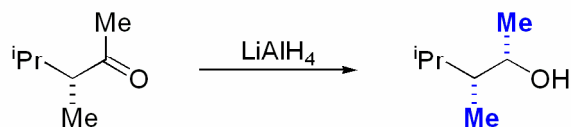# Carbonyl Addition Reactions

1. Introduction and History

1.1. Historic Models Developed for Carbonyl Addition Reactions

Example for diastereoselective reduction:

^{i}Pr — C(Me)(Me) — C(=O)Me $\xrightarrow{\text{LiAlH}_4}$ ^{i}Pr — CH(Me) — CH(Me)OH
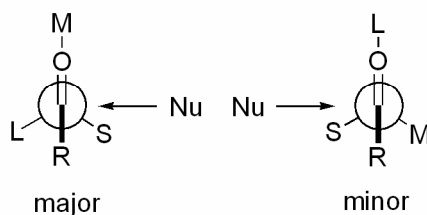
ca. 4:1 *syn*:*anti*

> diastereoselectivity needs to be accounted for; information on structure and reactivity obtained

historical: Felkin *Tetrahedron Lett.* **1963**, 2199.
Felkin *J. Am. Chem. Soc.* **1968**, *90*, 2199.
Anh & Eisenstein *Nouv. J. Chim* **1977**, 61.
Houk *J. Am. Chem. Soc.* **1981**, *103*, 2438.
Cram *J. Am. Chem. Soc.* **1952**, *74*, 5828.
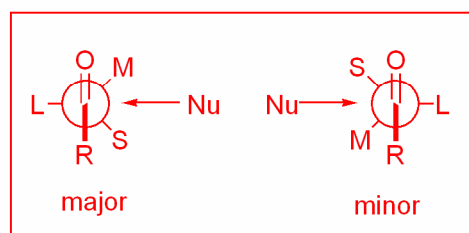Karabatsos *J. Am. Chem. Soc.* **1967**, *89*, 1367.

See also the monograph: *Asymmetric Organic Reactions;* Morrison and Mosher, ACS **1976**
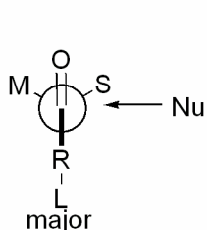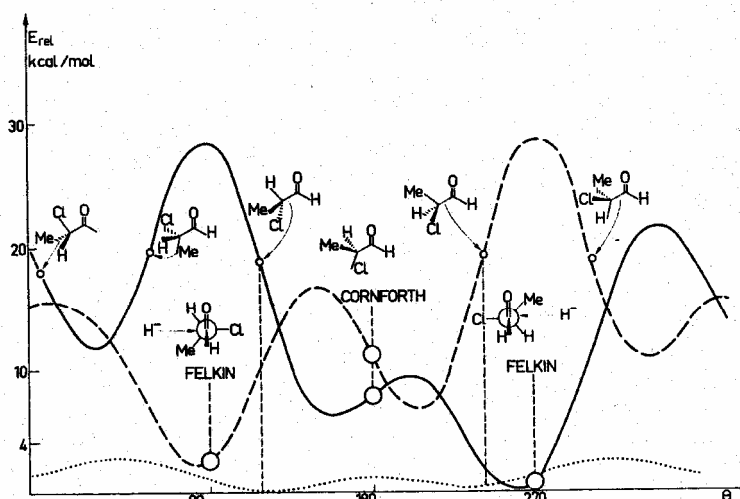
Cram (Cornforth) model   **Karabatsos model**   **Felkin model**

major   major   minor   major   minor

energy of the transition states for the models:

Reaction of H⁻ with Me—CHCl—CHO. Plot of transition states energies versus θ, angle of rotation around C1–C2. Full (dashed) line corresponds to transition states leading to the major (minor) product, according to Cornforth's rule. Dotted curve: conformational energy curve of Me—CHCl—CHO.
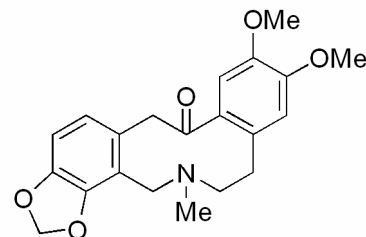
1.2. The Bürgi-Dunitz Study

compounds whose X-ray structures provided the basis for the 'Bürgi-Dunitz' trajectory:
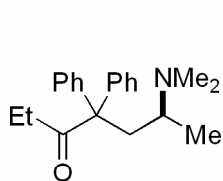
methadone
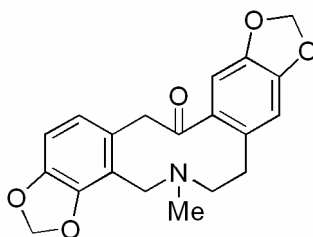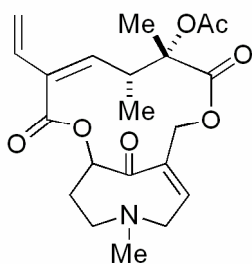
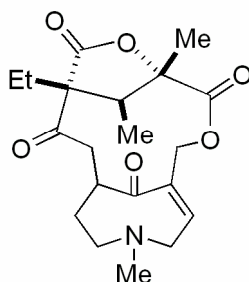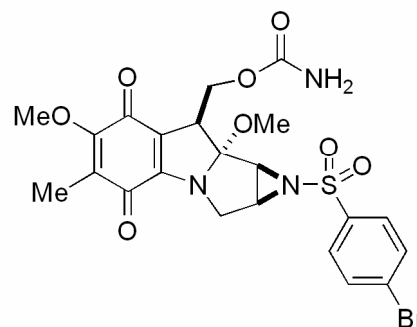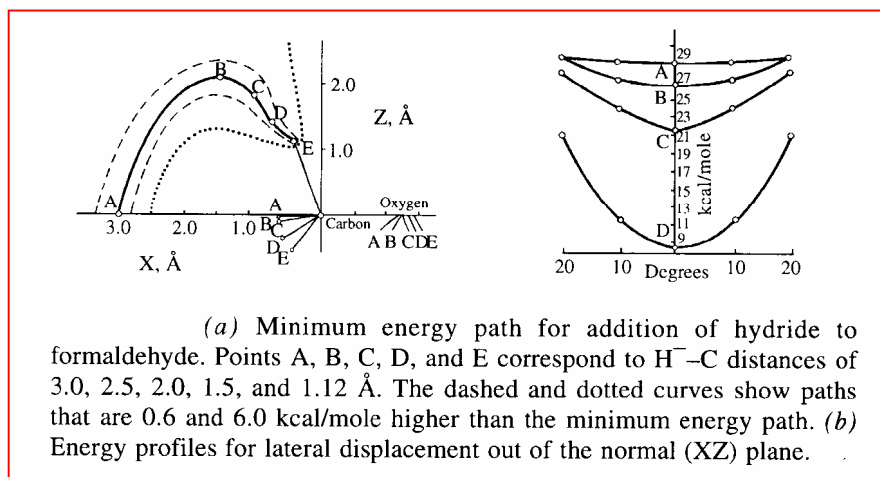**cryptopine**

protopine

clivorine

retusamine

N-brosylmitomycin A

Dunitz *J. Am. Chem. Soc.* **1973**, *95*, 5065.
Tetrahedron **1974**, *30*, 1563.

representation of the Bürgi-Dunitz trajectory:

(a) Minimum energy path for addition of hydride to formaldehyde. Points A, B, C, D, and E correspond to H⁻–C distances of 3.0, 2.5, 2.0, 1.5, and 1.12 Å. The dashed and dotted curves show paths that are 0.6 and 6.0 kcal/mole higher than the minimum energy path. *(b)* Energy profiles for lateral displacement out of the normal (XZ) plane.

simple representations of HOMO and LUMO:

HOMO   C—O   C—O   C—O   C—O   LUMO
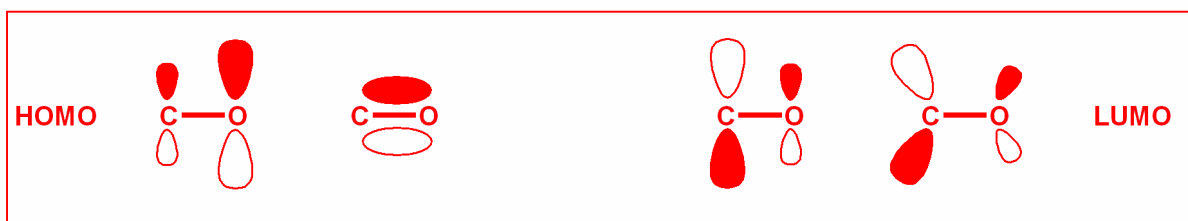
1.3. Houk's Rule

> ... the stereochemical rule found here can be stated in a much more general fashion to be a result of magnified torsional effects occurring in the transition states of addition reactions: **the tendency for staggering of vicinal bonds with respect to partially formed bonds is greater than for fully formed bonds.**

origin of π-facial stereoselectivity in additions to π-bonds: generality of the *anti*-periplanar effect
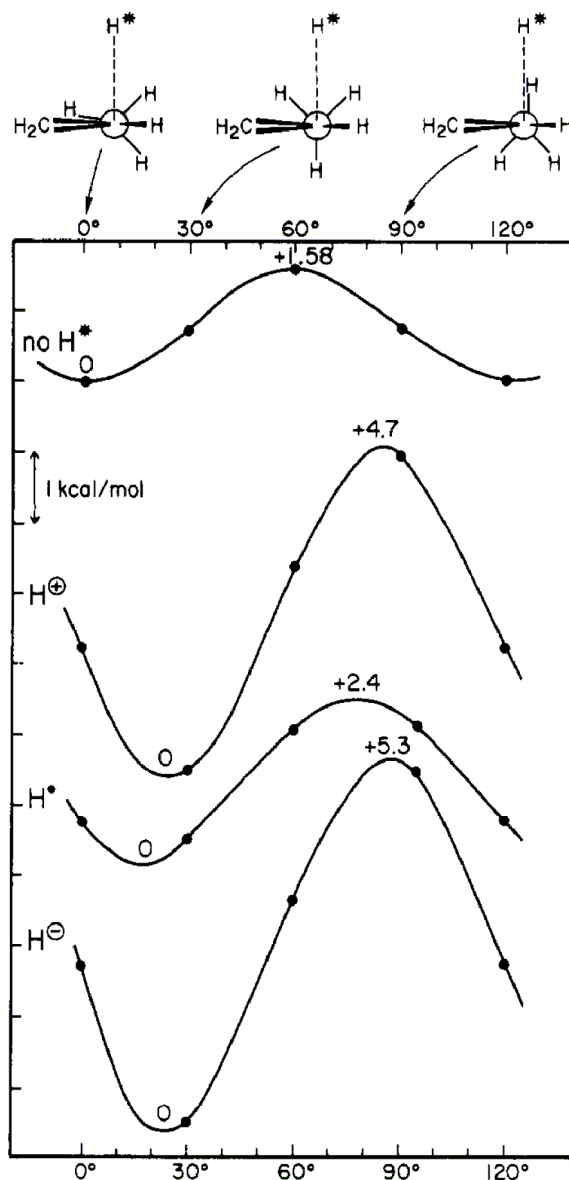

Figure 1. Energies as a function of methyl rotation.[8] Top curve: isolated propene. Second curve: propene plus H^+ placed 2 Å above C-2. Third curve: propene plus H· placed 2 Å above C-2. Bottom curve: propene plus H^- placed 2 Å above C-2.

Houk *J. Am. Chem. Soc.* **1981**, *103*, 2438.

2. Felkin-Anh: The Model

rules for cases in which steric effects dominate:

> **1. define R_S, R_M and R_L**
> **2. orient R_L perpendicular to plane of the carbonyl π-system and antiperiplanar to the incoming reagent**
> **3. apply Houk's rule**
> **4. look for non-bonding interactions between reagent and substrate**

preferred
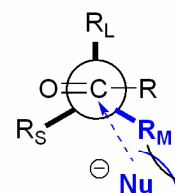
'Cram product'
Felkin-Anh product
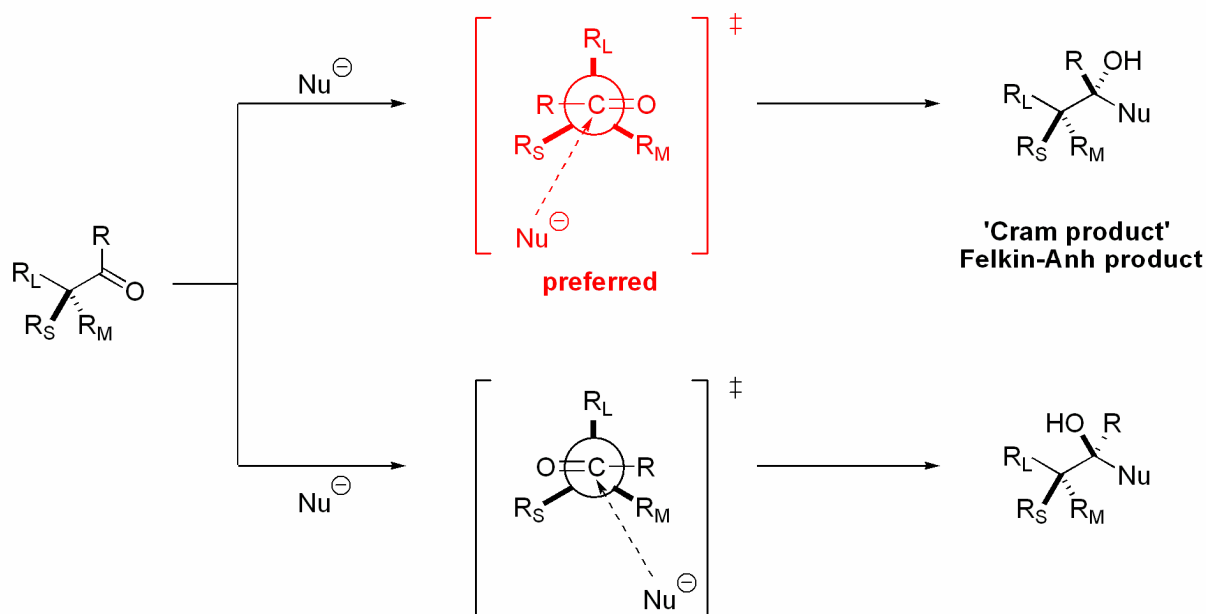
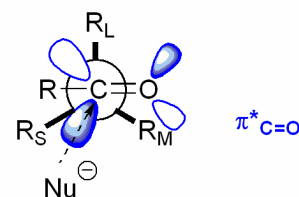**preference for transition state highlighted in red:**

1. The conformer shown gives fully staggered arrangement in the products (cp. Houk's rule).
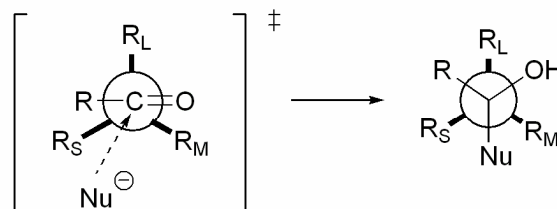
2. Unfavorable non-bonded interactions between Nu and R_L as well as Nu and R_M are minimized.
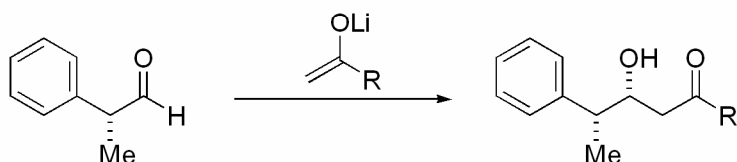

3. Trajectory is in agreement with the spatial requirements demanded by stereoelectronics: Bürgi–Dunitz trajectory.
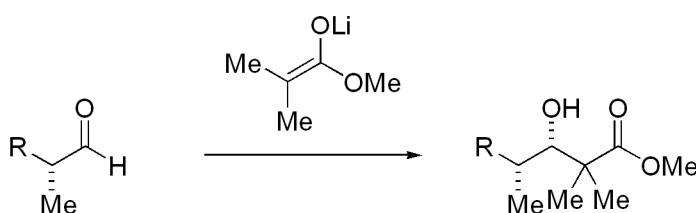

$\pi^*_{C=O}$

66

examples:

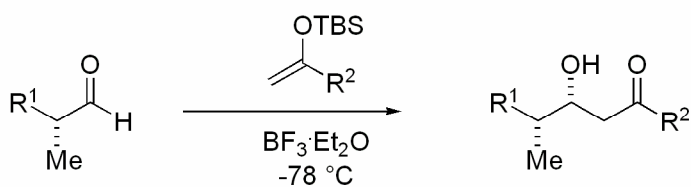| strength of the model lies in its ability to account for and predict the stereochemical outcome of many processes encompassing a broad range of nuclephiles |
|---|

R	ratio
Me	3 : 1
O^{t}Bu	4 : 1

Tetrahedron Lett. **1985**, *26,* 973.

R	ratio
Ph	>200 : 1
C$_6$H$_{11}$	9 : 1

Tetrahedron Lett. **1985**, *26,* 973.

TBS = ^{t}BuMe$_2$Si

R^1	R^2	ratio
Ph	Me	10 : 1
Ph	^{t}Bu	24 : 1
Ph	OMe	15 : 1
Ph	O^{t}Bu	36 : 1
C$_6$H$_{11}$	O^{t}Bu	16 : 1

Heathcock *J. Am. Chem. Soc.* **1983**, *105,* 1667.

titanium reagents: mild and selective organometallic nucleophiles
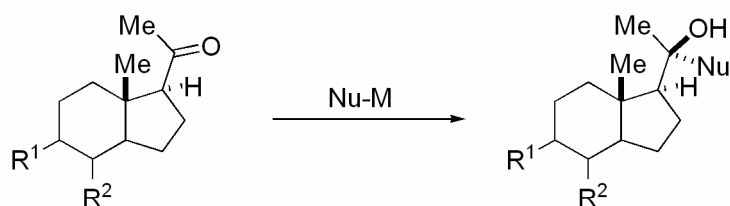
preferred conformation:
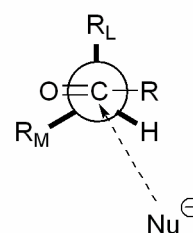
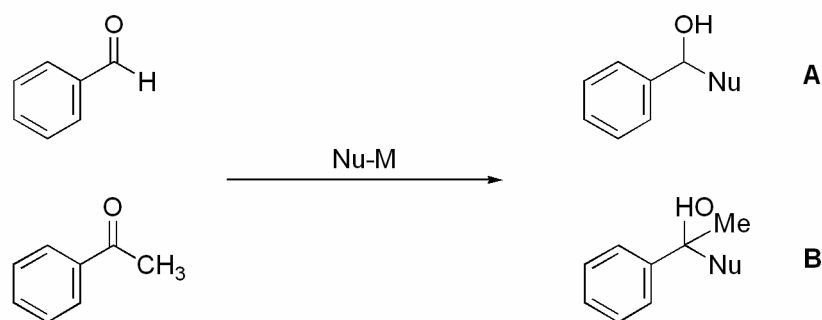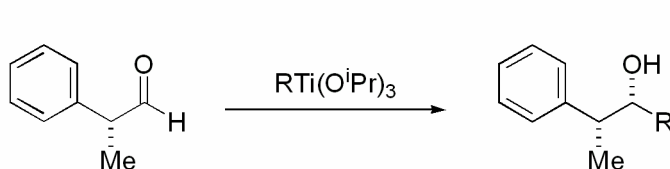| Nu-M	Felkin-Anh : *anti*-Felkin Anh
$CH_2=CHCH_2Ti(O^iPr)_3$	> 90:10
$CD_3Ti(O^iPr)_3$	96:4

competition experiment:

A

B

Nu-M	A : B
$C_6H_5\,Li$	~ 1:1
C_6H_5 -Ti $(O i prop)_3$	> 98:2

Seebach *Helv. Chim. Acta* **1981**, *64,* 357.

for additional examples, see: *Organotitanium Reagents for Organic Synthesis*, Berlin: Springer, **1985**.

$RTi(O^iPr)_3$

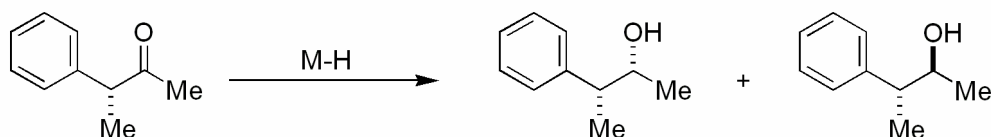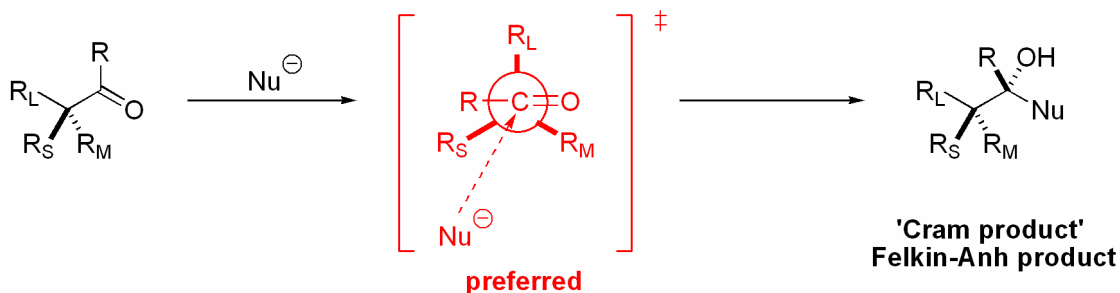| R	ratio
R = Me	> 90 : 10
R = ^nBu	> 90 : 10

RMgX gives near 3:1 ratios.

Reetz *Angew. Chem. Int. Ed. Engl.* **1982**, *21,* 135.

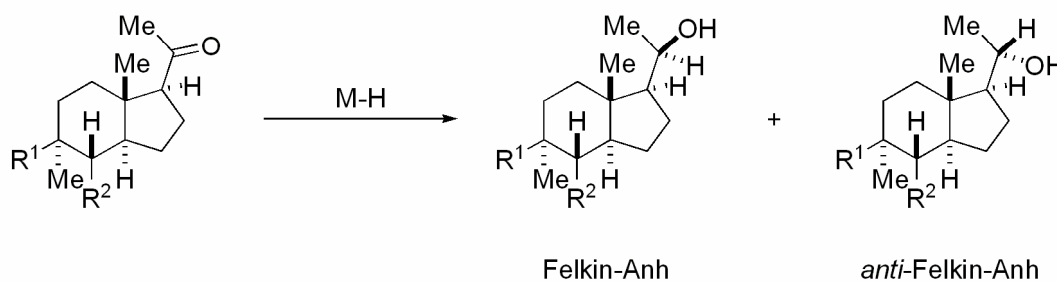# 3. Limitation and further Refinements of the Felkin-Anh Model

3.1. Diastereoselective Ketone Reduction: Borane vs Borohydride Reagents

in general:

'Cram product'
Felkin-Anh product

preferred

reagent	ratio	model
LiHB(ˢBu)$_3$	22 : 1	Felkin-Anh
HB(Sia)$_2$	1 : 4	*anti*-Felkin-Anh

consistent with Felkin-Anh Model

Felkin-Anh   *anti*-Felkin-Anh

reagent	ratio	model
LiHB(ˢBu)$_3$	54 : 1	Felkin-Anh
NaBH$_4$	5 : 1	Felkin-Anh
LiAlH$_4$	3 : 1	Felkin-Anh
HB(Sia)$_2$	1 : 10	**anti-Felkin-Anh**

**rationale for inconsistency
with HB(Sia)$_2$ needed**

oxidative work-up with H$_2$O$_2$

*J. Am. Chem. Soc.* **1983**, *105*, 3725.

differences between reductions using boron hydride reagents and reductions with boranes highlight some important features of the model

The model used is a simplification and therefore has its limitations. In this respect, the nature and structure of the reagents involved has been ignored. Moreover, in its current state, the model does not consider the effect of interactions between the carbonyl group and the metal.
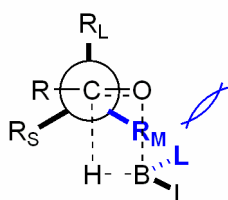
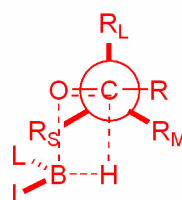**detailed analysis of the system:**
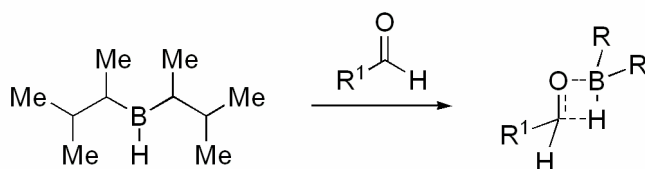
**boron is
Lewis acidic**
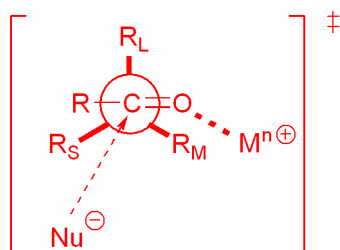
Felkin-Anh model

Felkin-Anh model does not imply any covalent connection between nucleophile and the metal center activating the carbonyl group
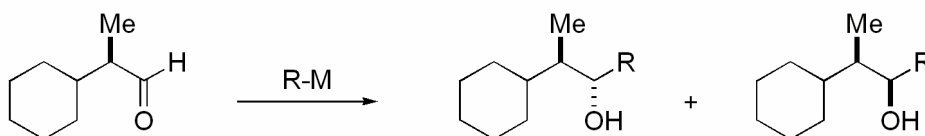

**non-bonding interaction
between R_M and L**

**non-bonding
interactions with
substituents on boron
minimized**

preferred

example:
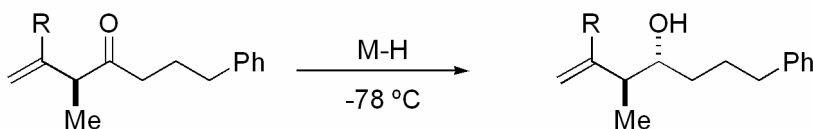

MAT = bis-(2,4,6-tri-*tert*-butyl-4-methylphenoxy)methyl aluminum

	anti Felkin-Anh : Felkin-Anh
MeMgI	28:72
MeMgBr	16:84
MeMgI + MAT	93:7
MeMgBr + MAD	80:20

J. Am. Chem. Soc. 1985, 107, 4753.

3.2. Diastereoselective Ketone Reduction with Non-Boron Reagents

R	reagent	ratio
H	LiHB(^{s}Bu)$_3$	96 : 4
H	DIBAL-H	47 : 53
Me	LiHB(^{s}Bu)$_3$	>99 : 1
Me	DIBAL-H	88 : 12

Tetrahedron Lett. **1984**, *25,* 2479.
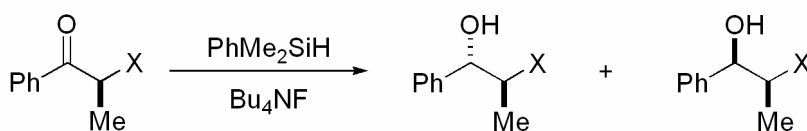
X	ratio
NMe$_2$	>99 : 1
OAc	95 : 5
OCOPh	96 : 1

J. Am. Chem. Soc. **1984**, *106,* 4629.

cyclic model for reduction
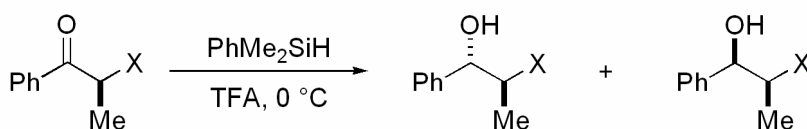
X	ratio
NHCO$_2$Et	>1 : 99
OCOPh	7 : 93

J. Am. Chem. Soc. **1984**, *106,* 4629.

3.3. Polar Felkin-Anh and Chelate Model

back to an analysis of the Felkin-Anh model:

$$\left[\begin{array}{c} R_L \\ R{-}C{=}O \\ R_S \qquad R_M \\ \\ Nu^{\ominus} \end{array} \right]^{\ddagger}$$

preferred

Me—C(=O)—C(=CH₂)—Me (with RO) ⟶ syn product (Me, OH, Me with RO) + anti product (Me, OH, Me with RO)
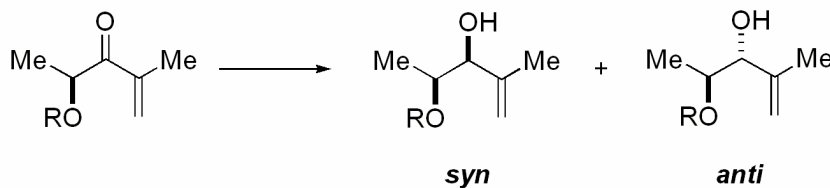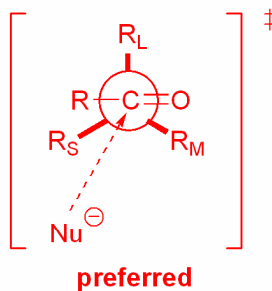
syn   *anti*

R	reagent	*syn* : *anti*
CH₂OBn	LiAlH₄ (-10 °C)	2 : 98
TBDPS	LiAlH₄ (-10 °C)	95 : 5

TBDPS = $^{t}BuPh_2Si$

explanation for experimental observations: Felkin-Anh model needs to incorporate steric and electronic effects

polar Felkin-Anh model:

> **When a polar electronegative substituent is present, stereoelectronic effects usually dominate over steric effects. In such cases, the polar substituent is placed in the position normally reserved for R_L.**

σ^{*}_{C-X} ... $\pi^{*}_{C=O}$

$$\begin{array}{c} X \\ R{-}C{=}O \\ R_S \qquad R_M \\ \\ Nu^{\ominus} \end{array}$$
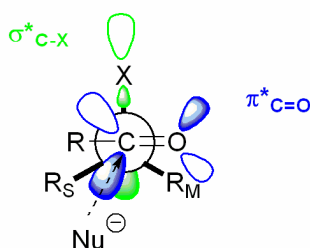
second result can be interpreted using the polar Felkin-Anh model, but the first one behaves differently

chelate effect:

chelate product
(opposite configuration at
new stereocenter for
Felkin-Anh control)
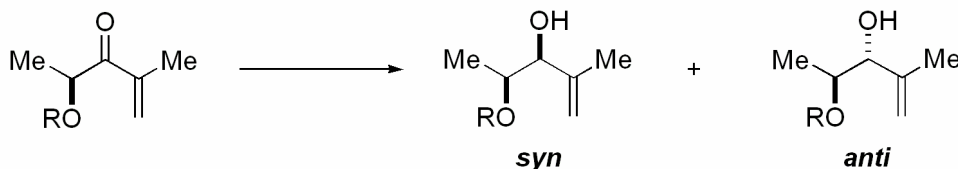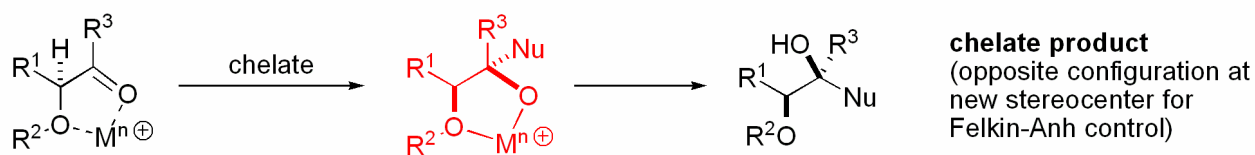
	syn	+	anti

R	reagent	solvent	syn : anti	
CH$_2$OBn	LiAlH$_4$ (-10°C)	THF	30 : 70	
CH$_2$OBn	**LiAlH$_4$ (-10°C)**	**Et$_2$O**	**2 : 98**	**chelate**
SiPh$_2$^{t}Bu	**LiAlH$_4$ (-10°C)**	**THF**	**95 : 5**	**Felkin-Anh**
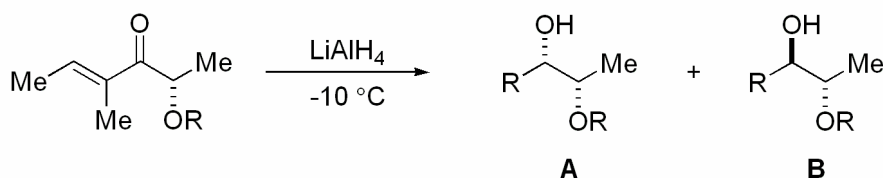
R	solvent	A : B	model
CH$_2$OBn	THF	30 : 70	chelate
CH$_2$OBn	Et$_2$O	2 : 98	chelate
SiPh$_2$^{t}Bu	THF	95 : 5	polar Felkin-Anh

Overman *Tetrahedron Lett.* **1982**, *23*, 2355.
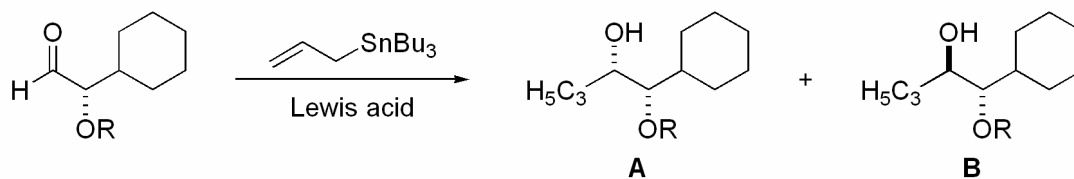
R	Lewis acid	solvent	A : B
CH$_2$OBn	MgBr$_2$	THF (0°)	20 : 80
CH$_2$OBn	MgBr$_2$	CH$_2$Cl$_2$ (-20°)	>250 : 1
CH$_2$OBn	TiCl$_4$	CH$_2$Cl$_2$ (-78°)	>250 : 1
SiPh$_2$^{t}Bu	BF$_3$·Et$_2$O	CH$_2$Cl$_2$ (-78°)	5 : 95

Keck *Tetrahedron Lett.* **1984**, *25*, 265.