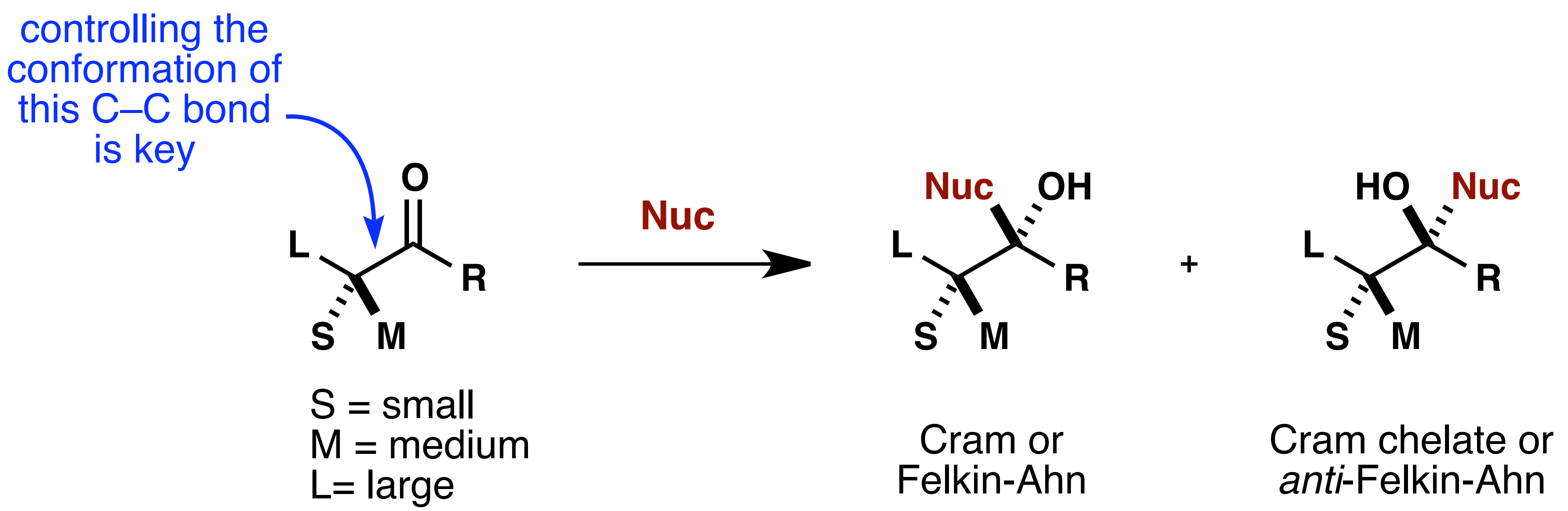
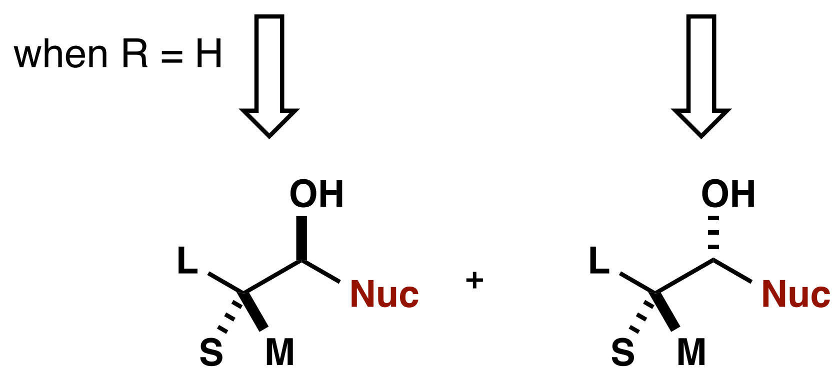
Stereoselectivity Models: α-Chiral Carbonyl Compounds





Reliable models that can be used for predictions and rationaluzations of stereoselective additions of a wide variety of nucleophiles into α-chiral carbonyl compounds.

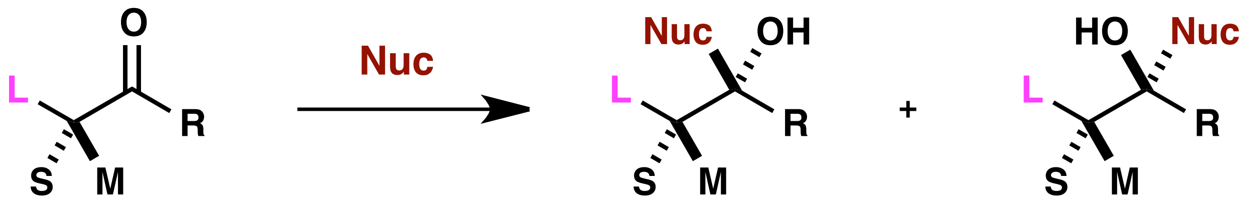
Carreira: Chapter 2.1 – 2.5

Review: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.

1,2-Asymmetric Induction: Cram-Chelate Rule

If the α-carbon has a group that can chelate metals the conformation will be locked. A very reliable model and no amendments have been made to the original proposal.

S = small
M = medium
L= large

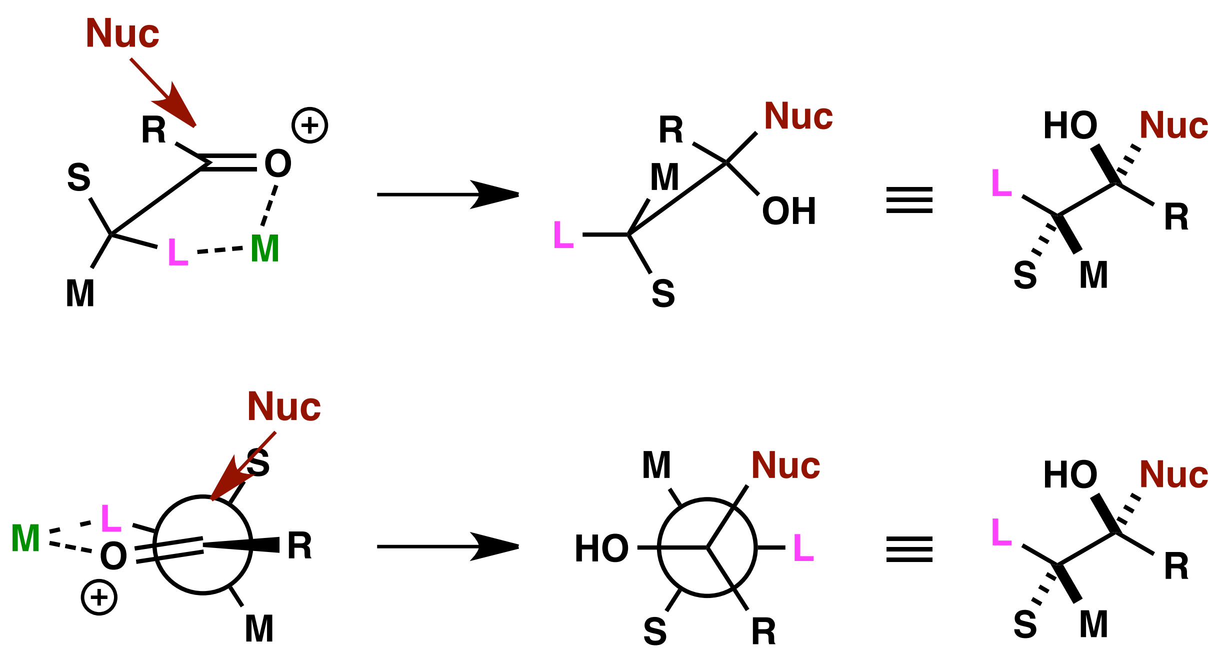


L = OR, NHR, etc.

Minor *Major*

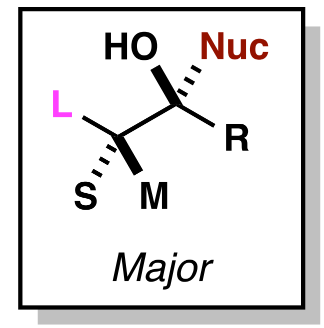
M = metal

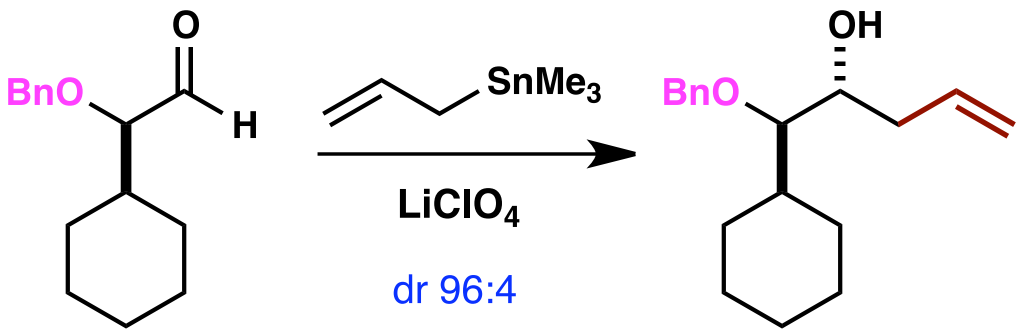
nucleophile approaches on the least sterically hindered face



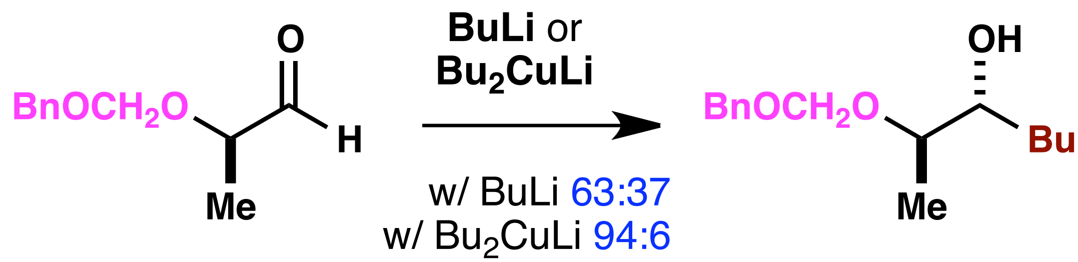
Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 5828.; *J. Am. Chem. Soc.* **1953**, *75*, 6005.; *J. Am. Chem. Soc.* **1963**, *85*, 1245.

Cram-Chelate Rule: Examples

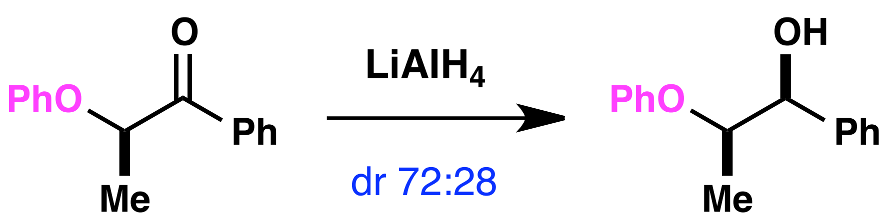




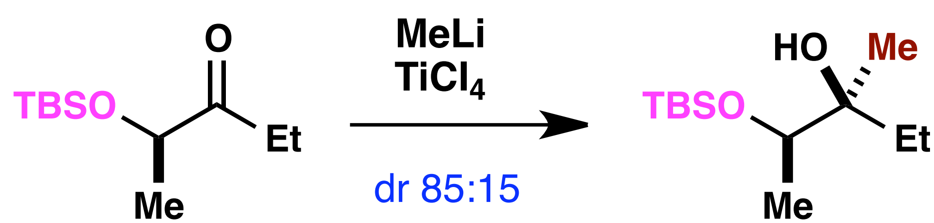
Tetrahedron Lett. **1992**, *33*, 1817.



Tetrahedron Lett. **1980**, *21*, 1035.



Tetrahedron Lett. **1986**, *27*, 3091.

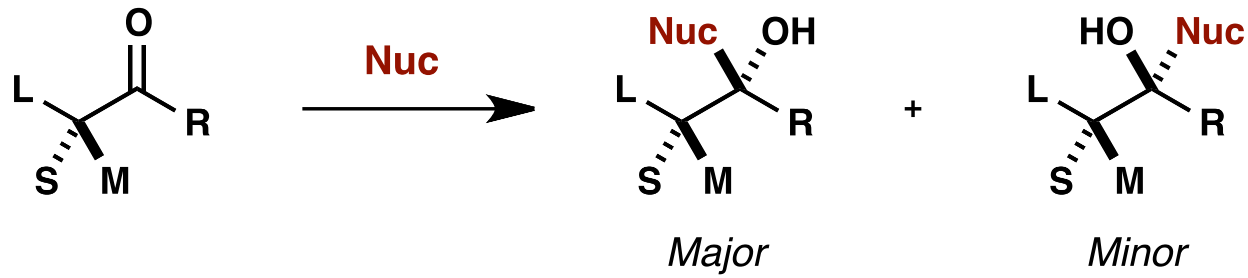


J. Chem. Soc., Chem. Commun. **1986**, 1600.

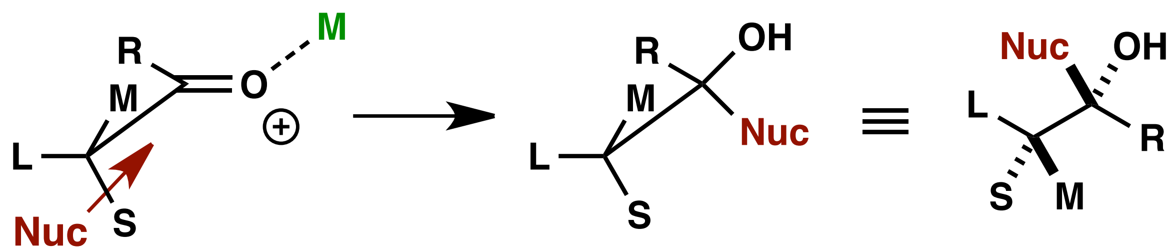
1,2-Asymmetric Induction: Cram Rule

Cram thought that in the absence of a chelating group sterics played the biggest role in limiting the conformation of the α-C–carbonyl bond.

S = small
M = medium
L= large

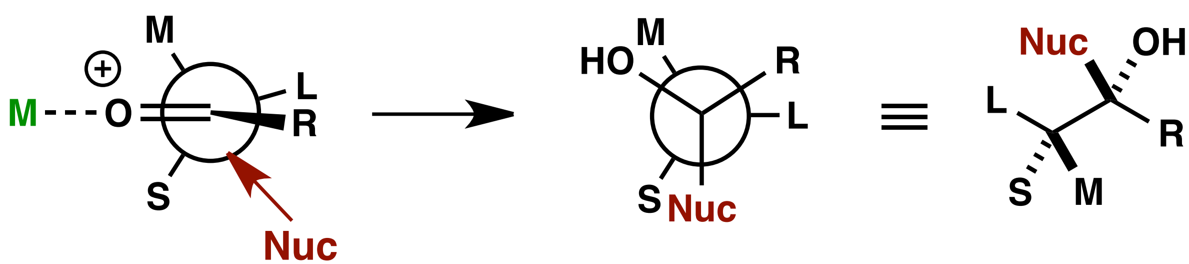


large group oriented *anti* to the carbonyl group



M = metal

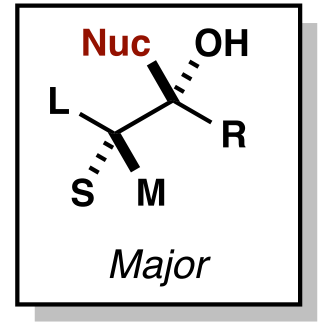
nucleophile approaches on the least sterically hindered face

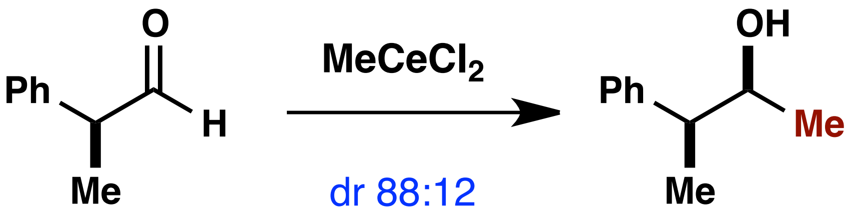


leads to eclipsed conformation

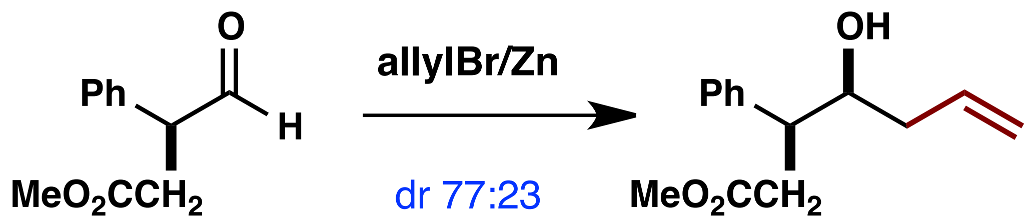
Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 5828.; *J. Am. Chem. Soc.* **1953**, *75*, 6005.; *J. Am. Chem. Soc.* **1963**, *85*, 1245.

Cram-Chelate Rule: Examples

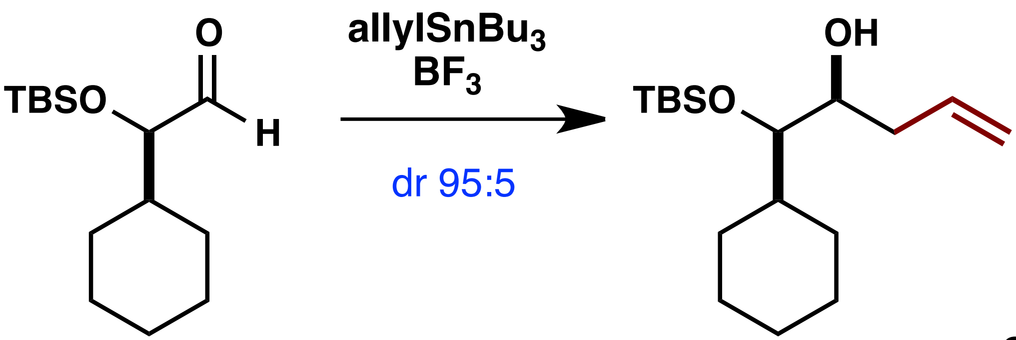




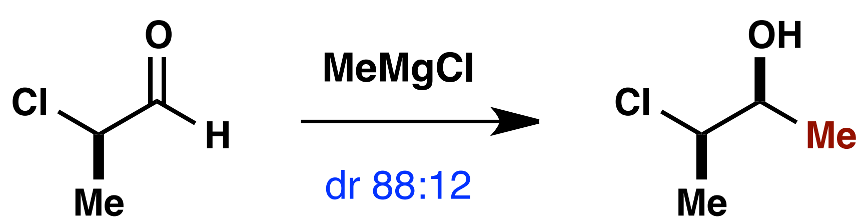
Tetrahedron Lett. **1994**, *35*, 285.



Liebigs Ann. Chem. **1989**, 891.



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

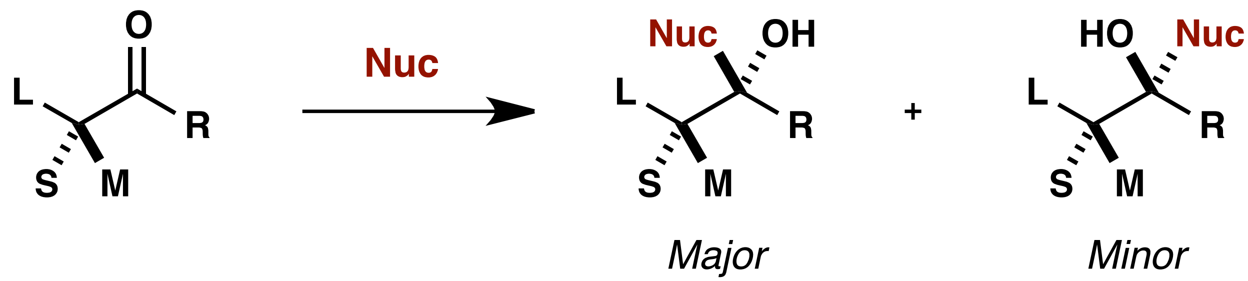


Tetrahedron **1991**, *47*, 9005.

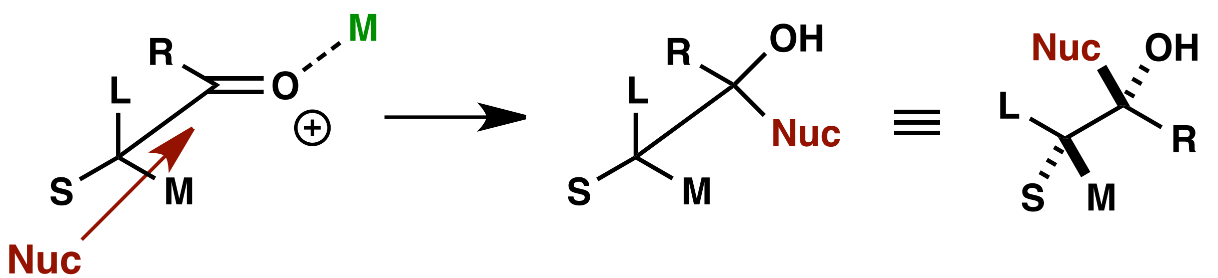
1,2-Asymmetric Induction: Felkin-Ahn Model

The Cram rule is reliable when there are nonpolar groups. If the α-carbon has polar (EWG) groups that are not able to chelate well (e.g., Cl, OTMS) the model breaks down. After contributions by Cornforth, Felkin, Ahn, and Eisenstein a new model emerged.

S = small
M = medium
L= large or EWG



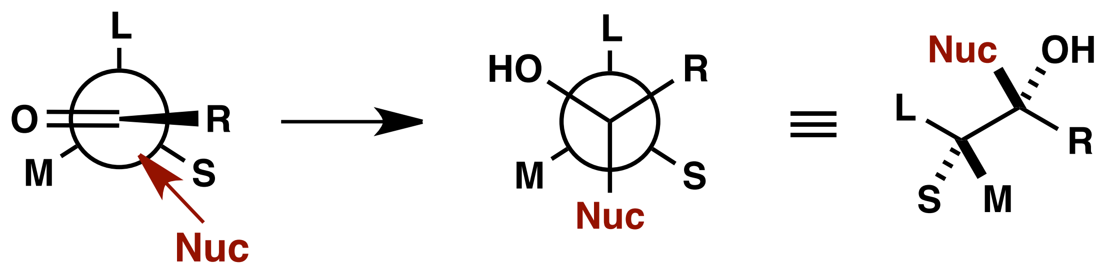
large group is placed orthogonal to the carbonyl, M group on the same side as the carbonyl



Cram & Felkin-Ahn predict the *same* product

M = metal

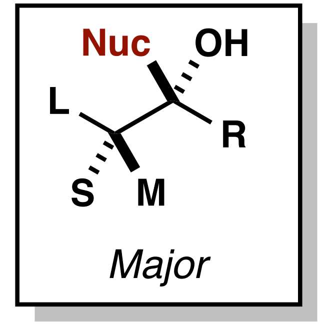
nucleophile approaches on the least sterically hindered face

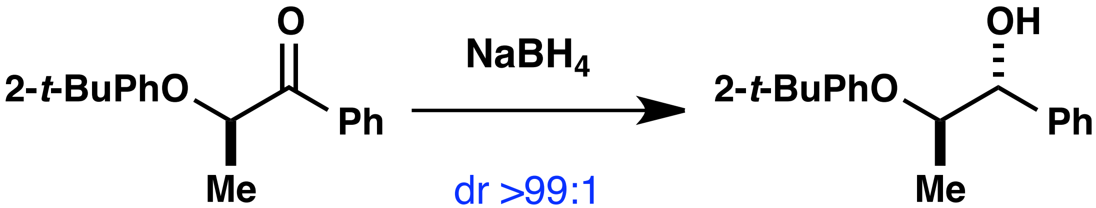


leads to staggered conformation

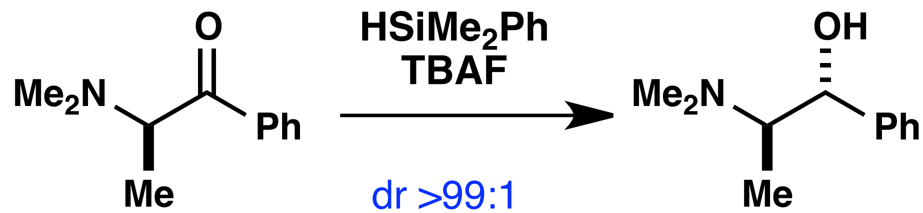
Cornforth, J. W. *J. Chem. Soc.* **1959**, 112.; Felkin, H. *Tetrahedron Lett.* **1968**, 2199.; Ahn, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155.; Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.; Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Felkin-Ahn: Examples

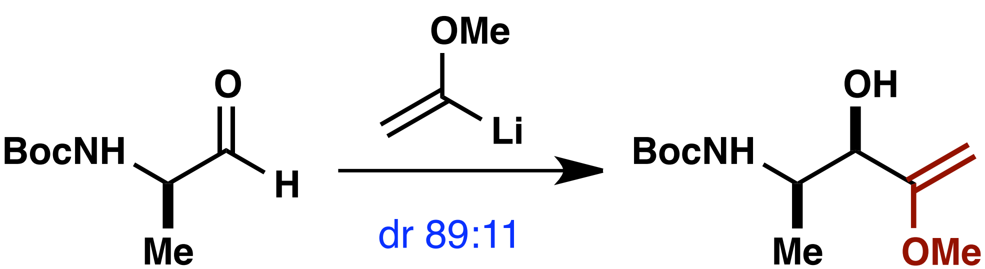




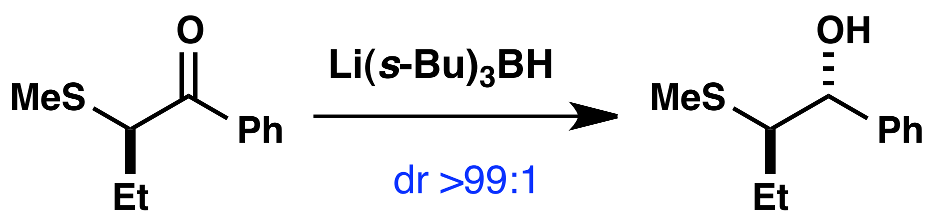
Tetrahedron Lett. **1986**, *27*, 3091.



Tetrahedron **1993**, *49*, 4293.



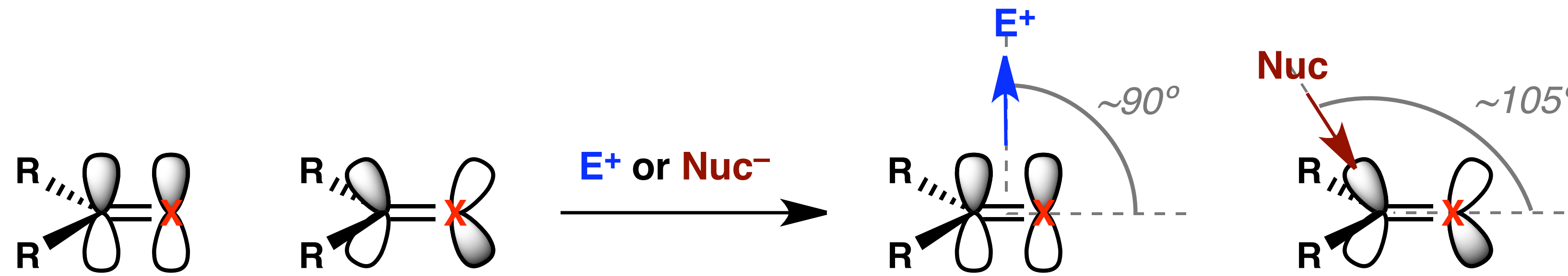
Liebigs Ann. Chem. **1994**, 121.



Tetrahedron Lett. **1984**, *25*, 4775.

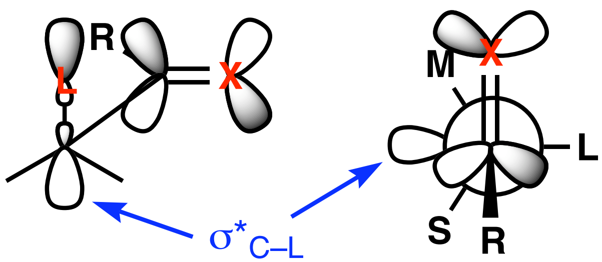
How the Reaction Partner Approaches: Orbital Control

The trajectory of the approach of both nucleophiles and electrophiles to a π-system can be rationalized by considering the orientation of the HOMO or LUMO of the π-system.

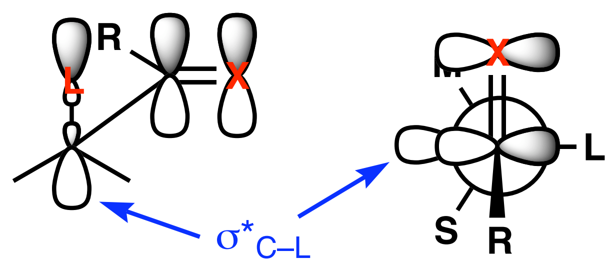


X = O, CH_2 HOMO LUMO **X** = O, CH_2 HOMO LUMO

The Felkin-Ahn model also has an orbital component that helps to explain the observed selectivity. Delocalization of electron density by hyperconjugation between the σ*C–L and the π-system.



Felkin models
with C=X LUMO



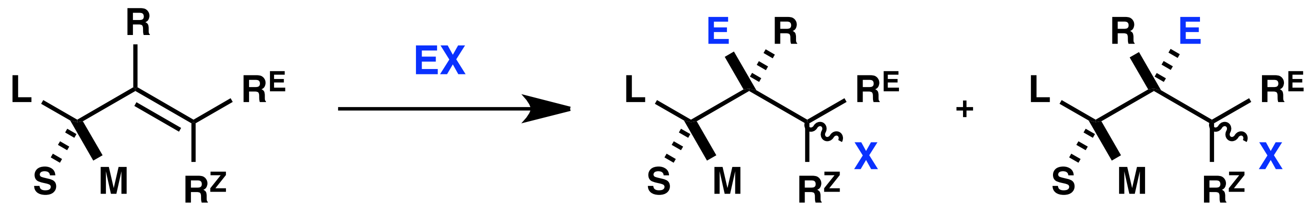
Felkin models
with C=X HOMO

Bürgi, H. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 5065; Bürgi, H. B.; Dunitz, J. D. *Tetrahedron* **1974**, *30*, 1563; Ahn, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155.; Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.; Ahn, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Addition to α-Chiral C–C Double Bonds

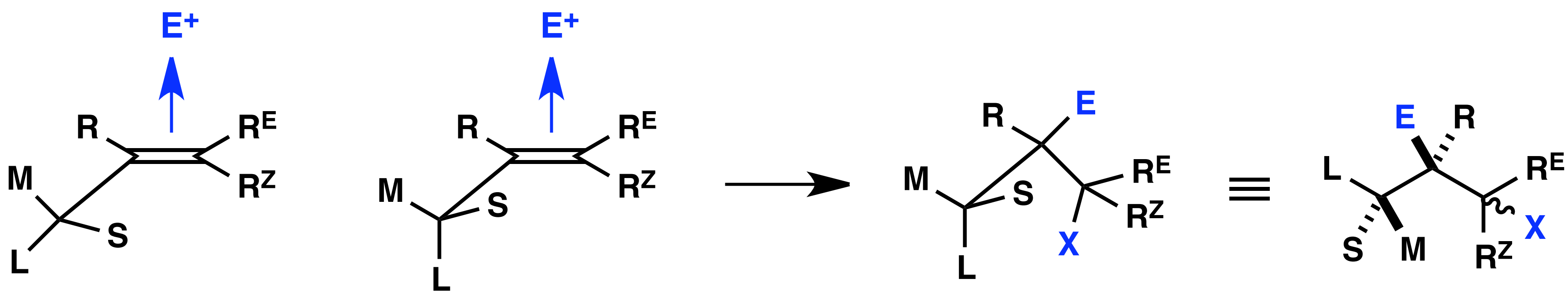
Two models can be used to explain the selectivity observed when electrophiles are added to α-chiral (allylic) C–C double bonds. Both give the same product.

S = small
M = medium
L= large or EDG



Major
(*anti*-Felkin)

Minor

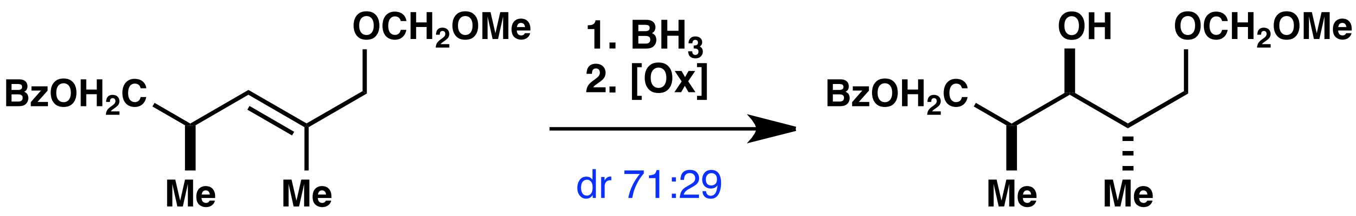


1,3-allylic strain model

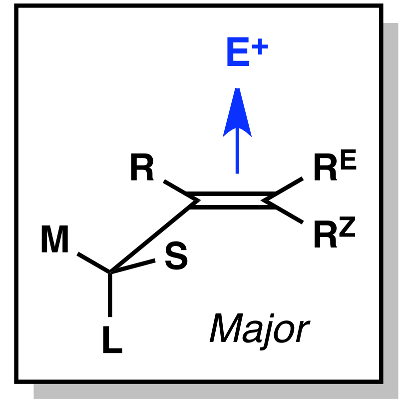
Houk model
S group is oriented on the same side as the electrophile (*anti*-Felkin)

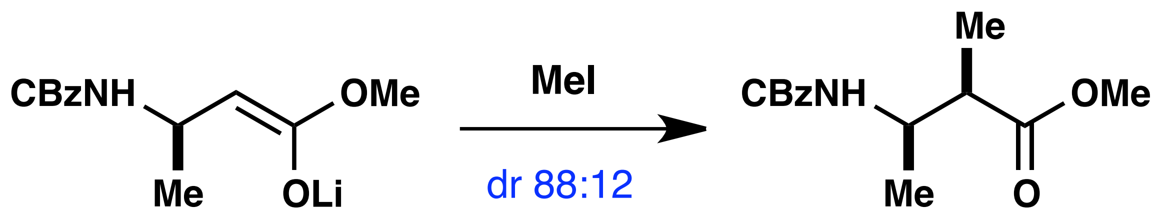
Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

Chiral Allylic: Examples

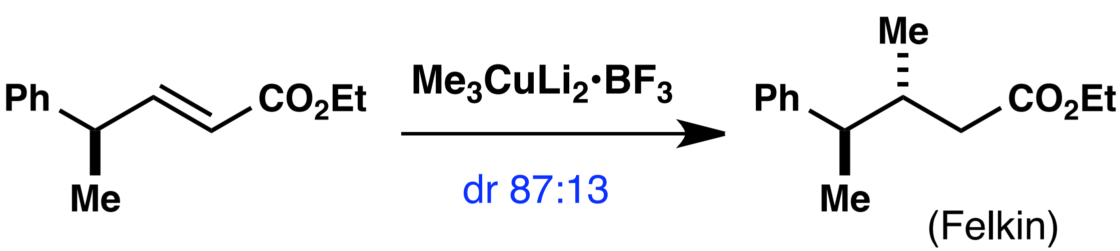


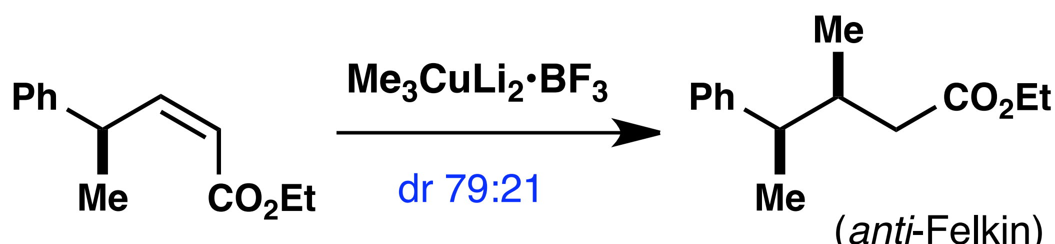
Tetrahedron **1984**, *40*, 2257. (*anti*-Felkin)





Helv. Chem. Acta **1988**, *71*, 1824. (*anti*-Felkin)



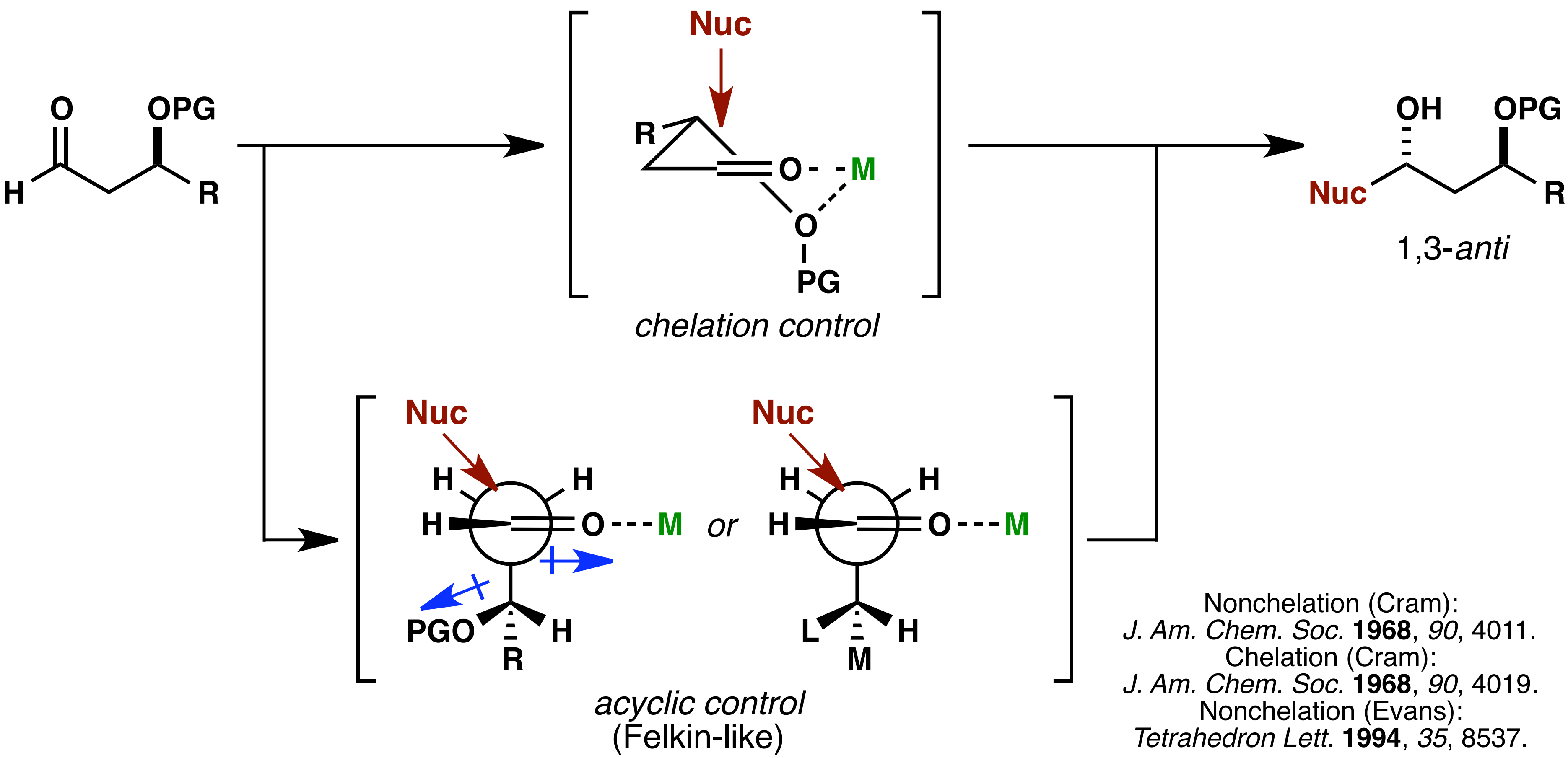


J. Chem. Soc., Chem. Commun. **1987**, 1572.

1,3-Asymmetric Induction

Stereogenic β-carbons can also exert an influence during nucleophilic additions to carbonyls. High selectivities are typically only observed with electronegative atoms on the β-carbon.

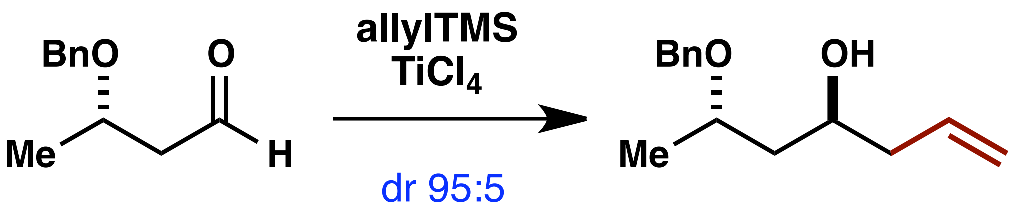
Two models have been proposed. One involves chelation. The other involves dipole minimization. *Both lead to the same outcome.* This is in contrast to the Cram chelation and Felkin-Ahn models.

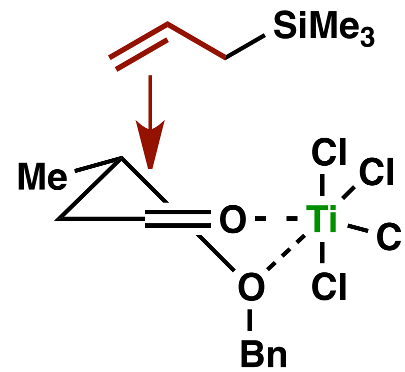


Nonchelation (Cram):
J. Am. Chem. Soc. **1968**, *90*, 4011.
Chelation (Cram):
J. Am. Chem. Soc. **1968**, *90*, 4019.
Nonchelation (Evans):
Tetrahedron Lett. **1994**, *35*, 8537.

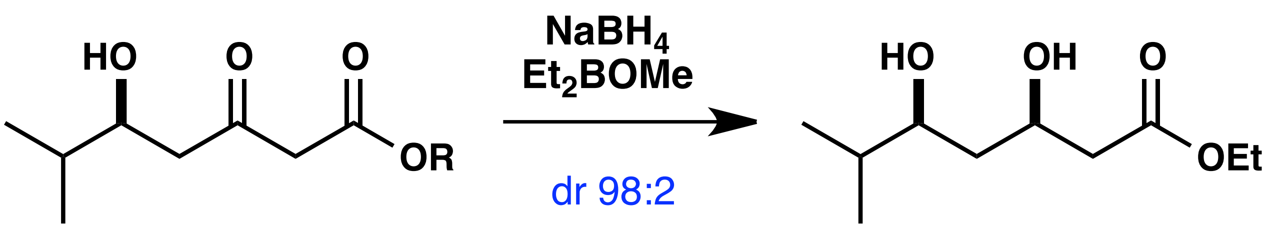
Chelation control requires two adjacent vacant coordination sites at the metal center *and* a protecting group that enables complexation with the Lewis acid.

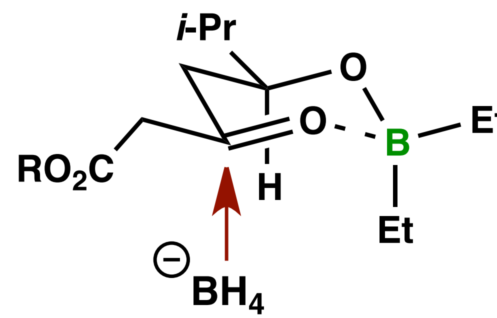
1,3-Asymmetric Induction: Examples



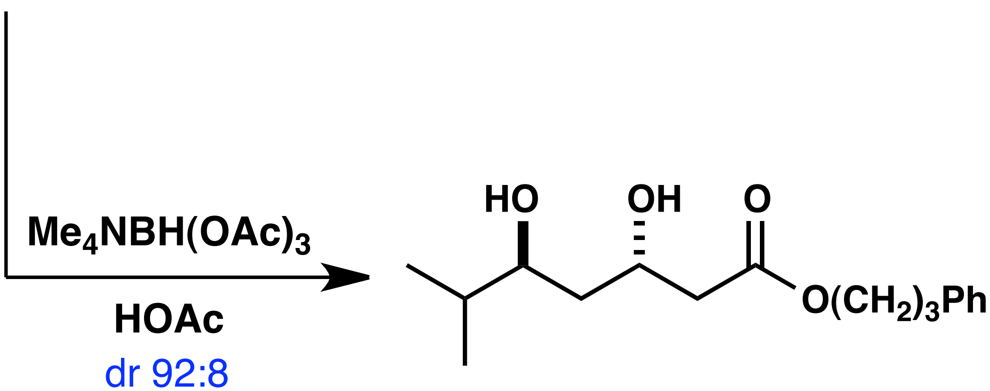


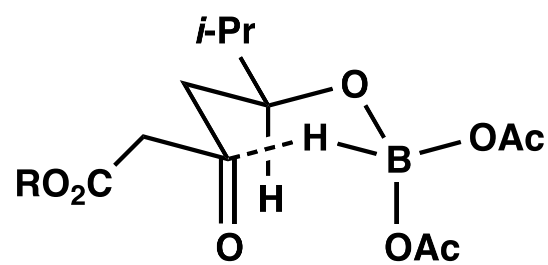
J. Am. Chem. Soc. **1983**, *105*, 4833.





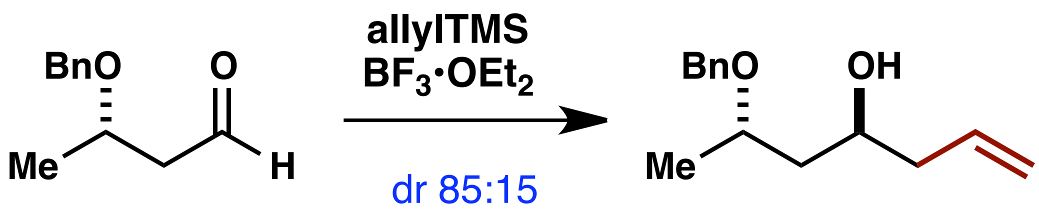
Tetrahedron Lett. **1987**, *28*, 155.

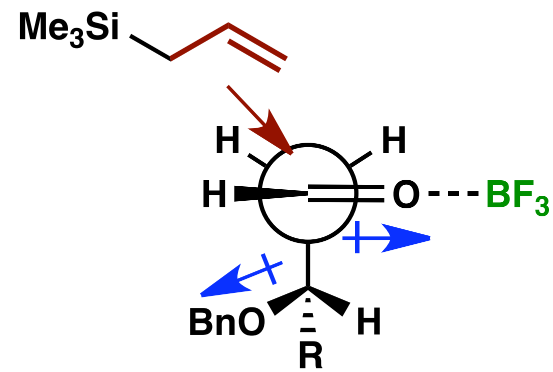




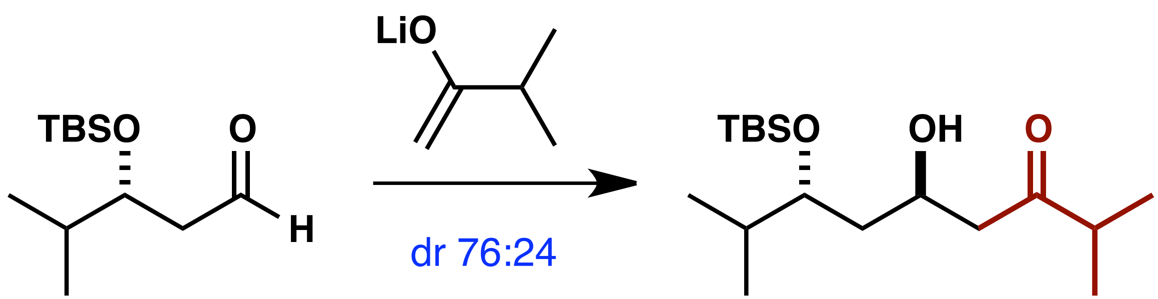
J. Am. Chem. Soc. **1988**, *110*, 3560.

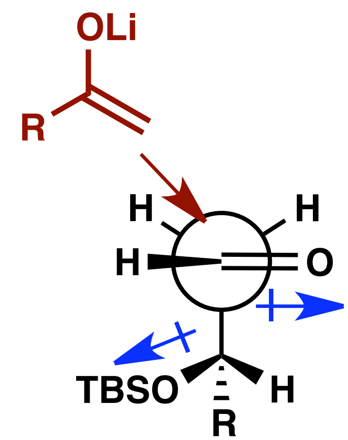
1,3-Asymmetric Induction: Examples





Tetrahedron Lett. **1984**, *25*, 729.



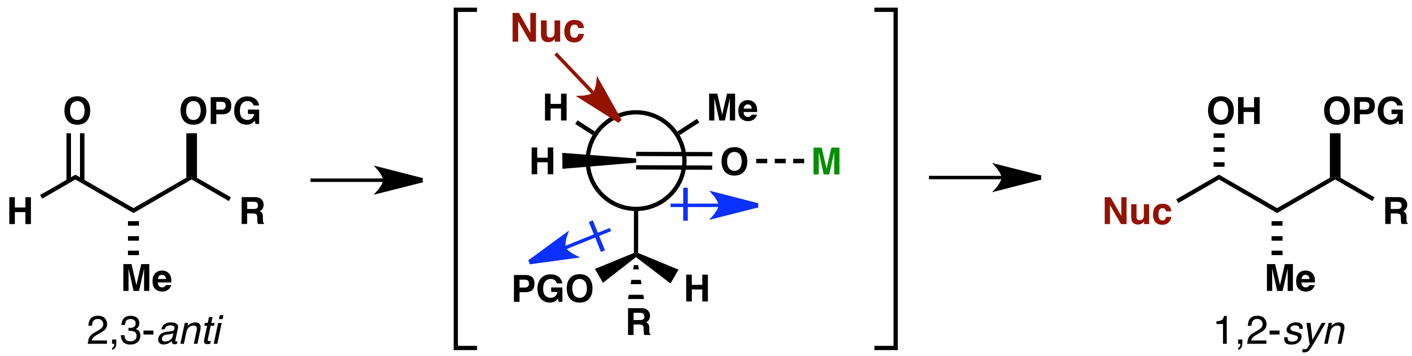


Tetrahedron Lett. **1994**, *35*, 8537.

1,3-Asymmetric Induction

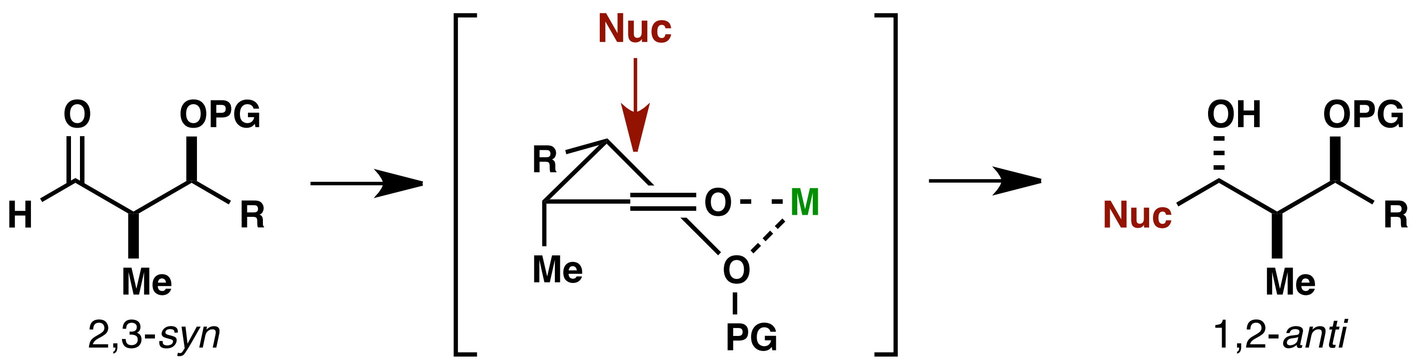
The situation is more complicated when both Cα and Cβ are stereogenic.

2,3-*anti*: stereocenters are reinforcing under nonchelating conditions; chelating conditions lead to opposing influences and are less predictable



acyclic control
(Felkin-like)

2,3-*syn*: stereocenters are reinforcing under chelating conditions; nonchelating conditions lead to opposing influences and are less predictable

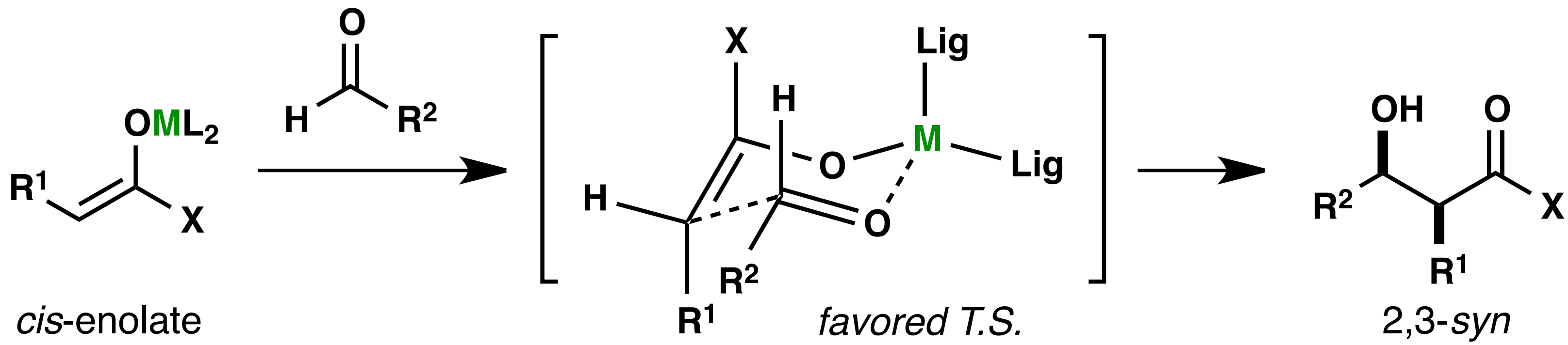


chelation control

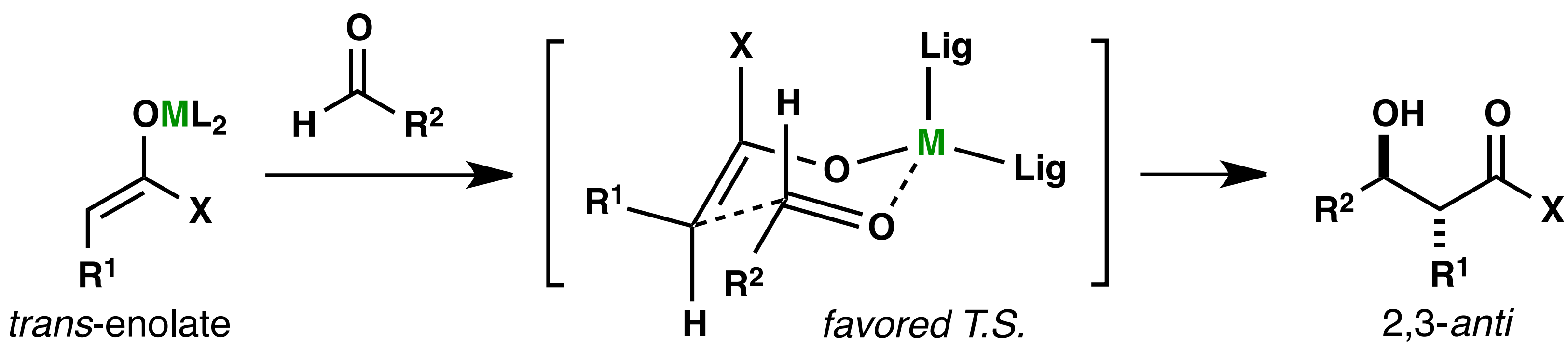
Notice that in both cases a 1,3-*anti* "diol" is produced

Closed Transition States: Zimmerman-Traxler

Closed transition state: both nucleophile and electrophile are joined by a metal or Lewis acid promoter. Commonly used in aldol reactions. Useful in many other reactions as well.



X = OR, SR, alkyl
M = Li, B, Ti, Sn, etc.



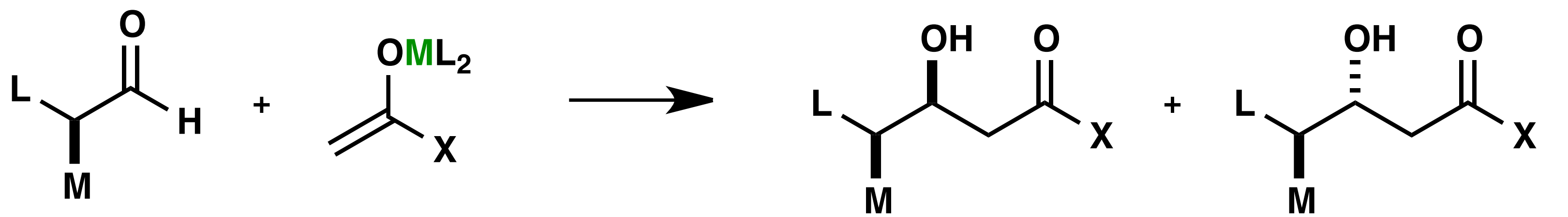
The diastereoselectivity at the 2- and 3-position is controlled by the configuration of the starting enolate.

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

Carreira: Ch. 4.1 – 4.3

Closed Transition States: Zimmerman-Traxler + Felkin

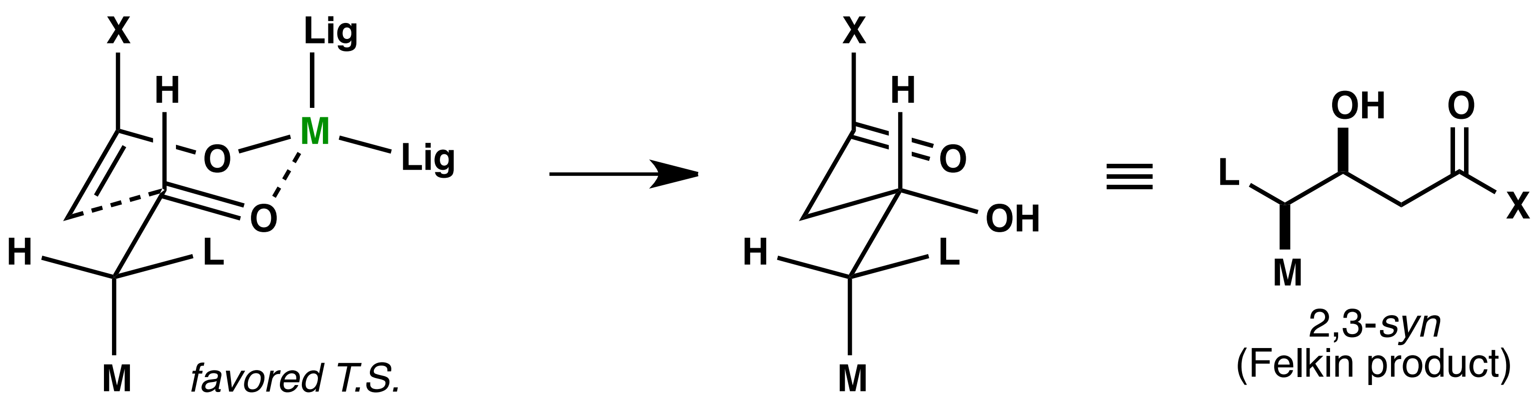
When α-chiral aldehydes are used, the Zimmerman-Traxler transition state must be used in concert with the Felkin model. The Felkin model only contributes to the facial selectivity of the electrophile. The selectivity is often not great, but the identity of the major diastereomer can be predicted.



unsubstituted enolate

3,4-*syn* (Felkin product) *Major*

3,4-*anti* (*anti*-Felkin product) *Minor*

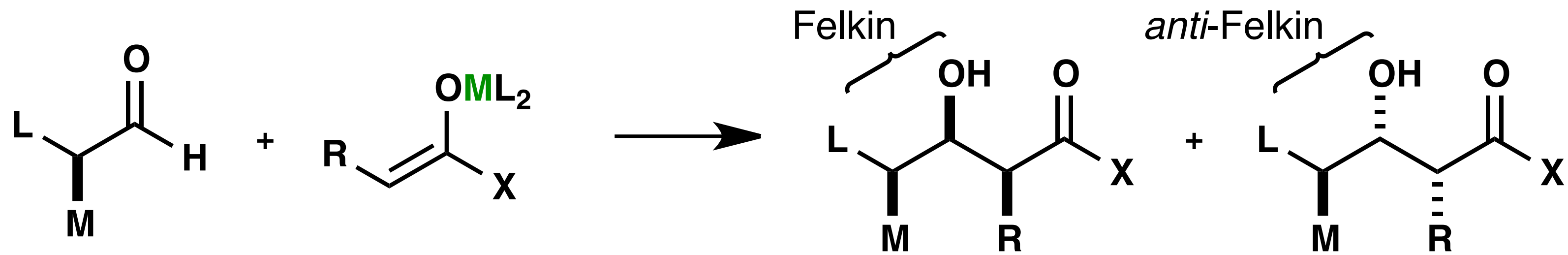


favored T.S.

2,3-*syn* (Felkin product)

Closed Transition States: Zimmerman-Traxler + Felkin

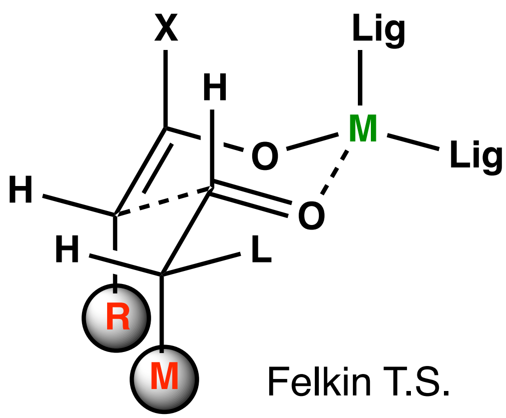
When α-chiral aldehydes are used, the Zimmerman-Traxler transition state must be used in concert with the Felkin model. The Felkin model only contributes to the facial selectivity of the electrophile. The selectivity is often not great, but the identity of the major diastereomer can be predicted.



cis-enolate

syn, syn
Minor

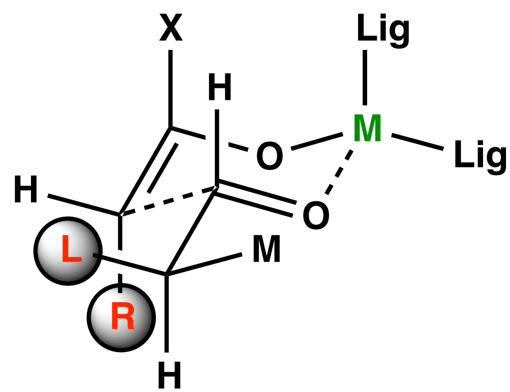
2,3-*syn*-3,4-*anti*
Major



Felkin T.S.

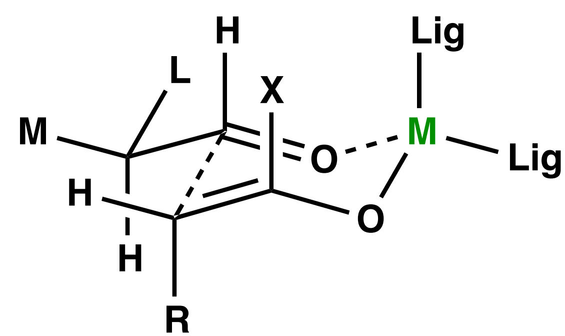
⇩

syn, syn



⇩

syn, syn



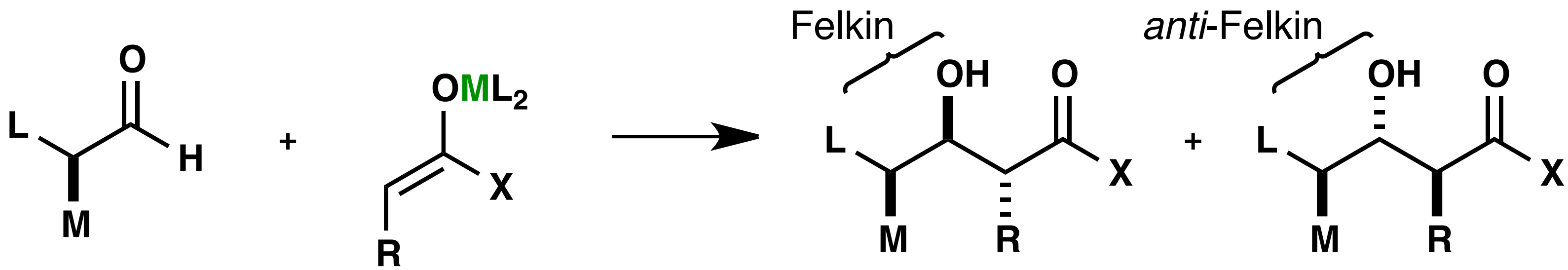
anti-Felkin T.S.

⇩

syn, anti

Closed Transition States: Zimmerman-Traxler + Felkin

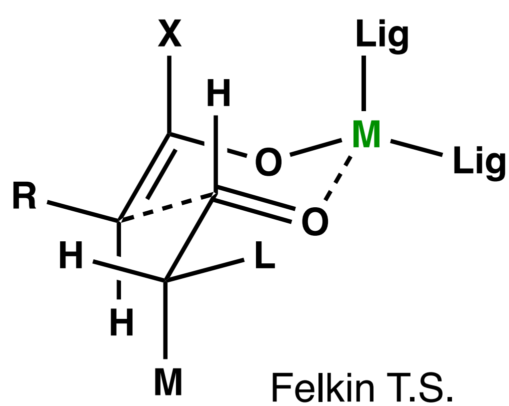
When α-chiral aldehydes are used, the Zimmerman-Traxler transition state must be used in concert with the Felkin model. The Felkin model only contributes to the facial selectivity of the electrophile. The selectivity is often not great, but the identity of the major diastereomer can be predicted.



trans-enolate

2,3-*anti*-3,4-*syn*
Major

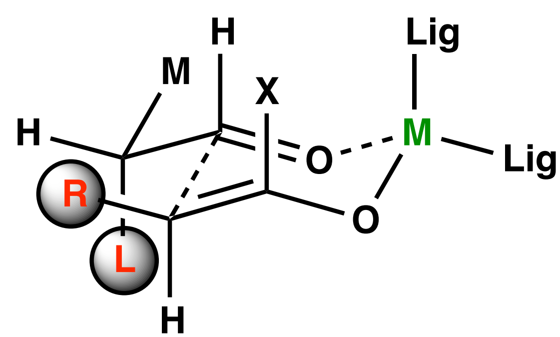
anti, *anti*
Major



Felkin T.S.

⇩

anti, *syn*

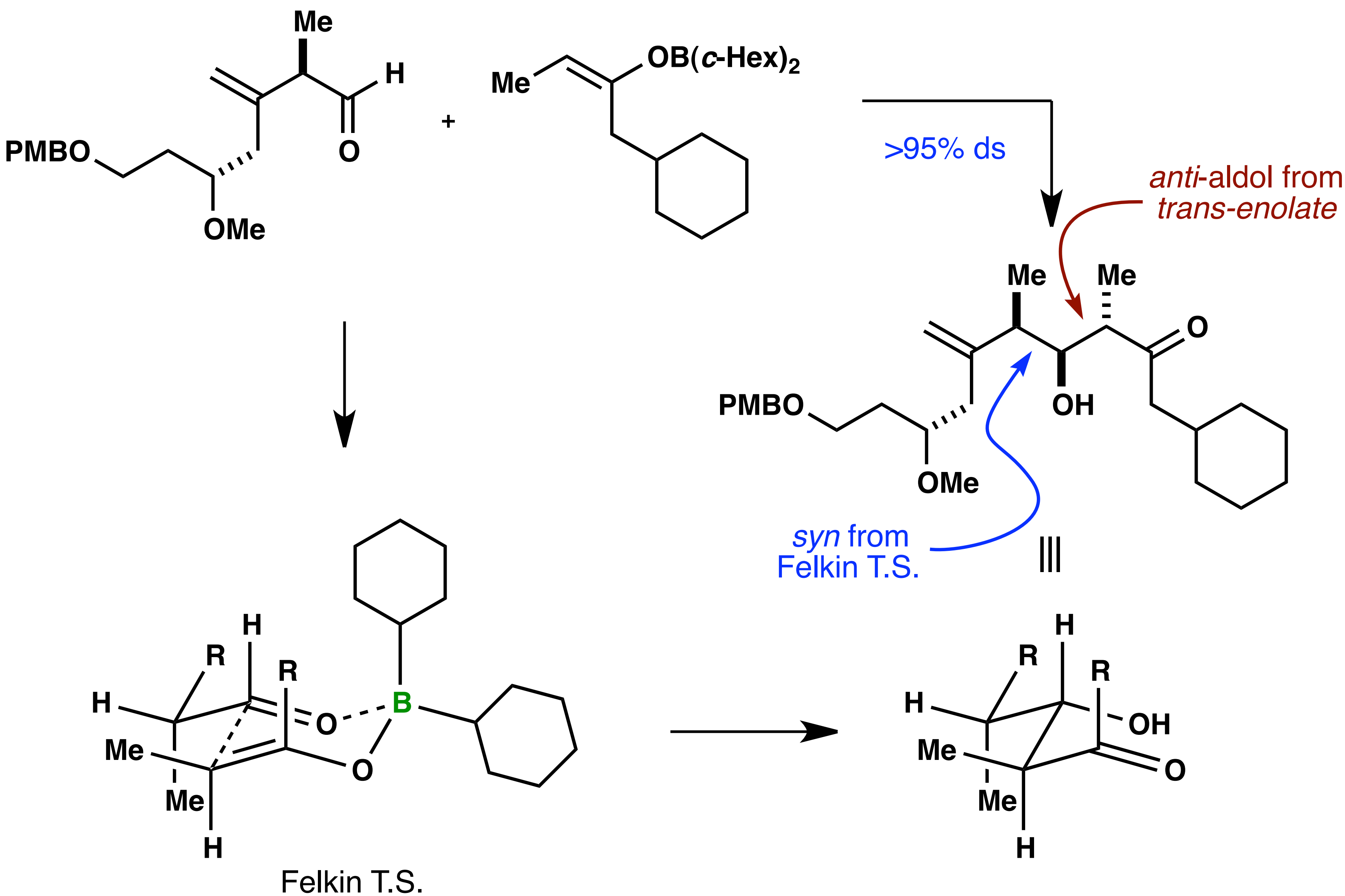


anti-Felkin T.S.

⇩

anti, *anti*

Zimmerman-Traxler + Felkin: Example



Tetrahedron Lett. **1997**, *38*, 8241.