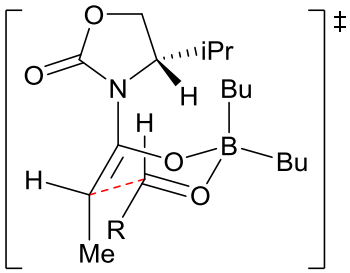
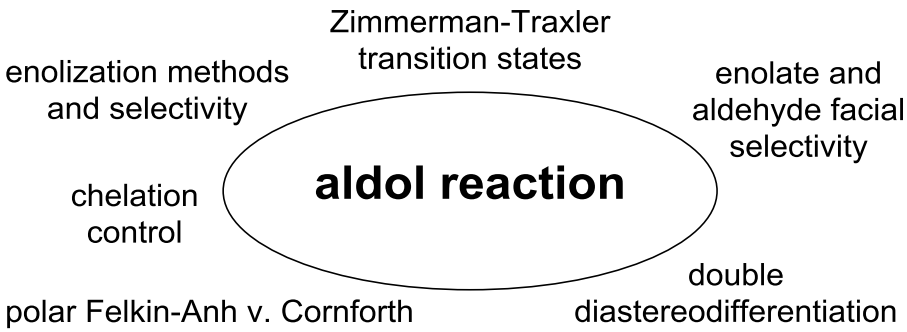
The Aldol Reaction

Jason J. Beiger



Scope of Lecture



Helpful References

1. "Stereoselective Aldol Condensations." Evans, D.A. et al. *Top. Stereochem.* **1982**, *13*, 1.

2. "Stereoselective Aldol Reactions." Chem 215 Handout, Harvard University, http://www.chem.harvard.edu/groups/myers/handouts/14_Stereoselective.pdf

3. "Diastereoselection in Lewis-Acid-Mediated Aldol Additions." Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.

4. "The Aldol Reaction..." Heathcock, C.H. *Comprehensive Organic Synthesis*. Trost, B.M.; Fleming, I., eds. Oxford, Pergamon Press, **1999**, *2*, 181.

5. "Stereoselective Aldol Reactions in the Synthesis of Natural Products." Paterson, I. *Modern Carbonyl Chemistry*. Otera, J., ed. Weinheim, Wiley-VCH, **2000**, 249.

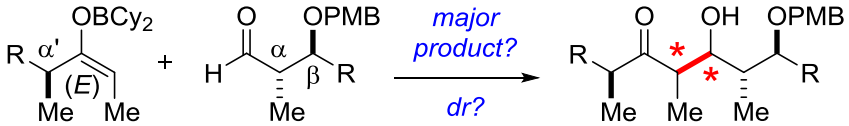
6. "Modern Aldol Reactions." Mahrwald, R., ed. Weinheim, Wiley-VCH, **2004**, *Vol. 1 & 2*.

7. "Modern Aldol Methods for the Total Synthesis of Polyketides." Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 7506.

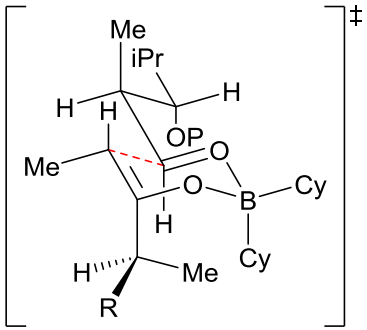
8. "Classics in Stereoselective Synthesis." Kværno, L.; Carreira, E.M. Weinheim, Wiley-VCH, **2004**, *Ch. 4*, 103.

Key Questions

1. How do pre-existing stereochemical elements on both enolate and aldehyde control aldol diastereoselectivity?



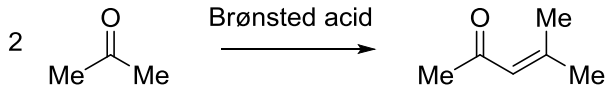
2. How do steric, electrostatic and stereoelectronic effects govern aldol reactivity and selectivity?



lecture notes edited by Richard Liu and Eugene Kwan

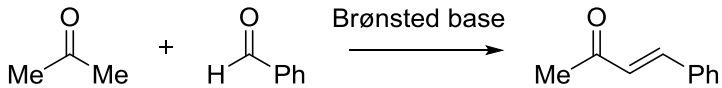
Discovery

- **Self-Condensation**



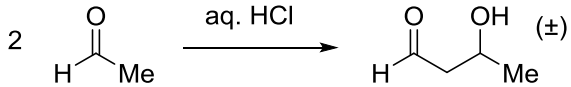
Kane, R. *J. Prakt. Chem.* **1838** *15* 129

- **Claisen-Schmidt Crossed (Mixed) Condensation**



Schmidt, J.G. *Ber. Dtsch. Chem. Ges.* **1880** *13* 2342; **1881** *14* 1459
Claisen, L.; Claparède, A. *Ber. Dtsch. Chem. Ges.* **1881** *14* 349

- **Self-Addition of Acetaldehyde**



aldol
(β-hydroxy aldehyde)

Wurtz, W. *J. Prakt. Chem.* **1872** *5* 457; *Comptes Rendus* **1872** *74* 1361
Borodin, A.P. (see: Gordin, M.D. *J. Chem. Ed.* **2006** *83* 561

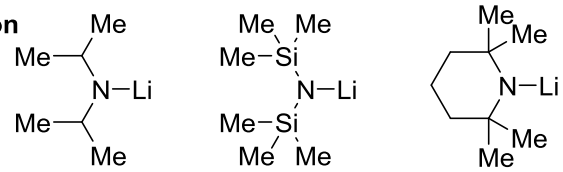
Enolization Methods

- **"Traditional" Brønsted Acid or Base Activation: Complications**
  - unfavorable equilibriums (reversibility)
  - condensation byproducts
  - poor regioselectivity when using unsymmetrical ketones
  - undesired enolization of electrophile
  - lack of stereochemical control

- **The Emergence of Preformed Enolates (1970s)**

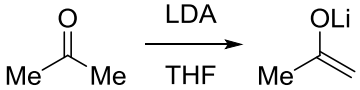
1) "hard" enolization

– deprotonation of a carbonyl compound with a strong base



	LDA	LiHMDS	LiTMP
pK_a	36 (THF)	26 (THF) 30 (DMSO)	37 (DMSO)

pK_a(DMSO) = 26.5

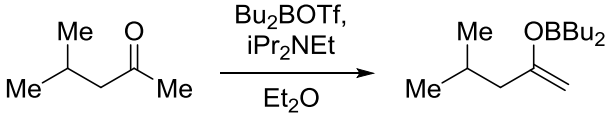


2) "soft" enolization

– deprotonation of a carbonyl compound through the use of a Lewis acid and a weak base

Lewis acids: boron, titanium(IV), tin(II), magnesium…
weak bases: Et_3N, iPr_2NEt, $EtNMe_2$, (–)-sparteine, pyridine…

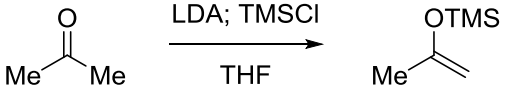
– complexation with Lewis acid increases acidity of carbonyl α-protons by ~20 pK_a units



Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976** 559

3) formation of silyl enol ethers (Mukaiyama aldol reaction)

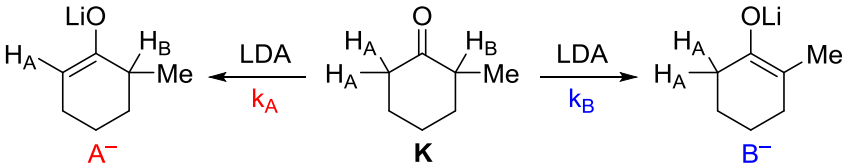
– preparation of stable and isolable enolate equivalents by the capture of enolate anions with silicon electrophiles



Brownbridge, P. *Synthesis* **1983** *1* 85

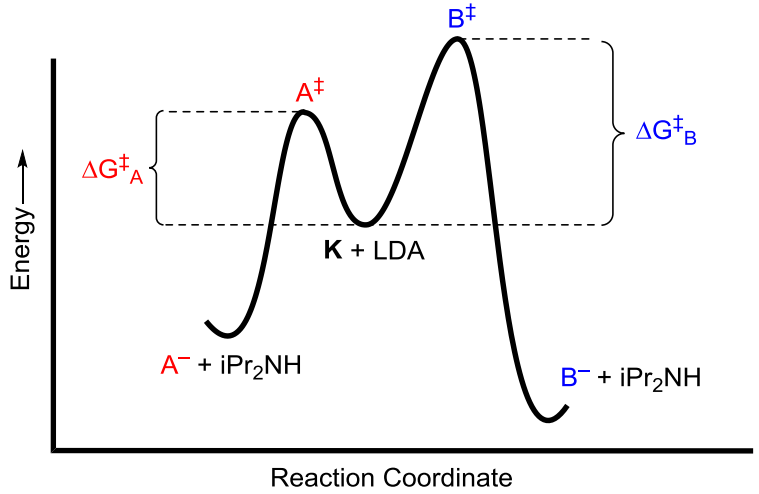
Enolization Regioselectivity

- **Kinetic Acidity**

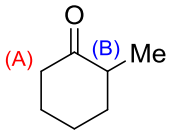
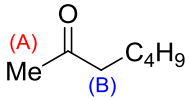
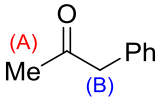


– differences in the rate of proton removal (k_A v. k_B) allow for regioselective deprotonation under non-equilibrating conditions

– the magnitudes of k_A and k_B are sensitive to structure (steric effects)

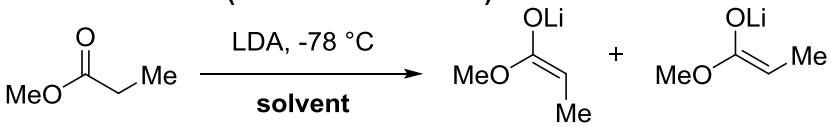


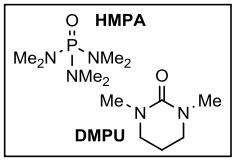
– kinetic control produces less-substituted enolates while equilibration over time and/or at higher temperatures favors more-substituted enolates

*Observed Deprotonation Ratio (**A**:**B**)*			
Kinetic (–78 °C)	99:01	84:16	86:14
Equilibrium (rt)	10:90	13:87	01:99

Control of Enolate Geometry

- **Lithium Enolates (and Polar Additives)**

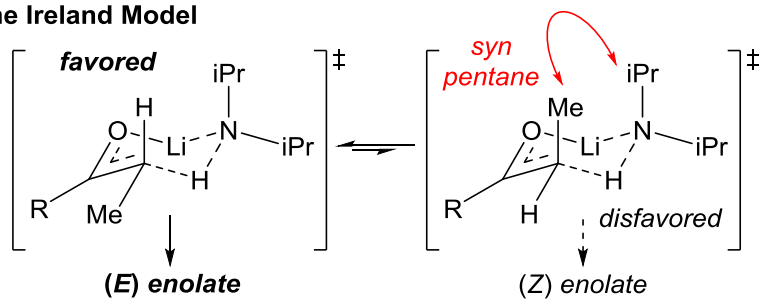




THF	**94**	:	06
23% **HMPA**-THF	15	:	**85**
45% **DMPU**-THF	07	:	**93**

Ireland, R.E.; Wipf, P.; Armstrong, J.D. *J. Org. Chem.* **1991** *56* 650

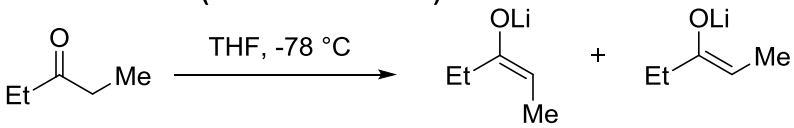
- **The Ireland Model**



– steric interactions minimized in pericyclic chair-like transition state
– poor orbital overlap suggests this model may not be realistic
– model does not account for *Z*-selective enolization methods

Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976** *98* 2868

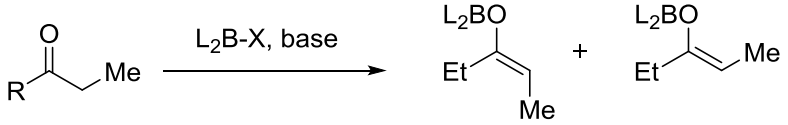
- **Lithium Enolates (and LiX Additives)**



conditions	***(E) enolate***		***(Z) enolate***
LDA	77	:	23
LiTMP	**86**	:	14
LiTMP, **10% LiBr**	**98**	:	02

Hall, P.L.; Gilchrist, J.H.; Collum, D.B. *J. Am. Chem. Soc.* **1991** *113* 9571

- **Boron Enolates**

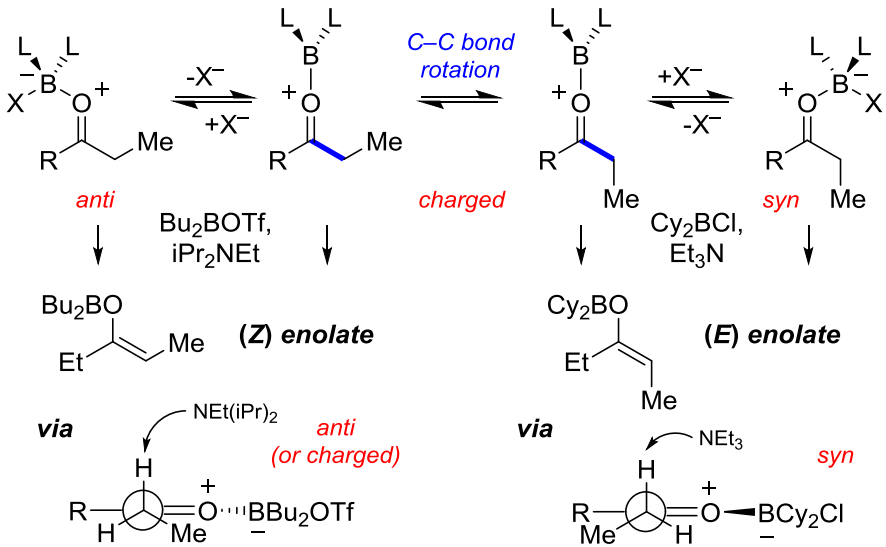


R	conditions	(*E*) *enolate*		(*Z*) *enolate*
Et	Bu_2BOTf, iPr_2NEt	<03	:	**>97**
	9-BBN-OTf, Et_3N	<03	:	**>97**
	Cy_2BCl, Et_3N	**79**	:	21
iPr	Cy_2BCl, Et_3N	**>97**	:	<03

Evans, D.A.; Vogel, E.; Nelson, J.V. *J. Am. Chem. Soc.* **1979** *101* 6120
Brown, H.C.; et al. *J. Am. Chem. Soc.* **1989** *111* 3441
Brown, H.C.; Ganesan, K.; Dhar, R.K. *J. Org. Chem.* **1993** *58* 147

– **L_2BOTf reagents favor the formation of (*Z*) enolates**
– **L_2BCl reagents favor the formation of (*E*) enolates**
– steric requirements of trialkylamine base and L in L_2B-X also impact ratio

- **The Paterson Model for Stereoselective Enolization**

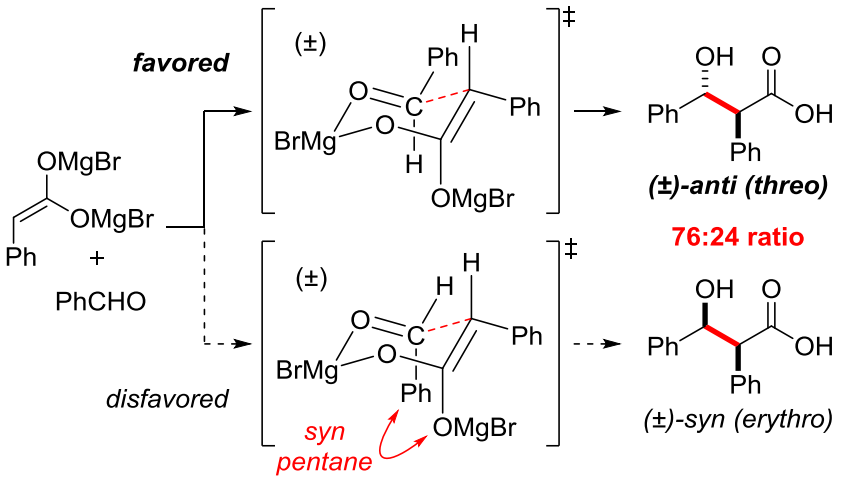


Goodman, J.M.; Paterson, I. *Tetrahedron Lett.* **1992** *33* 7223

Enolate Geometry is Linked to Product Stereochemistry

- **Zimmerman-Traxler Model for the Ivanov Reaction (1957)**

– proposed a cyclohexane chair-like transition state

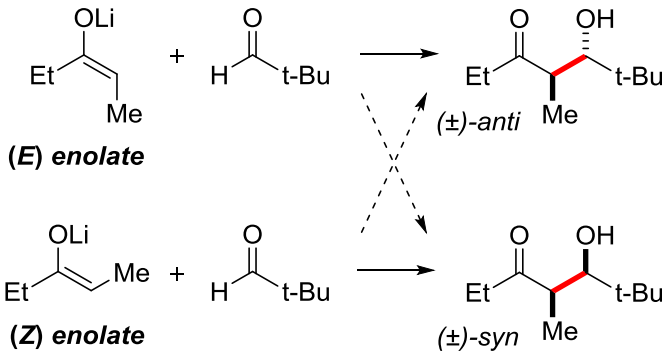


– diastereoselectivity is a function of the relative sizes of the substituents on the carbonyl electrophile (Ph v. H) and on the enolate

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

- **Dubois Aldol Experiments (1975)**

– noted rough correlation between enolate geometry and product stereochemistry for aldol reaction

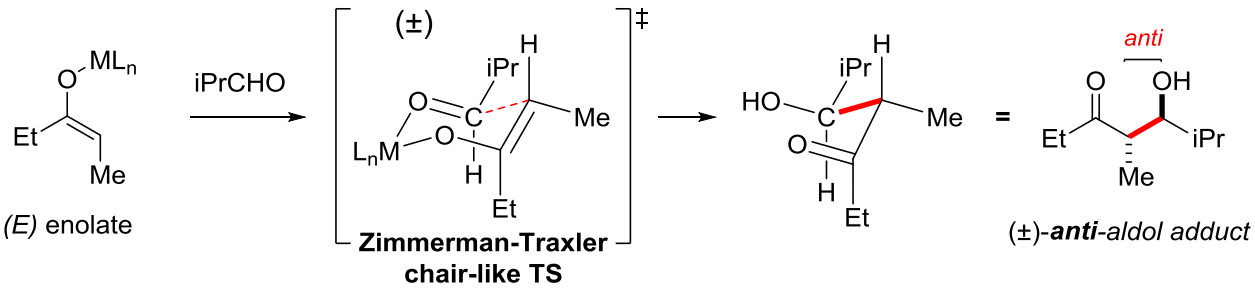


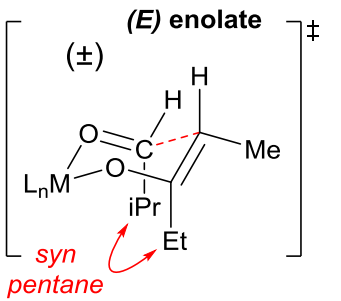
syn	:	anti
48	:	**52**
88	:	12

Dubois, J.E.; Fellman, P. *Tetrahedron Lett.* **1975** *14* 1225

Application of the Zimmerman-Traxler Transition State Model to the Aldol Reaction

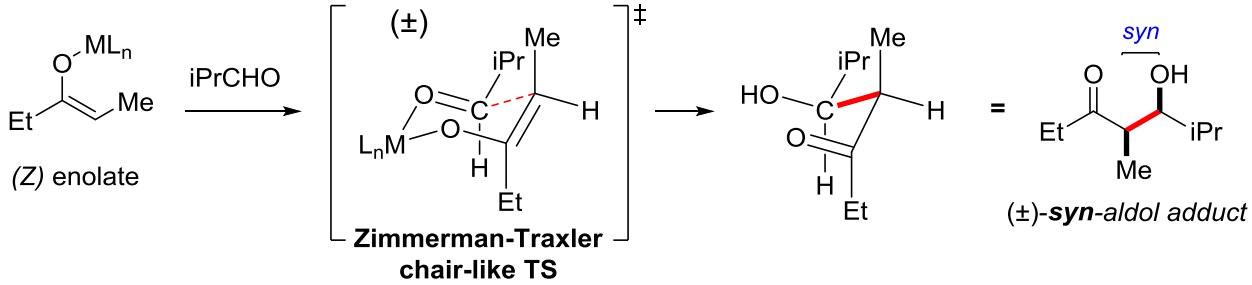
***(E) enolates** produce anti-aldol adducts:*

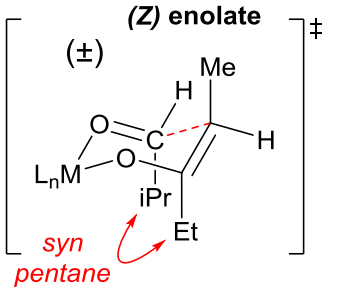




Disfavored Transition States

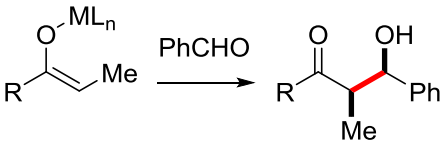
***(Z) enolates** produce syn-aldol adducts:*





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

- **Effect of Enolate Size**
  - diastereoselectivity results from the minimization of developing *syn* pentane (1,3-diaxial) interactions in each chair-like transition state (~3.7 kcal/mol)
  - as axially-oriented enolate substituent (above: Et) enlargens, the reaction diastereoselectivity often improves regardless of metal identity



R	ML_n	syn:anti
Et	Li	80:20
t-Bu	Li	>98:02
	MgBr	>95:05
	BBu_2	>97:03

Evans, D.A.; Vogel, E.; Nelson, J.V. *J. Am. Chem. Soc.* **1979** *101* 6120
Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *J. Am. Chem. Soc.* **1981** *103* 3099

- **Effect of Metal Identity**
  - diastereoselectivity can be highly metal dependent, with boron often providing the highest levels of stereocontrol
  - boron tightens transition states by virtue of the short bonds it forms:

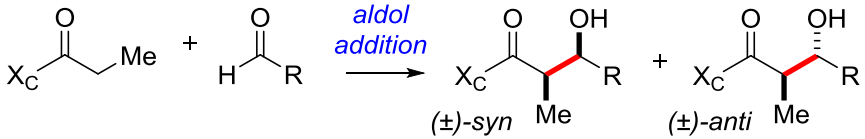
M–O 1.6-2.2 Å →	B–O **1.4-1.5 Å**
M–C 2.0-2.3 Å →	B–C **1.5-1.6 Å**

(same reaction as left)

R	ML_n	syn:anti
Et	Li	80:20
	BBu_2	>97:03
Ph	Li	80:20
	BBu_2	>97:03
	9-BBN	98:02
***via* (*E*) enolate →** Ph	BCy_2	05:95

Controlling Enolate Facial Selectivity

- **The Aldol Problem: Selecting for One Product Stereoisomer**

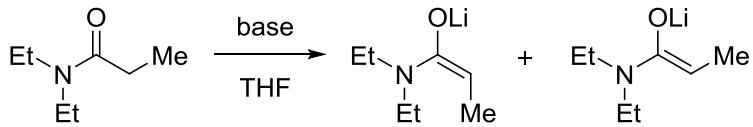


- **Chiral Auxiliary (X_C) Design Objectives**

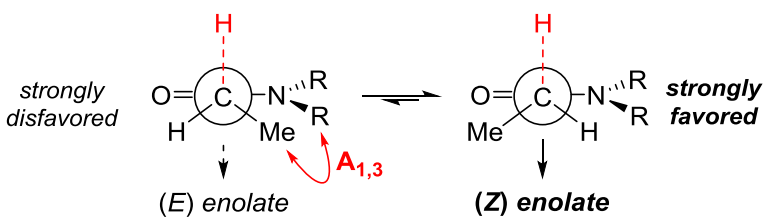
Evans, D.A. *Aldrichimica Acta* **1982** *15* 23

1) Control Enolate Geometry

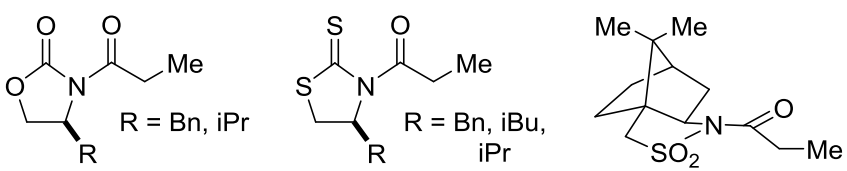
– use allylic strain ($A_{1,3}$) to control enolization selectivity



base	(*E*) *enolate*		(*Z*) *enolate*
LDA	0	:	**100**
sec-BuLi	25	:	**75**



– chiral auxiliaries that use allylic strain to control enolate geometry:



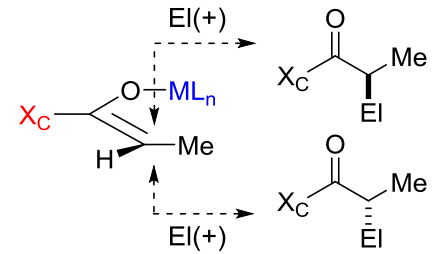
Evans *JACS* **1981** *103* 2127 | Crimmins *OL* **2000** *2* 775 | Oppolzer *JACS* **1990** *112* 2767

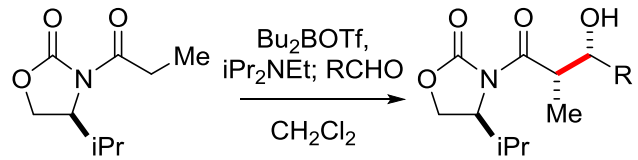
– *amide-based chiral auxiliaries are* ***limited*** *by (Z)-selective enolization**

2) Control Enolate Facial Selectivity

– provide a strong topological bias for enolate diastereoface selection

– diastereoselectivity may be induced by the **auxiliary (X_C)** or the **metal complex (ML_n)**

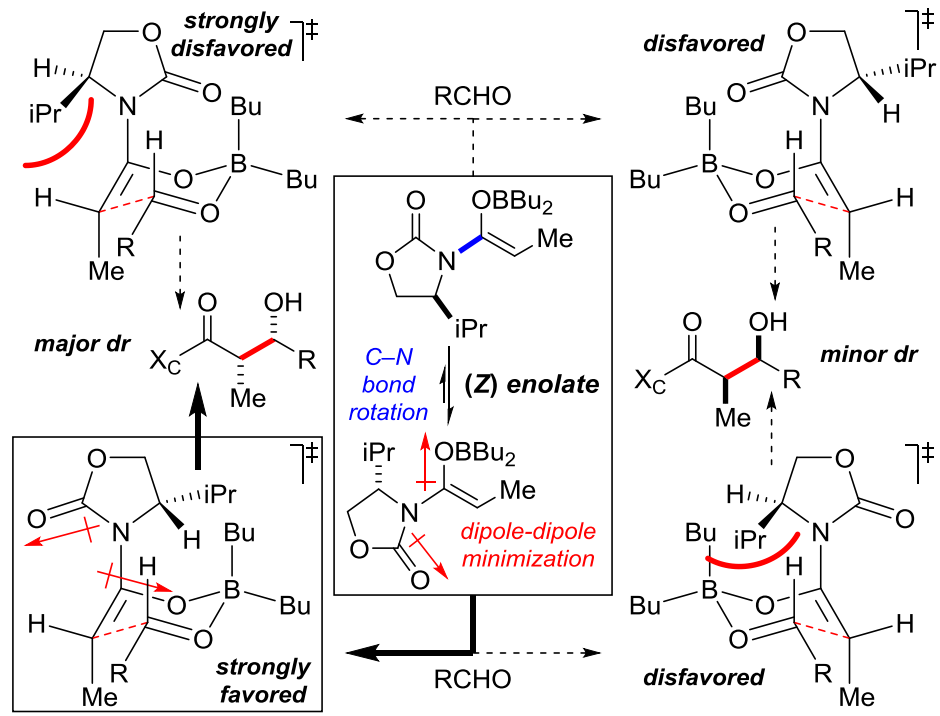




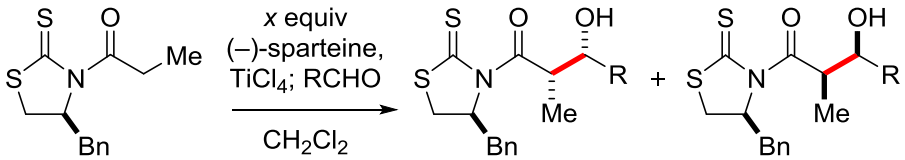
R	Yield	dr
Ph	88%	>500:1
Bu	75%	141:1
iPr	78%	497:1

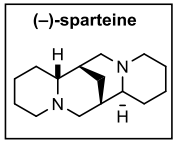
Evans, D.A.; Bartroli, J.; Shih, T.L. *J. Am. Chem. Soc.* **1981** *103* 2127

– **steric interactions** between the oxazolidinone iPr group and RCHO, and **dipole-dipole interactions** within the imide are minimized in favored TS



Evans, D.A.; et al. *Pure & Appl. Chem.* **1981** *53* 1109

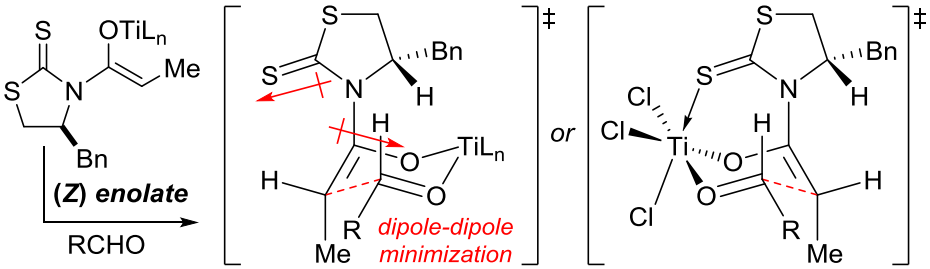




x	R	yield	"Evans" syn	:	"non-Evans" syn
1.0	CH_2=CH	49	<01	:	**>99**
	iPr	60	02	:	**98**
2.0	CH_2=CH	77	**>99**	:	<01
	iPr	75	**97**	:	03

Crimmins, M.T.; Chaudhary, K. *Org. Lett.* **2000** *2* 775

– both syn aldol adducts may be accessed from a common auxiliary simply by changing the amount of (–)-sparteine base



"Evans" syn aldol TS
[2 equiv. (–)-sparteine]

"non-Evans" syn aldol TS
[1 equiv. (–)-sparteine]

3) Limit Racemization Upon Removal

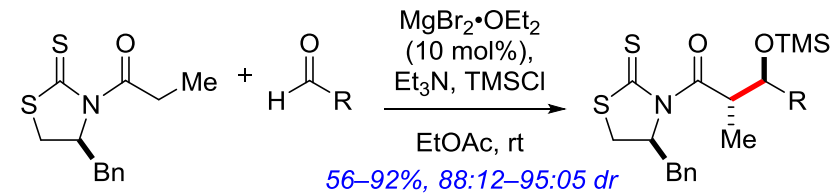
Auxiliary	Transformation	Reagents	Product
oxazolidinone	reduction	$LiBH_4$, ROH	1° alcohol
	hydrolysis	$LiOH.OH_2$	carboxylic acid
	trans-esterification	$Ti(OBn)_4$	benzyl ester
	trans-thioesterification	BnSLi or EtSLi	thioester
	trans-amidation	$Me(OMe)NH_2Cl$, $AlMe_3$	Weinreb amide
thiazolidinethione	reduction	DIBAl-H	**aldehyde**

• **The Anti-Aldol Problem**

Are amide-based chiral auxiliaries limited by *Z*-selective enolization?

71–92%, 86:14–97:03 dr

Evans, D.A.; et al. *J. Am. Chem. Soc.* **2002**, *124*, 392.



56–92%, 88:12–95:05 dr

Evans, D.A. *et al. J. Org. Lett.* **2002** *4* 1127

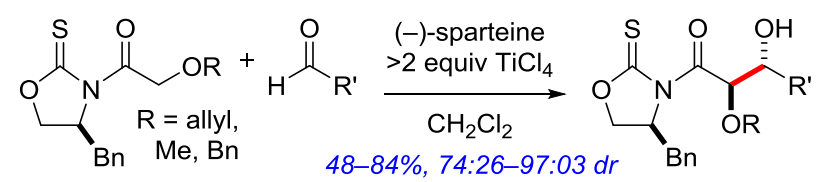
– reactions afford unexpected **anti aldol products from (*Z*)-enolates**

– speculated to proceed through **closed boat-like transition states**

– TMSCl silylates metal aldolate to turn catalytic cycle, but not enolate

- overcomes reversibility of C–C bond formation
- excludes Mukaiyama-type aldol pathway

– mainly limited to aromatic and unsaturated aldehydes (RCHO)



48–84%, 74:26–97:03 dr

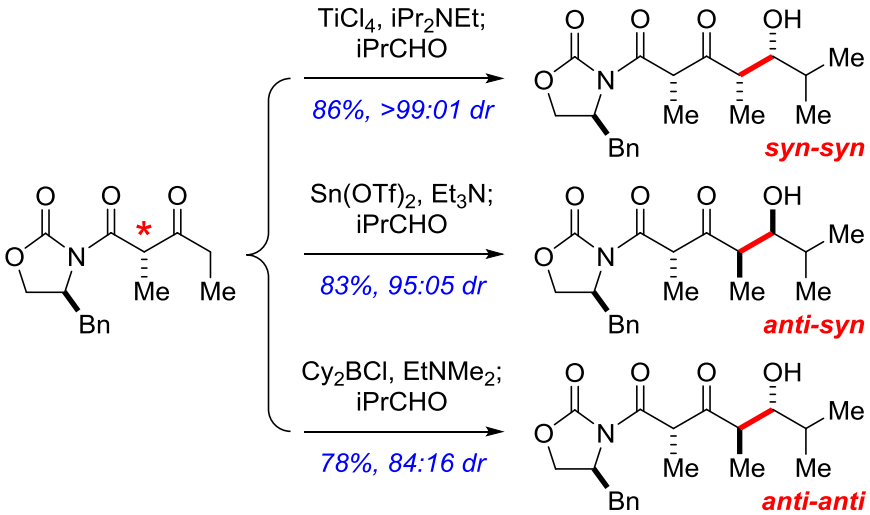
Crimmins, M.T.; McDougall, P.J. *Org. Lett.* **2003** *5* 591

– reactions afford unexpected **anti aldol products from (*Z*)-enolates**

– proposed to proceed via an **open transition state**

Enolate Facial Selectivity: Other Methods

- **Diastereoselective β-Ketoimide Aldol Reactions**



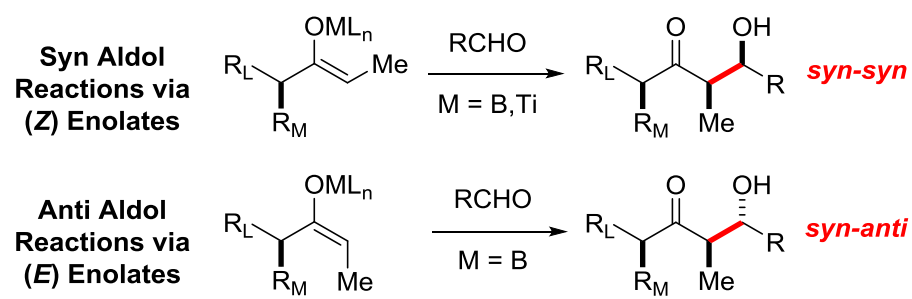
Evans, D.A. *et al. J. Am. Chem. Soc.* **1990** *112* 866
Evans, D.A.; Ng, H.P.; Clark, J.S.; Rieger, D.L. *Tetrahedron* **1992** *48* 2127

– kinetic lability of the Me-bearing stereocenter (*) attenuated by allylic strain

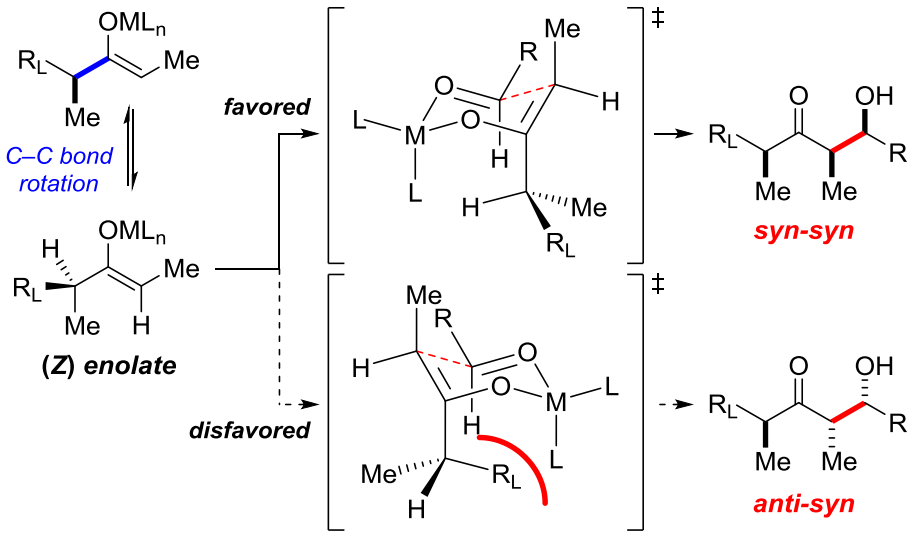
– stereochemical outcome dominated by the methyl-bearing stereocenter, with the chirality of the oxazolidinone playing a subordinate role

– **the sense of asymmetric induction observed in these reactions was opposite to that predicted by previously established models**

- **Aldol Reactions of Chiral Ethyl Ketones**



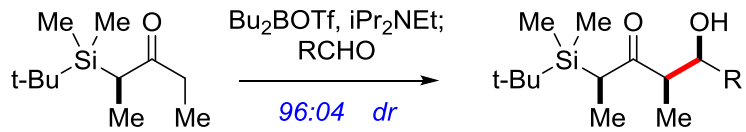
Syn Aldol Reactions via (*Z*) Enolates



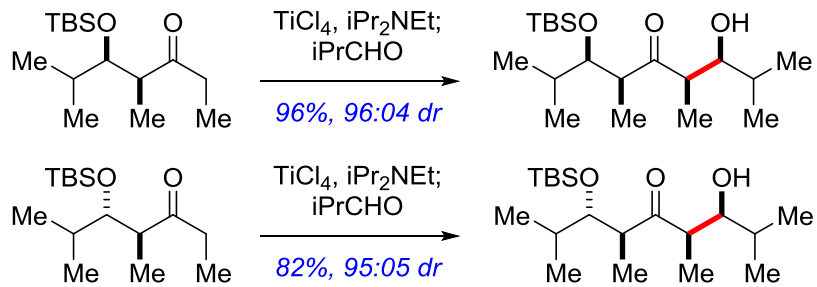
– R_L and Me (R_M) are the sterically dominant and subordinate substituents

– R_L is oriented away from the reactive enolate diastereoface

– nonbonding interactions between the metal center and Me (R_M) minimized

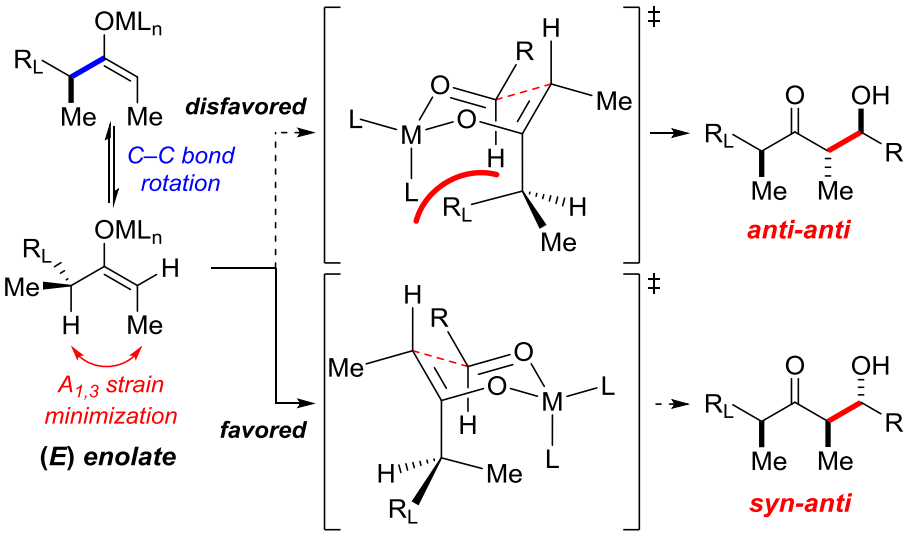


Enders, D.; Lohray, B.B. *Angew. Chem. Int. Ed.* **1988** *27* 581



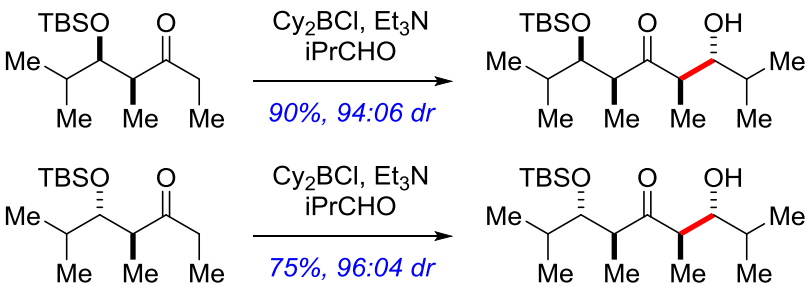
Evans, D.A.; Rieger, D.L.; Bilodeau, M.T.; Urpí, F. *J. Am. Chem. Soc.* **1991** *113* 1047

Anti Aldol Reactions via (*E*) Enolates



– allylic strain ($A_{1,3}$) minimized between enolate Me and α' stereocenter

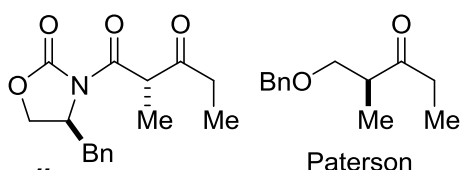
– sterically dominant R_L substituent oriented away from incoming electrophile



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

WARNING

(*E*) enolates of these chiral ethyl ketones **do not comply** with this allylic strain steric model (additional electrostatic effects?):

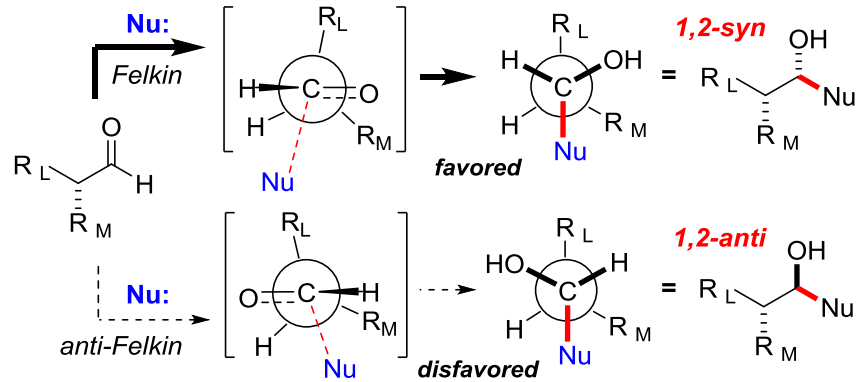


Paterson *TL* **1989** *30* 7121

***anti-anti* aldol adducts observed!**

Aldehyde Facial Selectivity

- **1,2-Stereoinduction: The Felkin-Anh Model (cf. previous lecture)**



Anh, N.T.; Eisenstein, O. *Nouv. J. Chim.* **1977** *1* 61

– Bürgi-Dunitz trajectory applied to nucleophile approach

– transition state stabilized by hyperconjugative interaction between the forming bond and the C–R_L antibonding orbital (**antiperiplanar effect**)

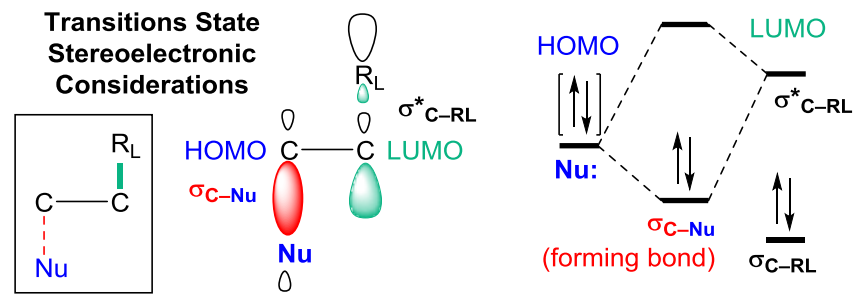
Theoretical Support for the Felkin-Anh Model

– **greater tendency of partially formed vicinal bonds to stagger** during transition state than for fully formed bonds in the ground state

Paddon-Row, M.N.; Rondan, N.G.; Houk, K.N. *J. Am. Chem. Soc.* **1982** *104* 7162
Houk, K.N.; et al. *Science* **1986** *231* 1108

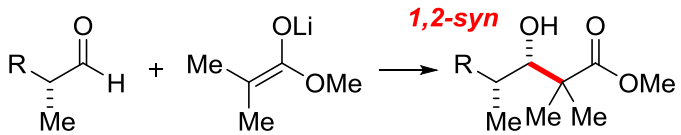
– **best acceptor orbital** (σ^*_{C-RL}) and **forming bond** ("σ_{C-Nu}") adopt antiperiplanar orientation (to optimize transition state stabilization)

Transitions State Stereoelectronic Considerations



Wong, S.S.; Paddon-Row, M.N. *J. Chem. Soc., Chem. Commun.* **1990** 456

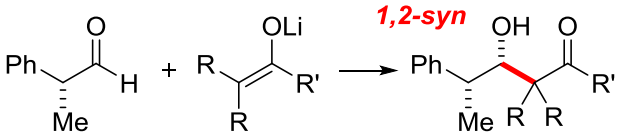
Experimental Observations



R	syn:anti
Cy	9:1
Ph	>200:1

Flippin, L.A.; Onan, K.D. *Tetrahedron Lett.* **1985** *26* 973

– better acceptor orbitals ($\sigma^*_{C-Ph} > \sigma^*_{C-Cy}$) provide greater transition state stabilization and result in higher Felkin selectivities

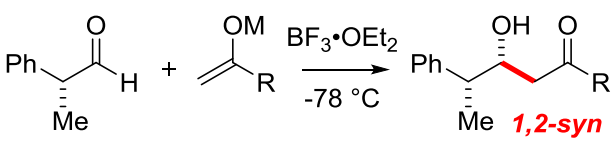


R	R'	syn:anti
H	Me	3:1
	O*t*-Bu	4:1
Me	OMe	>200:1

Flippin, L.A.; Onan, K.D. *Tetrahedron Lett.* **1985** *26* 973

– larger nucleophiles (sterically hindered enolates) generally result in enhanced Felkin selectivities

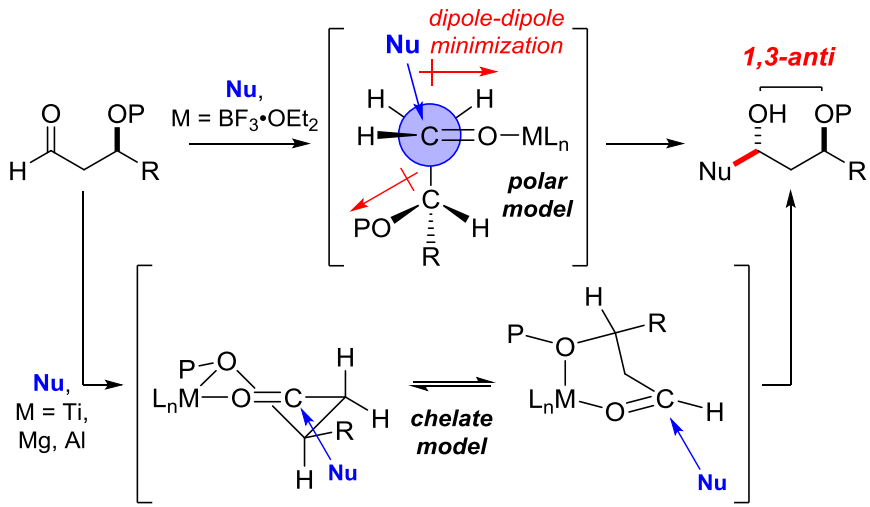
– Lewis acid-catalyzed aldol additions of silyl enol ethers tend to be more diastereoselective than their lithium enolate counterparts



R	M	syn:anti
Me	Li	3:1
	TBS	10:1
O*t*-Bu	Li	4:1
	TBS	36:1

Heathcock, C.H.; Flippin, L.A.
J. Am. Chem. Soc. **1983** *105* 1667

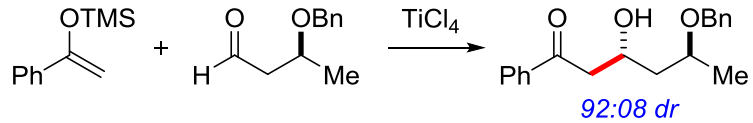
• **1,3-Stereoinduction: Polar and Chelate Models**



Polar Model: Evans, D.A.; et al. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
Chelate Model: Evans, D.A.; et al. *J. Am. Chem. Soc.* **2001**, *123*, 10840.

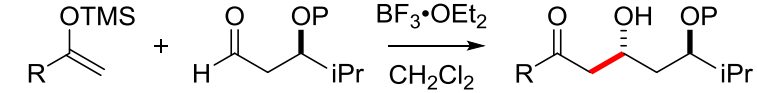
– 1,3-anti relationship is favored by both the polar and chelate models
– polar model minimizes internal electrostatic and steric repulsion

chelate model



92:08 dr

polar model

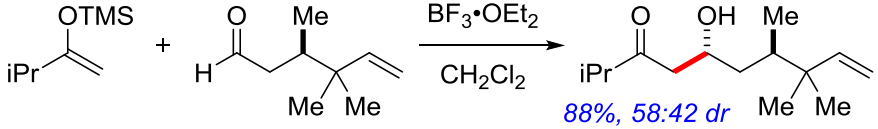


R = Me, iPr, *t*-Bu

P = PMB, TBS

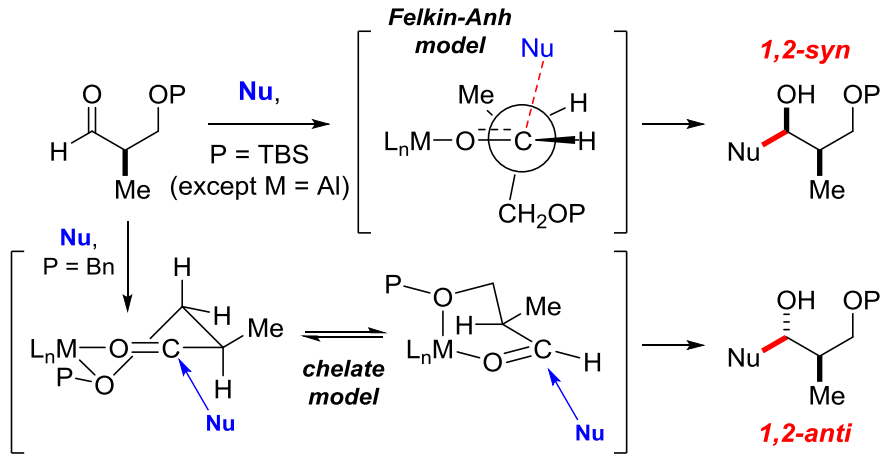
79–91%, 80:20–93:07 dr

– steric effects play a minor role in stereoinduction:

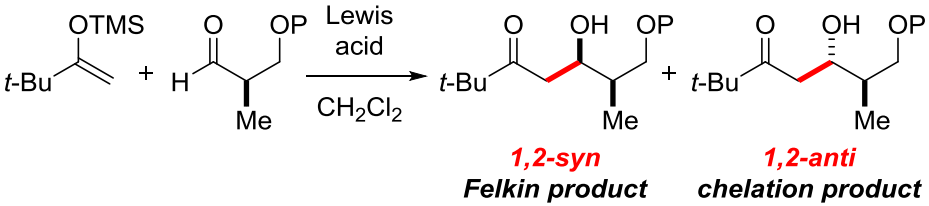


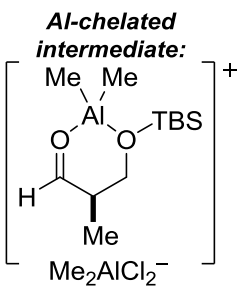
88%, 58:42 dr

• Using 1,3-Chelation to Overcome Felkin Selectivity



Evans, D.A.; et al. *J. Am. Chem. Soc.* **2001**, *123*, 10840.





Lewis acid	P = TBS	%	P = Bn	%
$BF_3{\bullet}OEt_2$	91 : 09	55	74 : 26	76
$SnCl_4$	93 : 07	41	50 : 50	87
$TiCl_4$	93 : 07	55	**03 : 97**	**74**
Me_2AlCl	**03 : 97**	62	10 : 90	45

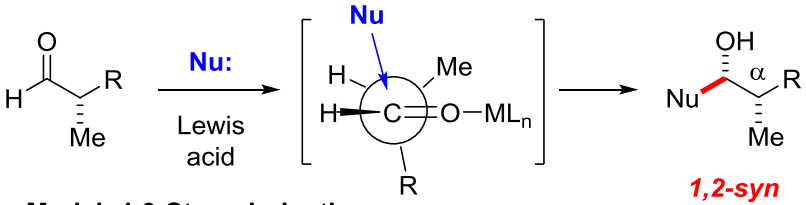
Felkin:chelation *product ratios and yields*

– good Felkin selectivity when P = TBS and M Al
– best diastereoselection for **chelation** products occur when **M = Ti, Al**
– only Me_2AlCl, $MeAlCl_2$, and $RZnX/ZnR_2$ chelate strongly to $OSiR_3$ groups

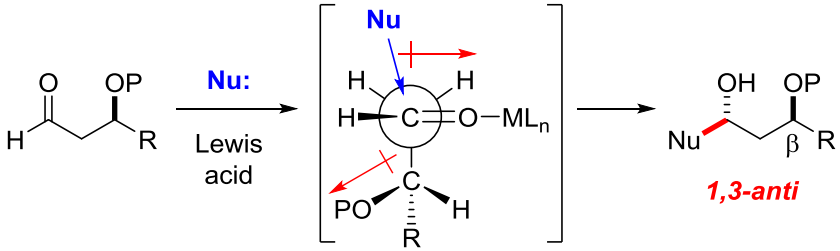
Zn chelation: Stanton, G.R.; Koz, G.; Walsh, P.J. *J. Am. Chem. Soc.* **2011** *133* 7969

• Merged 1,2- and 1,3-Stereoinduction Model

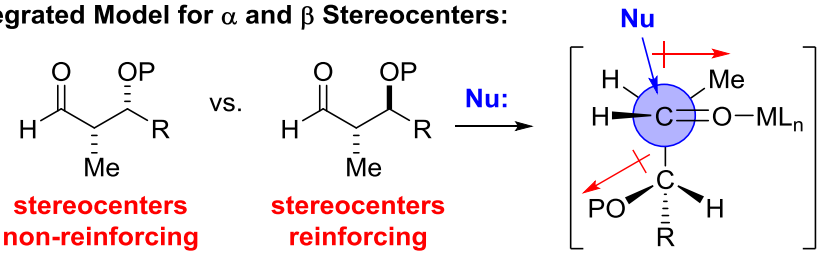
Felkin-Anh Model: 1,2-Stereoinduction



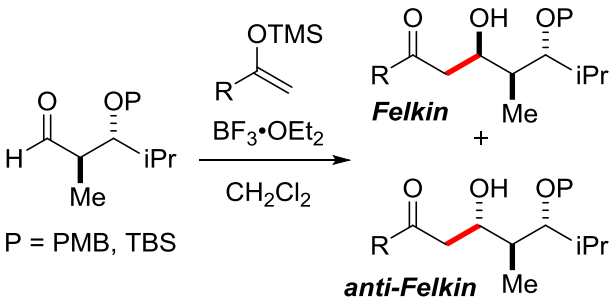
Polar Model: 1,3-Stereoinduction



Integrated Model for α and β Stereocenters:



The Anti Diasteromer: Reinforcing Stereocenters

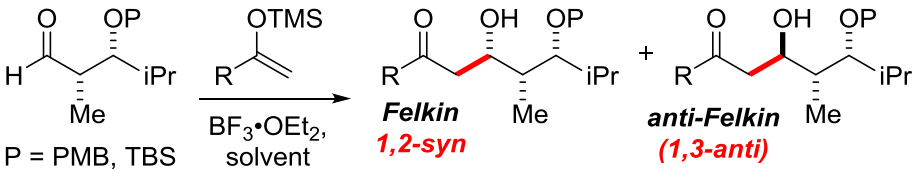


Felkin:anti-Felkin *product ratios*

R	P = PMB	P = TBS
t-Bu	99:01	99:01
iPr	98:02	95:05
Me	97:03	71:29

Evans, D.A. *et al. J. Am. Chem. Soc.* **2001** *123* 10840

The Syn Diasteromer: Non-Reinforcing Stereocenters



– stereoinduction primarily dependent upon the size of the silyl enol ether:

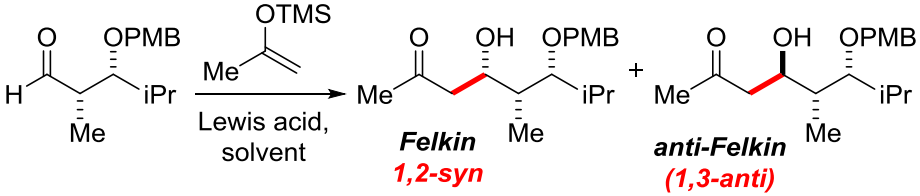
α substituent dominates for **large nucleophiles (Felkin control)**

β substituent dominates for **small nucleophiles (1,3-control)**

Felkin:anti-Felkin *product ratios*

R	solvent	P = PMB	P = TBS
t-Bu	CH_2Cl_2	**96 : 04**	**96 : 04**
	PhMe	88 : 12	94 : 06
iPr	CH_2Cl_2	56 : 44	87 : 13
	PhMe	32 : 68	75 : 25
Me	CH_2Cl_2	17 : 83	58 : 42
	PhMe	**06 : 94**	40 : 60

Evans, D.A.; et al. *J. Am. Chem. Soc.* **2001** *123* 10840



Lewis acid	solvent	Felkin product	:	anti-Felkin product
BF_3•OEt_2	PhMe	06	:	**94**
Ph_3CClO_4	CH_2Cl_2	**89**	:	11

– stereoinduction also influenced by the size of the Lewis acid:

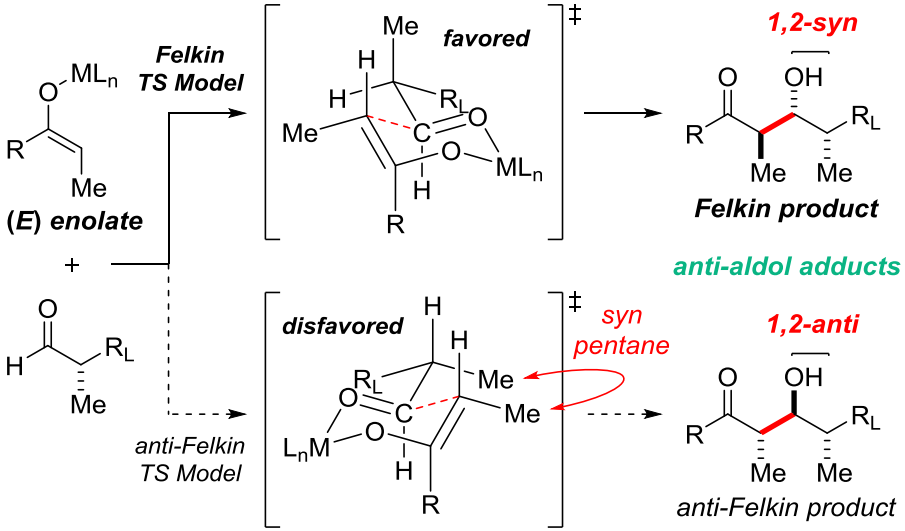
α substituent dominates for **large Lewis acids (Felkin control)**

β substituent dominates for **small Lewis acids (1,3-control)**

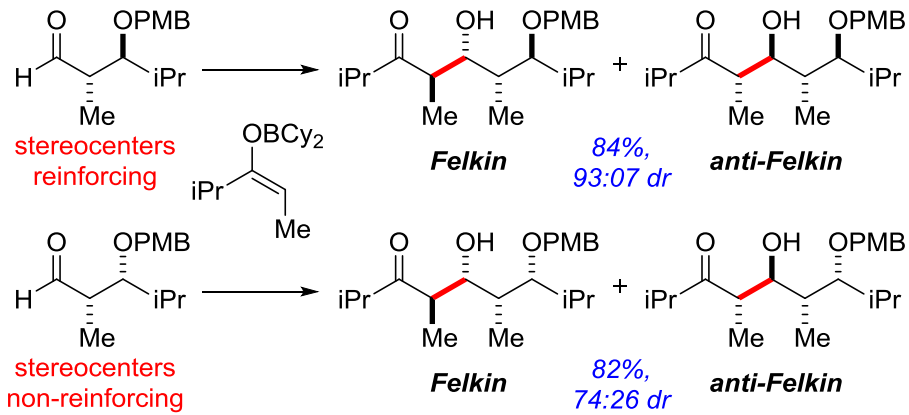
Evans, D.A. *et al. J. Am. Chem. Soc.* **1996** *118* 4322

• Inherent Enolate Bias

(*E*) Enolates Exhibit Felkin Aldehyde Diastereoface Selection



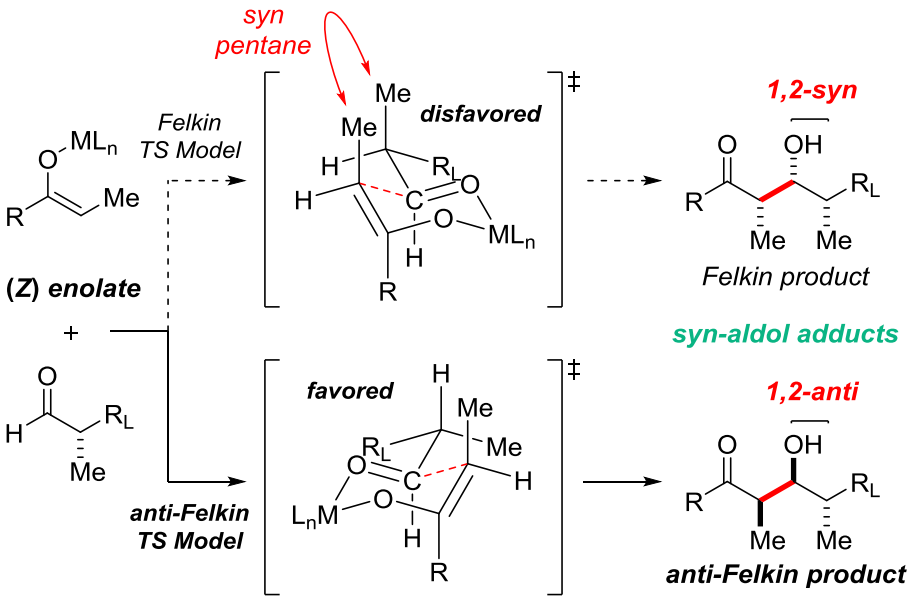
Aldol Reactions between Chiral Aldehydes and Achiral (*E*)-Enolates



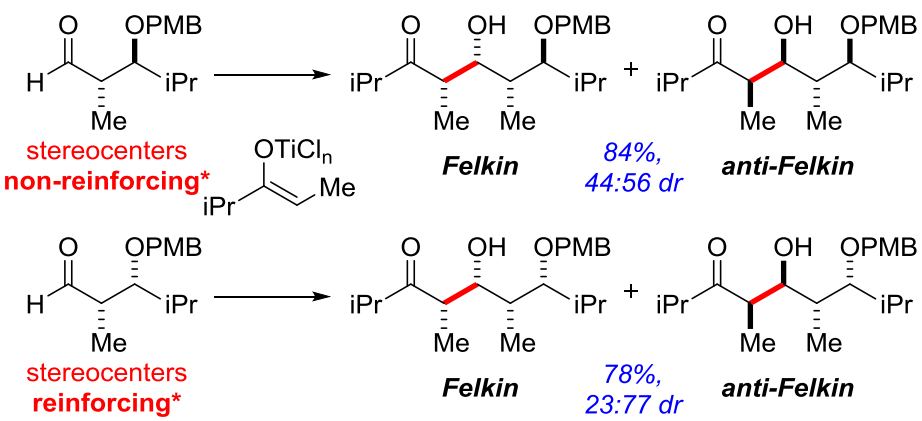
– **Felkin** selectivity correlates strongly with (***E***)-enolate geometry

Evans, D.A. *et al. J. Am. Chem. Soc.* **1995** *117* 9073
Evans, D.A. *et al. Topics in Stereochemistry* **1982** *13* 1
Roush, W.R. *J. Org. Chem.* **1991** *56* 4151

(*Z*) Enolates Exhibit Anti-Felkin Aldehyde Diastereoface Selection



Aldol Reactions between Chiral Aldehydes and Achiral (*Z*)-Enolates

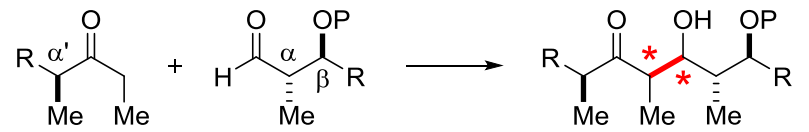


– **anti-Felkin** selectivity correlates *less strongly* with (*Z*)-enolate geometry
– boron and lithium enolates display similar levels of anti-Felkin selectivity

Evans, D.A. *et al. J. Am. Chem. Soc.* **1995** *117* 9073

Double Stereodifferentiating Aldol Reactions

- **Stereochemical Control Elements**

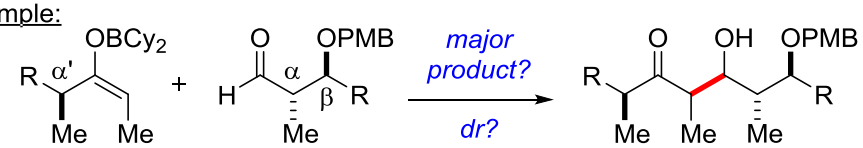


– enolate facial bias (α')
– aldehyde facial bias (α and β)
– enolate geometry (*E* or *Z*)

Objectives:
Extrapolate product stereochemistry and aldol diastereoselection

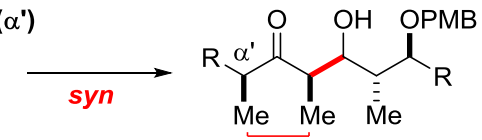
- **Determination of Matched and Mismatched Reactant Pairs**

Example:



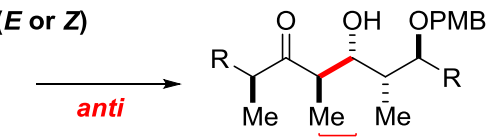
1) Consider enolate facial bias (α')

syn relationship across carbonyl preferred regardless of enolate geometry



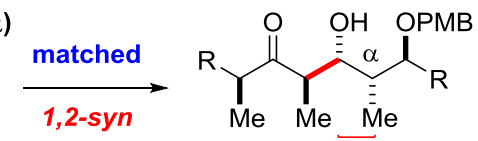
2) Consider enolate geometry (*E* or *Z*)

(*E*) enolates produce anti-aldol adducts



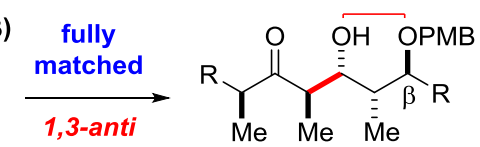
3) Check aldehyde facial bias (α) against enolate geometry

(*E*) enolates exhibit Felkin selectivity



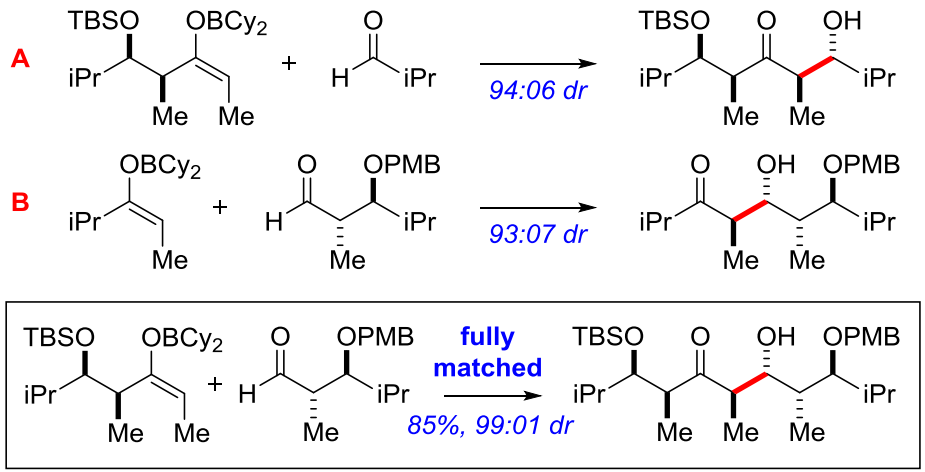
4) Check aldehyde facial bias (β)

anti relationship preferred according to polar model



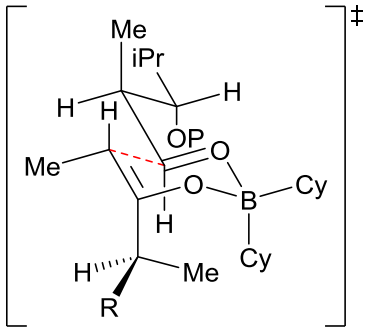
Evans, D.A. *et al. J. Am. Chem. Soc.* **1995** *117* 9073
Evans, D.A. *et al. Tetrahedron Lett.* **1996** *37* 1957

Use Reference Reactions to Predict Diastereoselectivity



Fully Matched Transition State

- chair-like geometry
- no syn pentane interactions
- dipole-dipole minimization
- $A_{1,3}$ strain minimization
- no additional destabilizing nonbonding (steric) interactions

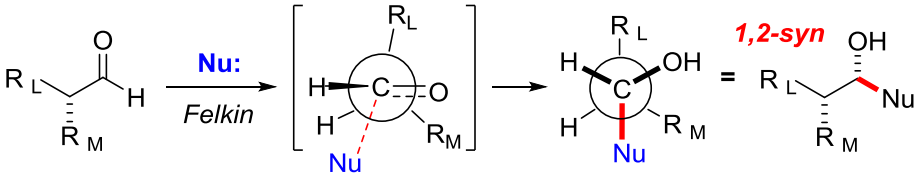


Empirical Observations

- when enolate and aldehyde α stereocenters are matched, good to excellent diastereoselection is observed regardless of aldehyde β center configuration
- **fully mismatched** reactions (wrt enolate) are generally nonselective
- **partially matched** reactions may exhibit useful levels of diastereoselectivity, but the relative influence of each control element depends upon metal choice

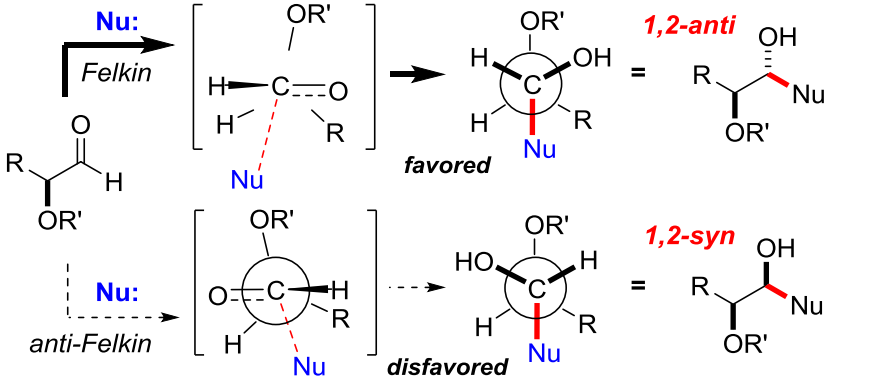
Electrostatic Effects

- **The Felkin-Anh Model** Anh, N.T.; Eisenstein, O. *Nouv. J. Chim.* **1977** *1* 61



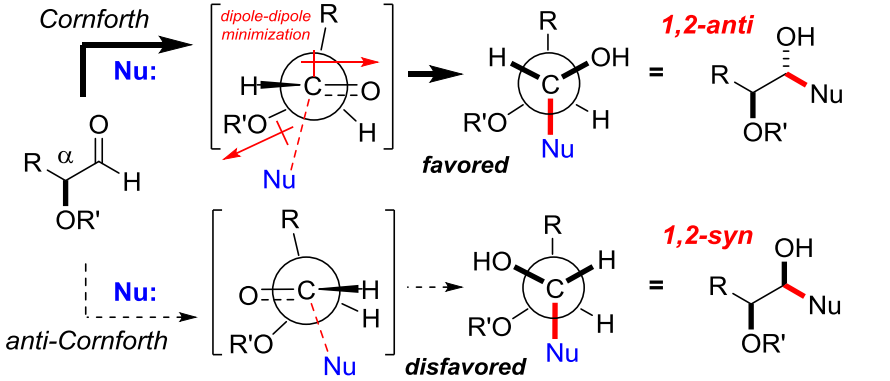
– best acceptor (antibonding) orbital ($\sigma^*_{C-R_L}$) and forming bond (σ_{C-Nu}) adopt antiperiplanar orientation (to optimize transition state stabilization)

- **The Polar Felkin-Anh Model**



– **asserts that transition state hyperconjugative interactions dominant**

- **The Modified Cornforth Model**



Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. *J. Chem. Soc.* **1959** 112

– transition state stabilized by dipole-dipole minimization between the transforming carbonyl group and the polar C_α–OR' bond

– **asserts that transition state electrostatic effects dominant**

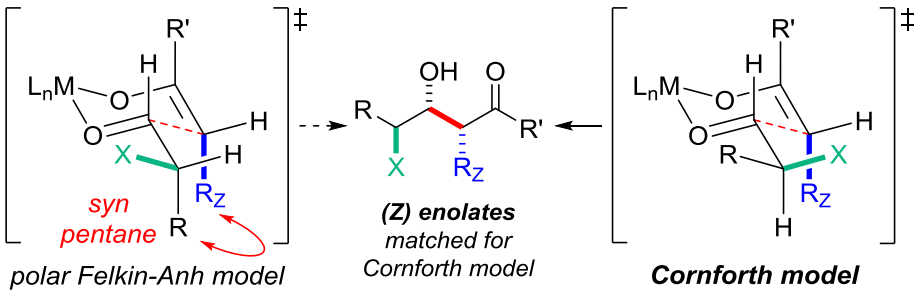
→ ***Both models lead to the same stereochemical prediction***

• **Distinguishing Between The Polar Felkin-Anh and Cornforth Models**

– may be distinguished when the nucleophile imposes a conformational constraint on the orientation of the aldehyde α-stereocenter

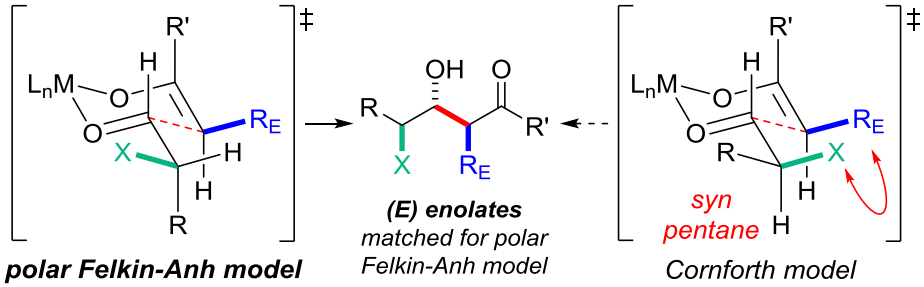
– **substituted enolates** used to reveal dependence of diastereoselectivity on enolate configuration

(*Z*) Enolates



– Cornforth model predicts high diastereoselection for (*Z*) enolates, whereas polar Felkin-Anh rotamer suffers destabilizing TS nonbonding interactions

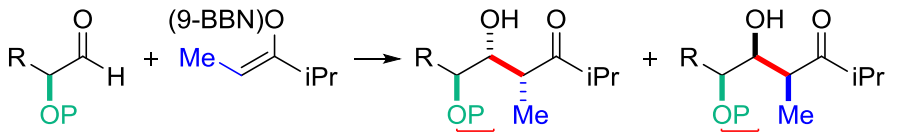
(*E*) Enolates



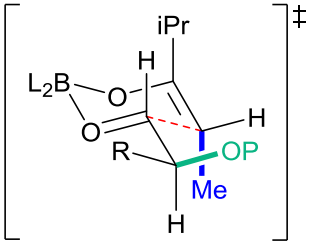
– Felkin-Anh model predicts high diastereoselection for (*E*) enolates, whereas Cornforth rotamer suffers destabilizing TS nonbonding interactions

Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* **2003** *42* 1761

(*Z*) Enolates



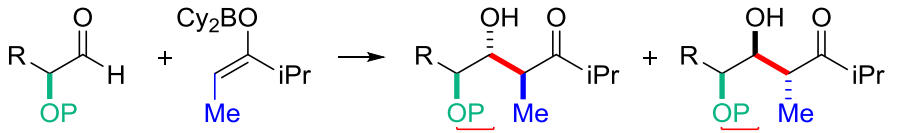
Cornforth model



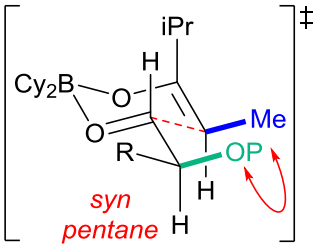
P	R	1,2-anti product	:	1,2-syn product
Bn	Me	89	:	11
	iPr	98	:	02
TBS	Me	98	:	02
	iPr	98	:	02

– (*Z*) enolates exhibit high levels of 1,2-anti diastereoselection

(*E*) Enolates



Cornforth model



P	R	1,2-anti product	:	1,2-syn product
Bn	Me	33	:	67
	iPr	67	:	33
TBS	Me	21	:	79
	iPr	43	:	57

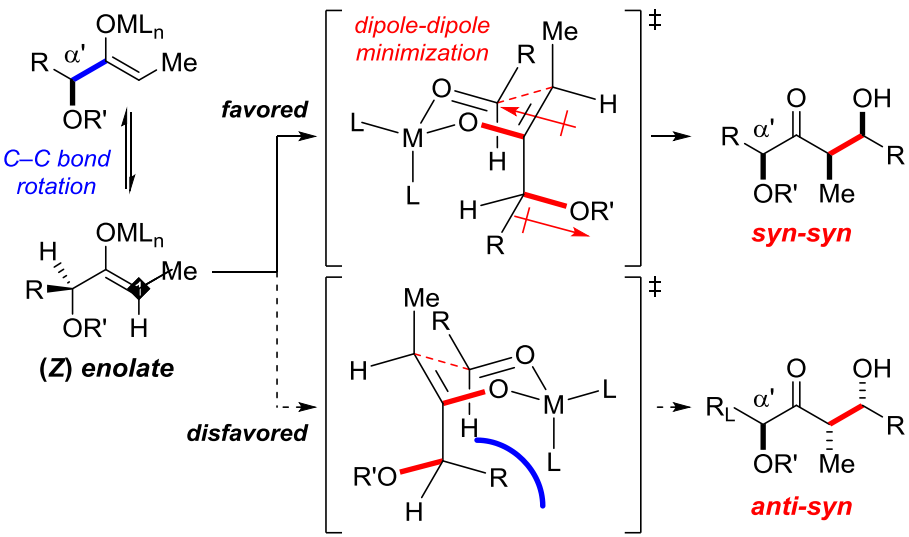
– (*E*) enolates exhibit diminished levels of 1,2-anti diastereoselection

– **experimental evidence supports modified Cornforth model** for the addition of enolate nucleophiles to α-oxygenated aldehydes

Enolates: Evans, D.A.; Siska, S.J.; Cee, V.J. *Angew. Chem. Int. Ed.* **2003** *42* 1761
Boranes: Evans, D.A.; Cee, V.J.; Cramer, C.J. *J. Am. Chem. Soc.* **2006** *128* 2920

- **Dipole-Dipole Minimization in α'-Oxygenated Ketone Aldol Reactions**

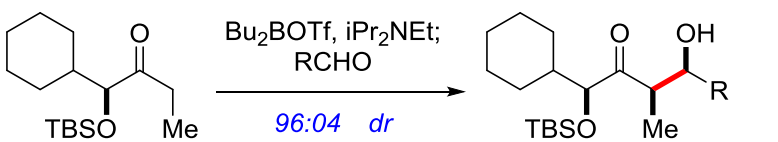
Syn Aldol Reactions via (*Z*) Enolates



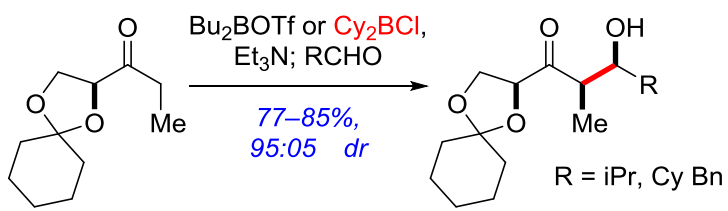
Gennari, C.; Paterson, I. *et al. Tetrahedron* **1991** *47* 3471

– transition state stabilized by **dipole-dipole minimization** between the transforming enolate (ketone carbonyl group) and the polar $C_{\alpha'}$–OR' bond

– R is oriented away from the reactive enolate diastereoface



Masamune, S. *et al. J. Am. Chem. Soc.* **1981**, *103*, 1566.



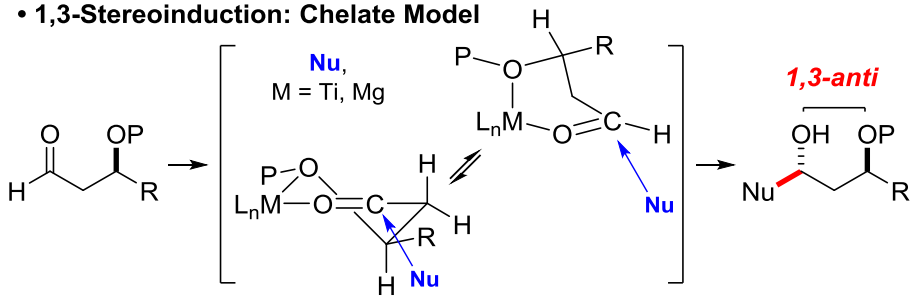
Carda, M.; Marco, J.A. *et al. Tetrahedron: Asymmetry* **2000** *11* 3211

– Cy$_2$BCl forms (*Z*) enolate via chelation with α' oxygen before deprotonation

Chelation Control

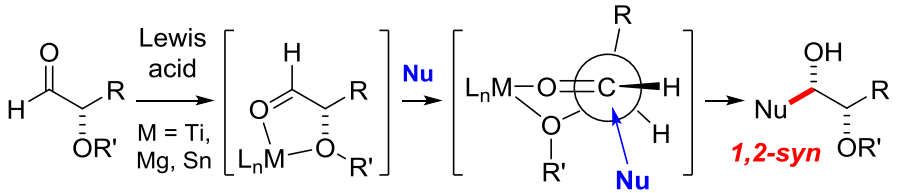
Reetz, M.T. *Acc. Chem. Res.* **1993** *26* 462
Reetz, M.T. *Angew. Chem. Int. Ed.* **1984** *23* 556

- **1,3-Stereoinduction: Chelate Model**



Evans, D.A.; et al. *J. Am. Chem. Soc.* **2001** *123* 10840

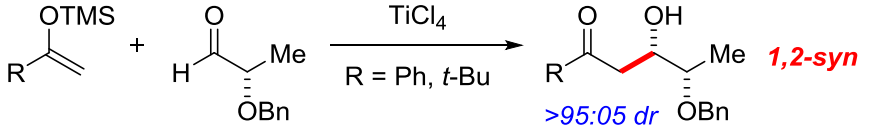
- **1,2-Stereoinduction: Chelate Model**



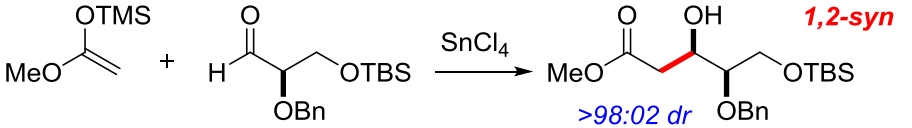
Cram, D.J.; Kopecky, K.R. *J. Am. Chem. Soc.* **1959** *81* 2748

– complementary sense of diastereoselection to Cornforth model (cf. *1,2-anti*)

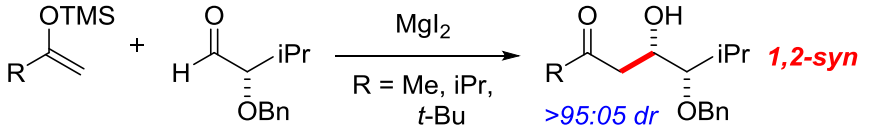
– chelation generally enhances reaction rates and stereoselectivity



Reetz, M.T.; et al. *Angew. Chem. Int. Ed.* **1983** *22* 989

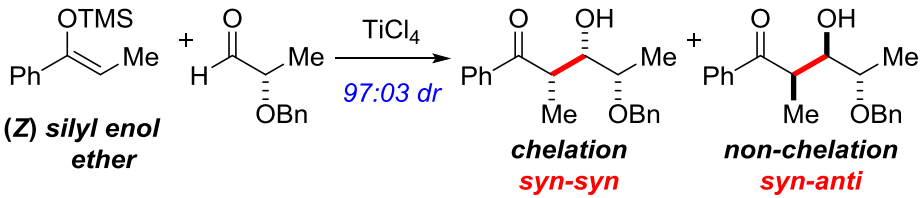


Reetz, M.T.; Kesseler, K. *J. Org. Chem.* **1985** *50* 5434



Siska, S.J. Ph.D. Thesis. Harvard University, 2005.

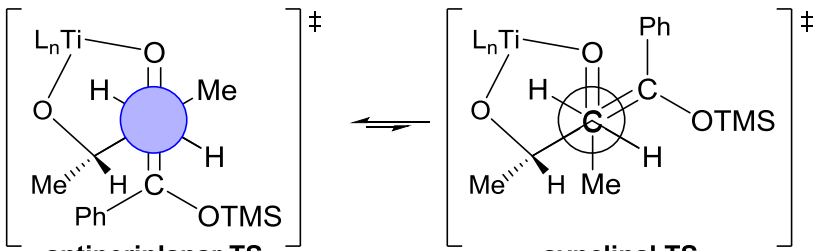
Mukaiyama Aldol Additions of Substituted Silyl Enol Ethers



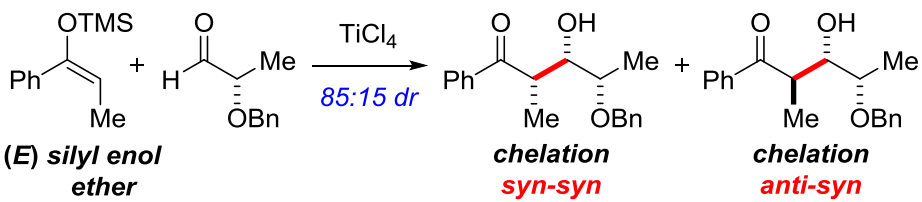
(Z) silyl enol ether

Reetz, M.T.; et al. *Angew. Chem. Int. Ed.* **1983** *22* 989

– Mukaiyama aldol additions proceed through **open transition states**

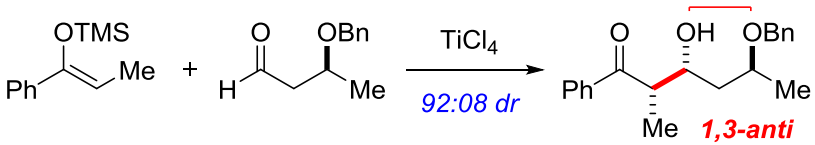


– steric interactions between silyl enol ether substituents and chelated aldehyde minimized (relative size of substituents and Lewis acid important)
– modest preference for antiperiplanar over synclincal transition states



(E) silyl enol ether

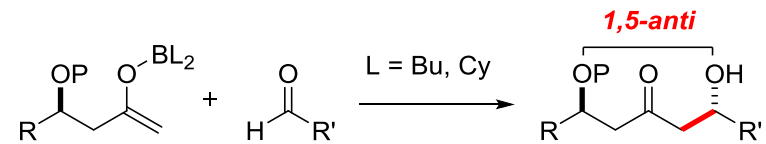
– chelation-controlled additions exhibit good syn aldol diastereoselection regardless of silyl enol ether geometry (*E* or *Z*)
– non-chelating aldehydes exhibit unpredictable syn/anti diastereoselectivity

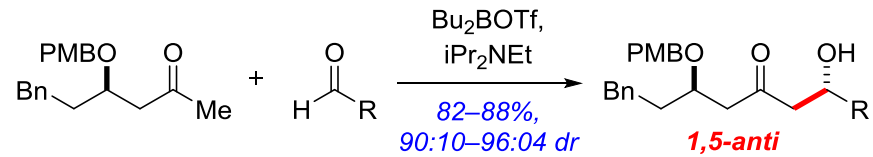


Reetz, M.T.; et al. *Angew. Chem. Int. Ed.* **1983** *22* 989

1,5-Stereoinduction

• **Boron-Mediated Aldol Additions of Methyl Ketones**

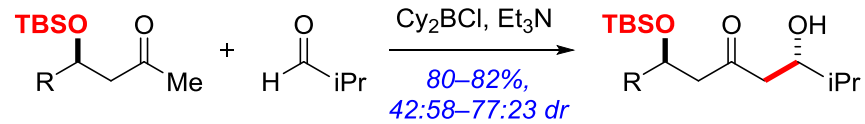




– Li enolate and Mukaiyama ($TMS/BF_3{\bullet}OEt_2$) additions were nonselective

– 1,5-anti enolate bias stronger than 1,3-anti aldehyde bias in double stereodifferentiating aldol reactions

Evans, D.A.; Coleman, P.J.; Côté, B. *J. Org. Chem.* **1997** *62* 788
Evans, D.A.; et al. *J. Am. Chem. Soc.* **2003** *125* 10893



– benzylic and benzylidene acetal protecting groups for the β-hydroxyl group tolerated, but **silyl groups** often exhibit poor diastereoselectivity

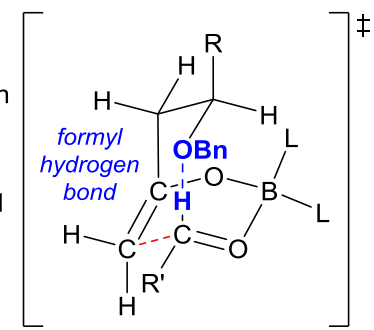
Paterson, I.; Gibson, K.R.; Oballa, R.M. *Tetrahedron Lett.* **1996**, *37*, 8585.

Proposed Boat-Like Transition State

– boron aldol reactions of methyl ketones may proceed through boat-like transition state structures

– transition state stabilized by **hydrogen bond** between the β-alkoxy oxygen and formyl hydrogen atoms

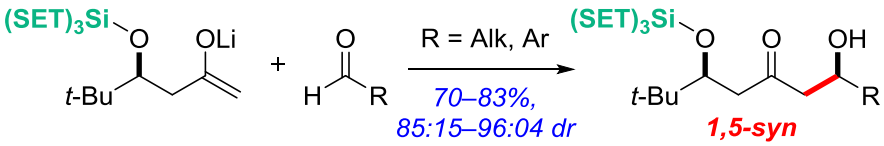
– steric interactions between enolate (R) and boron ligands (L) minimized



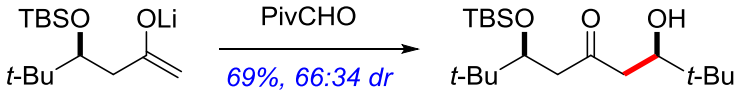
Paton, R.S.; Goodman, J.M. *Org. Lett.* **2006** *8* 4299

Yamamoto Aldol Additions of β-Super Siloxy Methyl Ketones

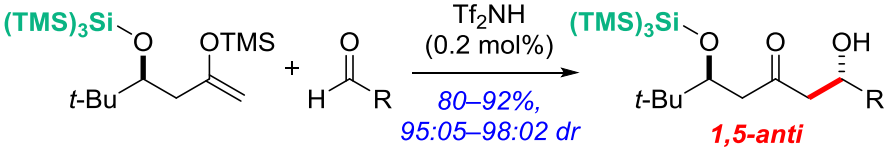
1,5-Stereoinduction



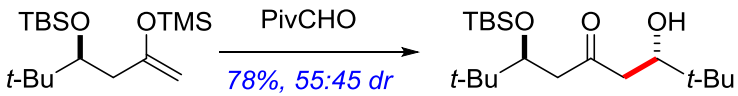
whereas



– steric effect of **super silyl group ($Si[SiR_3]_3$)** in combination with lithium enolate results in opposite selectivity to boron-mediated aldol (cf. *1,5-anti*)



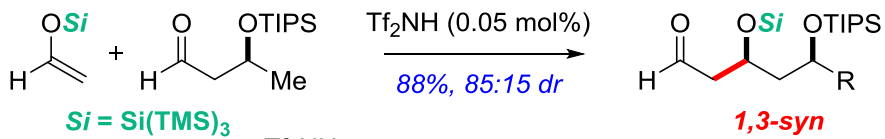
whereas

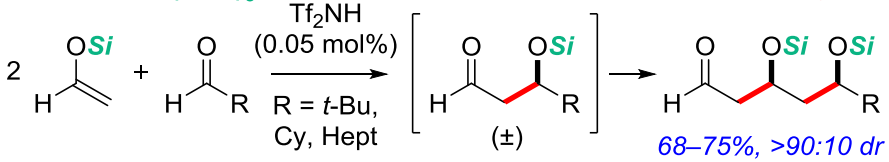


– Mukaiyama aldol restores high 1,5-anti selectivity via open transition state

Yamaoka, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2010** *132* 5354

1,3-Stereoinduction (Revisited)





– unfavorable steric interactions between **super silyl groups (*Si*)** in silyl enol ether, implicated Lewis acid catalyst (Tf_2*Si*), and cascade intermediate overturn 1,3-anti diastereoselection predicted by polar model

Boxer, M.B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006** *128* 48