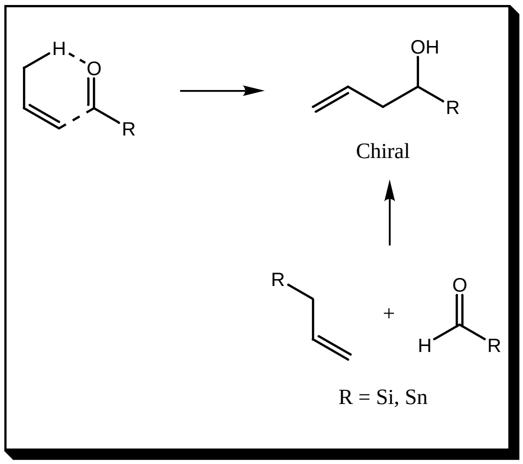
Asymmetric Ene Reaction

Evans Group Seminar
by
Steven Tregay

December 12, 1997

Seminar Topics



Covered in this Seminar:

Asymmetric Ene
(Metallo-Ene not covered)

Chiral Auxilaries

Catalytic/Promoted

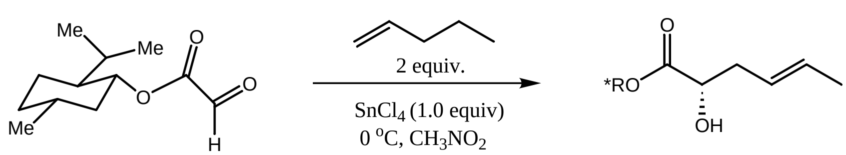
History:

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

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

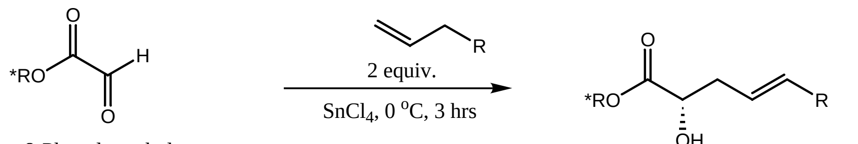


31 % ee, 87 % yield

Thermal reaction (160 ^{o}C) gave no induction

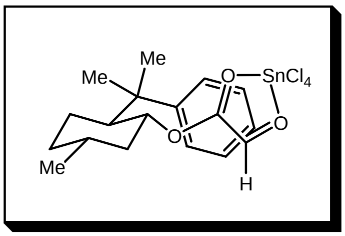
Achmatzowicz, JOC, **1972**, *37*, 964.

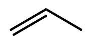
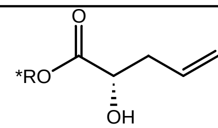
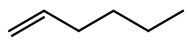
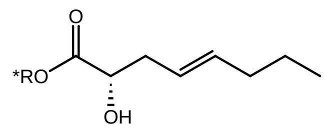
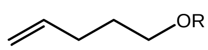
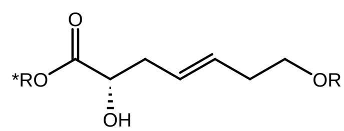
Ene reactions of 8-Phenylmenthol Glyoxylate Ester



*R = 8-Phenylmenthol

>97 % de
< 6 % *cis* olefin observed

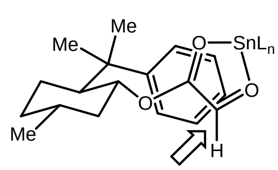


Alkene	Product	Yield
		99 %
		92 %
		R=H 100 % (2:1 *cis : trans)* R=OAc 59 % R=Bn 99 % R=TBS 89 %

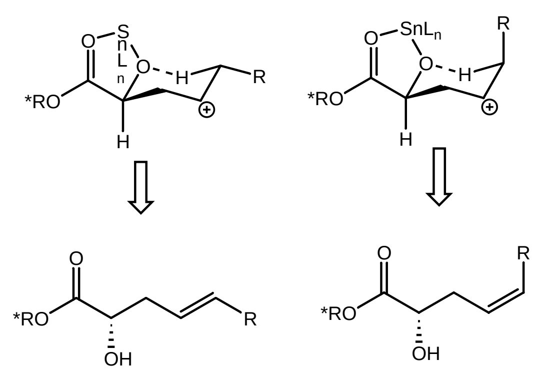
Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986,** *42,* 2993.

Mechanism for 1-Substituted Olefins

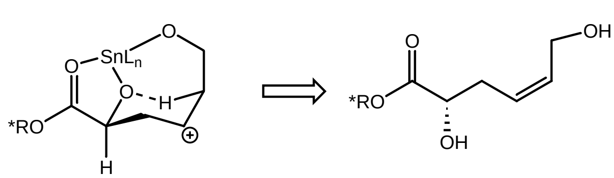
Absolute Configuration



Olefin Geometry

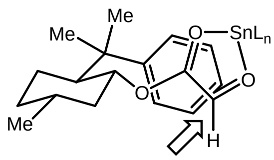


Competing Pathway for Free Hydroxyl

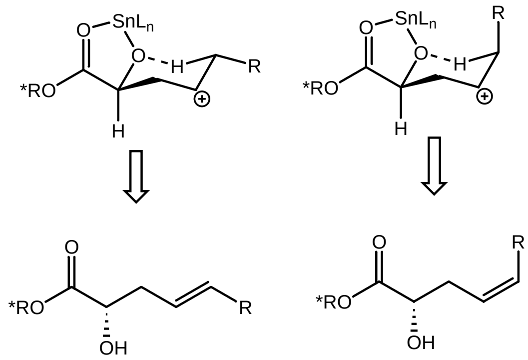


Mechanism for 1-Substituted Olefins

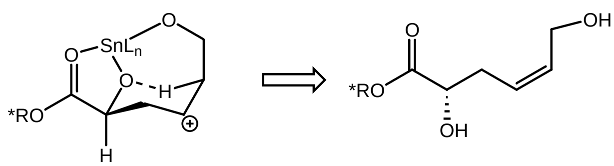
Absolute Configuration



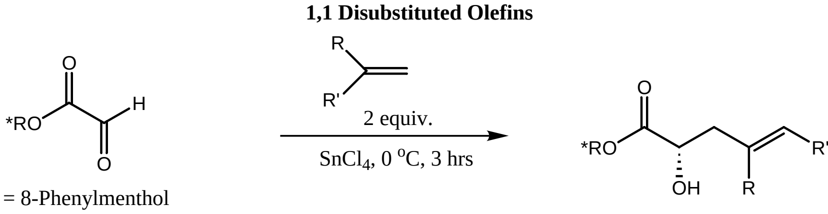
Olefin Geometry



Competing Pathway for Free Hydroxyl

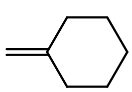
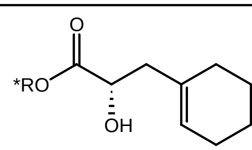
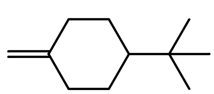
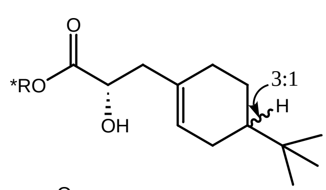
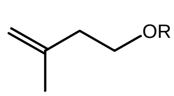
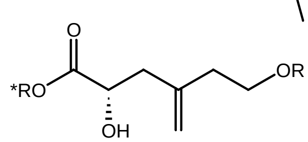


1,1 Disubstituted Olefins



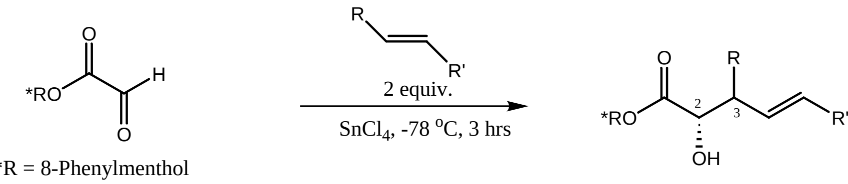
*R = 8-Phenylmenthol

>97 % de

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

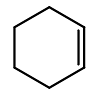
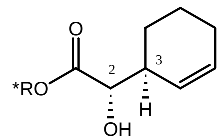
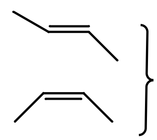
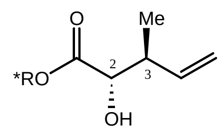
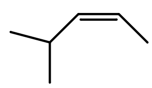
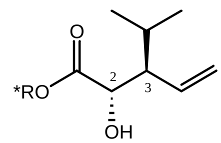
Whitesell, JCS CC, **1982**, 989.
Whitesell, Tetrahedron, **1986,** *42*, 2993.

1,2 Disubstituted Olefins



*R = 8-Phenylmenthol

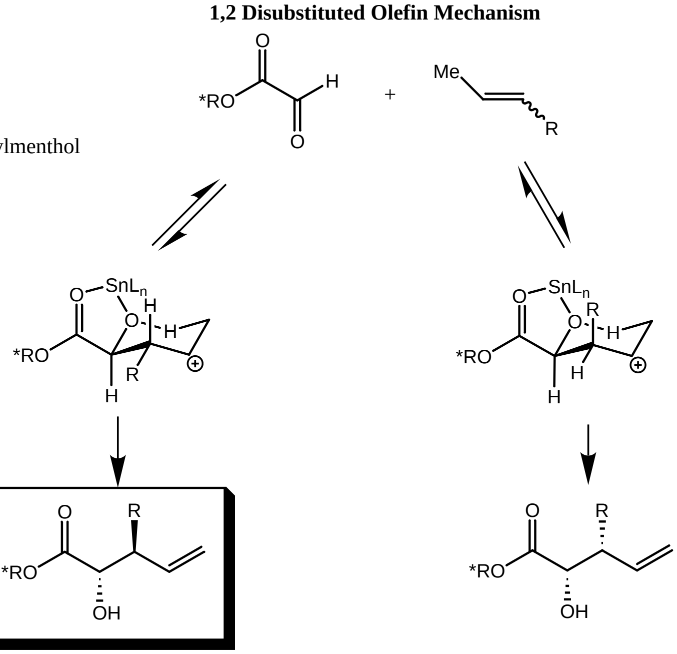
C-2 >97 % de

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

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

1,2 Disubstituted Olefin Mechanism

*R = 8-Phenylmenthol



R = Me

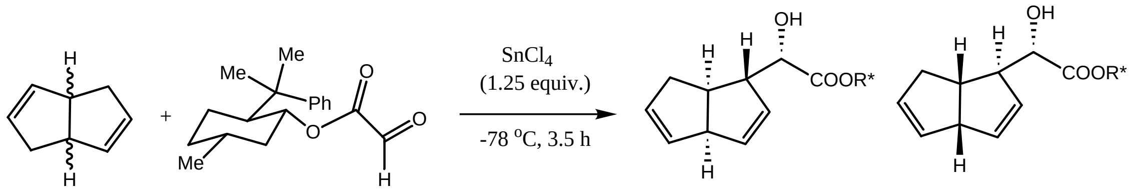
trans-butene 15 : 1
cis-butene 8 : 1

R = i-Pr

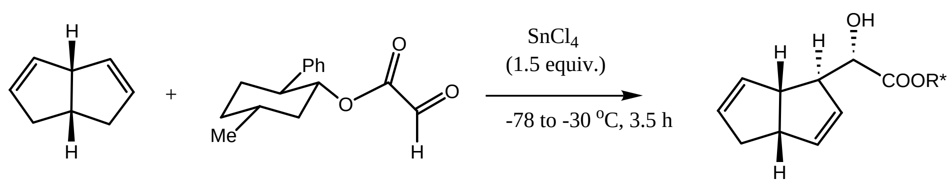
4-methyl-*cis*-2-pentene one compound

Note: *cis*-butene does not isomerize in presence of $SnCl_4$ or $SnCl_4$ / isopropyl alcohol at -78 ^oC
Isomerization does occur in the presence of gyloxylate

Asymmetric Desymmetrization using 8-Phenylmenthol Glyoxylate Ester



Excess 1 8 : 1 (72 % yield)



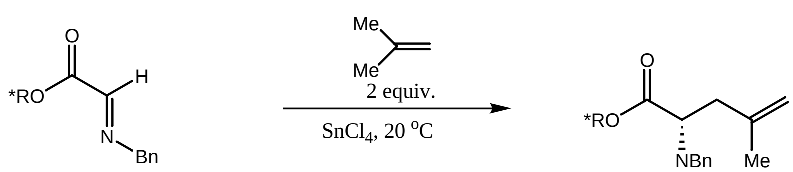
one diastereomer

(81 % yield)

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

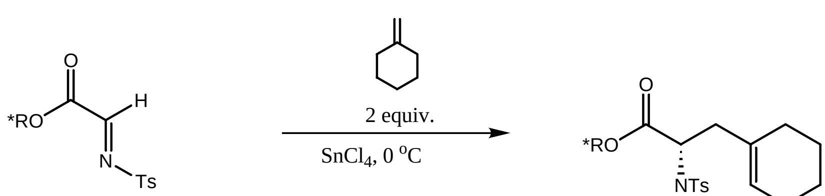
Note: 1 gives opposite bridgehead selectivity

Phenylmenthol Imine-Ene Reaction



*R = 8-Phenylmenthol

97 % de
76 % yield



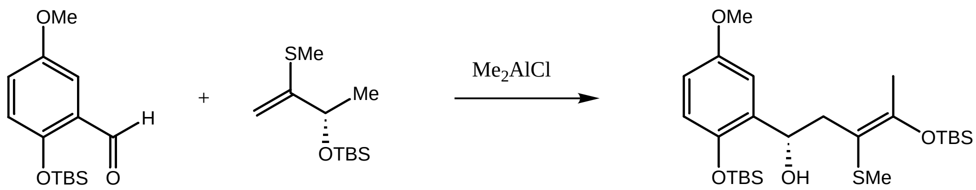
*R = 8-Phenylmenthol

> 98 % de
60 % yield

Use of Ts rather than Bn
was not discussed

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

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

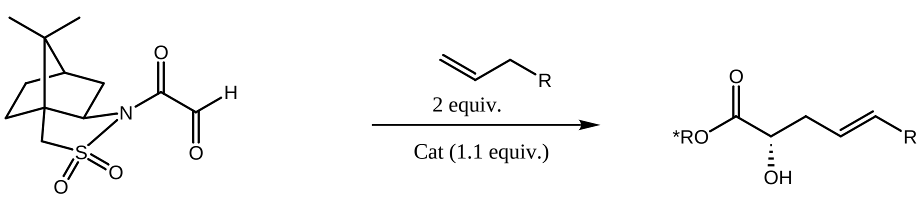


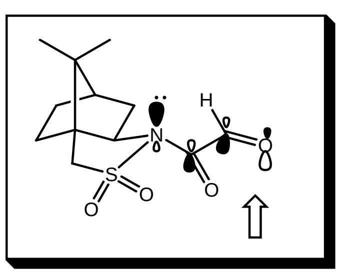
99 % ee
100 % yield

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



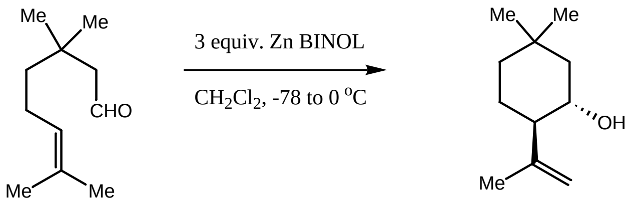


Most Reactive Conformation according to PM3 and *Ab initio* calculations
Chapuis, *Helv. Chim. Acta*, in preparation

R =	Catalyst	Temp (^{o}C)	% de	% Yield
Et	$SnCl_4$	-78	84 : 16	78
	$ZnBr_2$	5	90 : 10	50
n-Pr	$SnCl_4$	-78	75 : 25	93
	$ZnBr_2$	5	89 : 11	43

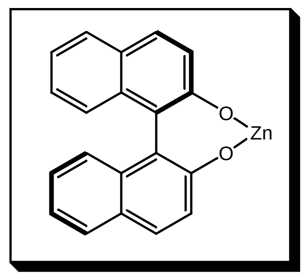
Jurczak, *Tet.: Asymm.*, **1997**, *8*, 1741.

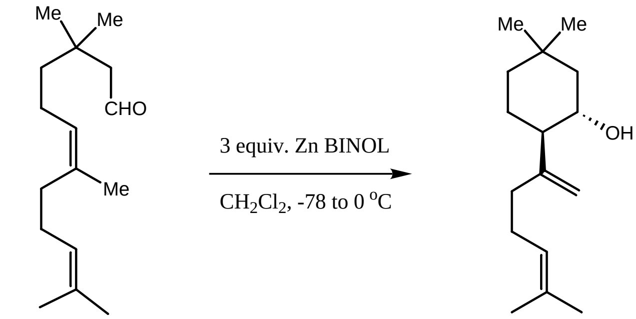
Zn BINOL Promoted Intramolecular Ene Cyclizations



88 % ee
86 % yield

Note: using 1.5 equiv. reagent lowers % ee





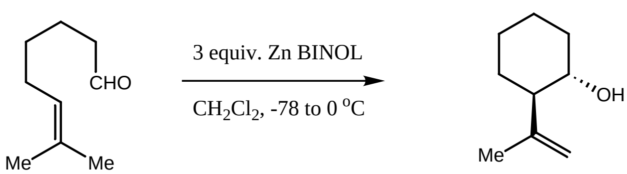
88 % ee
89 % yield

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

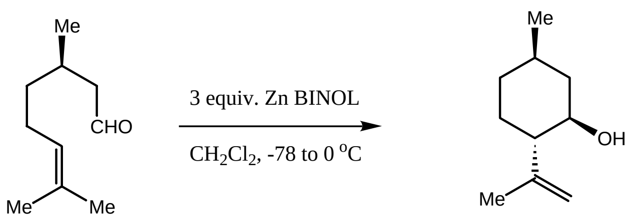
(*Z*)- methylfarnesal

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

Zn BINOL Promoted Intramolecular Ene Cyclizations



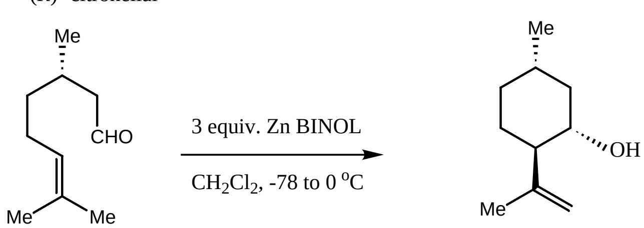
0 % ee
31 % yield



one compound

(*R*)- citronellal (*R*)-isopulegol

Note : $ZnBr_2$ gives 95:5 ratio of products of idenical configuration
See: Nakatani, *Syn. Comm.*, ***1978***, *147*.

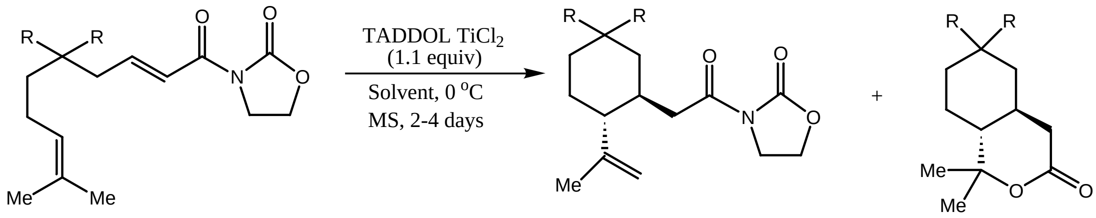


one compound

(*S*)- citronellal (*S*)-isopulegol

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

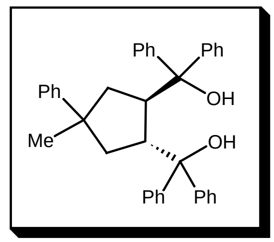
TADDOL Promoted Intramolecular Ene



1

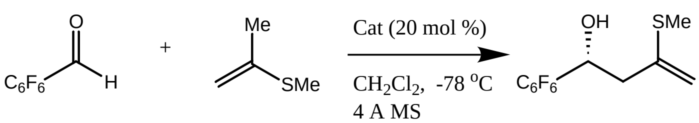
2

R =	Solvent	**1** % ee	(% yield)	**2** % ee	(% yield)
H	Toluene (20 days)	ND	(17)	ND	(37)
Me	Toluene	82	(39)	92	(36)
	1,3,5 Trimethylbenzene	86	(32)	>98	(37)
	$CFCl_2CF_2Cl/ CH_2Cl_2$	97	(47)	ND	(16)
$-SCH_2CH_2S-$	$CFCl_2CF_2Cl/ CH_2Cl_2$	84	(ND)	>98	(ND)

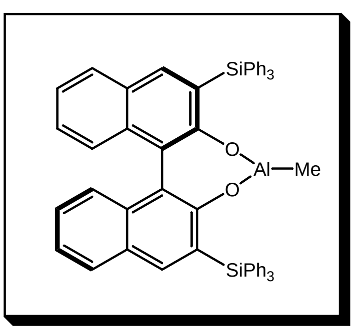


Narasaka, *Chem. Lett.*, **1988**, 1609.

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



88 % ee
88% yield



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

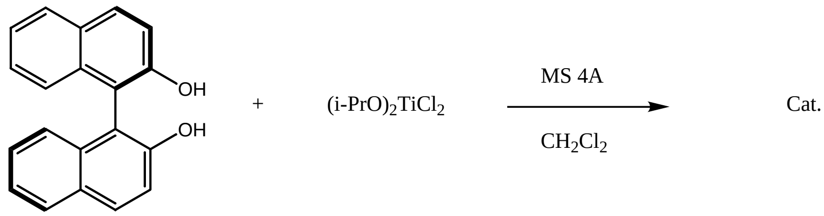
Use of MS is required for catalytic reaction

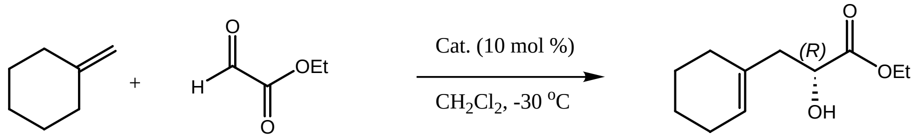
Use of 3-3'-diphenylbinaphthol complex gave 0 % ee

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

$(i\text{-}PrO)_2TiCl_2$ (*R*)-BINOL Catalyzed Ene Reaction

Preliminary Result:

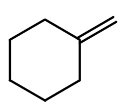
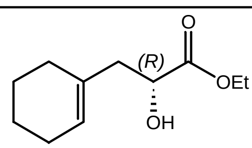
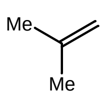
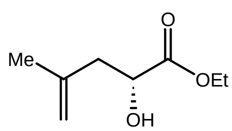
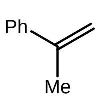
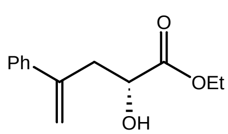
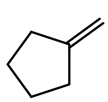
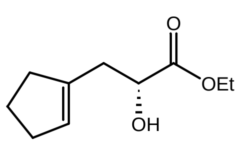




86 % ee
82 % yield

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

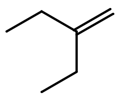
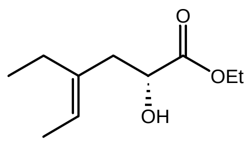
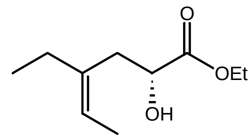
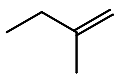
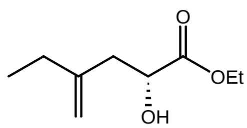
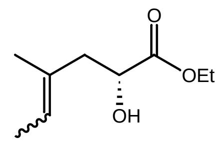
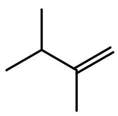
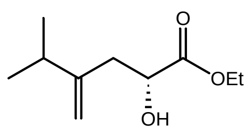
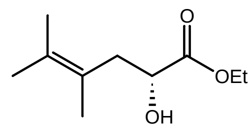
$(i\text{-}PrO)_2TiBr_2$ (*R*)-BINOL Catalyzed Ene Reaction : 1,1 Disubstituted

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

Reaction conditions: Ethyl glyoxylate, -30 ^{o}C, 3 hr, MS, CH_2Cl_2

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

$(i\text{-}PrO)_2TiBr_2$ (*R*)-BINOL Catalyzed Ene Reaction : More 1,1 Disubstituted

Olefin	Products				
		*E* 91 % yeild 98 % ee		*Z* 9 % yeild >90 % ee	
		39 % yeild 91% ee		*E* 57% yeild >98 % ee	*Z* 4% yeild >90 % ee
		83 % yeild 92% ee		17% yeild >98 % ee	

Reaction conditions: Ethyl glyoxylate, 5 -10 mol % cat., -30 ^{o}C, 3 hr, MS, CH_2Cl_2

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

Importance of Molecular Sieves

$BINOL\text{-}(OH)_2$ + $(i\text{-}PrO)_2TiCl_2$ —(Additive, CH_2Cl_2)→ Method **A**

$BINOL\text{-}(OLi)_2$ + $TiCl_4$ —(Additive, CH_2Cl_2)→ Method **B**   ref: Reetz, *Chem. Ind. (London)*, **1986**, 824.

For reaction of α-methyl Styrene and ethyl gloxylate (CH_2Cl_2, -30 ^{o}C)

Method **A**	Additive 4 A MS (g/mmol)	Yield	% ee
	5	100	97
	0	81	10
	5 then filter	96	97

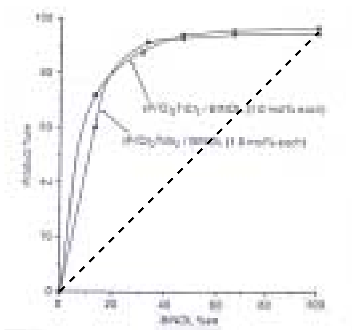
Note : By ^{13}C NMR no Ti BINOL complexation occurs until MS are added.
$(i\text{-}PrO)_2TiCl_2$ is a viable catalyst for the reaction.

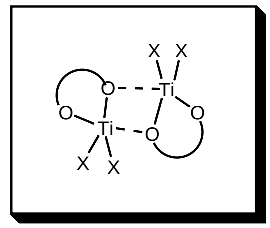
Method **B**	Additive i-PrOH	Additive 4 A MS (g/mmol)	Yield	% ee
	0	0	95	93
	10 mol %	0	90	95
	0	5	100	95
	10 mol %	5	98	96

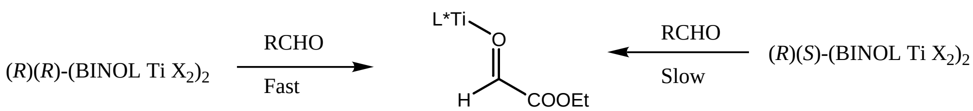
Note : MeOH, t-BuOH give similar results

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

NonLinear Effect in the(i-PrO)$_2$TiX$_2$ BINOL Catalyzed Ene Reaction







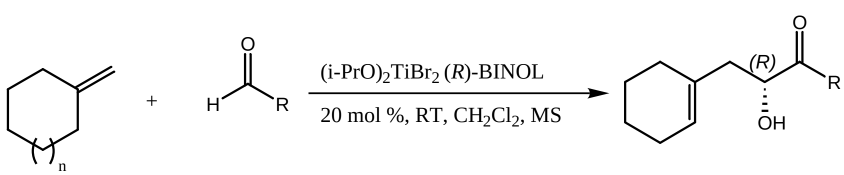
For chiral poisoning of racemic BINOL Complxes see:

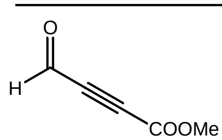
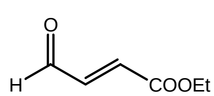
Faller, TL, **1996**, *37*, 3449.
Mikami, *Nature*, **1997,** *385*, 613.

Note : For X-ray crystal structure of dimeric ((PhO)$_2$TiCl$_2$)$_2$ See: Watenpaugh, *Inorg. Chem.* **1966**, *5*, 1782.

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

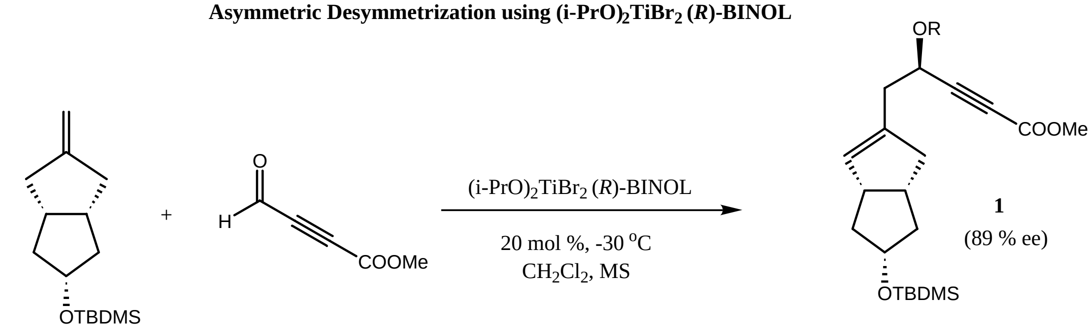
(i-PrO)$_2$TiBr$_2$ (*R*)-BINOL Catalyzed Ene Reaction : Other Enophiles



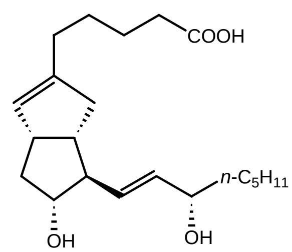
Enophile	n=	% Yield	% ee
	0	85	87
	1	70	94
	0	80	72
	1	60	86

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

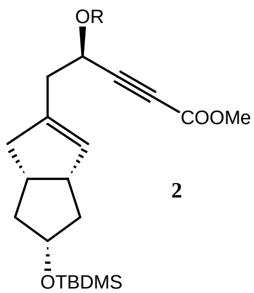
Asymmetric Desymmetrization using (i-PrO)$_2$TiBr$_2$ (*R*)-BINOL



1
(89 % ee)



isocarbacyclin

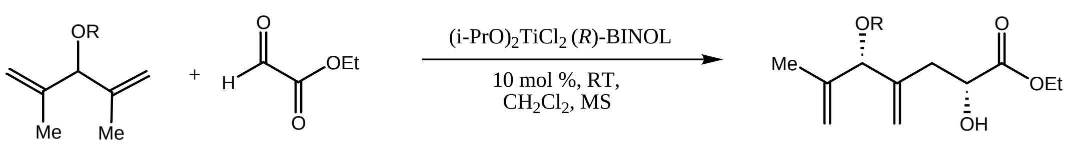


2

1 : 2 ratio 92 : 8

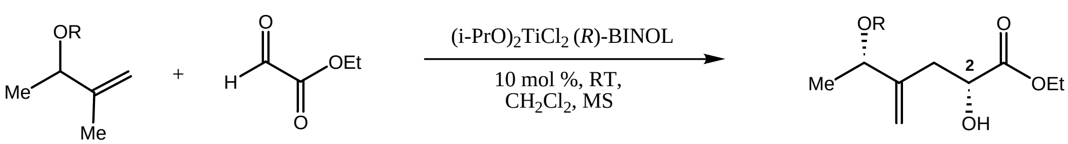
Mikami, TL, **1996**, *47*, 8515.
Mikami, Synlett, **1995**, 29.

Asymmetric Desymmetrization / Resolution using (i-PrO)$_2$TiCl$_2$ (*R*)-BINOL



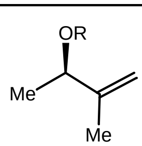
R = Dimethylthexylsilyl

> 99 % *syn*
(97 % ee)



1

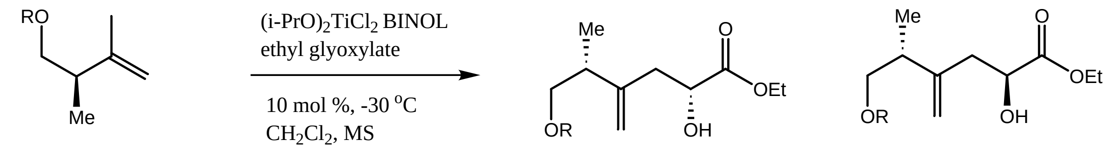
> 97% *syn*
(>95 % ee)



Catalyst	Product
(i-PrO)$_2$TiCl$_2$ (*S*)-BINOL	*ent*-**1** (>99 % *syn*, 71 % yield)
(i-PrO)$_2$TiCl$_2$ (*R*)-BINOL	*ent*-**1** (50 : 50 at C-2, 31 % yield)

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

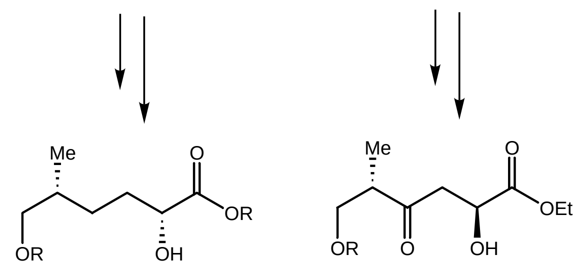
Synthesis of C_{10} - C_{15} and C_{30}- C_{35} fragments of Rapamycin



R= Dimethylthexylsilyl

(*R*)-BINOL (83 % yield)	>99	<1
(*S*)-BINOL (61 % yield)	3	97

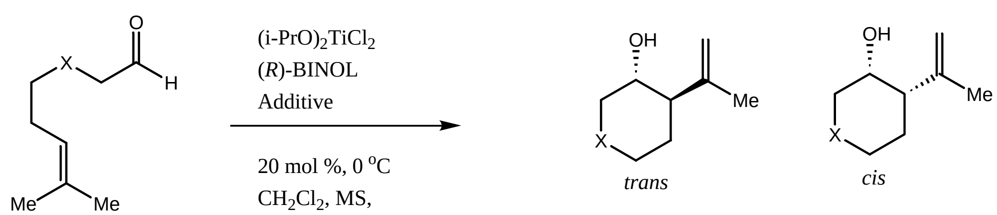
Mikami, TL, **1994**, *35*, 7793.

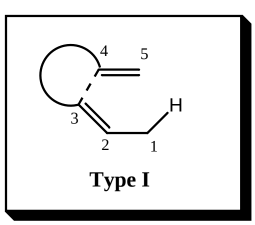


C_{10} - C_{15} fragment

C_{30}- C_{35} fragment

$(i\text{-}PrO)_2Ti(ClO_4)_2$ (*R*)-BINOL Catalyzed {3, 4} *exo, exo* Intramolecular Ene Reaction

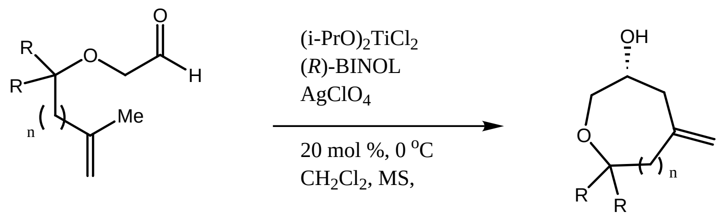


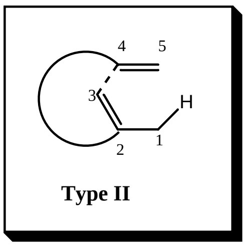


X =	Additive	time	% Yield	Ratio *trans : cis*	*trans* % ee
O	none	24 h	73	47 : 53	70
O	$AgClO_4$	24 h	50	80 : 20	84
$-CH_2-$	$AgClO_4$	48 h	66	69 : 31	55

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

(i-PrO)$_2$Ti(ClO$_4$)$_2$ (*R*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction

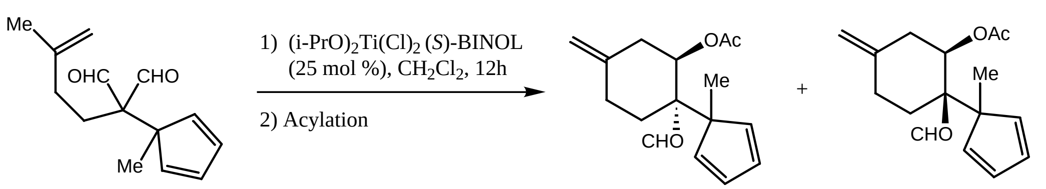




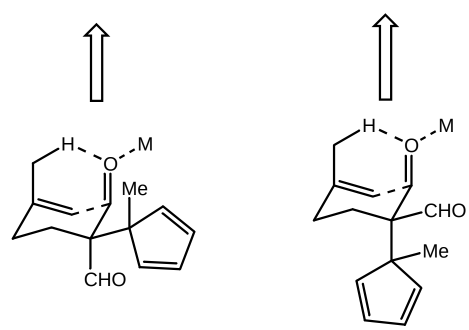
n=	R=	% yield	% ee
0	H or Me	NR	--
1	H	43	91
1	Me	40	82

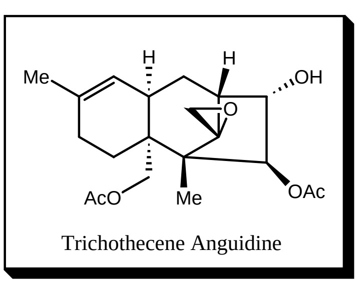
Mikami, TL, **1991**, *32*, 6571.
Mikami, *Tet. :Asymm.*, **1991,** *2*, 1403.

(i-PrO)$_2$Ti(Cl)$_2$ (*S*)-BINOL Catalyzed
{2, 4} *exo, exo* Intramolecular Ene Reaction



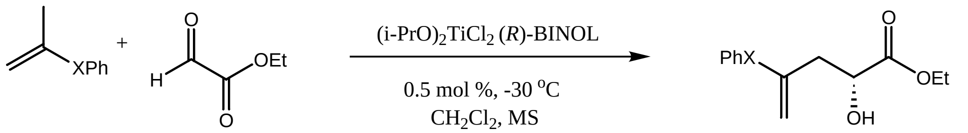
4.5 (38 % ee) : 1



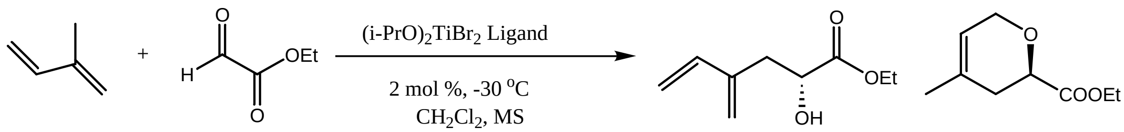


Ziegler, JACS, **1990**, *112*, 2749.

Approaches toward Ipsdienol

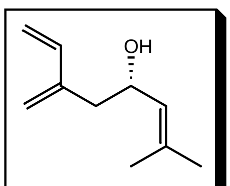


X= S	X= Se
94 % yield >99 % ee	95 % yield >99 % ee

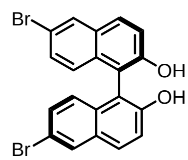


Ene

Hetero D.A.



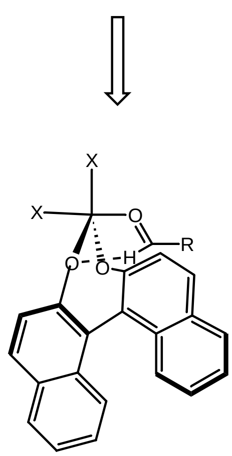
(*R*)-Ipsdienol

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

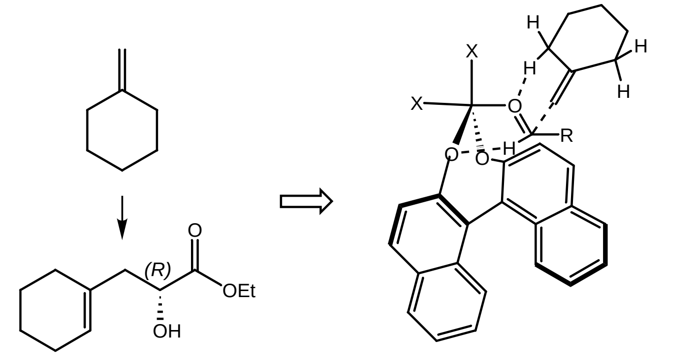
Mikami, JCS CC, **1995**, 2391.
Mikami, JCS CC, **1993**, 327.

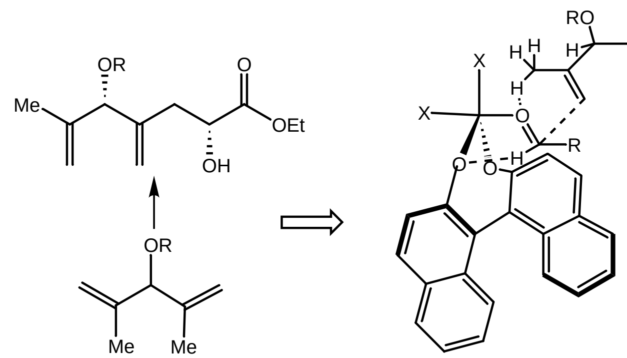
Corey's Model for Ti BINOL Ene Reactions

BINOL Ti X_2
Aldehyde Complex



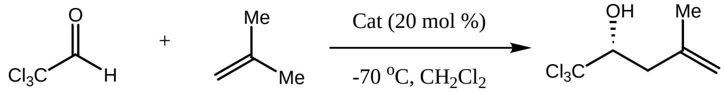
Corey, TL, **1997**, *38*, 6513.





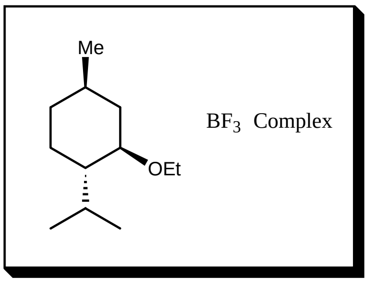
R= Dimethylthexylsilyl

BF_3 Menthylethyl Etherate catalyzed Ene reaction



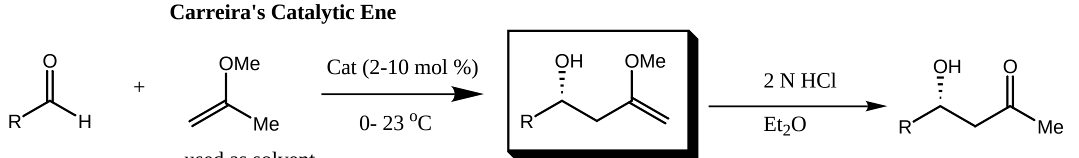
2 equiv.

22 % ee
55 % yield



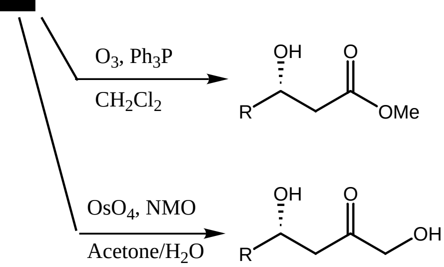
Demir, *Syn. Comm.* **1994**, *24*, 137.

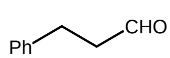
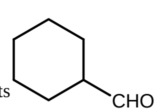
Carreira's Catalytic Ene



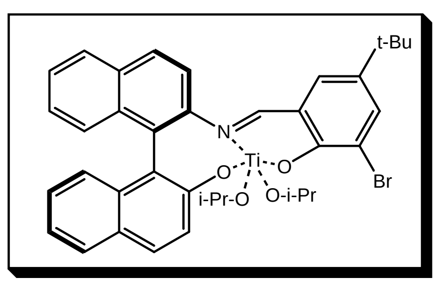
used as solvent

~ $50 per L
b.p. 34- 36 °C



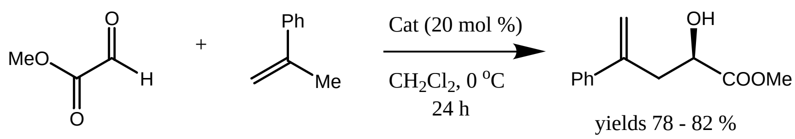
Aldehyde	% ee[a]	% yield
$Ph(CH_2)_3$–≡–CHO	98	99
$TBSOCH_2$–≡–CHO	93	85
Ph–≡–CHO	91	99
	90	98
PhCHO	66	83
Only α-branched aldehyde which reacts 	75	79

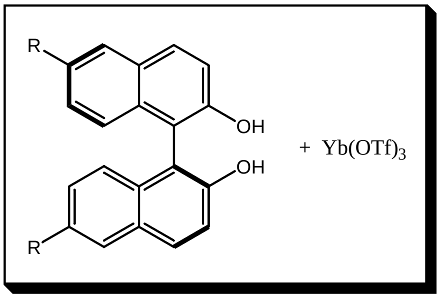
[a] % ee detrmind by NMR analysis of (*S*)-MPTA ester of methyl ketone



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

$Yb(OTf)_3$ BINOL Catalyzed Ene Reaction

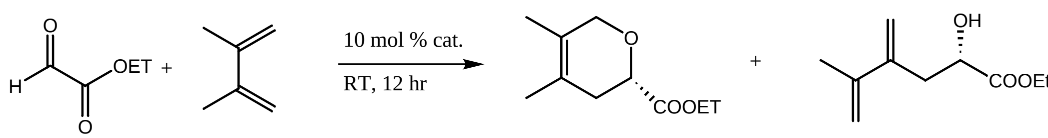


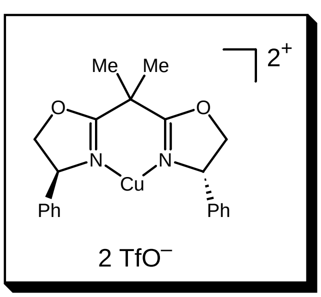


Ligand R=	% ee
H	12
Br	38
Ph	25
–≡–TMS	29

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

Jorgensen's Ene byproducts



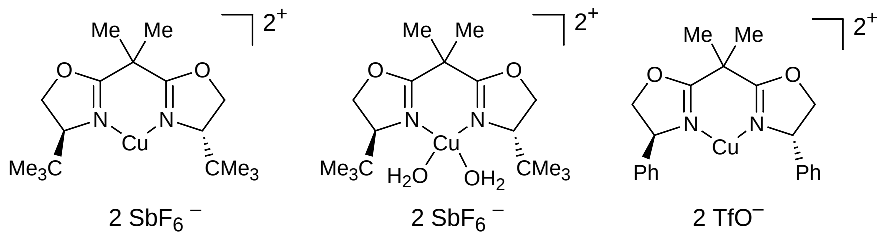


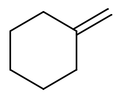
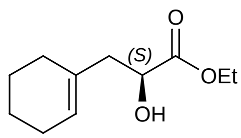
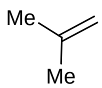
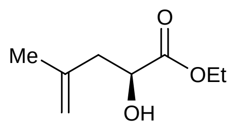
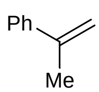
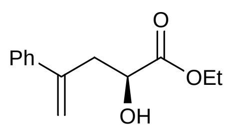
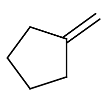
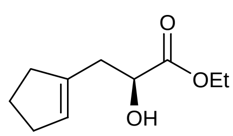
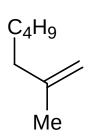
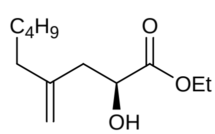
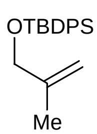
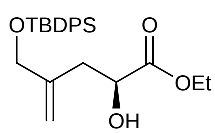
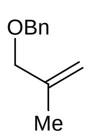
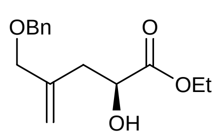
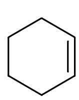
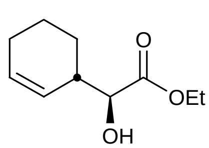
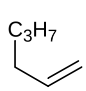
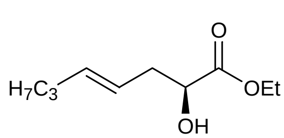
Solvent	Diels-Alder % ee	Ene Product % ee	DA :Ene Ratio
CH_2Cl_2	85	83	1 : 1.8
CH_3NO_2	90	78	1 : 0.8

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

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

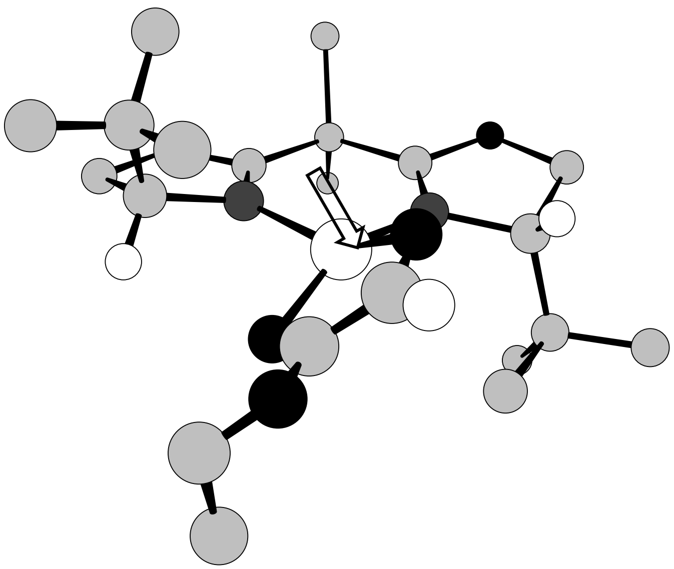
Work from the Evans Groups

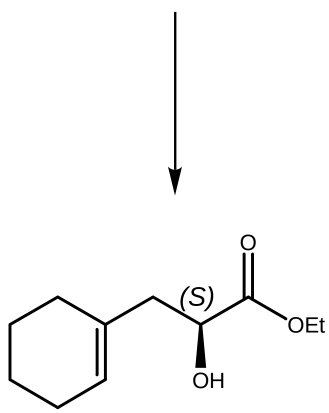


olefin	product[a]	catalyst	mol%	% yield	% ee	
		**2** **3**	1 10	90 99	97 (*S*) 87 (*R*)	
		**2** **3**	1 10	83 92	96 (*S*) 92 (*R*)	
		**2** **3**	1 10	97 99	93 (*S*) 89 (*R*)	
		**2** **3**	1 10	95 97	96 (*S*) 76 (*R*)	
		**2** **3**	1 10	89 81	96 (*S*) 92 (*R*)	Regiochemistry 75 : 25 90 : 10
		**2**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

Origins of Enantioselectivity in Cu Box Ene Reactions

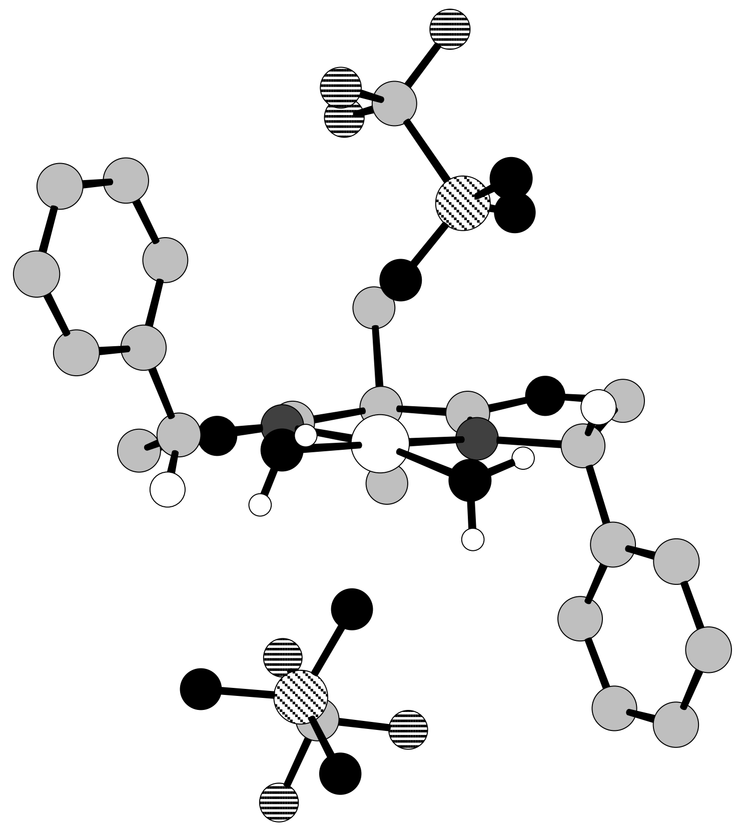
(*S,S*)-t-Bu Box Cu Glyoxylate (PM3[tm])





However, (*S*,*S*)-Ph-Box Cu $(OTf)_2$ gives (R) configured alcohols:

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



(*S*,*S*)-Ph Box Cu $(OTf)_2(H_2O)_2$ X-ray