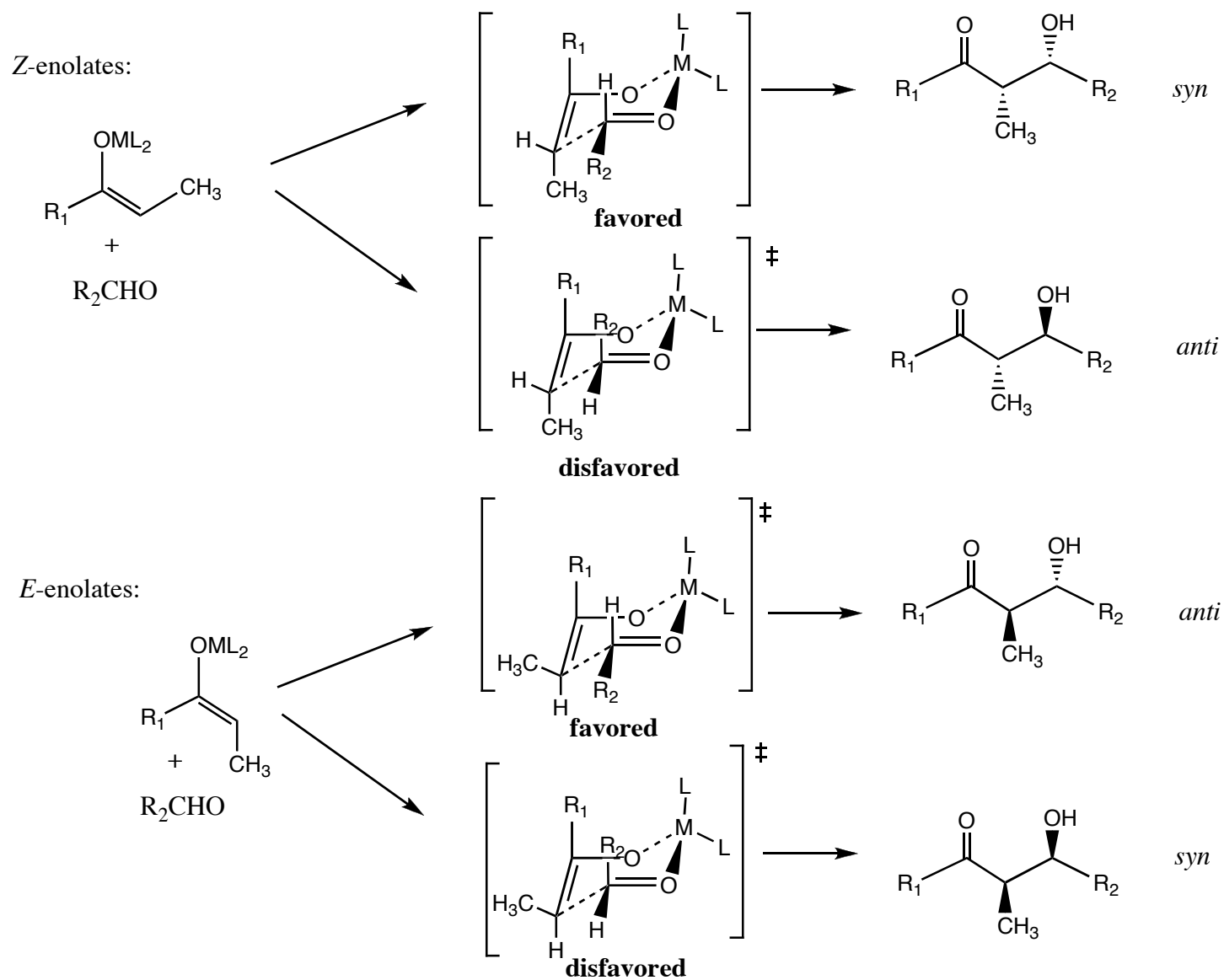
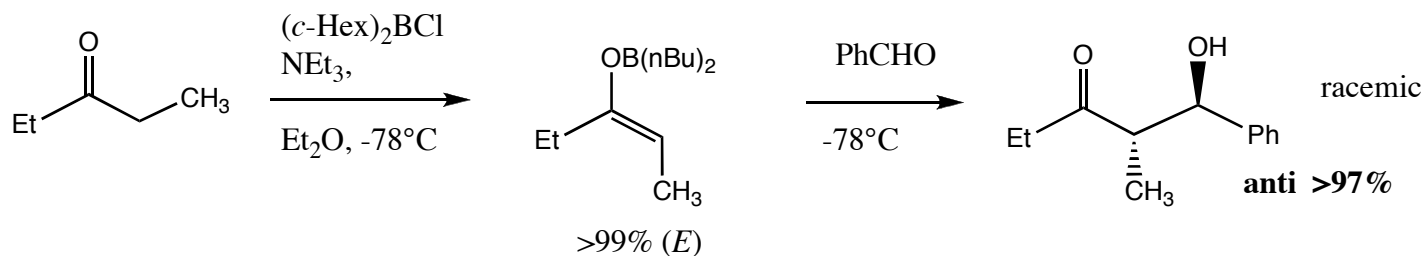
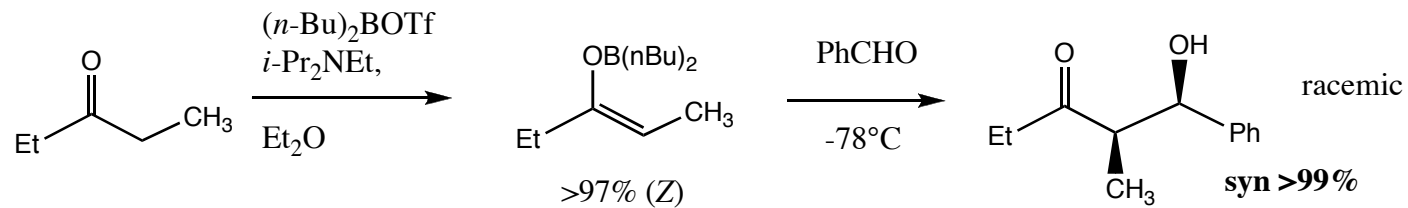


The aldol reaction with metal enolates proceeds by a chair-like, pericyclic process:



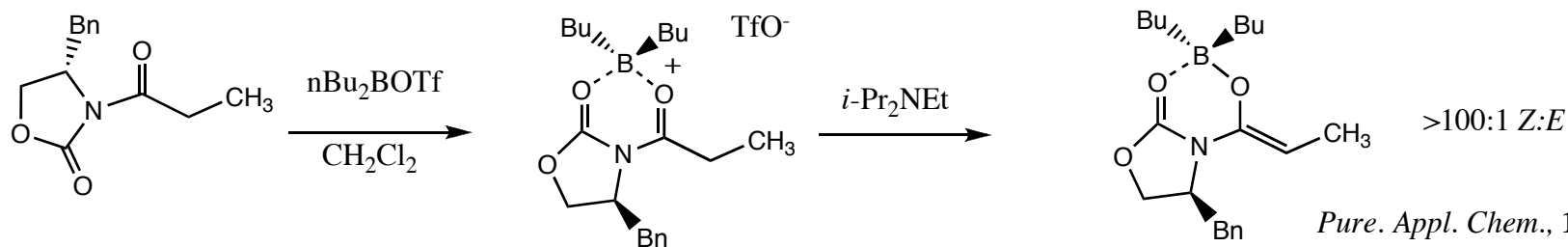
- In practice, the stereochemistry can be highly metal dependent; only boron reliably follows the indicated pathways
- *Z* and *E* enolates form *syn* and *anti* aldol adducts by minimizing the 1,3-diaxial interactions between  $R_1$  and  $R_2$  in each chair-like transition state.

### Preparation of (Z) and (E)- Boron enolates



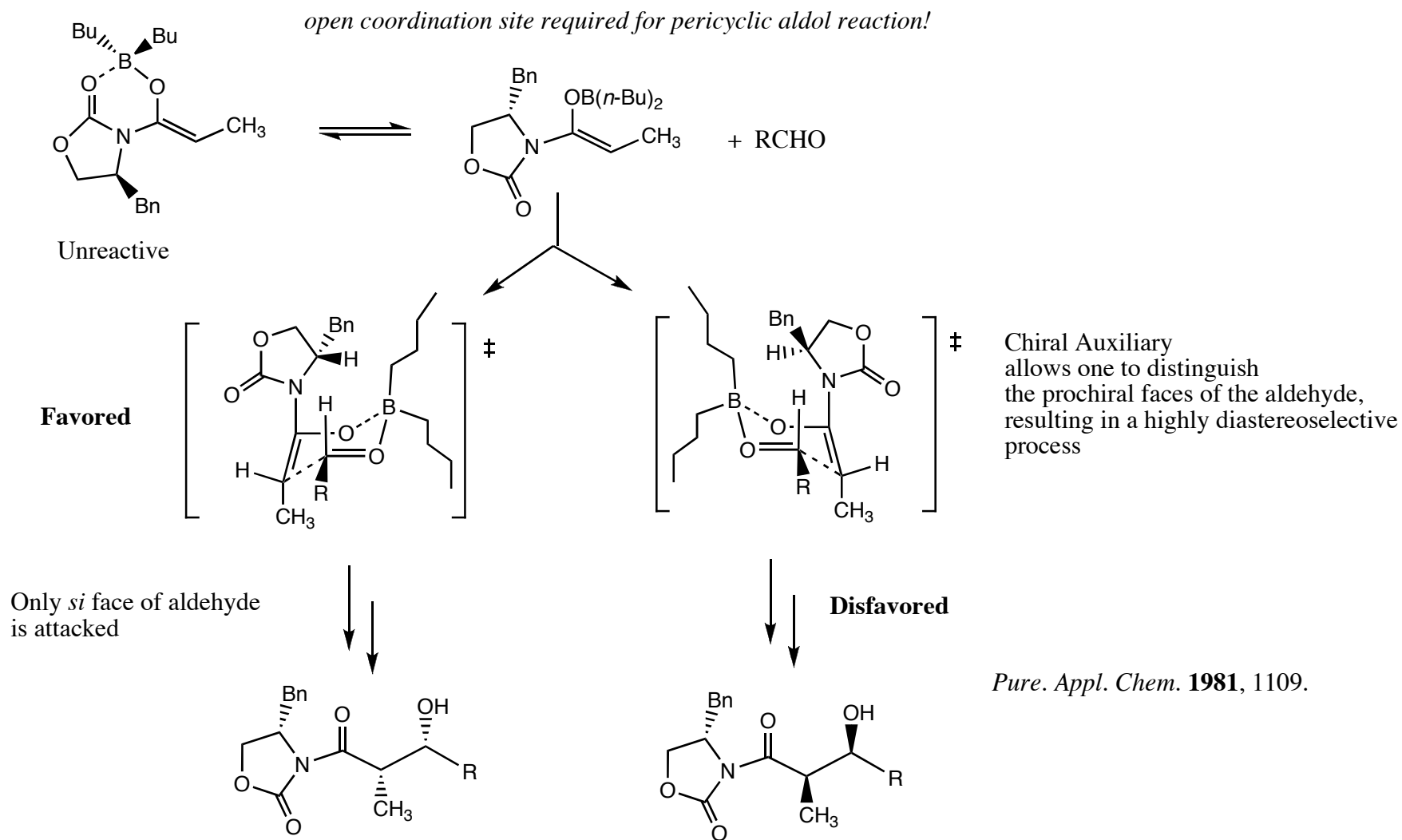
*JACS*, **1979**, 6120  
*JACS*, **1989**, 3441

### Z-selective preparation of boron enolates from Evans' Acyl oxazolidinones (Imides)



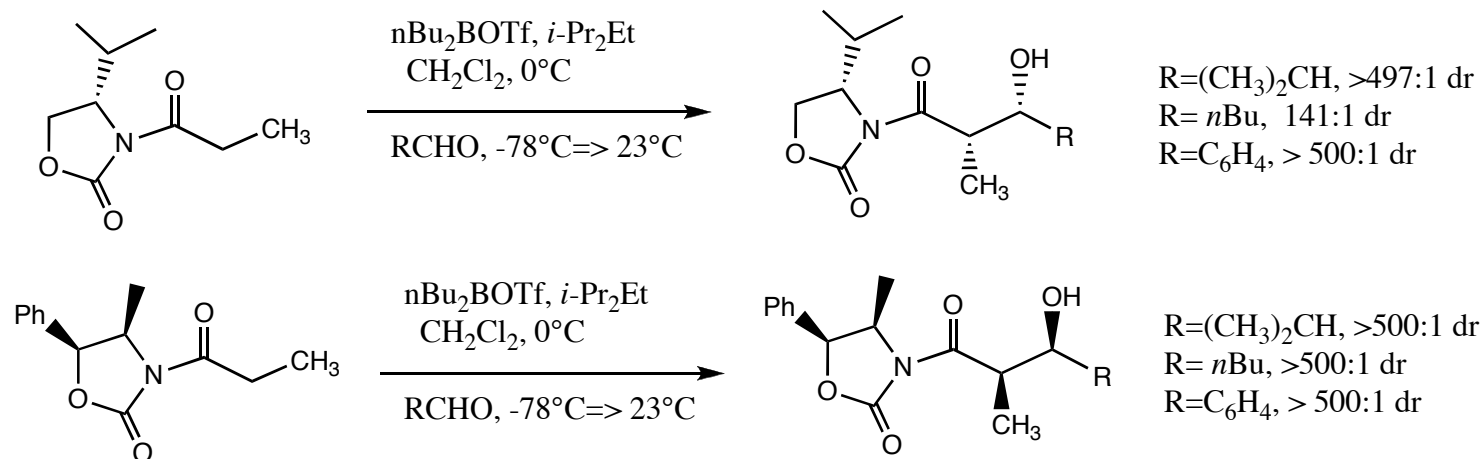
*Pure. Appl. Chem.*, **1981**, 1109.

## Syn-Selective Aldol Reactions of Imide-Derived Boron (Z)-Enolates

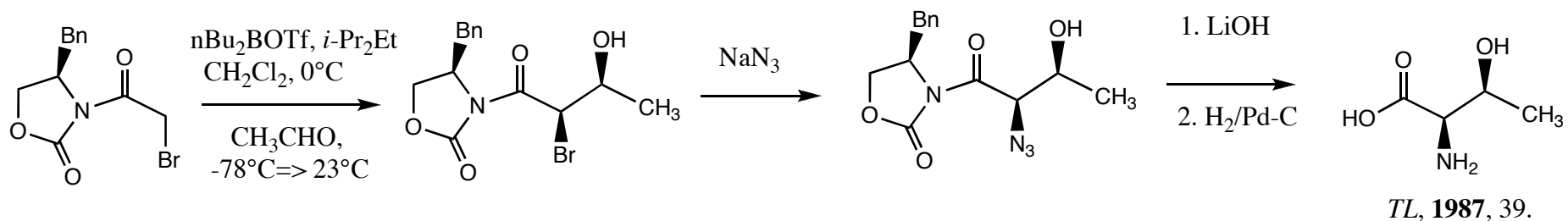


Diastereomeric transition states are of unequal energy, leading to the formation of one diastereomer of a pair preferentially

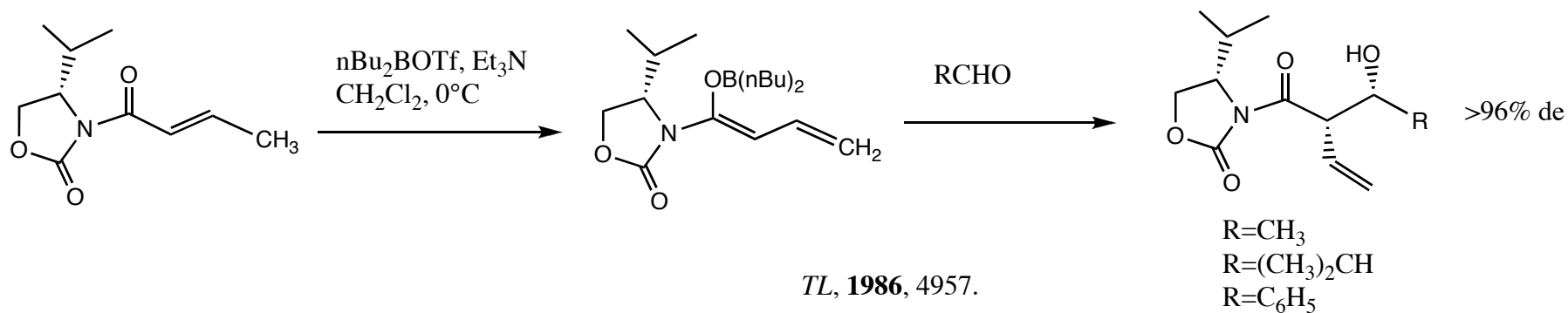
## Application of the Technology



## Amino Acid Synthesis:

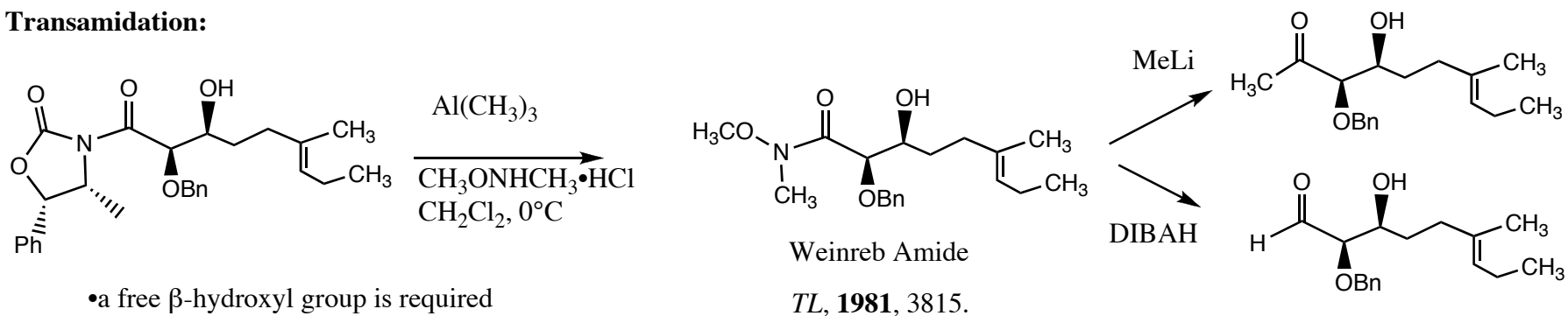


## Aldol Additions of Chiral Crotonate Imides

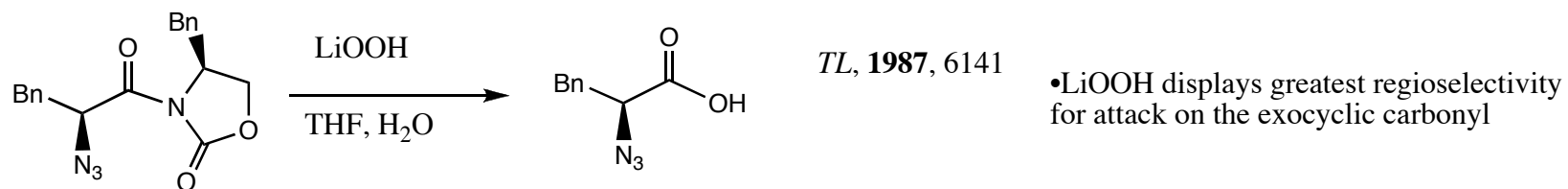


## Methods for Cleavage of Imide Auxiliaries

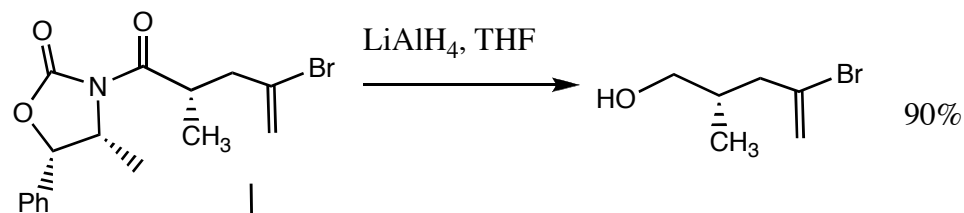
### Transamidation:



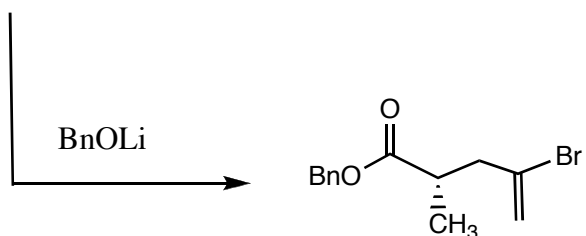
### Hydrolysis:



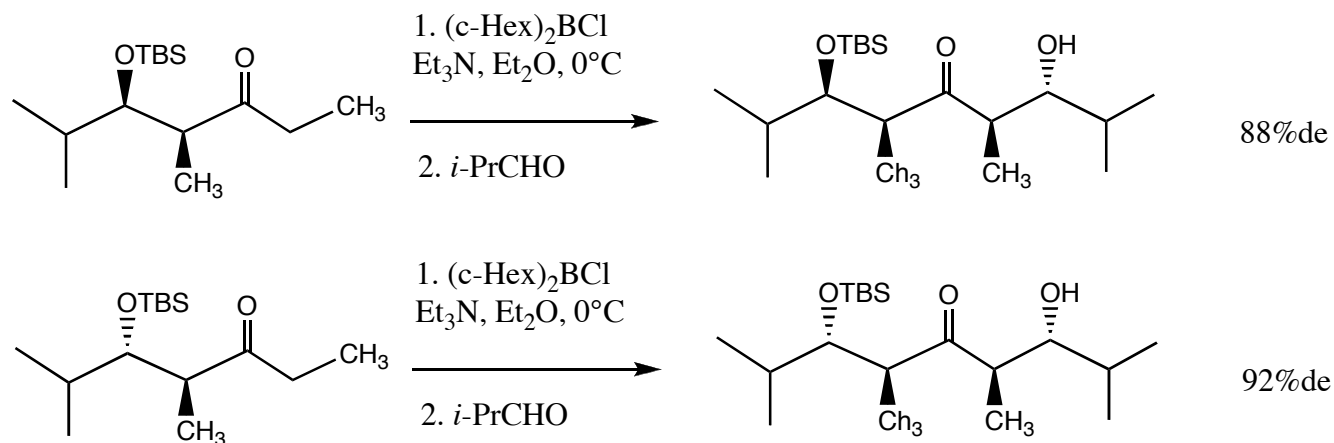
### Reductive Cleavage:



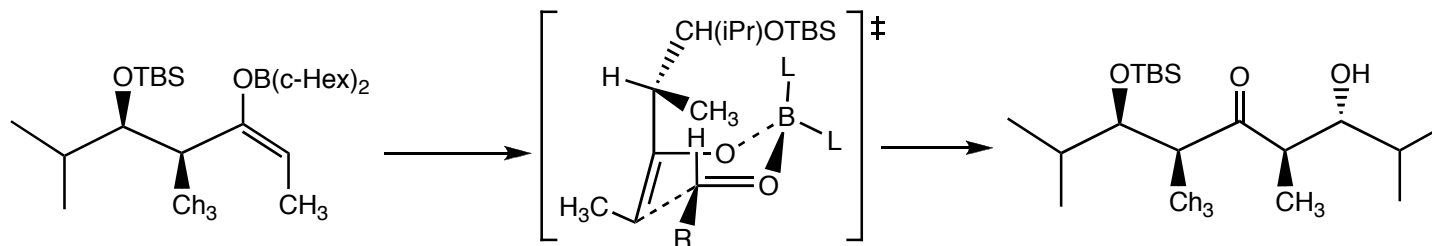
### Esterification:



## Anti-Selective Aldol Reactions in Related Systems



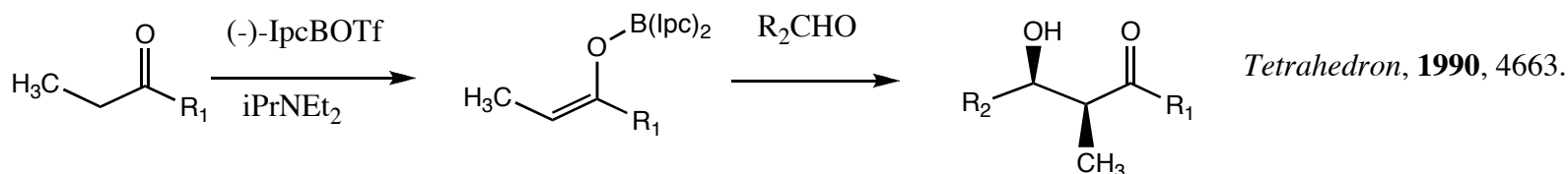
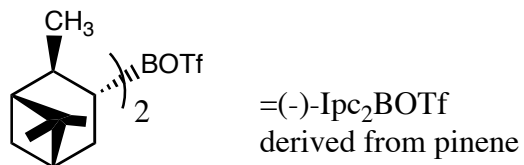
The C.2 stereocenter is the dominant control element for both substrates:



Minimization of A(1,3) interactions in the enolate biases the approach of the aldehyde to the methyl-bearing pi-face of the enolate, while the *E*-geometry afford *anti*-aldol products

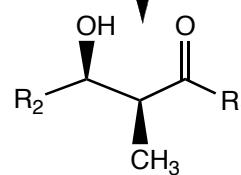
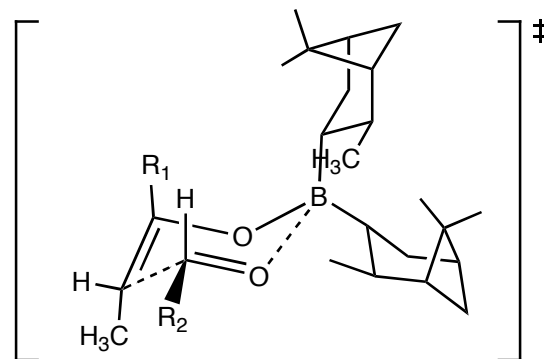
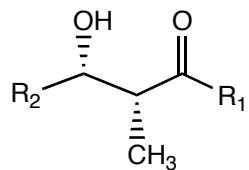
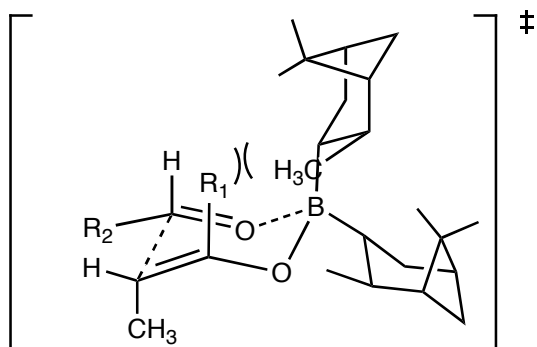
*Tetrahedron*, **1992**, 2127.

# Paterson Aldol, Part 1



- enolization on less hindered side of ketone with *Z* selectivity
- highest ee's with unhindered aldehydes
- aldol additions of methyl ketones not selective
- E*-enolate does not lead to a selective anti aldol reaction

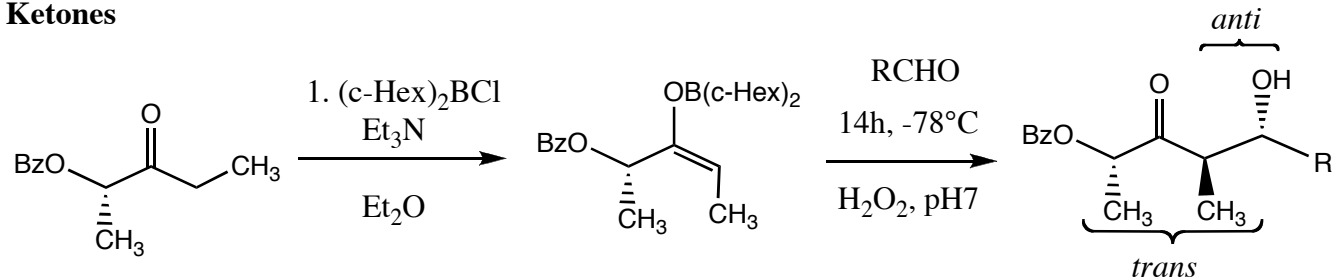
$\text{R}_1=\text{Et}, \text{R}_2=\text{iPr}$  66% ee, 96:4 syn:anti  
 $\text{R}_1=\text{iPr}, \text{R}_2=\text{CH}_2\text{C}(\text{CH}_3)_2$ , 88% ee, 95:5 syn:anti  
 $\text{R}_1=\text{Et}, \text{R}_2=\text{CH}_2\text{C}(\text{CH}_3)_2$ , 91% ee, 98:2 syn:anti



minimizes steric interactions between the Ipc ligand on boron and the  $\text{R}_1$  substituent on the ketone.

## Paterson Aldol, Part 2

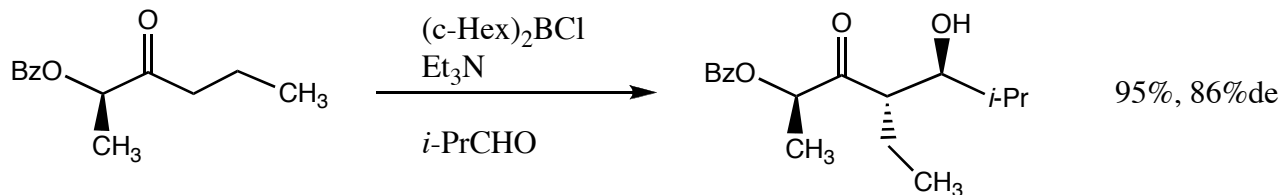
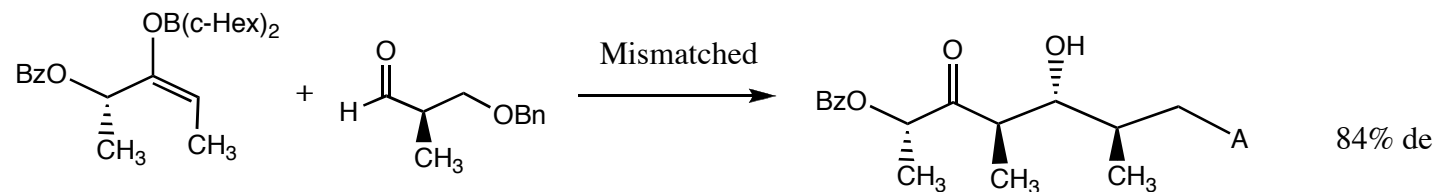
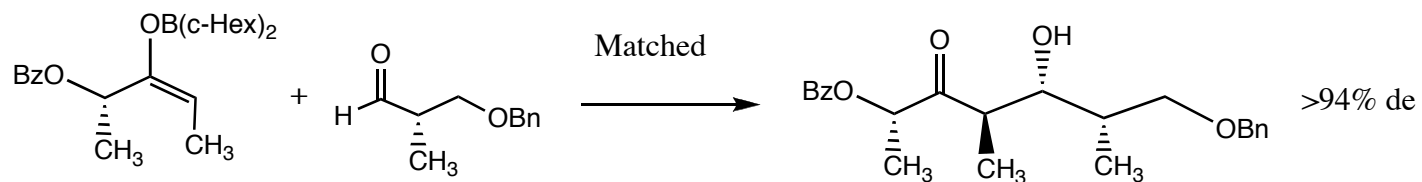
### Anti Aldol Reactions of Lactate-Derived Ketones



*Synthesis*, **1998**, 639.

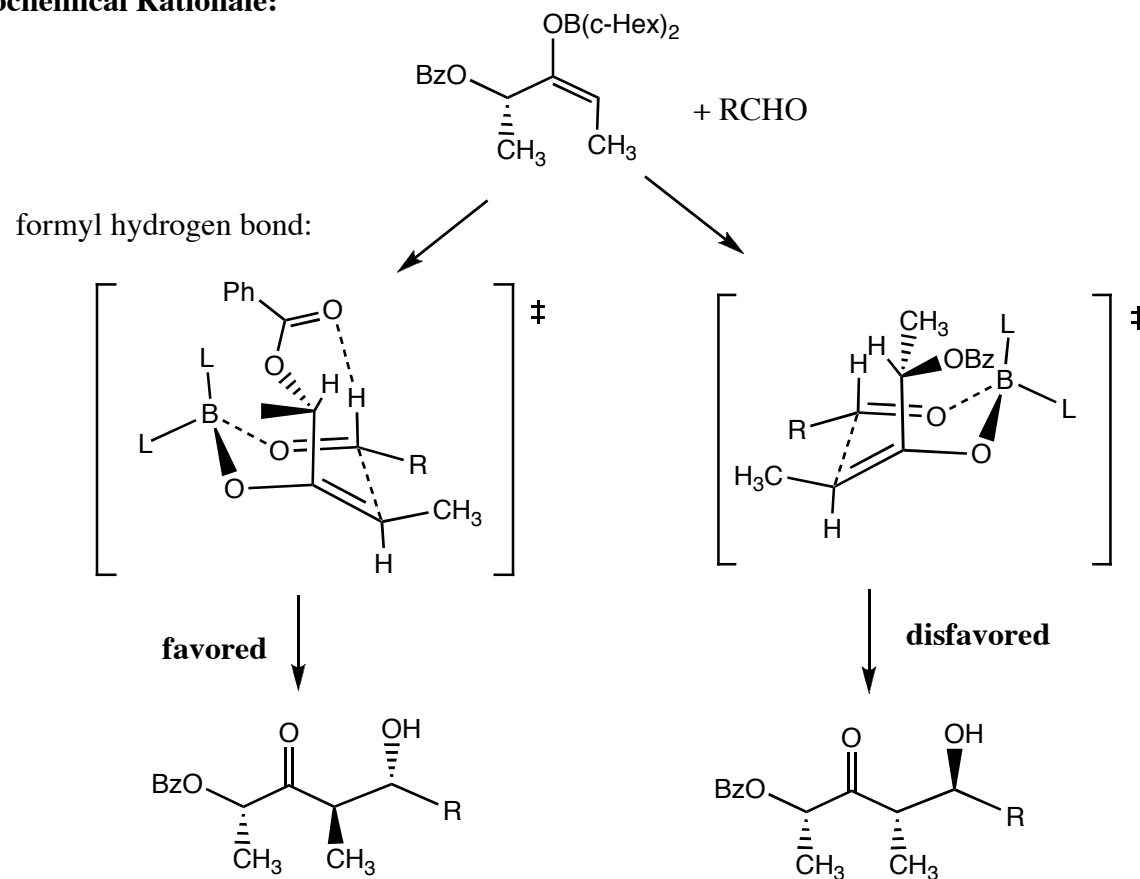
•diastereofacial selectivity is very high; alpha-chiral aldehydes afford anti-aldol adducts with high diastereoselectivity regardless of the stereochemistry.

R=*i*Pr, 94%de  
 R=Et, 99%de  
 R=Ph, 99%de  
 R=CH<sub>2</sub>CHCH, 90%de





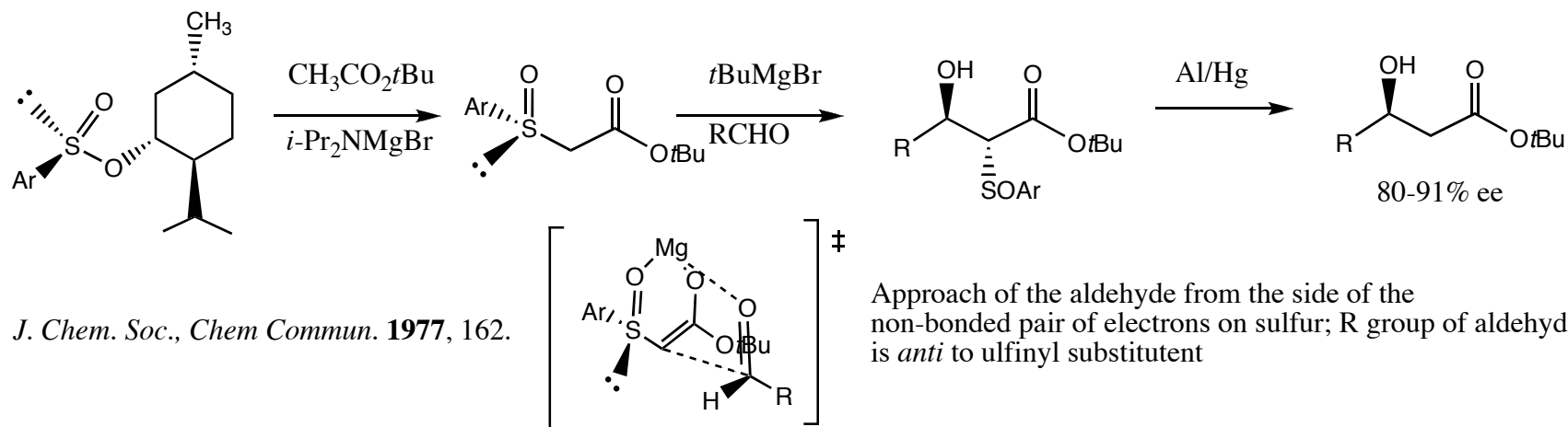
**Stereochemical Rationale:**



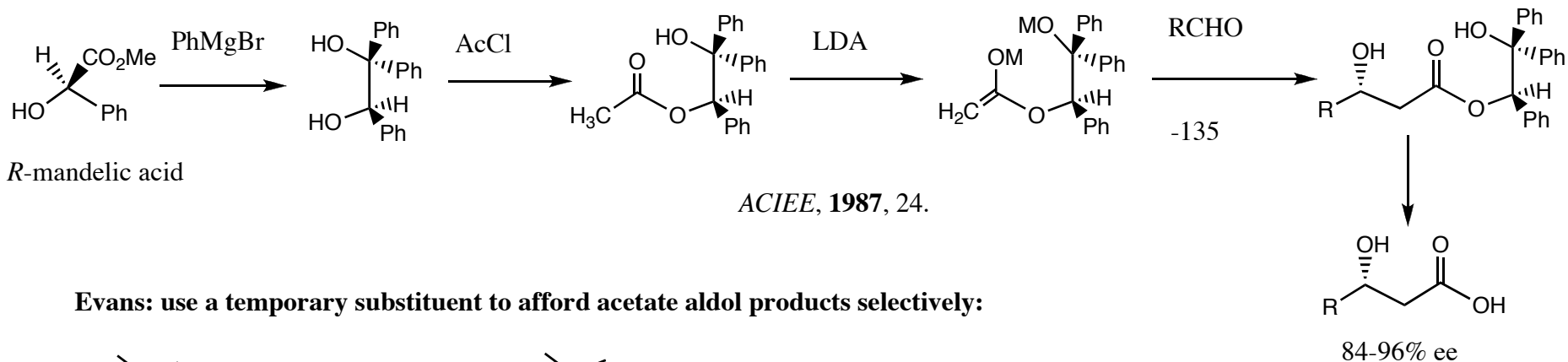
For the utility of these approaches, see Paterson's synthesis of Oleandolide: *JACS*, **1994**, 11287.

## Solutions for the Acetate Aldol Problem

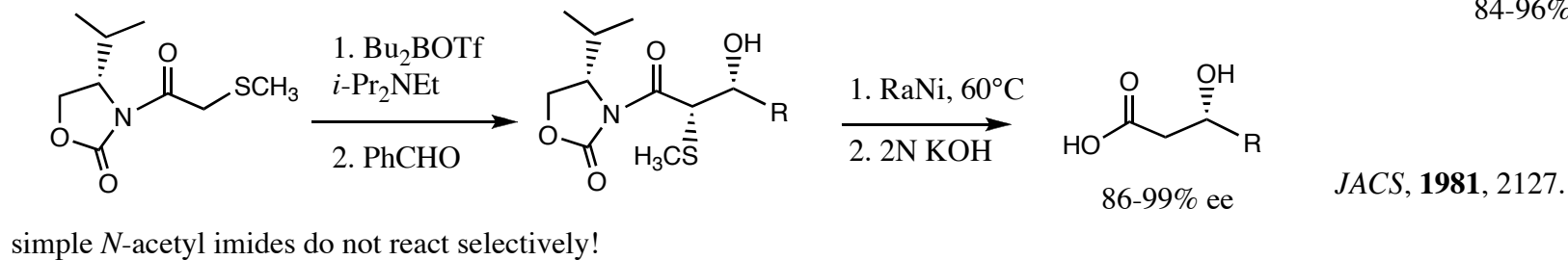
### Chiral alpha-sulfinyl ester:



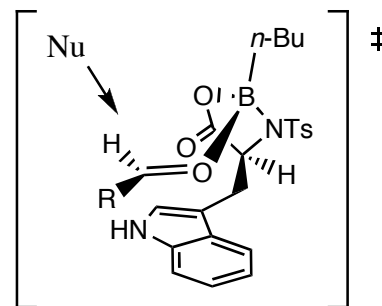
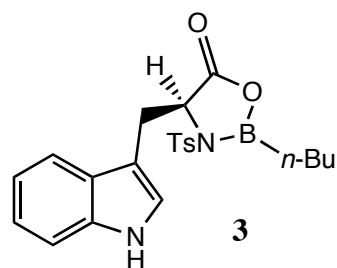
### Chiral Acetate Enolate addition to Aldehydes



### Evans: use a temporary substituent to afford acetate aldol products selectively:

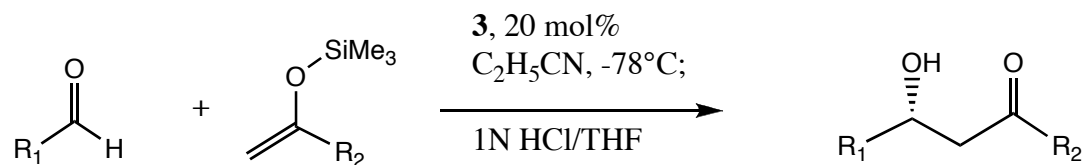


## Enantioselective Mukaiyama Aldol Reactions



*Si* face of aldehyde  
blocked by indole  
ring

*TL*, **1992**, 6907



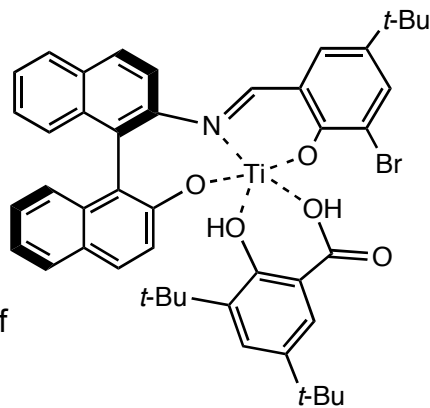
*Tetrahedron*, **1993**, 1761

R<sub>1</sub>=Ph, R<sub>2</sub>=Ph, 89%ee  
R<sub>1</sub>=c-Hex, R<sub>2</sub>=Ph, 93%ee  
R<sub>1</sub>=c-Hex, R<sub>2</sub>=Bu, 86%ee

# Catalytic, Enantioselective Acetate Aldol Additions with Silyl Ketene Acetals

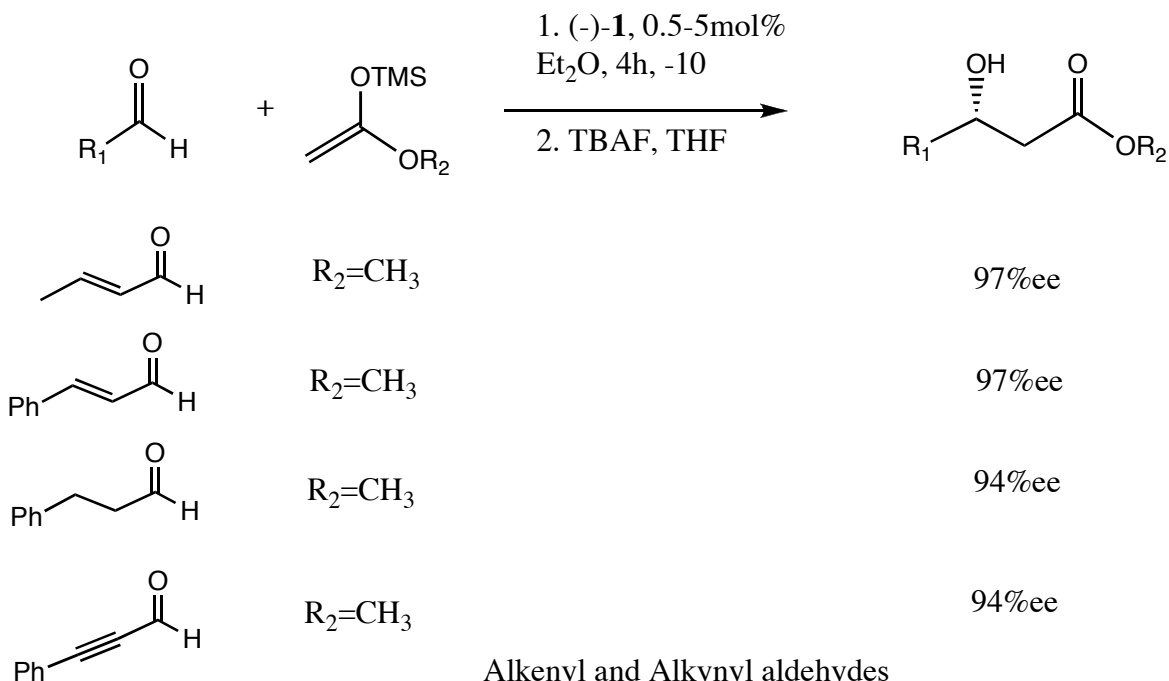
Carreira,  
*JACS*, **1994**, 8837  
*TL*, **1997**, 927  
*Tetrahedron*, **1998**, 7025

An Example of  
 Axial Chirality



(-)-1

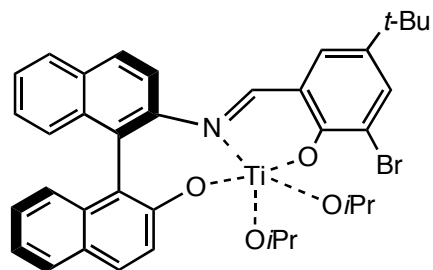
Only *re* face of aldehyde attacked  
 when (-)-1 is used  
 Only *si* face of aldehyde attacked  
 when (+)-1 is used



Alkenyl and Alkynyl aldehydes  
 are particularly good substrates for  
 this process

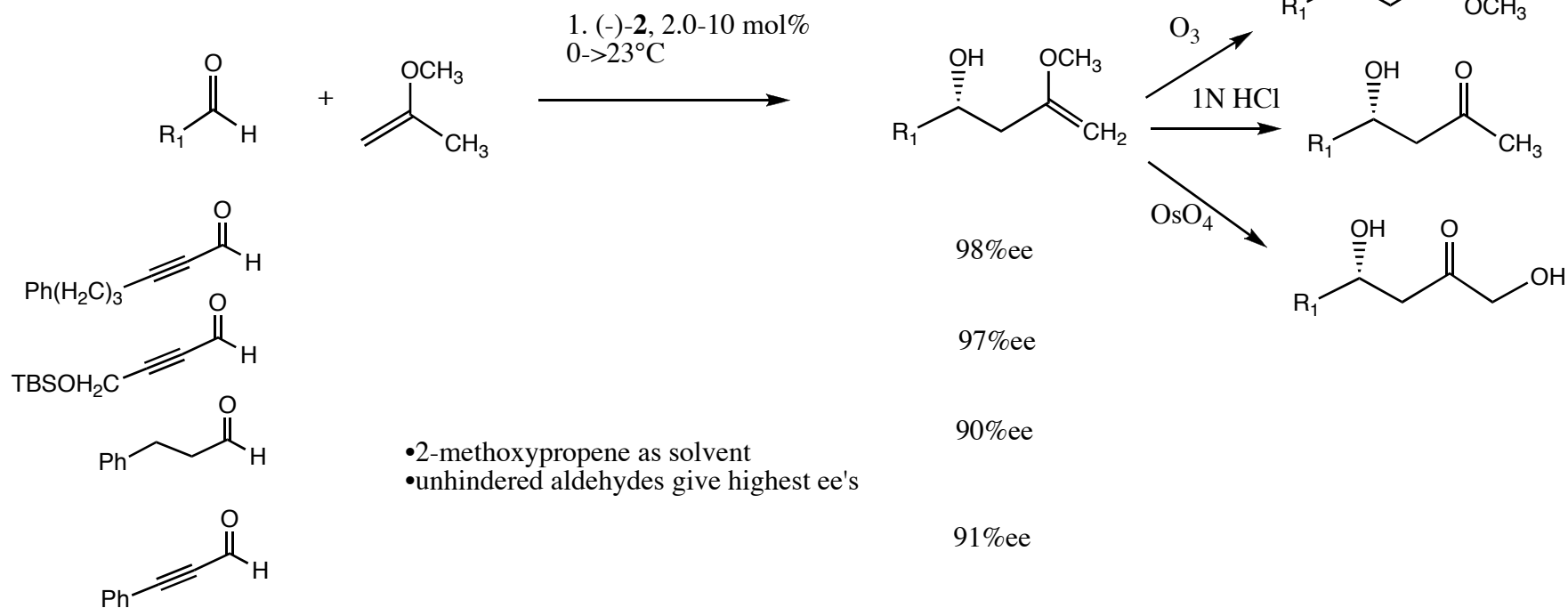
## Acetone Enolate Equivalent: 2-Methoxypropene Aldol Additions

Carreira,  
*JACS*, **1995**, 3649

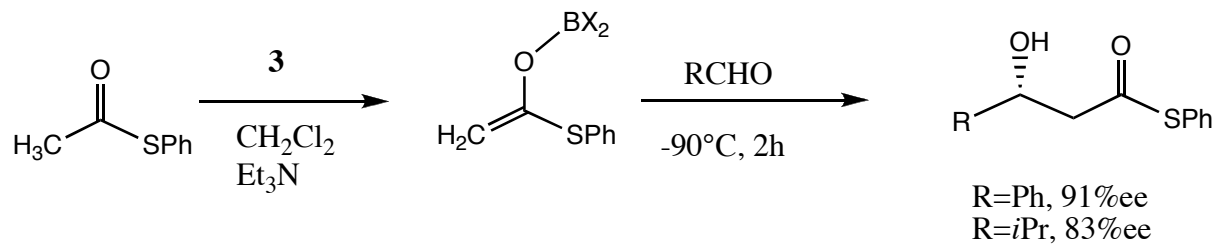
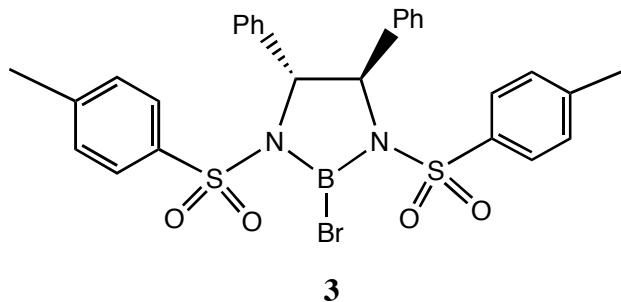


(-)-**2**

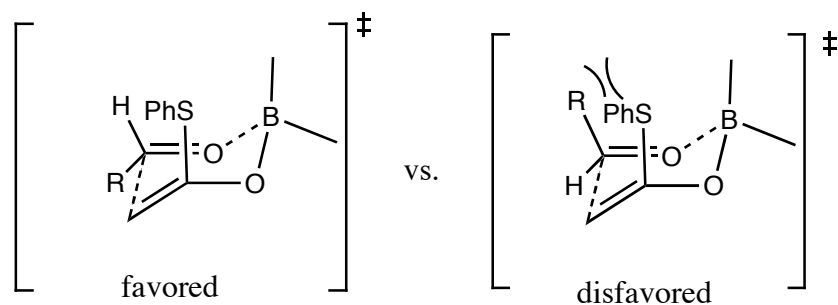
Only *re* face of aldehyde attacked when (-)-**2** is used  
Only *si* face of aldehyde is attacked when (+)-**2** is used



# Corey Enantioselective Acetate Aldol

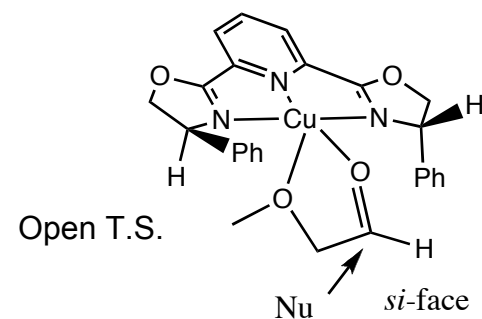
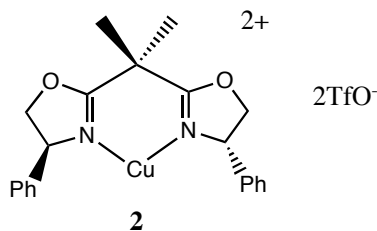
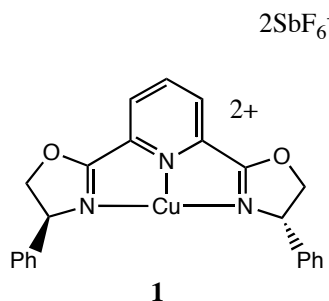


*JACS*, **1989**, 5493

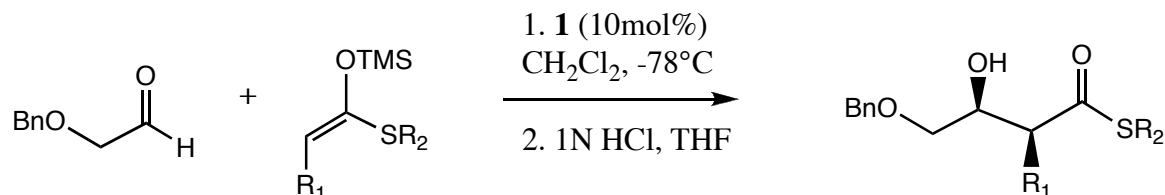


pi-facial selectivity dictated by the catalyst **3**

## Catalytic Enantioselective Aldol Additions



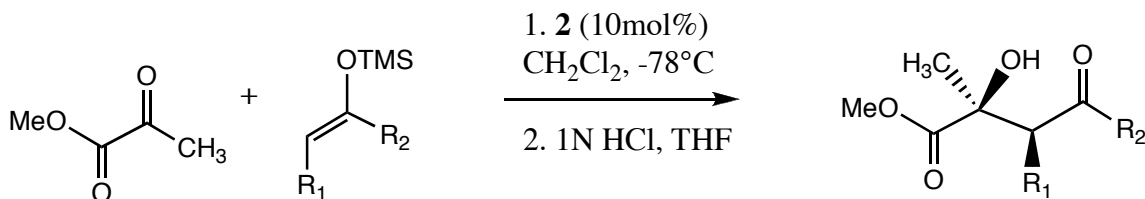
*JACS*, **1999**, 669.



Z or E geometry of enol  
Irrelevant in open T.S.

R<sub>1</sub>=H, R<sub>2</sub>=*t*Bu  
Z R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=Et  
E R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=Et

99% ee  
97% ee 97:3 syn:anti  
85% ee 86:14 syn:anti



Bidentate Coordination  
of the pyruvate is  
proposed

R<sub>1</sub>=H, R<sub>2</sub>=SEt  
R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=StBu  
R<sub>1</sub>=CH<sub>3</sub>, R<sub>2</sub>=SEt

97% ee  
96% ee, 94:6 syn:anti  
98% ee, 98:2 syn:anti

*JACS*, **1997**, 7893.