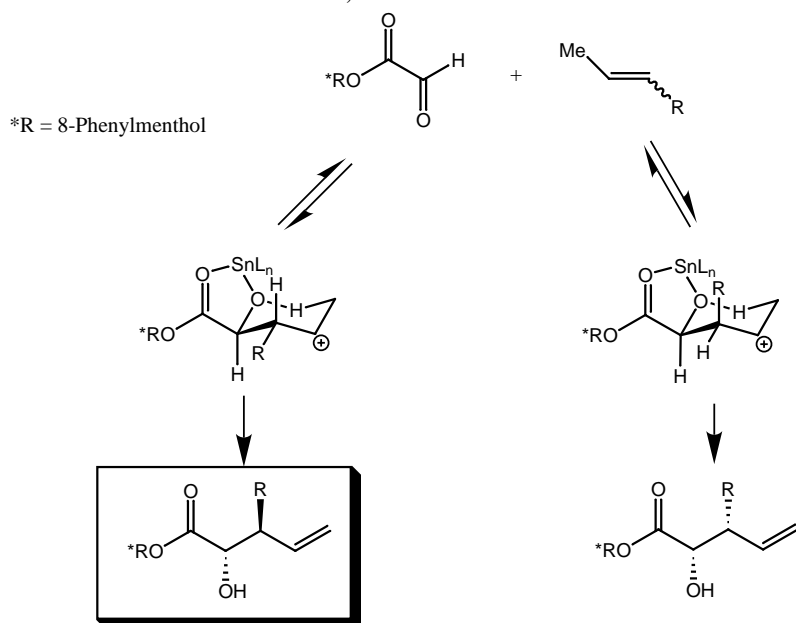
### 1,2 Disubstituted Olefins



Alkene	Product	Yield
		C-3 92% de "Exo TS" 90% yield
		C-3 15:1
		85% yield
		C-3 8:1 one compound 86% yield

Whitesell, JCS CC, **1982**, 989.  
Whitesell, Tetrahedron, **1986**, 42, 2993.

### 1,2 Disubstituted Olefin Mechanism

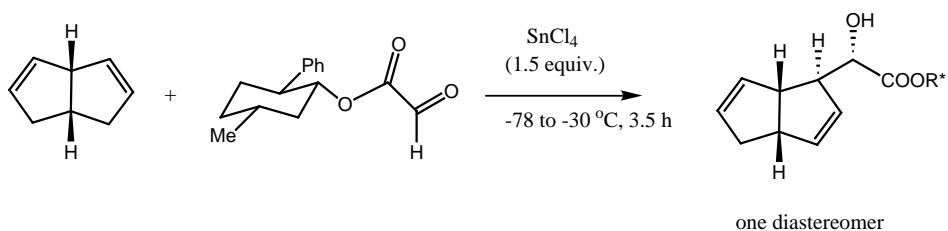
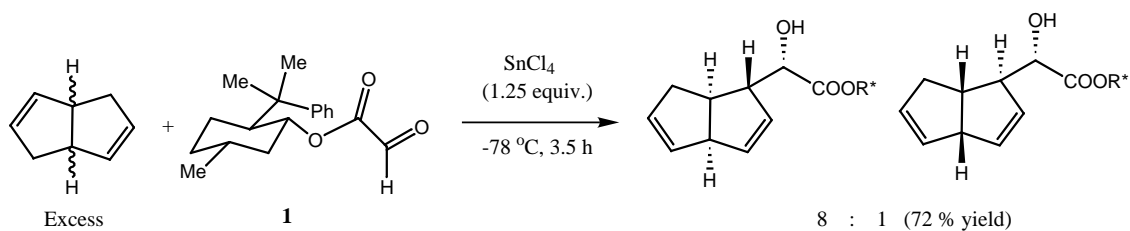


R = Me  
*trans*-butene 15:1  
*cis*-butene 8:1

R = i-Pr  
 4-methyl-*cis*-2-pentene one compound

**Note:** *cis*-butene does not isomerize in presence of SnCl<sub>4</sub> or SnCl<sub>4</sub>/isopropyl alcohol at -78 °C  
 Isomerization does occur in the presence of glyoxylate

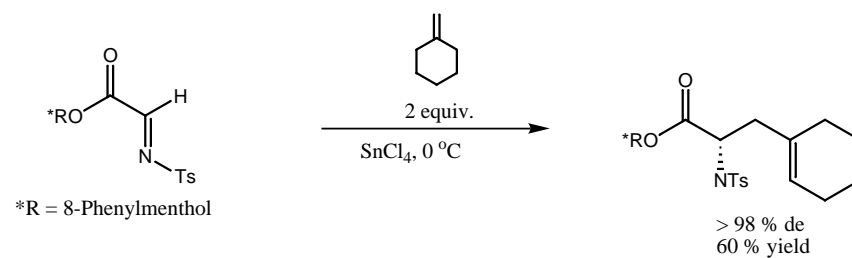
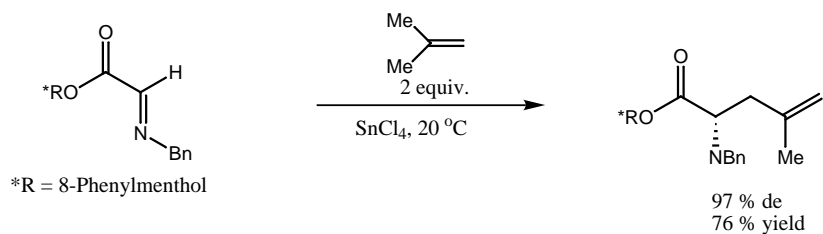
### Asymmetric Desymmetrization using 8-Phenylmenthol Glyoxylate Ester



Whitesell, JACS, **1988**, *110*, 3585.  
Whitesell, JACS, **1986**, *108*, 6802.  
Whitesell, JOC, **1985**, *50*, 3025.

**Note:** **1** gives opposite bridgehead selectivity

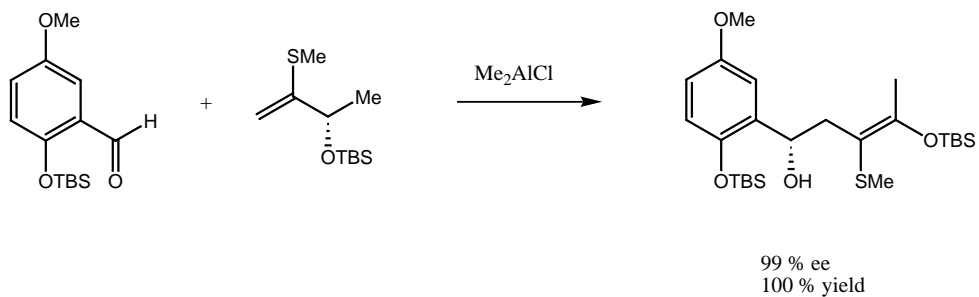
### Phenylmenthol Imine-Ene Reaction



Use of Ts rather than Bn was not discussed

Mikami, TL, **1993**, *34*, 4841.

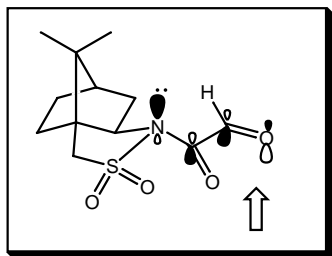
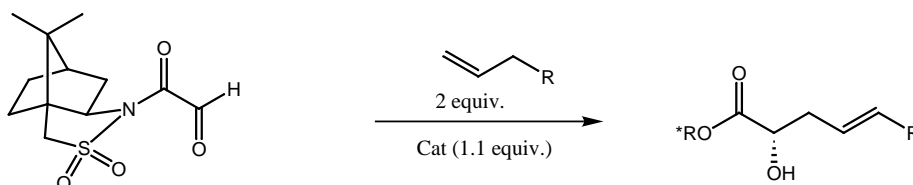
### Ene reaction of (S)-2-(Ethylthio)-3-siloxy-1-butene



Referenced in Mikami, *Chem. Rev.*, **1992**, 92, 1021

Kuwajima, Annual Meeting of the Chemical Society of Japan, 1991.

### Ene Reactions of N-Glyoxyloyl -(2R)-bornane-10,2-Sultam

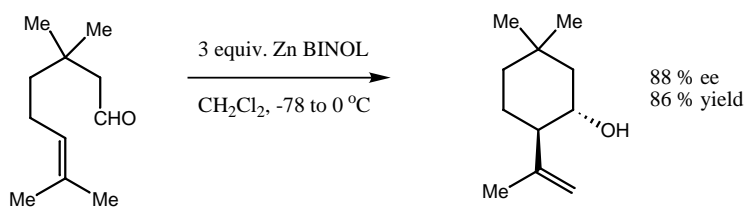


Most Reactive Conformation according to PM3 and *Ab initio* calculations  
Chapuis, *Helv. Chim. Acta*, in preparation

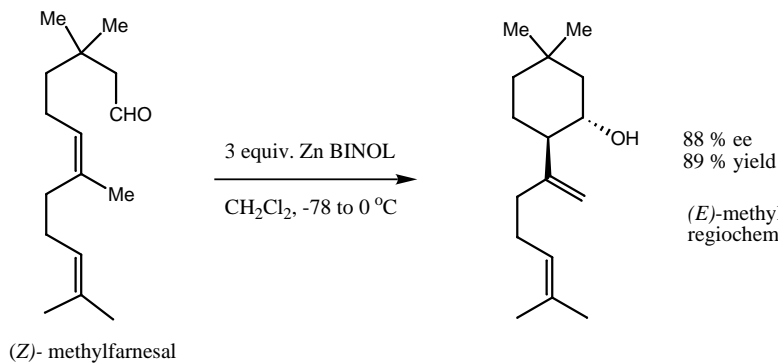
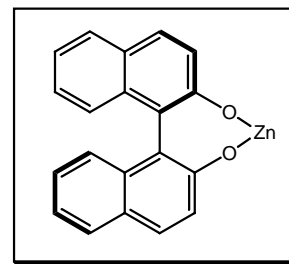
R =	Catalyst	Temp (°C)	% de	% Yield
Et	SnCl <sub>4</sub>	-78	84 : 16	78
	ZnBr <sub>2</sub>	5	90 : 10	50
<i>n</i> -Pr	SnCl <sub>4</sub>	-78	75 : 25	93
	ZnBr <sub>2</sub>	5	89 : 11	43

Jurczak, *Tet.: Asymm.*, **1997**, 8, 1741.

### Zn BINOL Promoted Intramolecular Ene Cyclizations



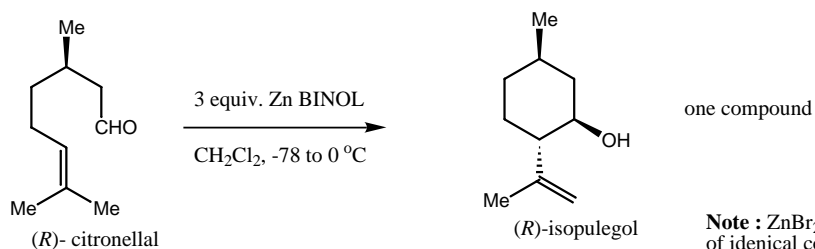
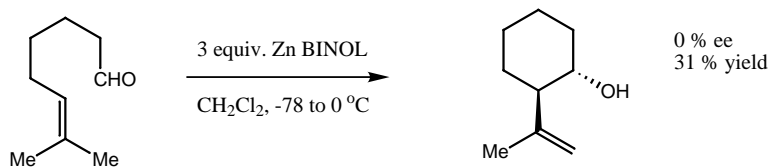
**Note:** using 1.5 equiv. reagent lowers % ee



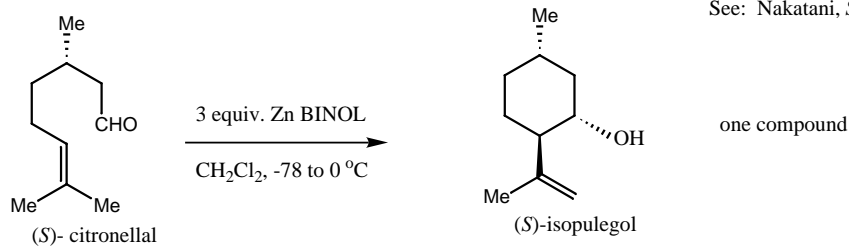
(E)-methylfarnesal afforded other regiochemistry in 20 % ee

Yamamoto, *Tetrahedron*, **1986**, 42, 2203.

### Zn BINOL Promoted Intramolecular Ene Cyclizations



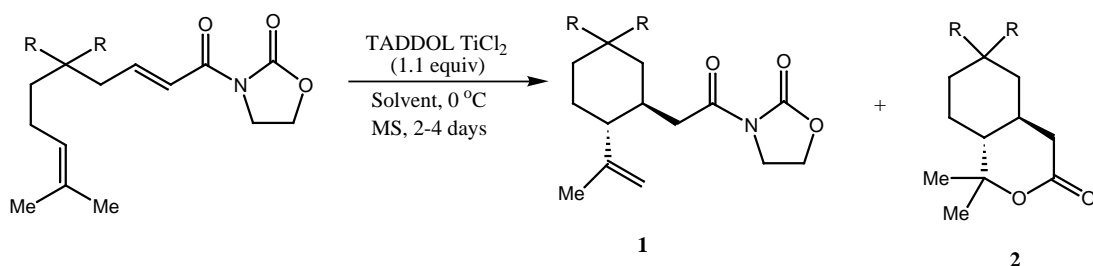
**Note :** ZnBr<sub>2</sub> gives 95:5 ratio of products of identical configuration  
 See: Nakatani, *Syn. Comm.*, **1978**, 147.



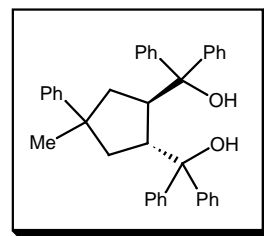
Yamamoto, *Tetrahedron*, **1986**, 42, 2203.



### TADDOL Promoted Intramolecular Ene

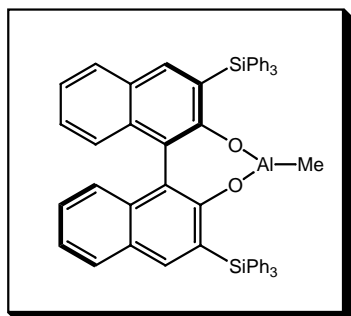
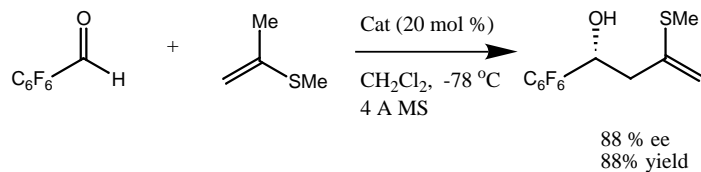


R =	Solvent	1 % ee (% yield)		2 % ee (% yield)	
H	Toluene (20 days)	ND	(17)	ND	(37)
	Toluene	82	(39)	92	(36)
Me	1,3,5 Trimethylbenzene	86	(32)	>98	(37)
	CFCl <sub>2</sub> CF <sub>2</sub> Cl/ CH <sub>2</sub> Cl <sub>2</sub>	97	(47)	ND	(16)
-SCH <sub>2</sub> CH <sub>2</sub> S-	CFCl <sub>2</sub> CF <sub>2</sub> Cl/ CH <sub>2</sub> Cl <sub>2</sub>	84	(ND)	>98	(ND)



Narasaka, *Chem. Lett.*, **1988**, 1609.

### 3-3'-bis(triphenylsilyl)BINOL Aluminium Catalyst



**Note:** Use of less reactive aldehydes (ie Chloral) afforded lower % ee and stoic. LA were required

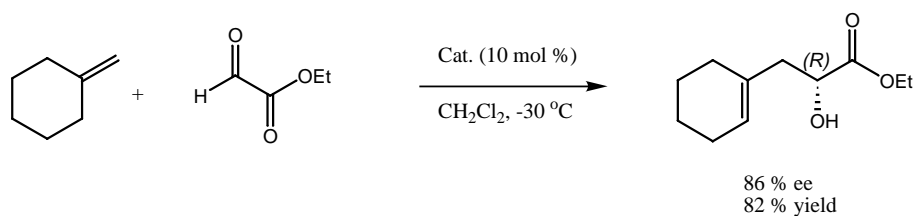
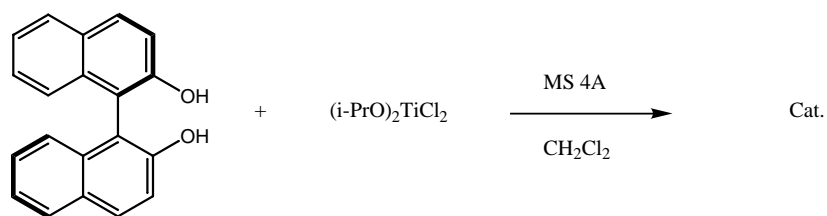
Use of MS is required for catalytic reaction

Use of 3-3'-diphenylbinaphthol complex gave 0 % ee

Yamamoto, *TL*, **1988**, 29, 3967.

(i-PrO)<sub>2</sub>TiCl<sub>2</sub> (R)-BINOL Catalyzed Ene Reaction

Preliminary Result:



Nakai, JACS, **1989**, *111*, 1940.  
Nakai; Mikami, JACS, **1990**, *112*, 3949.

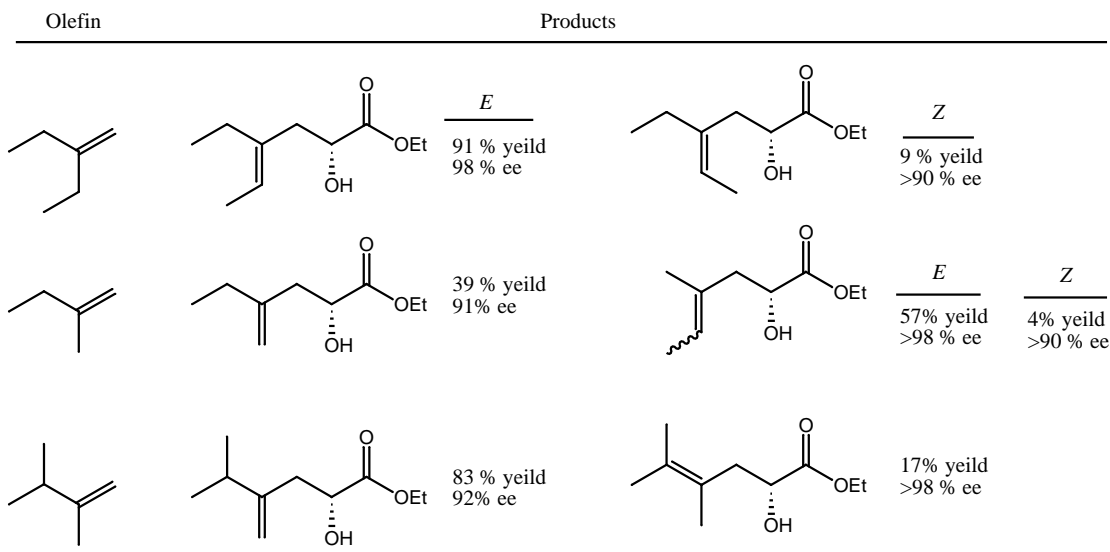
(i-PrO)<sub>2</sub>TiBr<sub>2</sub> (R)-BINOL Catalyzed Ene Reaction : 1,1 Disubstituted

Olefin	Product	Cat. Mol %	% yield	% ee
		5	73	98
		10	87	94
		1.0	98	94
		5	92	89

Reaction conditions: Ethyl glyoxylate, -30 °C, 3 hr, MS, CH<sub>2</sub>Cl<sub>2</sub>

Nakai, JACS, **1989**, *111*, 1940.  
Nakai; Mikami, JACS, **1990**, *112*, 3949.  
Nakai, *Org. Syn.*, **1993**, 14.

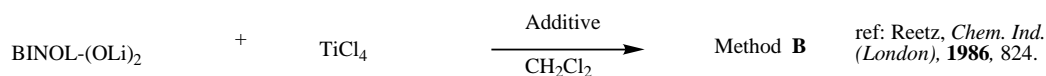
(i-PrO)<sub>2</sub>TiBr<sub>2</sub> (R)-BINOL Catalyzed Ene Reaction : More 1,1 Disubstituted



Reaction conditions: Ethyl glyoxylate, 5 -10 mol % cat., -30 °C, 3 hr, MS, CH<sub>2</sub>Cl<sub>2</sub>

Nakai, JACS, **1989**, *111*, 1940.  
Nakai; Mikami, JACS, **1990**, *112*, 3949.

Importance of Molecular Sieves



For reaction of  $\alpha$ -methyl Styrene and ethyl glyoxylate (CH<sub>2</sub>Cl<sub>2</sub>, -30 °C)

Method A	Additive	Yield	% ee	Method B	Additive	Yield	% ee
	4 A MS (g/mmol)				i-PrOH		
	5	100	97		0	95	93
	0	81	10		10 mol %	90	95
	5 then filter	96	97		0	100	95
					10 mol %	98	96

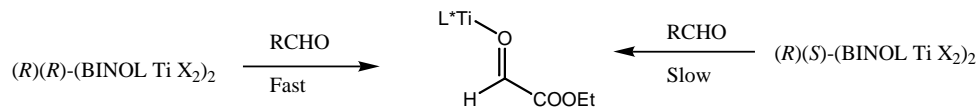
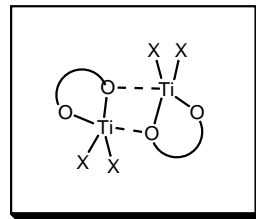
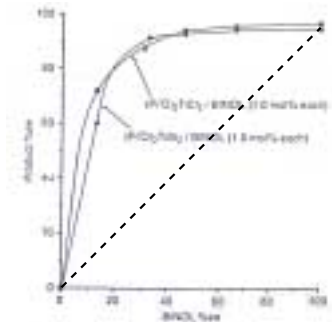
**Note :** By <sup>13</sup>C NMR no Ti BINOL complexation occurs until MS are added.

(i-PrO)<sub>2</sub>TiCl<sub>2</sub> is a viable catalyst for the reaction.

**Note :** MeOH, t-BuOH give similar results

Nakai; Mikami, JACS, **1990**, *112*, 3949.

### NonLinear Effect in the (i-PrO)<sub>2</sub>TiX<sub>2</sub> BINOL Catalyzed Ene Reaction



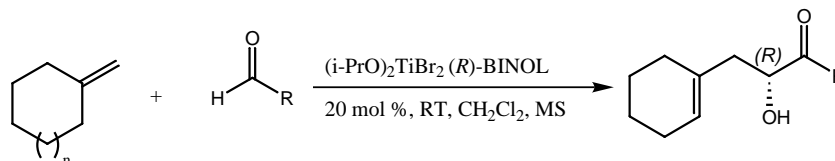
For chiral poisoning of racemic BINOL Complexes see:

Faller, TL, **1996**, 37, 3449.  
Mikami, *Nature*, **1997**, 385, 613.

**Note** : For X-ray crystal structure of dimeric ((PhO)<sub>2</sub>TiCl<sub>2</sub>)<sub>2</sub>  
See: Watenpaugh, *Inorg. Chem.* **1966**, 5, 1782.

Mikami, *Tetrahedron*, **1992**, 48, 5671.  
Mikami, *JACS*, **1994**, 116, 2812.

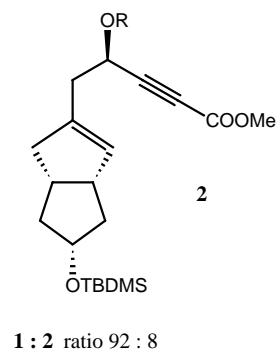
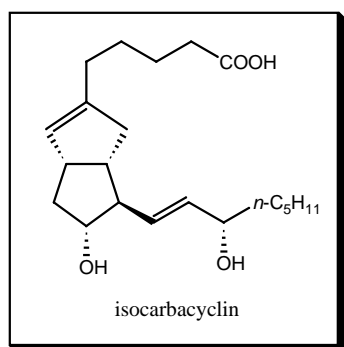
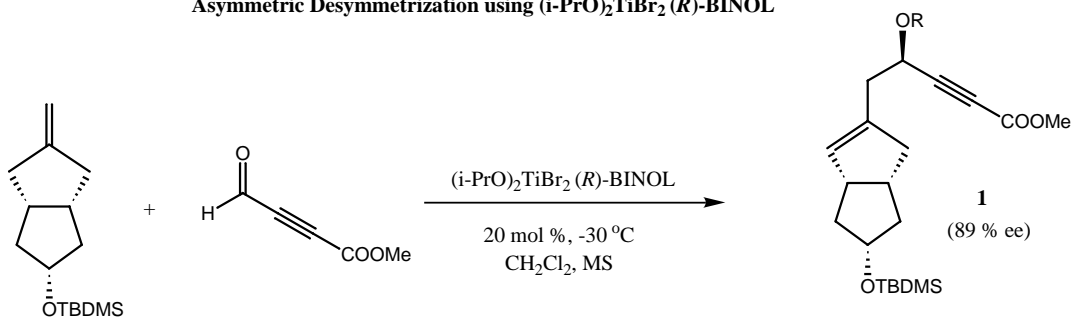
### (i-PrO)<sub>2</sub>TiBr<sub>2</sub> (R)-BINOL Catalyzed Ene Reaction : Other Enophiles



Enophile	n=	% Yield	% ee
	0	85	87
	1	70	94
	0	80	72
	1	60	86

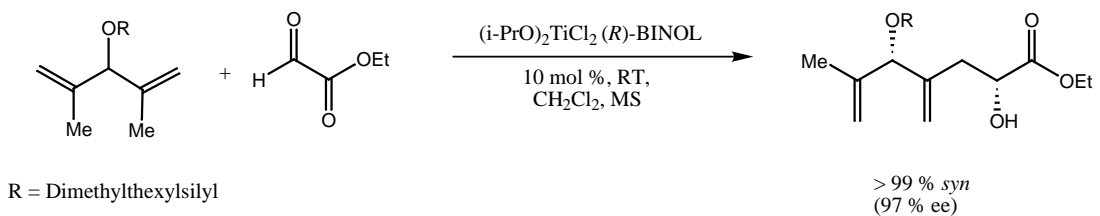
Mikami, TL, **1996**, 47, 8515.

Asymmetric Desymmetrization using (i-PrO)<sub>2</sub>TiBr<sub>2</sub> (R)-BINOL

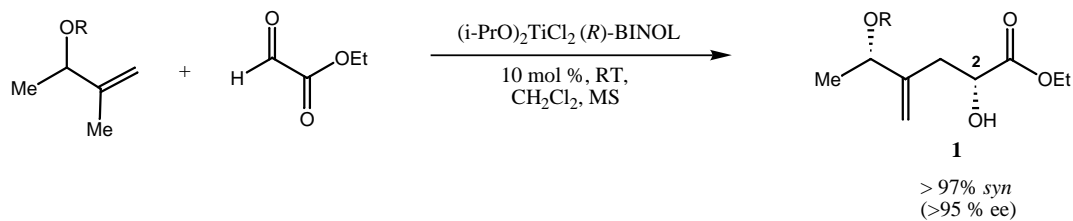


Mikami, TL, **1996**, 47, 8515.  
Mikami, Synlett, **1995**, 29.

Asymmetric Desymmetrization / Resolution using (i-PrO)<sub>2</sub>TiCl<sub>2</sub> (R)-BINOL



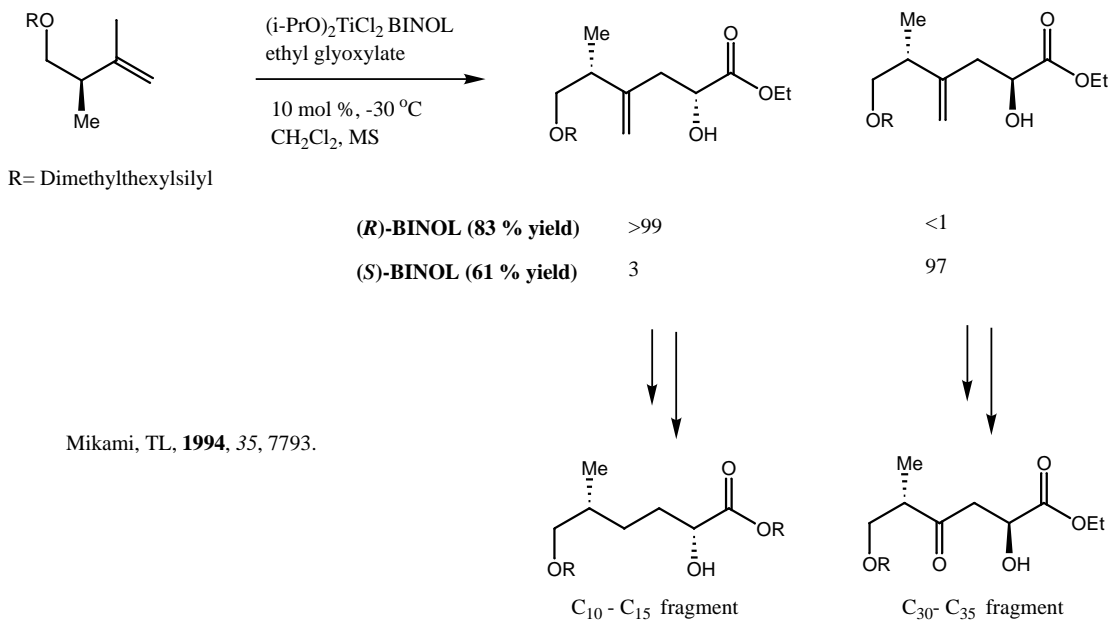
R = Dimethylhexylsilyl



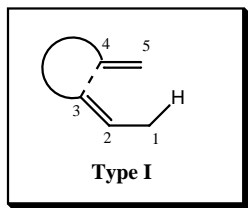
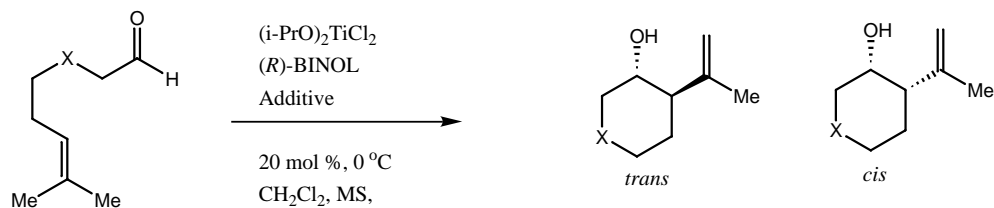
	Catalyst	Product
	(i-PrO) <sub>2</sub> TiCl <sub>2</sub> (S)-BINOL	<i>ent</i> - <b>1</b> (>99 % <i>syn</i> , 71 % yield)
	(i-PrO) <sub>2</sub> TiCl <sub>2</sub> (R)-BINOL	<i>ent</i> - <b>1</b> (50 : 50 at C-2, 31 % yield)

Mikami, Annual Meeting of the Chemical Society of Japan, **1990** and **1991**.  
See : Mikami, Synlett, **1992**, 255.

Synthesis of C<sub>10</sub> - C<sub>15</sub> and C<sub>30</sub>- C<sub>35</sub> fragments of Rapamycin



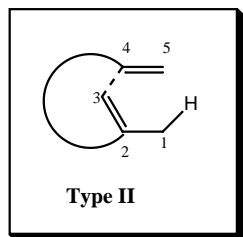
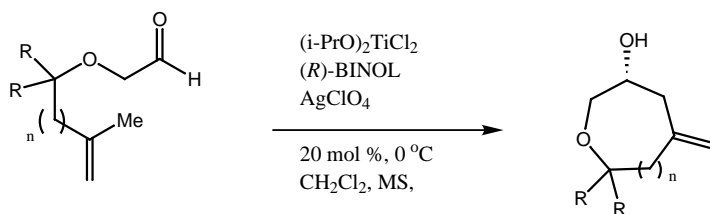
(i-PrO)<sub>2</sub>Ti(ClO<sub>4</sub>)<sub>2</sub> (*R*)-BINOL Catalyzed  
 {3, 4} *exo, exo* Intramolecular Ene Reaction



X =	Additive	time	% Yield	Ratio	
				<i>trans</i> : <i>cis</i>	<i>trans</i> % ee
O	none	24 h	73	47 : 53	70
O	AgClO <sub>4</sub>	24 h	50	80 : 20	84
-CH <sub>2</sub> -	AgClO <sub>4</sub>	48 h	66	69 : 31	55

Mikami, TL, **1991**, 32, 6571.  
 Mikami, *Tet. :Asymm.*, **1991**, 2, 1403.

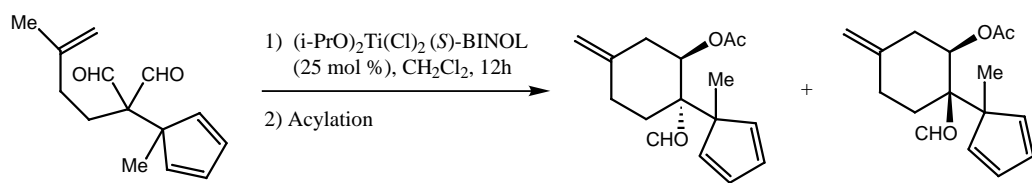
**(i-PrO)<sub>2</sub>Ti(ClO<sub>4</sub>)<sub>2</sub> (*R*)-BINOL Catalyzed  
{2, 4} *exo, exo* Intramolecular Ene Reaction**



n=	R=	% yield	% ee
0	H or Me	NR	--
1	H	43	91
1	Me	40	82

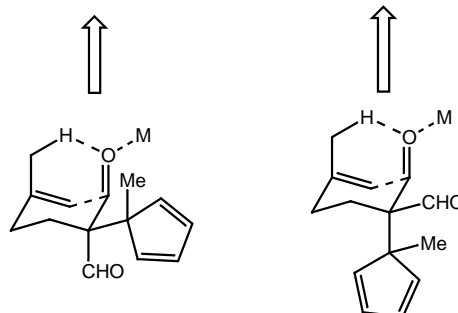
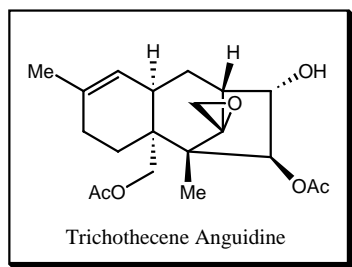
Mikami, TL, **1991**, 32, 6571.  
Mikami, *Tet. :Asymm.*, **1991**, 2, 1403.

**(i-PrO)<sub>2</sub>Ti(Cl)<sub>2</sub> (*S*)-BINOL Catalyzed  
{2, 4} *exo, exo* Intramolecular Ene Reaction**



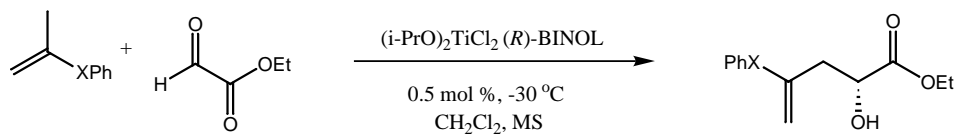
4.5 (38 % ee) :

1

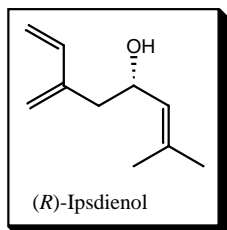
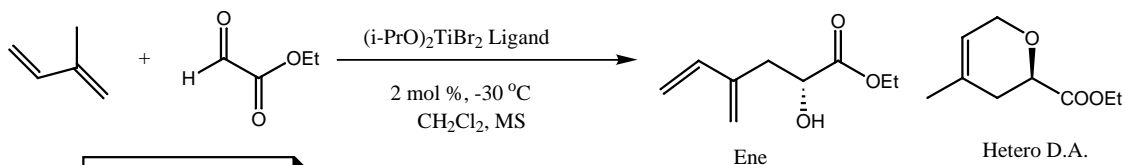


Ziegler, JACS, **1990**, 112, 2749.

### Approaches toward Ipsdienol



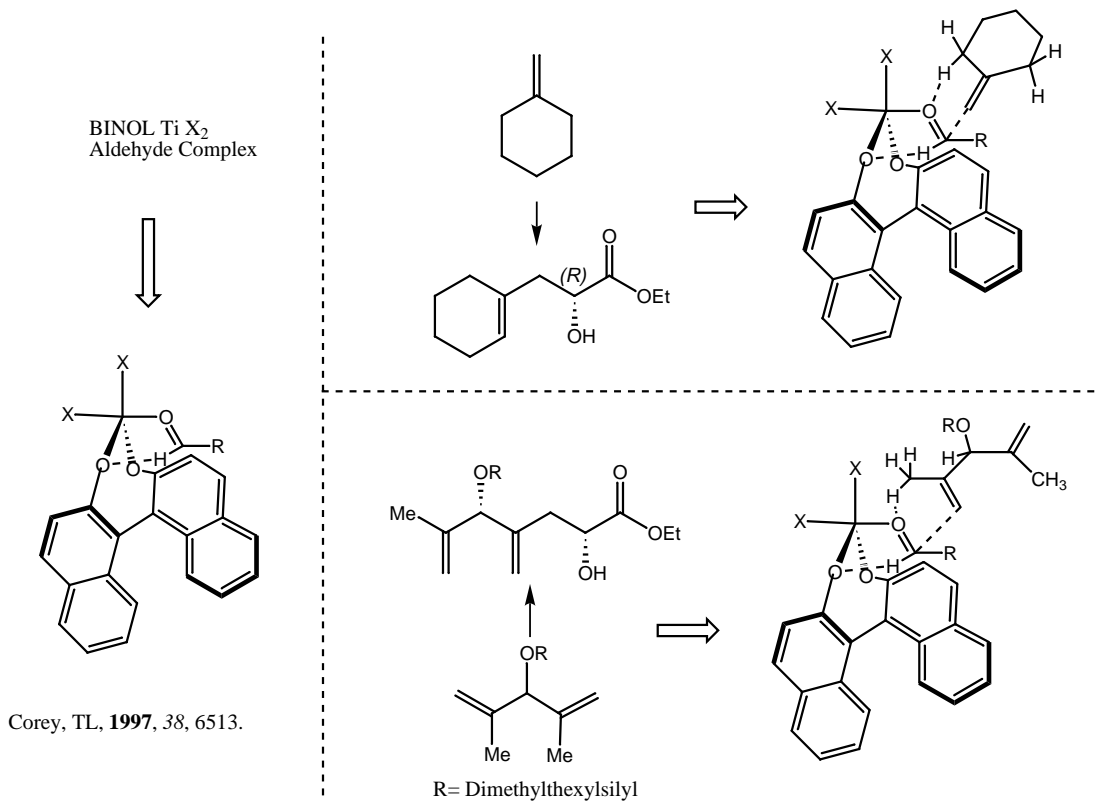
X = S      X = Se  
 94 % yield      95 % yield  
 >99 % ee      >99 % ee



Ligand	Yield	Product Ratio	
		Ene	Hetero D. A.
BINOL	94	79 (97 % ee)	21
	84	92 (>99 % ee)	8

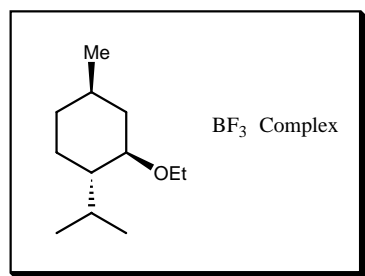
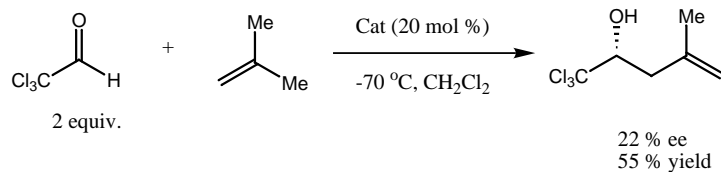
Mikami, JCS CC, **1995**, 2391.  
 Mikami, JCS CC, **1993**, 327.

### Corey's Model for Ti BINOL Ene Reactions



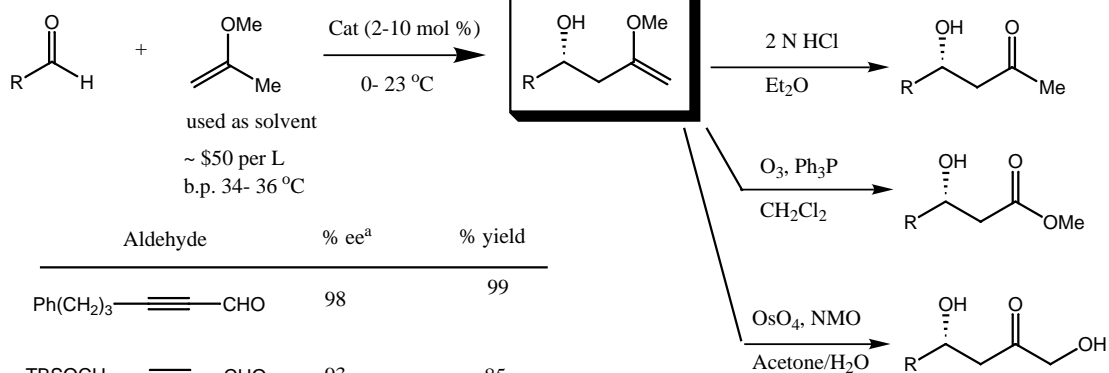


### BF<sub>3</sub> Menthylethyl Etherate catalyzed Ene reaction

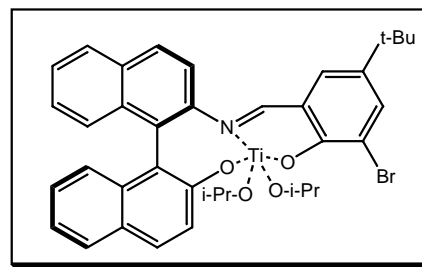


Demir, *Syn. Comm.* **1994**, 24, 137.

### Carreira's Catalytic Ene



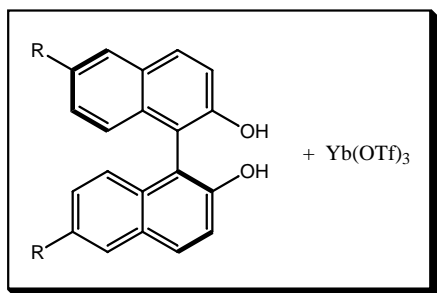
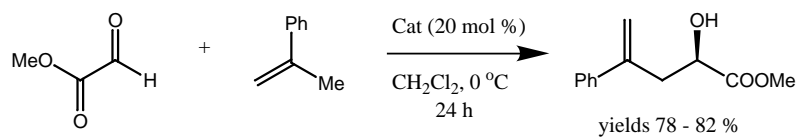
Aldehyde	% ee <sup>a</sup>	% yield
Ph(CH <sub>2</sub> ) <sub>3</sub> —C≡C—CHO	98	99
TBSOCH <sub>2</sub> —C≡C—CHO	93	85
Ph—C≡C—CHO	91	99
Ph—CH <sub>2</sub> —CH <sub>2</sub> —CHO	90	98
PhCHO	66	83
Only α-branched aldehyde which reacts 	75	79



Carreira, *JACS*, **1995**, 117, 3649.

<sup>a</sup> % ee detrmind by NMR analysis of (S)-MPTA ester of methyl ketone

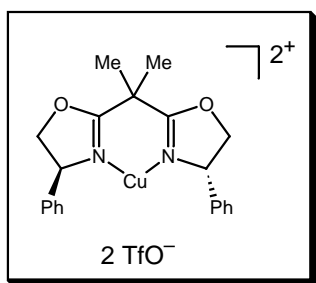
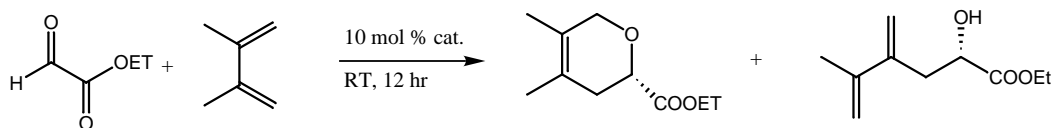
### Yb(OTf)<sub>3</sub> BINOL Catalyzed Ene Reaction



Ligand R=	% ee
H	12
Br	38
Ph	25
$\text{-}\overset{\text{R}}{\text{C}}\equiv\text{C-TMS}$	29

Qain, TL, **1997**, 38, 6721.

### Jorgensen's Ene byproducts

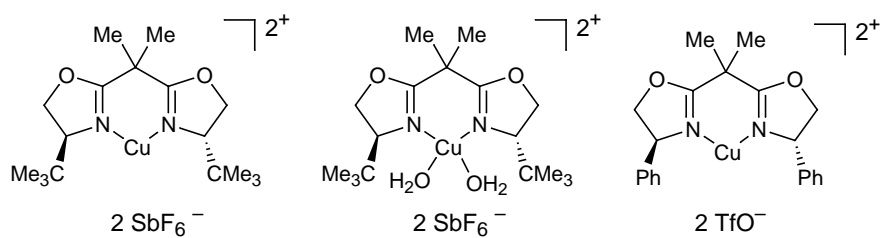


Solvent	Diels-Alder % ee	Ene Product % ee	DA :Ene Ratio
$\text{CH}_2\text{Cl}_2$	85	83	1 : 1.8
$\text{CH}_3\text{NO}_2$	90	78	1 : 0.8

Jorgensen, *Tetrahedron*, **1996**, 52, 7321.

For optimization of hetero Diels-Alder reaction products  
 See: Jorgensen, *JCS PT 2*, **1997**, 1183.

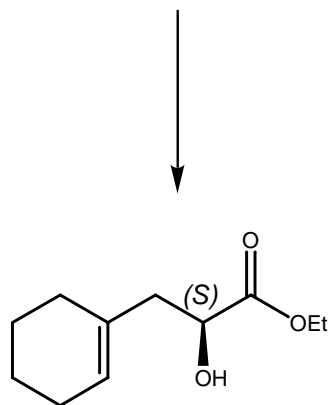
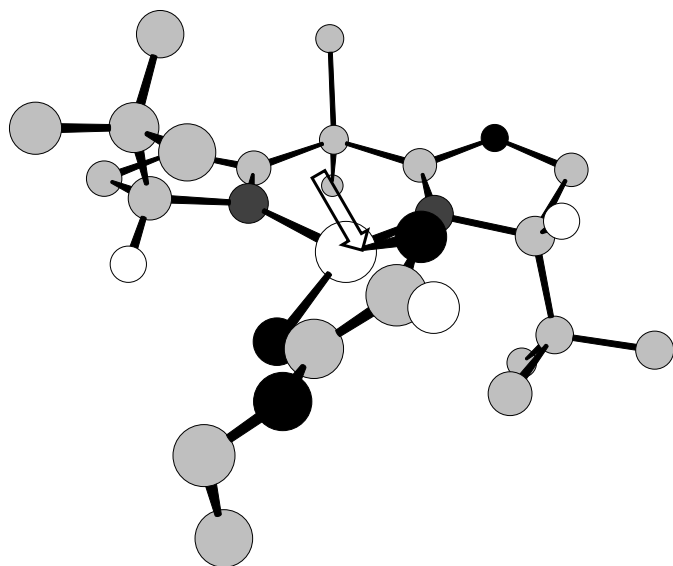
## Work from the Evans Groups



olefin	product <sup>a</sup>	catalyst	mol%	% yield	% ee	
		<b>2</b> <b>3</b>	1 10	90 99	97 ( <i>S</i> ) 87 ( <i>R</i> )	
		<b>2</b> <b>3</b>	1 10	83 92	96 ( <i>S</i> ) 92 ( <i>R</i> )	
		<b>2</b> <b>3</b>	1 10	97 99	93 ( <i>S</i> ) 89 ( <i>R</i> )	
		<b>2</b> <b>3</b>	1 10	95 97	96 ( <i>S</i> ) 76 ( <i>R</i> )	
		<b>2</b> <b>3</b>	1 10	89 81	96 ( <i>S</i> ) 92 ( <i>R</i> )	Regiochemistry 75 : 25 90 : 10
		<b>2</b> <b>3</b>	1 10	72 85	96 ( <i>S</i> ) 91 ( <i>R</i> )	one regioisomer
		<b>2</b> <b>3</b>	10 2	62 88	98 ( <i>S</i> ) 92 ( <i>R</i> )	one regioisomer
		<b>1</b> <b>3</b>	10 10	95 70	98 ( <i>S</i> ) 94 ( <i>R</i> )	<i>exo:endo</i> 86:14 95:5
		<b>1</b>	10	96	98 ( <i>S</i> )	<i>E:Z</i> 96 : 4

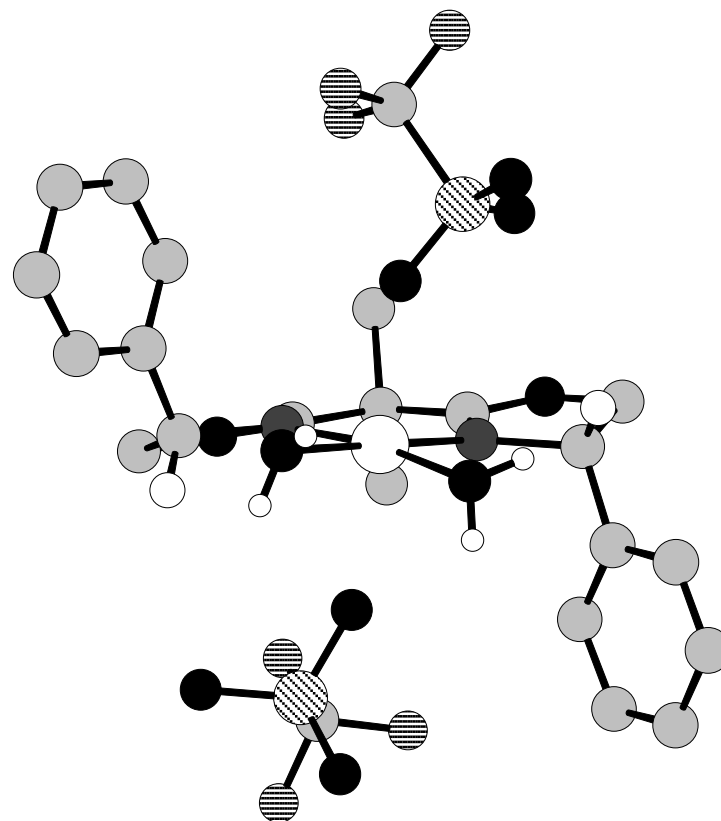
## Origins of Enantioselectivity in Cu Box Ene Reactions

**(*S,S*)-t-Bu Box Cu Glyoxylate (PM3<sup>tm</sup>)**



However, (*S,S*)-Ph-Box Cu (OTf)<sub>2</sub> gives (*R*) configured alcohols:

Tetrahedral Cu center??  
Jorgensen, JOC, 1995, 60, 5757.



**(*S,S*)-Ph Box Cu (OTf)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub> X-ray**