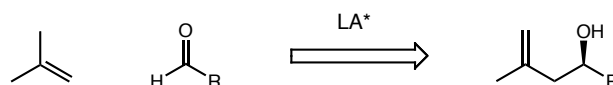
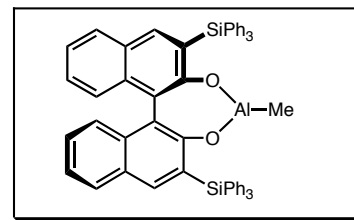
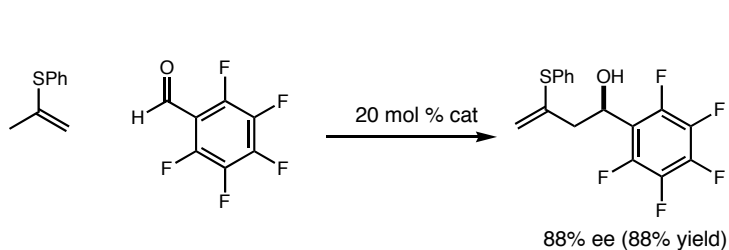


Enantioselective Catalysis of the Carbonyl-Ene Reaction



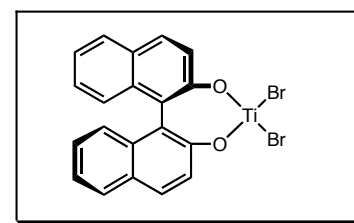
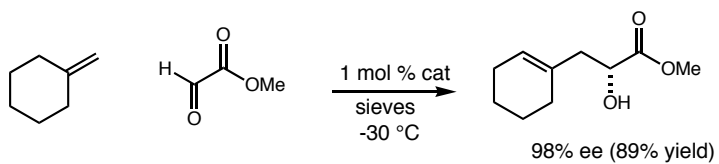
Nick Paras
Heathcock/MacMillan Group Meeting
March 7, 2000

Enantioselective Ene Reactions: Yamamoto and Mikami



H. Yamamoto, *Tet. Lett.*, **1988**, 3967.

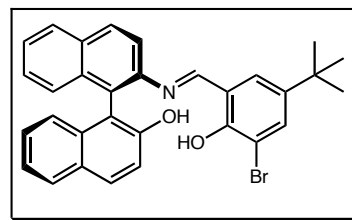
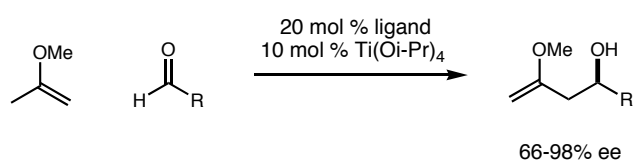
- Scope limited to highly electron deficient aromatic aldehydes or chloral



K. Mikami, *JACS*, **1989**, 1941.

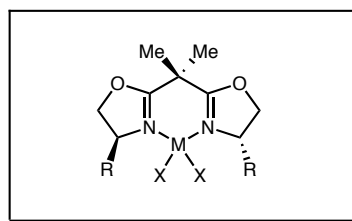
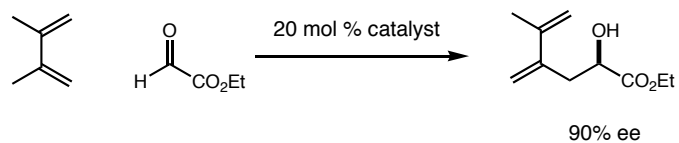
- Variety of 1,1-disubstituted olefins are effective

Enantioselective Ene Reactions: Carreira and Jørgensen



E. Carreira, *JACS*, **1995**, 3649.

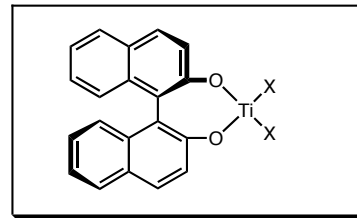
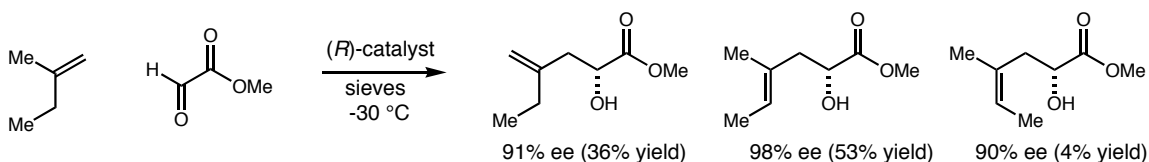
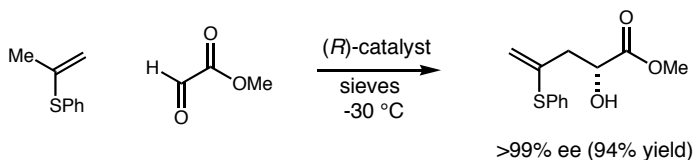
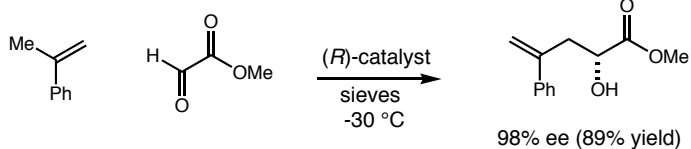
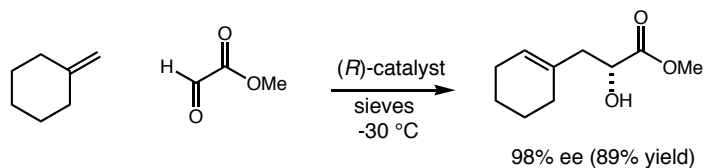
- Highest yields and ee's achieved with propargylic aldehydes.



K. Jørgensen, *JOC*, **1995**, 5759.

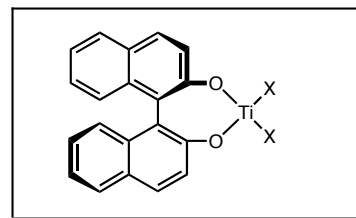
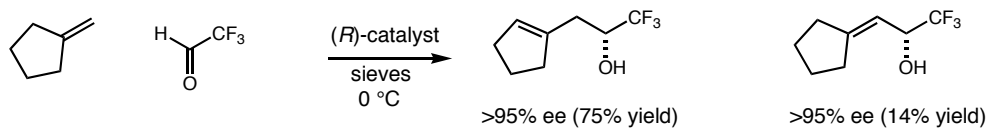
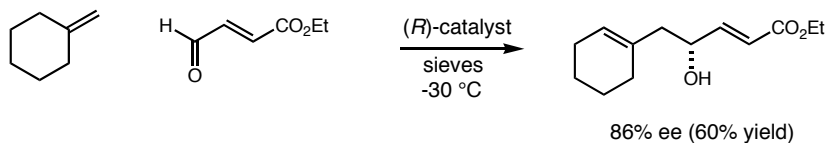
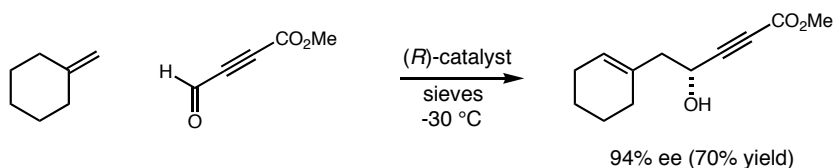
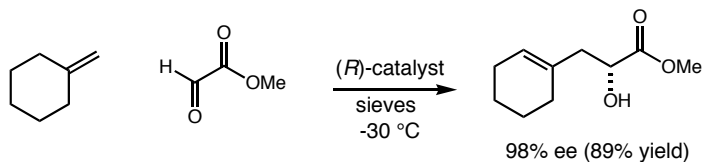
- Ene side products observed in up to 40% yield while attempting HDA.

Scope of Mikami Titanium BINOL Ene Reaction: Olefins



JACS, **1989**, 1941.
JACS, **1990**, 3949.
Chem. Comm., **1993**, 327.

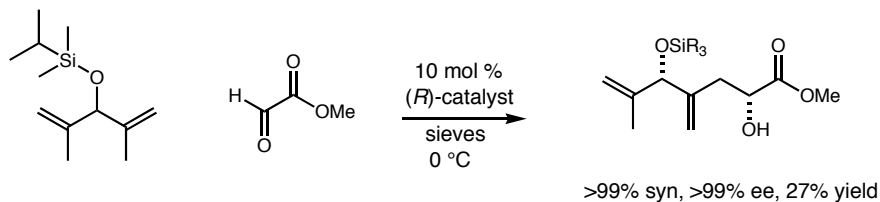
Scope of Mikami Titanium BINOL Ene Reaction: Electrophile



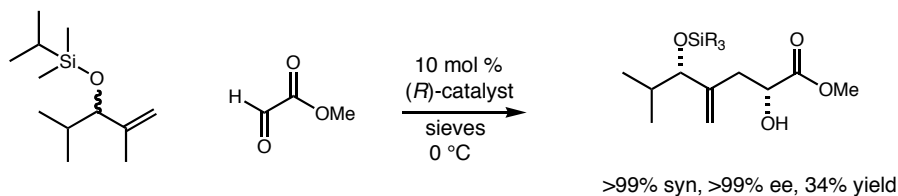
JACS, **1990**, 3949.
Tet. Lett., **1996**, 8515.
Tetrahedron, **1996**, 85.

Mikami Ene with New or Pre-existing Stereocenters on Nucleophile Component

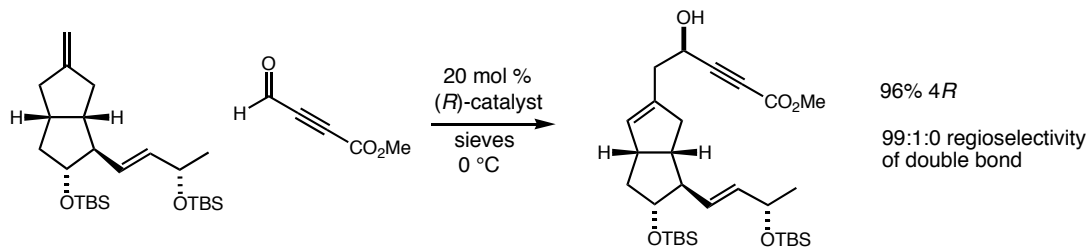
Desymmetrization:



Kinetic Resolution:

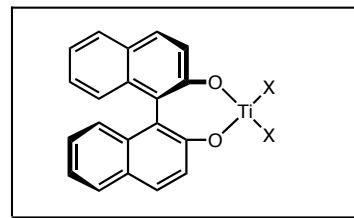


Selective Proton Abstraction:



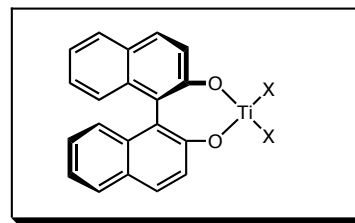
JACS, 1992, 6566.
Tet. Lett., 1996, 8515.

Understanding the BINOL-Ti Complex:
Positive Non-Linear Effect

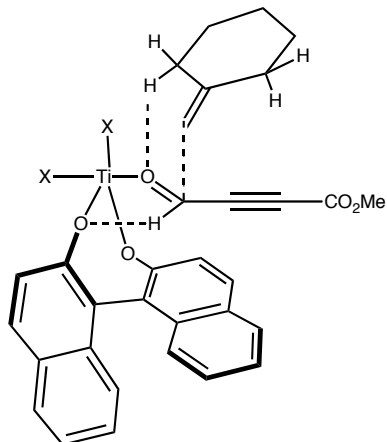


Tetrahedron, 1992, 5671.
Pur. Appl. Chem., 1996, 639.

*Understanding the BINOL-Ti Complex:
Corey Hydrogen Bond Model*

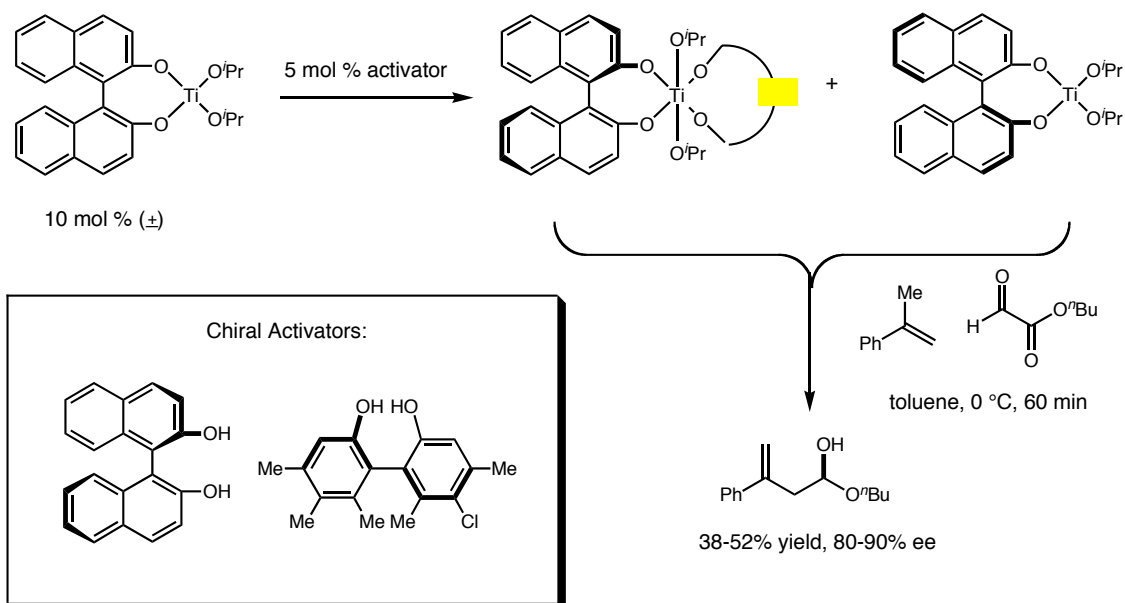


Tet. Lett., **1997**, 6513.



- Consistent with selectivity in monodentate electrophiles.
- TS organization based on association between BINOL oxygen and formyl hydrogen.
- Distorted trigonal bipyramidal Ti center with apical substituents being the coordinated aldehyde and the most electronegative of the remaining ligands.

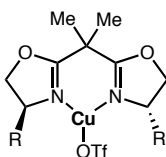
Understanding the BINOL-Ti Complex: Chiral Activation



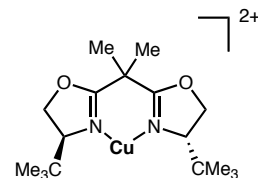
- (R,R) "Homo"Dimer shown to be up to 26 times faster than mono-BINOL complex.

Bis(oxazoline) & Pybox Complexes Are Valuable Catalysts...

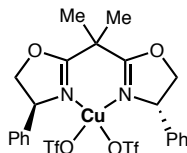
■ Cyclopropanation
JACS, **113**, 726 (1991)



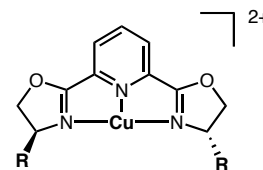
■ DA Cycloaddition
JACS, **115**, 6460 (1993)
Angew. Chem. Int. Ed., **34**, 798 (1995)



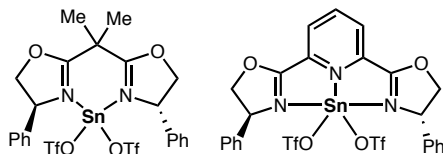
■ Aziridination
JACS, **115**, 5328 (1993)



■ Aldol Addition
JACS, **118**, 5814 (1996)
JACS, **119**, 7893 (1997)



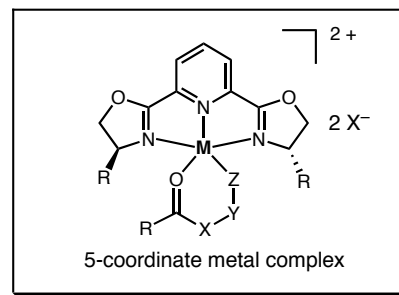
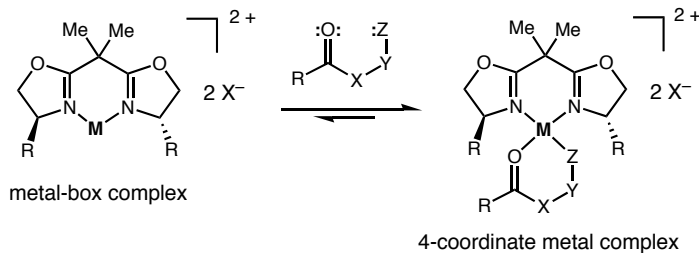
■ Anti-Aldol Addition
JACS, **119**, 10859 (1997)



Later incarnations:

Glyoxylate Ene Reactions
 Hetero Diels-Alder Reactions
 Enol Amination Reactions
 Michael Addition Reactions

Chelating Substrates for Chiral Lewis Acids

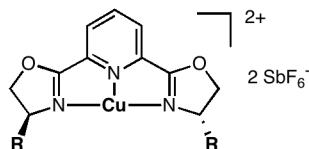
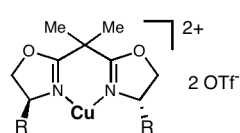
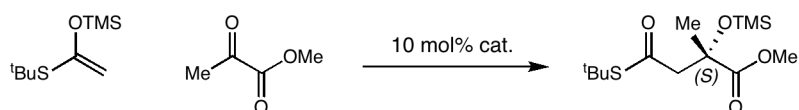


- Two point binding gives better organization about the metal center.
- Less ambiguity in understanding nature of catalyst-substrate complexation.
- Increased functionality allows greater elaboration of the products.

Readily Changed Variables

metal center:	Cu(II), Sn(II)
counterion X:	TfO ⁻ , SbF ₆ ⁻
Ligand coordinacy:	2 (box), 3 (pybox)
Ligand Substituent (R):	R = Ph, Bn, ⁱ Pr, ^t Bu

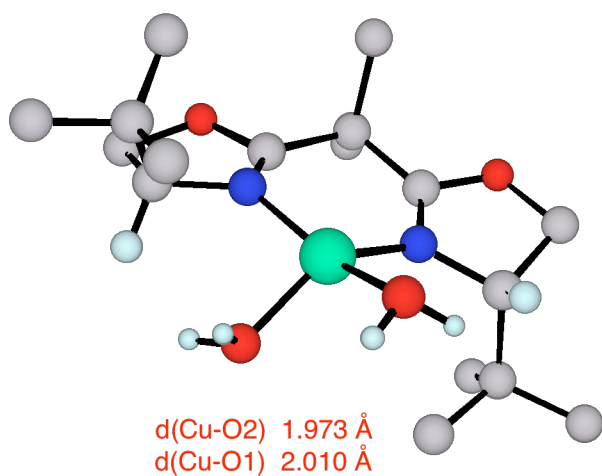
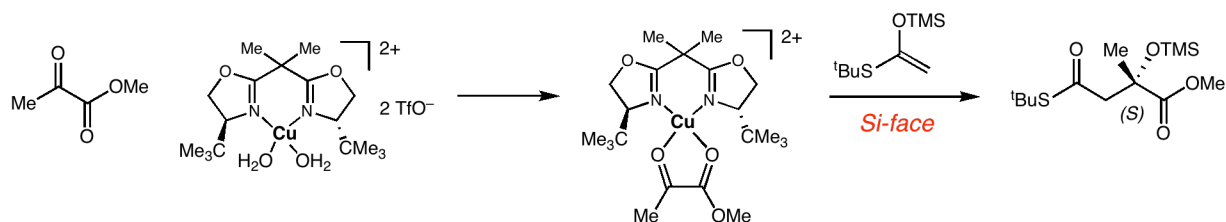
Catalysis of the Pyruvate Aldol Reaction



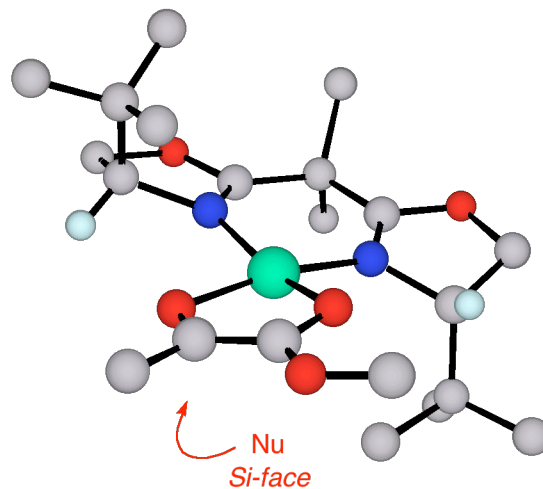
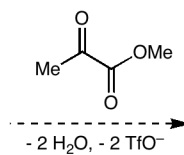
<i>R</i>	time/ <i>T</i>	<i>ee</i>	<i>R</i>	time/ <i>T</i>	<i>ee</i>
R = Ph	1.5 h/-78 °C	43%	R = Ph	15 min/-78 °C	62%
R = Bn	1.5 h/-78 °C	10%	R = Bn	15 min/-78 °C	77%
R = <i>i</i> Pr	1.5 h/-78 °C	23%	R = <i>i</i> Pr	15 min/-78 °C	95%
R = <i>t</i> Bu	30 min/-50 °C	98%	R = <i>t</i> Bu	2 h/-50 °C	4%

Drs. Christopher Burgey
and Marisa Kozlowski

Extrapolated Bis(oxazoline)Cu(2+)-Pyruvate Structure



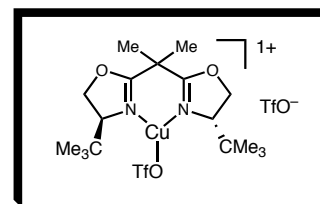
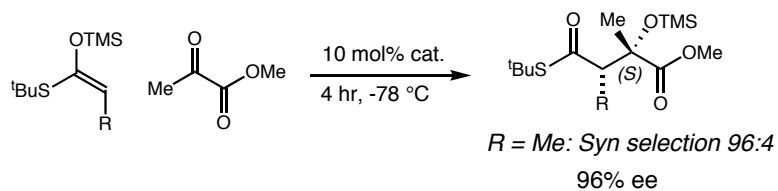
X-ray structure



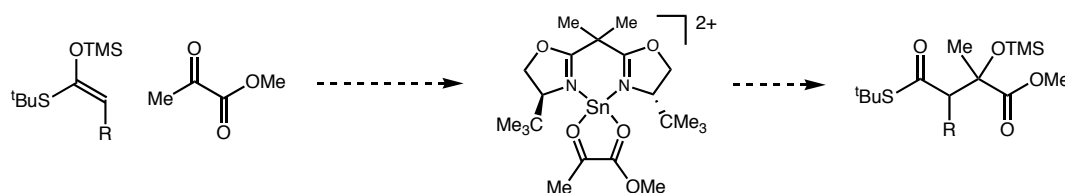
PM3tm calculated structure

Catalysis in Aldol Additions to Pyruvate Esters

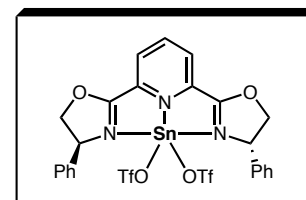
■ The analogy:



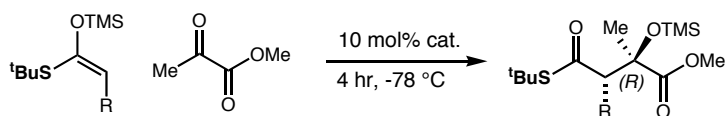
■ The extension:



Tin(II) Catalyzed Addition Reactions to Pyruvate

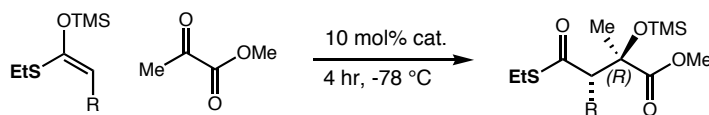


■ ^tButyl thio silylketene acetals



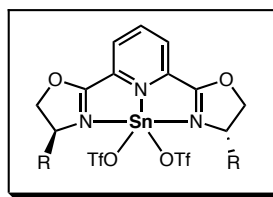
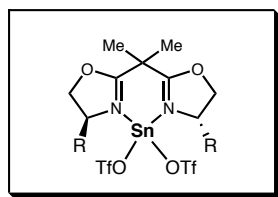
<i>R</i>	<i>anti:syn</i>	<i>anti ee</i>
<i>R</i> = Me	99:1	99%
<i>R</i> = Et	98:2	98%
<i>R</i> = ⁱ Bu	99:1	99%

■ Ethyl thio silylketene acetals

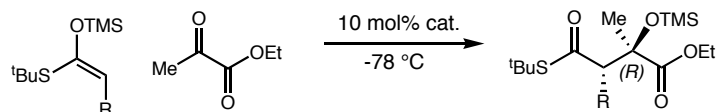


<i>R</i>	<i>anti:syn</i>	<i>anti ee</i>
<i>R</i> = Me	95:5	92%
<i>R</i> = Et	99:1	97%
<i>R</i> = ⁱ Bu	99:1	97%

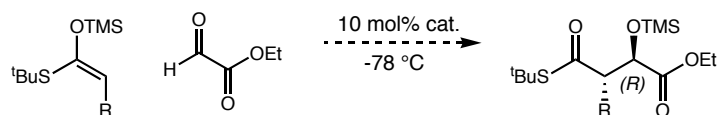
Extending the Aldol Additions to Glyoxylate



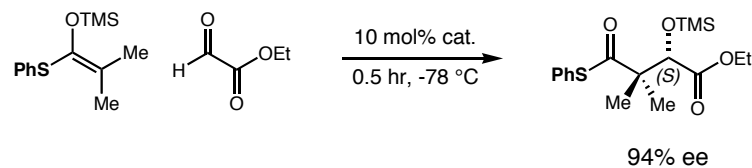
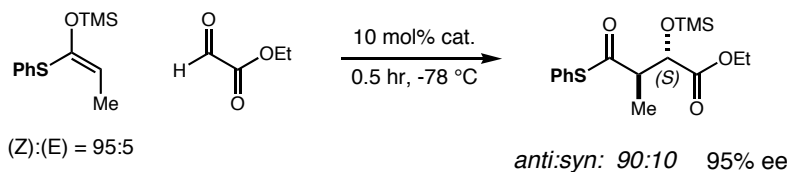
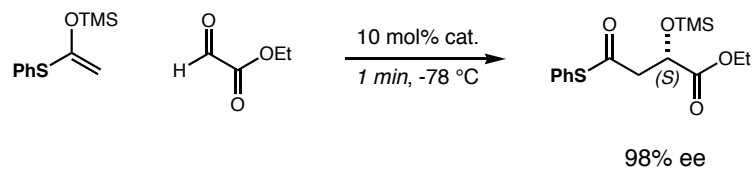
■ The analogy:



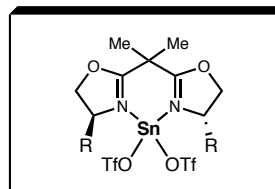
■ The prediction:



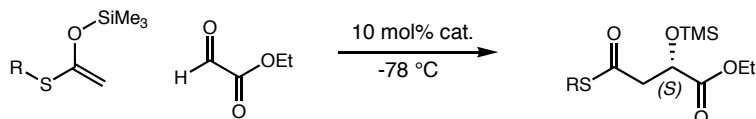
Sn(II) Catalysts are Effective in Anti Aldol Reactions: Addition to Glyoxylates



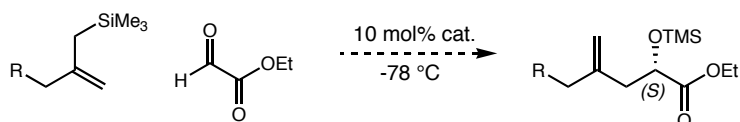
Allylsilane Additions to Glyoxylate Esters



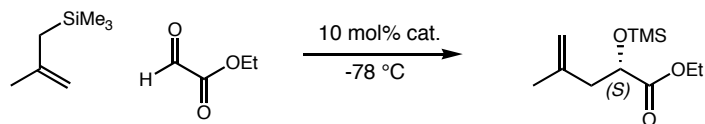
■ The analogy:



■ The extension:

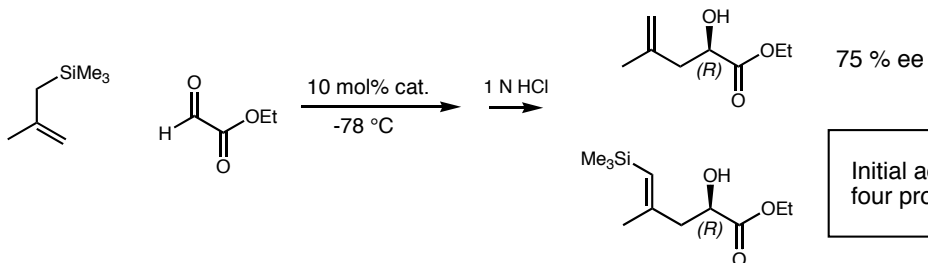
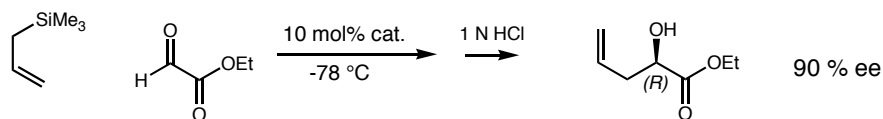
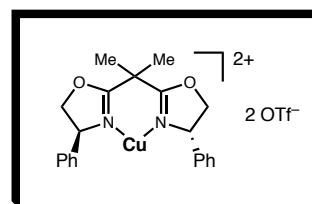


■ The result:



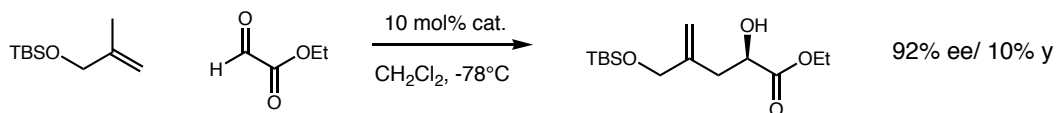
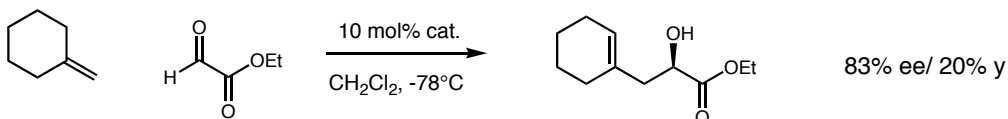
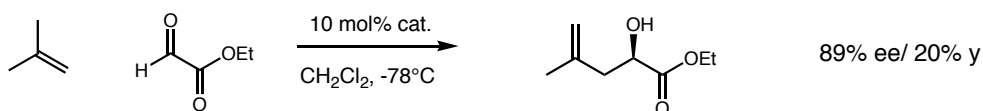
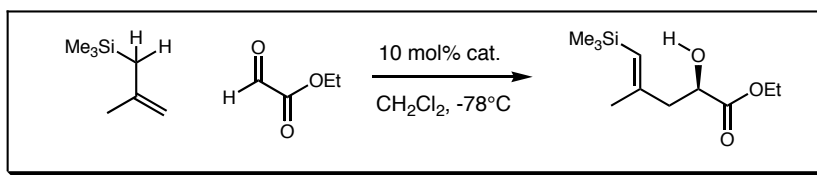
R=Ph, 90% ee

Adjusting for Reactivity: More Lewis Acidic Copper Catalysts



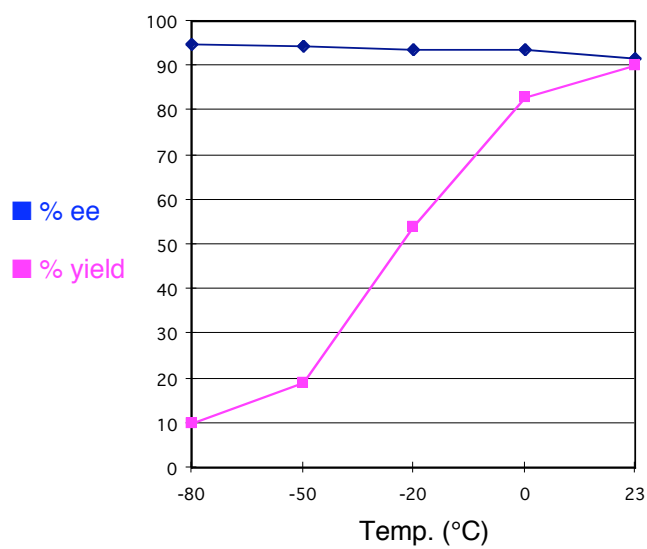
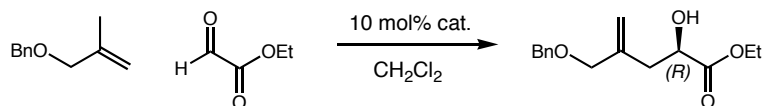
Initial addition gives four products.

*From Allylsilane Additions to Ene Reactions:
Catalyst Turnover Problems*

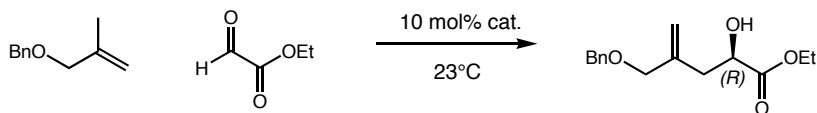
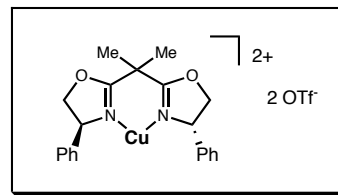


with Dr. Christopher Burgey

Glyoxylate Ene Temperature Profile for $[\text{Cu}(\text{Phbox})]^{2+}2(\text{OTf})^-$ Catalyst

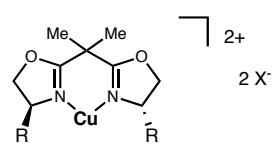
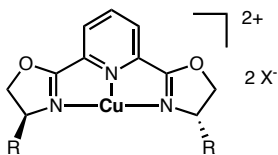
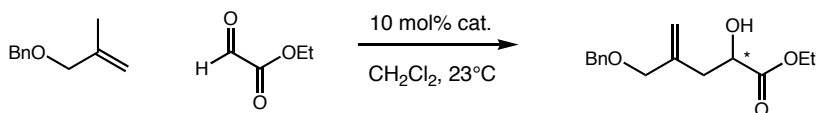


Solvent Effects on Rate, Yield and Selectivity



Solvent	time (h)	% yield	% ee
Toluene	40	82	92
Tol/CH ₂ Cl ₂	24	90	92
Et ₂ O/CH ₂ Cl ₂	24	88	93
PhCl	6	86	91
CH ₂ Cl ₂	5	90	90-92
1,2-DCE	5	90	91
THF	4.5	73	85

Reevaluation of Catalyst Architecture and Counterion Effects on Enantioselectivity



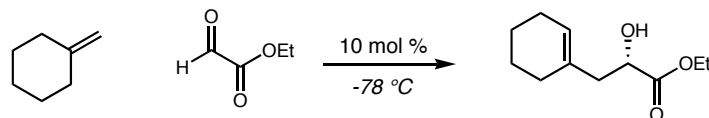
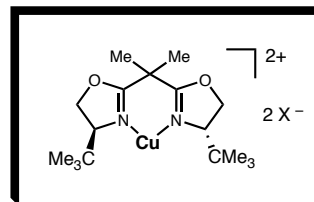
R	X=OTf	X=SbF ₆
iPr	21% ee	10% ee
Bn	8% ee	2% ee
^t Bu	7% ee	7% ee
Ph	53% ee	59% ee

R	X=OTf	X=SbF ₆
iPr	--	40% ee
Bn	--	34% ee
^t Bu	91% ee*	98% ee
Ph	92% ee	88% ee**

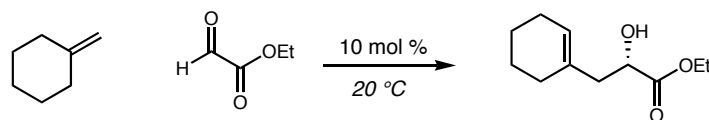
*after 24 hrs

**after 15 min

Catalysis of the Glyoxylate Ene Reaction:
Applying Optimized Conditions



X = OTf: 24 h, 96% ee, 8% yield

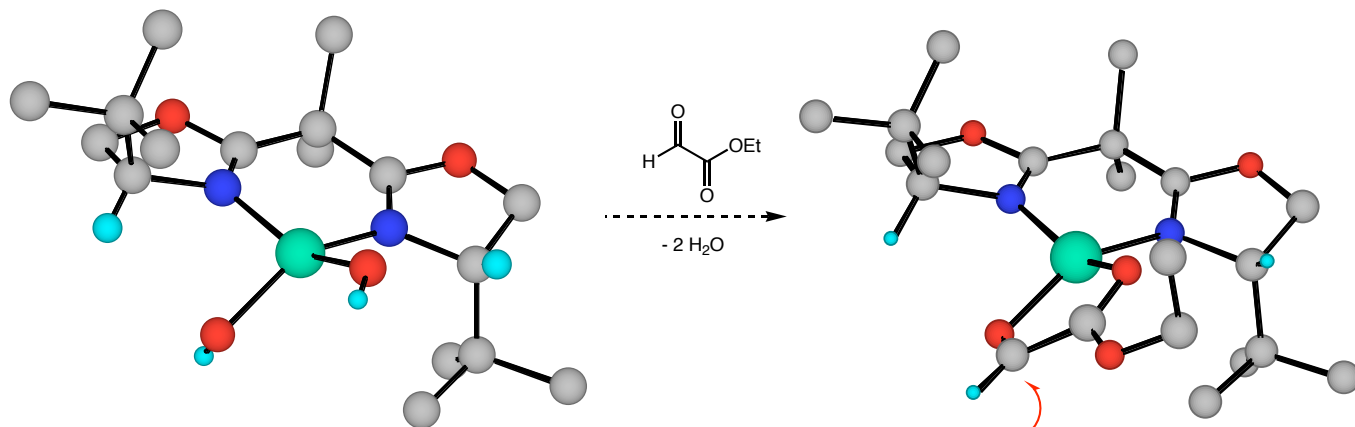
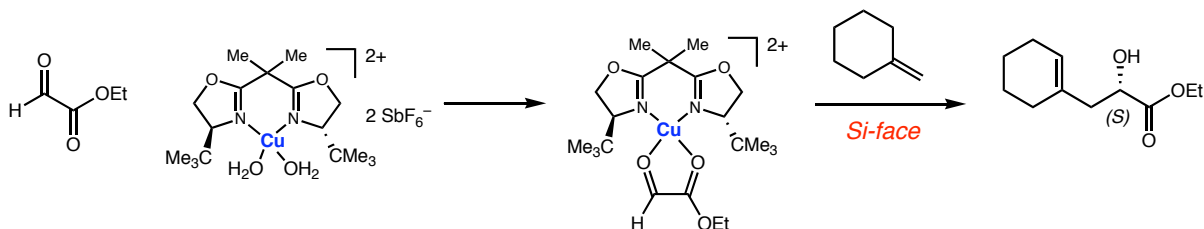


X = OTf: 20 h, 86% ee, 94% yield

X = SbF₆⁻: <3 h, 96% ee, 99% yield

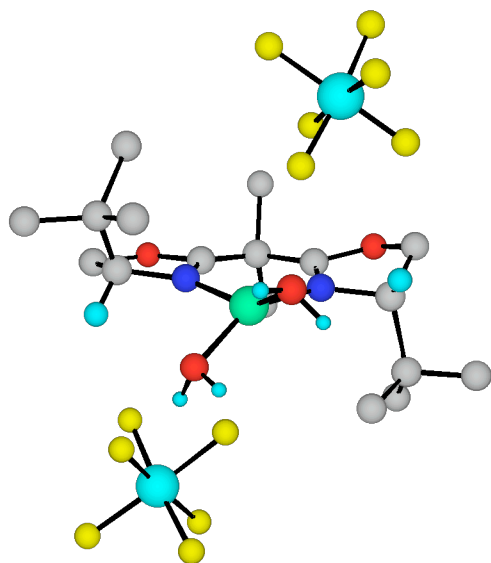
with Dr. Christopher Burgey

Extrapolated Bis(oxazoline)Cu(2+)-Glyoxylate Structure



d(Cu-O2) 1.973 Å
d(Cu-O1) 2.010 Å
X-ray structure

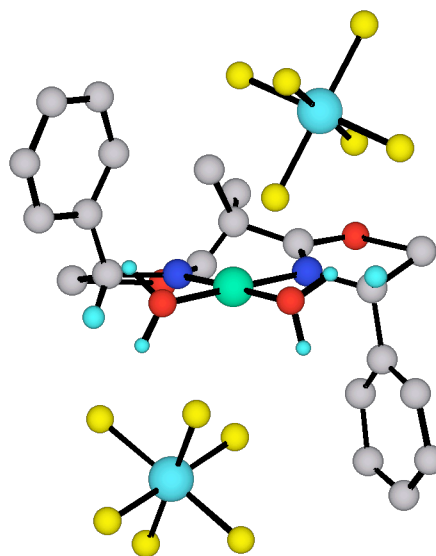
*Bis(oxazoline)Cu(SbF₆⁻)₂·2H₂O X-ray Structures:
Steric Induced Distortions*



H₂O-Cu-N-C Dihedral angle = 29.4 & 37.2 °

d(Cu-F₆Sb) = 3.260 Å
d(Cu-F₆Sb) = 3.500 Å

d(Cu-O1) = 1.92 Å
d(Cu-O2) = 1.94 Å



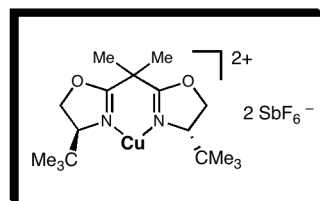
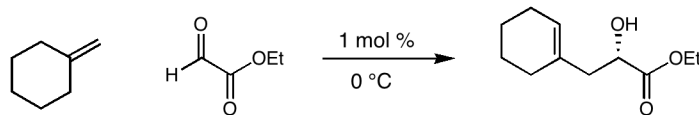
H₂O-Cu-N-C Dihedral angle = 5.3 & 14.0 °

d(Cu-F₆Sb) = 2.746 Å
d(Cu-F₆Sb) = 2.374 Å

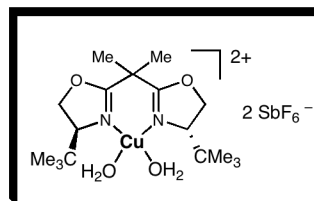
d(Cu-O1) = 1.90 Å
d(Cu-O2) = 1.90 Å

See also Evans, *Tet. Lett.*, 1999, 2879.

Bishydrate Cu(II)box Complexes Are Effective Catalysts



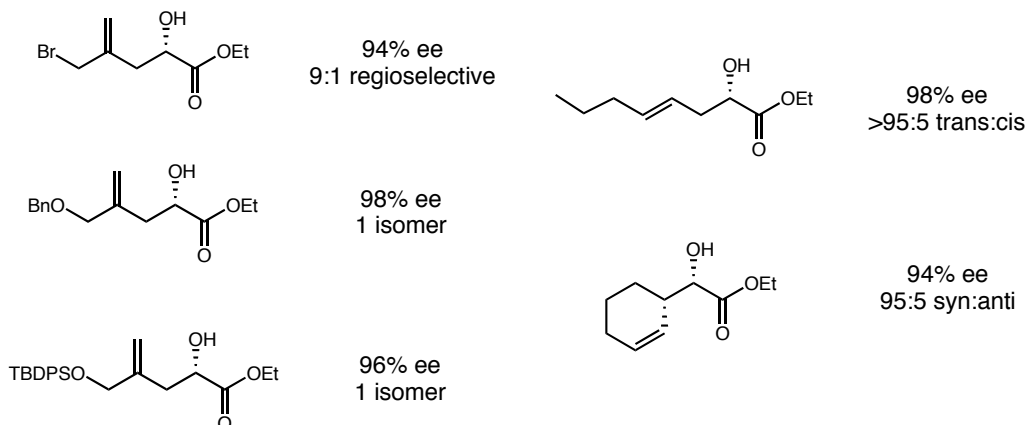
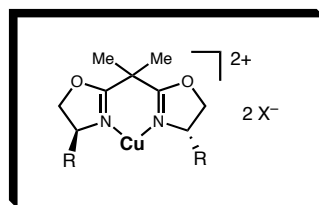
<3 h, 96% ee, 99% yield



<6 h, 97% ee, 97% yield

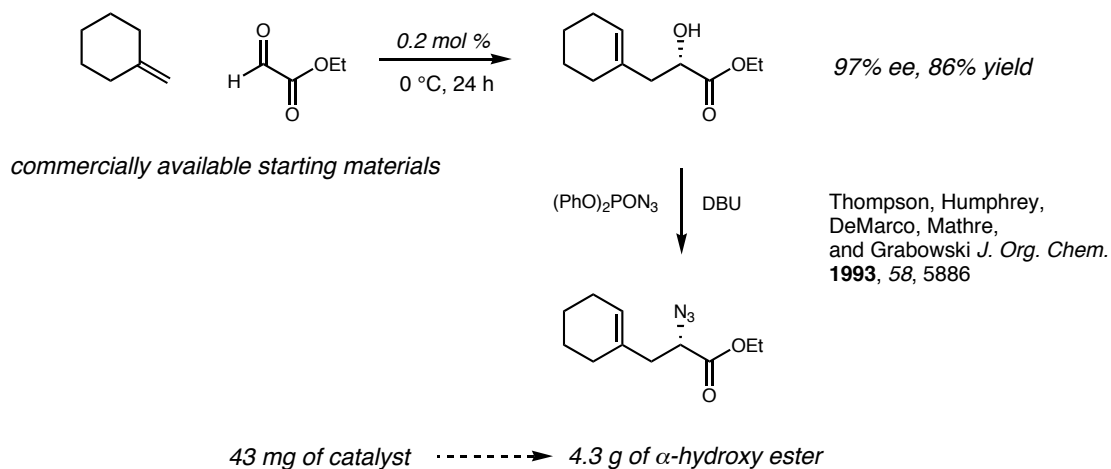
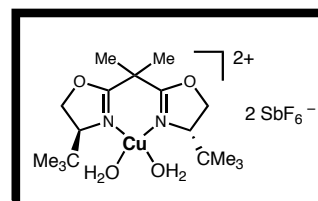
■ *Bishydrate is a bench-stable blue solid which tremendously increases ease of handling.*

*Scope of the Glyoxylate-Ene Reaction:
Less Nucleophilic Olefins*



with Dr. Chris Burgey, Steven Tregay

*Catalysis of the Glyoxylate Ene Reaction:
A Simple Entry Into α -Amino Acids*



with Dr. Chris Burgey