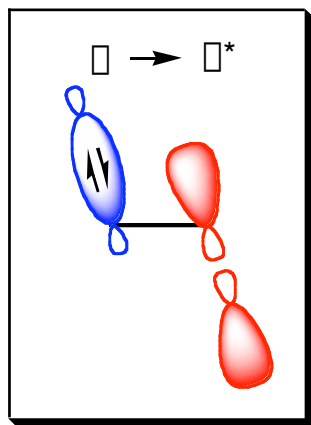


# Hyperconjugation



Alan B. Northrup

MacMillan Group Meeting

September 17, 2003

## Review of the Basics:

Kirby, A.J. "Stereochemical Effects," in *Oxford Chemistry Primers*, New York, 1996, Vol. 36, pp. 3-33.

## A semi-quantitative approach to frontier orbital size and application to pericyclic reactions:

Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley; New York, 1998.

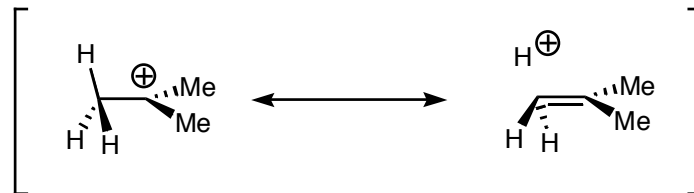
## Anomeric Effect in Detail:

Kirby, A.J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer-Verlag; New York, 1983.

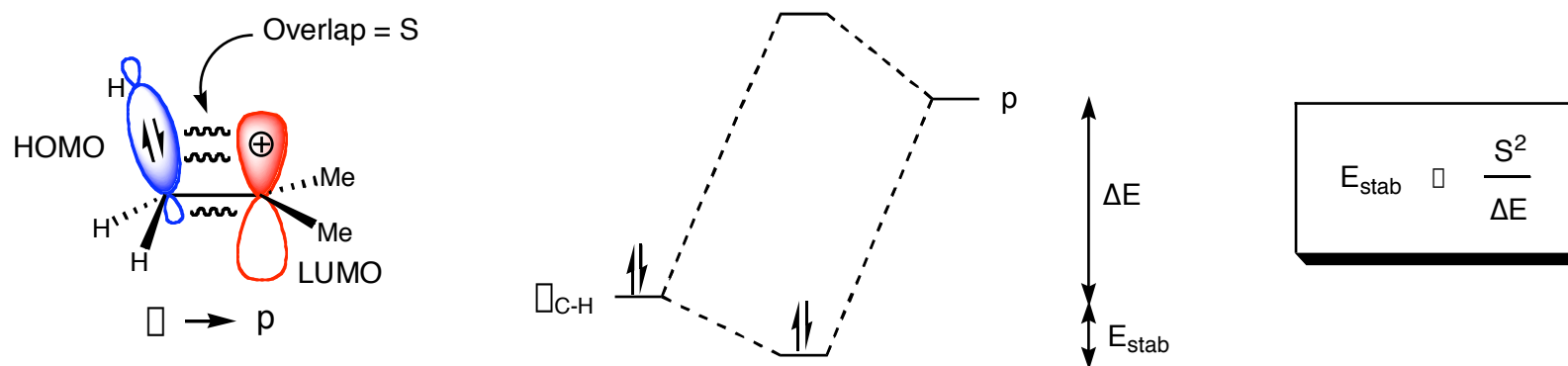
Graczyk, P.P.; Mikolajczyk, M. "Anomeric Effect: Origin and Consequences," in *Topics in Stereochemistry*, 1994, Vol. 21, p 159.

## What is Hyperconjugation?

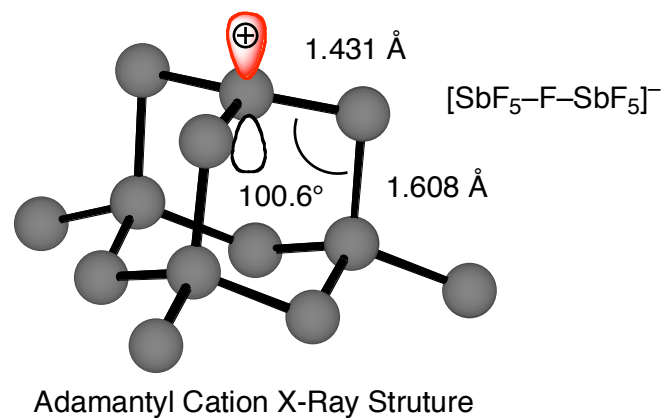
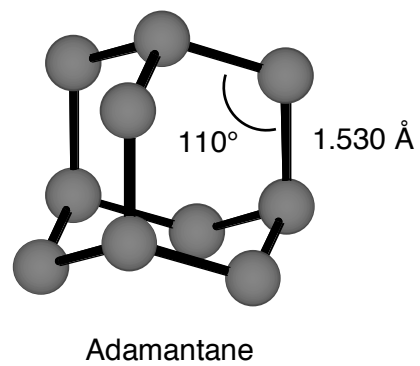
### ■ A Resonance View:



### ■ Frontier Molecular Orbital Depiction:

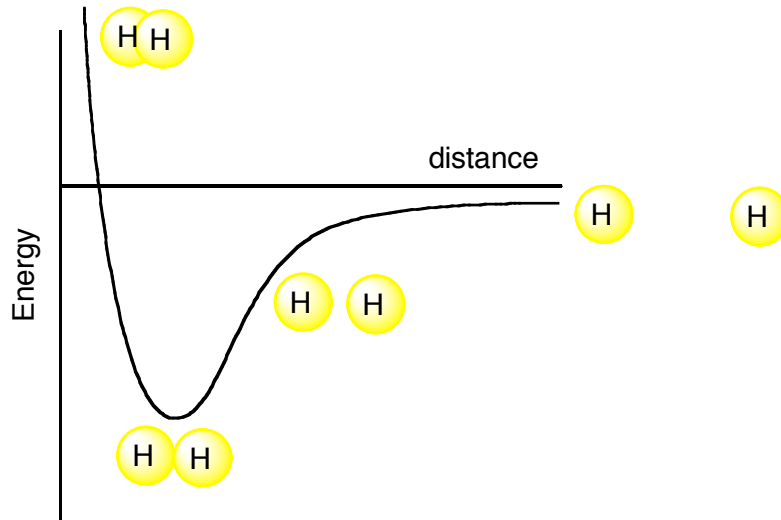


### ■ Physical Evidence for Hyperconjugation's Existence:



# Why is Hyperconjugation Stabilizing?

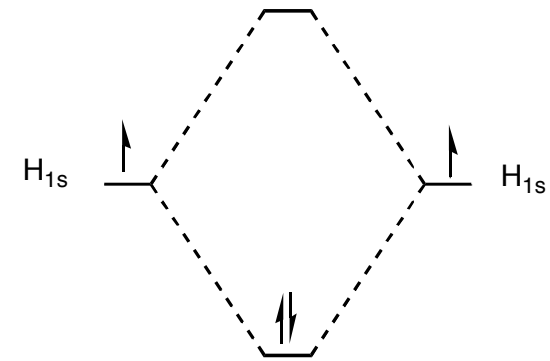
## Remember the H<sub>2</sub> Molecule:



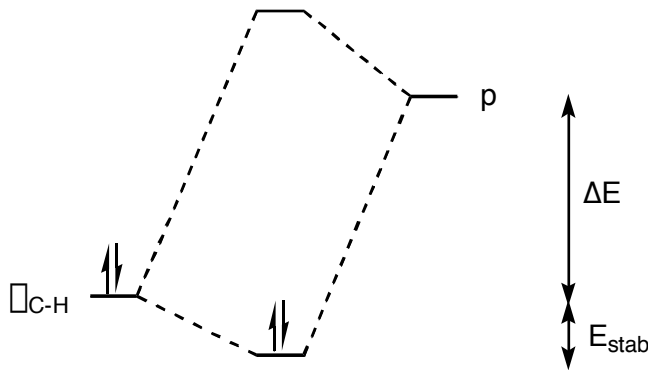
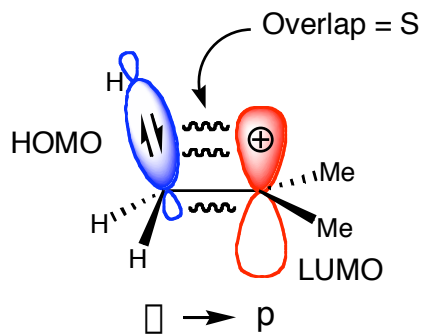
### One Central Postulate of FMO Theory

*Stabilization of the highest energy electrons stabilizes the entire system*

### The FMO View:



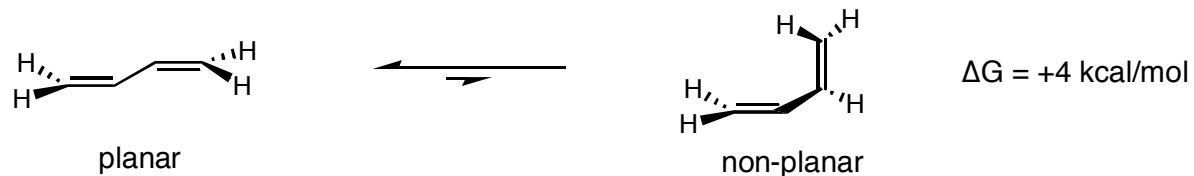
## Hyperconjugation Revisited:



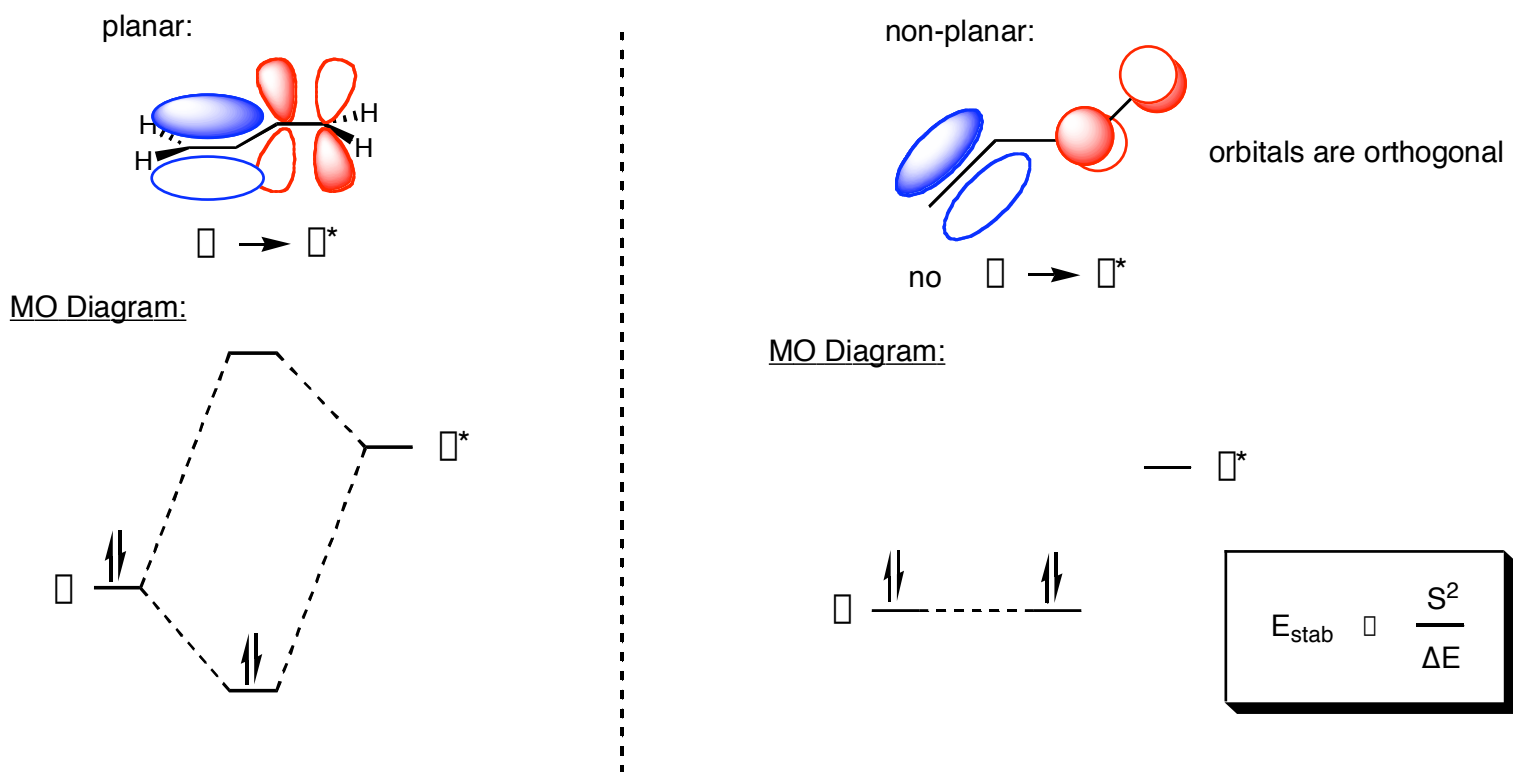
$$E_{\text{stab}} \propto \frac{S^2}{\Delta E}$$

## Conjugation vs. Hyperconjugation

- Butadiene shows a strong preference for planarity



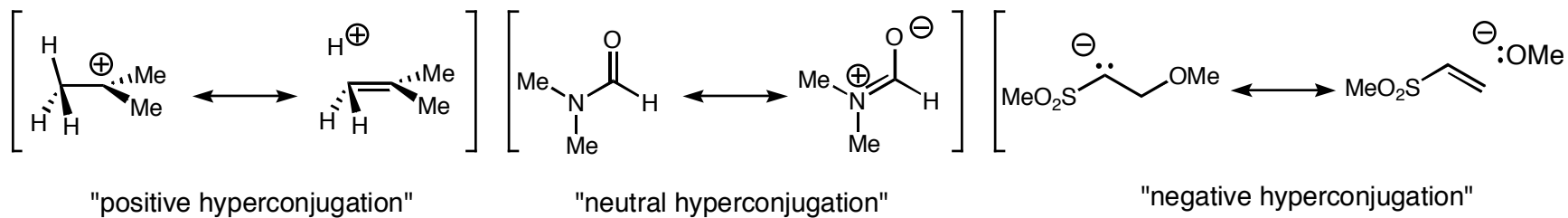
- Sterics alone cannot account for this large conformational bias



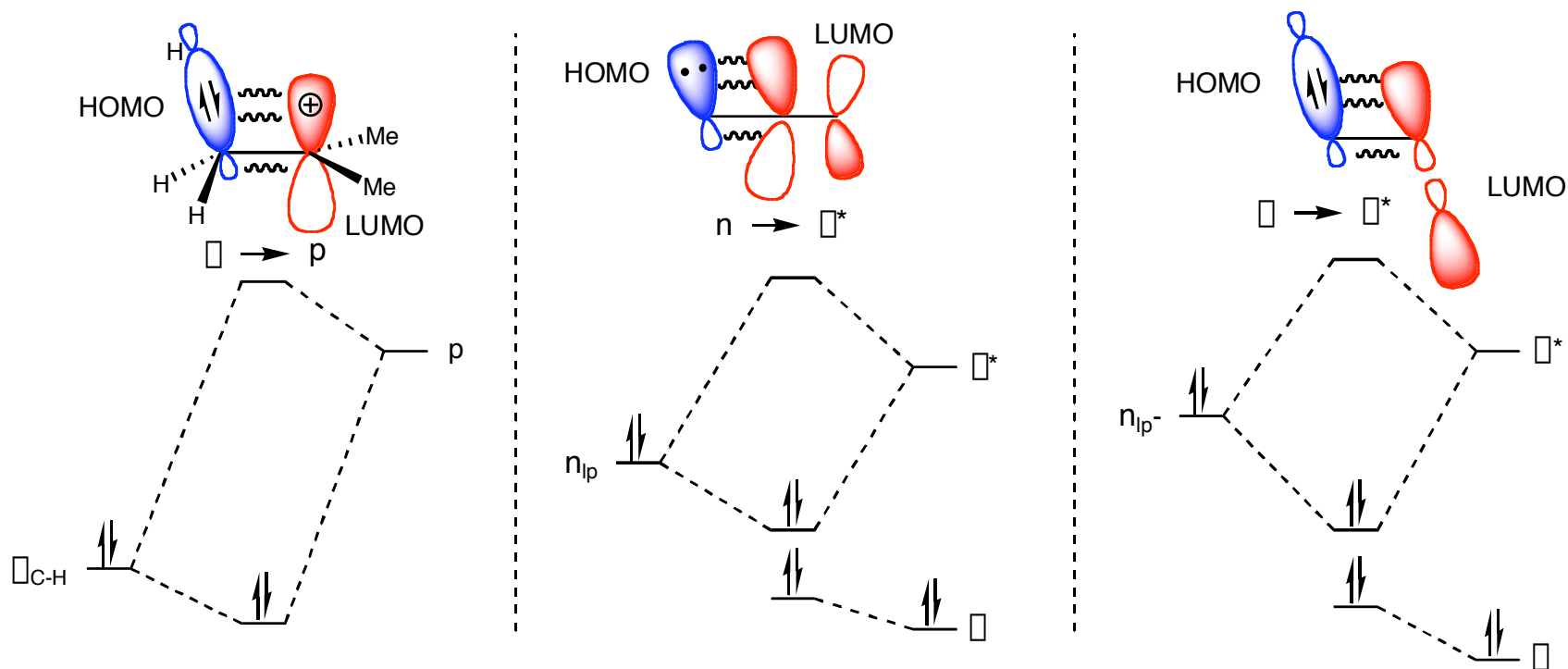
- Conjugation and Hyperconjugation are essentially the same phenomenon

## Positive, Neutral and Negative Hyperconjugation

- The literature is full of different descriptors for hyperconjugation



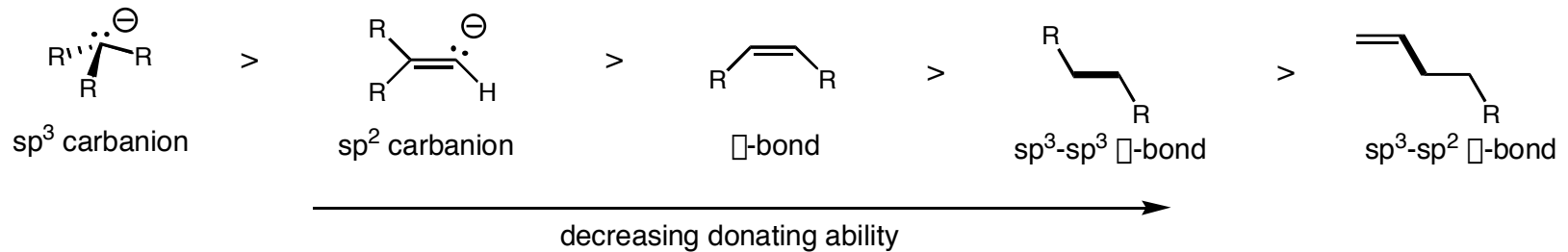
- Slight, but significant differences in MO diagrams



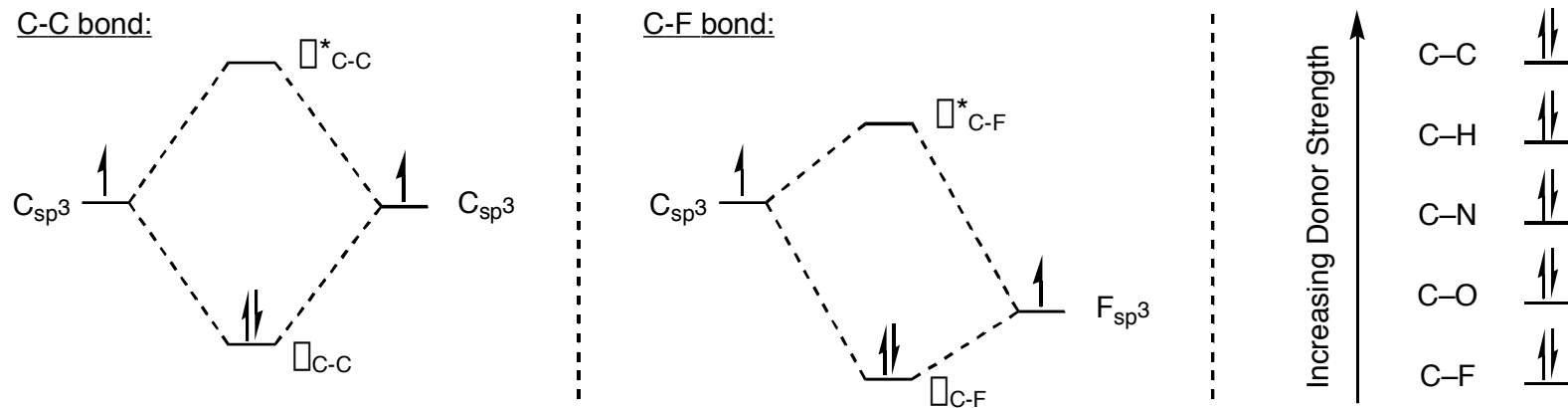
- "Hyperconjugation" will be used to refer to any of the above

## Ranking Electron-Donating Ability

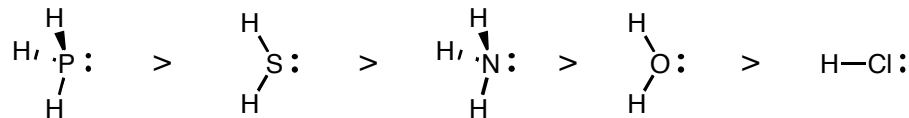
- Energies from PES provide a somewhat intuitive order for e- pairs on the same atom:



- C-X bonds, where X is electronegative lower both  $\sigma$  and  $\sigma^*$  orbitals, making them worse donors

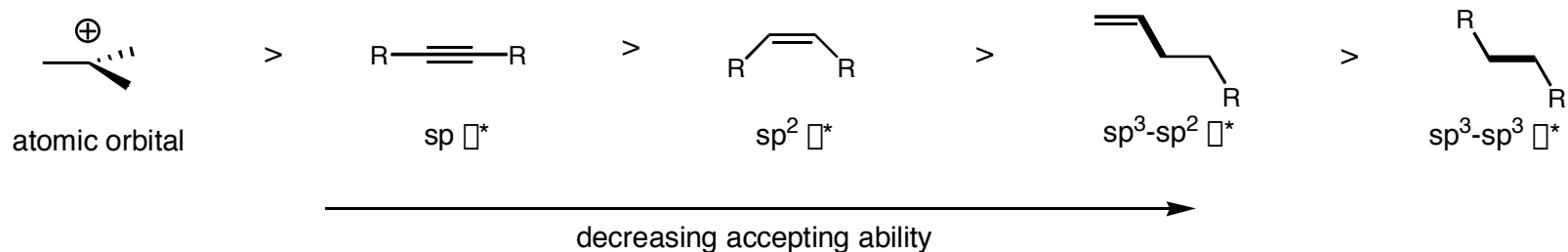


- Lone pair energies follow a similar trend

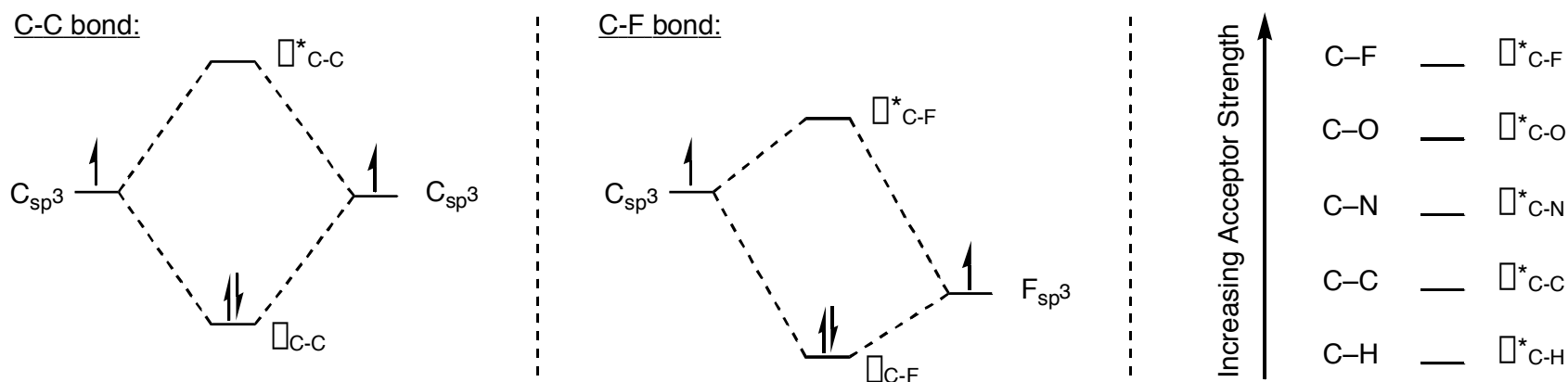


## Ranking Electron-Accepting Ability

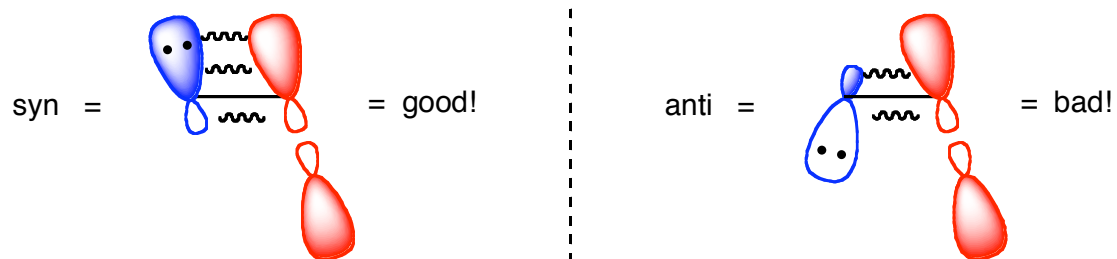
- Lower-lying LUMOs are better able to accept electron density



- C-X bonds, where X is electronegative lower both  $\sigma$  and  $\sigma^*$  orbitals, making them better acceptors

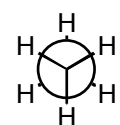


- A brief note on overlap:

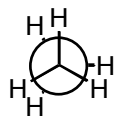


## Conformational Effects of Hyperconjugation: Single Bonds

### Staggered vs. Eclipsed Ethane Conformers



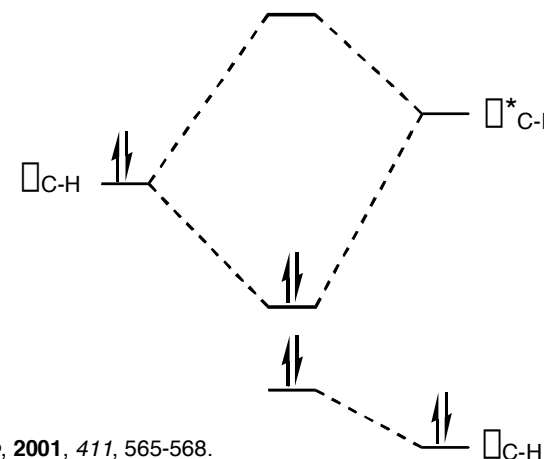
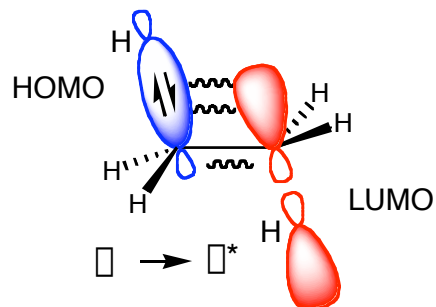
Staggered



Eclipsed

$$\Delta G = +3 \text{ kcal/mol}$$

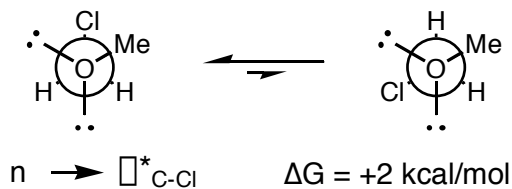
therefore, each interaction  $\approx 1 \text{ kcal/mol}$



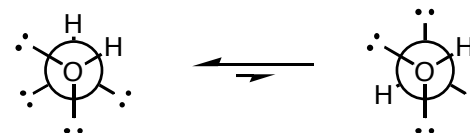
Pophristic, V.; Goodman, L. "Hyperconjugation not steric repulsion leads to the staggered structure of ethane." *Nature*, **2001**, 411, 565-568.  
See also: *Angew. Chem. Int Ed.* **2003**, 4183-4194 for one paper against and one paper for the above explanation

### The Gauche Effect

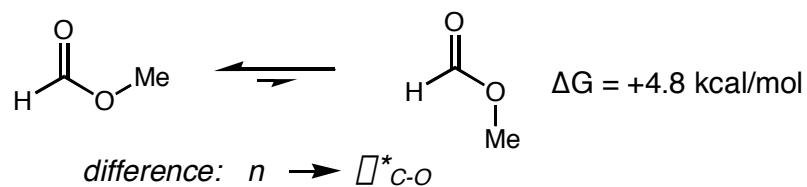
Example: MOM-Cl



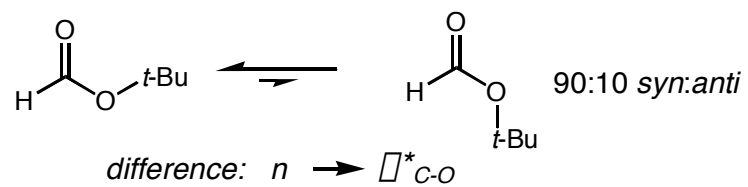
Example:  $\text{H}_2\text{O}_2$



### Conformational Preferences of Esters



Blom, Gunthard *Chem. Phys. Lett.* **1981**, 84, 267

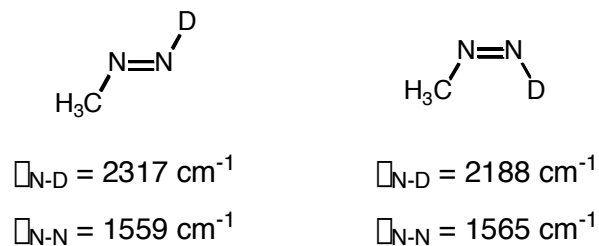


Oki, M.; Nakanishi, H *Bull. Chem. Soc. Jpn.* **1970**, 43, 2558

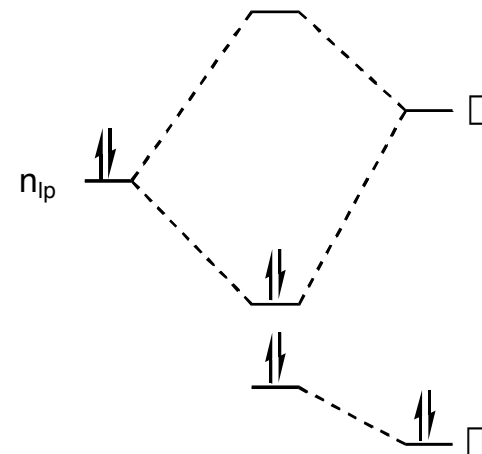
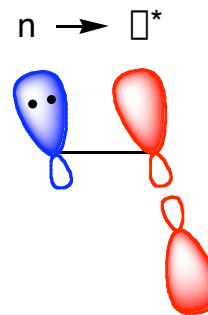


## Structural Effects of Hyperconjugation: Double Bonds

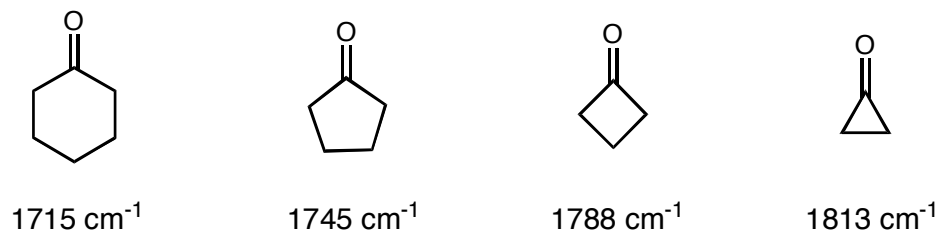
### IR Stretching Frequencies can Indicate the Degree of Hyperconjugation



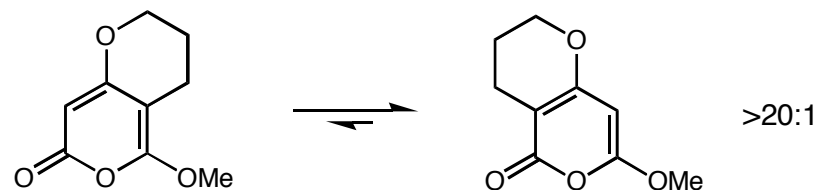
Craig, N. C., et al. *J. Am. Chem. Soc.* **1979**, *101*, 2408



### The Following can be Rationalized with Hyperconjugation



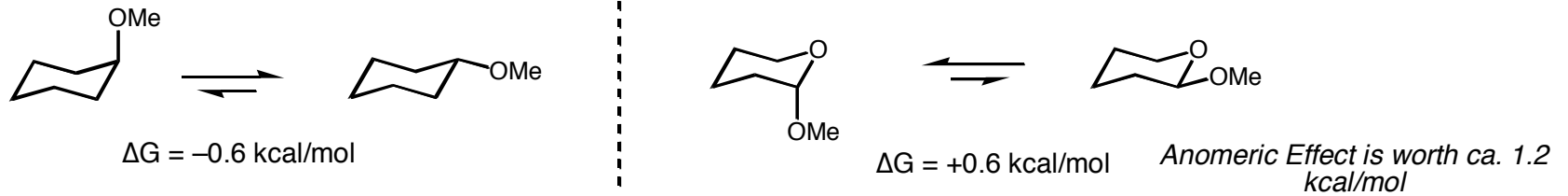
### Position of this Equilibrium Determined by an $n \rightarrow \pi^*$ Hyperconjugative Interaction



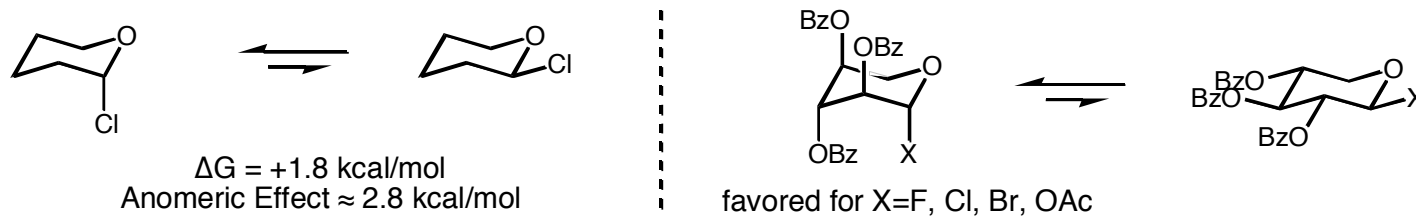
Vankataman, H; Cha, J.K. *Tet. Lett.* **1989**, *30*, 3509

# The Anomeric Effect: What is it?

- Anomeric Effect refers to the tendency of anomeric substituents to prefer an axial configuration

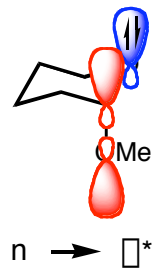


- Electron-Withdrawing Groups Increase the Magnitude of the Anomeric Effect

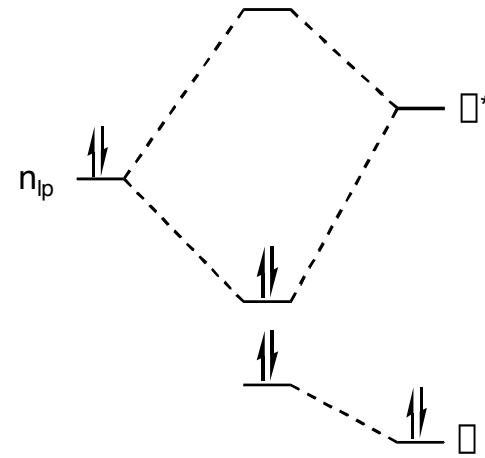
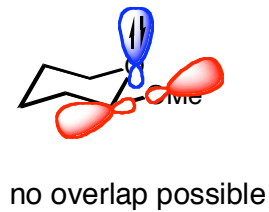


- Hyperconjugation Explains this Effect:

axial anomer:

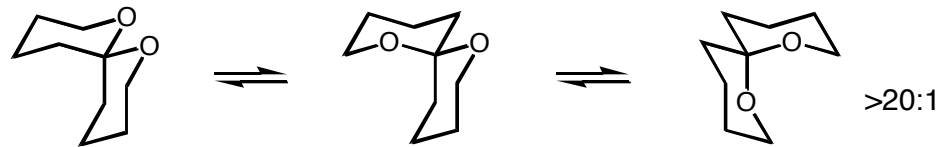


equatorial anomer:

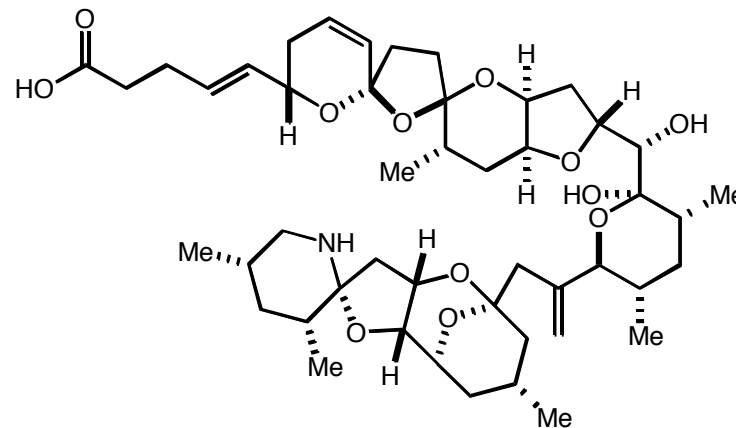


## The Anomeric Effect: Consequences

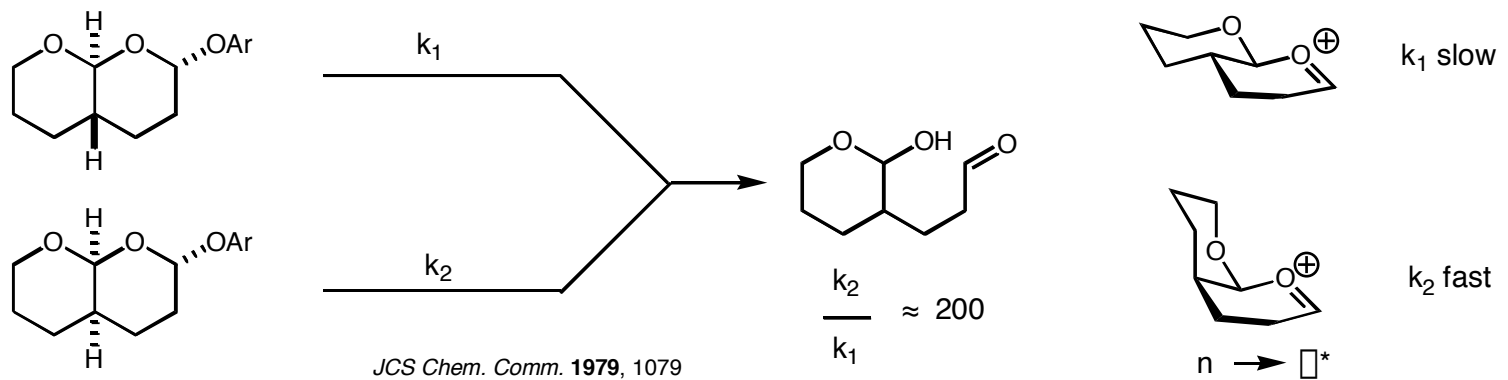
- Spiroketal Conformations are Controlled via the Anomeric Effect



- Azaspiracid Stereochemistry at all 5 Anomeric Centers is Predicted by the Anomeric Effect

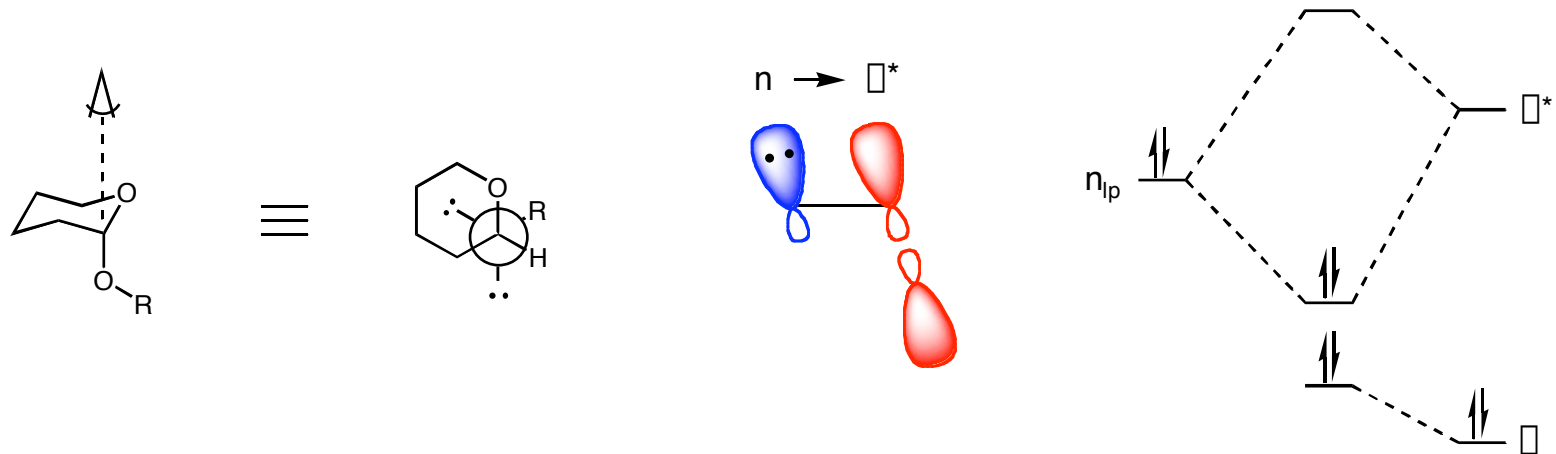


- Rate of Acetal Hydrolysis can be Impacted Considerably

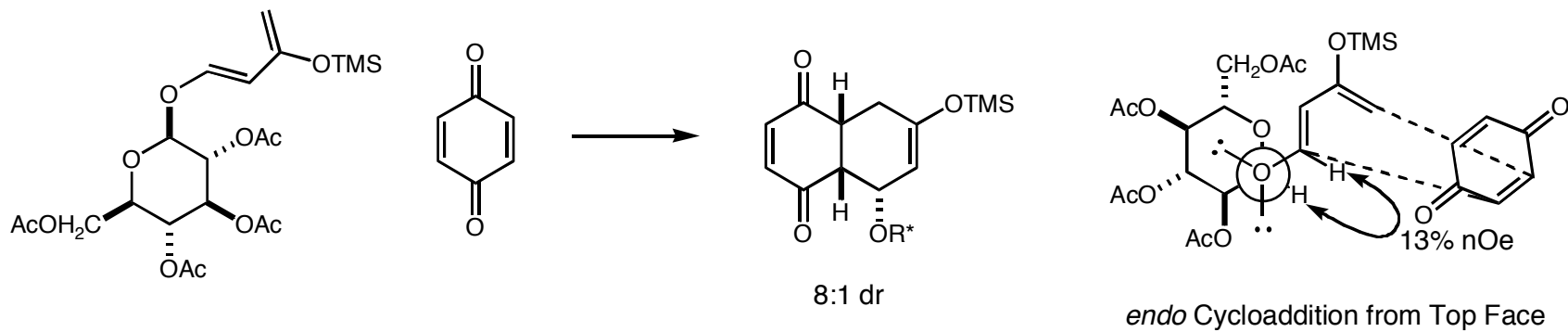


## The *exo*-Anomeric Effect

- The *exo*-Anomeric Effect Concerns the Conformation of an *O*-Glycosidic Linkage (*cf.* Gauche Effect)



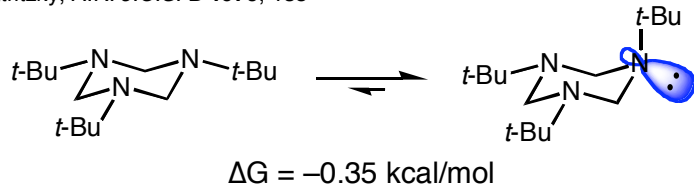
- While Important to Sugar Chemists, only Rarely Exploited in Synthesis:



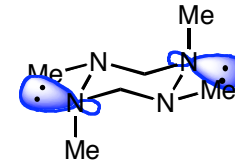
## The Anomeric Effect: It's not just for Oxygen Anymore

### Similar Effects are Noticed with Nitrogen

Katritzky, A.R. *J.C.S. B* **1970**, 135



Solution Structure (NMR):



Anderson, J. E.; Roberts, J.D. *J. Am. Chem. Soc.* **1967**, *96*, 4186

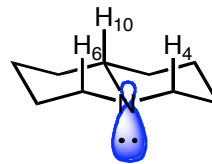
### Hyperconjugation has Large effects on Even C-H Bonds

IR: "Bohlmann Bands"

2700 to 2800  $\text{cm}^{-1}$   
for  $\text{H}_4$ ,  $\text{H}_6$ , and  $\text{H}_{10}$

Disappear when protonated

Bohlmann, *Ber.* **1958**, *91*, 2157



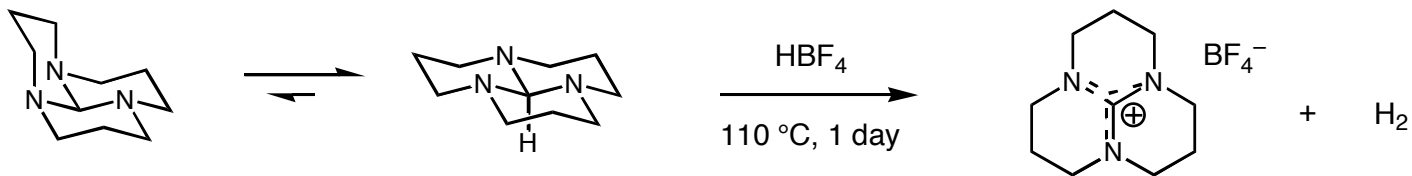
$^1\text{H}$  NMR: Extra Electron Density Causes Shielding

$\text{H}_{10}$  is furthest upfield

$\text{H}_4$  and  $\text{H}_6$  upfield by almost 1ppm  
of remaining protons

Only off by 0.5 ppm when acid is added

### Anomeric Effect in Orthoamides can Cause Strange Reactivity:

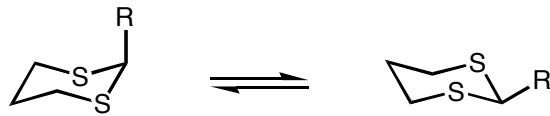


Illustrated proton  $\delta = 2.3 \text{ ppm}$

Erhardt, J.M; Wuest, J.D. *J. Am. Chem. Soc.* **1980**, *102*, 6363

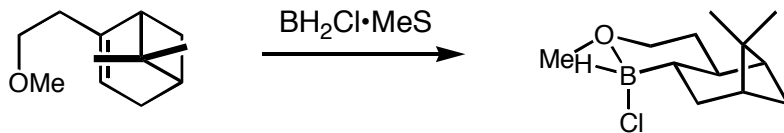
## The Anomeric Effect: It's not just for Oxygen Anymore

### Dithianes Allow the Study of this Effect for Sulfur



R	$\Delta G$ (kcal/mol)
SCH <sub>3</sub>	1.64
SPh	2.02
CO <sub>2</sub> Me	2.10
COPh	2.46
CO <sub>2</sub> H	>2.65
NMe <sub>2</sub>	≈ 0

### Carbon is not the only atom through which this effect may be transmitted!



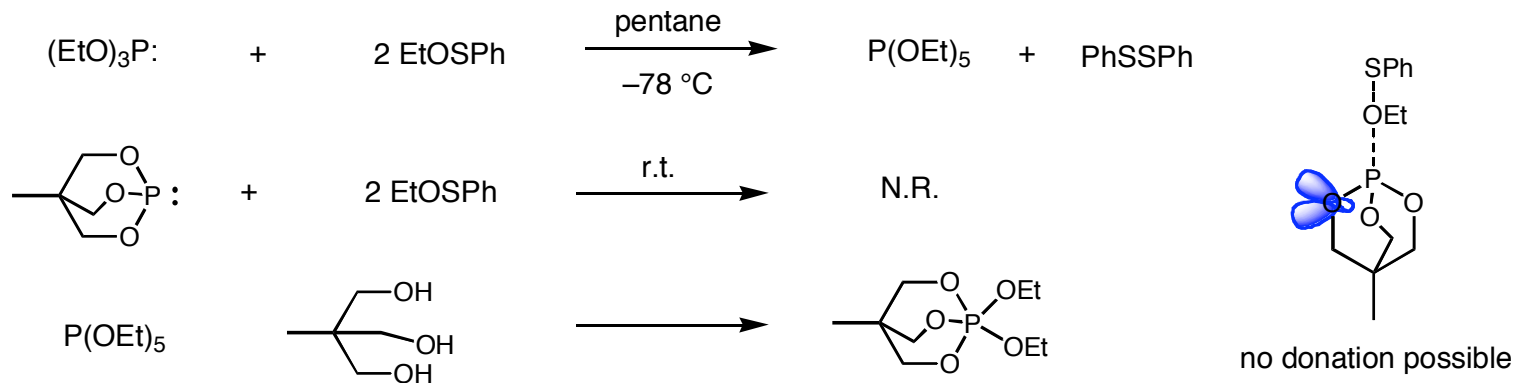
X-Ray Structure

Shiner, C.S.; Garner, C.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* **1985**, *107*, 7167

B-Cl bond = 1.890 Å

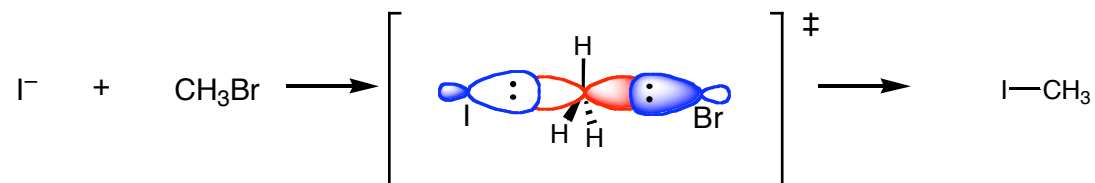
lit. range: 1.72-1.877 Å

### Anomeric Effect Through Phosphorous can be Significant for Phosphite Reactivity

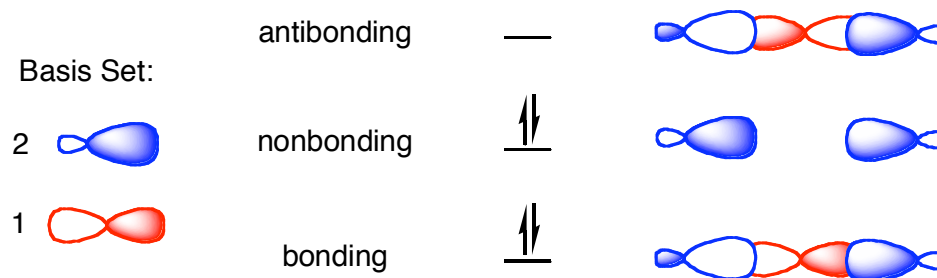


## The Role of Hyperconjugation in the Transition State: Theory

■ The  $S_N2$  Reaction TS looks like a 3c-4e<sup>-</sup> Bond:



■ MO Diagram for a 3c-4e<sup>-</sup> Bond:



*Prediction: Substituents with Low-Lying LUMOs will Accelerate the  $S_N2$  by Stabilizing Electron Density from Nucleophile and Leaving Group through Hyperconjugation*

Theoretical Support for the following Arguments: Houk, K. N., *et al. Science*, **1986**, 231, 1109

## Transition State Hyperconjugation Explains Substituent Effects in the $S_N2$ Reaction

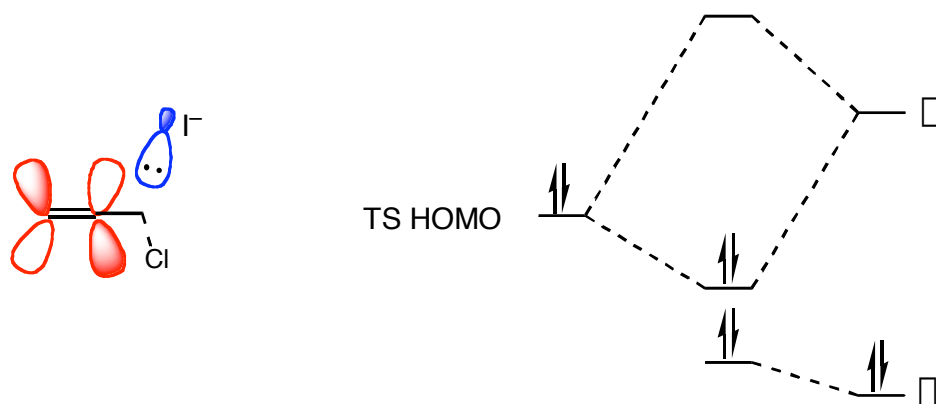
■ Here's the Rate Data on the  $S_N2$  Reaction:

$I^- + R-Cl \xrightarrow{\text{Acetone}} I-R$			
Entry	R	$k_{rel}$	$\sigma^*-LUMO$
1	<i>n</i> -Bu	1.0	$\sigma^*_{C-C}$
2	cyclohexyl	<0.0001	$\sigma^*_{C-C}$
3	PhCO <sub>2</sub> CH <sub>2</sub>	59.1	$\sigma^*_{C-O}$
4	Allyl	79	$\sigma^*_{C-C}$
5	Benzyl	195	$\sigma^*_{C-C}$
6	NCCH <sub>2</sub>	3,070	$\sigma^*_{C-N}$
7	PhCOCH <sub>2</sub>	105,000	$\sigma^*_{C-O}$

sterics are still important

Conant, J.B.; Kinner, W.R.; Hussey, R.E. *J. Am. Chem. Soc.* **1925**, 47, 488

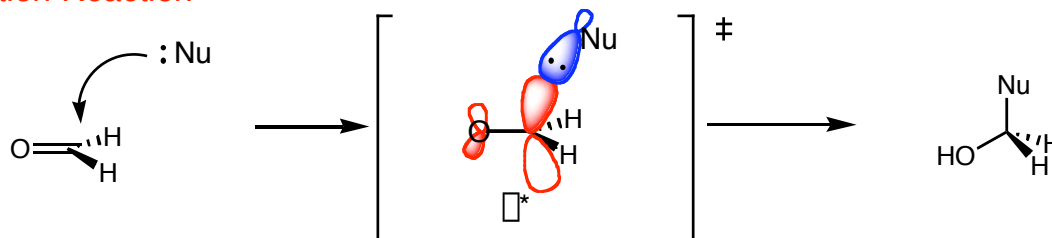
■ Data fits the Following Model





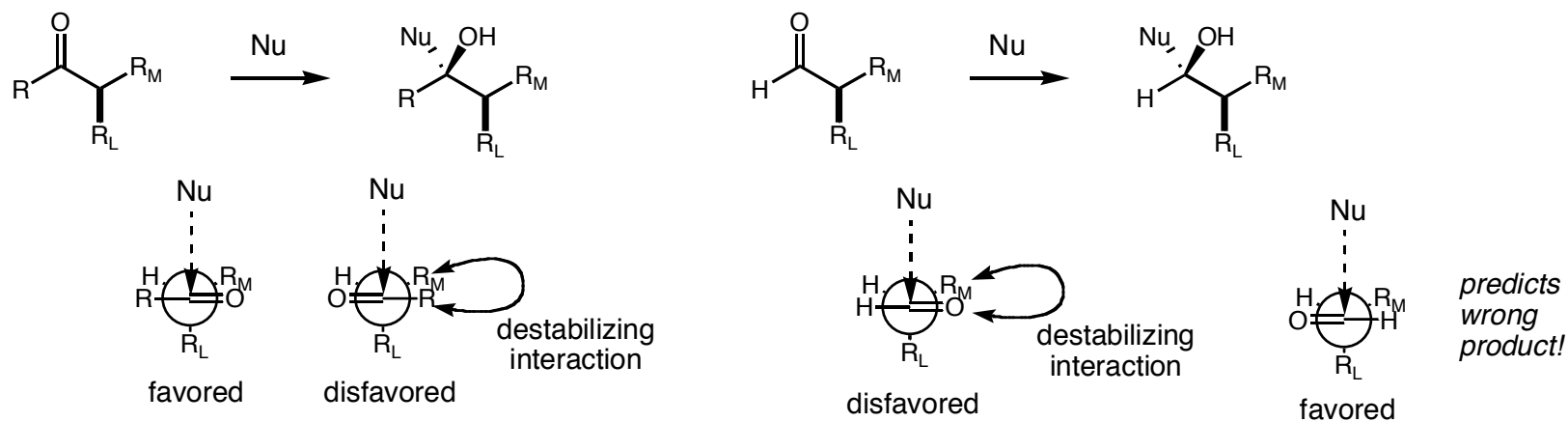
## Hyperconjugation in Carbonyl Addition Reactions

### ■ The Carbonyl Addition Reaction



### ■ Origin of Diastereoselectivity Subject of Much Debate (See NAP Group Meeting)

Felkin Model Predicts Ketones Well, Fails for Aldehydes:

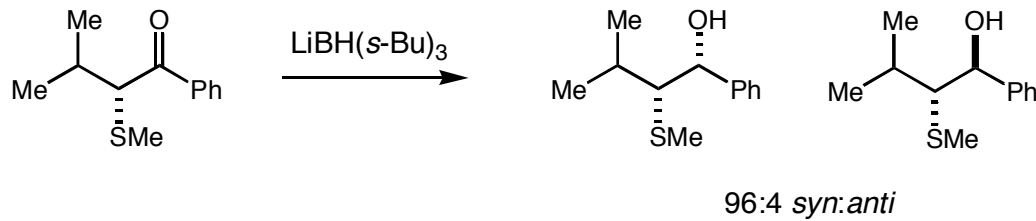


Ahn and Eisenstein add the Dunitz-Burgi Trajectory and the "Antiperiplanar Effect":

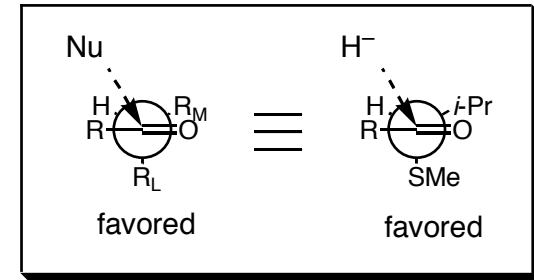


## The "Antiperiplanar Effect": Hyperconjugation in Action

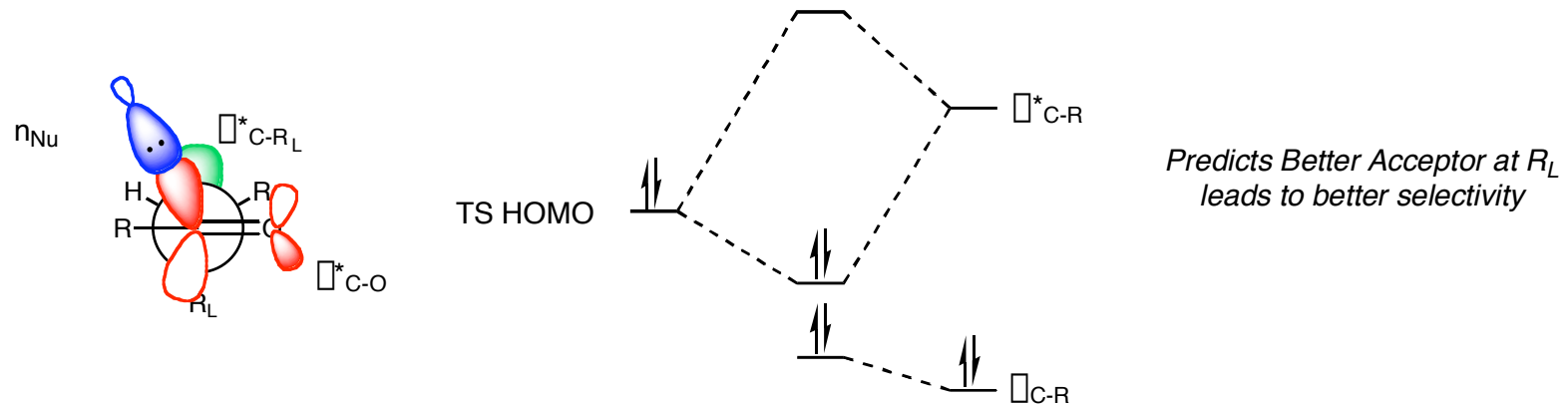
- Polar Substituents act as  $R_L$  in the Felkin-Ahn Model:



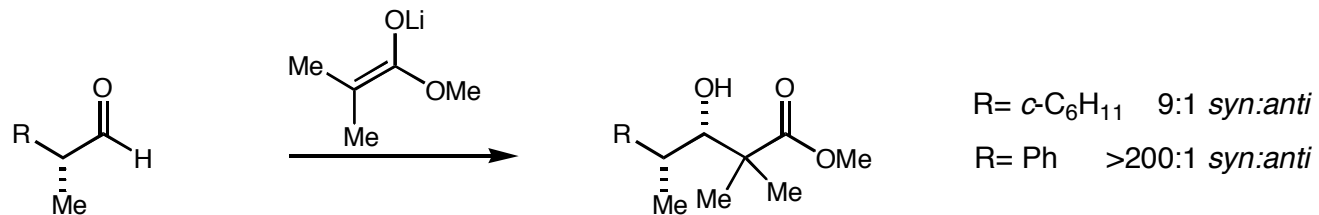
Shimagaki *Tet. Lett.* **1984**, 25, 4775



- Transition State Hyperconjugation, or How SMe can act Larger than *i*-Pr

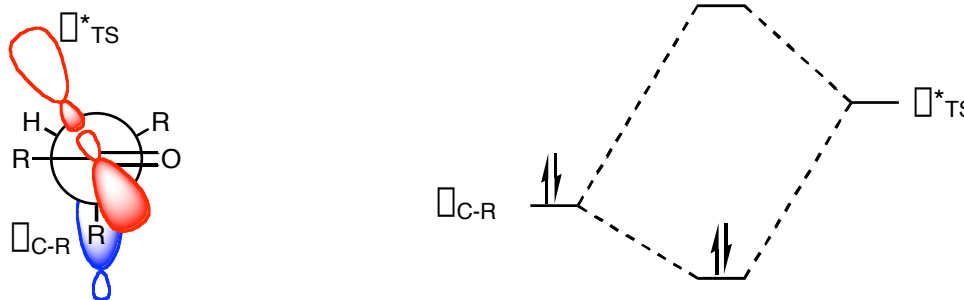


- Sterics Predicts the Opposite Trend:



## Transition State Hyperconjugation in C=O Additions: Cieplak

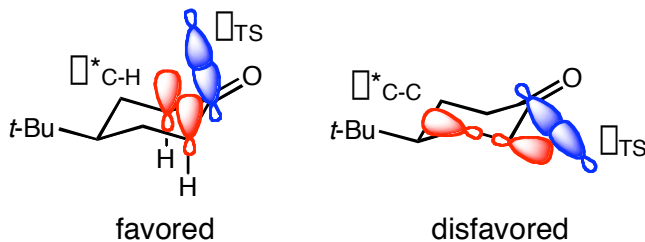
- Cieplak: Transition State is stabilized by an interaction between a filled substrate orbital and TS  $\sigma^*$  orbital



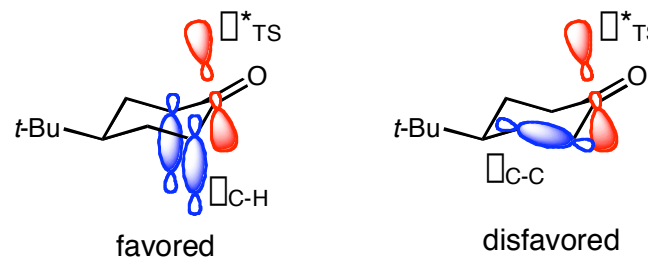
Cieplak, A.S. *J. Am. Chem. Soc.* **1981**, *103*, 4540

- Cieplak and Felkin-Ahn Both Usually Predict Same Sense of Diastereoselection

Felkin-Ahn: Axial Attack Favored



Cieplak: Axial Attack Favored



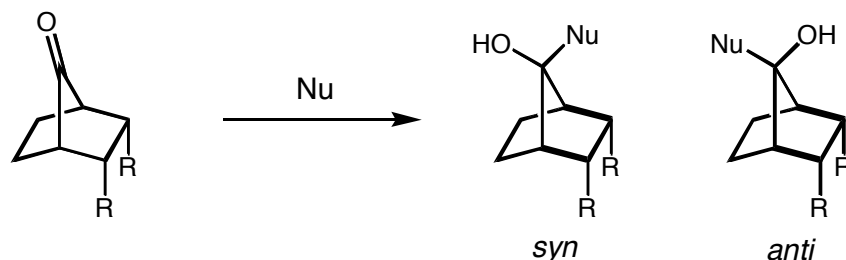
- A Much Maligned Theory:

"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."

—Prof. David A. Evans  
*Chem 206 Lecture Notes*

## Transition State Hyperconjugation in C=O Additions: Cieplak

### Examples consistent with Cieplak but not Felkin-Ahn



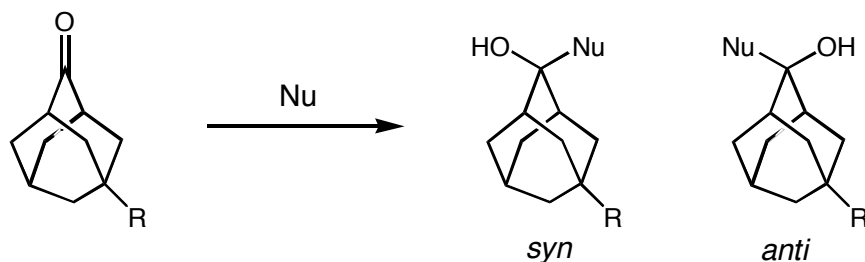
R=EWG, Shaded bond's  $\sigma^*$ , better acceptor, F-A predicts *anti*

R=EWG, Shaded bond's, worse donor, Cieplak predicts *syn*

R	Nu	<i>syn:anti</i>
CO <sub>2</sub> Me	LAH	87:13
	MeLi	>90:10
CH <sub>2</sub> OMe	NaBH <sub>4</sub>	40:60
	MeLi	34:66
CH <sub>2</sub> =CH <sub>2</sub>	LAH	35:65
	MeLi	27:73
Et	NaBH <sub>4</sub>	20:80
	MeLi	17:83

*Chem. Rev.* **1999**, *99*, 1387-1467

### Le Noble Has Many Examples with 2-Adamantanones:

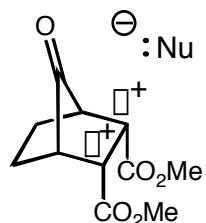


Same argument as above

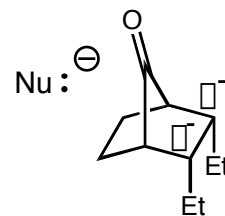
R	Nu	<i>syn:anti</i>
CO <sub>2</sub> Me	NaBH <sub>4</sub>	57:43
	MeLi	55:45
F	NaBH <sub>4</sub>	62:38
	MeLi	70:30
TMS	NaBH <sub>4</sub>	50:50
	MeLi	49:51
SnMe <sub>3</sub>	NaBH <sub>4</sub>	48:52
	MeLi	48:52

## Breakdown of the Cieplak Model: Is it Simply Electrostatics?

### ■ Critics of Cieplak Cite Role of Electrostatics in pro-Cieplak Examples:



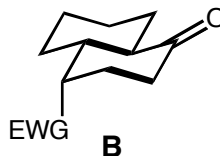
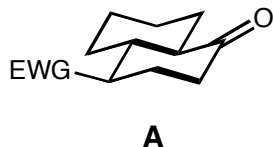
is *syn* product due to simple electrostatic attraction?



is *anti* product due to simple electrostatic repulsion?

### ■ Die-Hard Proponents of Cieplak Have a Hard Time Explaining This Houk Example:

Cieplak Prediction: Equatorial EWG should lower shaded bonds' donor strength, leading to more axial attack for **A** than **B**

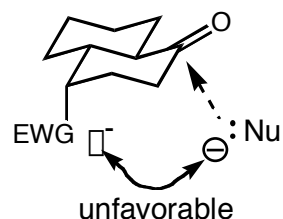


Houk, K.N., *et al.* *J. Am. Chem. Soc.* **1991**, *113*, 5018

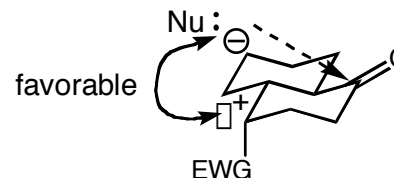
Diastereomer	EWG	axial:eq.
N.A.	H	60:40
<b>A</b>	OAc	71:29
<b>B</b>	OAc	83:17
<b>A</b>	Cl	71:29
<b>B</b>	Cl	88:12

### ■ Houk Invokes an Electrostatic Argument to Explain **B**'s Enhanced axial selectivity

Equatorial Approach Trajectory

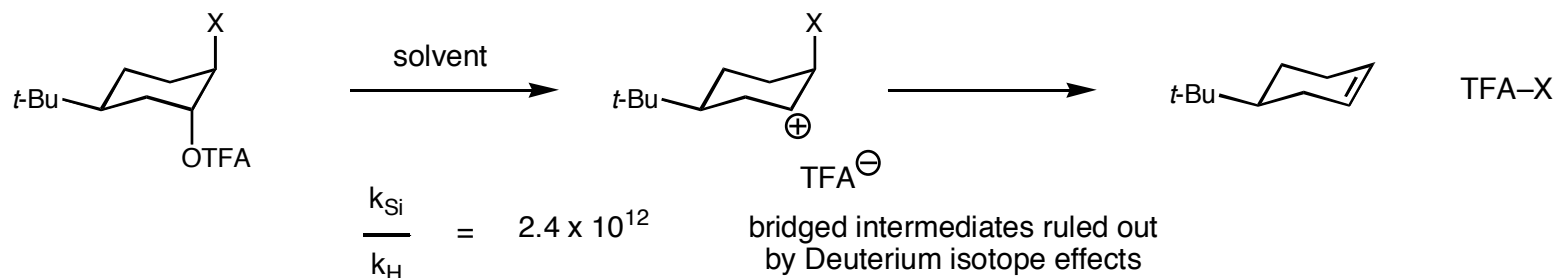


Axial Approach Trajectory



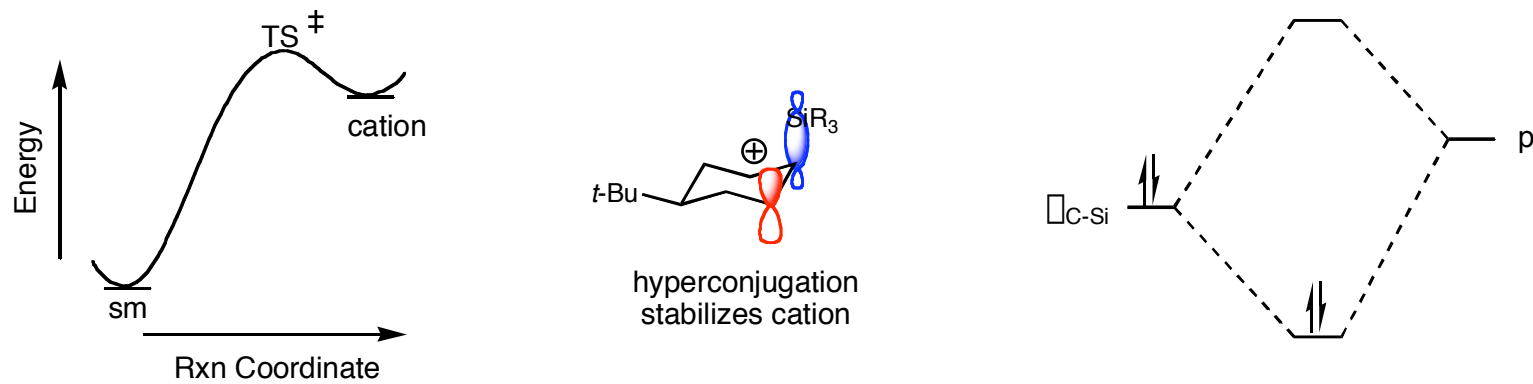
## The $\sigma$ -Silicon Effect: Hyperconjugation Yet Again

### ■ A Silicon $\sigma$ to a Leaving Group Greatly Enhances Ionization

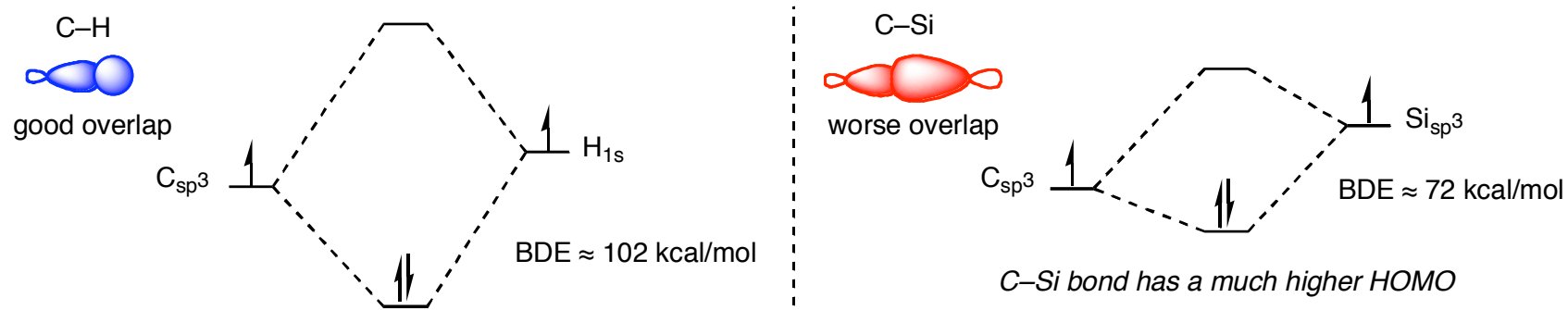


### ■ Late Transition State for Rate-Determining Ionization (Endothermic)

Lambert *et al.* *Acc. Chem. Res.* **1999**, *32*, 183

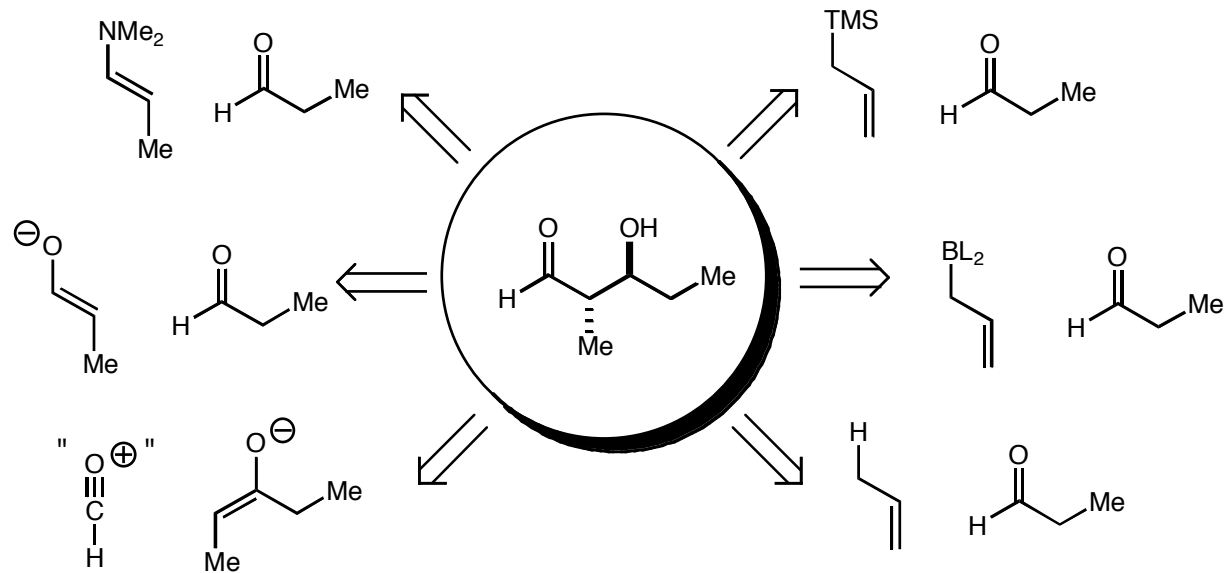


### ■ Why is C-Si so much better a donor than C-H? Look at the bonds!

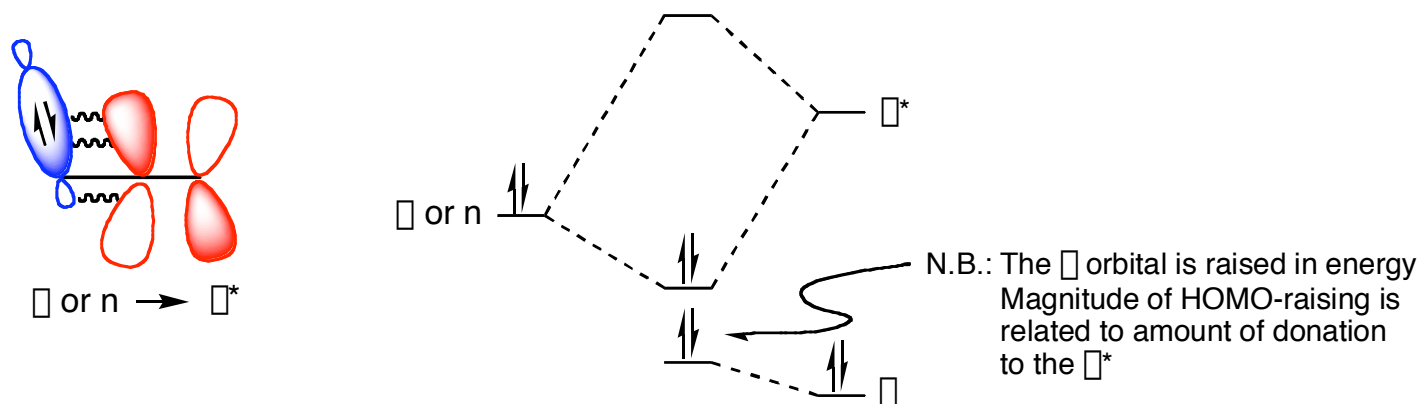


## Nucleophilic Olefin Addition Reactions: Homo-Raising Hyperconjugation

- Nucleophilic olefins constitute a key class of reagents

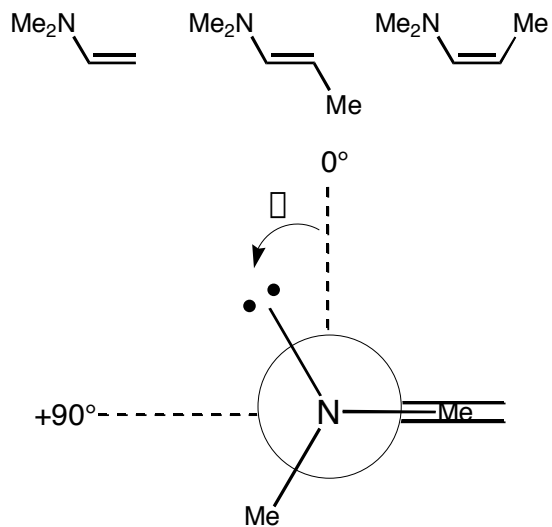


- Hyperconjugation Raises the  $\sigma$  HOMO of the alkene by donation to the  $\pi^*$

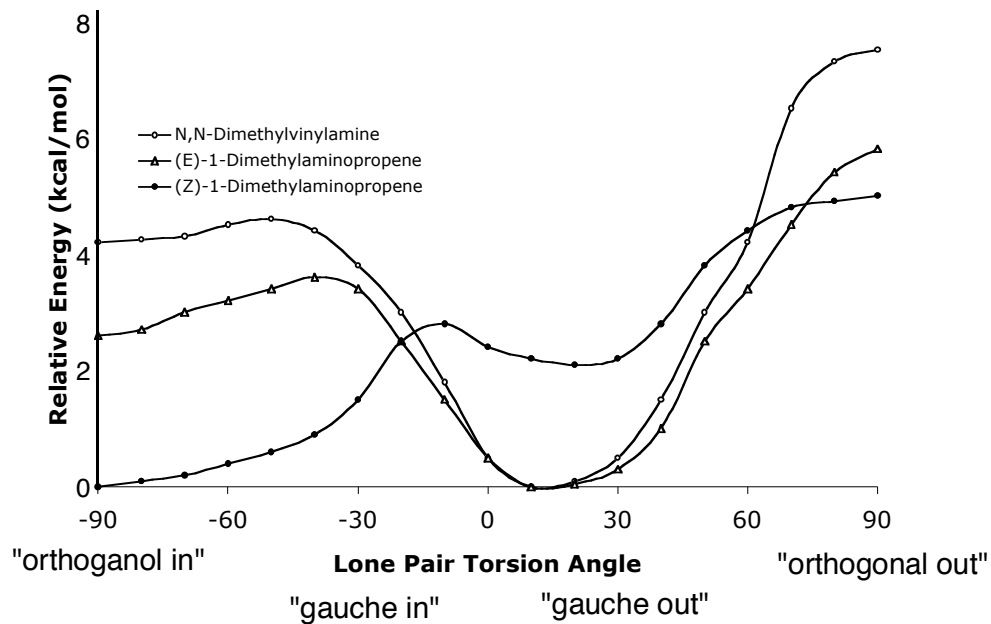


## Enamines: A Case Study in Hyperconjugation

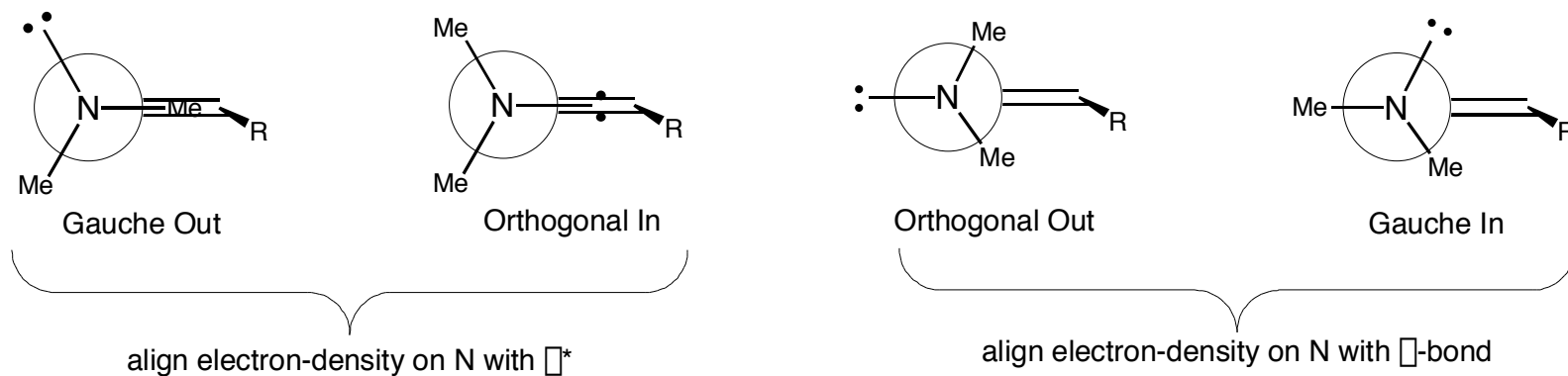
- Like amides there is restricted rotation about the C-N bond



Weston, J.W.; Albrecht, H. *J.C.S. Perkin 2*, 1997, 1003



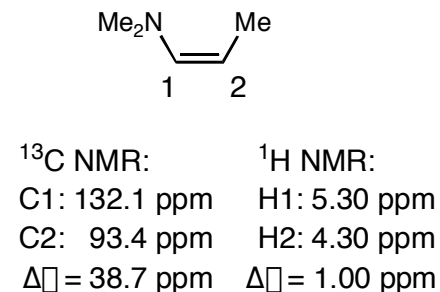
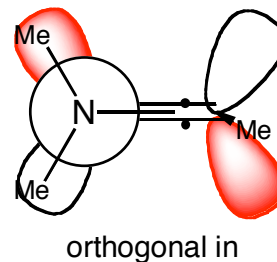
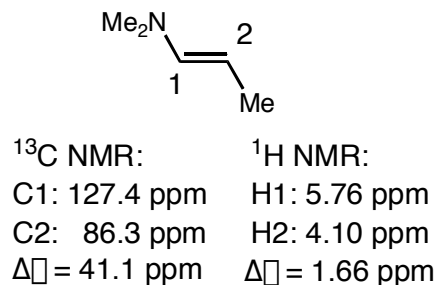
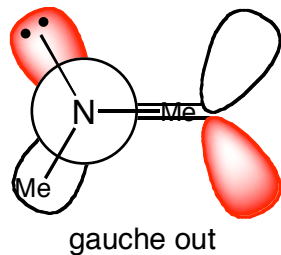
- E*-Enamines prefer a near Gauche-Out conformation While *Z*-Enamines prefer Orthogonal In





## Consequences of Enamine Conformation on Reactivity

- Hyperconjugation not only stabilizes "gauche out" but also makes it more reactive:



Lambert, J.B. *et al.* *J. Am. Chem. Soc.* **1980**, *102*, 6659

- Following MO Diagrams Illustrate the Difference

Gauche Out: 1  $n_{\text{N}}$  to  $\pi^*$  and 1  $\pi_{\text{C-N}}$  to  $\pi^*$

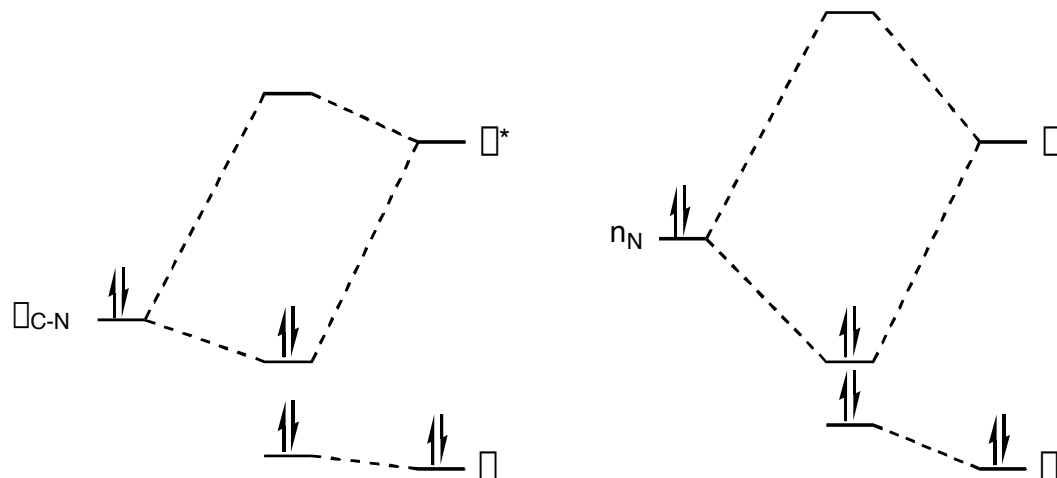
More hyperconjugation, higher  $\pi$  HOMO

$\implies$  alkene more reactive

Orthogonal In: 2  $\pi_{\text{C-N}}$  to  $\pi^*$ :

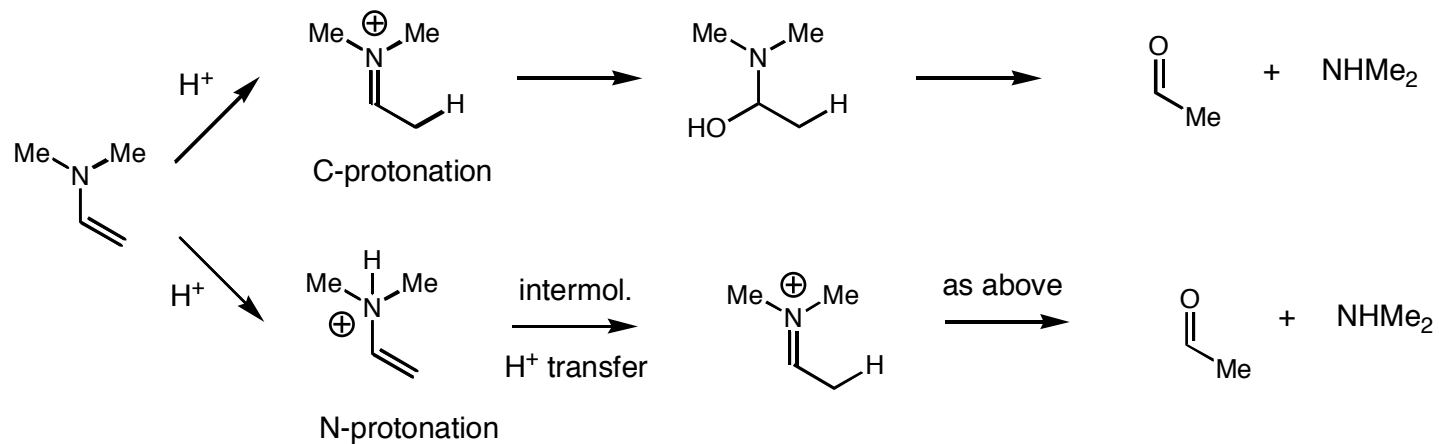
Less hyperconjugation, lower  $\pi$  HOMO

$\implies$  alkene less reactive

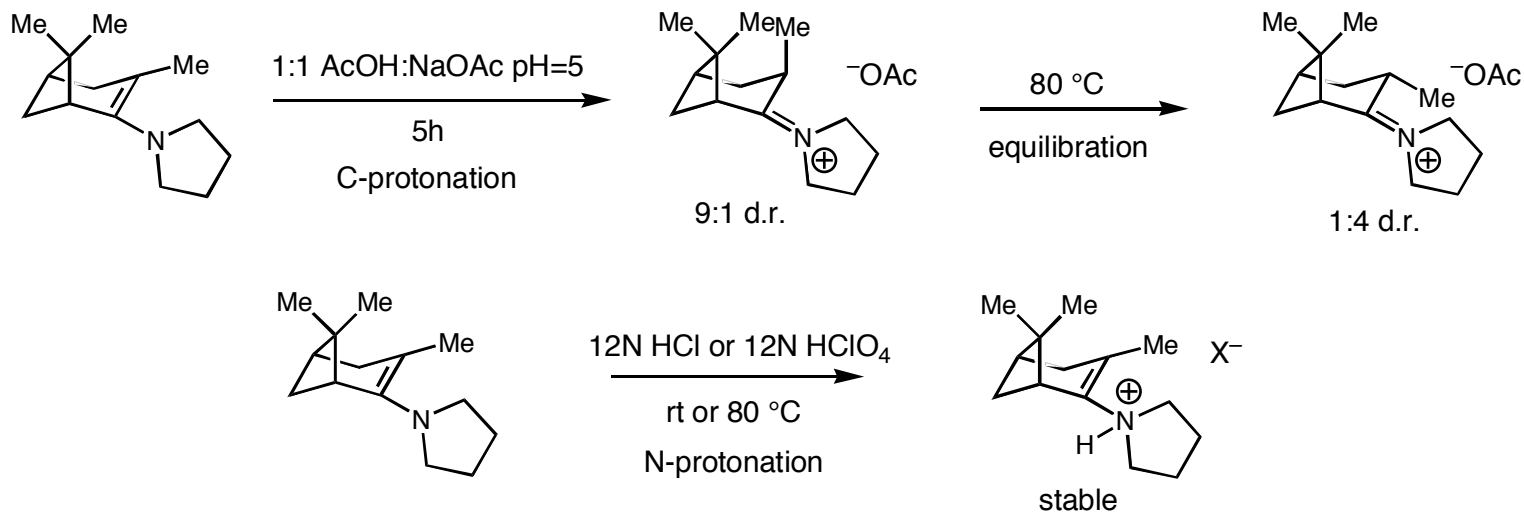


## Mechanism of Enamine Hydrolysis: Implications for Aldol Chemistry

### Two Competing Ideas for Enamine Hydrolysis

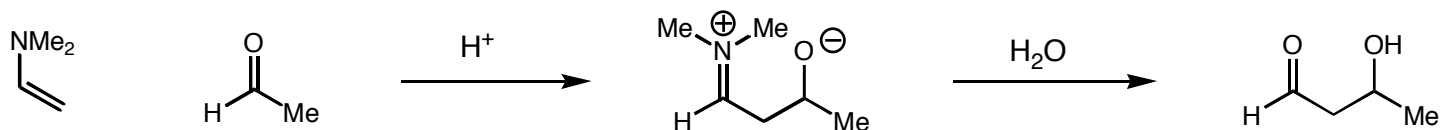


### Hyperconjugation makes N protonation difficult

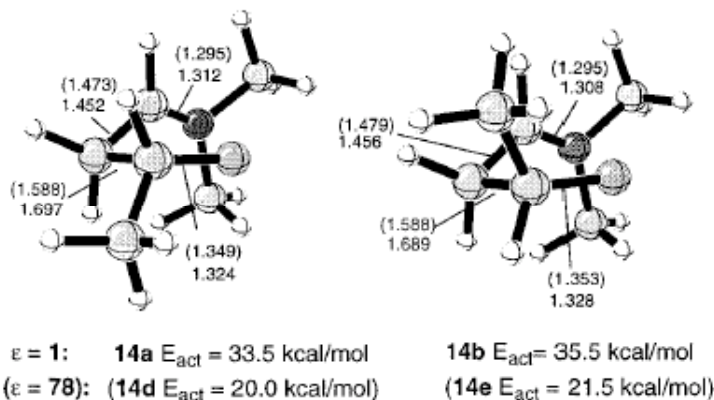


## Enamines in the Aldol Reaction: Computational Considerations

### The Enamine Aldol Reaction



### Computed Properties of the Transition State



A surprisingly late transition state:

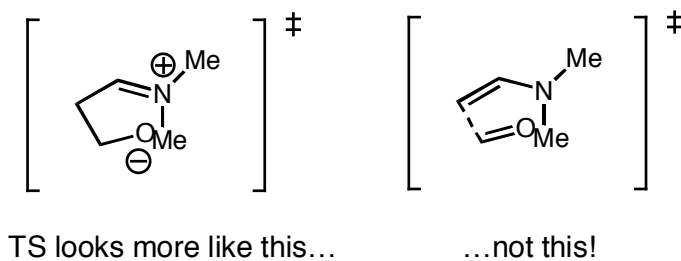
"Normal" Bond Lengths

C-C 1.544 Å

C-N 1.492 Å

C-O 1.470 Å

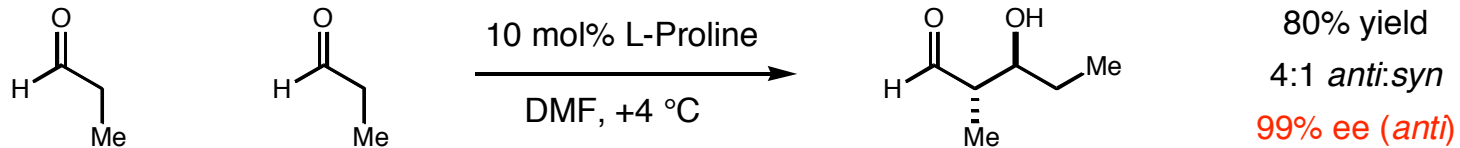
### What a Late Transition State Means for the Aldol



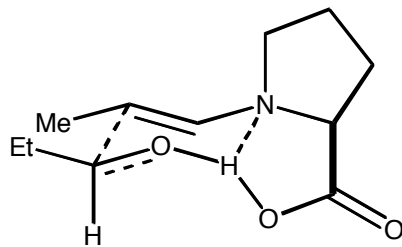
- Protonation only increases product level in TS
- Non-basic enamine N in TS (Hyperconjugation)
- C-N Conformation locked in "gauche out"

## Proline-Catalyzed Aldol Reaction Transition States

### ■ The Direct Aldehyde-Aldehyde Aldol Reaction

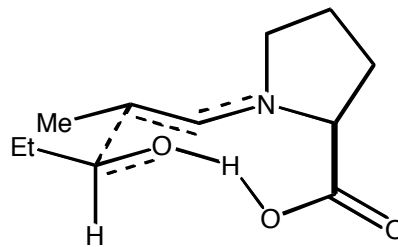


### ■ Barbas-List Transition State



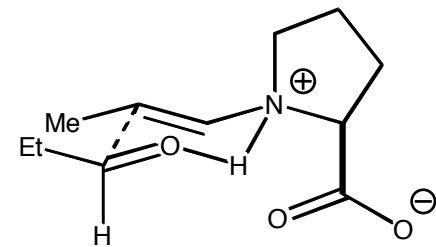
- First Model
- Correctly Predicts Stereochemistry
- Bifurcated H-bond
- Rigid 5-6 system
- Intimate Involvement of Chirality

### ■ Jorgenson's Transition State



- Second Model
- Correctly Predicts Stereochemistry
- Removes Bifurcated H-bond
- 9-membered Ring (8 planar centers)
- Intimate Involvement of Chirality
- Improves Hyperconjugation

### ■ MacMillan's Transition State



- Third Model
- Correctly Predicts Stereochemistry
- Removes Bifurcated H-bond
- Rigid 6 membered system
- No Intimate Involvement of Chirality
- Disregards Hyperconjugation

## Hyperconjugation Conclusions

It's a simple, but powerful theory.

