

## Reviews:

Heathcock, C. H. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 133-238.

Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 239-275.

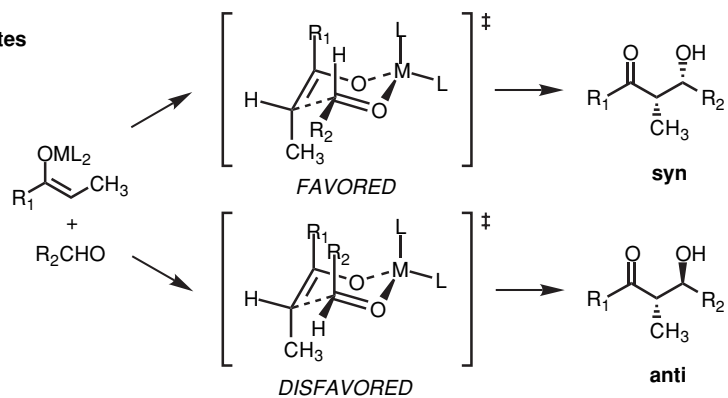
Paterson, I. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, Vol. 2, pp. 301-319.



- The aldol reaction was discovered by Aleksandr Porfir'evich Borodin in 1872 where he first observed the formation of "aldol", 3-hydroxybutanal, from acetaldehyde under the influence of catalysts such as hydrochloric acid or zinc chloride.

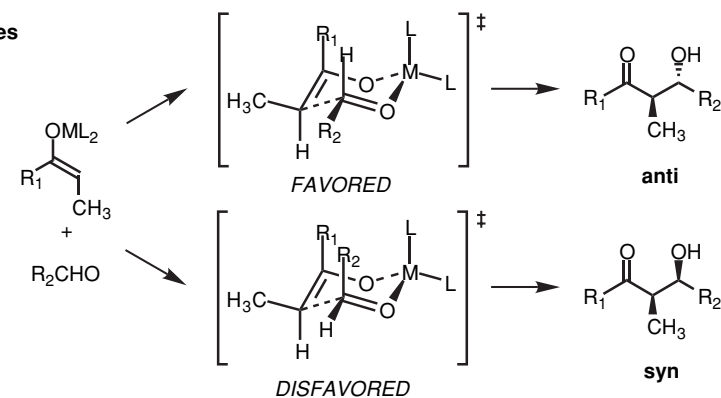
#### Diastereofacial Selectivity in the Aldol Addition Reaction- Zimmerman-Traxler Chair-Like Transition States

##### (Z)-enolates



- Note: the enantiomeric transition states (not shown) are, by definition, of equal energies. The pericyclic transition state determines syn/anti selectivity. To differentiate two syn or two anti transition states, a chiral element must be introduced (e.g., R<sub>1</sub>, R<sub>2</sub>, or L), thereby creating diastereomeric transition states which, by definition, are of different energies.

##### (E)-enolates



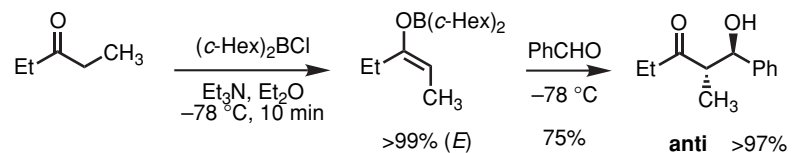
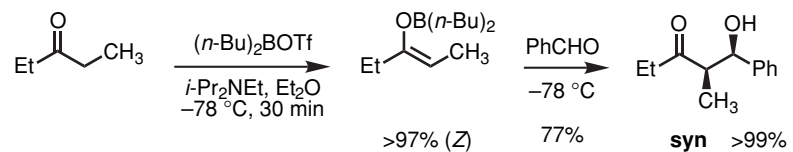
- Zimmerman and Traxler proposed that the aldol reaction with metal enolates proceeds via a chair-like, pericyclic process. In practice, the stereochemistry can be highly metal dependent. Only a few metals, such as boron, reliably follow the indicated pathways.
- (Z)- and (E)-enolates afford *syn*- and *anti*-aldol adducts, respectively, by minimizing 1,3-diaxial interactions between R<sub>1</sub> and R<sub>2</sub> in each chair-like TS<sup>‡</sup>.

Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.

Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225-1228.

Heathcock, C. H.; Buse, C. T.; Kleschnick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

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



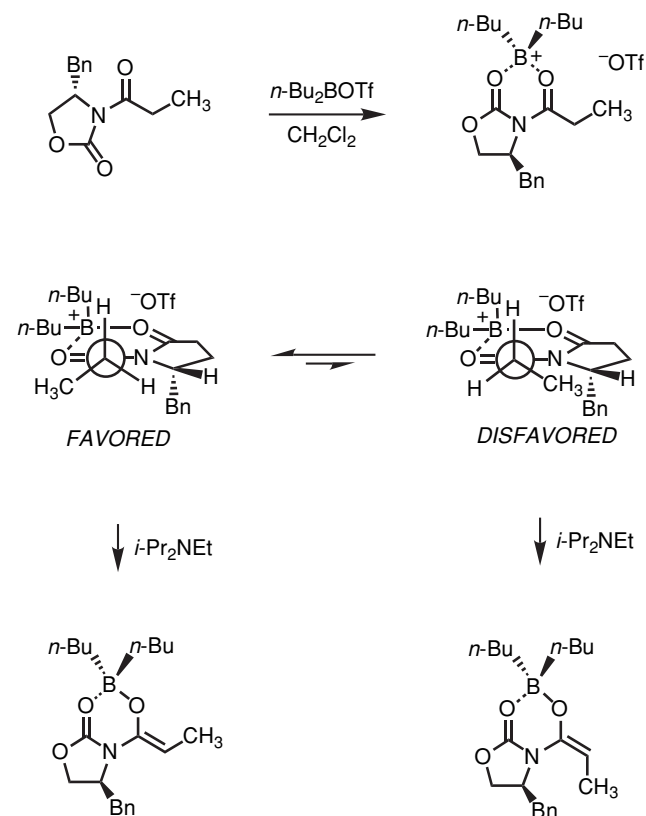
- Dialkylboron triflates typically afford (Z)-boron enolates, with little sensitivity toward the amine used or the steric requirements of the alkyl groups on the boron reagent.
- In the case of dialkylboron chlorides the geometry of the the product enolates is much more sensitive to variations in the amine and the alkyl groups on boron.
- The combination of (c-Hex)<sub>2</sub>BCl and Et<sub>3</sub>N provides the (E)-boron enolate preferentially.

Evans, D. A.; Vogel, E.; Nelson, J. V.; *J. Am. Chem. Soc.* **1979**, *101*, 6120.

Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

Brown, H. C.; Dhar, R. K. Bakshi, R. K. Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441-3442.

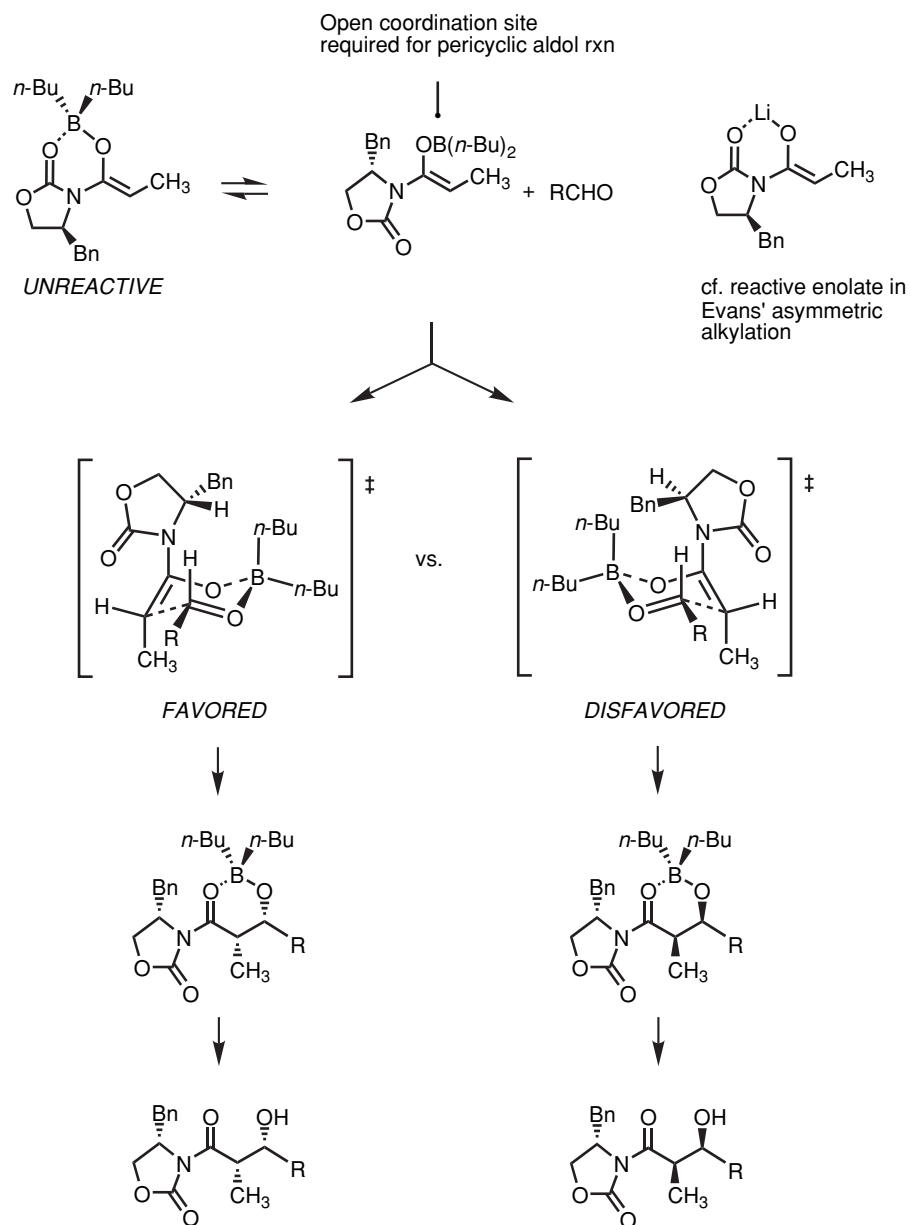
## (Z)-Selective Preparation of Boron Enolates from Evans' Acyl Oxazolidinones (Imides)



- Observed selectivity:  $\geq 100:1$  Z : E

Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

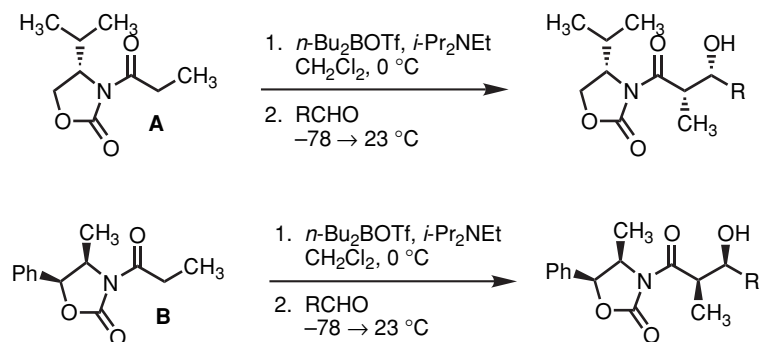
## Syn-Selective Aldol Reactions of Imide-Derived Boron (Z)-Enolates



Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J. Bartroli, J. *Pure & Appl. Chem.* **1981**, *53*, 1109-1127.

- Chiral controller group biases enolate  $\pi$ -faces such that one of the two diastereomeric (syn) transition states is greatly favored.

- Dipole-dipole interactions within the imide are minimized in the reactive conformation (see: Noe, E. A.; Raban, M. *J. Am. Chem. Soc.* **1975**, *97*, 5811-5820).



imide	aldehyde	diastereomeric <sup>a</sup>	
		ratio	yield
<b>A</b>	$(\text{CH}_3)_2\text{CHCHO}$	497:1	78
<b>B</b>	$(\text{CH}_3)_2\text{CHCHO}$	<1:500	91
<b>A</b>	$n\text{-C}_4\text{H}_9\text{CHO}$	141:1	75
<b>B</b>	$n\text{-C}_4\text{H}_9\text{CHO}$	<1:500	95
<b>A</b>	$\text{C}_6\text{H}_5\text{CHO}$	>500:1	88
<b>B</b>	$\text{C}_6\text{H}_5\text{CHO}$	<1:500	89

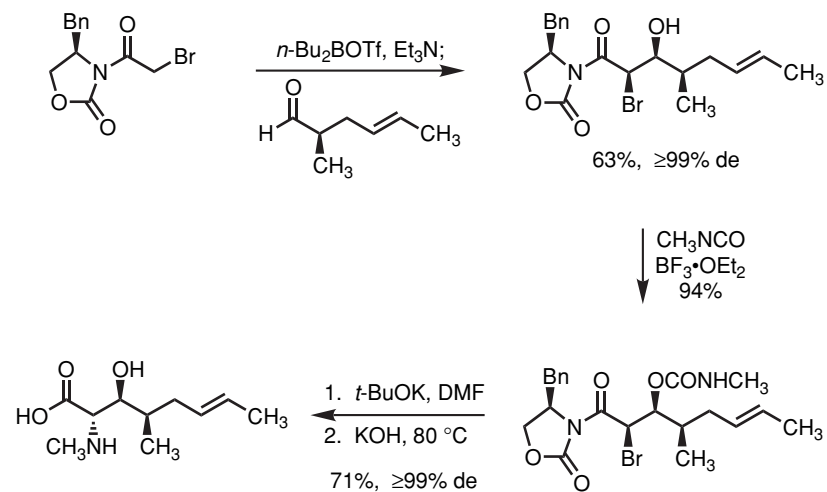
<sup>a</sup>Ratio of major syn product to minor syn product.

- A variety of chiral imides can be used for highly selective aldol reactions.
- Anti products are typically formed in less than 1% yield.
- Often, a single crystallization affords diastereomerically pure product.

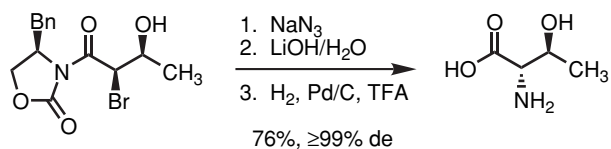
Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

Evans, D. A.; Gage, J. R. *Org. Syn.* **1990**, *68*, 83.

## Asymmetric Synthesis of Anti $\beta$ -Hydroxy- $\alpha$ -Amino Acids



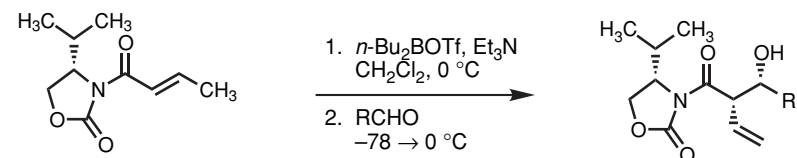
- 2-Chloro- and 2-Bromoacetyl imides undergo aldol addition with high diastereoselectivity (88-96% de, 63-79% yield).



- Bromide displacement occurs with clean inversion.

Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, 28, 39-42.

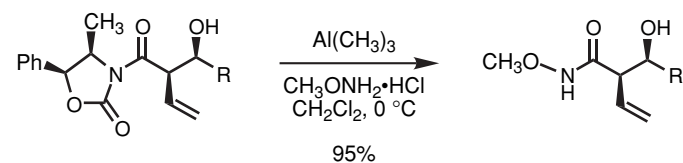
## Aldol Addition Reactions of Chiral Crotonate Imides



aldehyde	yield (%) <sup>a</sup>
$\text{CH}_3\text{CHO}$	82
$(\text{CH}_3)_2\text{CHCHO}$	90
$\text{C}_6\text{H}_5\text{CHO}$	92

<sup>a</sup>>96% de.

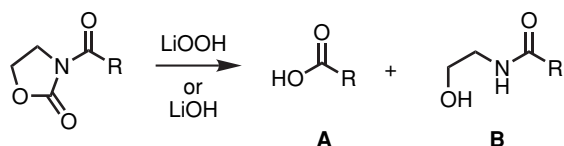
- The use of triethylamine rather than diisopropylethylamine is essential in these examples because self-condensation (Michael addition) can compete with enolization.



- Although the aldol adducts are sensitive to base-induced retro-aldol reaction, aluminum amides are found to cleave the auxiliary efficiently.

Evans, D. A.; Sjogren, E. B.; Bartoli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, 27, 4957-4960.

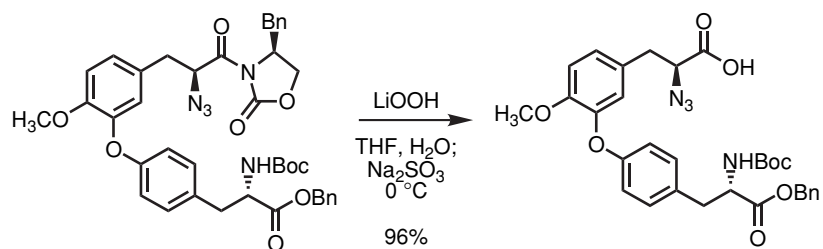
## Carboximide Hydrolysis with Lithium Hydroperoxide



substrate	reagent	yield of <b>A</b> (%) <sup>a</sup>	yield of <b>B</b> (%) <sup>a</sup>
	LiOOH	76	16
	LiOH	0	100
	LiOOH	98	<1
	LiOH	43	30

<sup>a</sup>Yield of diastereomerically pure (>99:1) product.

- LiOOH displays the greatest regioselectivity for attack of the exocyclic carbonyl group.
- This selectivity is most pronounced with sterically congested acyl imides.
- This is a general solution for the hydrolysis of all classes of oxazolidinone-derived carboximides and allows for efficient recovery of the chiral auxiliary.

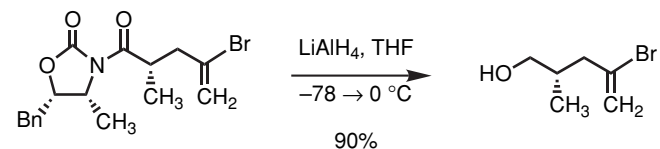


- The selective hydrolysis of carboximides can be achieved in the presence of unactivated esters using LiOOH.

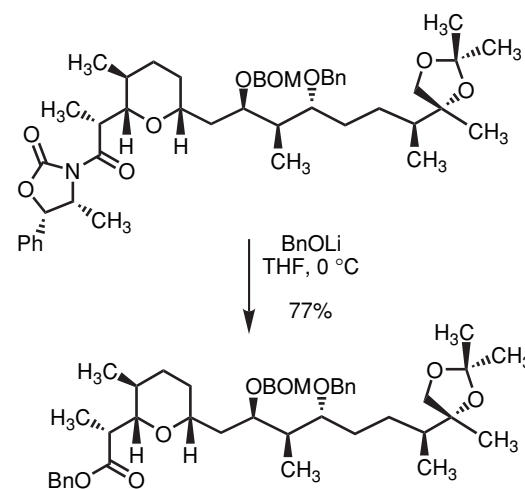
Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.  
Gage, J. R.; Evans, D. A. *Org. Syn.* **1990**, *68*, 83-91.

## Other Methods for Removal of the Chiral Auxiliary

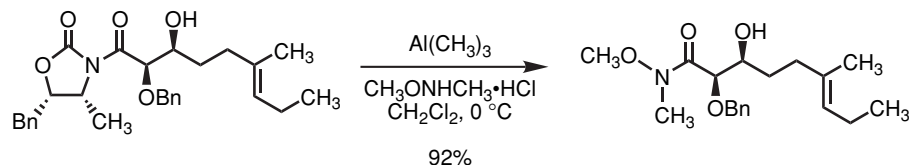
- Reductive cleavage:



- Esterification:



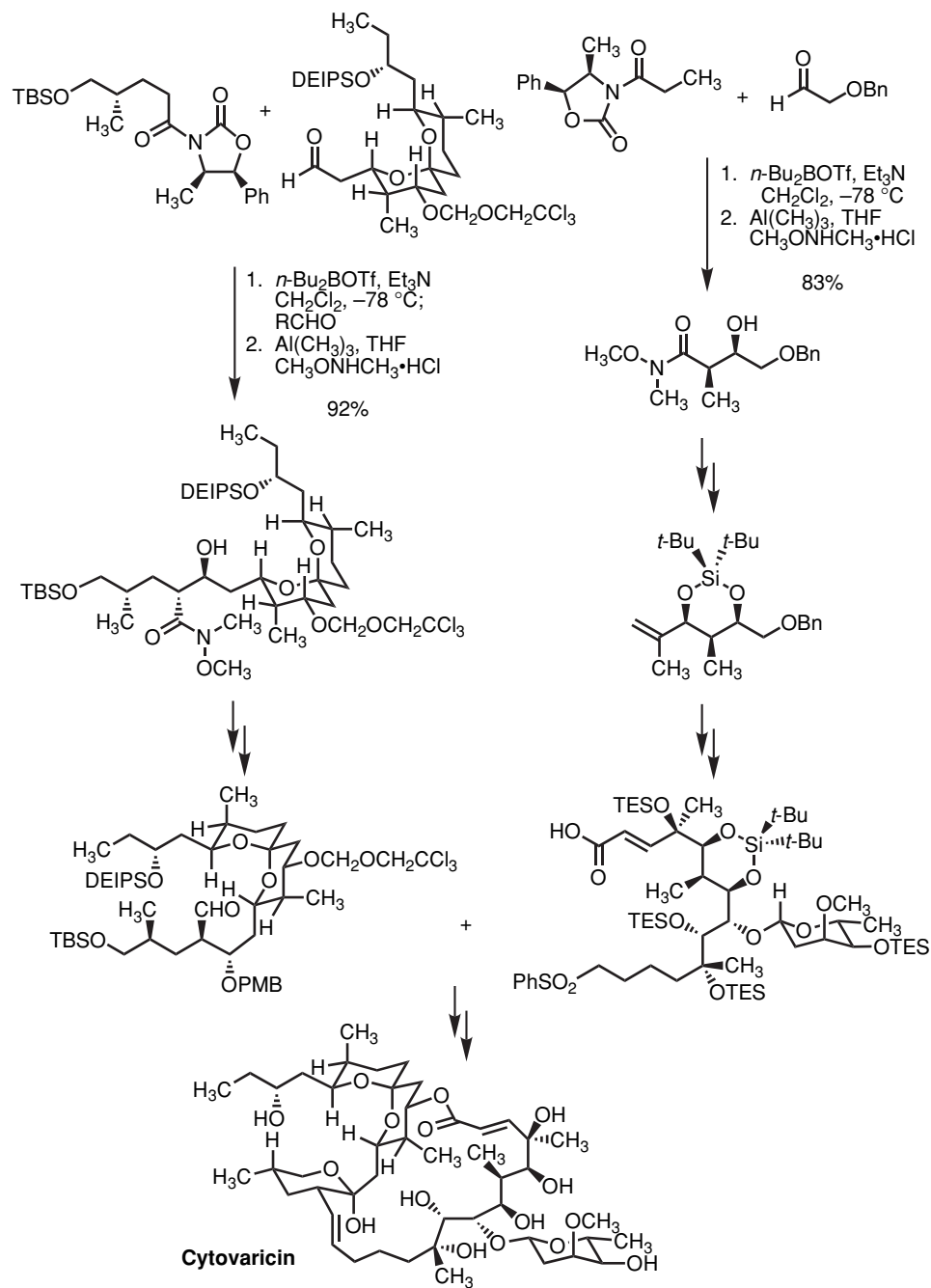
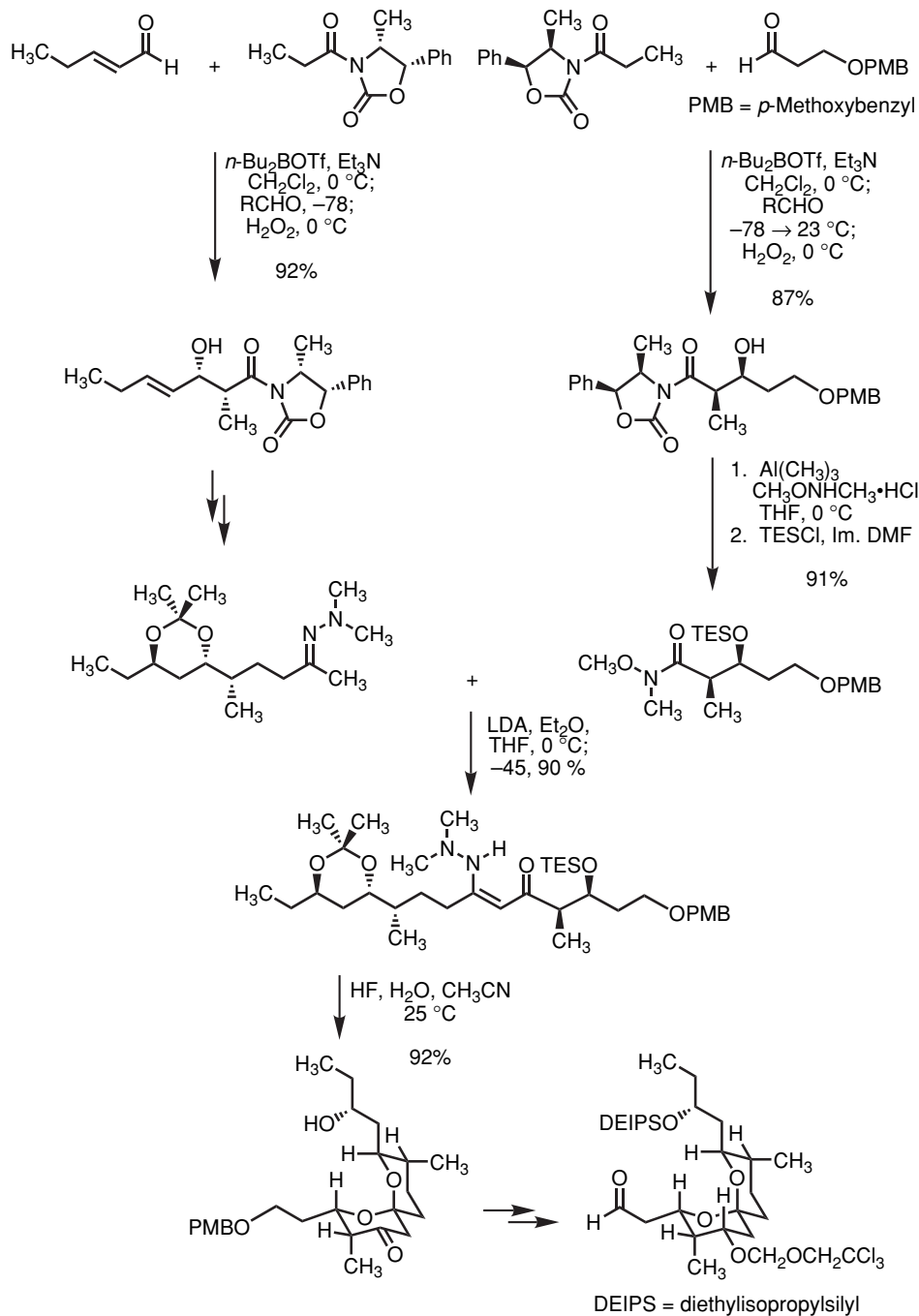
- Transamination (as before):



- A free  $\beta$ -hydroxyl group is required.
- Weinreb amides can be readily converted into ketones or aldehydes (see: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818).

Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526.

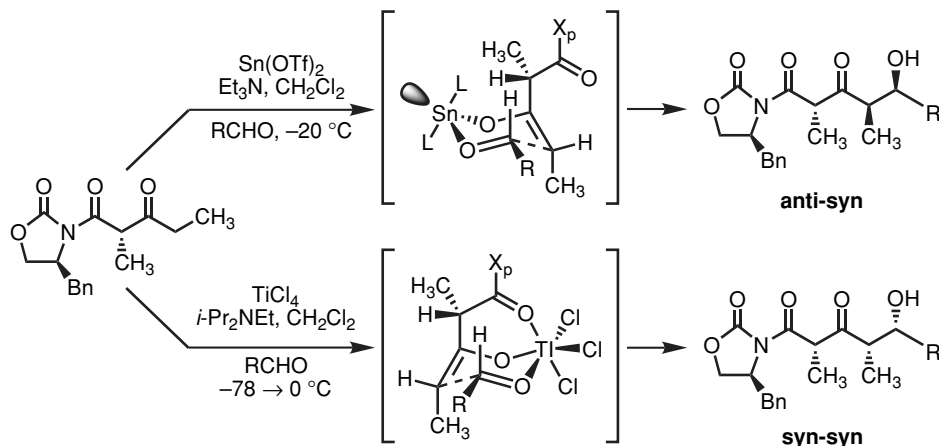
**Cytovaricin:**



Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

M. Movassaghi

### Diastereoselective *Syn*-Aldol Reaction of $\beta$ -Ketoimides



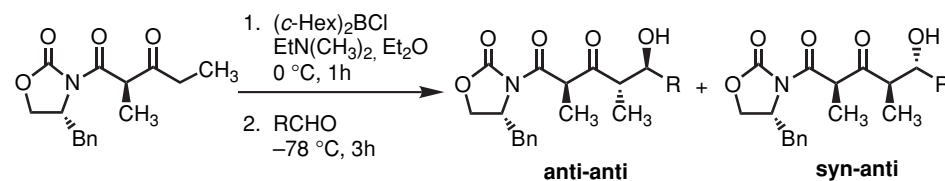
enolization conditions	RCHO <sup>a</sup>	yield % <sup>b</sup>	ratio anti-syn : syn-syn
A		83	95:5
B		86	<1:99
A		77 <sup>c</sup>	95:5
B		64 <sup>c</sup>	2:98
A		71	79:21
B		86	<1:99
A		85	89:11
B		81	4:96

A: Sn(OTf)<sub>2</sub>, Et<sub>3</sub>N; B: TiCl<sub>4</sub>, *i*-Pr<sub>2</sub>NEt. <sup>a</sup>1.0-1.1 equiv  
<sup>b</sup>isolated yield of major diastereomer (>99% purity). <sup>c</sup>3-5 equiv of RCHO was used.

- Both enolization methods provide (*Z*)-enolates and (diastereomeric) *syn* aldol products.
- The stereochemical outcome of both reactions is dominated by the C<sub>2</sub> methyl-bearing stereocenter, as shown in the proposed transition states above.
- Use of excess aldehyde (3-5 equiv) is necessary where polymerization of the aldehyde is a problem (i.e.,  $\alpha$ -methacrolein).
- The chirality of the oxazolidinone has little influence on the diastereoselectivity of these reactions.

Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868.

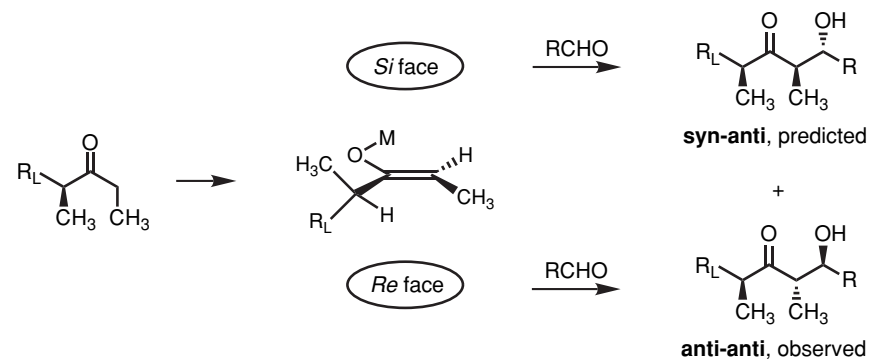
### Diastereoselective *Anti*-Aldol Reactions of $\beta$ -Ketoimides



aldehyde	yield % <sup>a</sup>	ratio anti-anti : syn-anti
(CH <sub>3</sub> ) <sub>2</sub> CHCHO	78	84:16
CH <sub>2</sub> =C(CH <sub>3</sub> )CHO	72	92:8
CH <sub>3</sub> CH <sub>2</sub> CHO	70 <sup>b</sup>	80:20
PhCH <sub>2</sub> CH <sub>2</sub> CHO	84 <sup>b</sup>	88:12
	84	97:3

<sup>a</sup>Isolated yield of major diastereomer. <sup>b</sup>Yield of purified mixture of diastereomers.

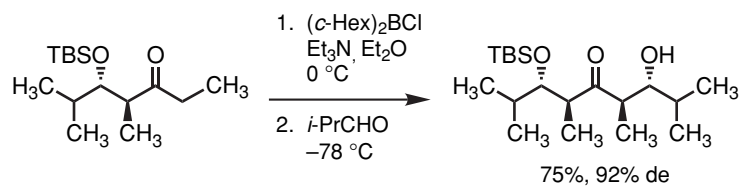
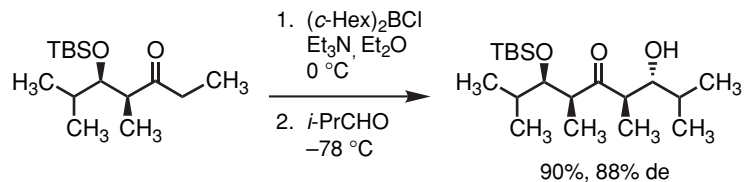
- Enolization of the less hindered side of the ketone under Brown's conditions affords the (*E*)-boron enolate.
- The C<sub>2</sub> stereocenter is the dominant control element in these aldol reactions; "matched" vs. "mismatched" effects of the remote auxiliary are negligible.



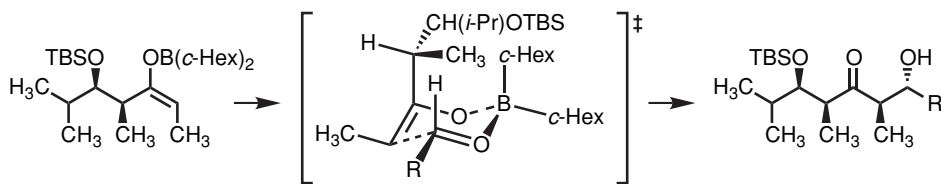
- The sense of asymmetric induction observed in these reactions was unexpected and opposite to a prediction based on a reactant-like transition state model minimizing A<sub>(1,3)</sub> strain.

Evans, D. A.; Ng, H. P.; Clark, J. S.; Reiger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.

## Anti-Selective Aldol Reactions in Related Systems



- The C2 stereocenter is believed to be the dominant control element for both substrates.

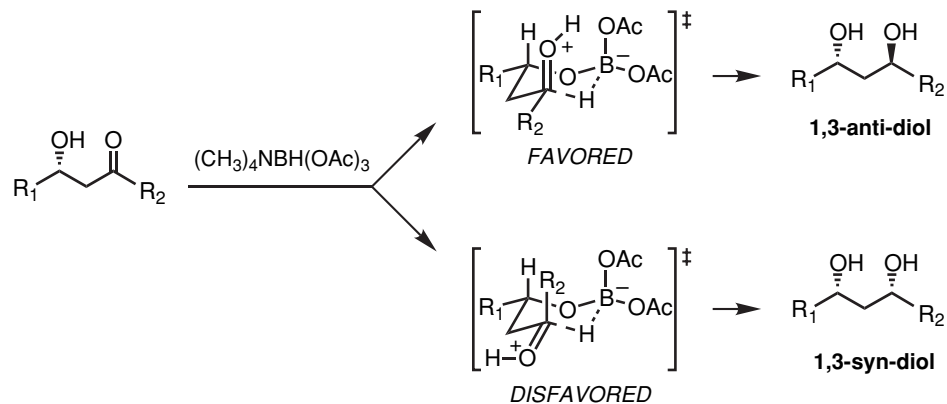


- Minimization of  $A_{(1,3)}$  interactions in the enolate biases the approach of the aldehyde to the methyl-bearing  $\pi$ -face of the enolate, while the (*E*)-enolate geometry affords anti-aldol products.

Evans, D. A.; Ng H. P.; Clark, J. S.; Reiger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.

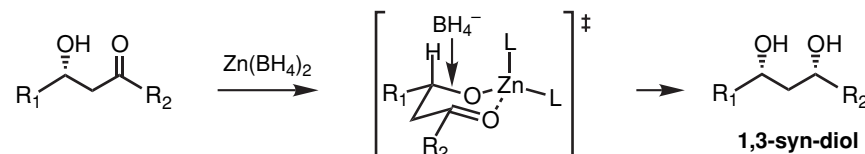
## Directed Reduction of $\beta$ -Hydroxy Ketones

Internal hydride delivery:

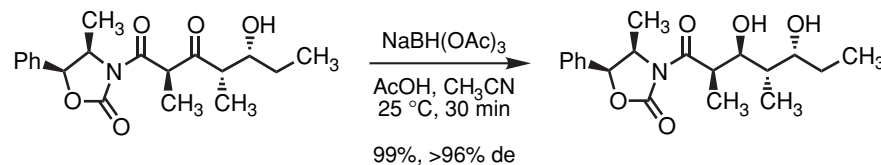


- The reactivity of the reagent is attenuated such that the reduction of ketones proceeds at convenient rates only intramolecularly, favoring formation of 1,3-anti-diols.

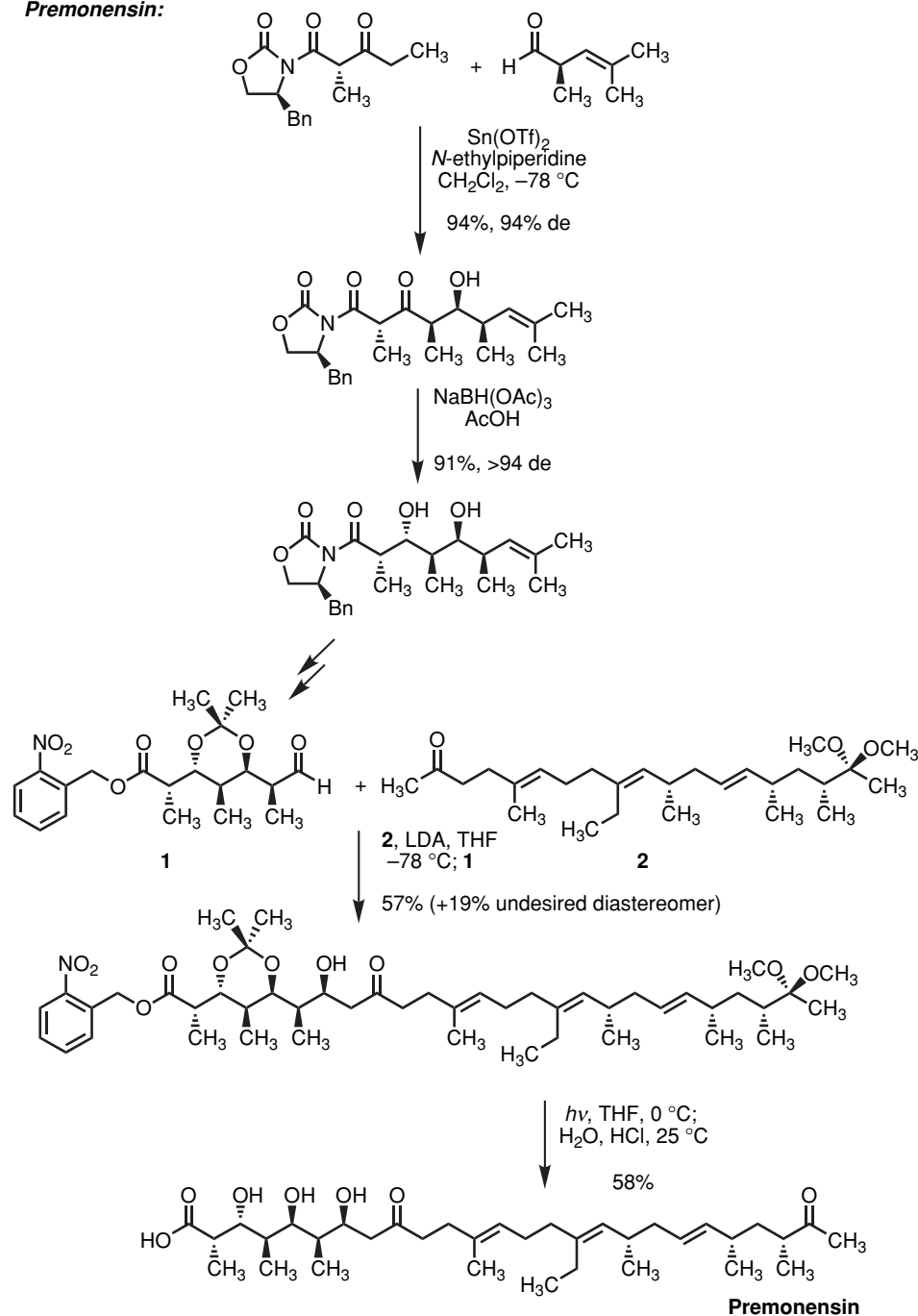
External hydride delivery:



- Chelated transition state, axial attack provides 1,3-syn-diol.
- These directed reductions are applicable to  $\delta$ -hydroxy- $\beta$ -ketoimides:



Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

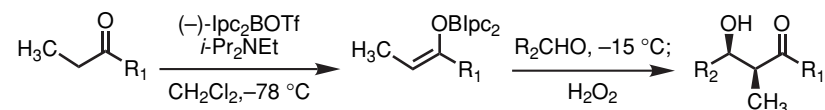
**Premonensin:**

Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476-2478.

**Paterson Aldol****Reviews:**

Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317.

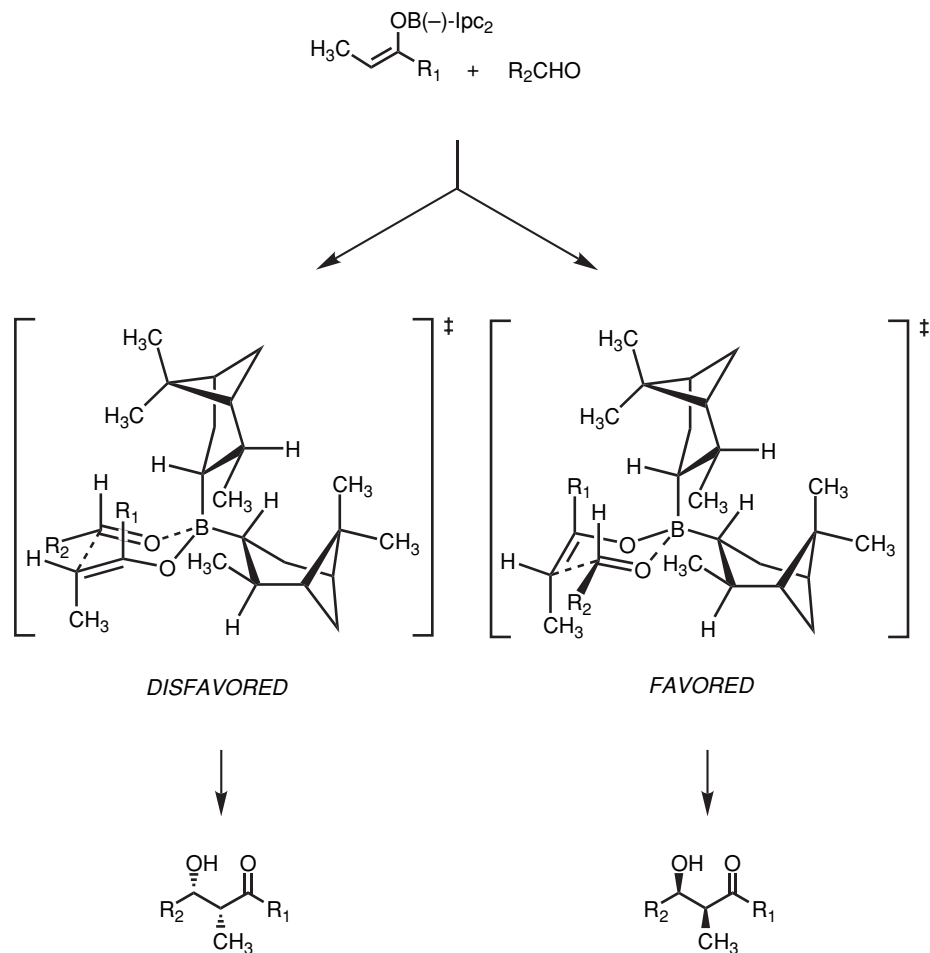
**Syn-Aldol Adducts via Enol Disopinocampheylborinates**

ketone	aldehyde	syn:anti	ee (%)	yield (%)
		98:2	91	78
		96:4	66	45
		96:4	80	84
		95:5	88	99
		97:3	86	79

- Enolization occurs selectively on the less hindered side of the ketone and with (*Z*)-selectivity.
- The (*E*)-Enolate, generated in low yield using  $(-)\text{-Ipc}_2\text{BCl}$ , does not lead to a selective *anti*-aldol reaction.
- Highest enantioselectivities are obtained with unhindered aldehydes.
- Aldol additions of methyl ketones are not highly enantioselective (53-73%).

Paterson, I.; Goodman, J. M.; Lister, M. A.; Scumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663-4684.

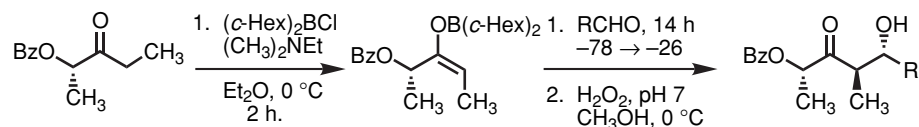
### Proposed Origin of Selectivity:



- Diastereofacial selectivity is believed to be due to a favored transition state wherein steric interactions between the (-)-Ipc ligand on boron and the R<sub>1</sub> substituent on the ketone are minimized.

Paterson, I.; Goodman, J. M.; Lister, M. A.; Scumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663-4684.

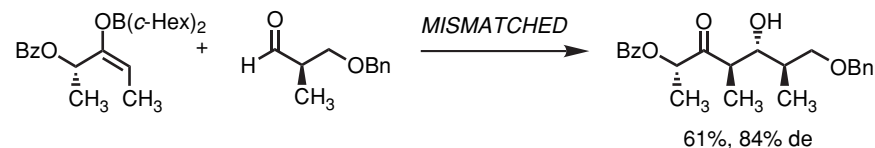
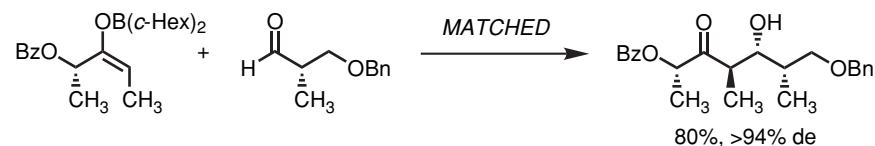
### Anti-Aldol Reactions of Lactate-Derived Ketones



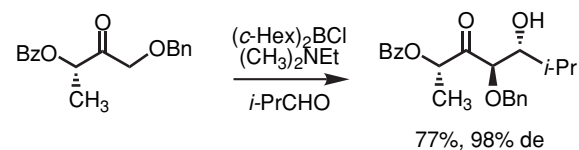
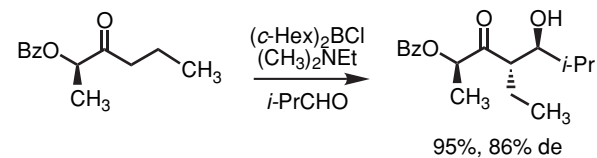
aldehyde	de (%)	yield (%) <sup>a</sup>
	94	95
	99	82
	90	97
	96	97
	99	85

<sup>a</sup>Isolated yield for 3 steps.

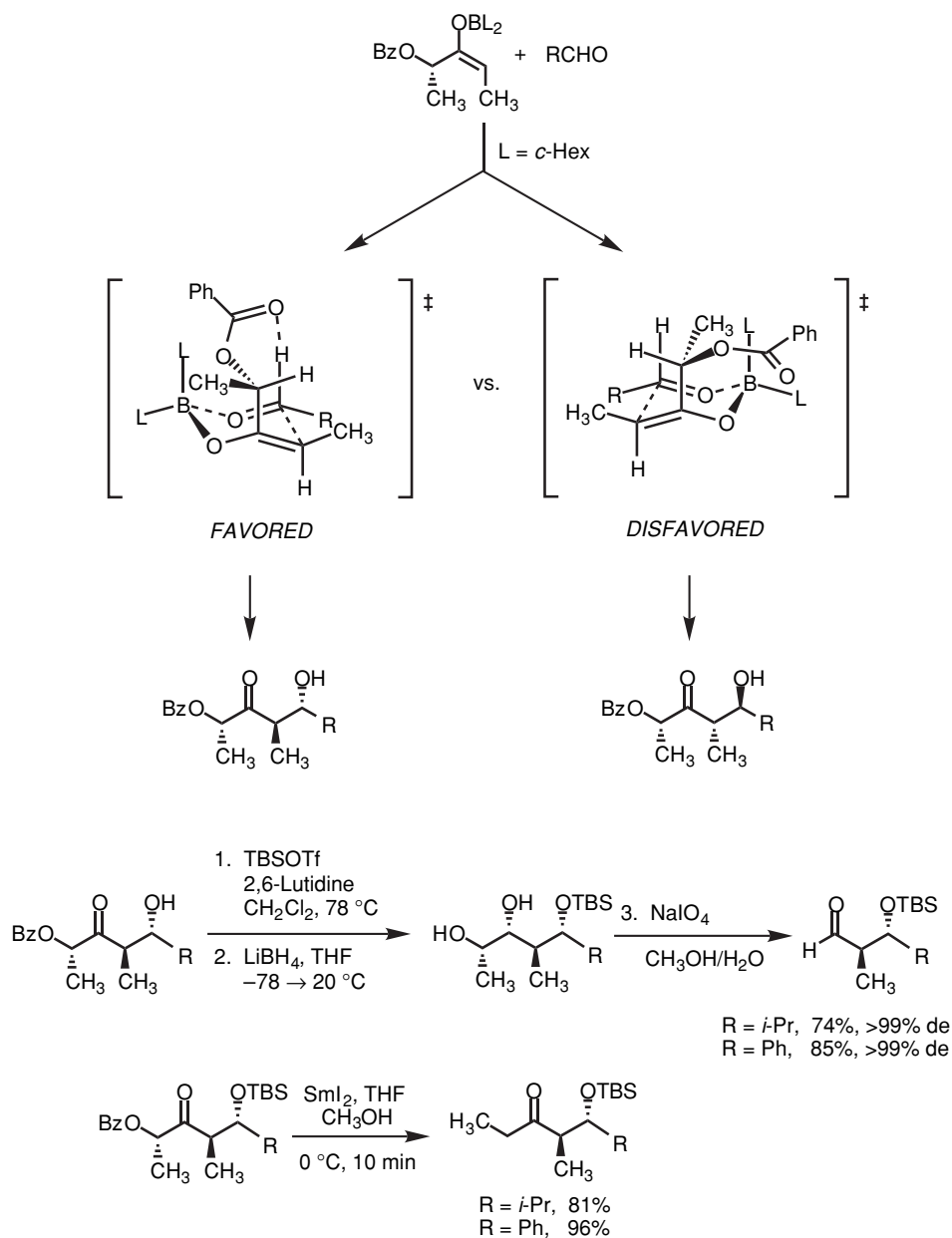
- Diastereofacial selectivity is very high; α-chiral aldehydes afford anti-aldol adducts with high diastereoselectivity regardless of their stereochemistry.



- Other examples:

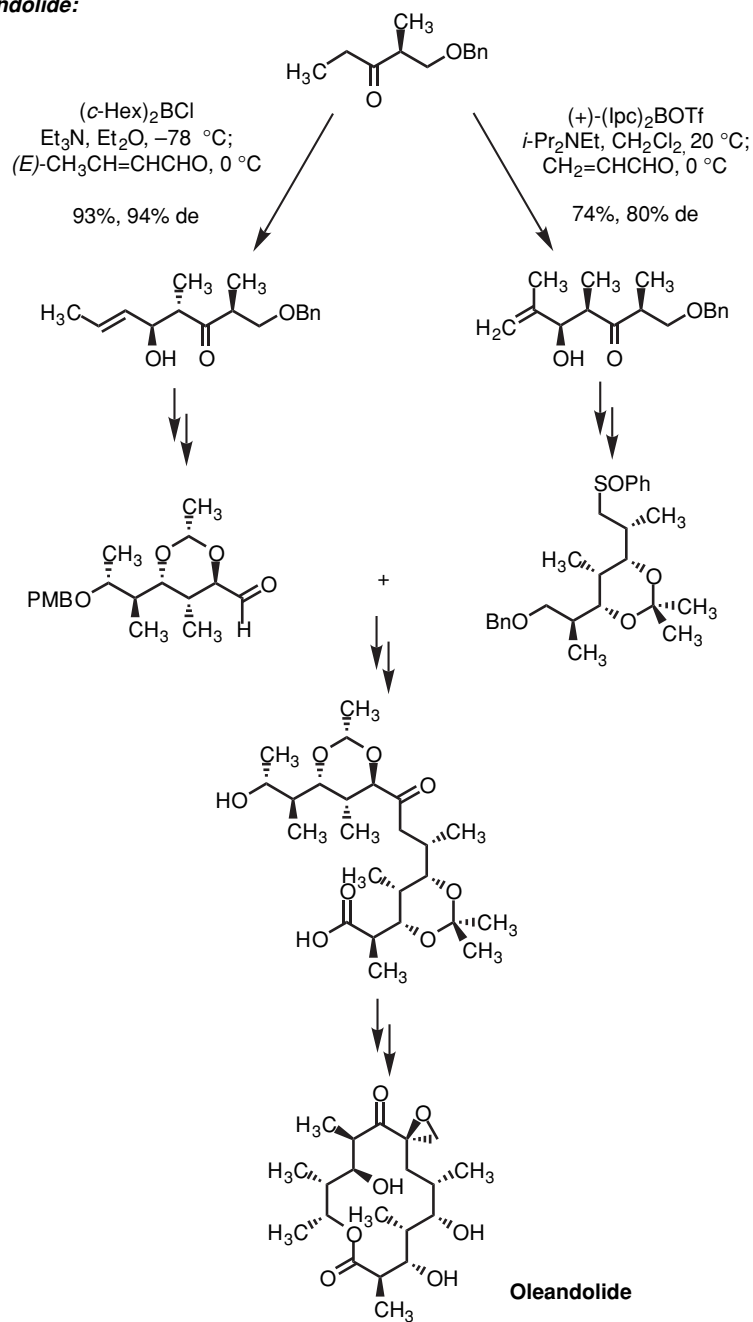


- The origin of the diastereoselectivity is proposed to be due to a formyl hydrogen bond in the favored transition state.



- Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639-652.

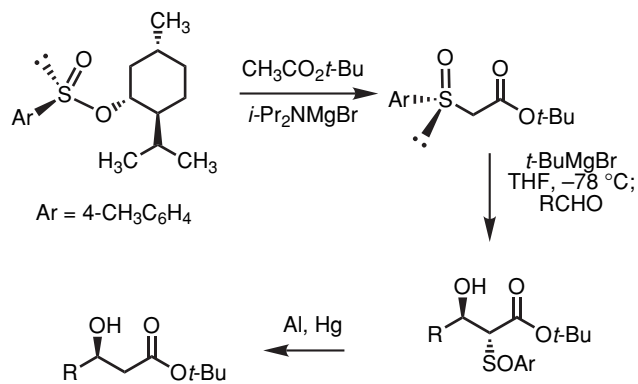
#### Oleandolide:



Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287-11314.

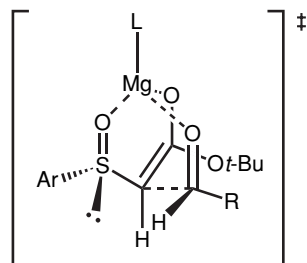
## Acetate Aldol

### Addition of a Chiral $\alpha$ -Sulphinylester Enolate to Aldehydes



- The  $\beta$ -hydroxy ester products are isolated in 50-85% yield and 80-91% ee.

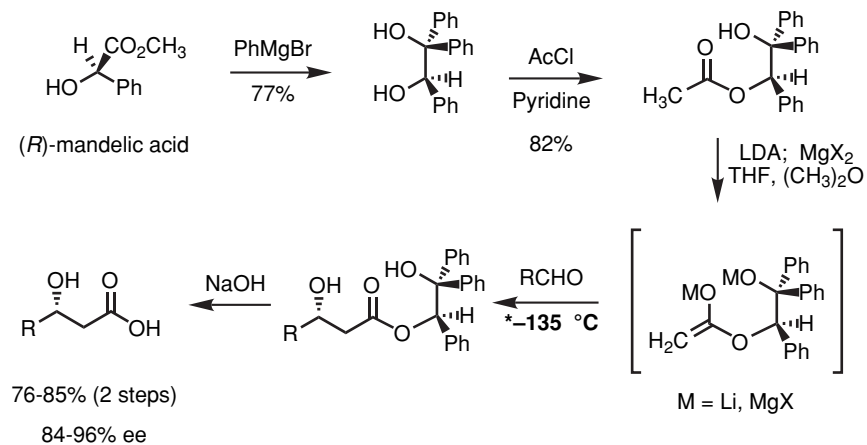
### Proposed Transition State



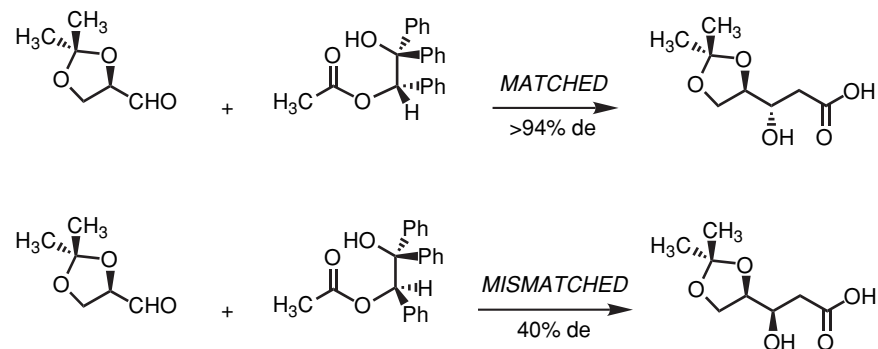
- Approach of the aldehyde is proposed to occur from the side of the non-bonding electron pair of the sulfur atom with the R-group of the aldehyde anti to the sulfinyl substituent. A chelated enolate is proposed.

Mioskowski, C.; Solladie, G. *J. Chem. Soc., Chem. Commun.* **1977**, 162-163.

### Addition of a Chiral Acetate Enolate to Aldehydes



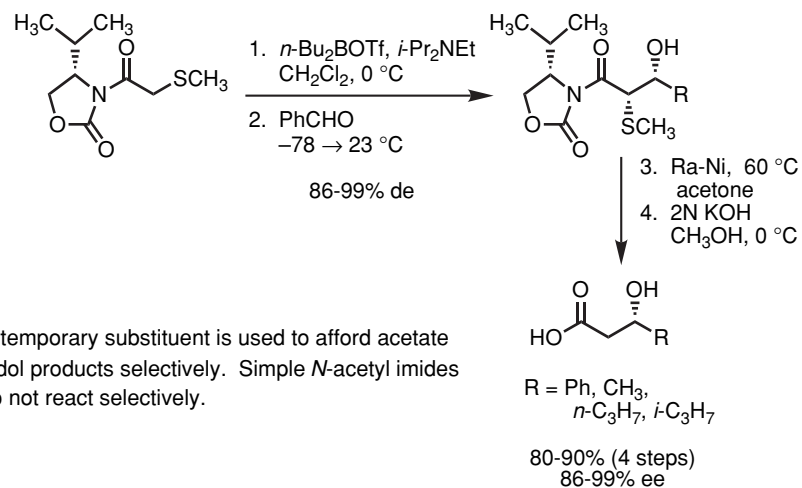
- Both (*R*)- and (*S*)-mandelic acids are commercially available.



- Low diastereoselectivities are obtained with mismatched chiral aldehydes.
- A mechanistic rationale has not been proposed.

Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 24-37.

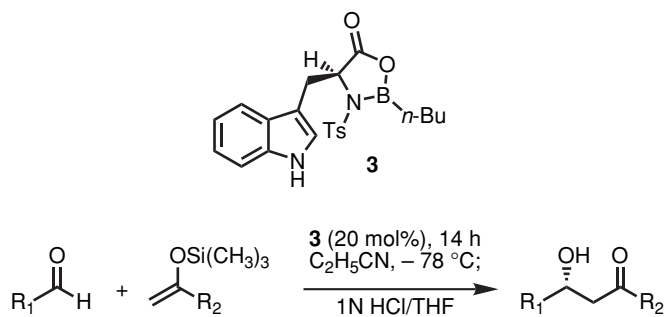
### An Approach to the Acetate Aldol Problem



- A temporary substituent is used to afford acetate aldol products selectively. Simple *N*-acetyl imides do not react selectively.

Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

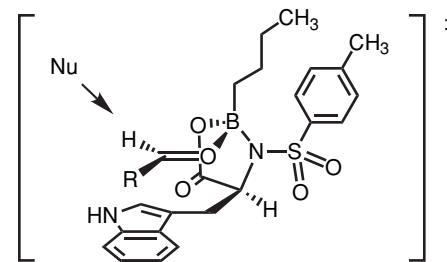
### An Enantioselective Mukaiyama Aldol Reaction Catalyzed by a Tryptophan-Derived Oxazaborolidine



$\text{R}_1$	$\text{R}_2$	yield (%)	ee (%)
Ph	$\text{C}_6\text{H}_5$	82	89
$c\text{-C}_6\text{H}_{11}$	$\text{C}_6\text{H}_5$	67	93
2-furyl	$\text{C}_6\text{H}_5$	100	92
$c\text{-C}_6\text{H}_{11}$	$n\text{-C}_4\text{H}_9$	56	86

- The Lewis-acid catalyzed addition of silyl enol ethers to aldehydes is known as the Mukaiyama Aldol reaction: Kobayashi, S.; Uchiro, H.; Shina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761-1772.

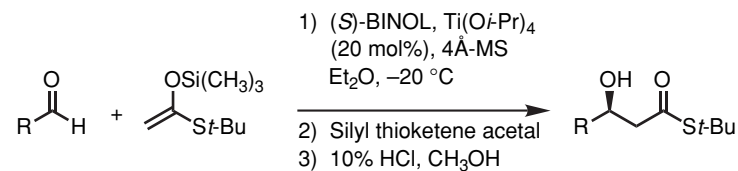
- Use of terminal trimethylsilyl enol ethers provide the highest level of enantioselectivities.



- A transition state is proposed in which the *si* face of the aldehyde is blocked by the indole ring.

Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907-6910.

### Catalytic, Enantioselective Mukaiyama Aldol Condensation of Silyl Thioketene Acetals



aldehyde	yield (%)	ee (%)
PhCHO	90	97
$\text{PhCH}_2\text{CH}_2\text{CHO}$	80	97
furylCHO	88	>98
$c\text{-C}_6\text{H}_{11}\text{CHO}$	70	89
$\text{PhCH}_2\text{OCH}_2\text{CHO}$	82	>98

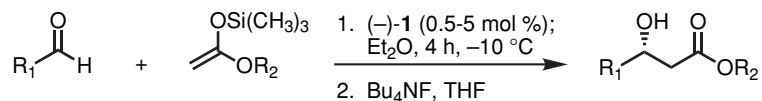
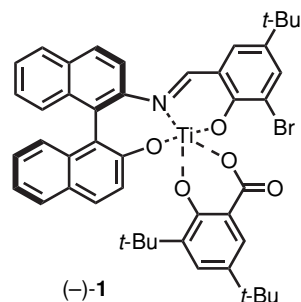
- This reaction is highly sensitive to the solvent and to reactant concentrations.

Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364.

## Catalytic, Enantioselective Acetate Aldol Additions with Silyl Ketene Acetals

### Review

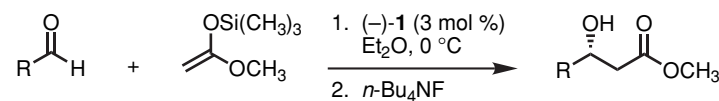
Carreira, E. M.; Singer, R. A. *Drug Discovery Today* **1996**, *1*, 145.



Aldehyde	%ee: R <sub>2</sub> = Et	%ee: R <sub>2</sub> = CH <sub>3</sub>	%ee: R <sub>2</sub> = Bn
	92	97	-
	88	95	-
	93	97	96
	89	94	91
	94	95	-
	93	96	96

Yields for two steps (addition and desilylation) range from 72-98%.

- Catalyst **1** is formed by condensation of the chiral amino alcohol with 3-bromo-5-tert-butylsalicylaldehyde followed by complexation with Ti(O*i*-Pr)<sub>4</sub> and 3,5-di-tert-butylsalicylic acid. Both enantiomeric forms are available.
- Complete removal of *i*-PrOH during catalyst preparation is key to achieving high yields and selectivities. This may be done by azeotropic removal of *i*-PrOH with toluene or by its silylation in an in situ catalyst preparation (TMSCl, Et<sub>3</sub>N).
- The reaction can be carried out in a variety of solvents, such as toluene, benzene, chloroform, diethyl ether, and *tert*-butyl methyl ether.
- Alkenyl and alkynyl aldehydes are particularly good substrates for this catalytic process.



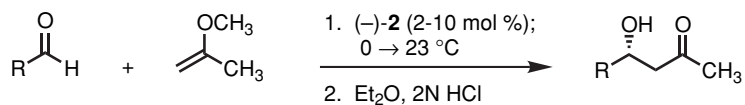
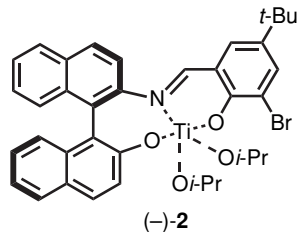
aldehyde	yield (%)	%ee
	88	96
	96	94
	88	97
	88	96

Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838.

Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927-930.

Singer, R. A.; Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1998**, *54*, 7025-7032.

## Catalytic, Enantioselective Aldol Additions of an Acetone Enolate Equivalent

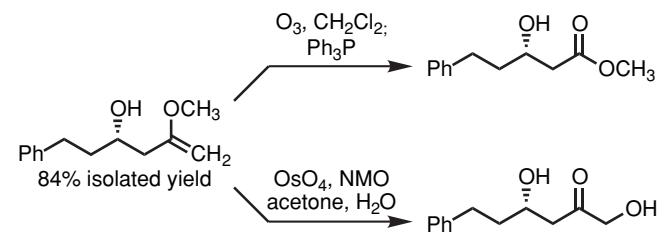


aldehyde	temp. (°C)	yield	%ee
Ph(CH <sub>2</sub> ) <sub>3</sub> -C≡C-CHO	0	99	98
TBSOCH <sub>2</sub> -C≡C-CHO	0	85	93
Ph-C≡C-CHO	0	99	91
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO	0 → 23	98	90
PhCHO	0 → 23	83	66
<i>c</i> -C <sub>6</sub> H <sub>11</sub> CHO	0 → 23	79	75

- 2-methoxypropene is used as the reaction solvent.
- Unhindered aldehydes afford products with the highest enantioselectivities.
- 2,6-di-*tert*-butyl-4-methylpyridine (0.4 equiv) is used in the reaction to prevent decomposition of the product by adventitious acid.

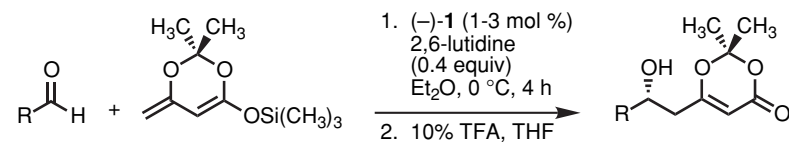
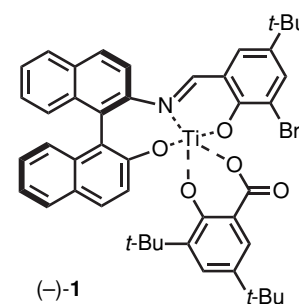
Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649-3650.

- The vinyl ether products can be isolated, or transformed into other useful products:



Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649-3650.

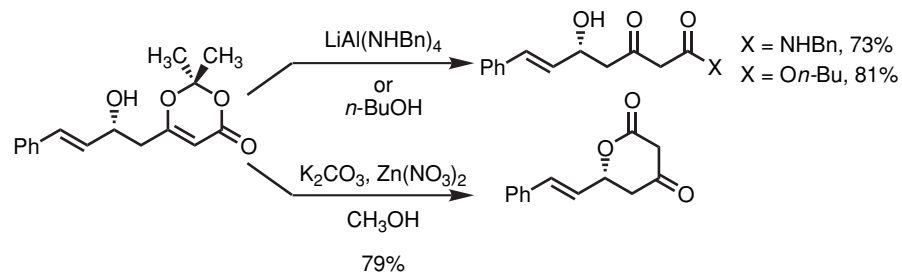
## Catalytic, Enantioselective Dienolate Additions to Aldehydes



aldehyde	yield (%)	%ee
TIPS-C≡C-CHO	86	91
TBSO-CH=CH-CHO	97	94
CH <sub>3</sub> -CH=CH-CH=CH-CHO	88	92
<i>n</i> -Bu <sub>3</sub> Sn-CH=CH-CHO	79	92
Ph-CH <sub>2</sub> -CH <sub>2</sub> -CHO	97	80
PhCHO	83	84 (96) <sup>a</sup>

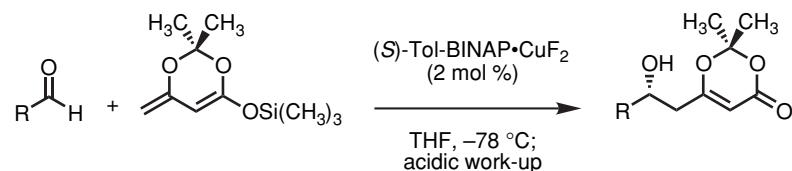
<sup>a</sup>after recrystallization.

- The silyl dienolate is easily prepared, purified by distillation, and is stable to storage.
- The absolute sense of induction parallels that of acetate-derived silyl enol ether and 2-methoxypropene addition reactions.
- The protected acetoacetate adducts are versatile precursors for the preparation of optically active  $\delta$ -hydroxy- $\beta$ -keto esters, amides, and lactones.



Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360-12361.

#### Catalytic, Enantioselective Dienolate Additions to Aldehydes Using a Nucleophilic Catalyst.



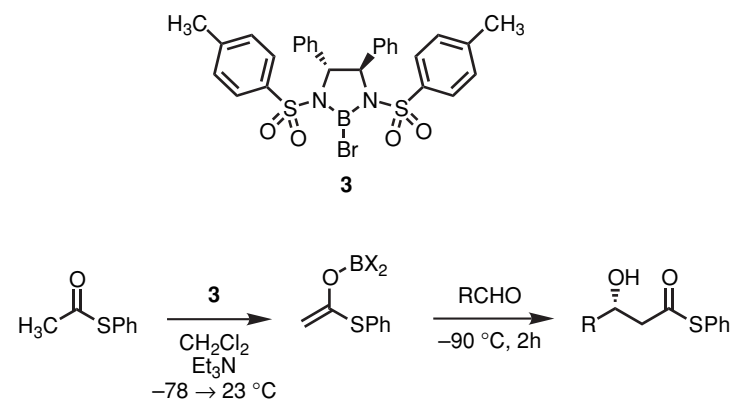
aldehyde	yield (%)	%ee
PhCHO	92	94
	98	95
	82	90
	48	91
	81	83
	74	65

- $(S)\text{-Tol-BINAP}\cdot\text{CuF}_2$  is readily prepared in situ by mixing  $(S)\text{-Tol-BINAP}$ ,  $\text{Cu}(\text{OTf})_2$ , and  $(n\text{-Bu}_4\text{N})\text{Ph}_3\text{SiF}_2$  in THF.
- This process is efficient for non-enolizable ( $\alpha,\beta$ -unsaturated, aromatic, and heteroaromatic) aldehydes.
- Enolizable, aliphatic aldehydes give products with high enantioselectivity, but in poor yield (<40%).
- Spectroscopic evidence supports a catalytic process involving a chiral transition metal dienolate as an intermediate.

Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837-838.

Pagenkopt, B. L.; Kruger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 3124-3126.

#### Enantioselective Acetate Aldol Addition Using a Chiral Controller Group

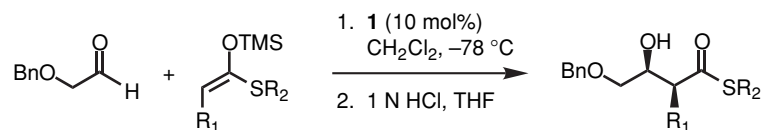
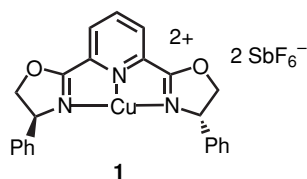


aldehyde	yield (%)	ee (%)
$\text{C}_6\text{H}_5\text{CHO}$	84	91
$i\text{-PrCHO}$	82	83

- Bromide **3** is produced from the corresponding  $(R,R)$ -bissulfonamide by reaction with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$ .
- Upon completion of the reaction the  $(R,R)$ -bis-sulfonamide can be recovered and reused.

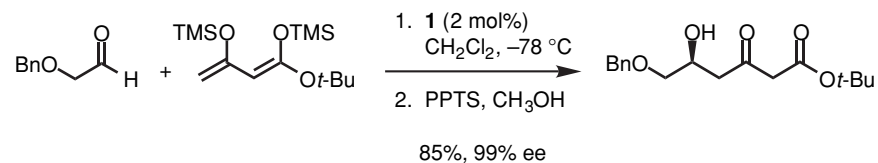
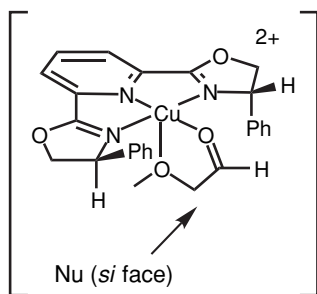
Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493-5495.

Catalytic, Enantioselective Aldol Additions of Silyl Thioketene Acetals and Silyl Enol Ethers

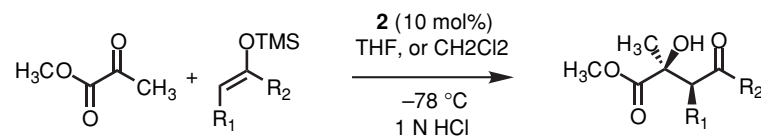
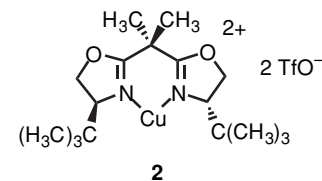


R <sub>1</sub>	R <sub>2</sub>	enol silane geometry	time (h)	T (°C)	syn:anti	%ee	yield (%)
H	<i>t</i> -Bu		24	-78		99	99
CH <sub>3</sub>	Et	( <i>Z</i> )	4	-78	97:3	97	90
CH <sub>3</sub>	Et	( <i>E</i> )	1d	-50	86:14	85	48
<i>i</i> -Bu	Et	( <i>Z</i> )	2d	-50	95:5	95	85

- Experimental data, including an X-ray structure of a catalyst-substrate complex, suggest a two-point binding model for the aldehyde during catalysis.



Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.



R <sub>1</sub>	R <sub>2</sub>	syn:anti	%ee	yield (%)
H	SEt		97	97
H	Ph		99	77
CH <sub>3</sub>	<i>S</i> <i>t</i> -Bu	94:6	96	96
CH <sub>3</sub>	SEt	98:2	98	91
<i>i</i> -Bu	SEt	90:10	93	88

- Based on structural data acquired with catalyst **1**, a bidentate coordination of methyl pyruvate to the copper complex **2** has been proposed.

Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893-7894.