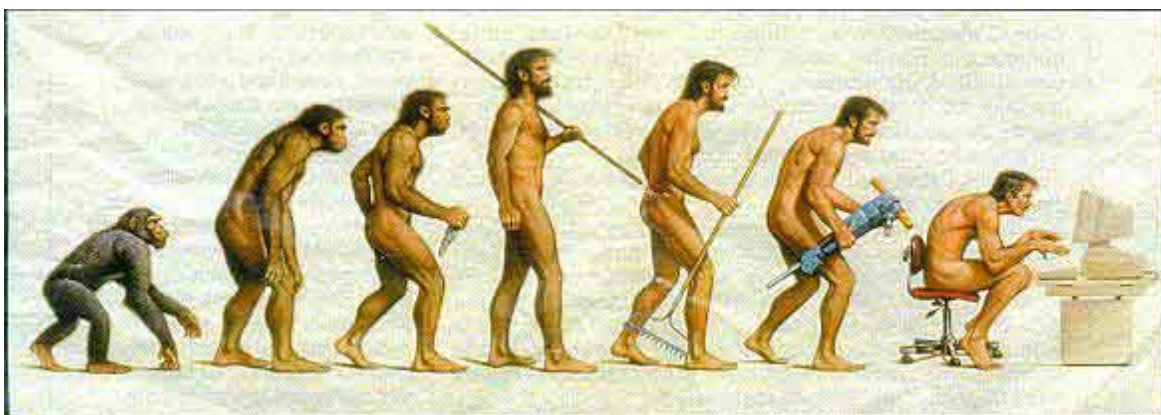


The Evolution of Models for Carbonyl Addition

Evans Group Afternoon Seminar
Sarah Siska
February 9, 2001



Fischer Cram Cornforth Felkin Anh/Eisenstein Cieplak Tomoda

The Evolution of Models for C=O Addition

Reviews

- Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, 99, 1191-1223
Gung, B. W. *Tetrahedron* **1996**, 52, 5263-5301
Ager, D. J.; East, M. B. *Tetrahedron* **1992**, 48, 2803-2894
Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 556-569
Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*;
Prentice Hall Inc.: **1971**
Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, 116, 11678-16888, ref. 1-5, 7

SJS Commentary

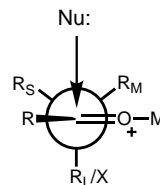
- great overview
thorough comparison of more recent models
1,2 and 1,3 difunctionality
chelation vs. non-chelation control
older models; historical perspective
excellent collection of references

Outline

- I. 1,2-Asymmetric Induction Models
 - A. Historical Perspective
 - B. Evolution: from empirical to computational
 1. Steric models
 2. Electronic models
 3. Polar models; recent support for electrostatics
- II. 1,3-Asymmetric Induction Models
 - A. Chelation model
 - B. Non-chelation models
 1. Steric model
 2. Polar model
- III. Merged 1,2- and 1,3-Asymmetric Induction
- IV. Unpredicted, highly selective carbonyl additions
 - A. Rapamycin (Smith)
 - B. Carbohydrate derivatives (Kobayashi)

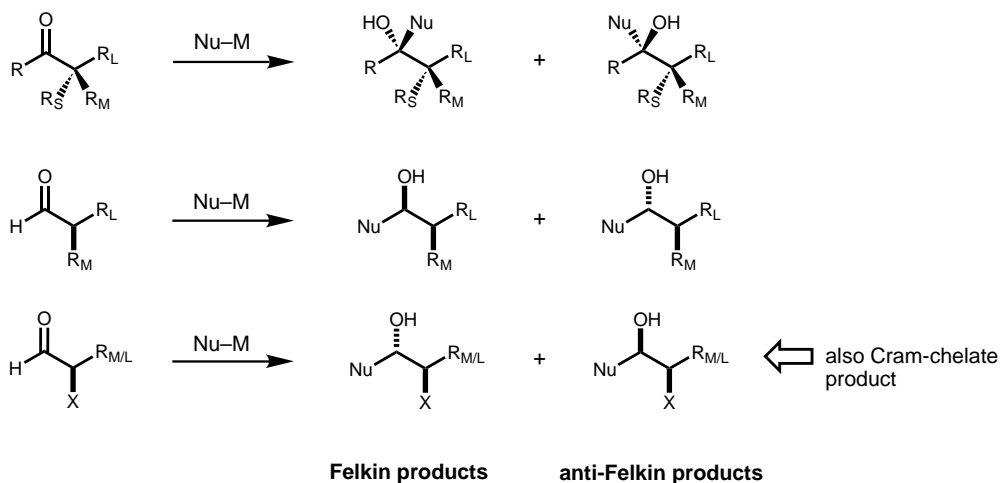
Definition of Terms

Felkin product = commonly accepted term for the major carbonyl addition product predicted by the Felkin-Anh model; also predicted by Cram and Karabatsos for steric cases, Cornforth and Evans for α -heteroatom (non-chelating) cases

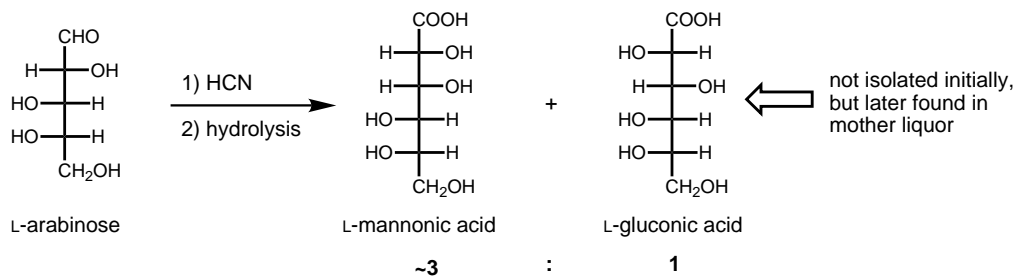


Examples:

Felkin-Anh model



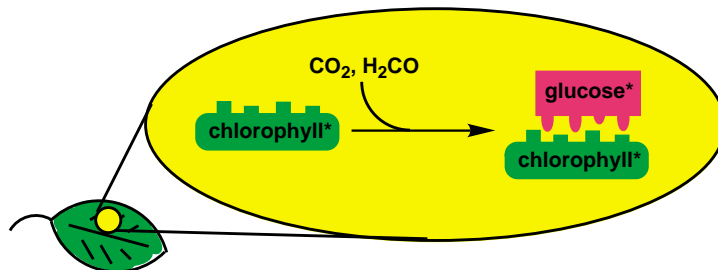
Fischer, and the Dawn of Asymmetric Induction



"To my knowledge these observations furnish the first definitive evidence that further synthesis with asymmetric systems proceeds in an asymmetric manner."
-Emil Fischer, 1894

Fischer, E. *Ber.* **1890**, 23, 2611
Fischer, E. *Ber.* **1894**, 27, 3189

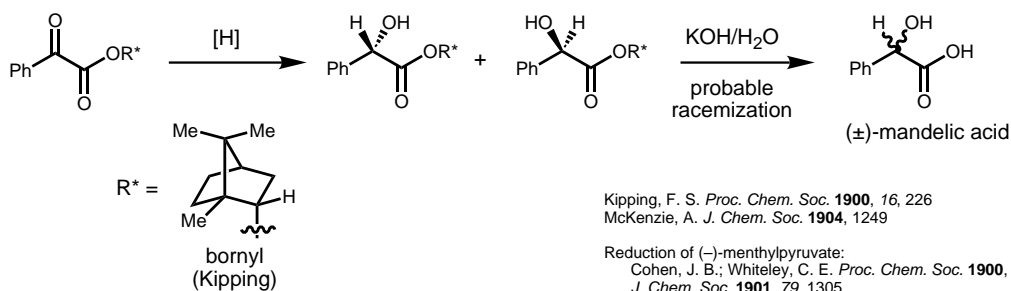
Assimilation in nature: propagation of asymmetry from one chiral molecule to another



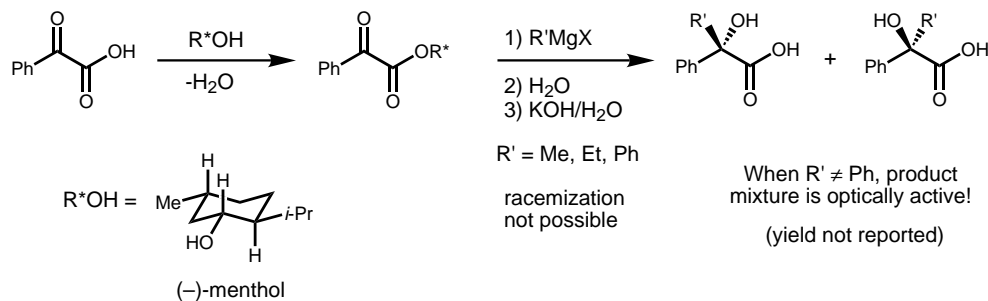
Fischer, E. *Ber.* **1894**, 27, 3189
Freudenberg, K. *Adv. in Carbohydrate Chem.* **1966**, 21, 1

McKenzie: Detection of Asymmetric Induction

The problematic mandelic acid synthesis

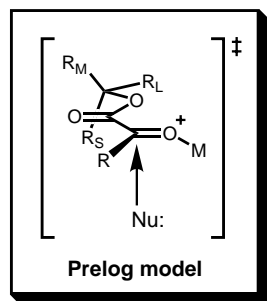


Grignard addition: a solution



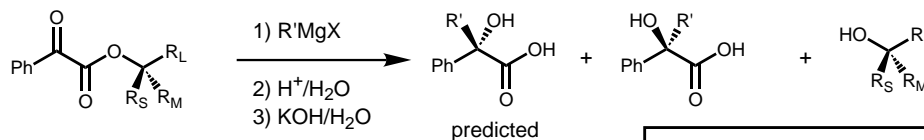
McKenzie, A. J. *Chem. Soc.* **1904**, 1249

Prelog's Generalization for α -Keto Esters



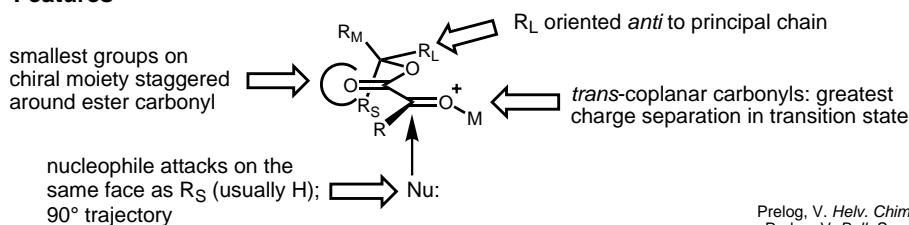
- First suggested in 1951 at the XIth International Congress of Pure and Applied Chemistry
- An empirical model: orientations of alkyl substituents and carbonyls were largely intuitive
- Rules established for assessing stereoselectivity:
 - ee's <5% disregarded
 - saponification yields <80% unreliable
 - optical rotations uniformly performed
 - R_S , R_M , and R_L hydrocarbon residues
 - when $\text{R}_\text{M} \approx \text{R}_\text{L}$, selectivity often poor

Basis for Rule



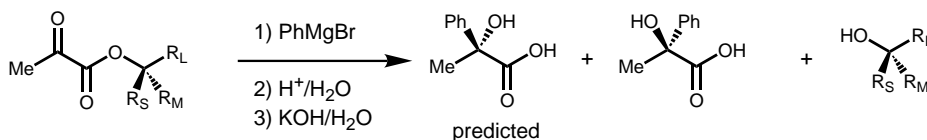
selectivities ranged from 8% to 69% ee, determined by polarimetry

Features



Prelog, V. *Helv. Chim. Acta* **1953**, 36, 308
 Prelog, V. *Bull. Soc. Chim. Fr.* **1956**, 987

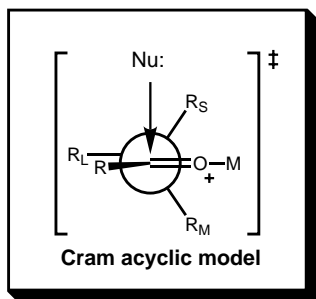
Atrolactic Acid Synthesis



Chiral Alcohol	% "asymmetric synthesis" (determined by optical rotation)	Original Prelog model
	25% (-)	
	12% (+)	
	69% (+)	
	13% (-)	

Prelog, V. *Helv. Chim. Acta* **1953**, 36, 308
Prelog, V. *Bull. Soc. Chim. Fr.* **1956**, 987

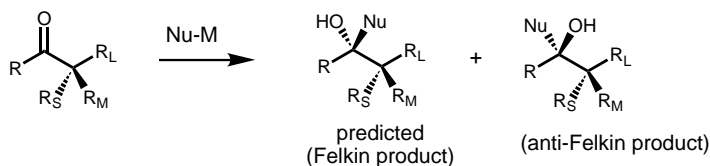
Cram: 1952



Cram's Rule: "In reactions of the following type, that diastereomer will predominate which would be formed by the approach of the entering group from the *least hindered side* of the double bond when the rotational conformation of the C-C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center."

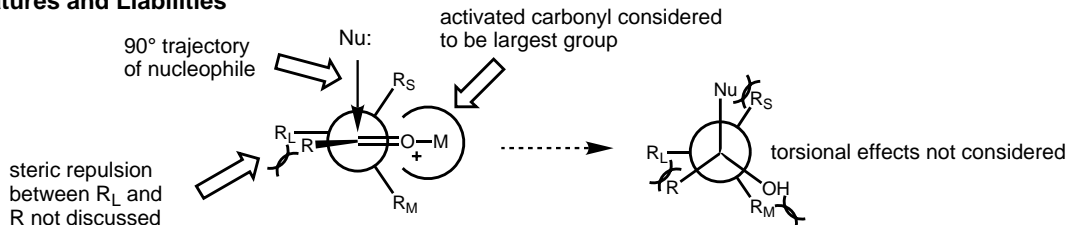
Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, 74, 5828

Basis for Model



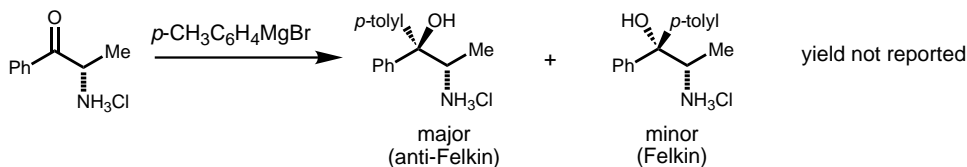
Nu-M = RMgX, LAH
R_L = Ph
R_M = Me, Et
R_S = H
R = H, Ph, Me, Et
selectivities ranging from 2:1 to >4:1, favoring Felkin product

Features and Liabilities



Cram: 1952

Among the 27 cited reactions whose stereoselection is "predicted" by Cram's acyclic rule:

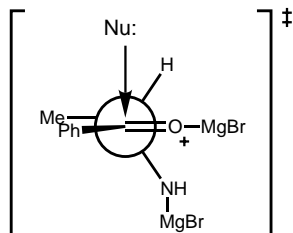


Curtin, D. Y.; Pollak, P. I. *J. Am. Chem. Soc.* **1951**, 73, 992

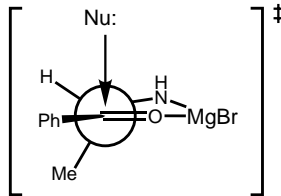
Ranking of steric bulk of α -substituents is somewhat arbitrary:

Me > NH_3Cl due to the amino group's formation of a non-rigid "more adaptable" ion pair

one proposed transition state:



in the end, a suggestion of a chelate . . .



Possible Pitfalls

- Low or unreported yields may result in misleading selectivities
- Model based on qualitative assessment of steric bulk

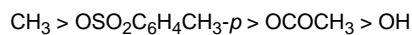
Bottom Line

Cram's acyclic model is a convenient mnemonic that predicts Felkin products in α -alkyl or aryl aldehydes or ketones.

Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, 74, 5828

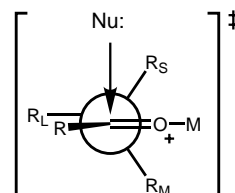
Cram: 1959

Methyl has greater *effective bulk* than OH; Cram cites "A-values" of Winstein, who compares the relative tendency of groups to occupy the equatorial position on a cyclohexane ring.

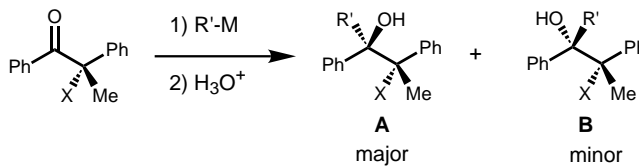
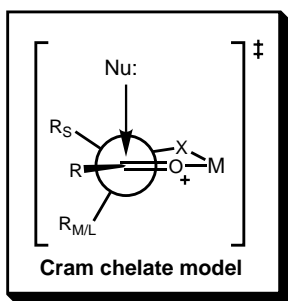


The acyclic model would predict the opposite product in the case of an α -heteroatom -- a new model is needed!

Winstein, S.; Holmes, N. J. *J. Am. Chem. Soc.* **1955**, 77, 5562

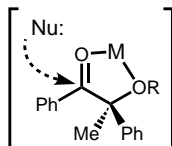


Cram acyclic model



R'-M	X	A : B	yield of A (%)
CH_3MgI	OH	11.5 : 1	20
CH_3Li	OMe	9 : 1	50

nucleophile approaches from the back face

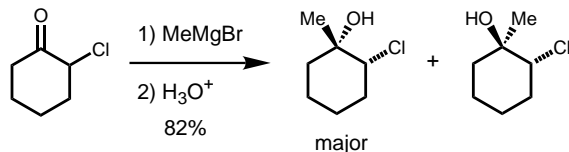


- expects groups OH, OR, OAc, NR_2 , NHAc to chelate

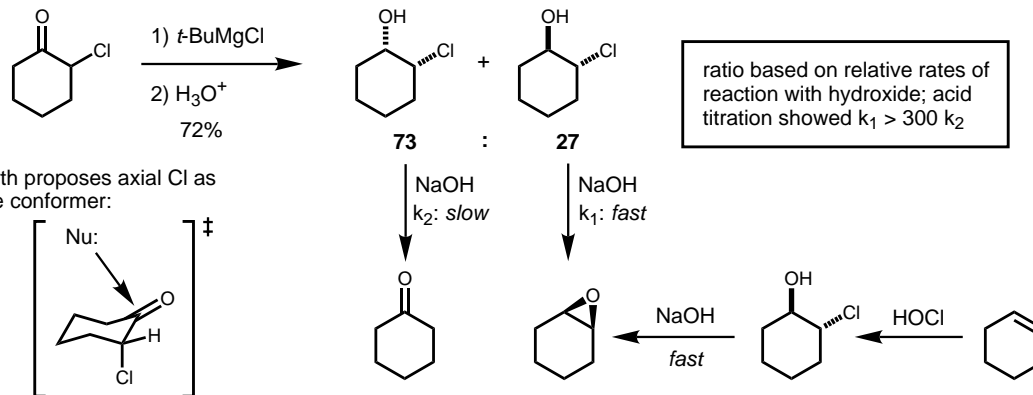
"The open-chain model applies to systems which contain only groups attached to asymmetric carbon of the starting material which are incapable of complexing with organometallic reagents."

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

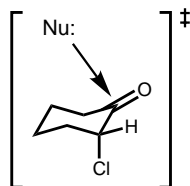
Bartlett: Early Chlorohydrin Work



Bartlett, P. D.; Rosenwald, R. H. *J. Am. Chem. Soc.* **1934**, *56*, 1990

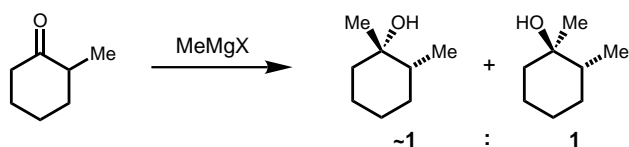


Cornforth proposes axial Cl as reactive conformer:



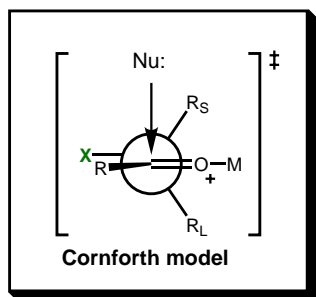
Bartlett, P. D. *J. Am. Chem. Soc.* **1935**, *57*, 224

In contrast:



Chiurdoglu, G. *Bull. Soc. Chim. Belges* **1938**, *47*, 241

Cornforth: 1959

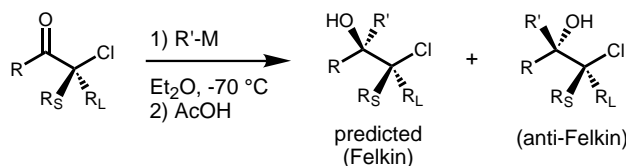


- argument based on importance of polarization in transition state, and evidence of selectivity in α -chlorocyclohexanone additions

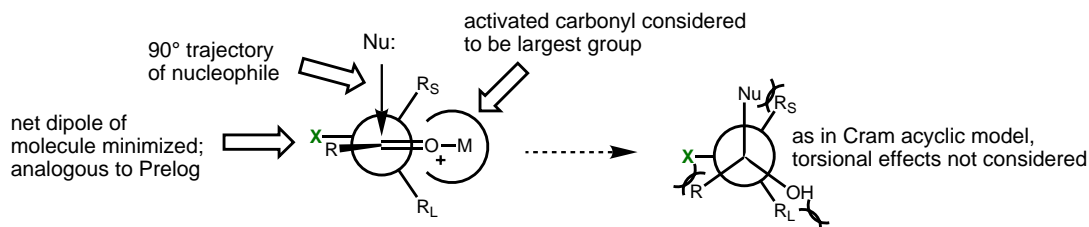
- "... where the dipoles are antiparallel, the polarization of the carbonyl group would be easiest," thereby lowering transition state energy

- a modification of Cram's rule for electronegative, non-chelating α -substituents X

Additions to α -Chloro Carbonyls



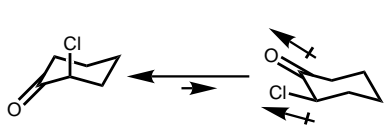
Features



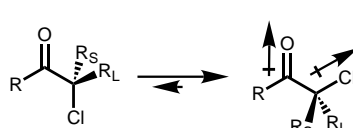
Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112

Cornforth: Rationalization and Evidence

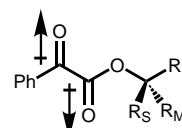
Support and Contradiction for Dipole Minimization



Corey, E. J. *J. Am. Chem. Soc.* **1953**, 75, 2301
Corey, E. J.; Burke, H. J. *ibid.* **1955**, 77, 5418

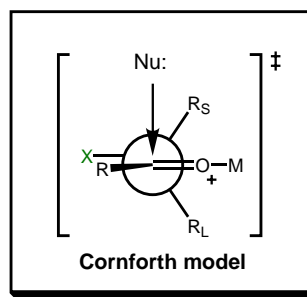
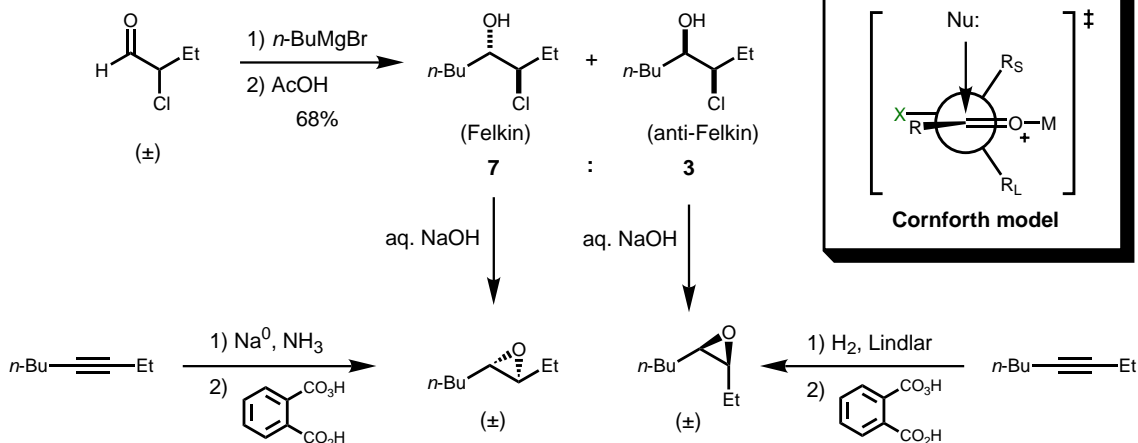


Bellamy, L. J.; Thomas, L. C.; Williams, R. L. *J. Chem. Soc.* **1956**, 3704
Bellamy, L. J.; Williams, R. L. *ibid.* **1957**, 4294



Prelog, V. *Bull. Soc. Chim. Fr.* **1956**, 987
(note: methylpyruvate does not adopt this conformation)

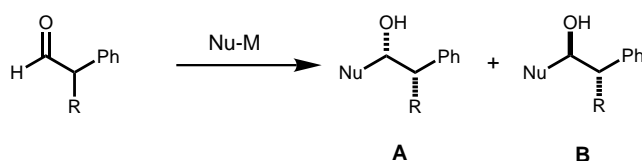
Chlorohydrin Synthesis



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

Karabatsos: 1967

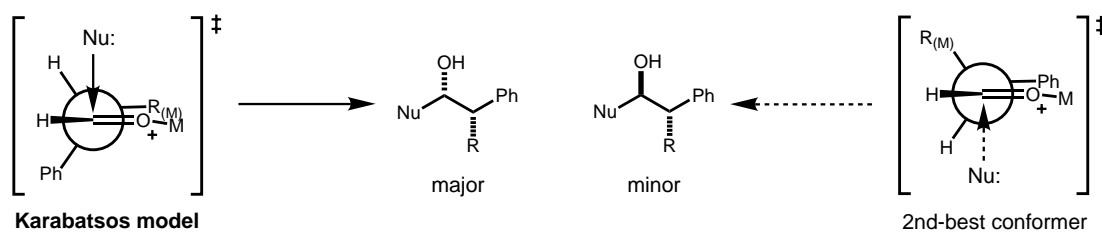
Given Cram's acyclic model, Karabatsos is surprised by the following selectivities:



R	A : B
Me	2-4 : 1
i-Pr	1-2 : 1

• it appears that i-Pr is effectively smaller than Me, if Ph = R_L

Karabatsos' explanation: Cram transition states are incorrect

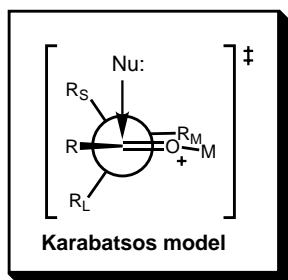


• ratios depend not on Nu ↔ H and Nu ↔ R_M,
but instead on R_M ↔ O vs. R_L ↔ O

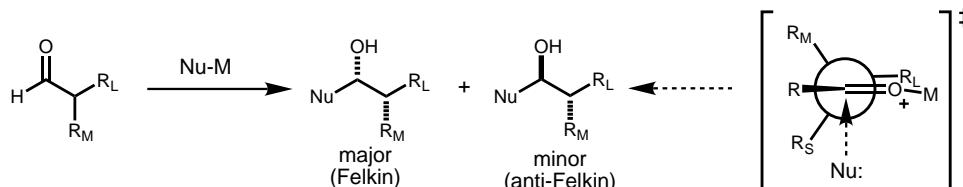
Compared Interaction	ΔΔH°
Me ↔ O - Ph ↔ O	0.6 kcal/mol
i-Pr ↔ O - Ph ↔ O	0.2 kcal/mol

Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, 89, 1367

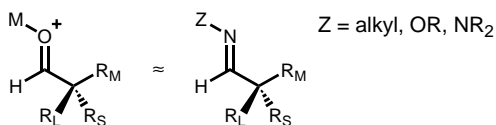
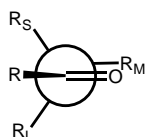
Karabatsos: 1967



- energy difference ($\Delta\Delta H^\circ$) between interactions of $R_M \leftrightarrow O$ and $R_L \leftrightarrow O$ determines product ratio
- reactant-like transition state
- model based on most stable ground-state conformation
- energy differences between major and minor conformations are <1 kcal/mol



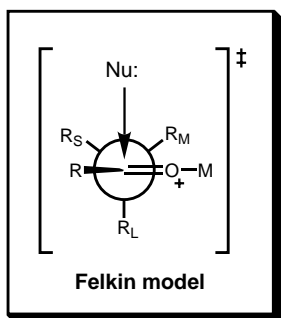
Rationalizations



- a) $\Delta H^\circ(\text{imine } N \leftrightarrow R) \approx \Delta H^\circ(\text{carbonyl } O \leftrightarrow R)$
 b) imine geometry \approx complexed C=O geometry
 $\therefore \Delta H^\circ(\text{imine } N \leftrightarrow R) \approx \Delta H^\circ(\text{complexed } C=O \leftrightarrow R)$

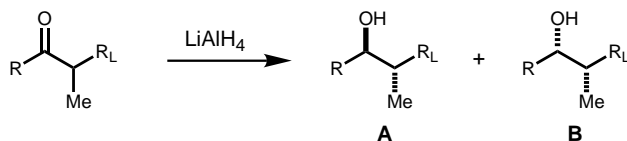
Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367

Felkin: 1968



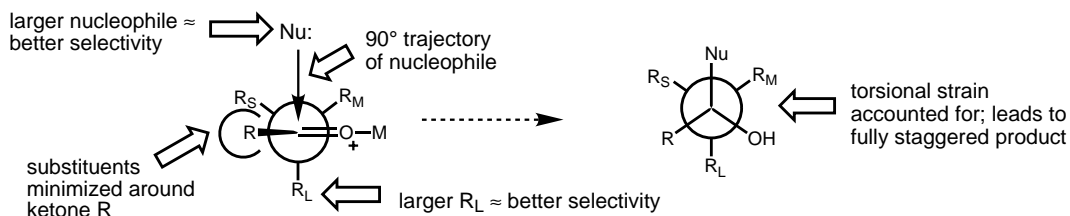
- "reactant-like" transition state
- assumption of torsional strain in partially formed or broken bonds: first fully staggered acyclic model
- substituents minimized around R; leads to inconsistency in aldehyde substrates
→ see DAE Chem 206 Lecture Notes (2000), 18-08
- polar effect: maximize separation between incoming anionic nucleophile and electronegative α -substituent (R_S , R_M , or R_L)

Reduction of α -Methyl Ketones



	A / B	
R	$R_L = \text{Cy}$	$R_L = \text{Ph}$
Me	1.6	2.8
Et	2.0	3.2
<i>i</i> -Pr	4.1	5.0
<i>t</i> -Bu	1.6	49

Features

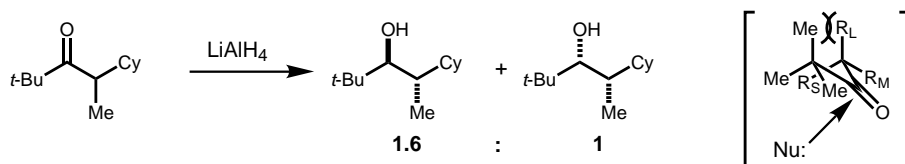


Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199

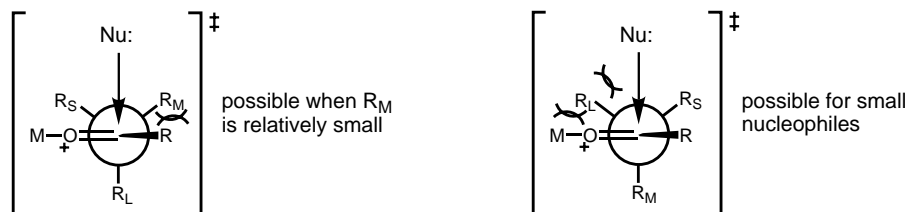
Felkin: Accounting for Less Selective Reactions

1) The *t*-butyl ketone case

- with α -branching, in any staggered conformation, *syn*-pentane is impossible to avoid

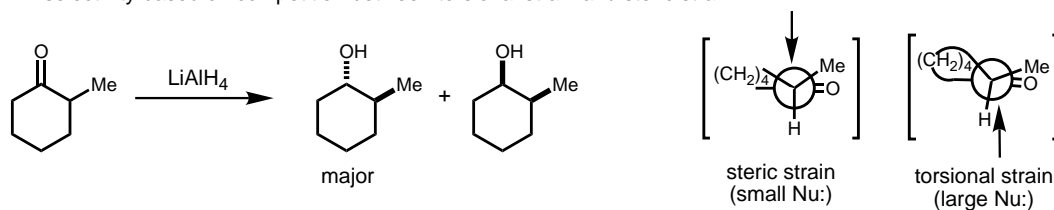


2) Transition states for minor products (does not consider conformers with R_L next to R)



3) 2-methylcyclohexanone

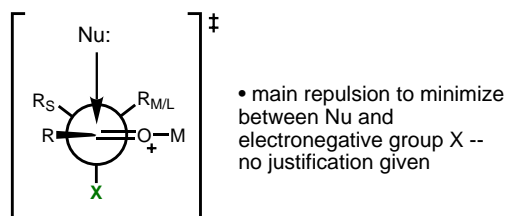
- cannot adopt Felkin-type conformation; still considered as a reactant-like transition state
- selectivity based on competition between torsional strain and steric strain



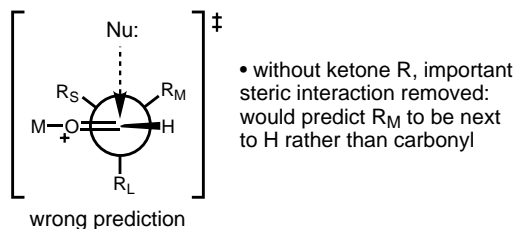
Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 18, 2199; 2205

Weaknesses in Felkin's Argument

1) Polar effect



2) Breakdown for aldehydes

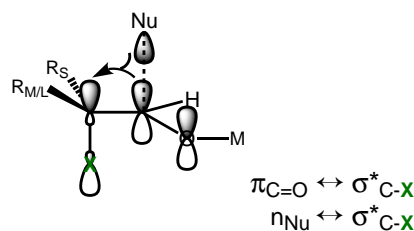


Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 18, 2199

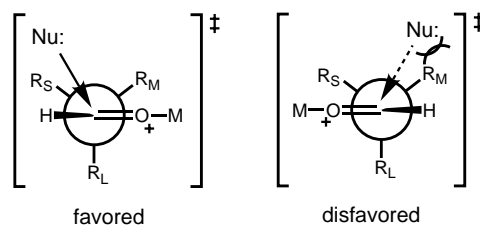
Anh's Solutions

1) Antiperiplanar effect

- best acceptor σ^* orbital aligned parallel to π and π^* orbitals of carbonyl; stabilization of incoming anion



2) Non-perpendicular attack

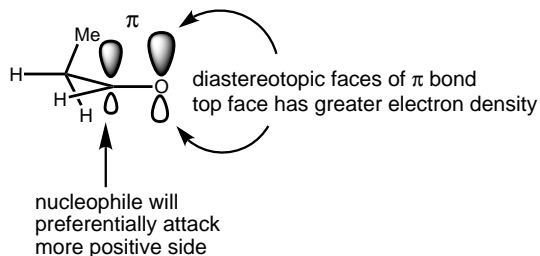


- incorporation of the Bürgi-Dunitz trajectory

Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, 1, 61
 Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, 95, 5065
 Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, 30, 1563

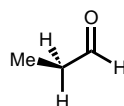
Anh: Orbital Factors

Hypothesis: The conformer with greatest dissymmetry will give greatest relative ratio of diastereomers.

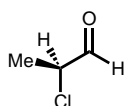


- suggests that both steric and orbital factors control asymmetric induction
- "at longer distances, orbital factors might be more effective than steric factors"

Conformers with large π orbital dissymmetry



propanal
Cram



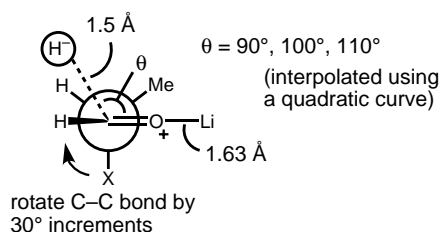
2-chloropropanal
Cornforth

Felkin conformers
not considered

Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dâu, M.-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146

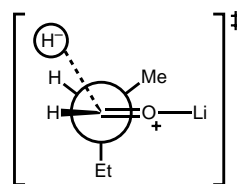
Anh's Calculated Transition State Energies

The model:

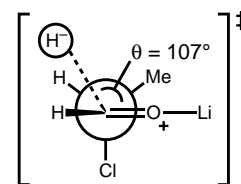


STO-3G *ab initio* method (low level)

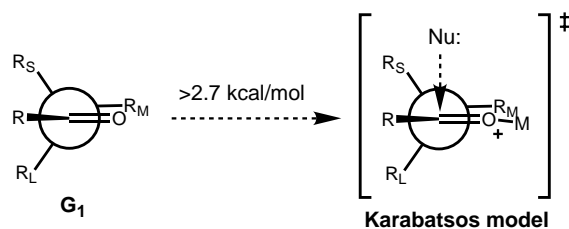
Lowest energy transition states:



2-methylbutanal
(Felkin-Anh model)



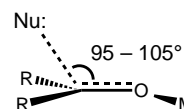
2-chloropropanal
(Felkin-Anh polar model)



most stable
ground state
conformer

$$E_{\text{Felkin model}} \approx E_{\text{G1}}$$

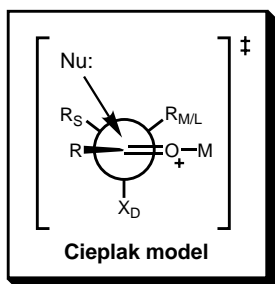
Non-perpendicular attack



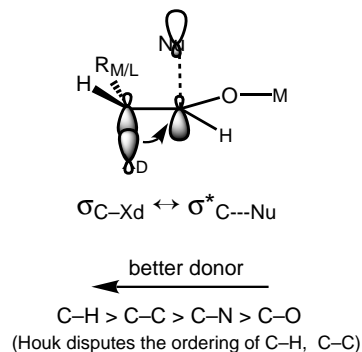
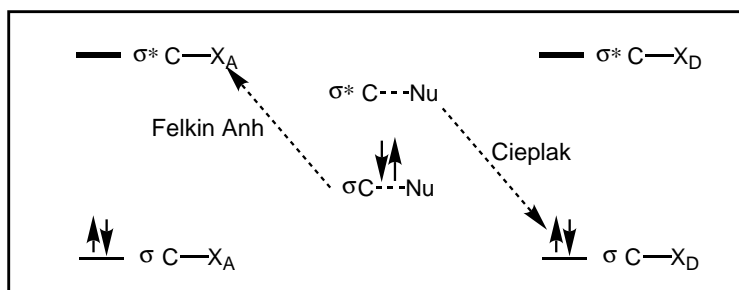
a range of angles for optimum overlap

Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155
Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61
Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 146

Cieplak Model for Carbonyl Addition



- similar to Anh-Eisenstein modification of the Felkin model: stabilization of nucleophile via antiperiplanar C-X_D bond
- assumes an electron-poor transition state: aligns best donor C-X_D *anti* to incoming nucleophile to stabilize σ* of forming bond
- a model generated to explain unexpected selectivities
- importance of torsional effects (Felkin, Anh, Houk, Paddon-Row) disputed



"Structures are stabilized by stabilizing their highest energy filled states. This is one of the fundamental assumptions in frontier molecular orbital theory. The Cieplak hypothesis is nonsense."

"Just because a hypothesis correlates a set of observations doesn't make that hypothesis correct."

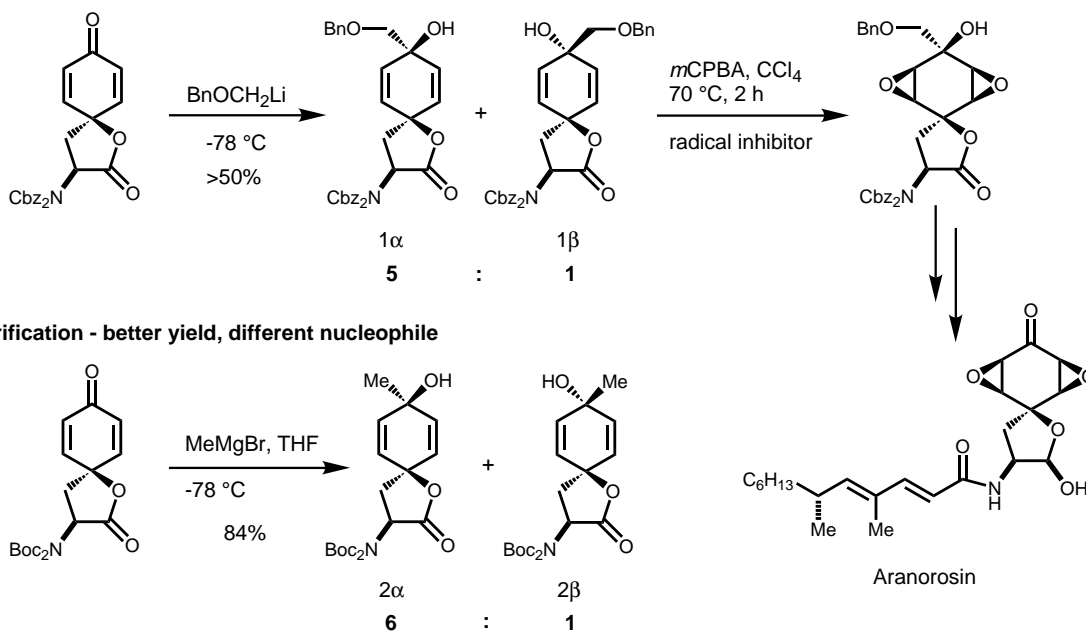
DAE, Chem 206 2000, Lecture 18

Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540; Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447

Wipf: 4,4-Disubstituted Cyclohexadienones

Preliminary Results

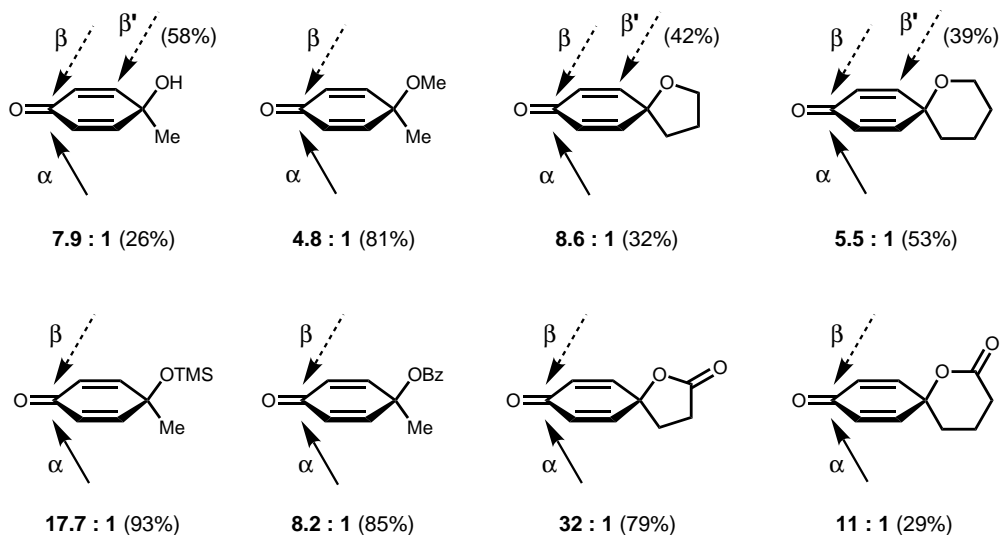
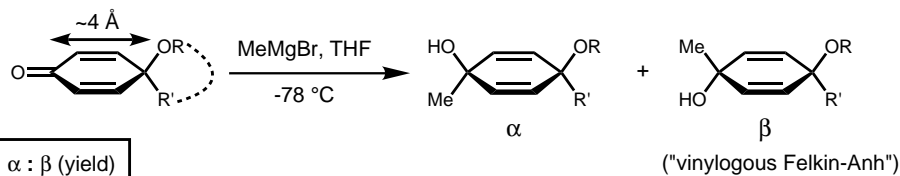
An interesting selectivity *en route* to a total synthesis



- little steric bias as determined by molecular mechanics minimization of geometry
- likely to be an electrostatic or stereoelectronic (hyperconjugation, orbital distortion, etc) explanation

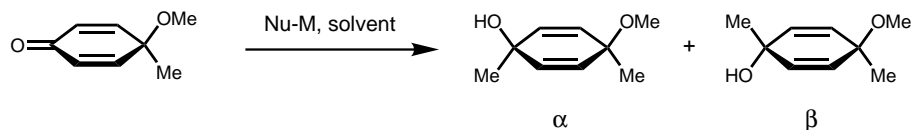
Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
Wipf, P.; Jung, J-K. *Chem. Rev.* **1999**, *99*, 1469

4,4-Disubstituted Cyclohexadienones: Experimental Data



Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
 Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469

Effect of Changing Nucleophile



Nu-M	yield (%)	α : β	solvent
MeMgBr	81	4.8 : 1	THF
NaBH ₄ or LAH	100	1 : 1	MeOH or THF
HC≡CMgBr	70	1 : 1	THF
H ₉ C ₄ C≡CLi	26	1.1 : 1	THF
PhMgBr	83	3.6 : 1	THF
MeLi	87	2.1 : 1	THF
MeLi	77	3.3 : 1	Et ₂ O
BnOCH ₂ Li	84	3 : 1	THF

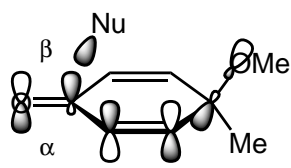
- C-sp² and C-sp³ nucleophiles exhibit facial selectivity, while C-sp and hydride donors are non-selective
- stereoselectivity highly sensitive to nature of nucleophile (electronic structure, aggregation state)
- any selectivity observed is in favor of α attack, *anti* to the 4-oxygen substituent

Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
 Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469

Wipf Seeking an Explanation

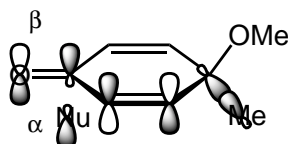
Stereoelectronic effect?

Neither vinylogous Felkin nor vinylogous Cieplak sufficiently explains or predicts selectivity.



"vinylogous Anh-Eisenstein" model

- stabilizing HOMO of nucleophile
- predicts β attack -- wrong product!

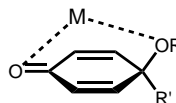


"vinylogous Cieplak" model

- stabilizing σ^* of the incipient bond
- predicts α attack, but no qualitative correlation between ratio of isomers and σ energy of donor C-C bonds

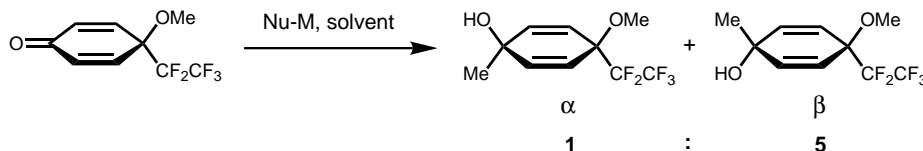
LUMO of enone has phase inversion due to double bond between carbonyl and donor/acceptor orbital

Chelate shielding of the β face is not likely, since 1,4-addition, when it does occur, is β -selective.



Electrostatic effect?

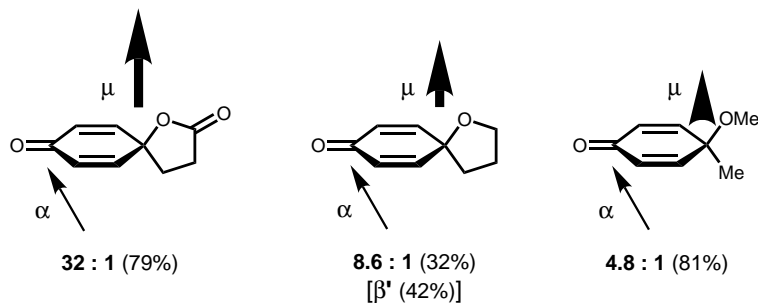
Substrate with inverted dipole exhibits good β selectivity!



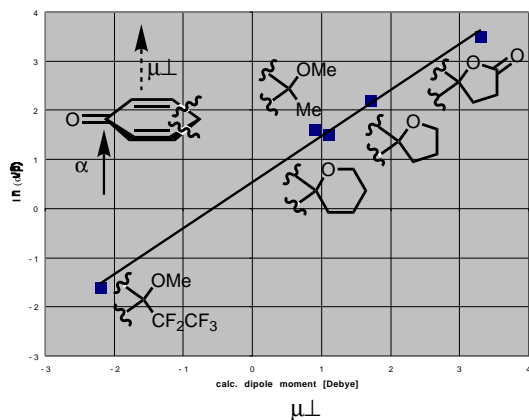
Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
Wipf, P.; Jung, J-K. *Chem. Rev.* **1999**, *99*, 1469

Quantitative Correlation Between Facial Selectivity and Dipole Moment

Qualitative Assessment



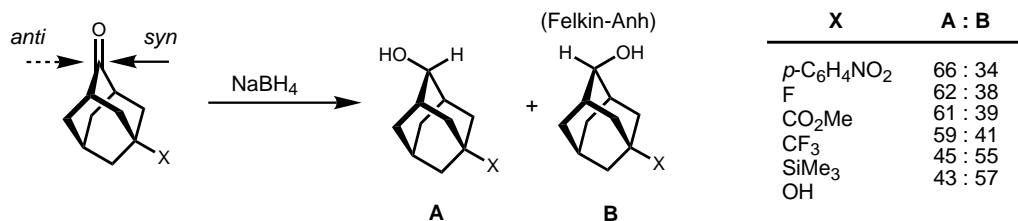
Dipole Moment Calculations



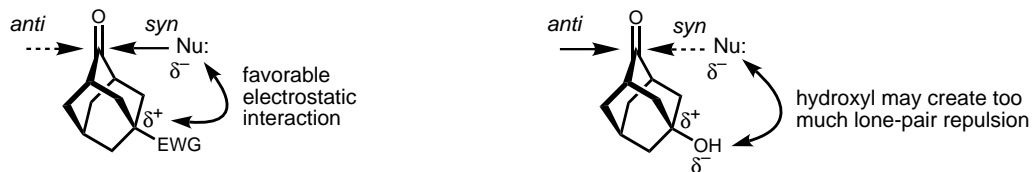
- calculated dipole moments of five representative dienones using SPARTAN
- linear correlation between perpendicular vector of dipole moment and natural log of facial selectivity
- validity of ground-state dipole moment: complexed carbonyl should affect dipoles of all dienone substrates in same manner
- approach of nucleophile toward positive end of dipole favored

Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678
Wipf, P.; Jung, J-K. *Chem. Rev.* **1999**, *99*, 1469

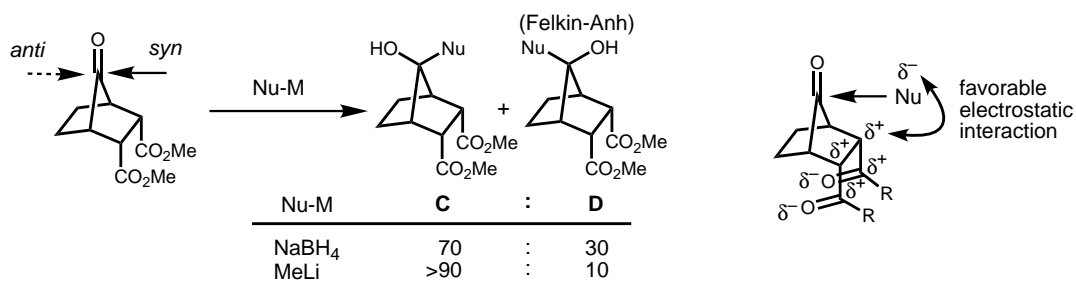
An Electrostatic Take on Some Controversial Cases



Cheung, C. K.; Tseng, L. T.; Lin, M-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598

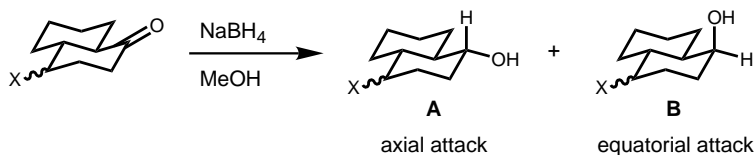


Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867



Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140
 Paddon-Row, M. N.; Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638
 Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734

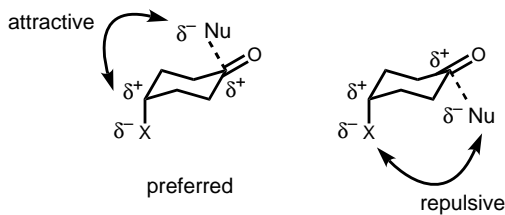
Houk: Axial Effect



X	A : B
H	60 : 40
eq OH	61 : 39
eq OAc	71 : 29
eq Br	66 : 34
eq Cl	71 : 29
ax OH	85 : 15
ax OAc	83 : 17
ax Cl	88 : 12
ax F	87 : 13

Rationalization:

a remote electrostatic effect



Wu, Y-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018
 Paddon-Row, M. N.; Wu, Y-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638

Tomoda: The Exterior Frontier Orbital Extension (EFOE) Model

The EFOE model is a *quantitative*, ground-state model for carbonyl addition based on the Salem-Klopman equation, which has an exchange repulsion (steric) term, an electrostatic term, and a donor-acceptor orbital interaction term. The EFOE model combines the steric term with the orbital term, leaving out coulombic interactions.

Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223
Salem, L. *J. Am. Chem. Soc.* **1968**, *90*, 543

Assumption: the volume of the outer (exterior) space nearest to a reaction center should contain steric information of the substrate, since it is the space which a nucleophile must occupy.

Calculates PDAS, a steric factor, and EFOE density, an electronic factor, for ground states:

π -plane-divided accessible space (PDAS) = the space outside the van der Waals radii of the atoms nearest the reaction center; calculated by integrating the space within 2.65 Å of the molecular surface

exterior frontier orbital electron (EFOE) density = the π -plane-divided electron density of a frontier orbital (LUMO of carbonyl) summed over points that satisfy the following condition: the absolute total value of the wave functions belonging to the carbonyl carbon makes a maximum contribution to the total value of FMO wave function at the point.

$$\lambda = \text{EFOE (a)}^2 - \text{EFOE (b)}^2$$

Relates activation enthalpy (or product ratio) to EFOE density: $\Delta\Delta H^\ddagger = m\lambda + n$ ($m > 0$; $n = \text{a constant}$)

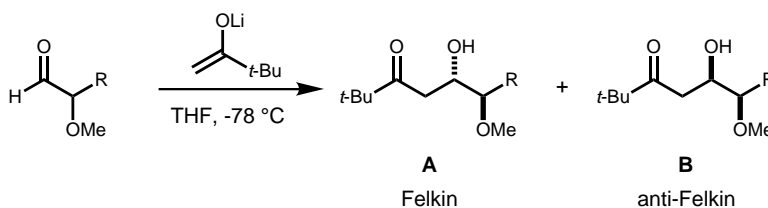
- claims linear correlations between $\ln(\text{ax}/\text{eq})$ and λ for 4-substituted-*trans*-decalone reductions, but data are somewhat scattered
- claims to predict kinetics from ground-state effects

The "axial effect" of 4-substituted cyclohexanones "could be reasonably explained by ground-state factors - the extension of LUMO and the molecular conformation - without invoking other influences."

(generated to explain selectivities often explained by the Cieplak model)

Tomoda, S.; Senju, T. *Tetrahedron* **1997**, *53*, 9057
Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 3871
Tomoda, S.; Senju, T. *J. Chem. Soc. Chem. Commun.* **1999**, 621
→ Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243

Heathcock: α -Alkoxy Lithium Aldol

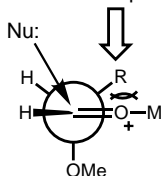


R	A : B
Me	58 : 42
Et	76 : 24
<i>i</i> -Pr	92 : 08
Ph	83 : 17
<i>t</i> -Bu	93 : 07

"Quite simply, we believe our data show that the Anh-Eisenstein hypothesis is only partly correct."

Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353

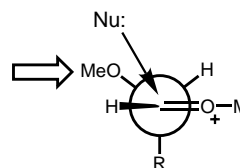
steric effect on Nu:
is underemphasized



Felkin-Anh polar model

- Would expect some erosion of selectivity as size of R increases -- observe just the opposite!

steric effect on Nu:
is overemphasized



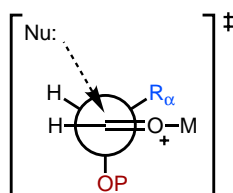
Evans electrostatic model

- As R is anti to incoming nucleophile, increasing size of R should not erode selectivity
- As R gets larger, conformation may be more "locked" in the Evans conformer

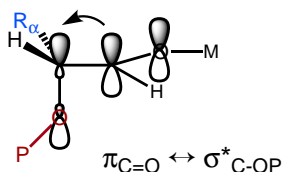
In both models, the stereoelectronic or electrostatic control element is not consistently dominant!
Both the size and the electronic properties of the α -substituents must be considered.

Are Felkin-selective reactions of α -heteroatom aldehydes going through the Felkin-Anh transition state?

Felkin-Anh model

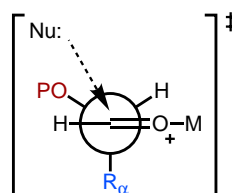


- leads directly to staggered conformation, Felkin product
- best acceptor σ^* orbital aligned parallel to π and π^* orbitals of carbonyl: hyperconjugative stabilization

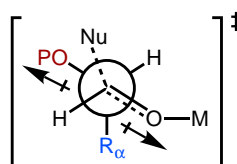


- assumes a covalent transition state in which FMO stabilization dominates

Evans electrostatic model



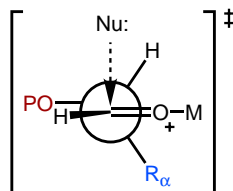
- leads directly to staggered conformation, Felkin product
- dipoles of carbonyl and α -C-O are minimized, with increasing stabilization as pyramidalization occurs at the reactive center



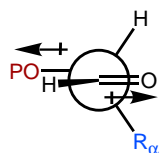
- assumes a more ionic transition state in which coulombic interactions dominate
- larger π^* coefficient on C of oxocarbenium species may enable a wider range of angles for nucleophilic trajectory

How does the Cornforth model compare to the Evans electrostatic model?

Cornforth model

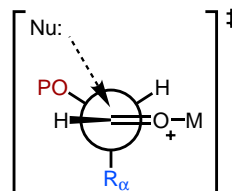


- leads to torsionally strained conformation, Felkin-Anh product
- dipoles of carbonyl and α -C-O are minimized for the ground state: reactant-like transition state

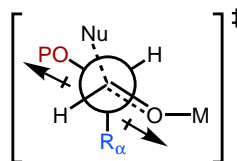


- assumes a more ionic transition state in which coulombic interactions dominate
- perpendicular trajectory of nucleophile

Evans electrostatic model

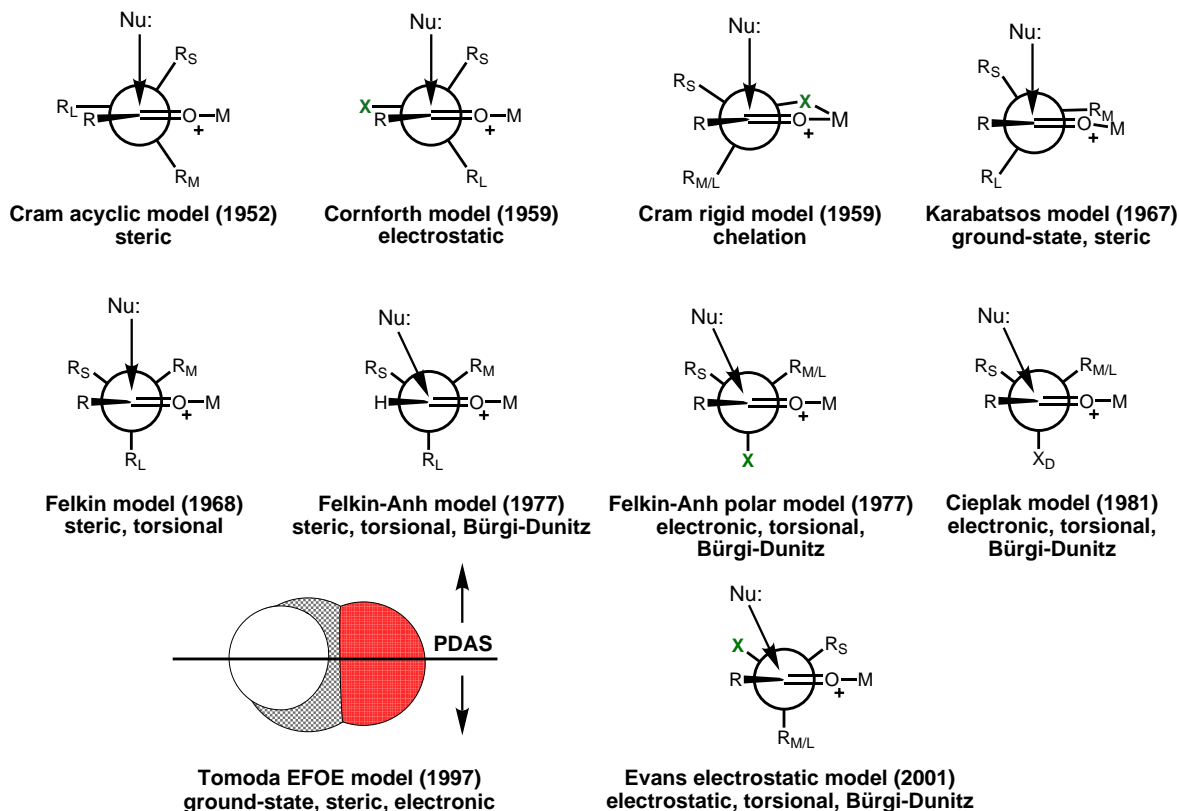


- leads directly to staggered conformation, Felkin-Anh product
- dipoles of carbonyl and α -C-O are minimized, with increasing stabilization as pyramidalization occurs at the reactive center

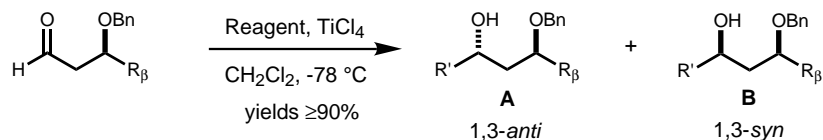


- assumes a more ionic transition state in which coulombic interactions dominate
- larger π^* coefficient on C of oxocarbenium species may enable a wider range of angles for nucleophilic trajectory

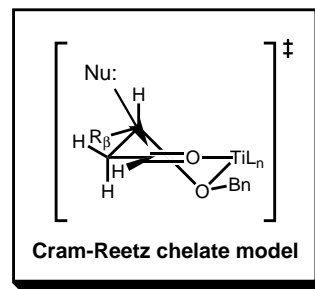
Models Proposed for 1,2-Asymmetric Induction



Reetz: Chelation in β -Alkoxy Aldehydes



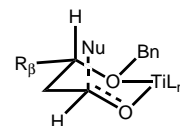
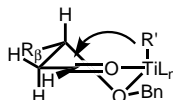
Reagent	R_β	R'	A : B
	Me		95 : 05
	Me		95 : 05
$n\text{-Bu}_2\text{Zn}$	Me	$n\text{-Bu}$	90 : 10
	$n\text{-Bu}$		95 : 5
	$n\text{-Bu}$		99 : 01



RMgX , RLi , and R_2CuLi fail to give high chelation selectivities for β -alkoxy aldehydes.

Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011, 4019
Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035

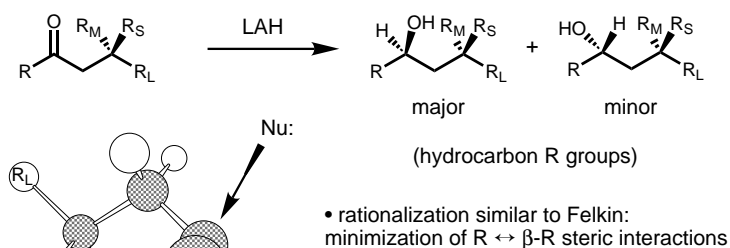
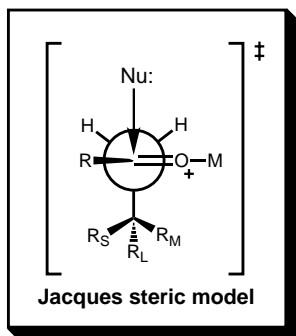
Reetz proposes possible transmetalation event of nucleophile: internal delivery.



• leads to a chair-like intermediate

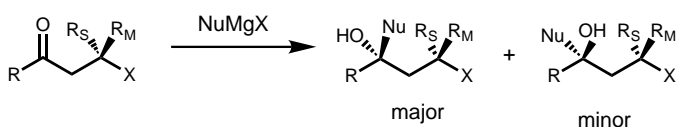
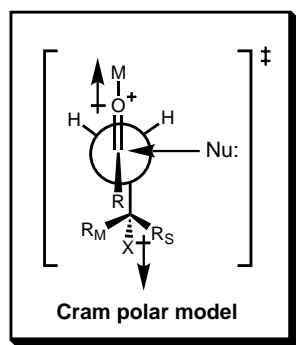
Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833

1,3-Asymmetric Induction: Open-Chain Models



3-D depiction of Jacques model

Brienne, M-J.; Ouannès, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1968**, 3, 1036

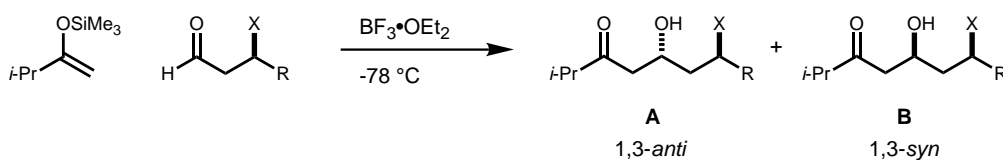


- an adaptation of the Cram steric model, with the key feature being dipole minimization of electronegative substituent X and carbonyl

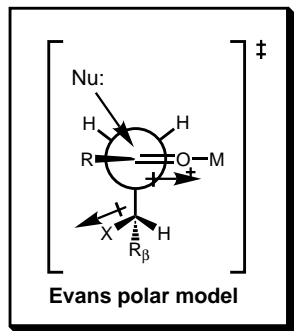
Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, 90, 4011, 4019

1,3-Asymmetric Induction: Open-Chain Models

Evans: Mukaiyama Aldols



X	R	A : B	yield (%)
OPMB	<i>i</i> -Pr	92 : 08	91
OTBS	<i>i</i> -Pr	80 : 20	84
OPMB	CH ₂ CH ₂ Ph	81 : 19	87
OTBS	CH ₂ CH ₂ Ph	73 : 27	90
OAc	CH ₂ CH ₂ Ph	43 : 57	79
Cl	CH ₂ CH ₂ Ph	83 : 17	84
Me	C(Me ₂)CHCH ₂	58 : 42	88

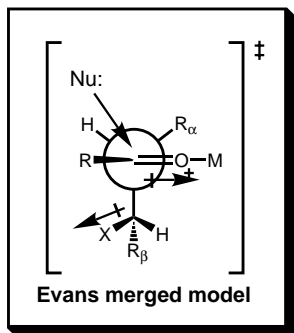


- staggered to avoid torsional strain
- dipoles of C_β-X and carbonyl minimized
- non-perpendicular nucleophile trajectory

Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, 35, 8537
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, 116, 4322

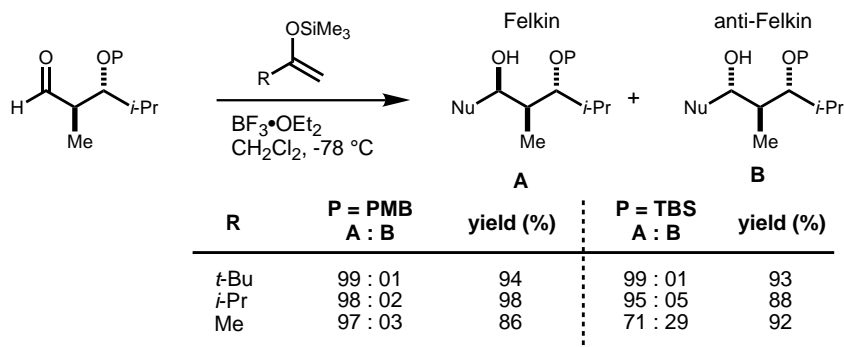
See also: Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, 53, 13419

Evans Merged Model for 1,2- and 1,3-Asymmetric Induction



- for non-chelating conditions
- a merger of the Felkin-Anh (1,2) model and the Evans polar (1,3) model
 - minimized dipole moment
 - non-perpendicular trajectory
 - R_L *anti* to incoming nucleophile
- predicts 1,2-Felkin control and 1,3-*anti*

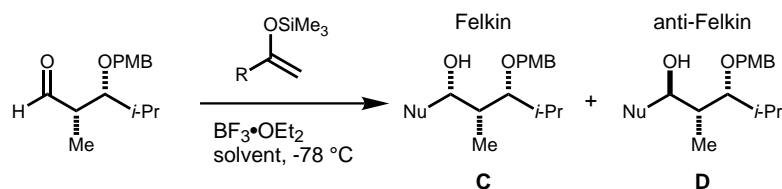
The stereoreinforcing case (Felkin and 1,3-*anti* induction coincide)



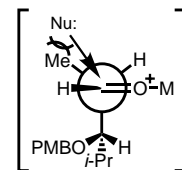
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322

Evans Merged Model for 1,2- and 1,3-Asymmetric Induction

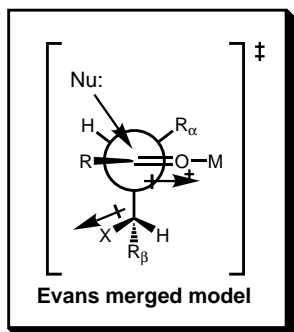
The non-stereoreinforcing case: Felkin control opposes 1,3-stereocontrol



R	C : D CH ₂ Cl ₂	yield (%)	C : D toluene	yield (%)
<i>t</i> -Bu	96 : 04	89	88 : 12	75
<i>i</i> -Pr	56 : 44	98	32 : 68	86
Me	17 : 83	82	06 : 94	92



non-stereoreinforcing transition state



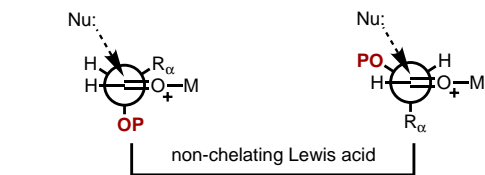
- with a small nucleophile, β -stereocenter becomes the dominant control element
- 1,3-induction is enhanced in nonpolar media

Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619
Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322

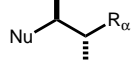
Integration of α - and β -Alkoxy Aldehyde Models in Non-chelating Systems

For α -alkoxy aldehydes:

Felkin-Anh model Evans electrostatic model



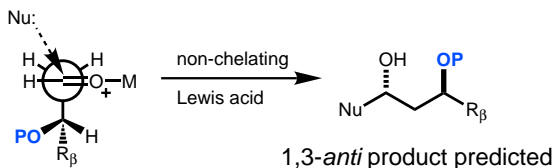
• no systematic electronic + steric study has been done



"Felkin" product predicted

For β -alkoxy aldehydes:

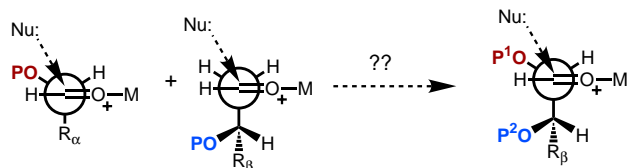
Evans model



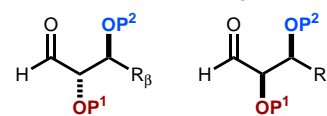
• under non-chelating conditions, 1,3-*anti* selectivity is observed

Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, 35, 8537-8540

For α,β -bisalkoxy aldehydes:

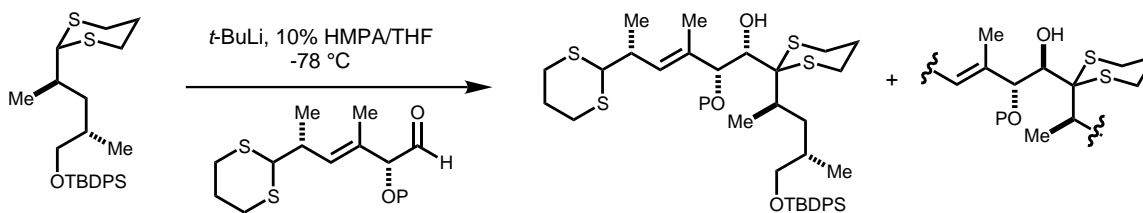


Which is stereoreinforcing, *anti* or *syn*?



How does the α -alkoxy substituent affect the conformation of the β -stereocenter?

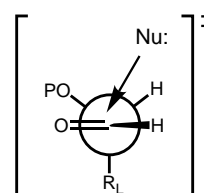
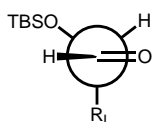
Smith: Rapamycin



A anti-Felkin **B** Felkin

P	A : B	yield (%)
MOM	2 : 1	32
TBS	5 : 1	75
TBDPS	>20 : 1	60

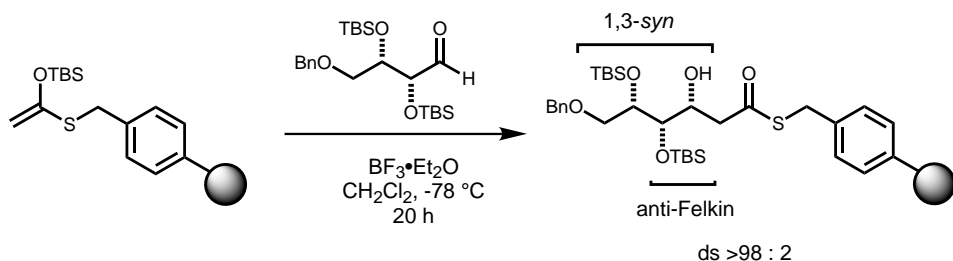
solid state conformation of TBS-protected aldehyde (X-ray structure) resembles Evans electrostatic model conformation:



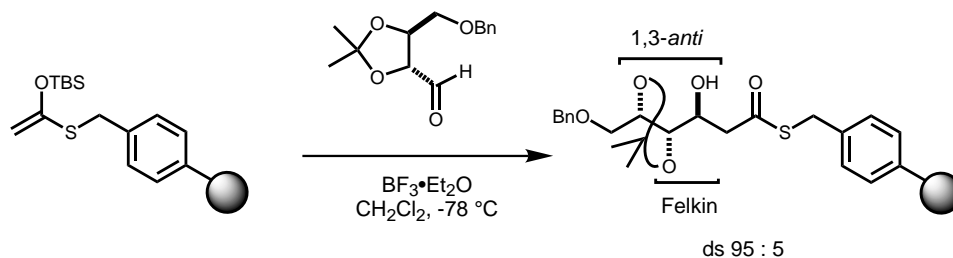
suggested as reactive conformer

Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, 119, 947

Kobayashi: Monosaccharide Derivatives on the Solid Phase



after cleavage from resin, 61% over 4 steps, the third of which is the aldol



after cleavage from resin, 61% over 4 steps, the third of which is the aldol

Kobayashi, S.; Wakabayashi, T.; Yasuda, M. *J. Org. Chem.* **1998**, *63*, 4868

Final Thoughts

Factors affecting preferred conformation

1) Solvent effects

- more polar solvent (higher dielectric constant): increase in induced dipole moment of solute
- also can reduce the value of dipole-dipole or dipole-point charge interactions
- in β -alkoxy non-chelation cases, less polar solvent correlates with better diastereoselectivity
- results may be unpredictable

2) Anionic character of reagent

Electrostatically-controlled processes: "increasing the more favorable electrostatic interaction should accelerate the reaction rate and the selectivity." -P. Wipf

Processes not governed by electrostatics: usually run at low temperatures to slow down the reaction to improve the selectivity

3) Size of nucleophile, size of protecting group, size of other α -substituent

While the Felkin-Anh model has withstood the test of time for hydrocarbon α -substituents, the number of exceptions to the electronic model have sparked a flurry of new explanations, beginning with Cieplak in 1981. The debate continues, between steric, torsional, electronic, and electrostatic effects.

Judging by the Smith and Kobayashi results, as well as many others, it remains a challenge to predict the stereochemical outcome of addition to α - and β -heteroatom-substituted carbonyl compounds. It may be that more than one model is operational in a single system.

