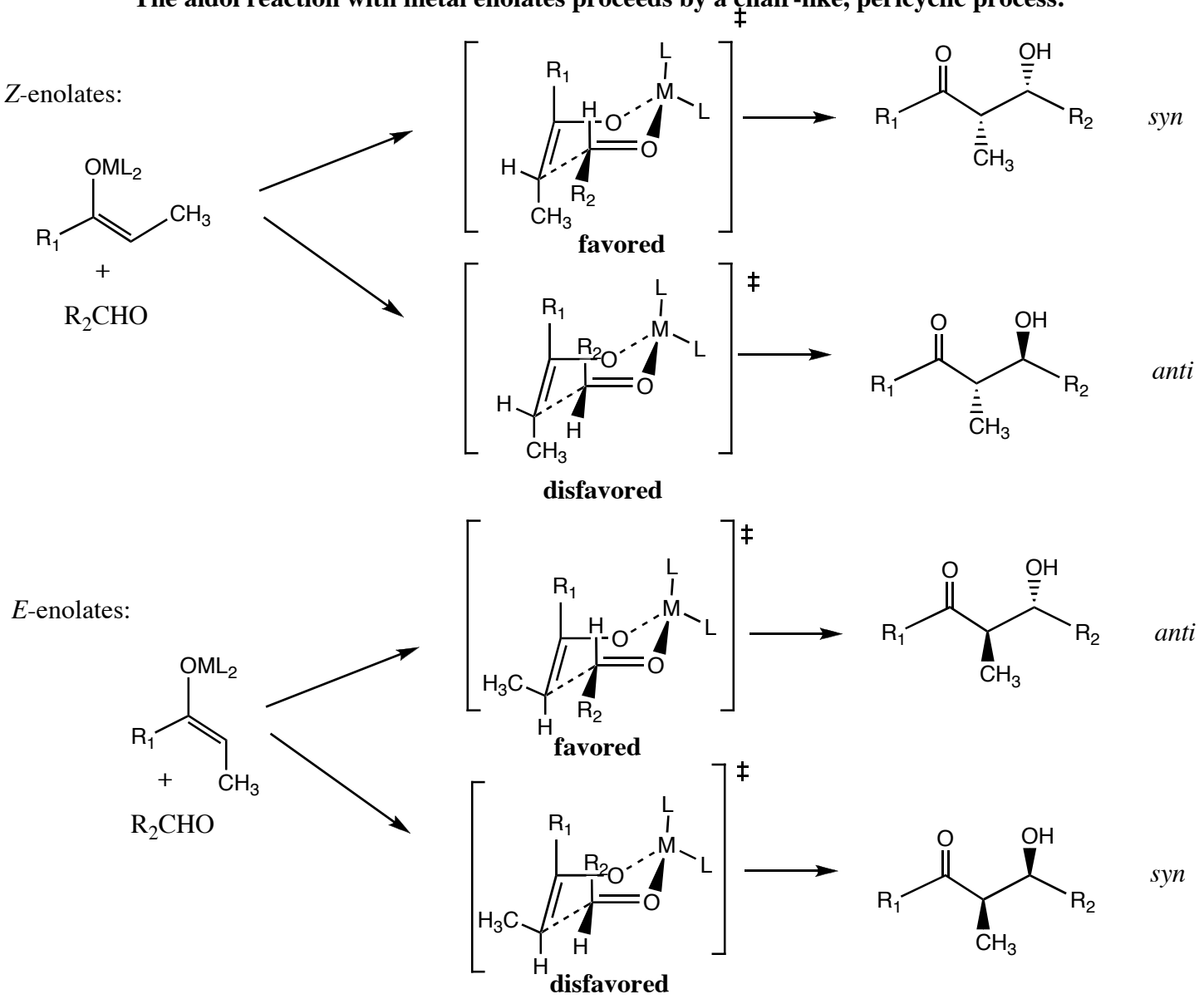
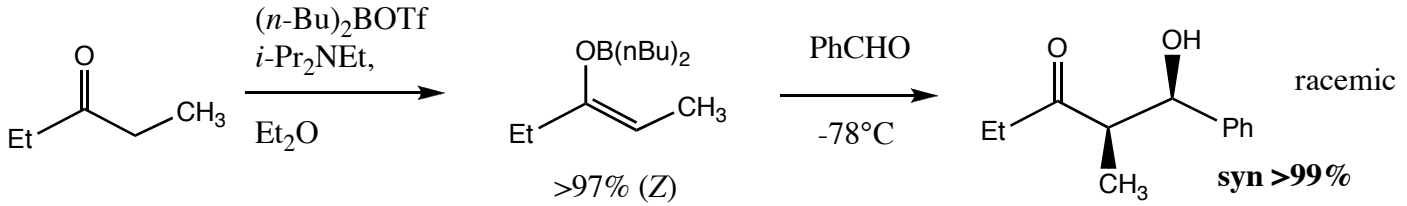
The aldol reaction with metal enolates proceeds by a chair-like, pericyclic process:



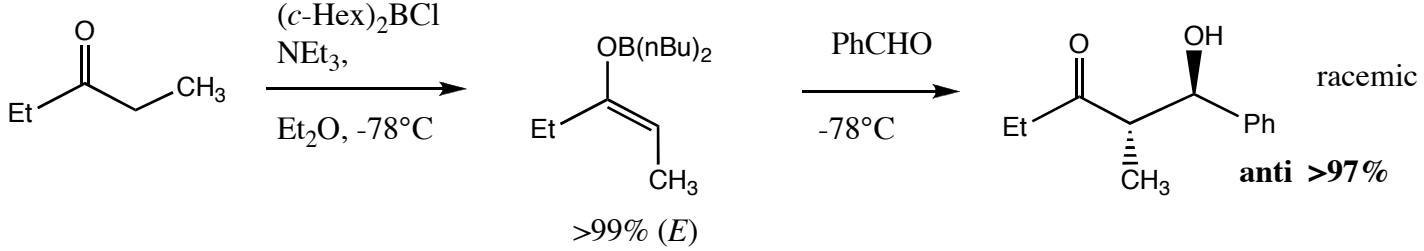
JACS, **1957**, 1920
TL, **1975**, 1225
JOC, **1980**, 1066.

- 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.

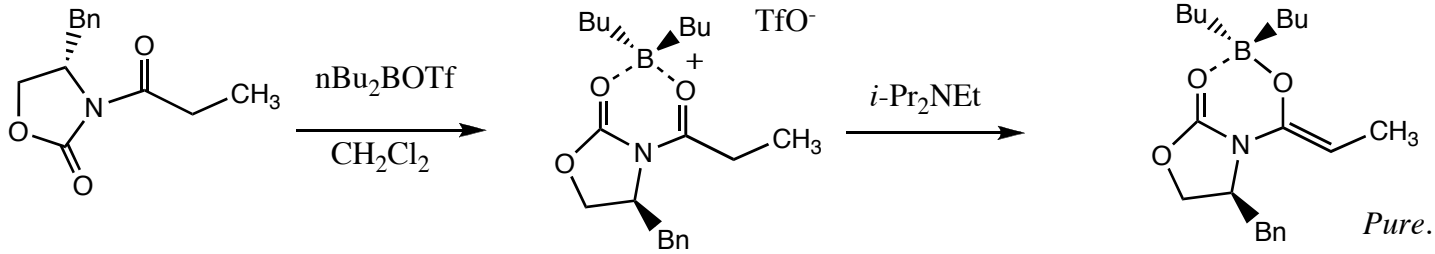
Preparation of (*Z*) and (*E*)- Boron enolates



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



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

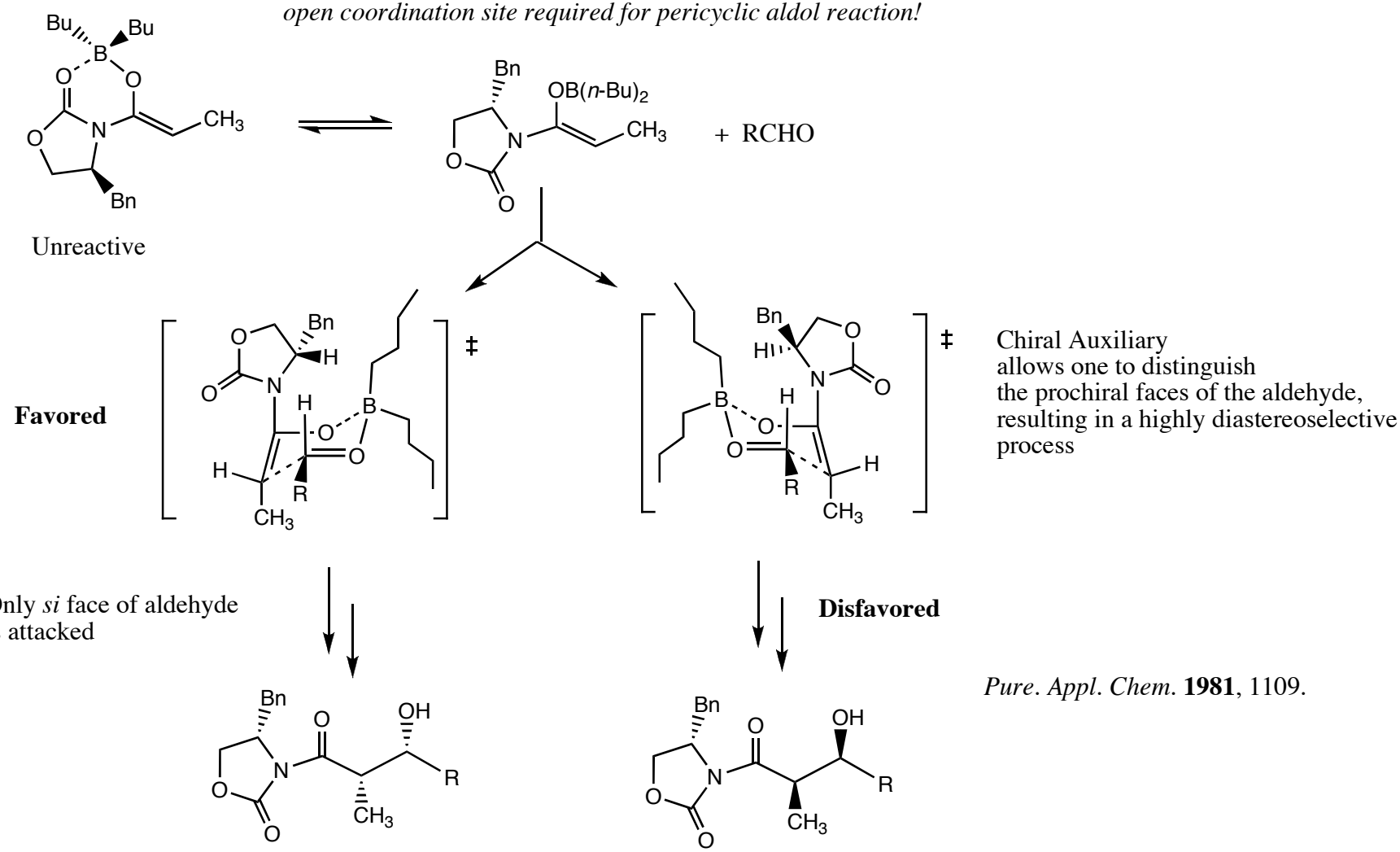


>100:1 *Z:E*

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

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

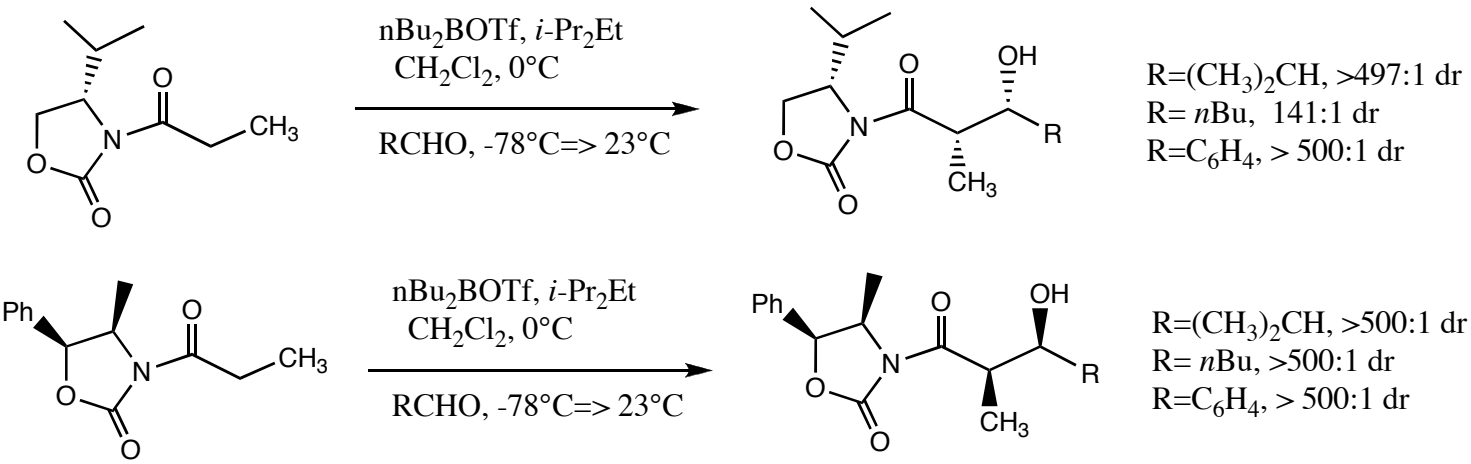
open coordination site required for pericyclic aldol reaction!



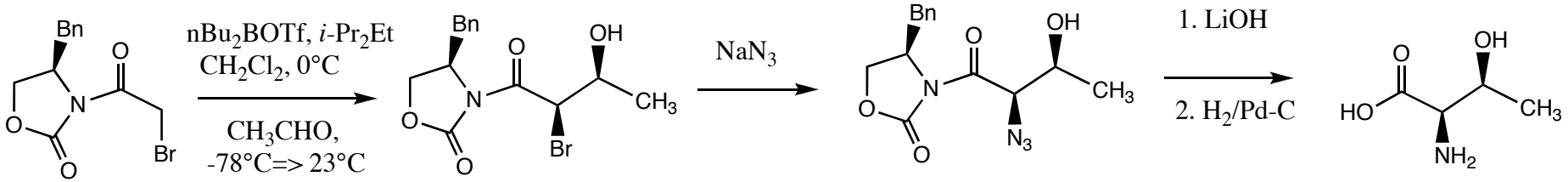
Pure. Appl. Chem. **1981**, 1109.

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

Application of the Technology

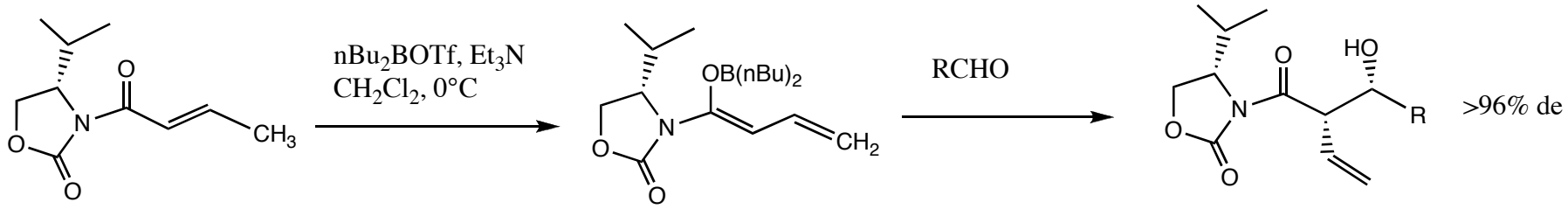


Amino Acid Synthesis:



TL, **1987**, 39.

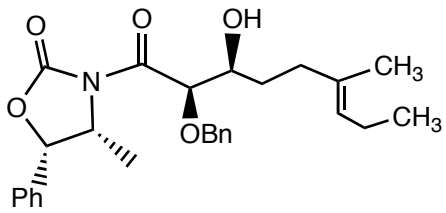
Aldol Additions of Chiral Crotonate Imides



TL, **1986**, 4957.

Methods for Cleavage of Imide Auxiliaries

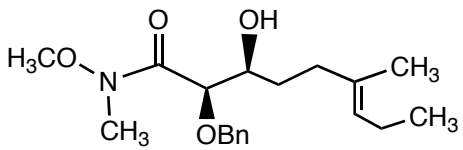
Transamidation:



$Al(CH_3)_3$

$CH_3ONHCH_3 \bullet HCl$

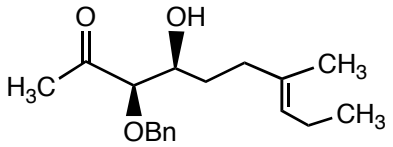
CH_2Cl_2, 0°C

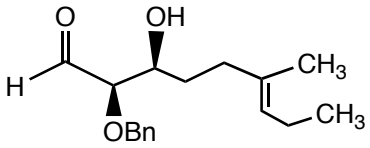


Weinreb Amide

MeLi

DIBAH

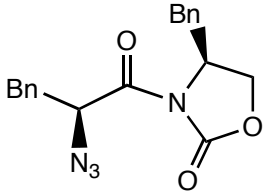




•a free β-hydroxyl group is required

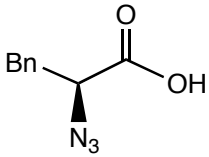
TL, **1981**, 3815.

Hydrolysis:



LiOOH

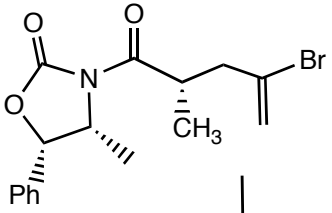
THF, H_2O



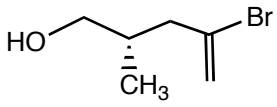
TL, **1987**, 6141

•LiOOH displays greatest regioselectivity for attack on the exocyclic carbonyl

Reductive Cleavage:



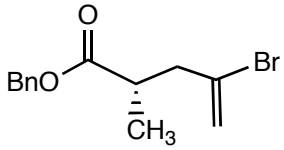
$LiAlH_4$, THF



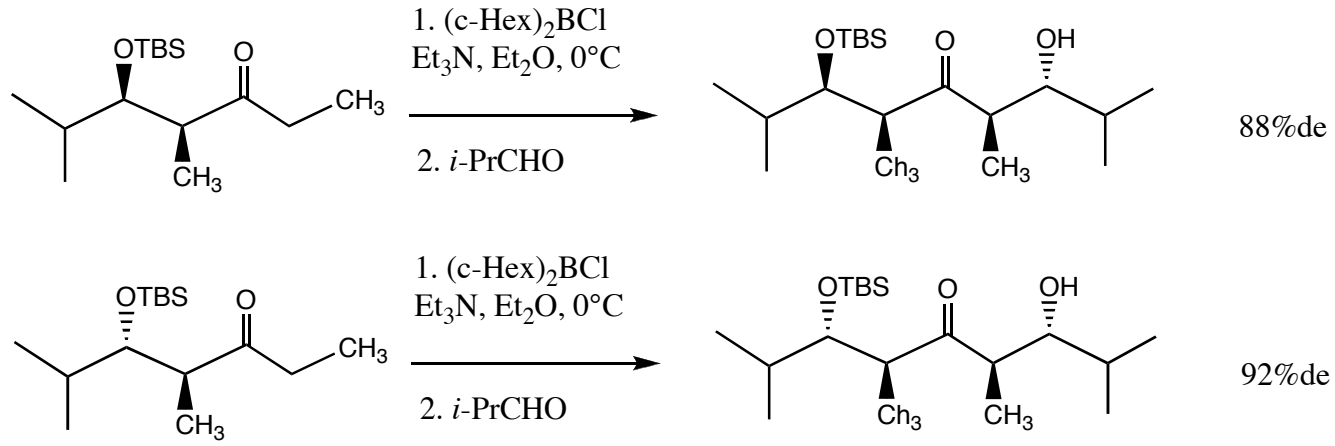
90%

Esterification:

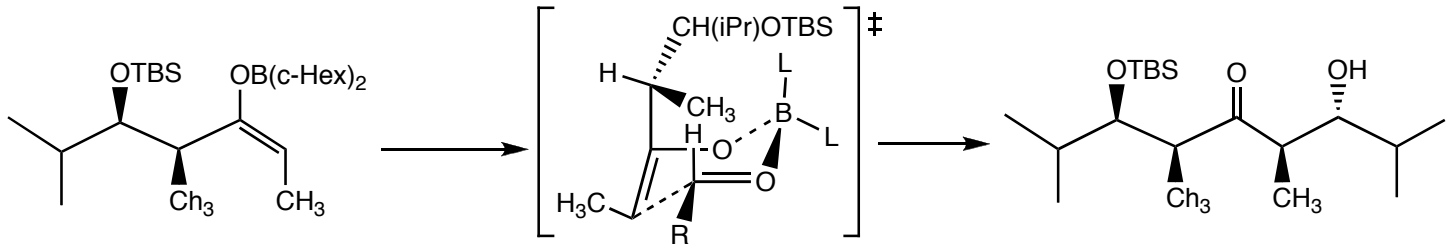
BnOLi



Anti-Selective Aldol Reactions in Related Systems



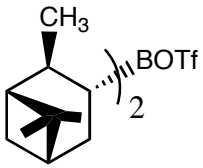
The C.2 stereocenter is the dominant control element for both substrates:



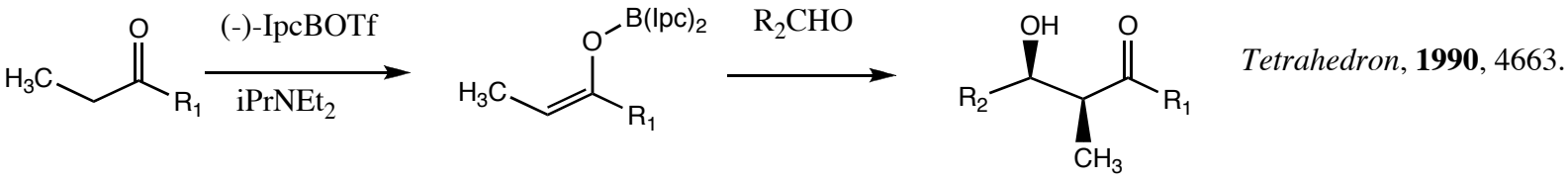
Minimization of A(1,3) interactions in the enolate biases the approach of the aldehyde to the methyl-bearing pi-face of the enolate, while the *E*-geometry afford *anti*-aldol products

Tetrahedron, **1992**, 2127.

Paterson Aldol, Part 1



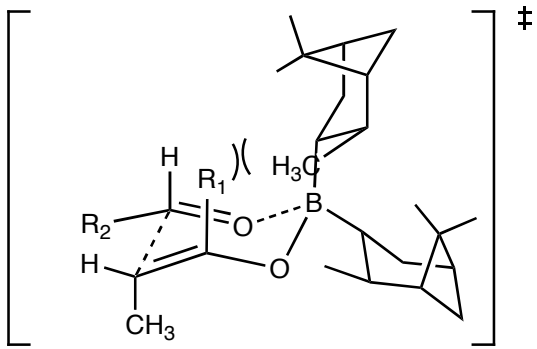
=(-)-Ipc$_2$BOTf
derived from pinene



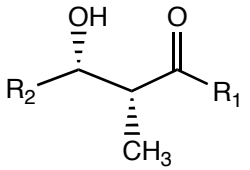
Tetrahedron, **1990**, 4663.

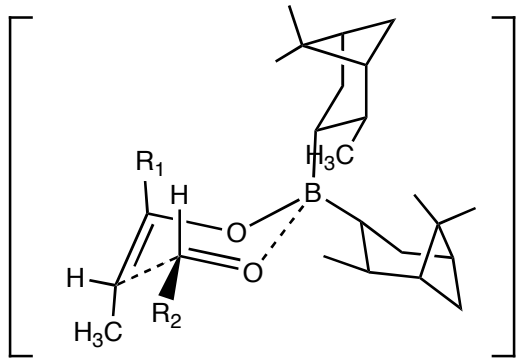
- enolization on less hindered side of ketone with *Z* selectivity
- highest ee's with unhindered aldehydes
- aldol additions of methyl ketones not selective
- *E*-enolate does not lead to a selective anti aldol reaction

R_1=Et, R_2= iPr 66% ee, 96:4 syn:anti
R_1=*i*Pr, R_2 = $CH_2C(CH_3)$, 88% ee, 95:5 syn:anti
R_1=Et, R_2= $CH_2C(CH_3)$, 91% ee, 98:2 syn:anti



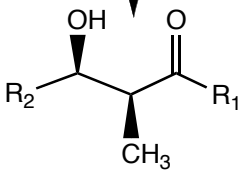
Disfavored





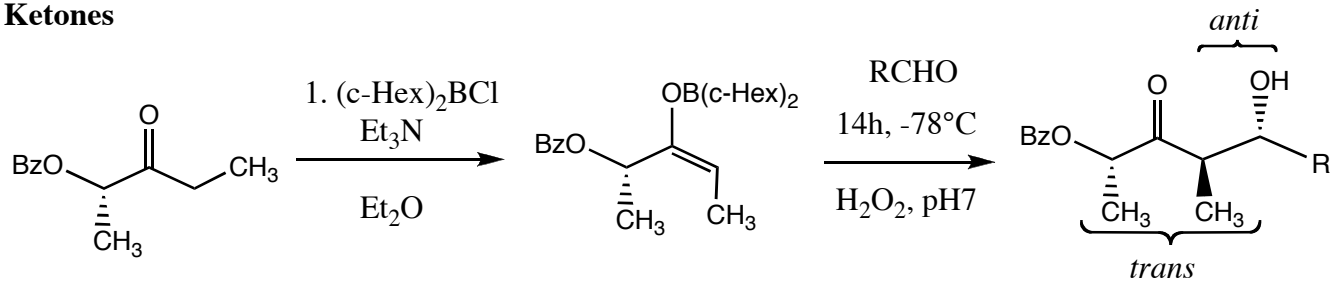
minimizes steric interactions between the Ipc ligand on boron and the R_1 substituent on the ketone.

Favored



Paterson Aldol, Part 2

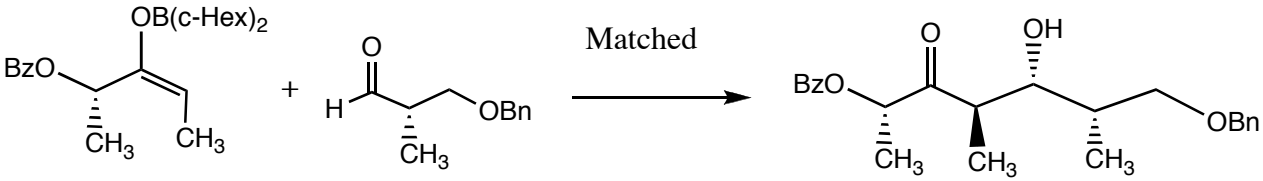
Anti Aldol Reactions of Lactate-Derived Ketones



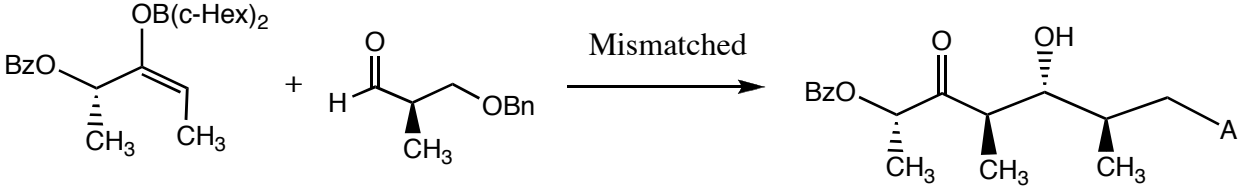
Synthesis, **1998**, 639.

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

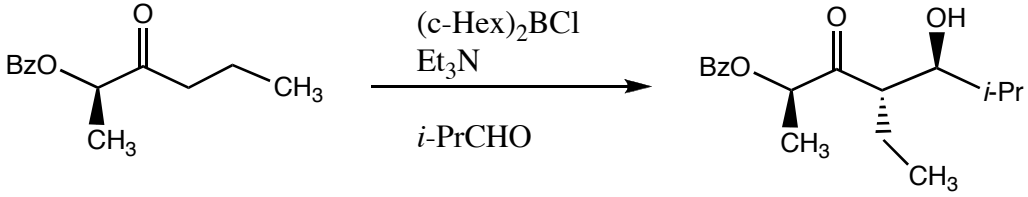
R=*i*Pr, 94%de
R=Et, 99%de
R=Ph, 99%de
R=CH_2CHCH, 90%de



>94% de

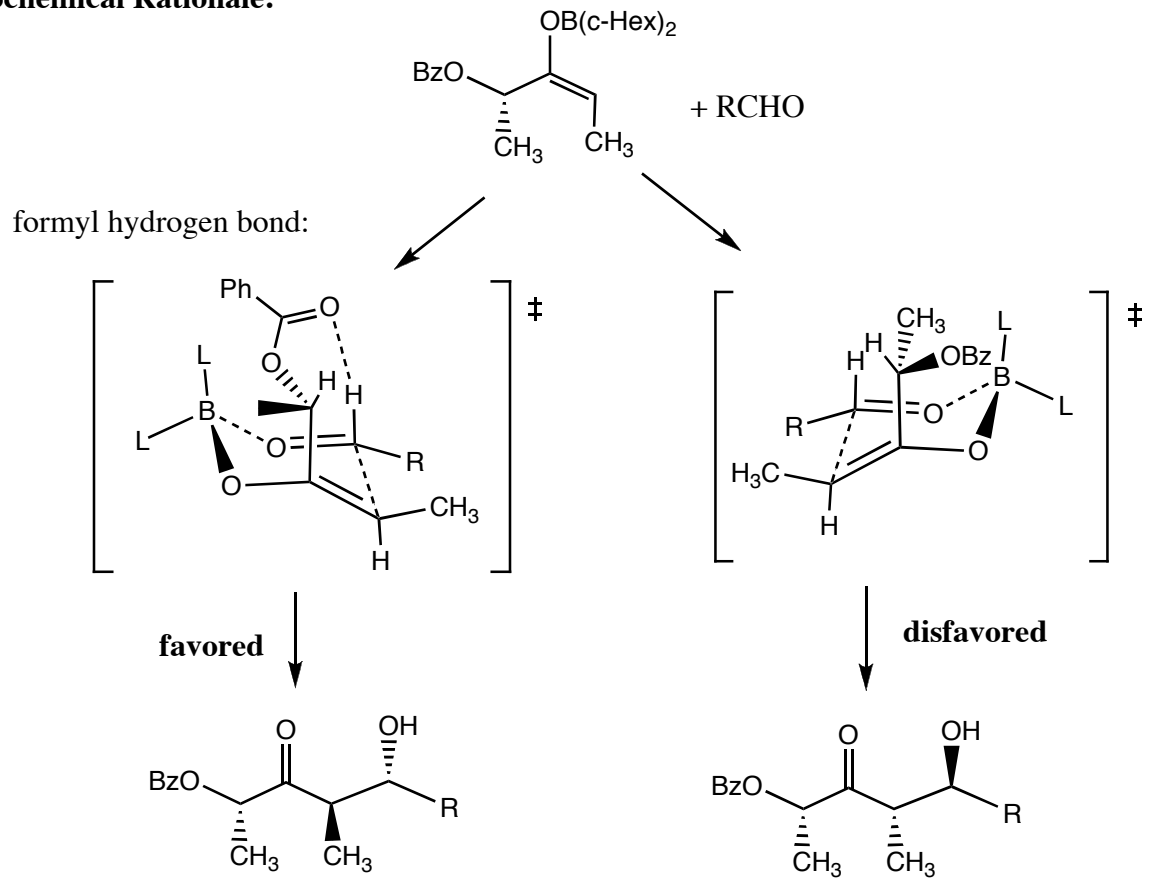


84% de



95%, 86%de

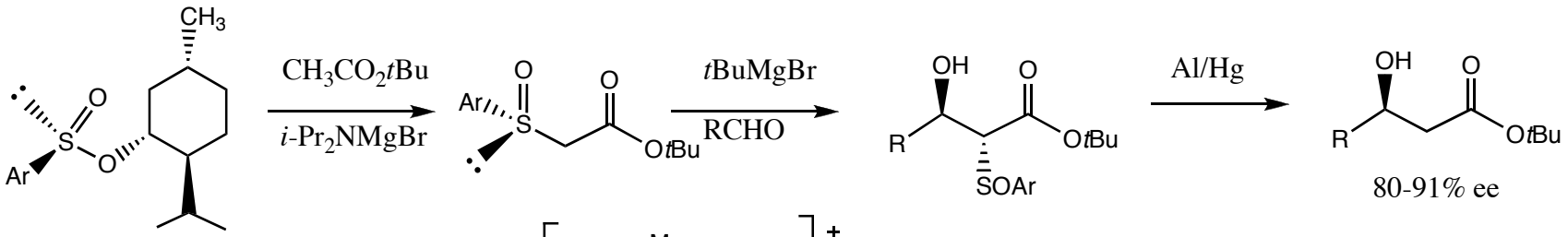
Stereochemical Rationale:



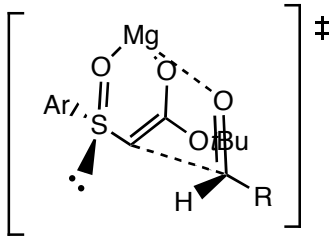
For the utility of these approaches, see Paterson's synthesis of Oleandolide: *JACS*, **1994**, 11287.

Solutions for the Acetate Aldol Problem

Chiral alpha-sulfinyl ester:

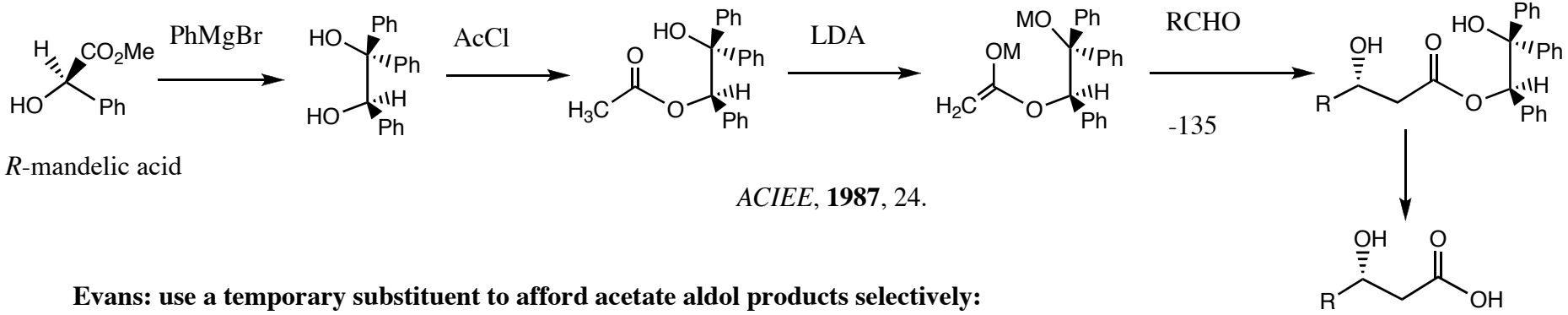


J. Chem. Soc., Chem Commun. **1977**, 162.



Approach of the aldehyde from the side of the non-bonded pair of electrons on sulfur; R group of aldehyde is *anti* to ulfinyl substitutent

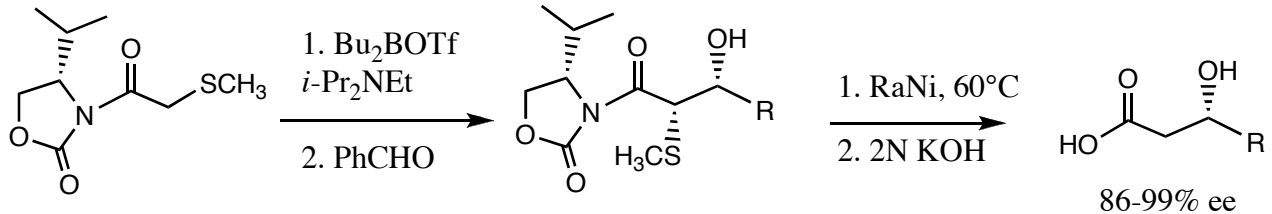
Chiral Acetate Enolate addition to Aldehydes



R-mandelic acid

ACIEE, **1987**, 24.

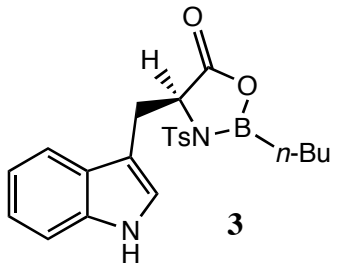
Evans: use a temporary substituent to afford acetate aldol products selectively:



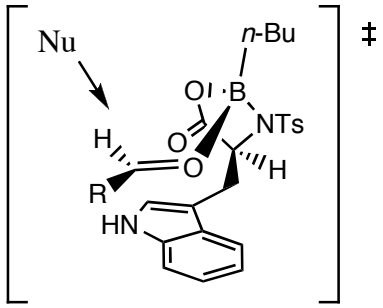
JACS, **1981**, 2127.

simple *N*-acetyl imides do not react selectively!

Enantioselective Mukaiyama Aldol Reactions

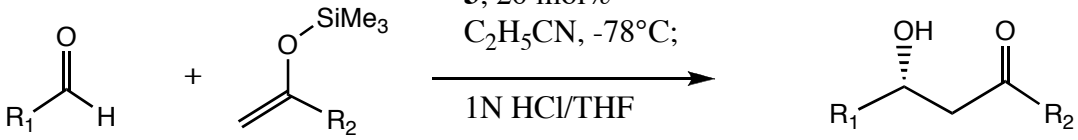


3



Si face of aldehyde blocked by indole ring

TL, **1992**, 6907



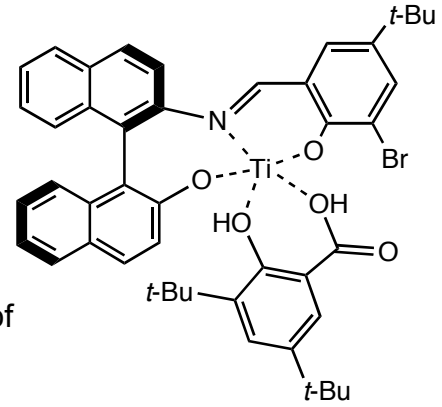
Tetrahedron, **1993**, 1761

R_1=Ph, R_2=Ph, 89%ee
R_1=c-Hex, R_2=Ph, 93%ee
R_1=c-Hex, R_2=Bu, 86%ee

Catalytic, Enantioselective Acetate Aldol Additions with Silyl Ketene Acetals

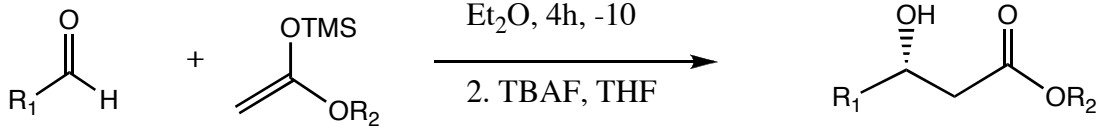
Carreira,
JACS, **1994**, 8837
TL, **1997**, 927
Tetrahedron, **1998**, 7025

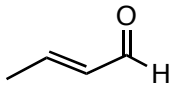
An Example of Axial Chirality



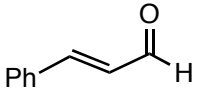
(-)-**1**

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

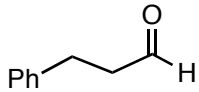




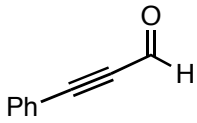
$R_2=CH_3$ 97%ee



$R_2=CH_3$ 97%ee



$R_2=CH_3$ 94%ee

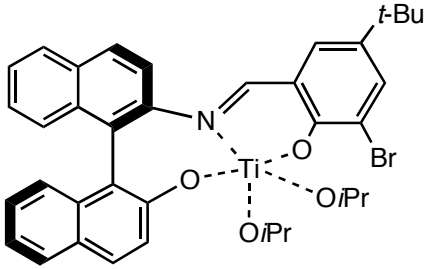


$R_2=CH_3$ 94%ee

Alkenyl and Alkynyl aldehydes are particularly good substrates for this process

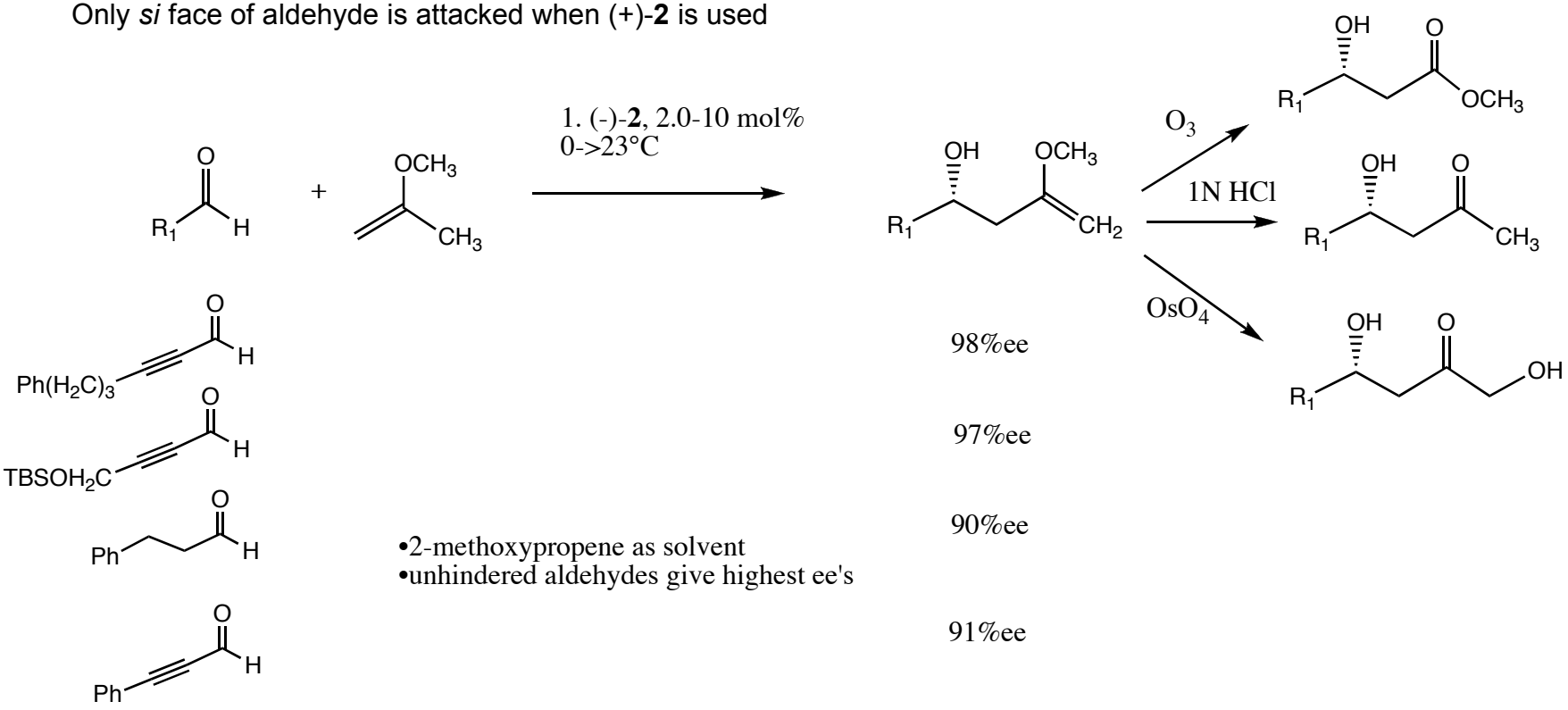
Acetone Enolate Equivalent: 2-Methoxypropene Aldol Additions

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



98%ee

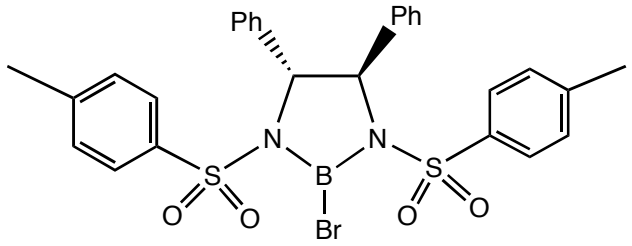
97%ee

90%ee

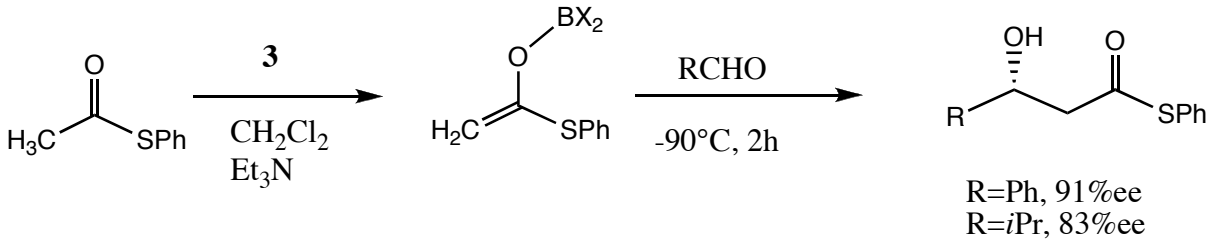
91%ee

- 2-methoxypropene as solvent
- unhindered aldehydes give highest ee's

Corey Enantioselective Acetate Aldol

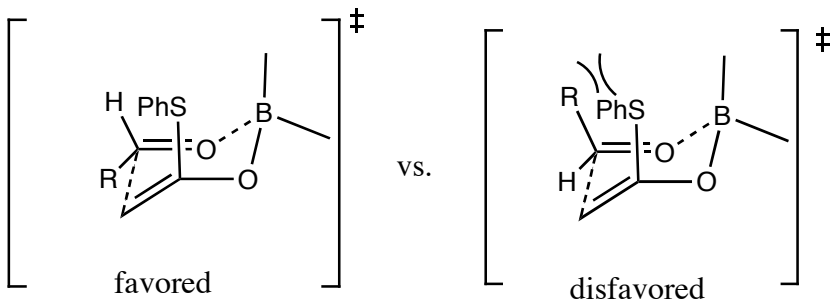


3



R=Ph, 91%ee
R=*i*Pr, 83%ee

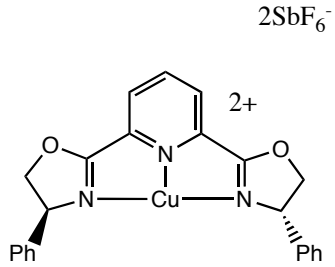
JACS, **1989**, 5493



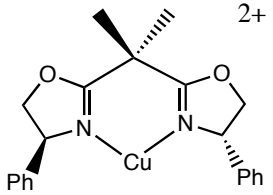
favored disfavored

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

Catalytic Enantioselective Aldol Additions

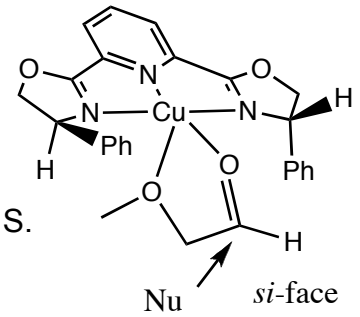


1



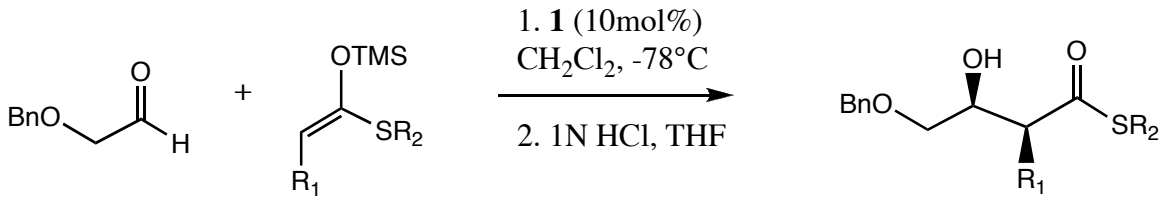
2

$2TfO^-$

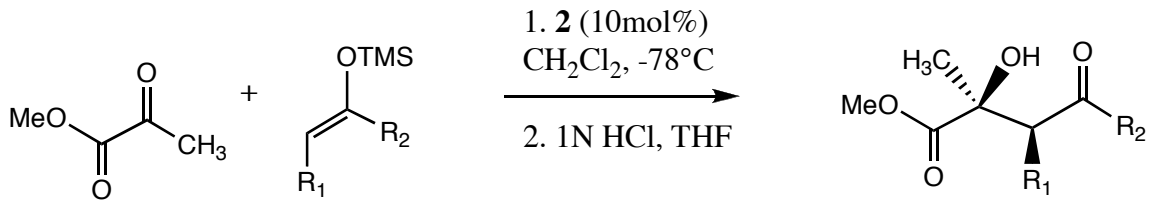


Open T.S.

JACS, **1999**, 669.



	R_1=H, R_2=*t*Bu	99%ee
Z or E geometry of enol Irrelevant in open T.S.	*Z* R_1=CH_3, R_2=Et	97%ee 97:3 syn:anti
	E R_1=CH_3, R_2=Et	85% ee 86:14 syn:anti



	R_1=H, R_2=SEt	97%ee
Bidentate Coordination of the pyruvate is proposed	R_1=CH_3, R_2=StBu	96%ee, 94:6 syn:anti
	R_1=CH_3, R_2=SEt	98% ee, 98:2 syn:anti

JACS, **1997**, 7893.