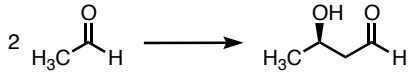
Reviews:

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.

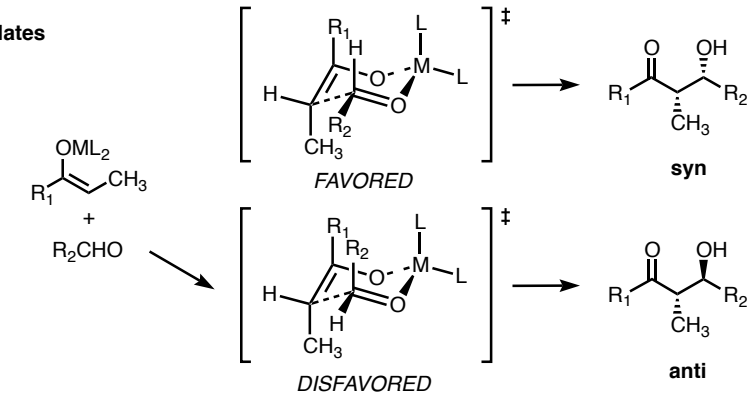
Paterson, I. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds., Pergamon Press: New York, **1991**, *Vol. 2*, pp. 301-319.



- 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.

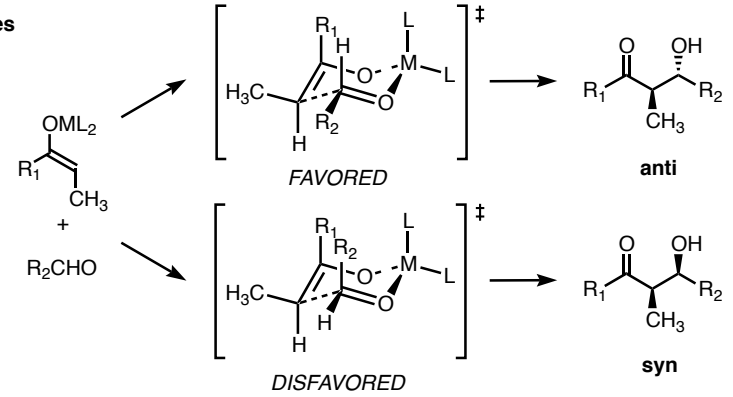
Diastereofacial Selectivity in the Aldol Addition Reaction-
Zimmerman-Traxler Chair-Like Transition States

(*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_1, R_2, 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_1 and R_2 in each chair-like TS‡.

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.

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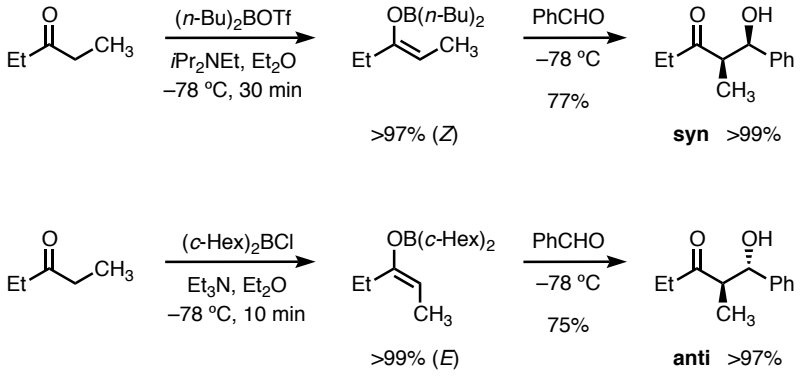
Preparation of (*Z*)- and (*E*)-Boron Enolates



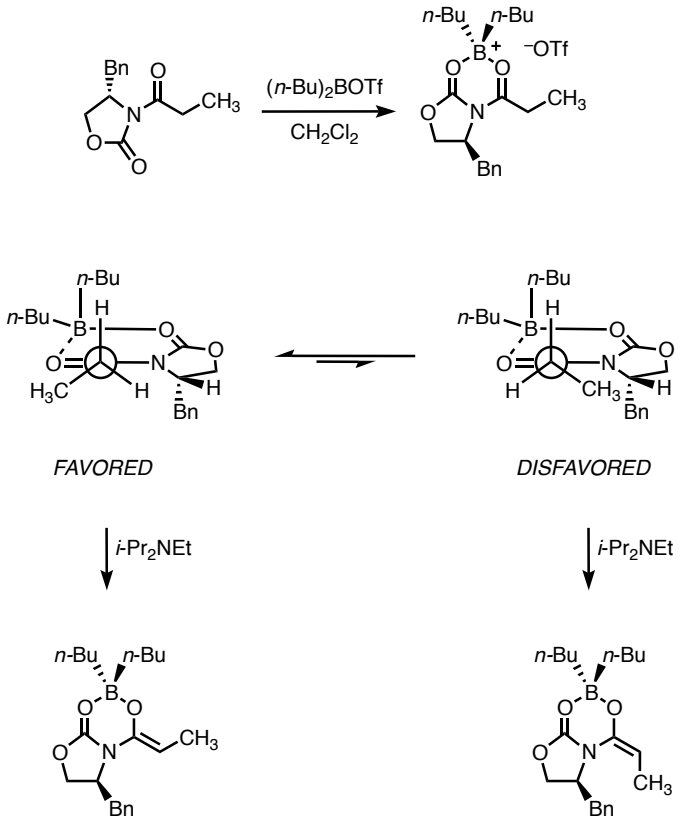
- Dialkylboron triflates typically afford (*Z*)-boron enolates, with little sensitivity toward the amine used or the steric requirements of the alkyl groups on the boron reagent.
- In the case of dialkylboron chlorides the geometry of the product enolates is much more sensitive to variations in the amine and the alkyl groups on boron.
- The combination of $(c\text{-Hex})_2BCl$ and Et_3N provides the (*E*)-boron enolate preferentially.

Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120-6123.

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 > 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.

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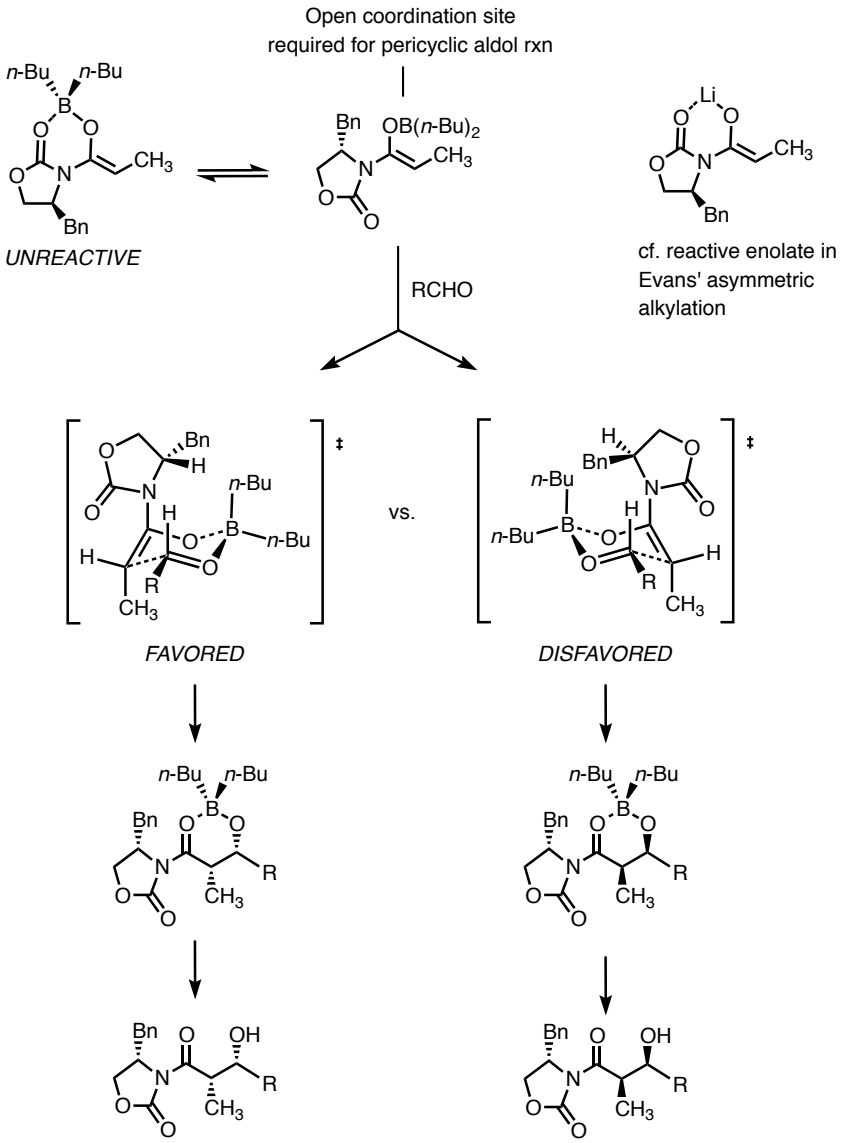
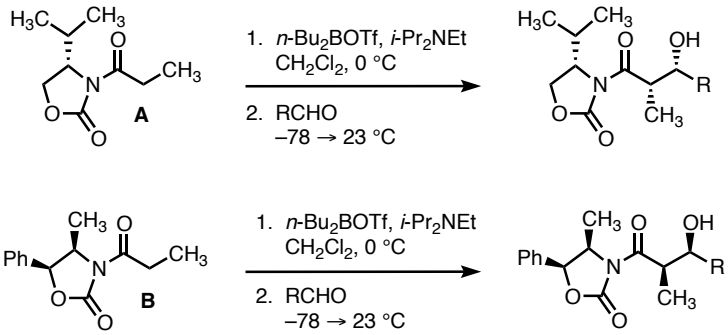
Syn-Selective Aldol Reactions of Imide-Derived Boron (_Z_)-Enolates



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 π-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[a] ratio	yield (%)
A	$(CH_3)_2CHCHO$	497:1	78
B	$(CH_3)_2CHCHO$	<1:500	91
A	n-C_4H_9CHO	141:1	75
B	n-C_4H_9CHO	<1:500	95
A	C_6H_5CHO	>500:1	88
B	C_6H_5CHO	<1:500	89

[a]Ratio of major syn product to minor syn product.

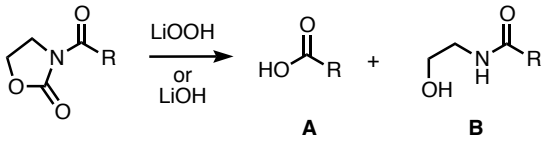
- A variety of chiral imides can be used for highly selective aldol reactions.
- Anti products are typically formed in less than 1% yield.
- Often, a single crystallization affords diastereomerically pure product.

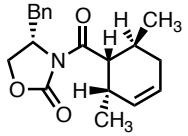
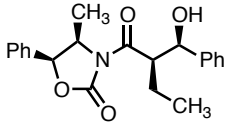
Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

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

M. Movassaghi

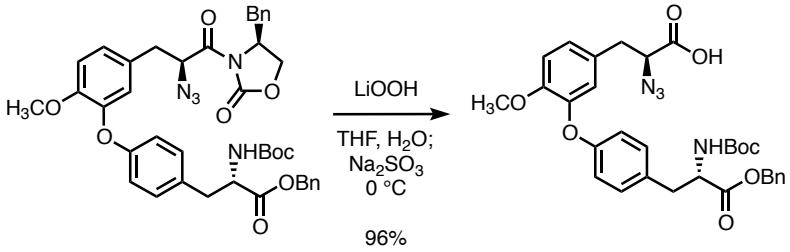
Carboximide Hydrolysis with Lithium Hydroperoxide



substrate	reagent	yield of **A** (%)[a]	yield of **B** (%)[a]
	LiOOH	76	16
	LiOH	0	100
	LiOOH	98	<1
	LiOH	43	30

[a]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.

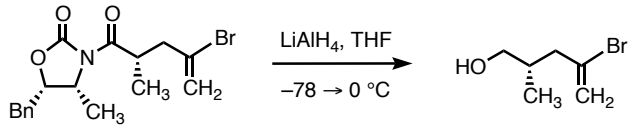


- The selective hydrolysis of carboximides can be achieved in the presence of unactivated esters using LiOOH.

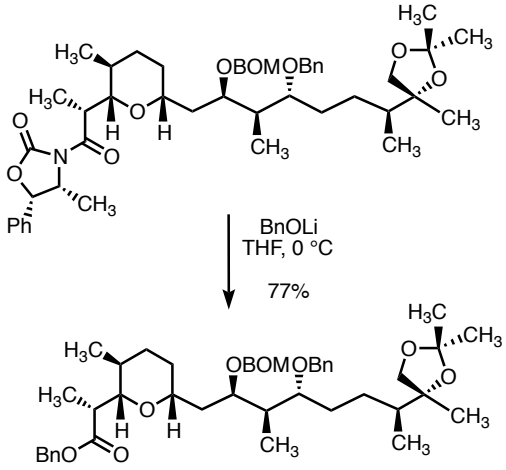
Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141-6144.
Gage, J. R.; Evans, D. A. *Org. Syn.* **1990**, *68*, 83-91.

Other Methods for Removal of the Chiral Auxiliary

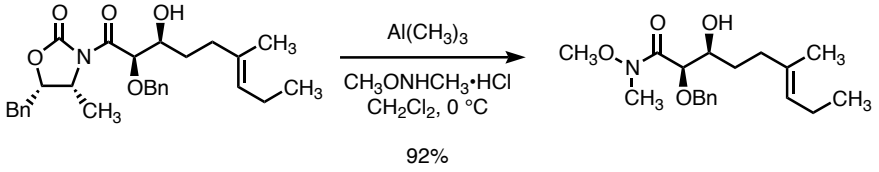
- Reductive cleavage:



- Esterification:



- Transamination:



- A free β-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.

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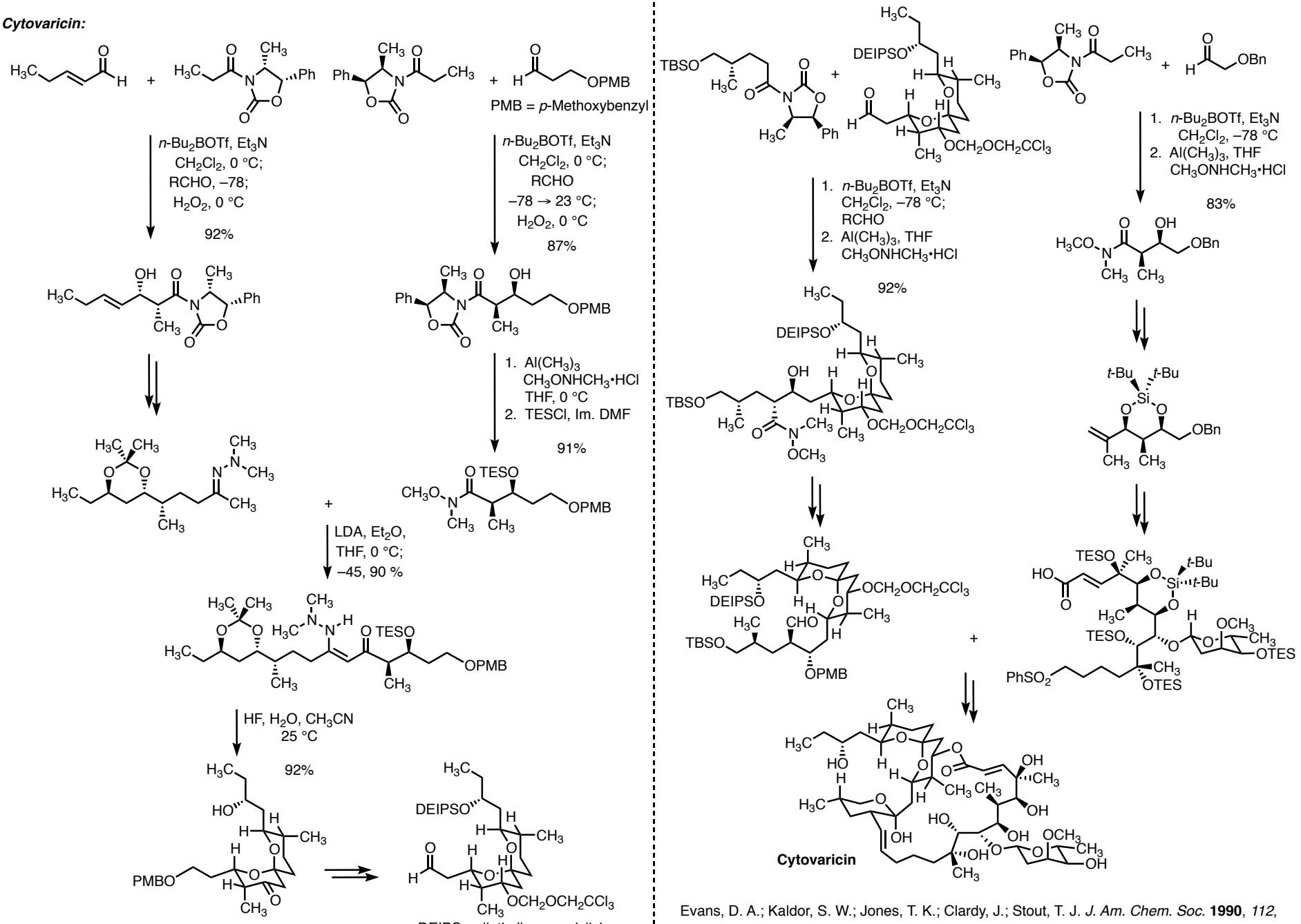
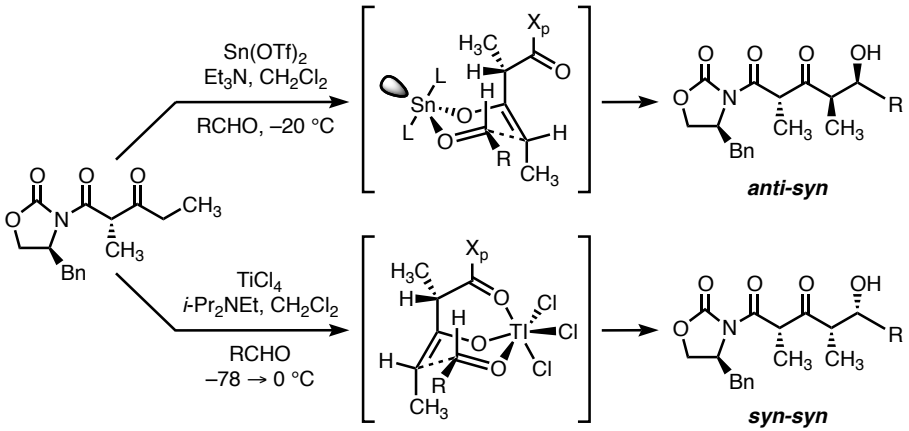
Cytovaricin:

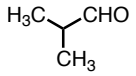
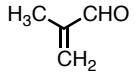
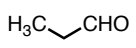
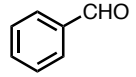


Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7031.

M. Movassaghi

Diastereoselective *Syn*-Aldol Reaction of β-Ketoimides



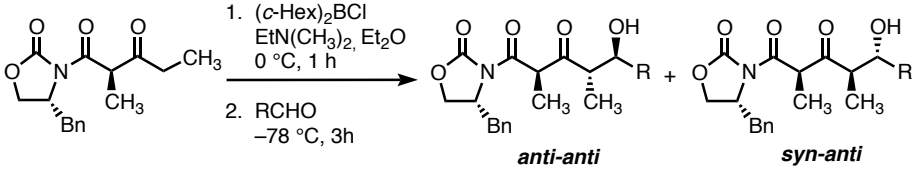
enolization conditions	RCHO[a]	yield %[b]	ratio *anti-syn* : *syn-syn*
A		83	95:5
B		86	<1:99
A		77[c]	95:5
B		64[c]	2:98
A		71	79:21
B		86	<1:99
A		85	89:11
B		81	4:96

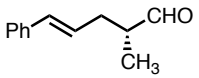
A: $Sn(OTf)_2$, Et_3N; B: $TiCl_4$, *i*-Pr_2NEt. [a]1.0-1.1 equiv [b]Isolated yield of major diastereomer (>99% purity). [c]3-5 equiv of RCHO was used.

- Both enolization methods provide (*Z*)-enolates and (diastereomeric) *syn* aldol products.
- The stereochemical outcome of both reactions is dominated by the C_2 methyl-bearing stereocenter, as shown in the proposed transition states above.
- 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.

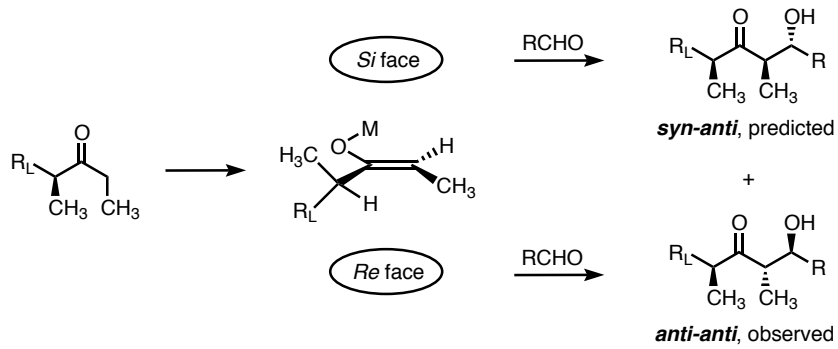
Diastereoselective *Anti*-Aldol Reaction of β-Ketoimides



aldehyde	yield %[a]	ratio anti-anti : syn-anti
$(CH_3)_2CHCHO$	78	84:16
$CH_2=C(CH_3)CHO$	72	92:8
CH_3CH_2CHO	70[b]	80:20
$PhCH_2CH_2CHO$	84[b]	88:12
	84	97:3

[a]Isolated yield of major diastereomer. [b]Yield of purified mixture of diastereomers.

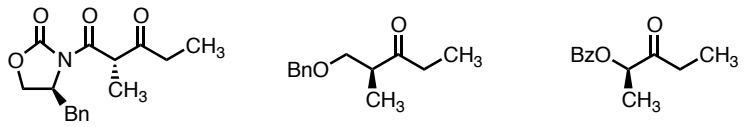
- Enolization of the less hindered side of the ketone under Brown's conditions affords the (*E*)-boron enolate.
- The C2 stereocenter is the dominant control element in these aldol reactions; "matched" vs. "mismatched" effects of the remote auxiliary are negligible.



- 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 $A_{(1,3)}$ strain.

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

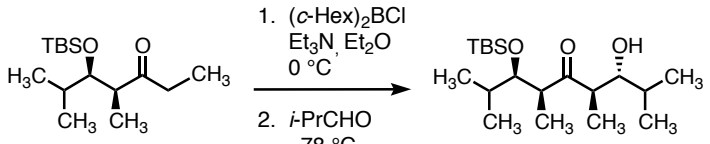
M. Movassaghi

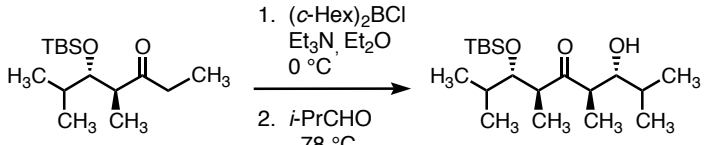


- In addition to β-ketoimides, the two chiral ethyl ketones above are known to undergo aldol reactions at the unexpected *Re* face of the enolate, deilvering *anti-anti* aldol products.

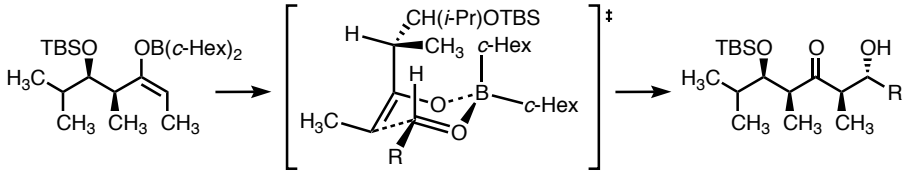
Paterson, I.; Goodman, J. M.; Isaka, M. *Tet. Lett.* **1989**, *30*, 7121-7124.
Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639-652.

Syn-Anti-Selective Aldol Reactions of Chiral Ethyl Ketones





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

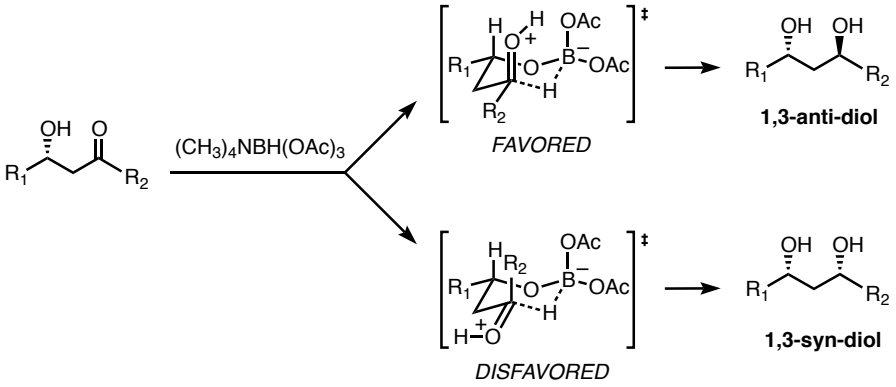


- Minimization of $A_{(1,3)}$ interactions in the enolate biases the approach of the aldehyde to the methyl-bearing π-face of the enolate, while the (*E*)-enolate geometry affords *anti*-aldol products.

Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.

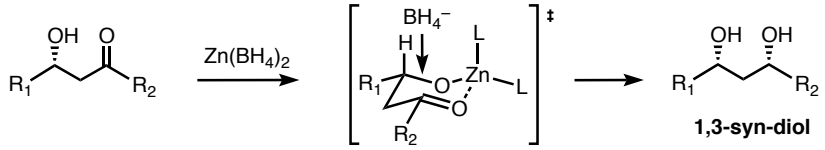
Directed Reduction of β-Hydroxy Ketones

Internal hydride delivery:

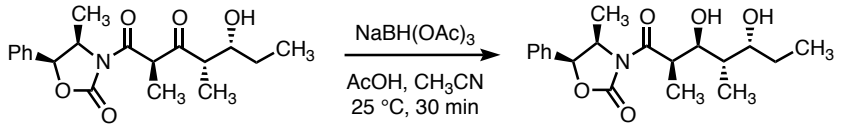


- The reactivity of the reagent is attenuated such that the reduction of ketones proceeds at convenient rates only intramolecularly, favoring formation of 1,3-anti-diols.

External hydride delivery:



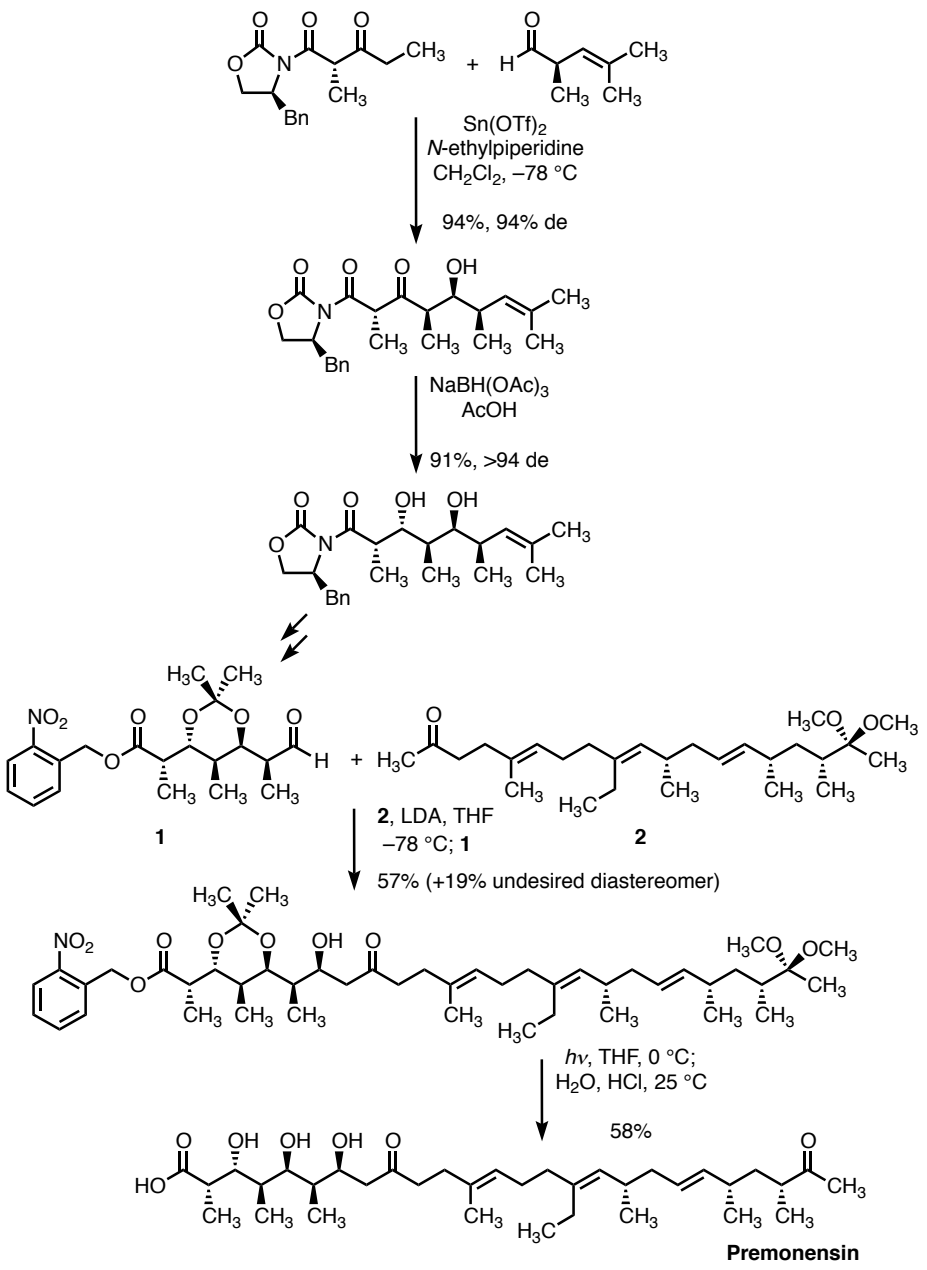
- Chelated transition state, axial attack provides 1,3-syn-diol.
- These directed reductions are applicable to δ-hydroxy-β-ketoimides:



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

Jaron Mercer, M. Movassaghi

Premonensin



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

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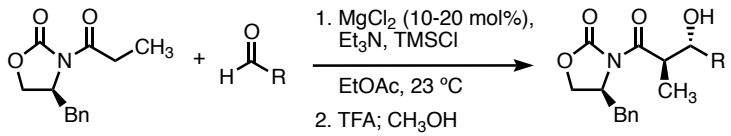
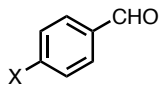
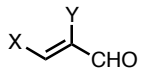
***Anti*-Aldols with Magnesium Enolates**

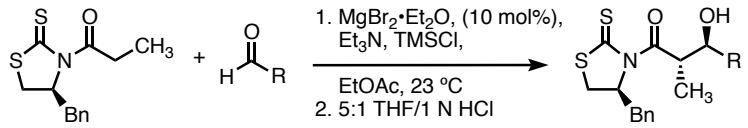


aldehyde		dr	yield (%)
	X = CH_3	24:1	-
	X = OCH_3	32:1	91
	X = NO_2	7:1	71
	X = Ph, Y = H	21:1	92
	X = Ph, Y = CH_3	28:1	92
	X = H, Y = CH_3	16:1	77
α-napthaldehyde		14:1	91
furfural		6:1	80

- Silylation of the magnesium alkoxide in the aldol product turns over the magnesium.
- The aldehyde component is limited to non-enolizable aromatic and α,β-unsaturated aldehydes.

Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

- Use of the analogous N-acylthiazolidinethione chiral auxiliary affords products of the opposite *anti*-stereochemistry in comparable yields and with high selectivities.

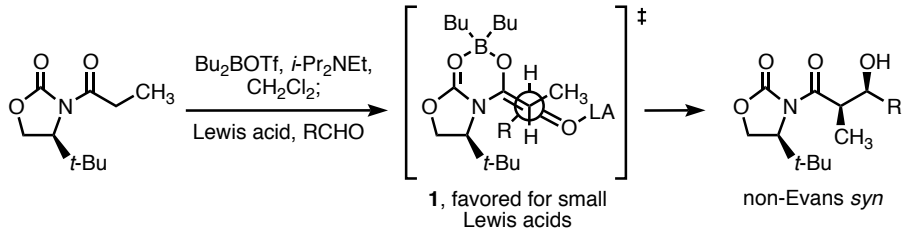


- Both reactions are proposed to proceed through boat transition states. See: Evans, D. A.; Downey, W. C.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127-1130.

Chris Coletta, Jaron Mercer

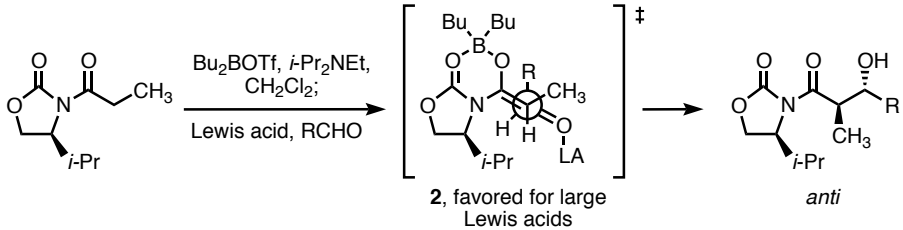
Open Transition State Aldol Reactions

- Heathcock and coworkers reported that complexation of the aldehyde with an added Lewis acid allows access to non-Evans *syn* and *anti* aldol products via open transition states.



1, favored for small Lewis acids

aldehyde	Lewis acid	*anti:syn**	yield (%)*
H_3C⌒CHO	$SnCl_4$	10:90	66
	$TiCl_4$	12:88	72
Ph–CHO	$TiCl_4$	8:92	65



2, favored for large Lewis acids

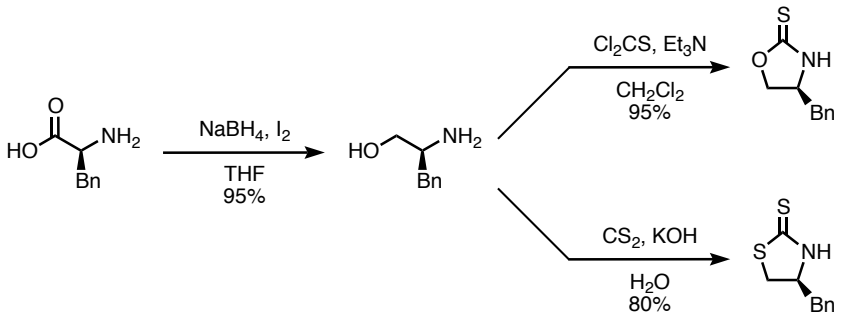
aldehyde	Lewis acid	*anti:syn**	yield (%)*
H_3C⌒CHO	Et_2AlCl	88:12	81
PhCHO	Et_2AlCl	74:26	62

*Determined by ^1H NMR. Yield given is the total yield of diastereomeric aldol mixture.

- Gauche interactions around the forming C-C bond dictate which face of the aldehyde reacts. For small Lewis acids, transition state **1** is favored. For large Lewis acids, transition state **2** is favored.

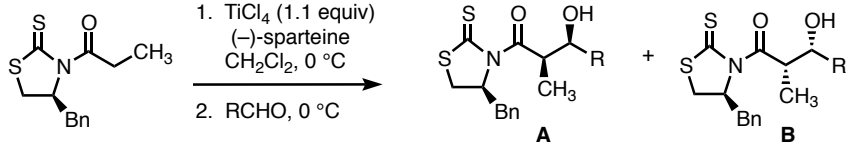
Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747-5750.

Synthesis of Oxazolidinethione and Thiazolidinethione Chiral Auxiliaries



Crimmins, M. T; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

Asymmetric Aldol Reactions with Titanium Enolates of *N*-Acylthiazolidinethiones



RCHO	(–)-sparteine (equiv)	yield (%)	**A** : **B**
CH_2=CHCHO	1.0	49	>99:1
i-PrCHO	1.0	60	98:2
CH_2=CHCHO	2.0	77	<1:99
i-PrCHO	2.0	75	3:97

- Selectivities are generally >95:5 for syn:anti products.
- Both the yield and diastereoselectivities are high and synthetically useful, although they are typically lower than the corresponding oxazolidine aldol reactions.
- An advantage of this method is that a single acyloxazolidinethione can provide either syn aldol product by changing the amount of sparteine in the reaction mixture.

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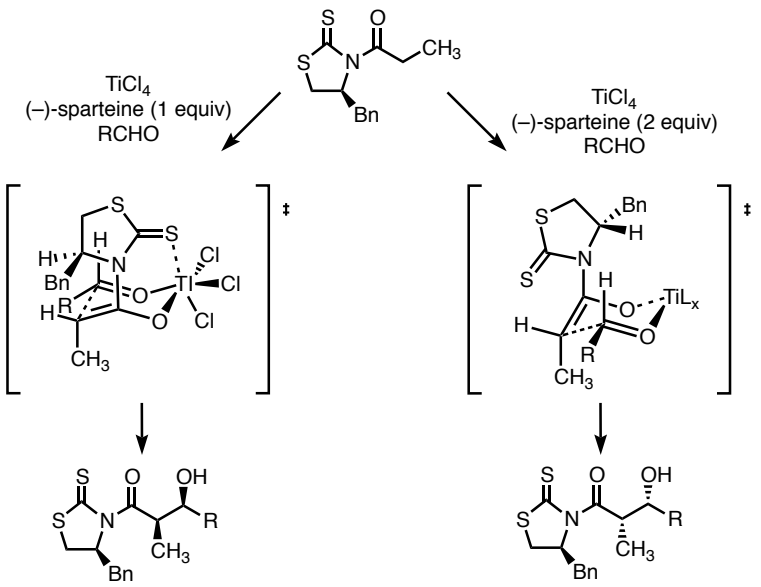
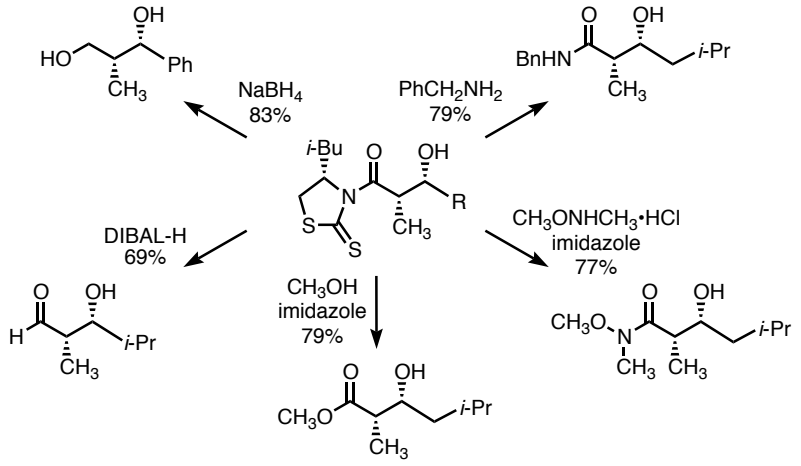
- Proposed transition states provide a rationale for the selectivity dependence on amine equivalents:



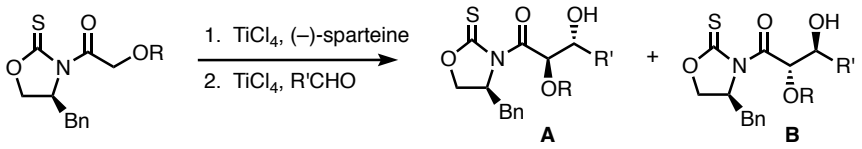
- The thiazolidinethione auxiliary is easily removed under mild conditions:

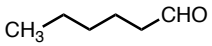
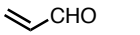
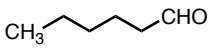
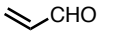
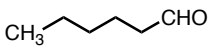
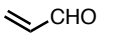


- The thiazolidinethione auxiliary is recovered by basic extraction (1 M NaOH) of the product mixture.

Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884.
Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775-777.

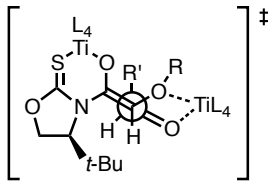
Anti-Selective Aldol Reactions with Titanium Enolates of _N_-Glycolyloxazolidinethiones



R	aldehyde	**A** : **B** : *syn*	yield (%)
allyl	H_3CCHO	94 : 6 : 0	84
allyl	Ph–CHO	65 : 24 : 11	56
allyl		94 : 6 : 0	74
allyl		95 : 5 : 0	58
Bn		88 : 12 : 0	64
Bn		74 : 26 : 0	48
CH_3		84 : 11 : 5	63
CH_3		88 : 12 : 0	59

- Complexation of the aldehyde with excess titanium occurs *in situ* to give *anti* products with high selectivity.

- The proposed transition state is analogous to that of the *anti*-selective Heathcock aldol.

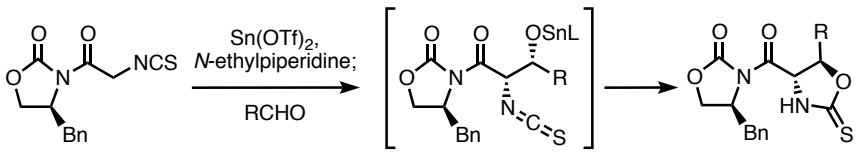


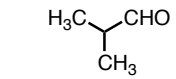
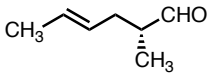
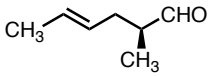
Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591-594.

M. Movassaghi, Jaron Mercer

Asymmetric Synthesis of *Syn*-β-Hydroxy-α-Amino Acids

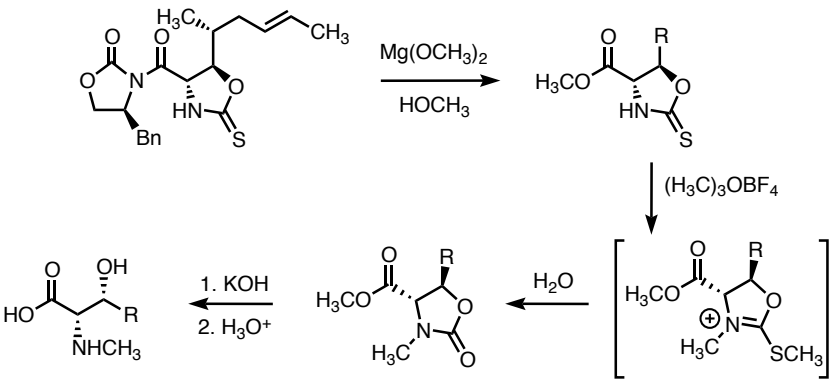
- The isothiocyanate below serves as a chiral glycine equivalent. Stannous triflate-mediated aldol reactions give cyclized aldol adducts in high yield and diastereoselectivity.



aldehyde	ratio*	yield (%)
H_3CCHO	91:9	75
PhCHO	99:1	91
	99:1	92
	94:6	73
	97:3	71

*Ratio of desired (illustrated) stereoisomer to the sum of all other stereoisomers.

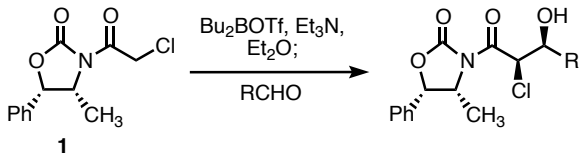
- The *N*-methyl amino acid can be reached in 4 steps.



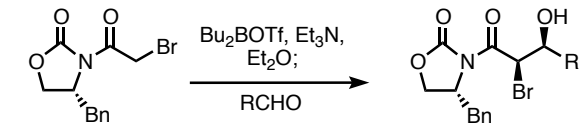
Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757-6761.

Asymmetric Synthesis of *Anti*-β-Hydroxy-α-Amino Acids

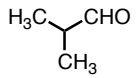
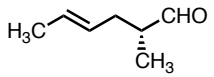
- 2-Chloro- and 2-Bromoacetyl imides undergo aldol addition with high diastereoselectivity.



1

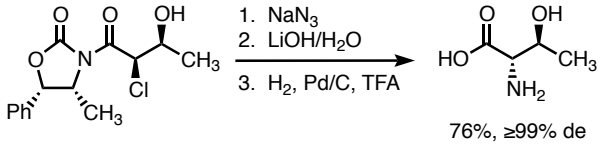


2

imide	aldehyde	ratio*	yield (%)
1	H_3CCHO	95:5	67
1	PhCHO	97:3	79
1		96:4	75
2		98:2	63
2		94:6	63

*Ratio of desired (illustrated) stereoisomer to the sum of all other stereoisomers.

- Halide displacement with NaN_3 occurs with inversion of stereochemistry. Hydrolytic removal of the auxiliary followed by hydrogenation of the azide delivers the amino acid.

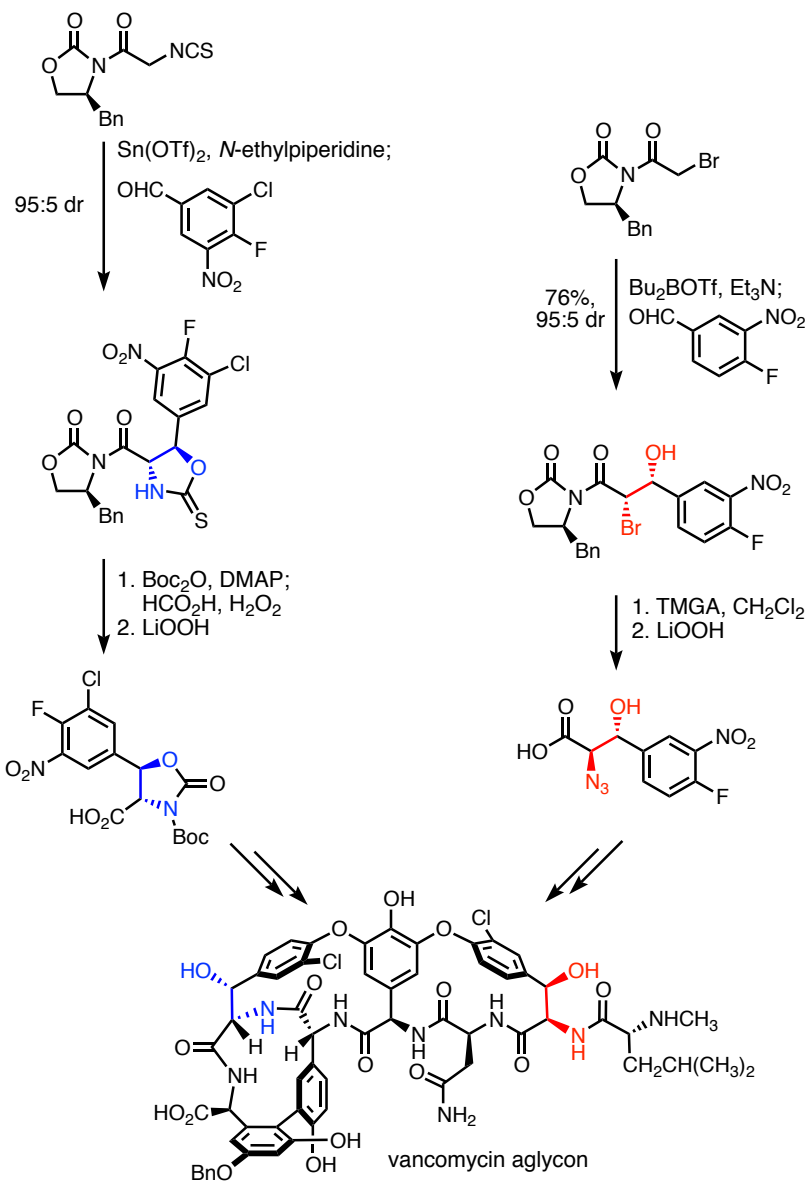


76%, ≥99% de

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

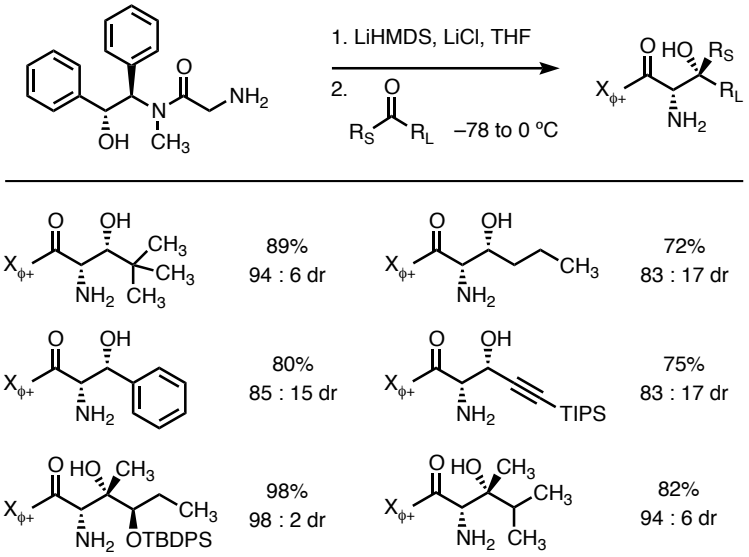
Jaron Mercer

Vancomycin Aglycon:



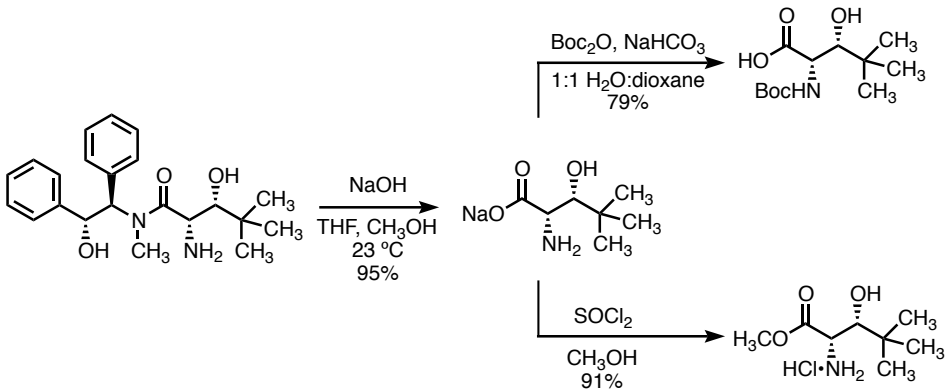
Evans, D. A.; Wood, R. W.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.
Evans, D. A.; Watson, P. S. *Tet. Lett.* **1996**, *37*, 3251-3254.

Direct Aldolization of Pseudoephenamine Glycinamide



Isolated yields of stereoisomerically pure products. Diastereomeric ratios reported as major isomer : sum of all other diastereomers.

- Pseudoephenamine glycinamide undergoes a direct aldol addition with both aldehyde and ketone substrates.
- The corresponding *N*-Boc-protected or methyl ester hydrochloride derivatives can be prepared in two steps from the aldol products.



Seiple, I. B.; Mercer, J. A. M.; Sussman, R. J.; Myers, A. G. *Unpublished.*

Jaron Mercer

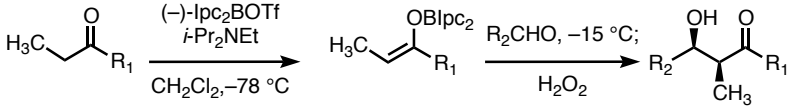
Paterson Aldol

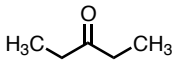
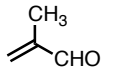
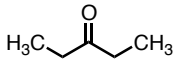
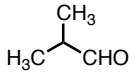
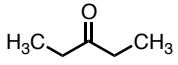
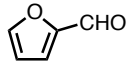
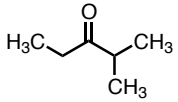
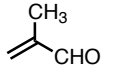
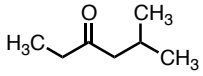
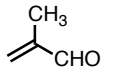
Reviews:

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 Diisopinocampheylborinates**

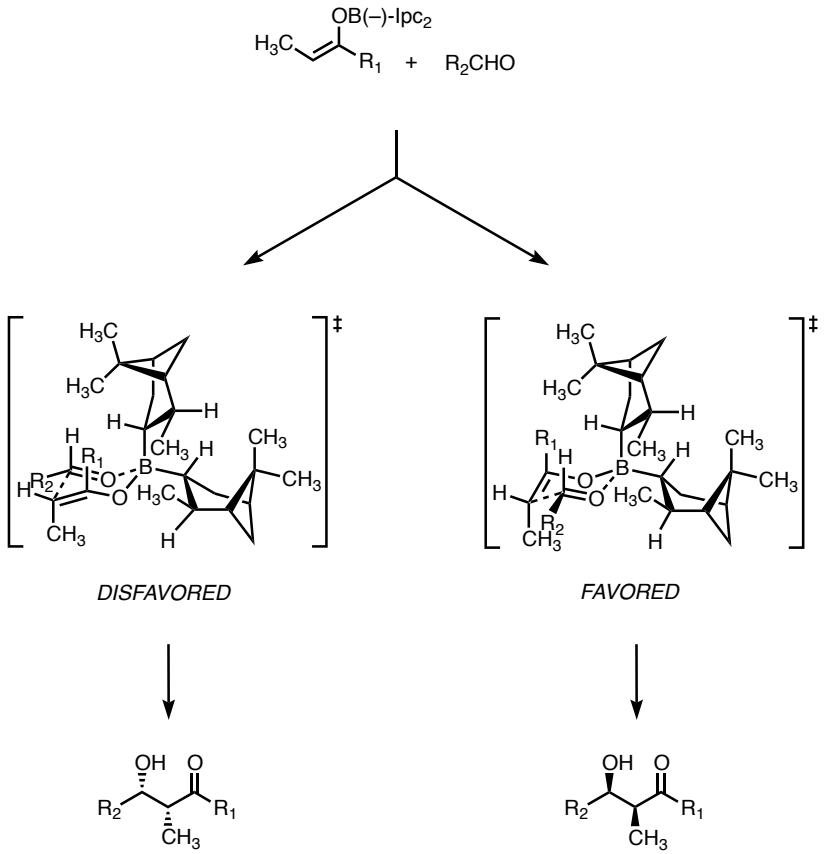


ketone	aldehyde	syn:anti	ee (%)	yield (%)
		98:2	91	78
		96:4	66	45
		96:4	80	84
		95:5	88	99
		97:3	86	79

- Enolization occurs selectively on the less hindered side of the ketone and with (*Z*)-selectivity.
- The (*E*)-Enolate, generated in low yield using (–)-Ipc_2BCl, 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% ee).

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:

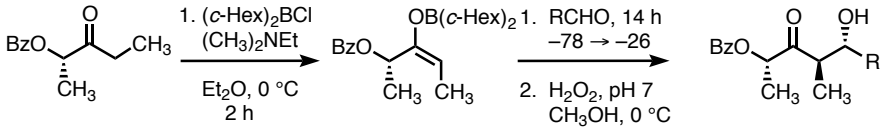


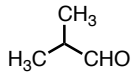
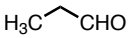
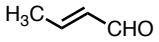
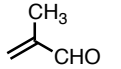
- Diastereofacial selectivity is believed to be due to a favored transition state wherein steric interactions between the (–)-Ipc ligand on boron and the R_1 substituent on the ketone are minimized.

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

M. Movassaghi

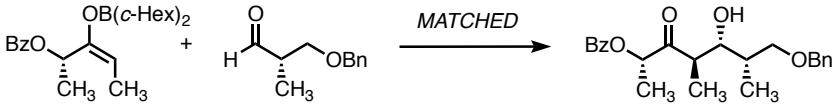
Anti-Aldol Reactions of Lactate-Derived Ketones

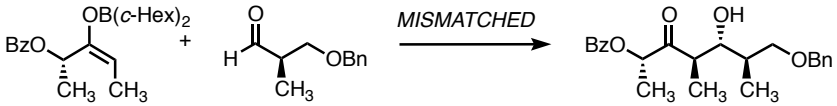


aldehyde	de (%)	yield (%)[a]
	94	95
	99	82
	90	97
	96	97
PhCHO	99	85

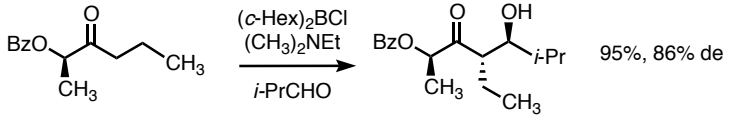
[a]Isolated yield for 3 steps.

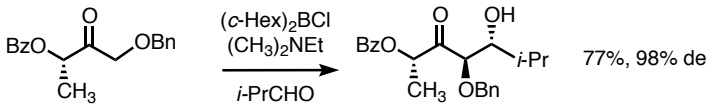
- Diastereofacial selectivity is very high; α-chiral aldehydes afford anti-aldol adducts with high diastereoselectivity regardless of their stereochemistry.



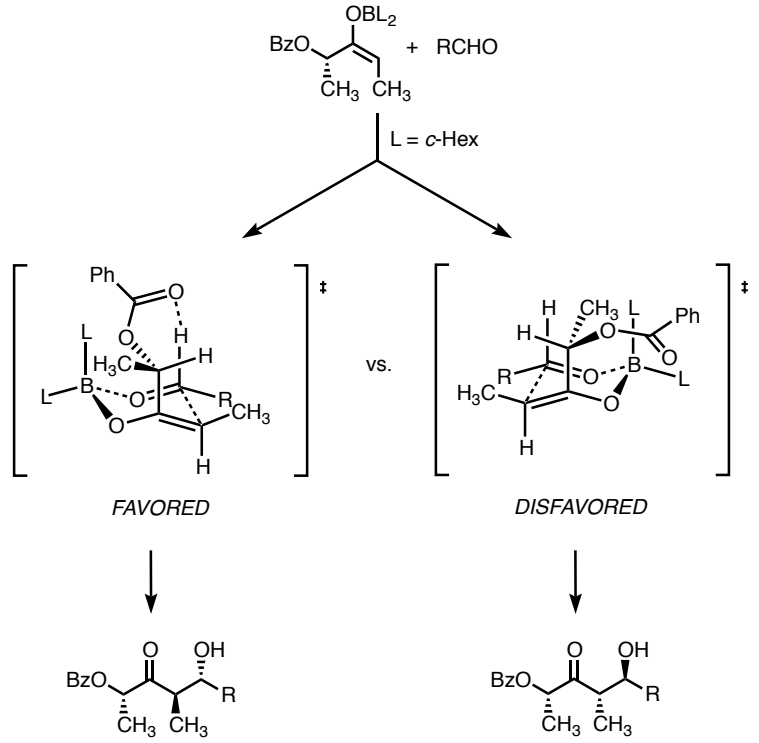


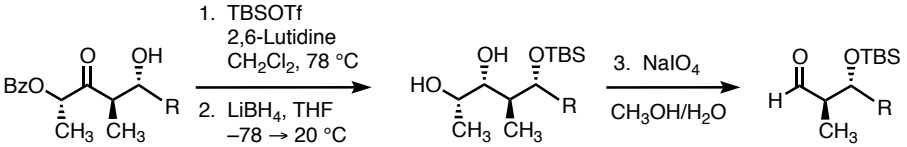
- Other examples:

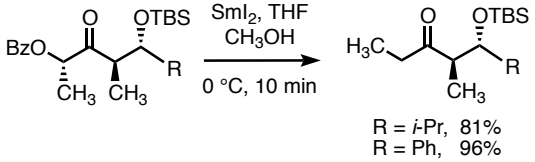




- The origin of the diastereoselectivity is proposed to be due to a formyl hydrogen bond in the favored transition state.







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

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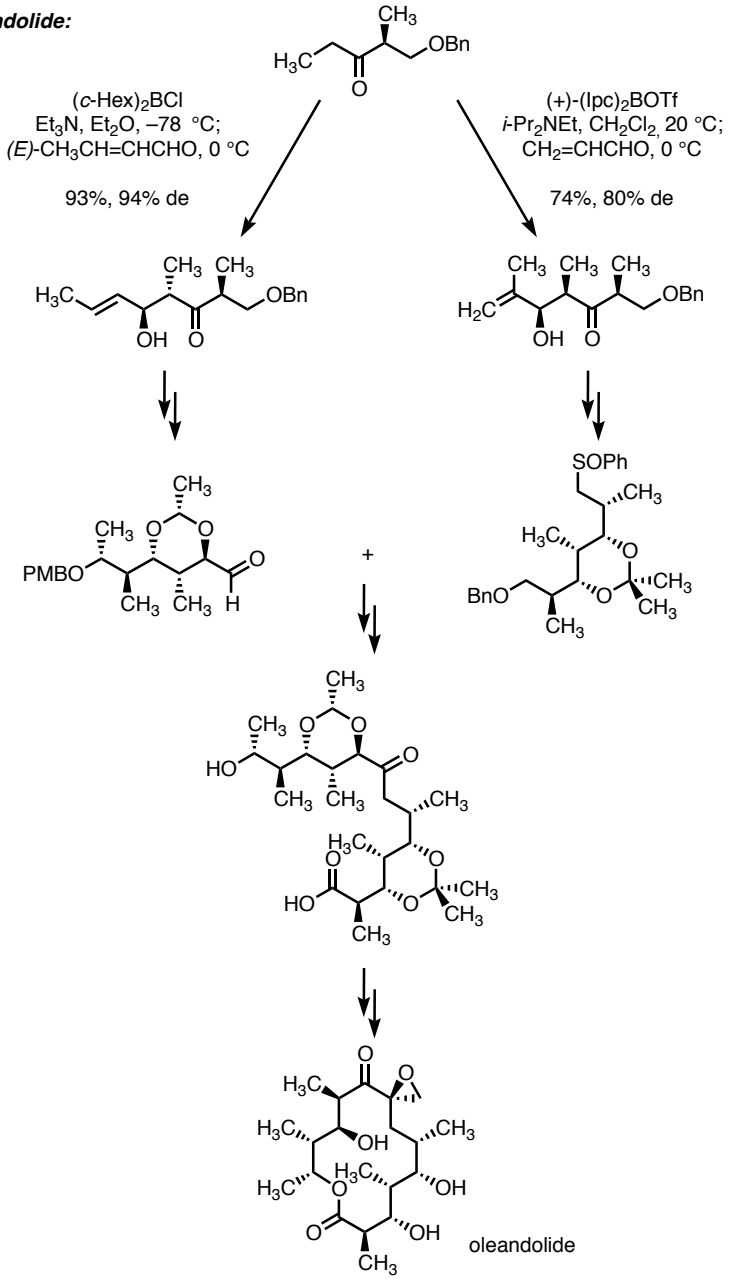
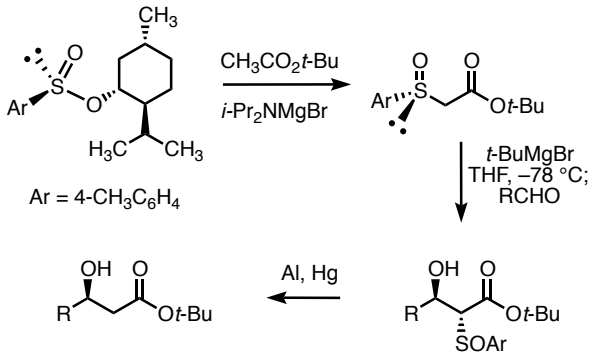
Oleandolide:



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

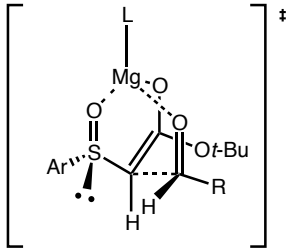
Acetate Aldol

Addition of a Chiral α-Sulphinylester Enolate to Aldehydes



- The β-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.

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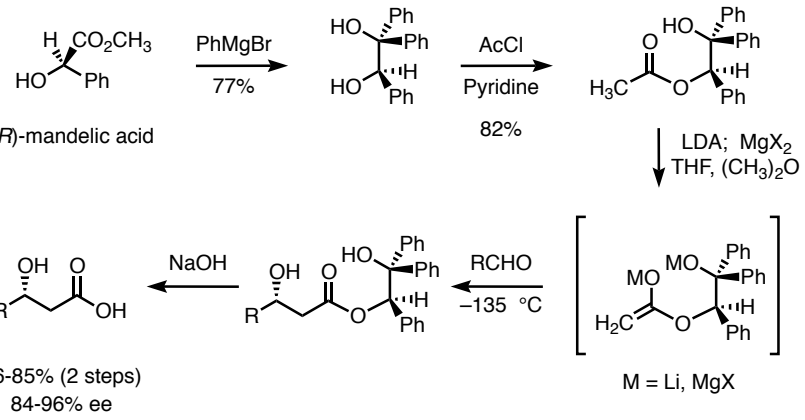
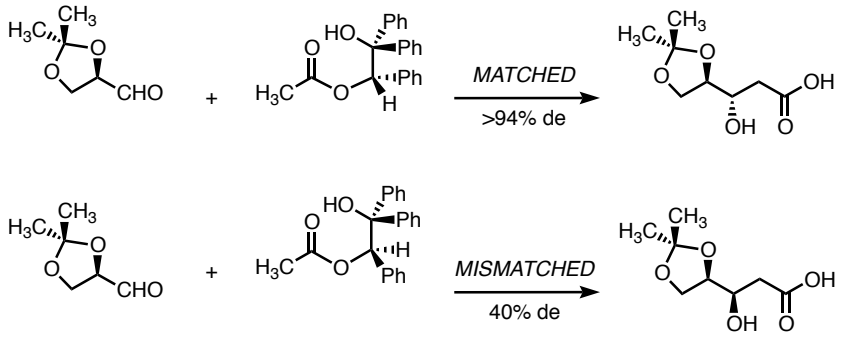
Addition of a Chiral Acetate Enolate to Aldehydes



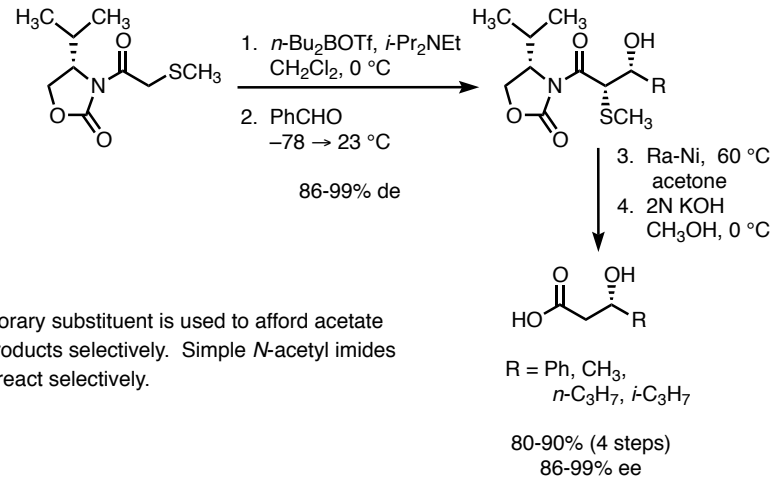
- Both (*R*)- and (*S*)-mandelic acids are commercially available.



- 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.

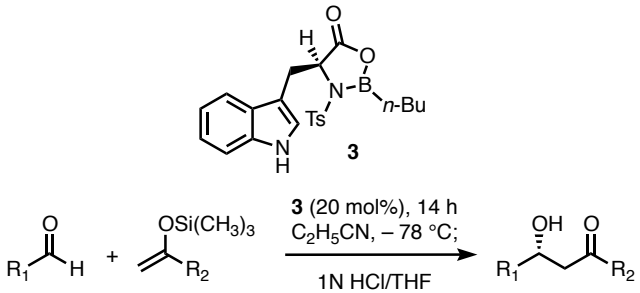
An Approach to the Acetate Aldol Problem



- 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



R_1	R_2	yield (%)	ee (%)
Ph	C_6H_5	82	89
c-C_6H_{11}	C_6H_5	67	93
2-furyl	C_6H_5	100	92
c-C_6H_{11}	*n*-C_4H_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.

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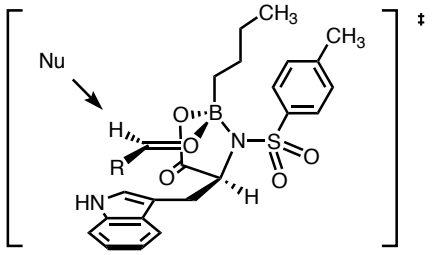
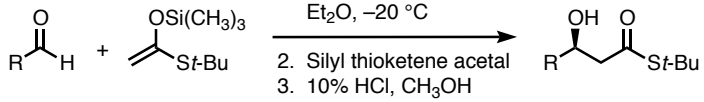
• Use of terminal trimethylsilyl enol ethers provide the highest level of enantioselectivities.



• 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



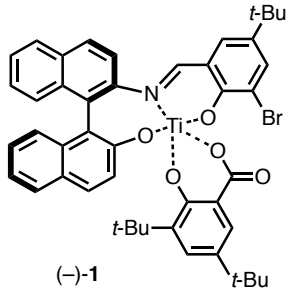
aldehyde	yield (%)	ee (%)
PhCHO	90	97
$PhCH_2CH_2CHO$	80	97
furylCHO	88	>98
c-$C_6H_{11}CHO$	70	89
$PhCH_2OCH_2CHO$	82	>98

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

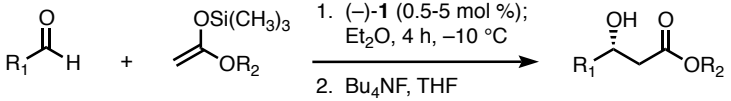
Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364.

Catalytic, Enantioselective Acetate Aldol Additions with Silyl Ketene Acetals

Review: Carreira, E. M.; Singer, R. A. *Drug Discovery Today* **1996**, *1*, 145-150.



(–)-**1**



Aldehyde	%ee: R_2 = Et	%ee: R_2 = CH_3	%ee: R_2 = Bn
CH_3 CHO	92	97	-
CH_3 CHO	88	95	-
Ph CHO	93	97	96
Ph CHO	89	94	91
CHO	94	95	-
CHO	93	96	96

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

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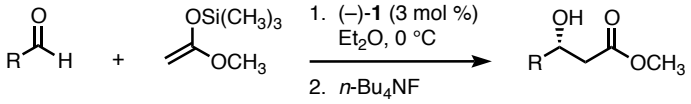
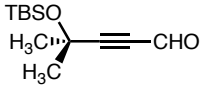
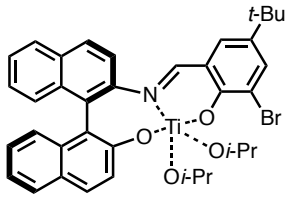
- Catalyst **1** is formed by condensation of the chiral amino alcohol with 3-bromo-5-*tert*-butylsalicylaldehyde followed by complexation with $Ti(O\textit{i}\text{-}Pr)_4$ and 3,5-di-*tert*-butylsalicylic acid. Both enantiomeric forms are available.
- Complete removal of *i*-PrOH during catalyst preparation 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_3N).
- 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.



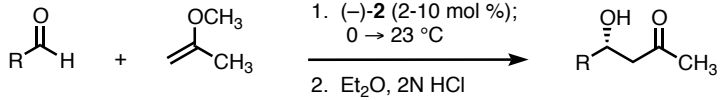
aldehyde	yield (%)	%ee
$TBSOCH_2{-}{\equiv}{-}CHO$	88	96
$Ph{-}{\equiv}{-}CHO$	96	94
$TIPS{-}{\equiv}{-}CHO$	88	97
	88	96

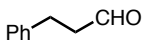
Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837-8838.
Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927-930.
Singer, R. A.; Shepard, M. S.; Carreira, E. M. *Tetrahedron* **1998**, *54*, 7025-7032.

Catalytic, Enantioselective Aldol Additions of an Acetone Enolate Equivalent



(–)-**2**



aldehdye	temp. (°C)	yield	%ee
$Ph(CH_2)_3{-}{\equiv}{-}CHO$	0	99	98
$TBSOCH_2{-}{\equiv}{-}CHO$	0	85	93
$Ph{-}{\equiv}{-}CHO$	0	99	91
	0 → 23	98	90
PhCHO	0 → 23	83	66
$c\text{-}C_6H_{11}CHO$	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.

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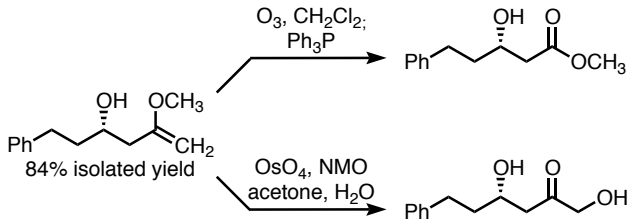
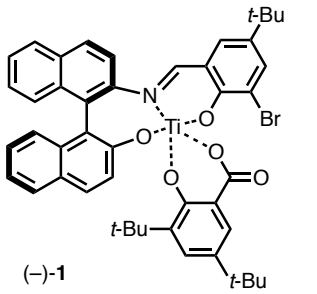
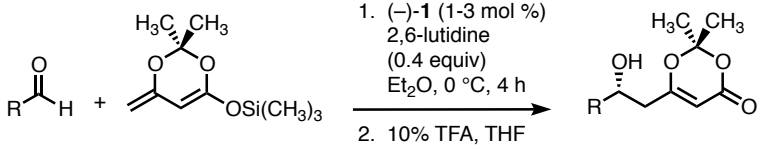
- The vinyl ether products can be isolated, or transformed into other useful products:



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

Catalytic, Enantioselective Dienolate Additions to Aldehydes

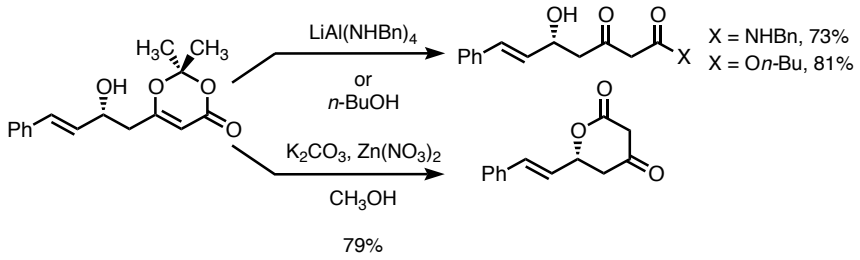




aldehyde	yield (%)	%ee
TIPS—≡—CHO	86	91
TBSO—CHO	97	94
CH_3—CHO	88	92
n-Bu_3Sn—CHO	79	92
Ph—CHO	97	80
PhCHO	83	84 (96)[a]

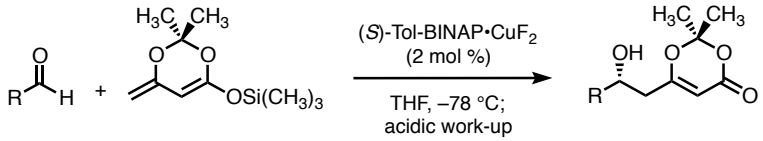
[a]after recrystallization.

- 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 δ-hydroxy-β-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
S—CHO	98	95
CHO, OCH_3	82	90
Ph—CHO	48	91
CH_3, Ph—CHO	81	83
Ph—CHO, CH_3	74	65

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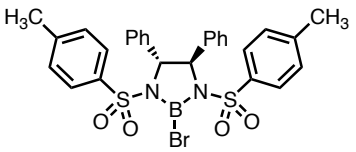
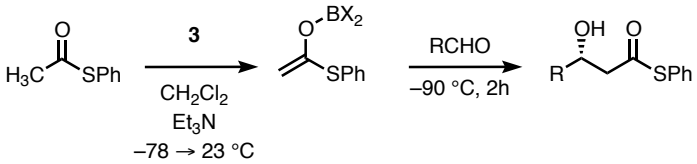
- (*S*)-Tol-BINAP-CuF_2 is readily prepared in situ by mixing (*S*)-Tol-BINAP, $Cu(OTf)_2$, and (n-Bu_4N)Ph_3SiF_2 in THF.
- This process is efficient for non-enolizable (α,β-unsaturated, aromatic, and heteroaromatic) aldehydes.
- Enolizable, aliphatic aldehydes give products with high enantioselectivity, but in poor yield (<40%).
- Spectroscopic evidence supports a catalytic process involving a chiral transition metal dienolate as an intermediate.

Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837-838.
Pagenkopt, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Engl. Ed.* **1998**, *37*, 3124-3126.

Enantioselective Acetate Aldol Addition Using a Chiral Controller Group



3

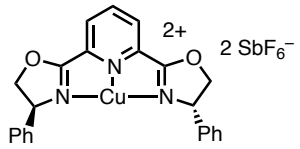


aldehdye	yield (%)	ee (%)
C_6H_5CHO	84	91
i-PrCHO	82	83

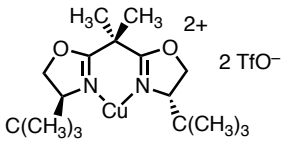
- Bromide **3** is produced from the corresponding (*R*,*R*)-bissulfonamide by reaction with BBr_3 in CH_2Cl_2.
- Upon completion of the reaction, the (*R*,*R*)-bis-sulfonamide can be recovered and reused.

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

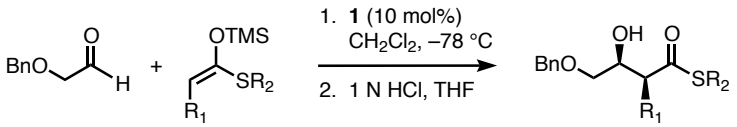
Catalytic, Enantioselective Aldol Additions of Silyl Thioketene Acetals and Silyl Enol Ethers



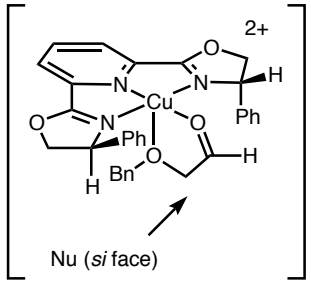
1



2



R_1	R_2	enol silane geometry	time (h)	T (°C)	syn:anti	%ee	yield (%)
H	*t*-Bu	–	24	–78	–	99	99
CH_3	Et	(*Z*)	4	–78	97:3	97	90
CH_3	Et	(*E*)	1d	–50	86:14	85	48
i-Bu	Et	(*Z*)	2d	–50	95:5	95	85



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.

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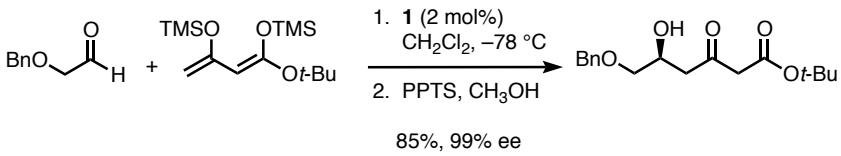
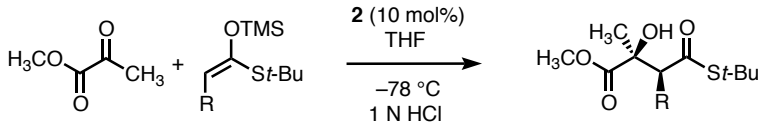


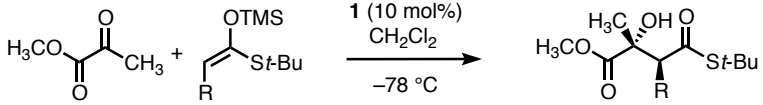
Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685.



R = H, CH_3, Et, *i*-Bu
77-97%
≥96% ee
≥94:6 syn:anti

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

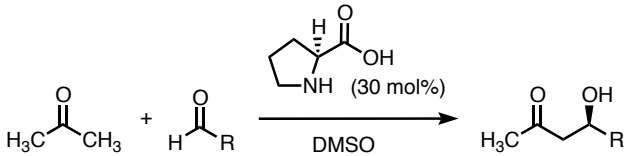
Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893-7894.

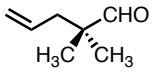


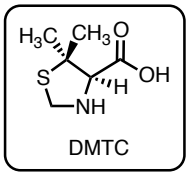
R = CH_3, Et, *i*-Bu
81-94%
≥96% ee
≥98:2 anti:syn

Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859-10860.
Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325-335.

Proline-Catalyzed Asymmetric Aldol Reaction of Acetone



aldehyde	yield	%ee
p-$NO_2C_6H_4CHO$	68 (60)	76 (86)
C_6H_5CHO	62 (60)	60 (89)
p-BrC_6H_4CHO	74 (85)	65 (67)
o-CCl_6H_4CHO	94 (71)	69 (74)
α-napthaldehyde	54 (60)	77 (88)
i-PrCHO	97 (65)	96 (96)
c-$C_6H_{11}CHO$	63 (45)	84 (83)
t-BuCHO	81	>99
	85	>99

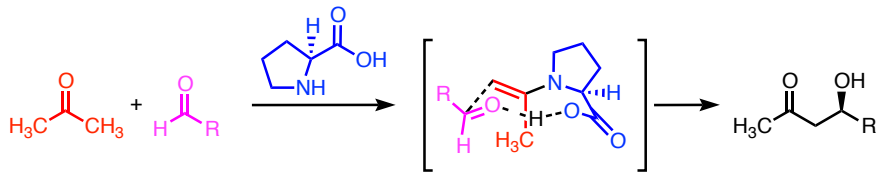


- Typically a 20–30 equivalent excess of acetone is used in relation to the aldehyde.
- Tertiary and α-branched aldehydes result in the highest yields and enantioselectivities, while unbranched aliphatic aldehydes give poor yields and enantioselectivities.
- 5,5-Dimethyl thiazolidinium-4-carboxylate (DMTC) has also been found to be an efficient amino acid catalyst for the acetone aldol reaction. Results with DMTC are in parentheses.

List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

Kandasamy, S.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

Proposed transition state:

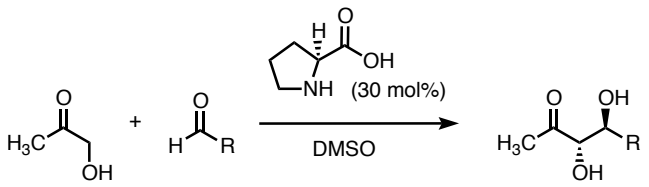


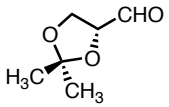
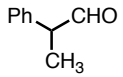
Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem. A.* **2002**, *106*, 5155-5159.
Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

For a discussion on the involvement of oxazolidinones in the mechanism, see: Seebach, D.; Beck, A. K.; Badine, M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425–471.

M. Movassaghi, Chris Coletta

Proline-Catalyzed Asymmetric Aldol Reaction of Hydroxyacetone

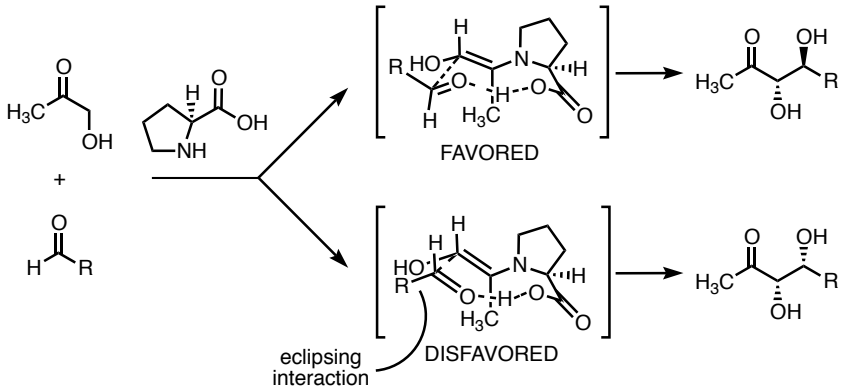


aldehyde	yield (%)	*anti:syn*	%ee
c-$C_6H_{11}CHO$	60	>20:1	>99
i-PrCHO	62	>20:1	>99
o-ClC_6H_4CHO	95	1.5:1	67
t-$BuCH_2CHO$	38	1.7:1	>97
	40	2:1	>97
	51	>20:1	>95

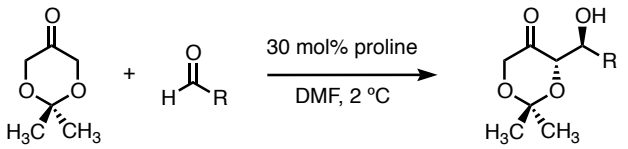
- The anti-diol product formed is not readily accessible via asymmetric dihydroxylation, making this reaction complementary to the Sharpless asymmetric dihydroxylation.
- The reaction is highly regioselective, and with suitable substrates (α-branched aliphatic aldehydes) the *anti:syn* ratio (dr) and enantioselectivity are excellent. In the case of α-unbranched aldehydes and aromatic aldehydes, the poor *anti:syn* selectivity is thought to result from a decrease in an eclipsing interaction between the alcohol and the aldehyde in the disfavored boat transition state shown below.

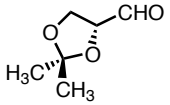
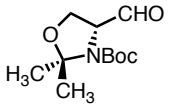
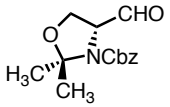
Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387.

Proposed origin of selectivity:

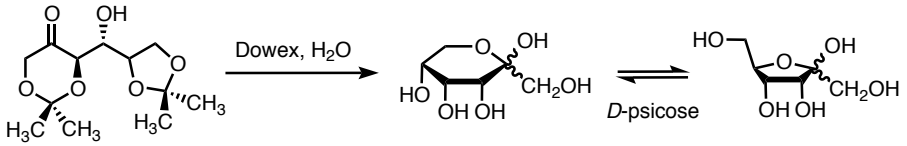


Proline-Catalyzed Asymmetric Aldol Reaction of Acetonide Protected Dihydroxyacetone



aldehyde	catalyst	yield	*anti/syn*	%ee
i-PrCHO	(*S*)-proline	97	>98:2	94
c-$C_6H_{11}CHO$	(*S*)-proline	86	>98:2	90
$BnOCH_2CHO$	(*S*)-proline	40	>98:2	97
$(CH_3O)_2CHCHO$	(*S*)-proline	69	94:6	93
	(*R*)-proline	76	>98:2	>98
	(*S*)-proline	80	>98:2	>96
	(*R*)-proline	31		>96
	(*S*)-proline	80	>98:2	>96

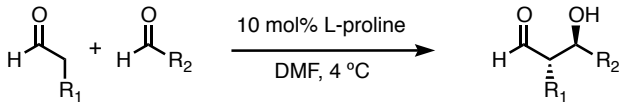
- The use of linear aldehydes in this reaction leads to poor yields, likely due to self condensation.
- Aromatic aldehydes form products with low diastereoselectivity (e.g., a 4:1 *anti:syn* ratio was reported for *ortho*-chlorobenzaldehyde).
- With the α-chiral α-aminoaldehyde shown above, the mismatched case results in a poor yield,
  but excellent dr and ee.
- Certain hexoses have been synthesized by this method.



Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210-1212.

Chris Coletta

Proline-Catalyzed Enantioselective Cross-Aldol Reaction of Aldehydes



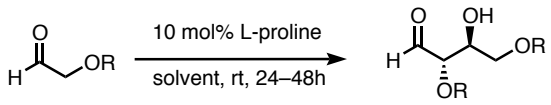
R_1	R_2	yield (%)	*anti*:*syn*	%ee
Me	Et	80	4:1	99
Me	*i*-Bu	88	3:1	97
Me	*c*-C_6H_{11}	87	14:1	99
Me	Ph	81	3:1	99
Me	*i*-Pr	82	24:1	>99
n-Bu	*i*-Pr	80	24:1	98
Bn	*i*-Pr	76	19:1	91

- Slow addition via syringe pump of the donor aldehyde to a solution of the acceptor aldehyde and proline is required in order to avoid dimerization of the donor aldehyde.

- Either non-enolizable aldehydes or aldehydes containg α- or β-branching are suitable acceptor aldehydes for this reaction.

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

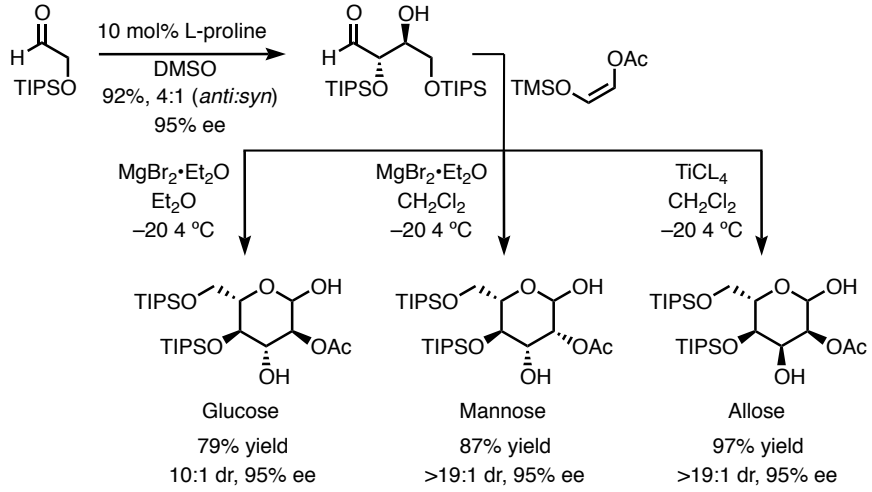
Proline-Catalyzed Direct and Enantioselective Aldol Reaction of α-Oxyaldehydes



R	solvent	yield (%)	*anti*:*syn*	%ee
Bn	DMF	73	4:1	98
PMB	DMF	64	4:1	97
MOM	DMF	42	4:1	96
TBDPS	DMF/dioxane	61	9:1	96
TIPS	DMSO	92	4:1	95
TBS	dioxane	62	4:1	88

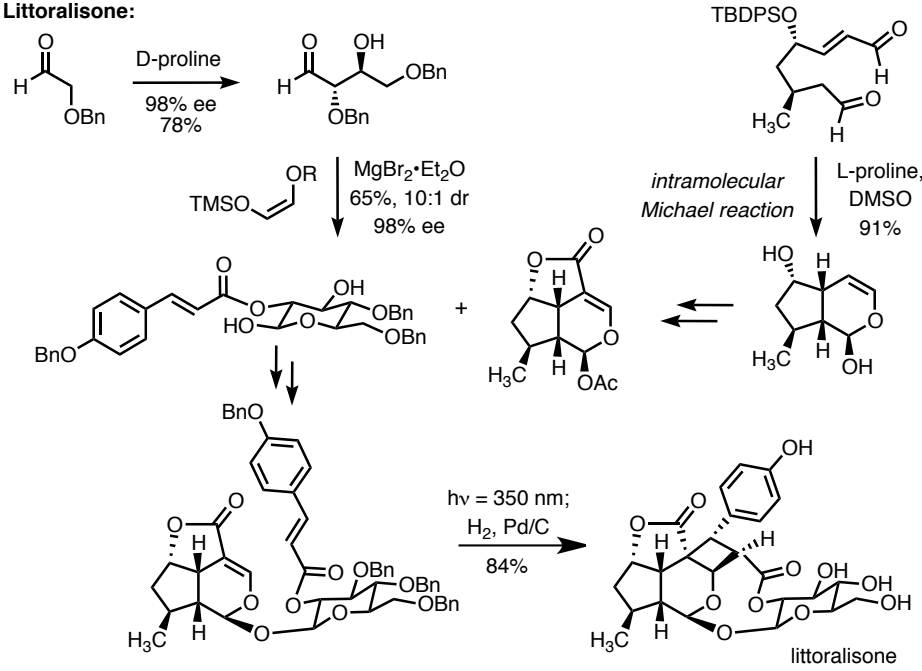
Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

- The aldol products from α-oxyaldehydes can be further elaborated as part of a two-step synthesis of carbohydrates.



Northrup, A. B.; MacMillan, D. W.C. *Science* **2004**, *305*, 1752-1755.

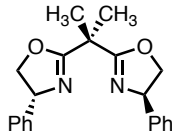
Littoralisone:



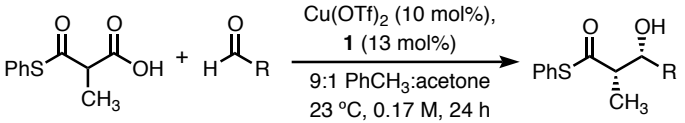
Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696-3697.

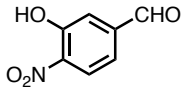
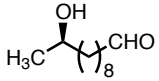
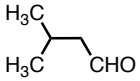
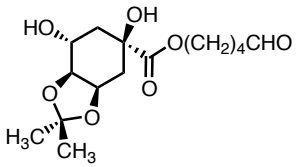
Chris Coletta, Jaron Mercer

Catalytic, Enantioselective Thioester Aldol Reactions



1

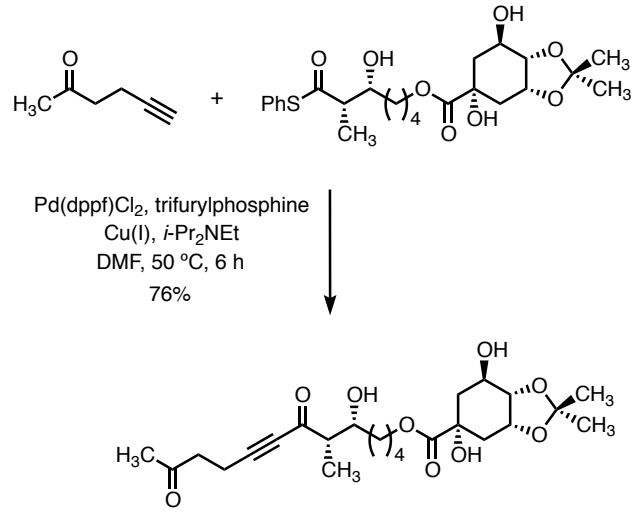


aldehyde	yield (%)	*syn:anti*	%ee
$CH_3(CH_2)_6CHO$	80	9:1	92 (R)
$CH_3O_2C(CH_3)_4CHO$	83	10:1	94
	83	9:1	93 (S)
	79	8:1	91
$CH_3(CH_2)_5{-}{\equiv}{-}CHO$	59	2.2:1	96 (S)
	73	7.5:1	89
c-$C_6H_{11}CHO$	48 (71[a])	36:1	93
	70	5.5:1	92

[a]two equiv of aldehyde was used.

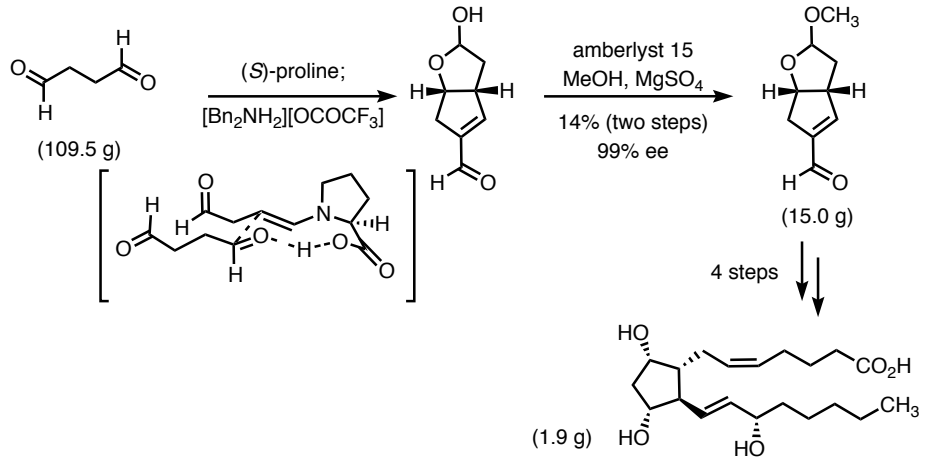
- This method is compatible with aldehyde substrates containing unprotected hydroxyl groups, including phenols.
- Aromatic aldehydes and β-branched aldehydes are generally poor substrates.

- The thioester group of the aldol products can be transformed by Pd-catalyzed cross coupling to give ketones.



Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284-3695.

- A recent example of proline-catalyzed aldol reaction in the synthesis of prostaglandin $PGF_{2\alpha}$:



Coulthard, G; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278-281.

Chris Coletta, Fan Liu