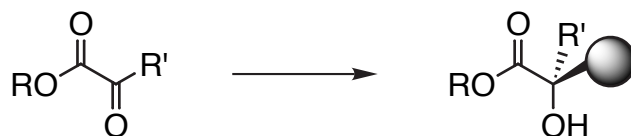


## Asymmetric Transformations of $\alpha$ -Ketoesters

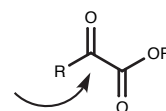


- I. Introductory remarks
- II. Reductions
- III. Organometallic additions
- IV. Aldol transformations
- V. Miscellaneous items of interest

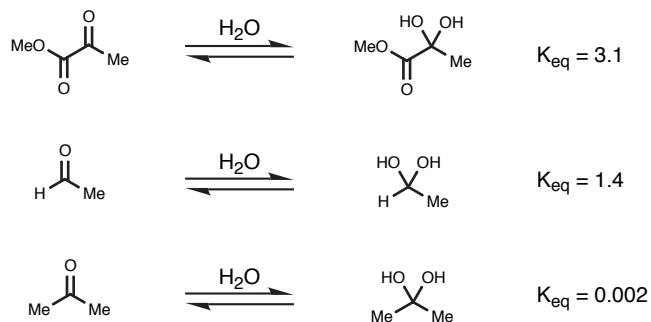
Wes Trotter  
May 10, 1996

### *The bare essentials*

- Nucleophilic reagents react selectively with  $\alpha$ -ketoesters at the ketone carbonyl.

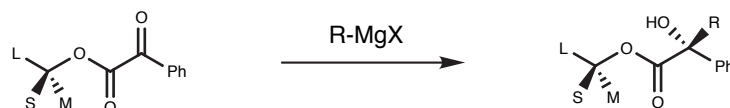


- $\alpha$ -Ketoesters behave kinetically and thermodynamically more like aldehydes than like ketones.

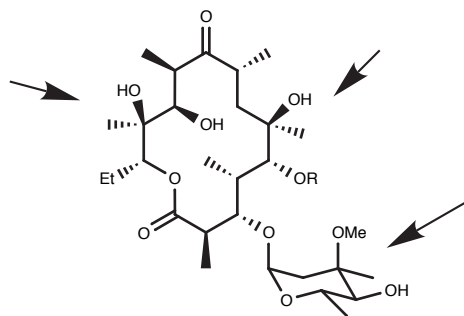


Greenzaid, *J. Am. Chem. Soc.*, **92**, 749 (1967)

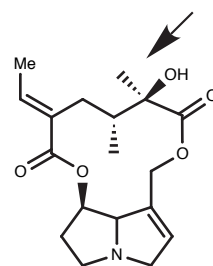
- Empirical data suggest that  $\alpha$ -ketoesters prefer a transoid conformation.



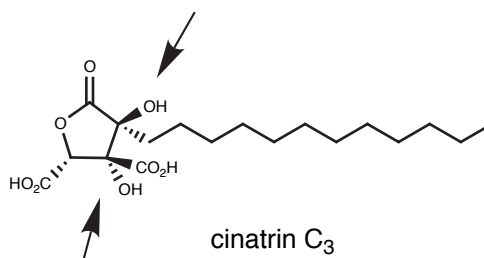
## Tertiary alcohols in nature



erythromycin A



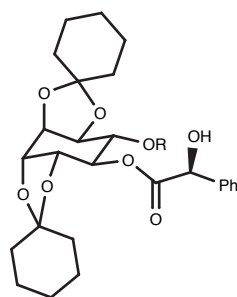
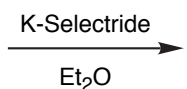
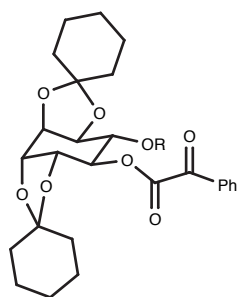
integerrimine



cinatrin C<sub>3</sub>

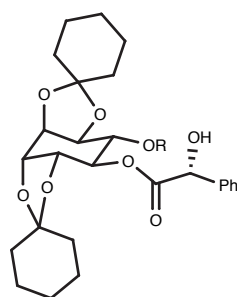
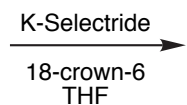
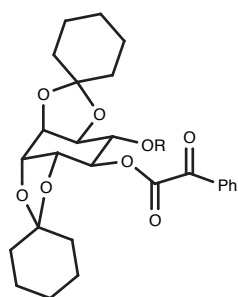
---

## Selective Reductions



R = MOM: 94% de, 78% yield

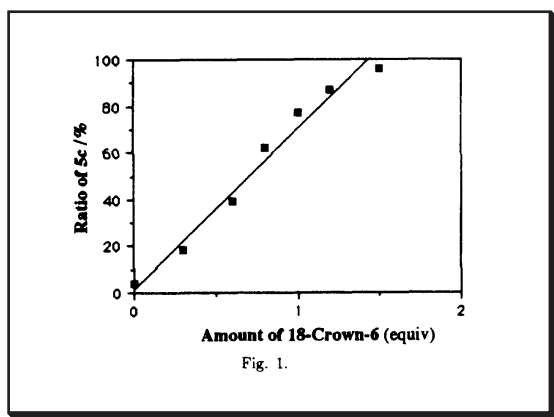
R = TBS: 96% de, 54% yield



R = MOM: 80% de, 78% yield

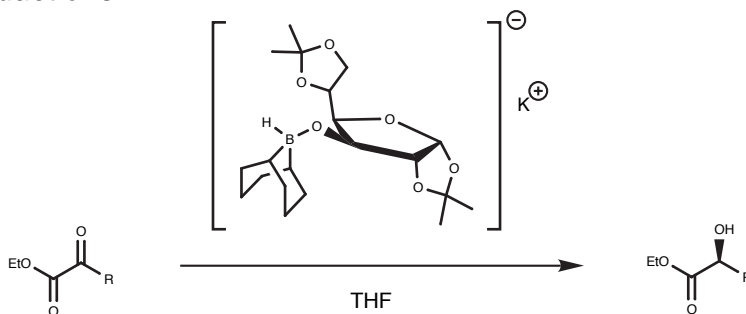
R = TBS: 92% de, 66% yield

## Selective Reductions: An Empirical Conformational Principle



Akiyama, *Bull. Chem. Soc. Jpn.*,  
**67**, 180-188 (1994)  
*Tet. Lett.*, **32**,  
 1335-1338  
 (1991)

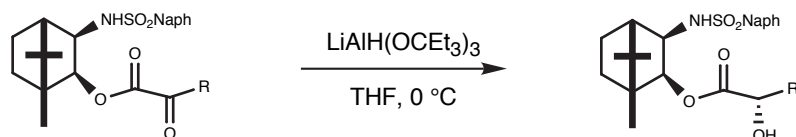
## Selective Reductions



R	yield, %	% ee
CH <sub>3</sub>	75	86
CH <sub>2</sub> CH <sub>3</sub>	80	92
CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	81	94
CH(CH <sub>3</sub> ) <sub>2</sub>	85	97
C(CH <sub>3</sub> ) <sub>3</sub>	87	98
CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	83	93
Ph	80	94
1-naphthyl	78	96

Brown, *J. Org. Chem.*, **51**, 3398-3400  
 (1986)

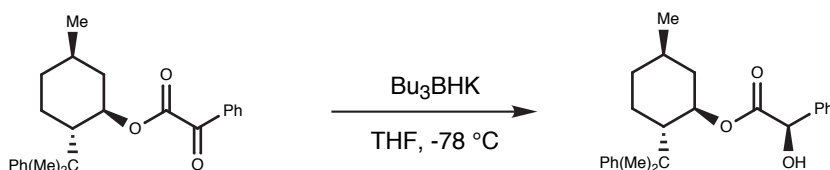
## Selective Reductions: Chiral Auxiliaries Aplenty



98% de, 84-97% yield

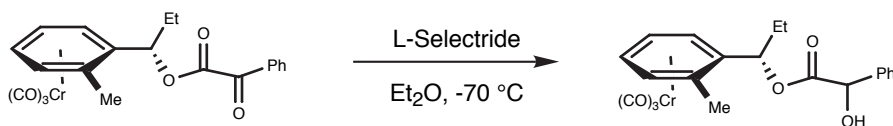
(R = Ph, Et, *n*-Pr)

Xiang, *J. Org. Chem.*, **58**, 993-994 (1993)



94% de, 95% yield

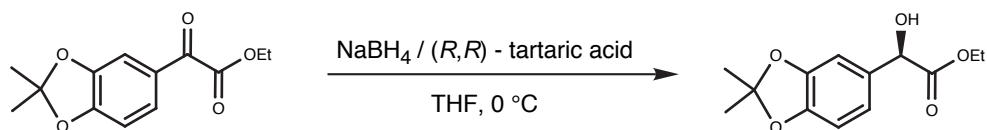
Solladie-Cavallo, *Tet. Asym.*, **2**, 1165-1171 (1991)



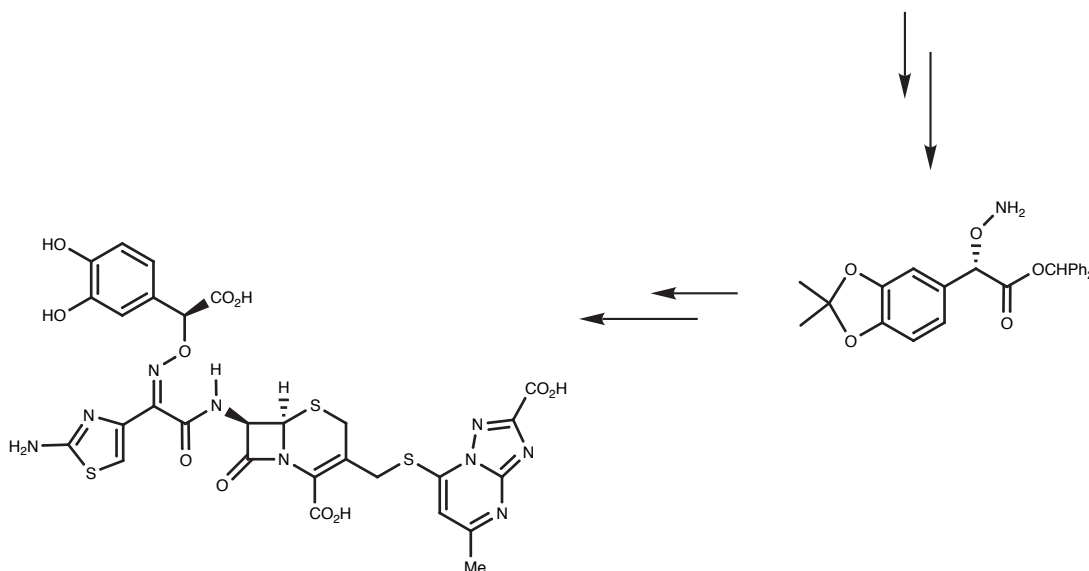
90% de, 90% yield

Solladie-Cavallo, *Tet. Lett.*, **26**, 429-430 (1985)

## Selective Reductions



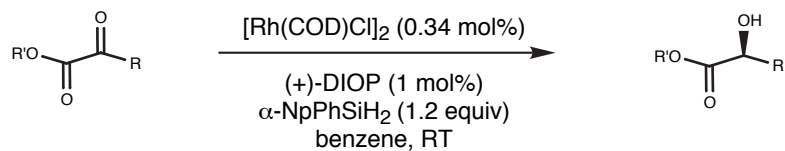
70% ee, 96% yield



"M-14659"

Iwagami, *Bull. Chem. Soc. Jpn.*, **64**, 175-182 (1991)

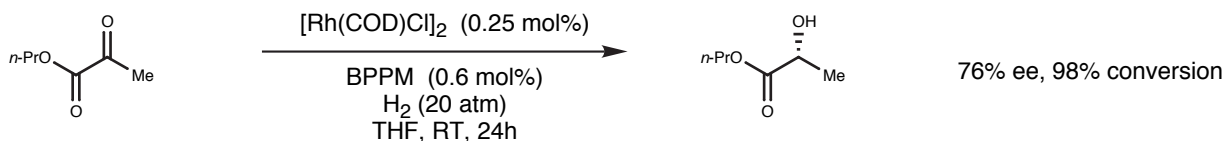
## Catalytic Hydrosilylation



R	R'	%ee	yield, %
CH <sub>3</sub>	<i>n</i> -Pr	85	90
CH <sub>3</sub>	<i>n</i> -Bu	83	83
CH <sub>3</sub>	<i>i</i> -Bu	72	84
Ph	Et	39	87
Ph	<i>c</i> -Hex	47	85

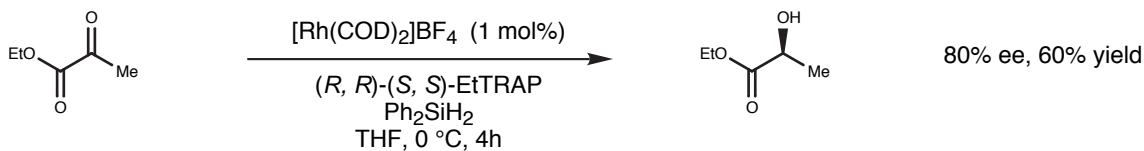
Ojima, *J. Org. Chem.*, **42**, 1671-1679 (1977)

## Catalytic Reduction



- ❑ Simple ketones are not hydrogenated by neutral rhodium catalysts.

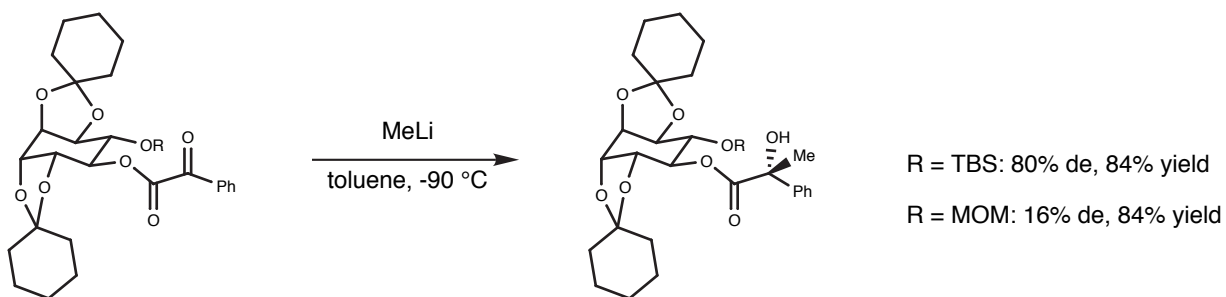
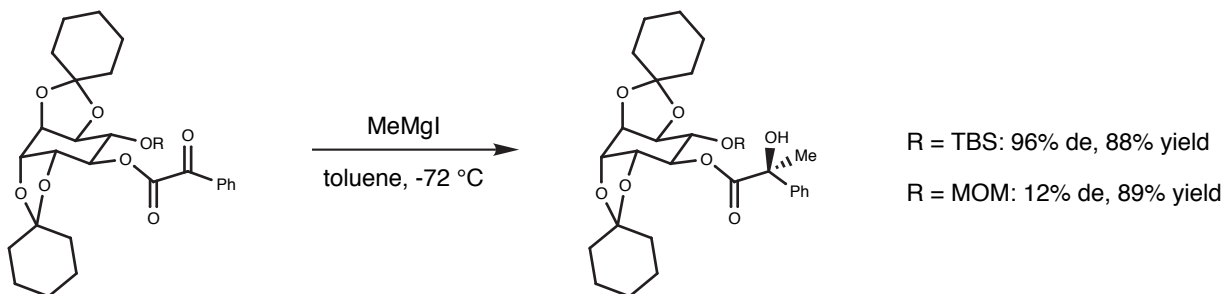
Ojima, *JCS Chem. Comm.*, 428-430 (1977)



- ❑ Simple ketones underwent hydrosilylation at -40 °C.
- ❑ The authors propose that the electron-withdrawing effect of the ester moiety may weaken the binding of the keto carbonyl to rhodium.

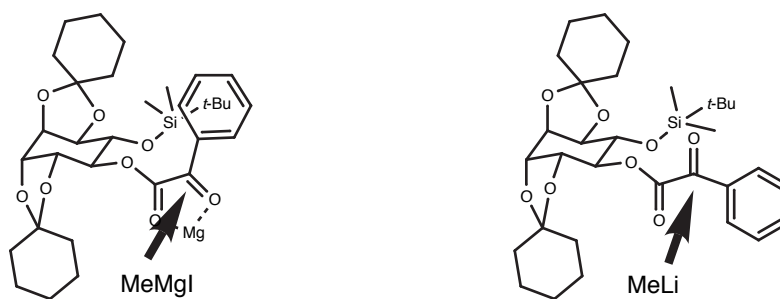
Sawamura, *Synlett*, 347-348 (1995)

## Organometallic Additions



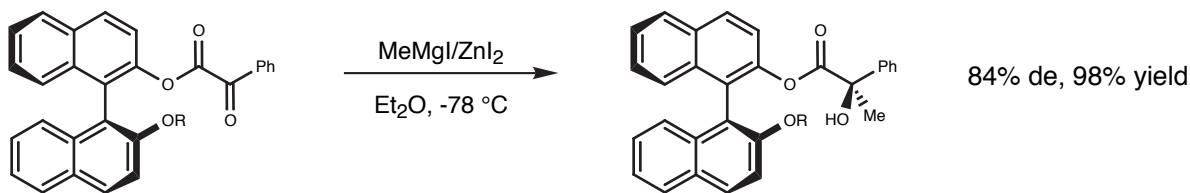
Akiyama, *Chem. Lett.*, 447-450 (1992)

## Organometallic Additions

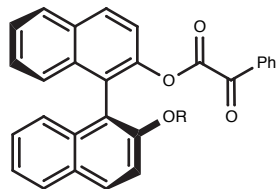
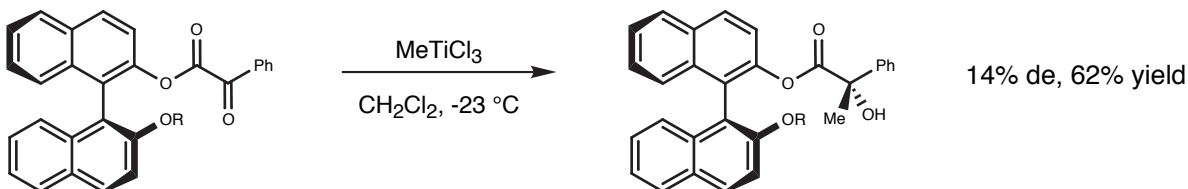


Akiyama, *Chem. Lett.*, 447-450 (1992)

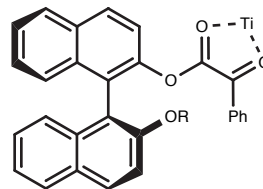
## Organometallic Additions



R = TBS



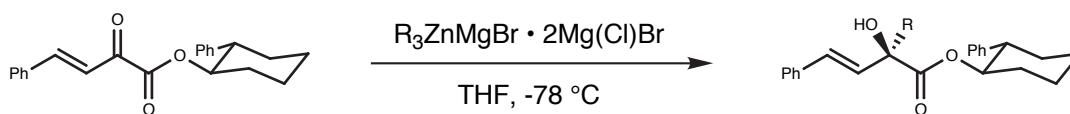
vs.



?

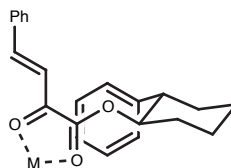
Tamai, *J. Chem. Soc. Perkin Trans. I*, 439-445 (1994)

## Organometallic Additions

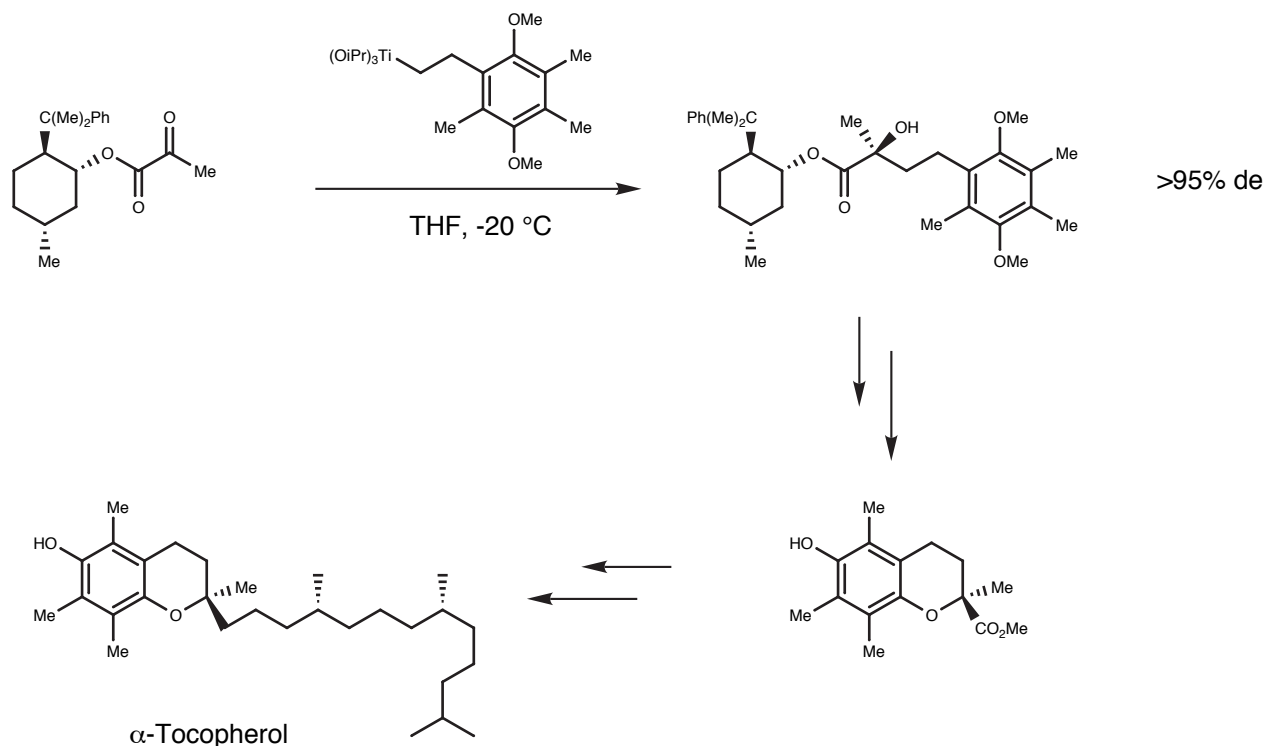


R	%de	%yield
Et	94	98
<i>n</i> -Bu	96	96
<i>i</i> -Bu	92	84
<i>t</i> -Bu	6	68
Bn	94	84
vinyl	88	79
allyl	70	79

- The use of triorganozincates reduces side products resulting from reduction and 1,4 addition.

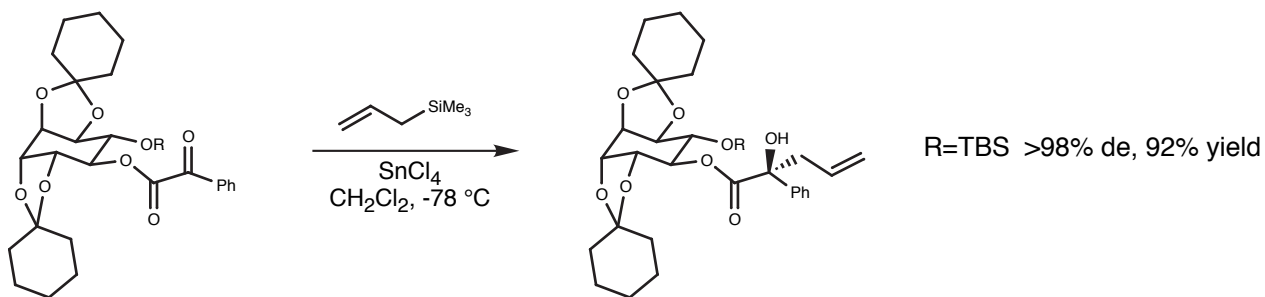


## Organometallic Additions



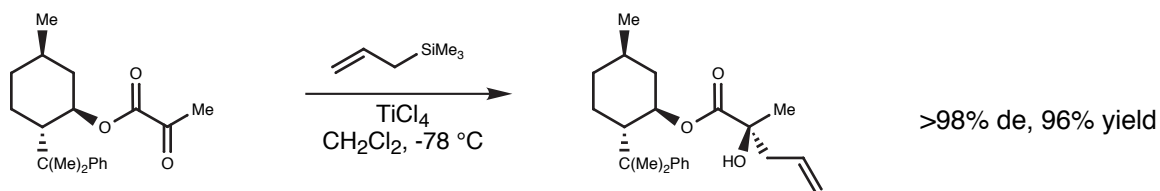
Barner, *Helv. Chim. Acta*, **73**, 1068-1087 (1990)

## Allylsilane Additions



□ Use of  $\text{TiCl}_4$  or  $\text{BF}_3 \cdot \text{OEt}_2$  gave no desired product.

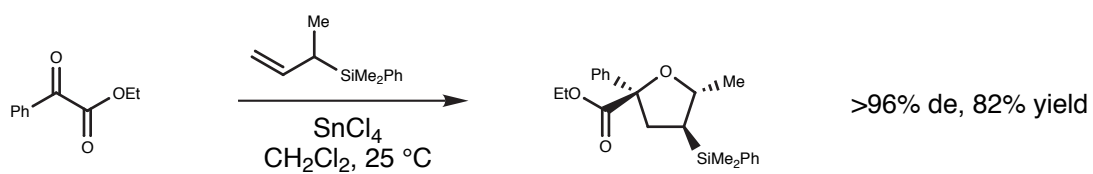
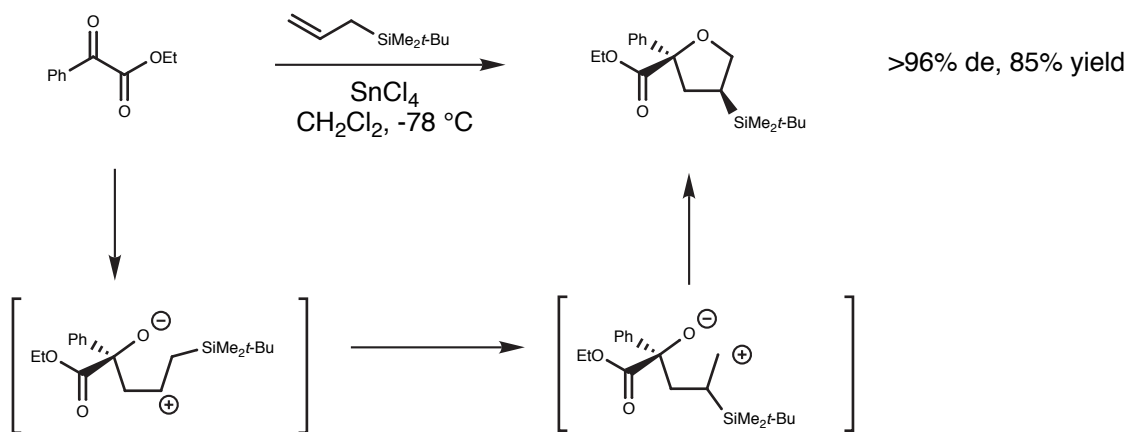
Akiyama, *Chem. Lett.*, 447-450 (1992)



Fang, *J. Chem. Soc. Perkin Trans.*, 1737-1741 (1993)

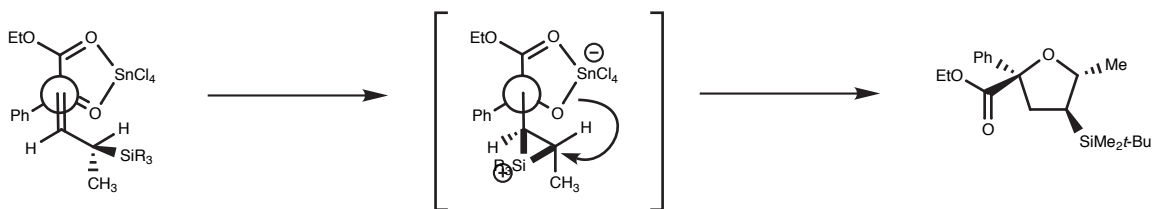
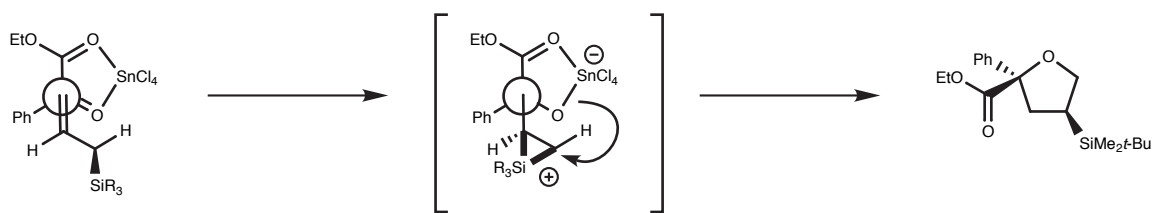


## Allylsilane [3+2] Cycloadditions

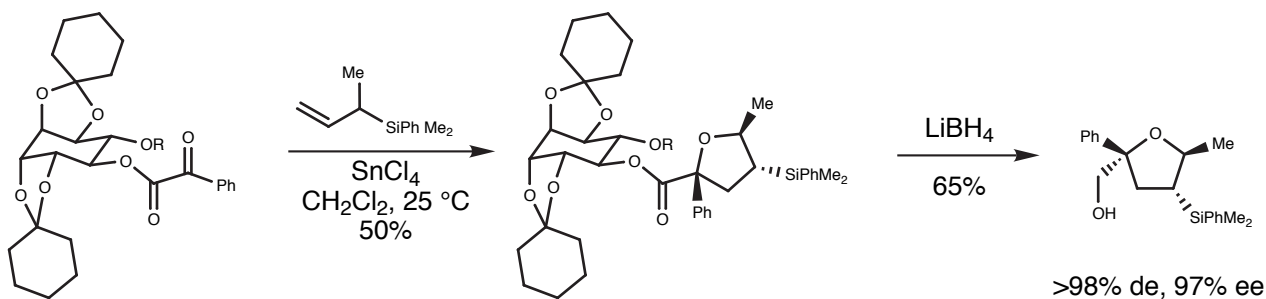
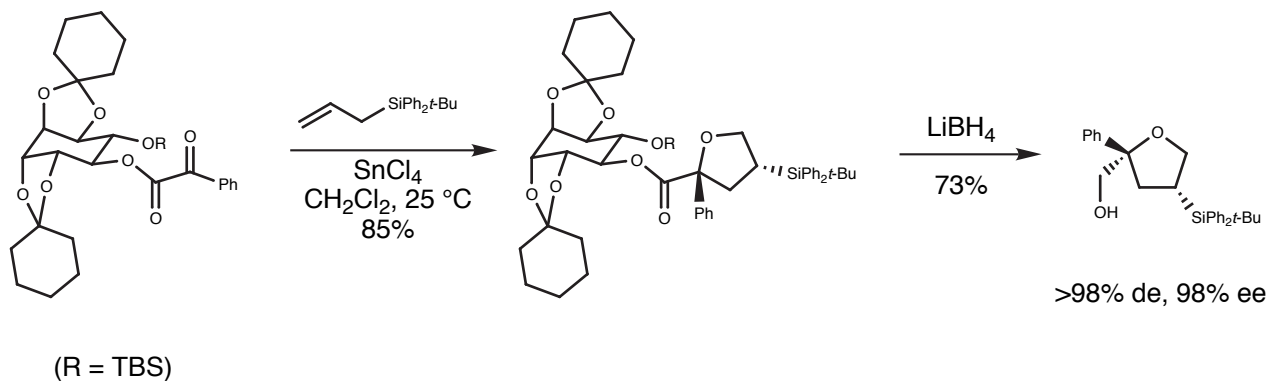


Akiyama, *Chem. Lett.*, 627-630 (1994)

## Allylsilane [3+2] Cycloadditions

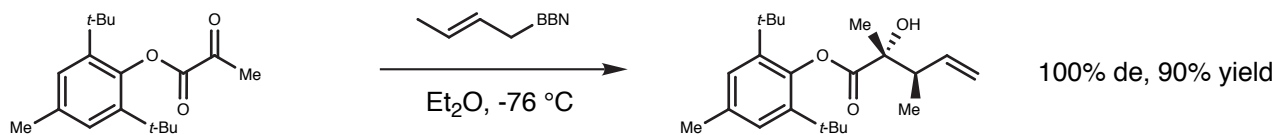


## Allylsilane [3+2] Cycloadditions

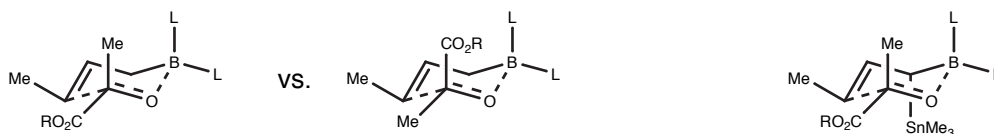
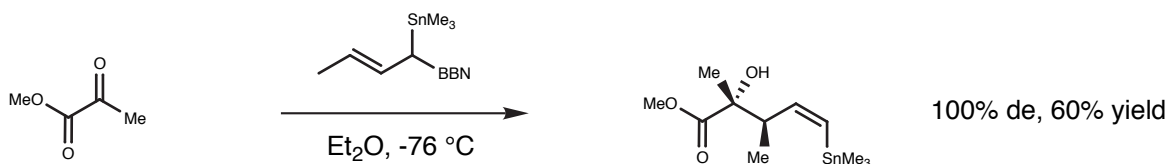


Akiyama, *Tet. Lett.*, **35**, 8401-8404 (1994)

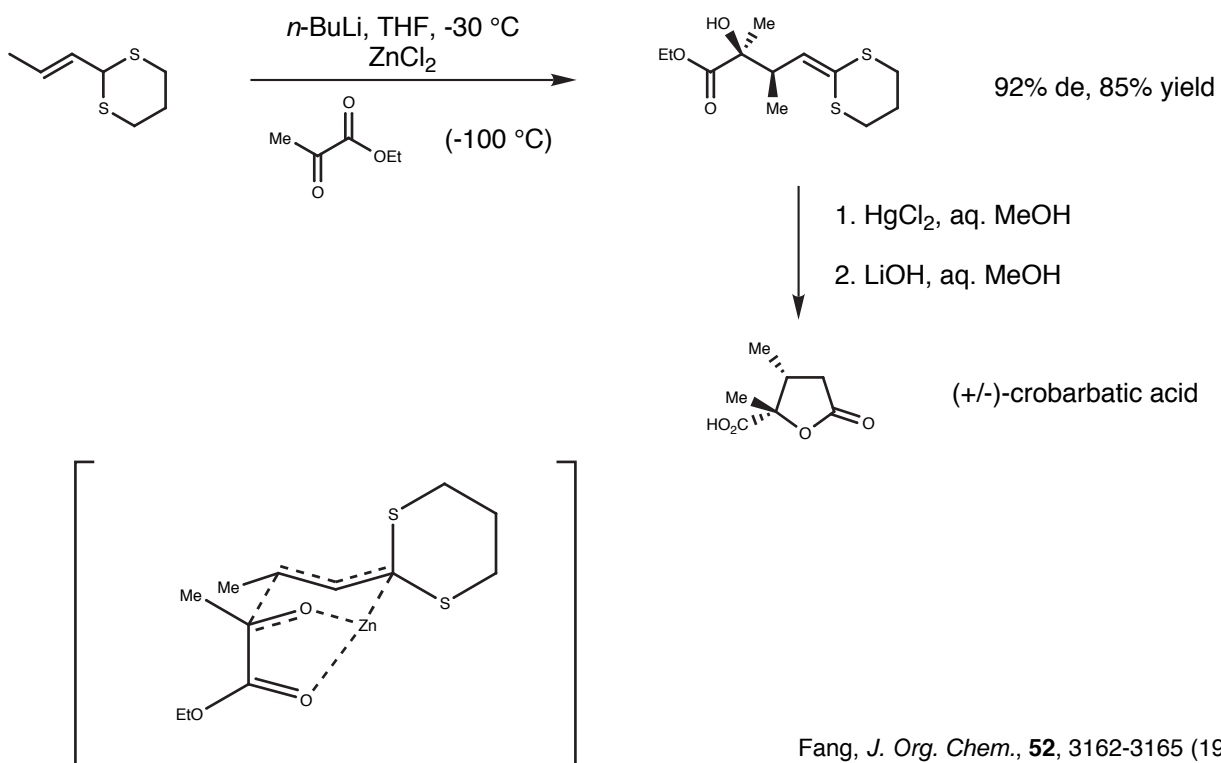
## Diastereoselective Crotylborane Additions



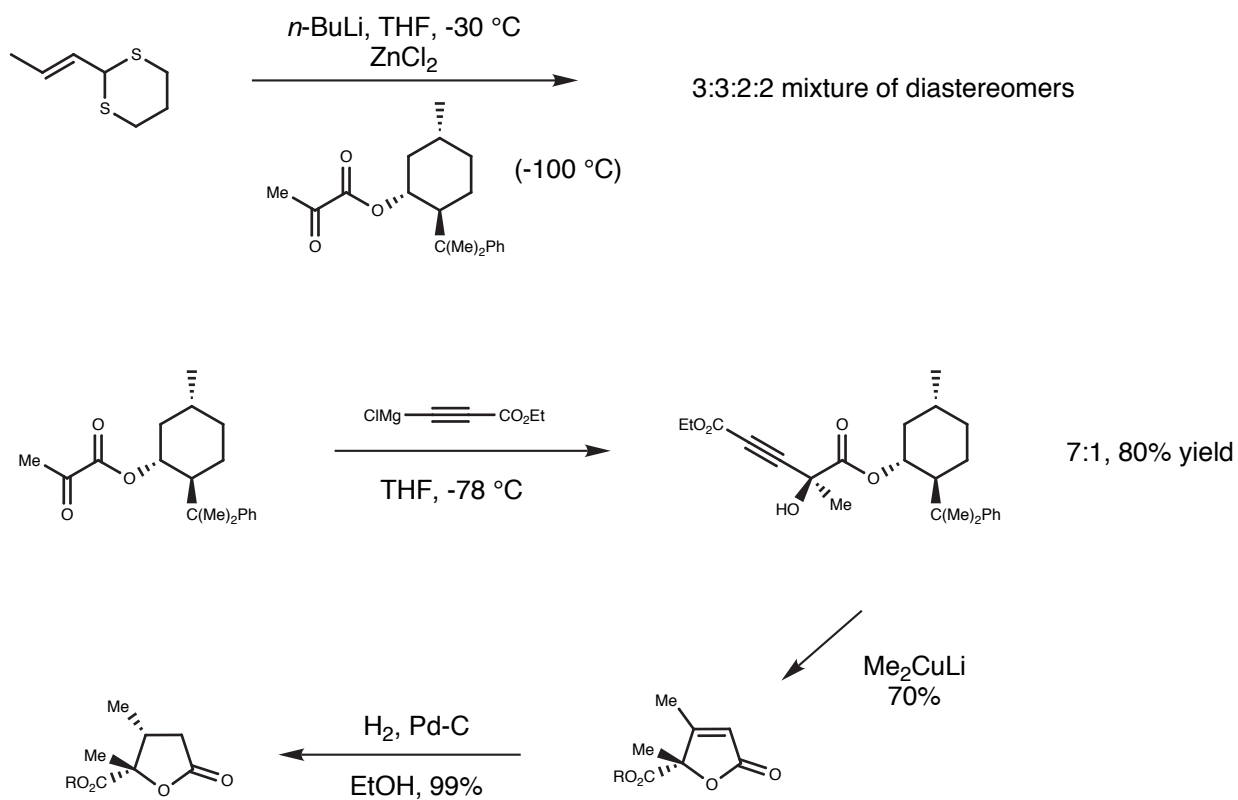
- The observed diastereoselectivity depends on the steric bulk of the ester moiety (methyl pyruvate gives a 70:30 mixture).



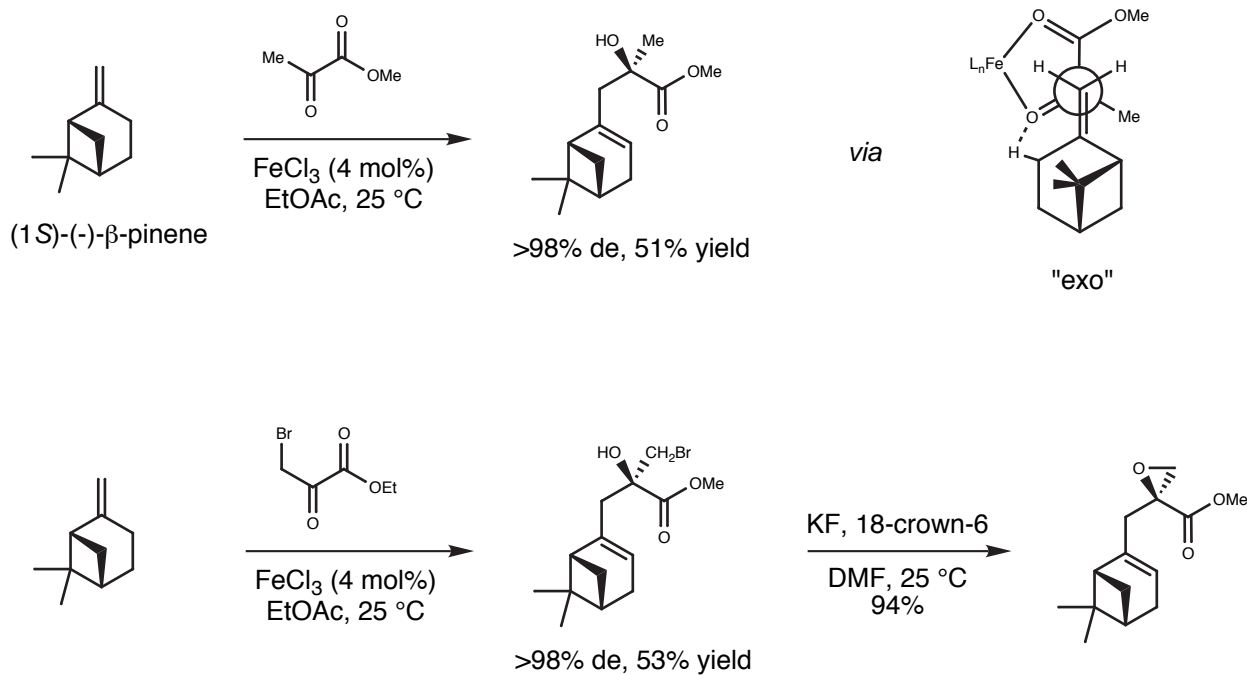
## Diastereoselective Crotyl Additions



## Synthesis of a (+)-crobarbatic acid ester

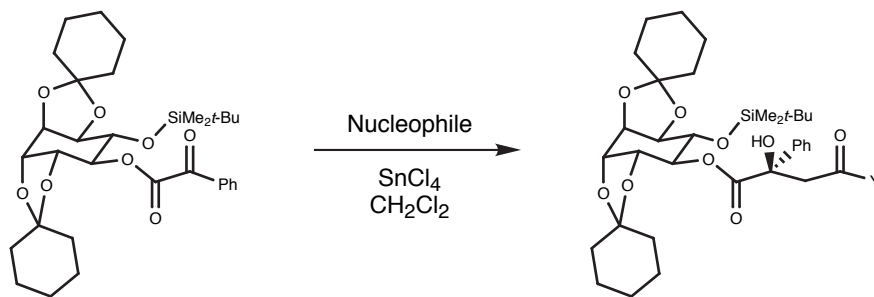


## Ene Reactions



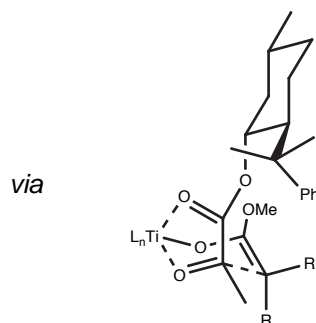
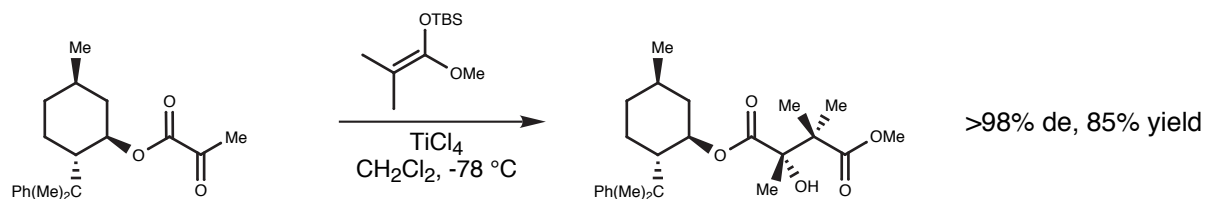
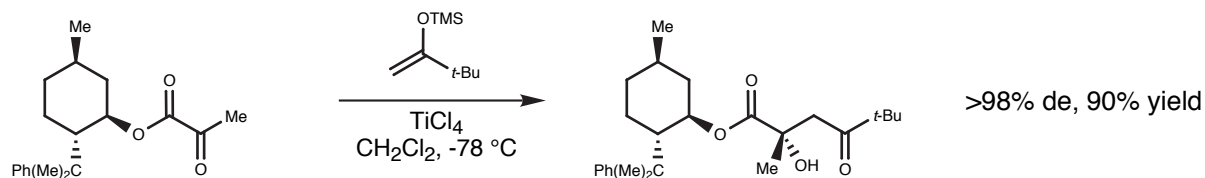
Palmisano, *J. Chem. Soc. Perkin Trans. I*, 1875-1880 (1990)

## Aldol Reactions



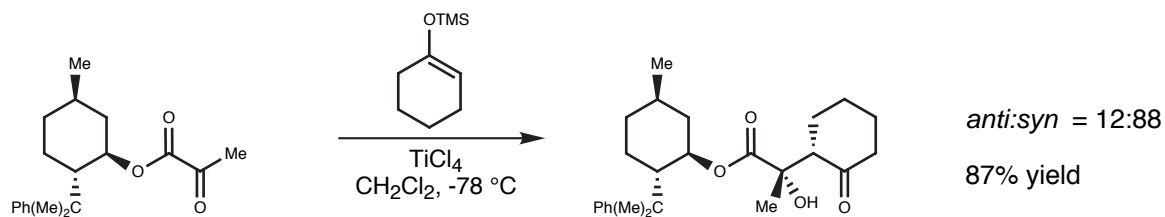
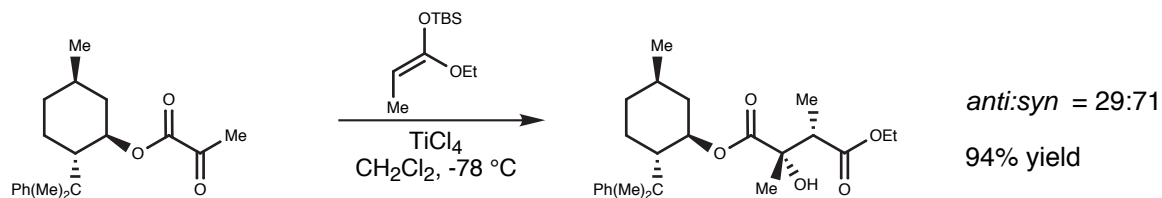
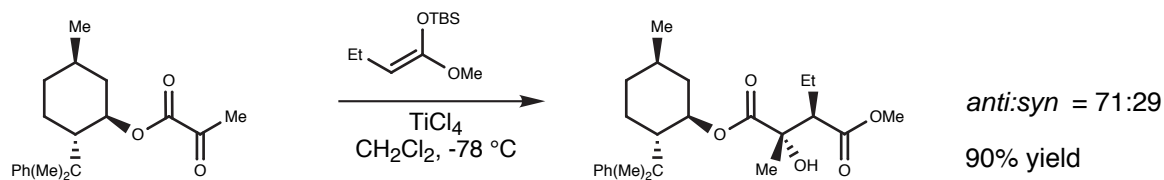
Nucleophile	Temperature	Y	%de	yield, %
	-78 °C	t-Bu	>98	89
	-78 °C	Ph	>98	70
	-20 °C	OEt	>98	92

## Aldol Reactions



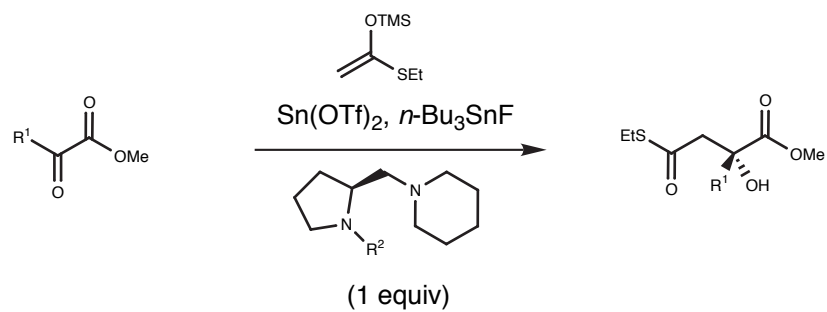
Fang, *J. Chem. Soc. Perkin Trans.*, 1737-1741 (1993)

## Aldol Reactions



□ The tertiary alcohol center is established with complete selectivity in all cases.

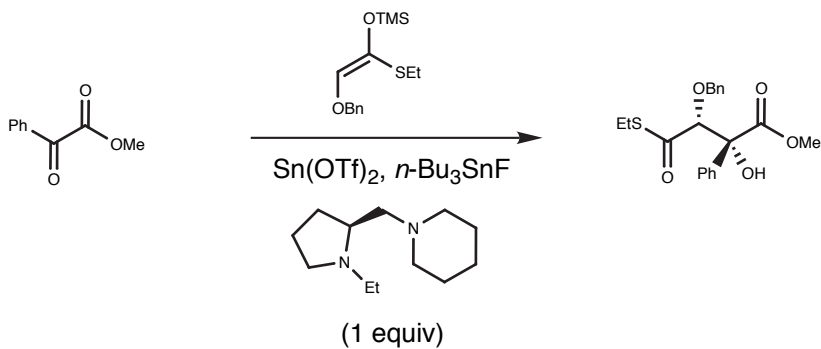
## Aldol Reactions



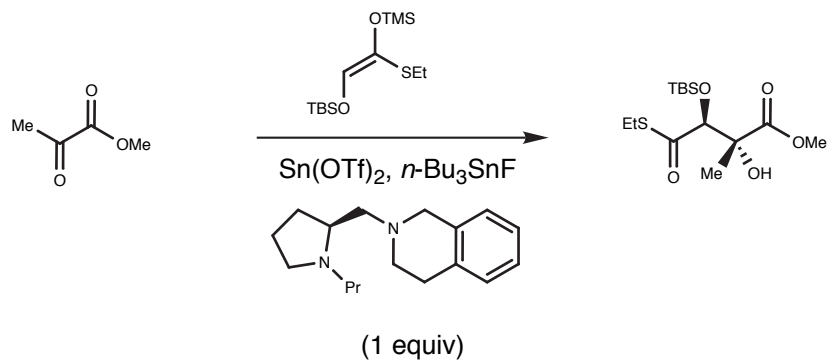
$\text{R}^1$	$\text{R}^2$	%ee	yield, %
Me	<i>n</i> -Pent	92	78
<i>i</i> -Pr	Me	>98	76
<i>i</i> -Pr	<i>n</i> -Pent	>98	81
Ph	Me	>98	74
Ph	<i>n</i> -Pent	>98	74

Kobayashi, *Chem. Lett.*, 2069-2072 (1989)

## Aldol Reactions

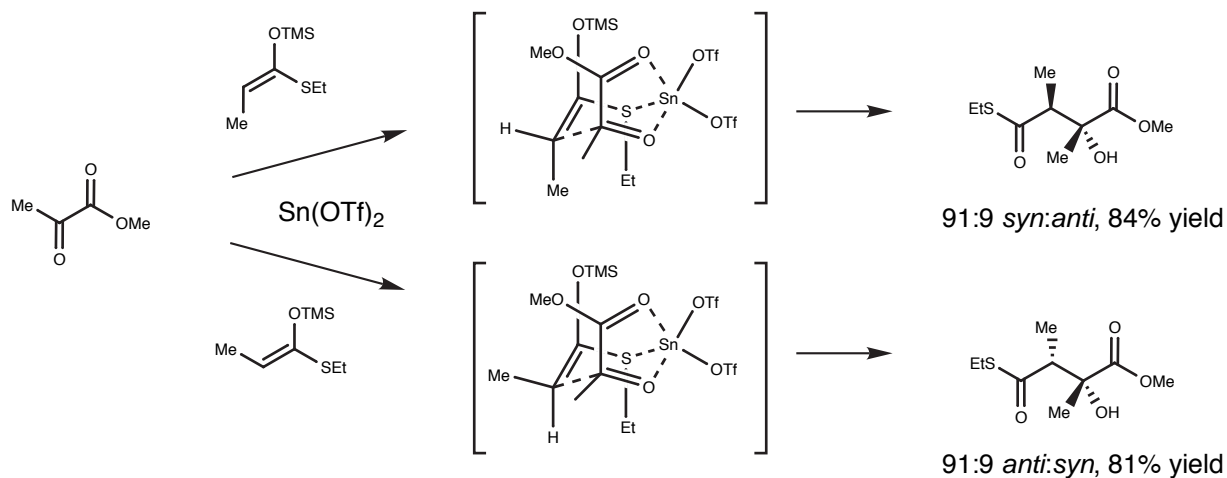


93:7 *anti:syn*, 92% ee, 70% yield



94:6 *syn:anti*, 88% ee, 89% yield

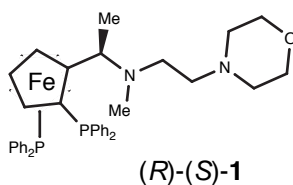
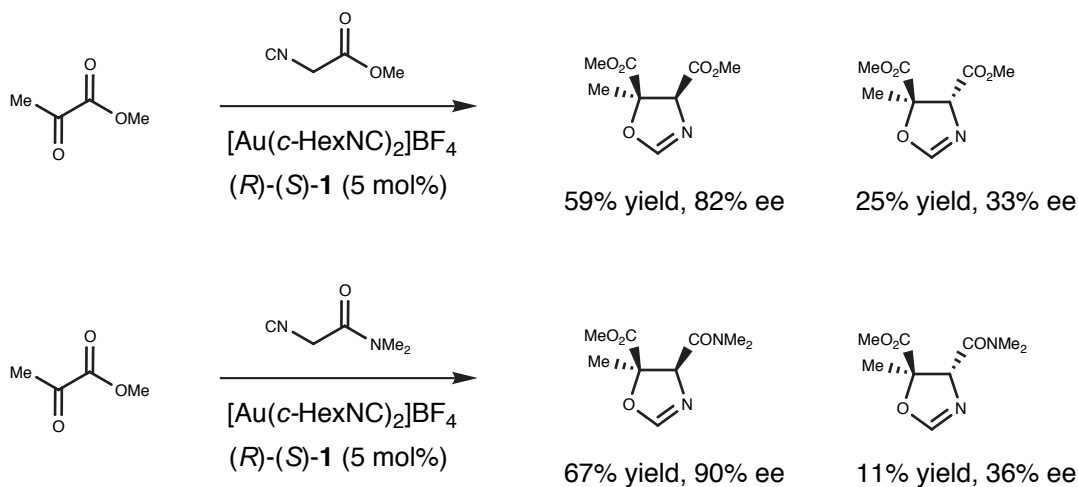
## Aldol Reactions



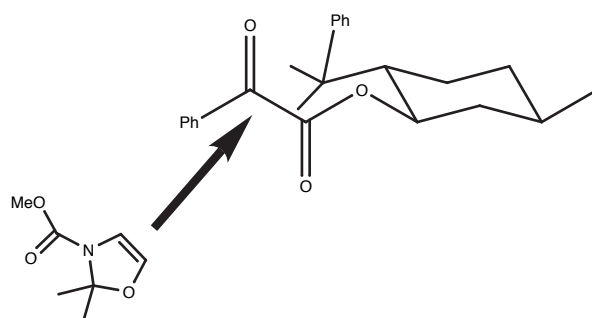
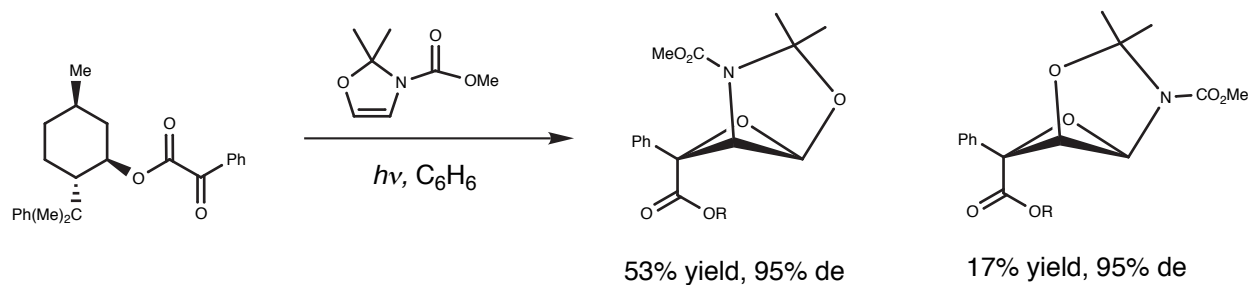
□ *Anti* adducts cannot be obtained enantioselectively in this manner.

Kobayashi, *J. Org. Chem.*, **57**, 1324-1326 (1992)

## Isocyanoacetate Aldol

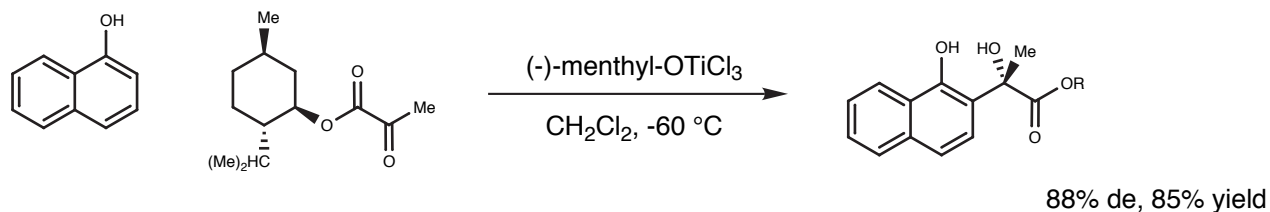


## Paterno-Büchi Reaction

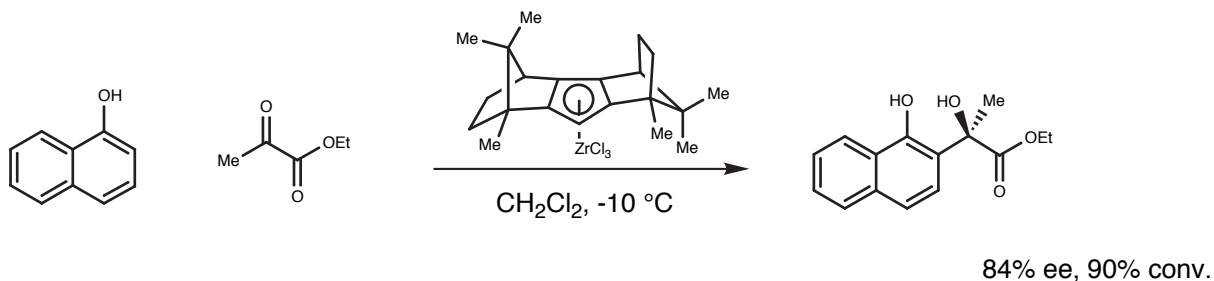


Scharf, *Chem. Ber.*, **121**, 971-976 (1988)

## Asymmetric electrophilic aromatic substitution



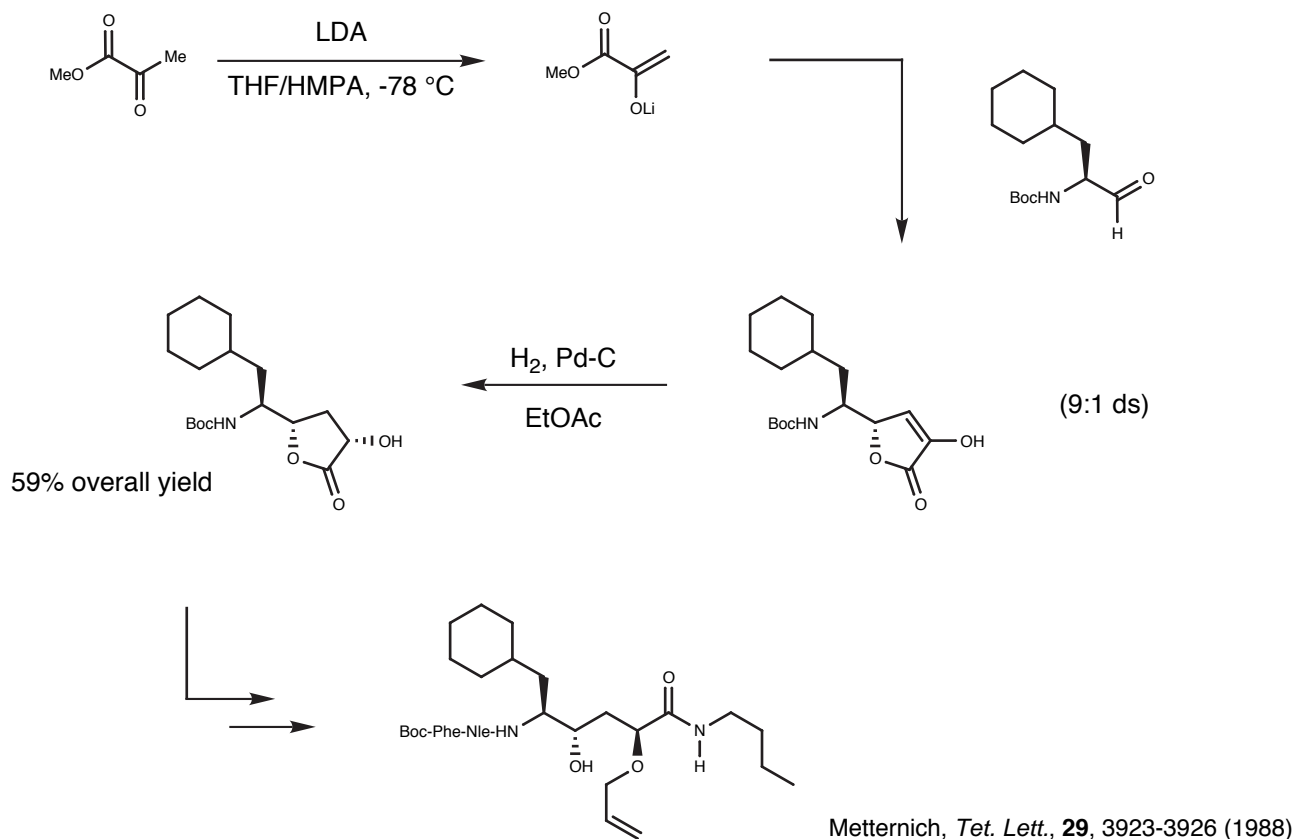
Casiraghi, *J. Org. Chem.*, **53**, 1779-1785 (1988)



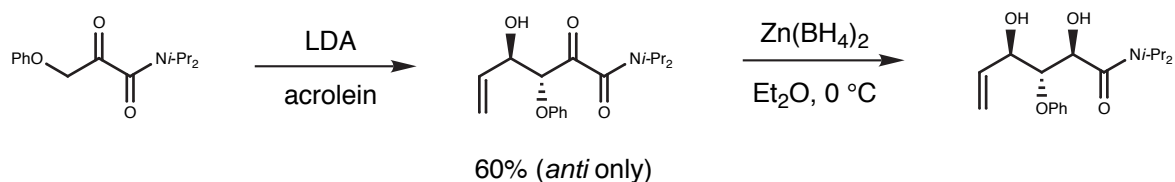
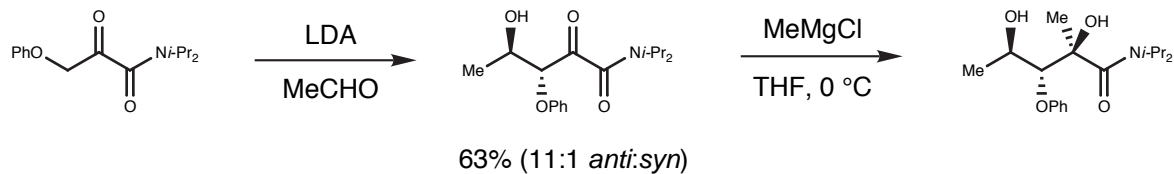
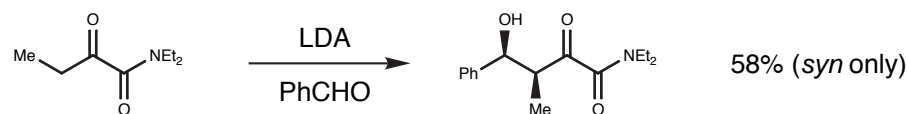
Ecker, *Angew. Chem. Int. Ed. Engl.*, **29**, 512 (1990)



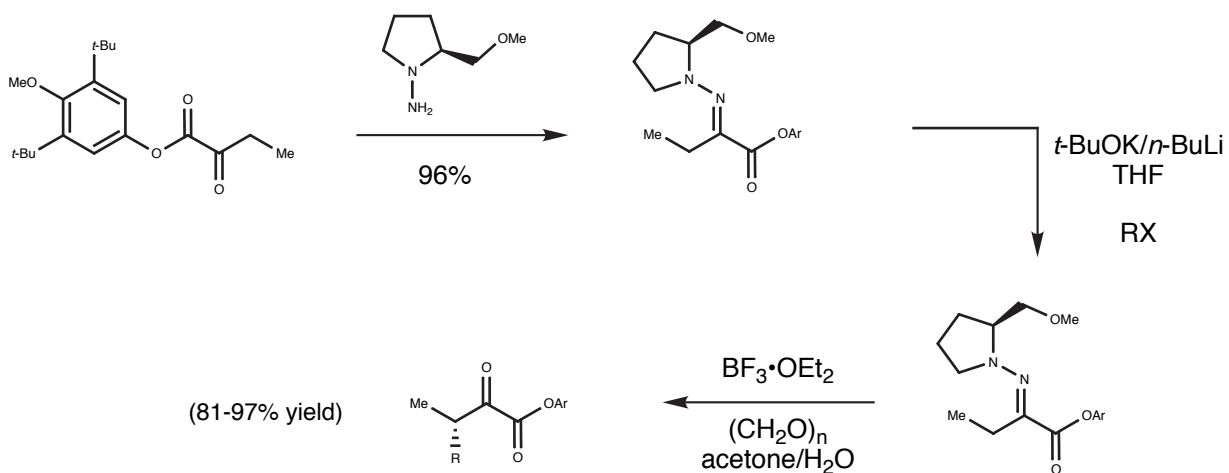
## Pyruvate enolates



## $\alpha$ -Ketoamide enolates



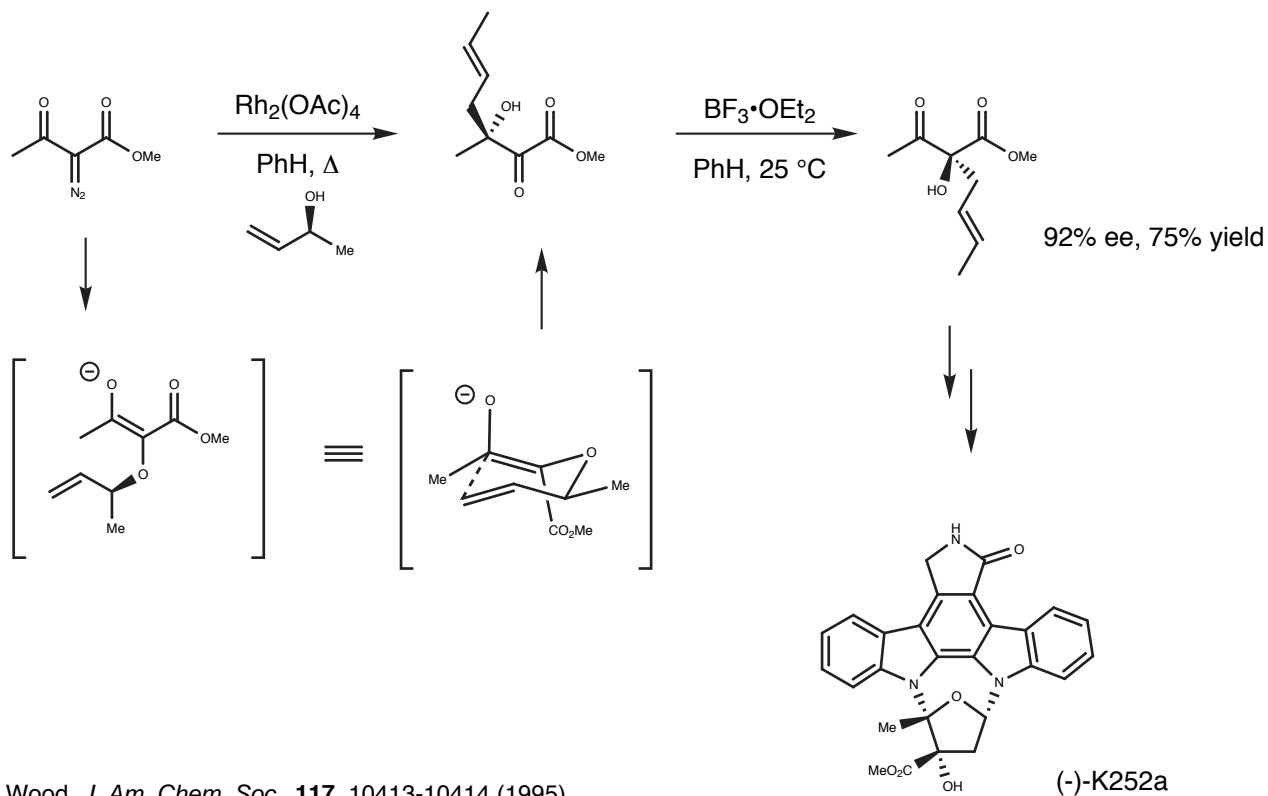
### $\alpha$ -Ketoester enolates



RX	Yield, %	%ee
Etl	63	93
<i>n</i> -BuI	55	>95
<i>i</i> -PrI	59	93
BnBr	58	>95
BOMCl	72	92
BnO(CH <sub>2</sub> ) <sub>2</sub> I	63	88

Enders, *Angew. Chem. Int. Ed. Engl.*, **31**, 618-619 (1992)

### Tandem [3,3]/[1,2] rearrangement



Wood, *J. Am. Chem. Soc.*, **117**, 10413-10414 (1995)