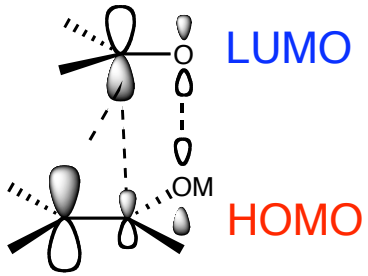
Frontier Orbital Interactions: Stereoselectivity



Phong V. Pham

MacMillan Group

Group Meeting

Princeton, Feb. 27, 2008

Frontier Orbital Interactions and Applications

Pericyclic Reaction

Addition Reactions

Substitution Reactions

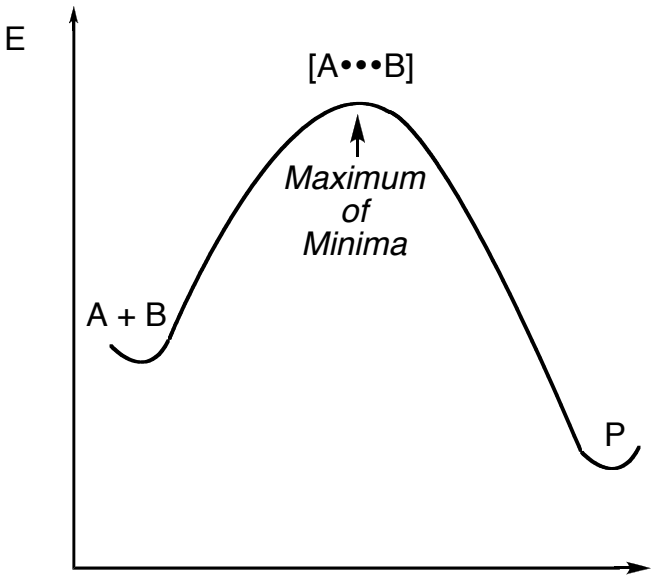
Limitation & Conclusion

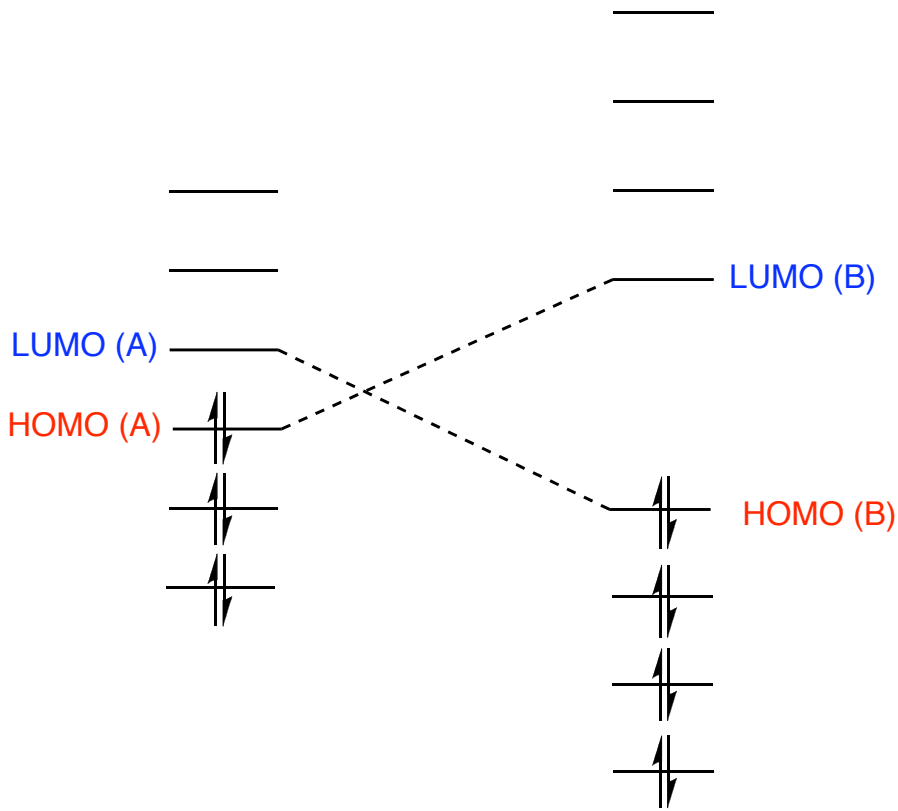
Leading Reference:

Anh T. Nguyen, *Frontier Orbitals*, Wiley, England, 2007

Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, England, 2006

Frontier Orbital Interactions and What We Can Do with Them?





HOMO: Highest Occupied Morlecular Orbital

LUMO: Lowest Unoccupied Morlecular Orbital

*"... majoyity of chemical reactions should take place at the position and in the direction of **maximum overlapping** of the **HOMO** (or high-lying occupied MO's) and the **LUMO** (or low-lying unoccupied MO's) of the reacting species; in reacting species possessing a singly occupied (SO) MO, this plays the part of the HOMO or of the LUMO, or of both"*

Fukui K., *Acc. Chem. Ress.* **1971**, *4*. 57

Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

Standard FO Treatments of **Structure**

Stable Conformations

Q: Which is the most stable conformation?

Reactive Conformation

Q: Which is the most reactive conformation?

Structural Anomalies

Q: When might structural anormalies occur?

Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

Standard FO Treatments of **Structure**

Stable Conformations

Q: Which is the most stable conformation?

A: Formally divide the molecule into two fragments, the most stable conformation will be the one having the smallest HOMO-HOMO interaction.

Reactive Conformation

Q: Which is the most reactive conformation?

A: It is the one having highest lying HOMO and lowest lying LUMO in the transition state.

Structural Anomalies

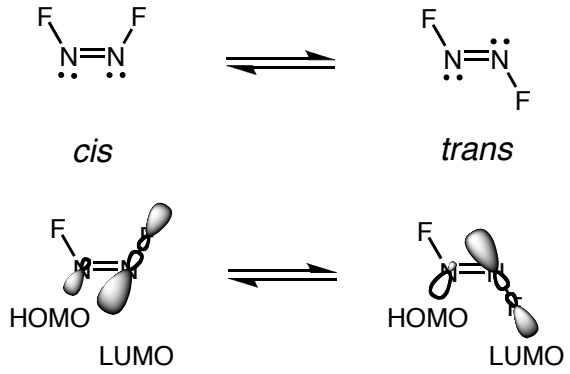
Q: When might structural anormalies occur?

A: A bond will shorten (or lengthen) if bonding electron density increases (or decreases) and/or antibonding electron density decreases (or increases) between the extremities.

Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

Standard FO Treatments of **Structure**



The *cis* isomer is 3 kcal/mol favored at 25 ^{o}C

Frontier Orbital Interactions and What We Can Do with Them?

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Absolute Reactivity

Q: Will A react with B?

Relative Reactivity

Q: Will A react preferentially with B_1 or B_2?

Regioselectivity

Q: Which reactive site of B will A react preferentially with?

Stereoselectivity

Q: Which is the best approach for A to attach a given site of B?

Frontier Orbital Interactions and What We Can Do with Them?

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Q: Which reactive site of B will A react preferentially with?

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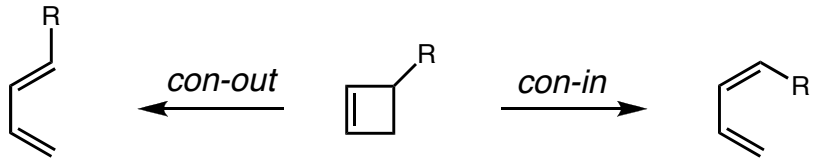
Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

Electrocyclic reactions

Torquoselectivity, basic Rondan-Houk treatment



Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

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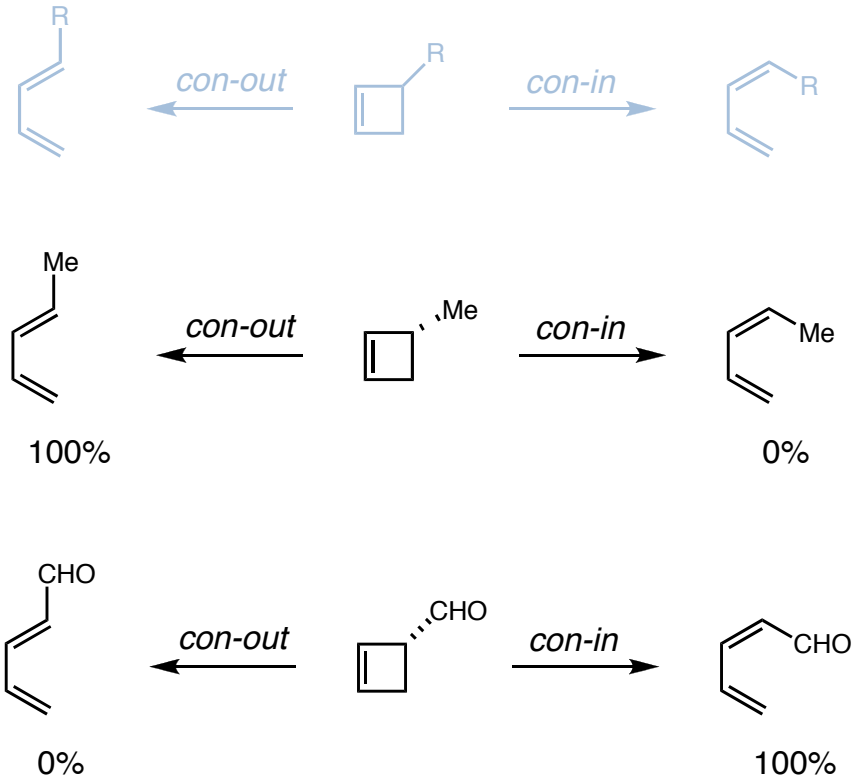

Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

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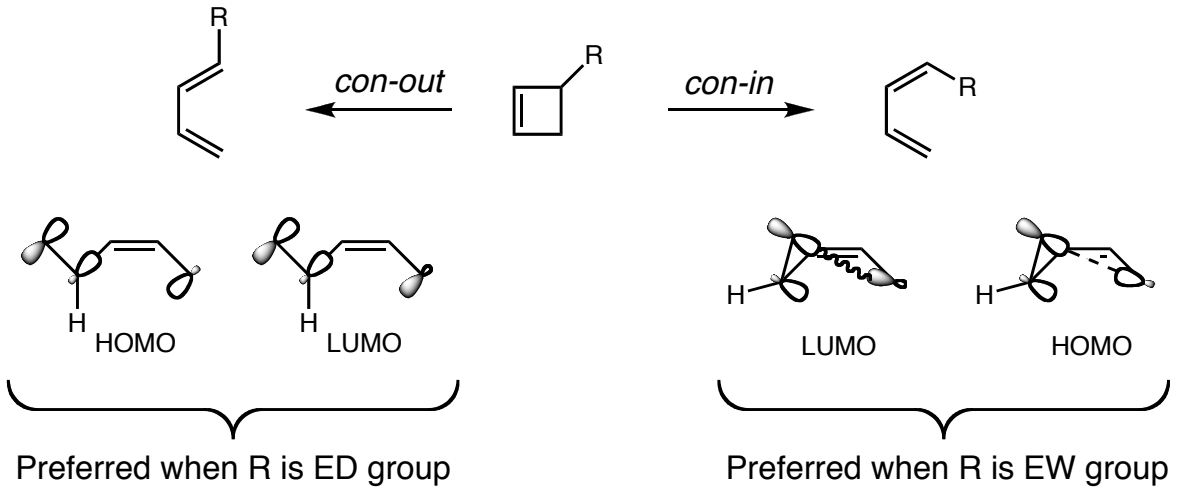
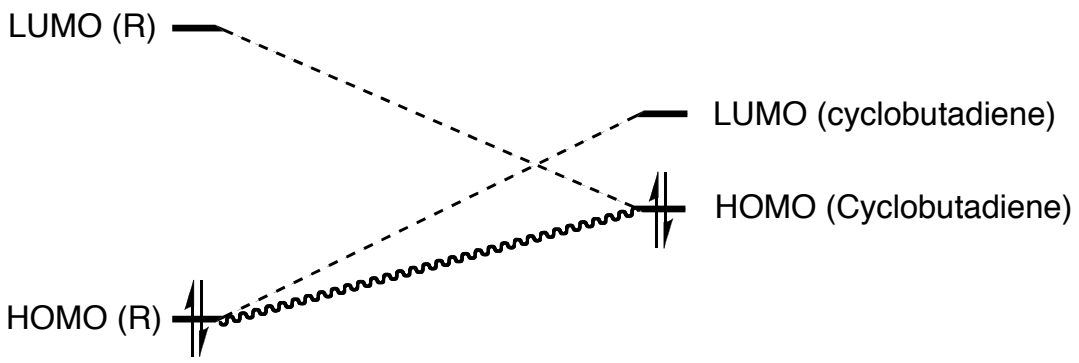


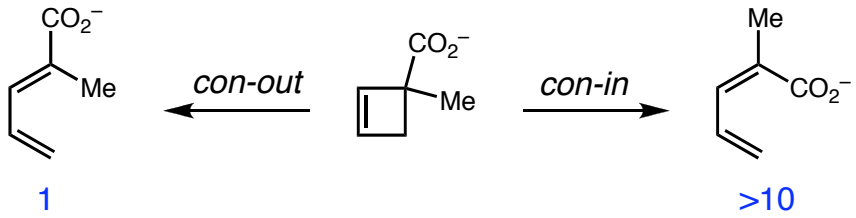


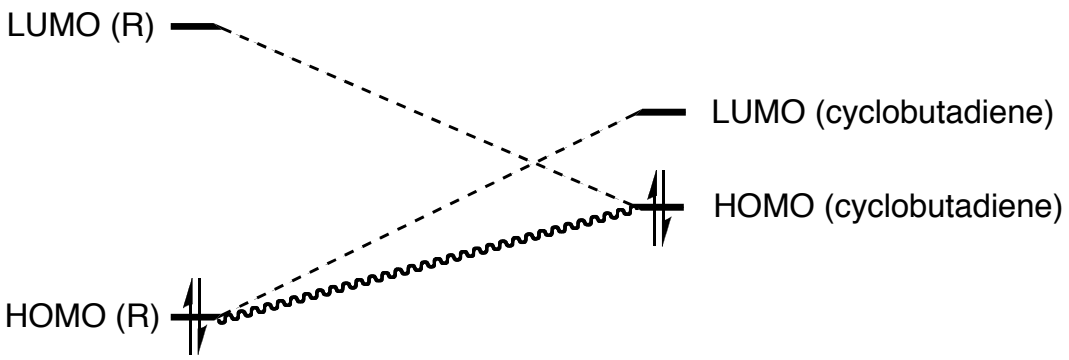
Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

Electrocyclic reactions

Torquoselectivity, quantitative analysis





Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

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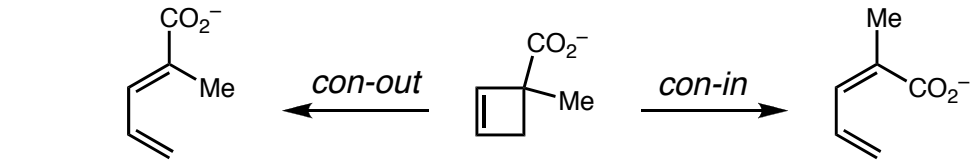


1 >10

+5.7 kcal/mol (Me)

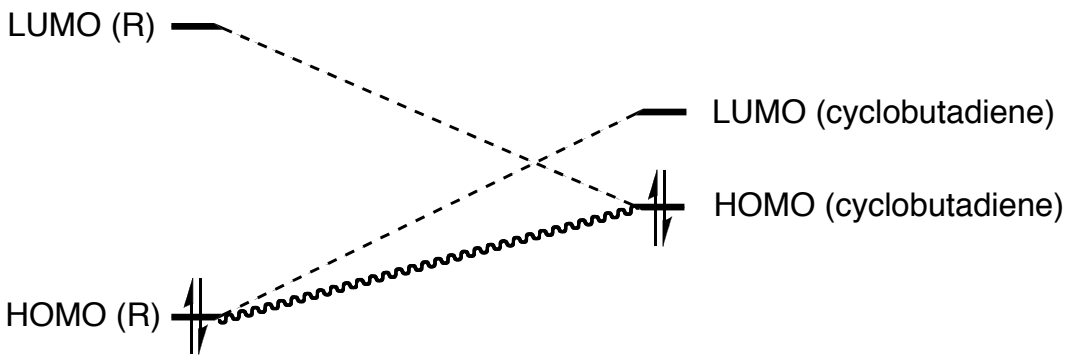
–4.4 kcal/mol (CO_2^-)

+1.3 kcal/mol

–1.2 kcal/mol (Me)

+0.7 kcal/mol (CO_2^-)

–0.5 kcal/mol



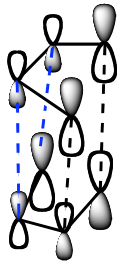
Houk K.N. *et al, Tet. Let.* **1995**, *36*, 6201

Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

Endo-Exo orientation, secondary orbital intereactions are important

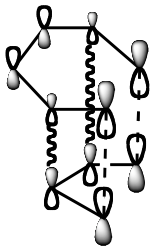
[4 + 2] and [8 + 2] prefers *Endo* orientation



LUMO

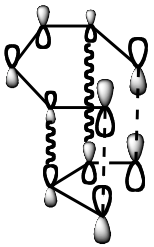
HOMO

[6 + 4] prefers *Exo* orientation



HOMO

LUMO



LUMO

HOMO

Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

Endo-Exo orientation, secondary orbital interactions are important

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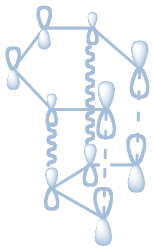
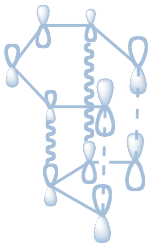
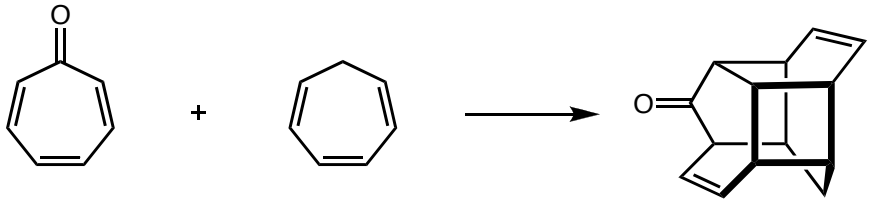
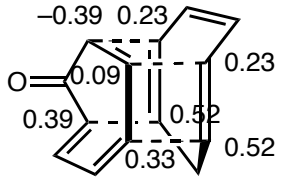
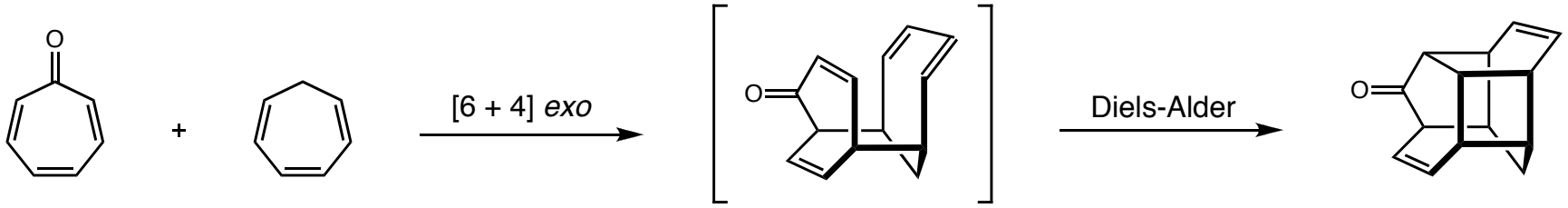




What do you think about the mechanism of this reaction?





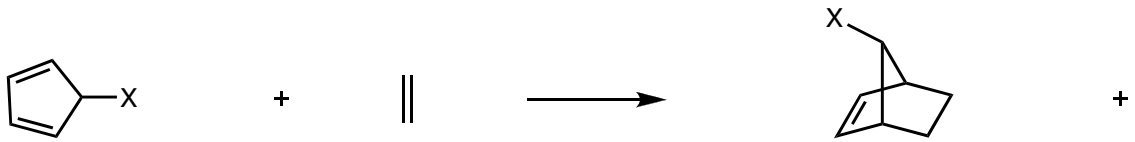


Woods M.C. *et al*, *Tet. Let.* **1967**, *8*, 1059

Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

Syn-Anti orientation, steric effect vs. secondary orbital interactions



syn

Steric control

anti

Secondary orbital overlap control

Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

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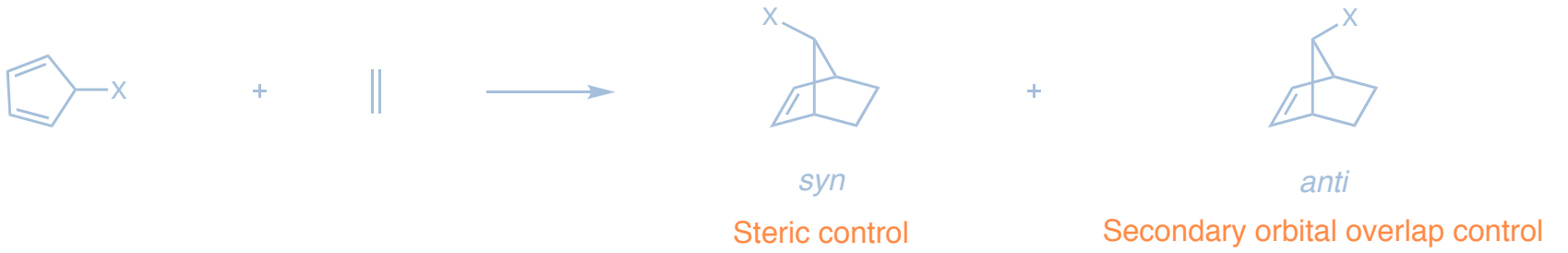
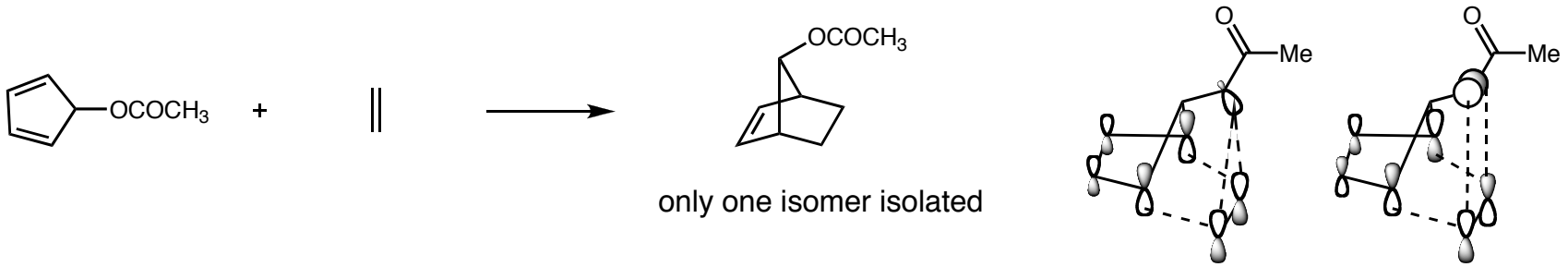
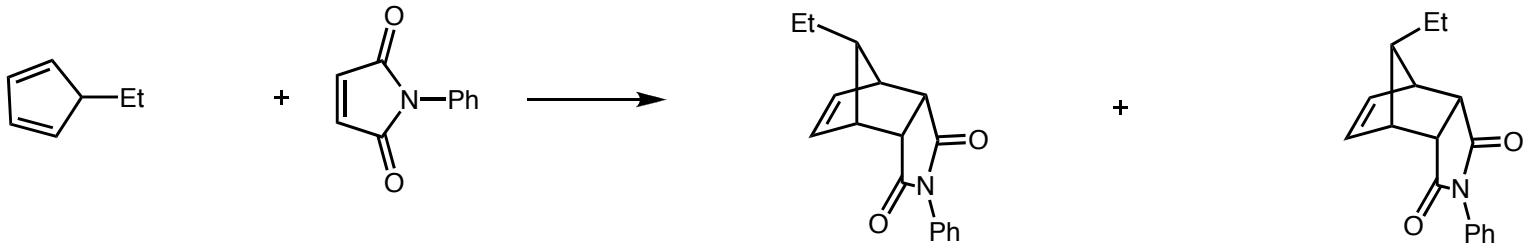




Woodward R.B., *J. Am. Chem. Soc.* **1955**, *77*, 4183



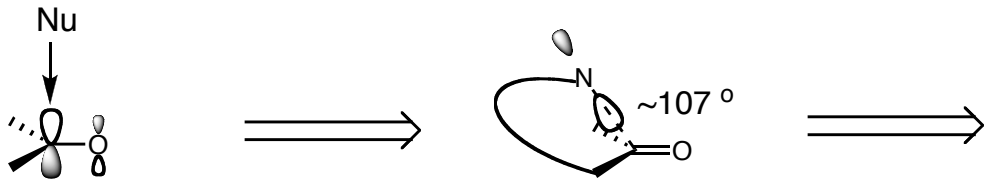
2.2 1

Burnell J.D, *J. Org. Chem.* **1997**, *62*, 7272

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

The non-perpendicular Dunitz-Burgi attack



Traditional model

Dunitz-Burgi study

Burgi H.B. *et al*, *JACS* **1973**, *95*, 5065

Nguyen A.T., *TCC* **1980**, *88*, 145

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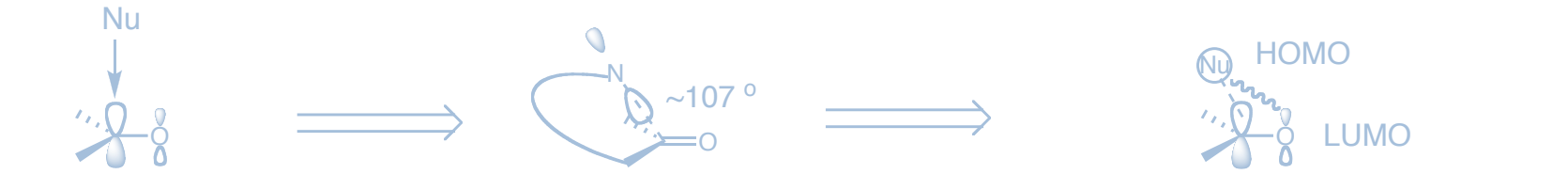

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Houk and co-workers showed on their calculation that the angles of nucleophilic attacks on alkenes and alkynes lie in the range 115–130 º (lager than the angle of attack on carbonyls.) Can you rationalize the result? (*JACS* **1982**, *104*, 7162)

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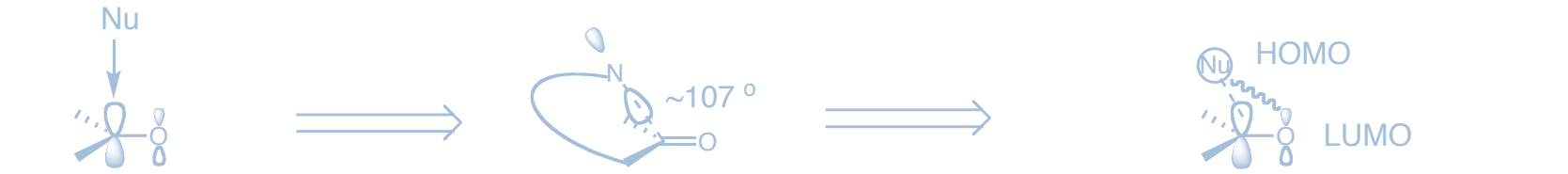

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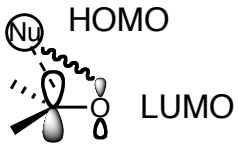
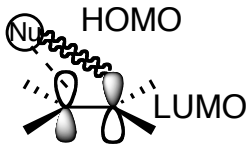


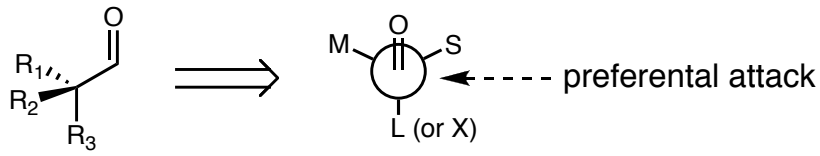


Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Cram model



(I)

L: the bulkiest group

X: electronegative group

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

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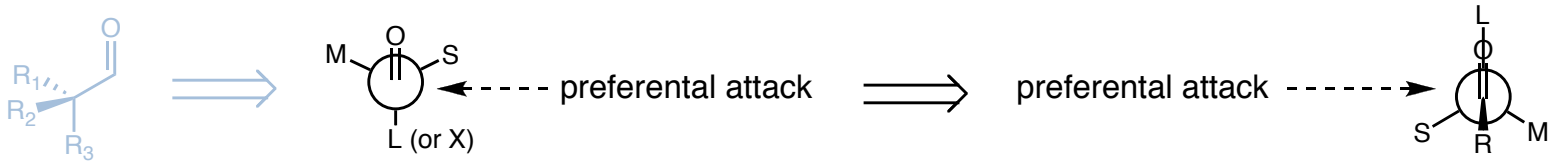


(I) (II)

L: the bulkiest group

X: electronegative group

Increase the size of R make II become more competitive with I

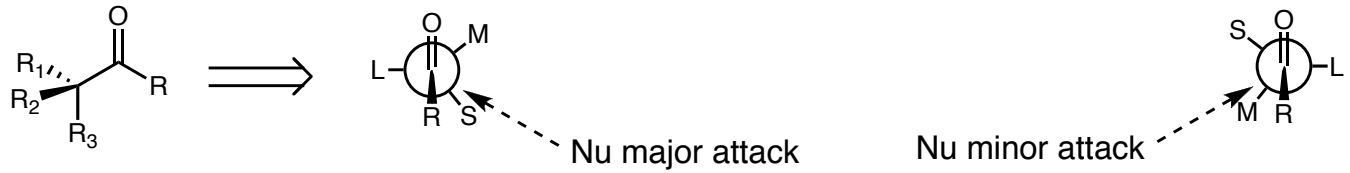
Cram model cannot explan the outcome of the reduction of 4–*tert*butylcyclohexanone by $LiAlH_4$

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Felkin model



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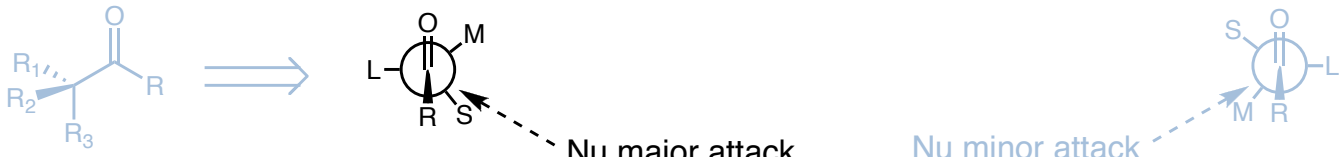

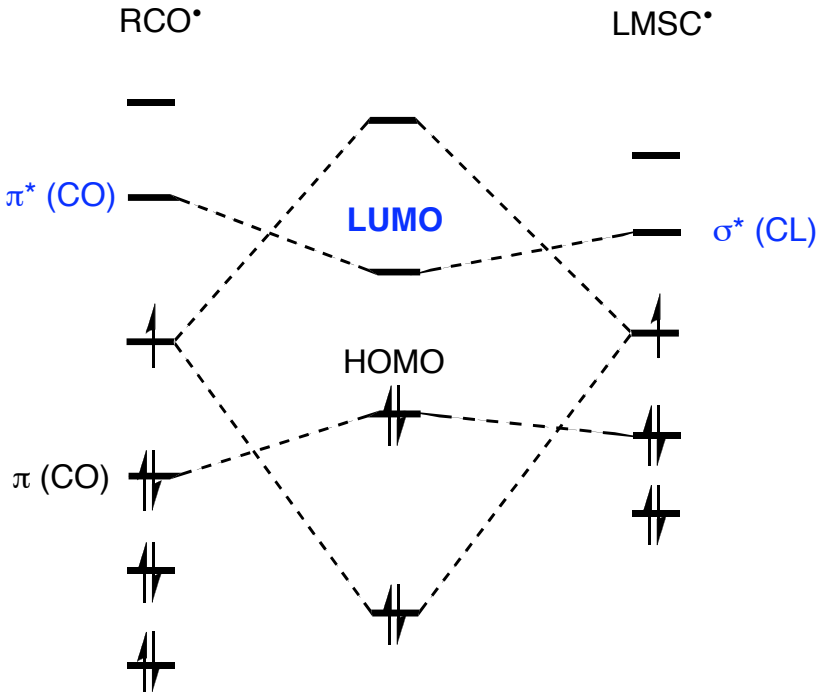

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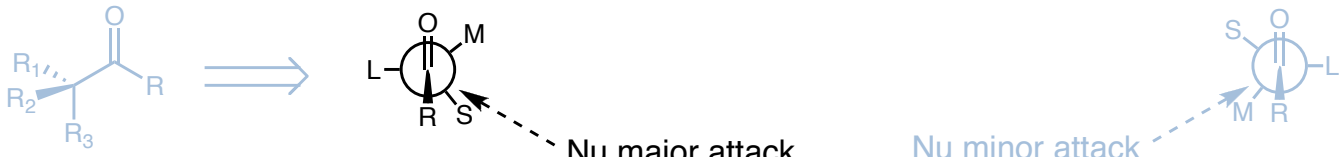
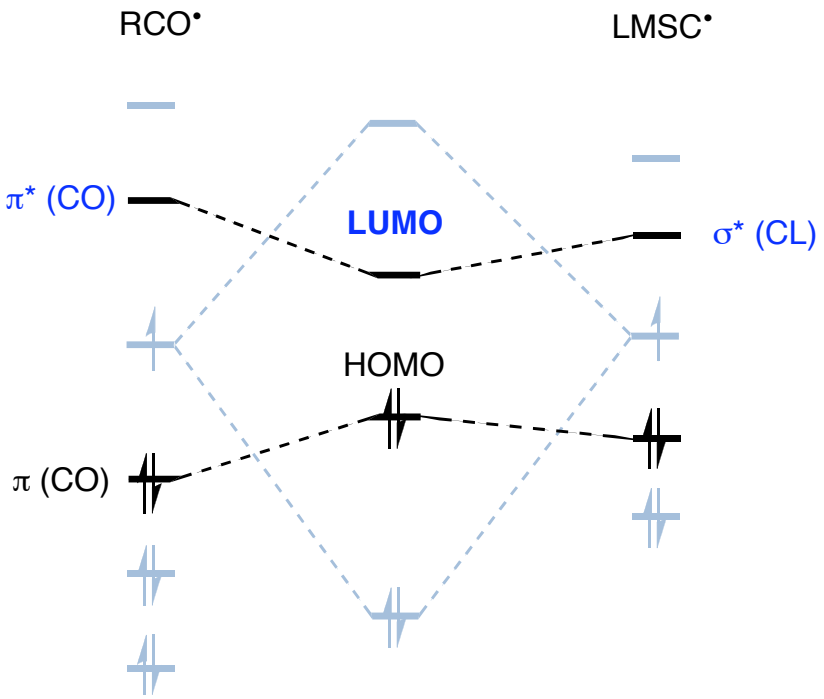




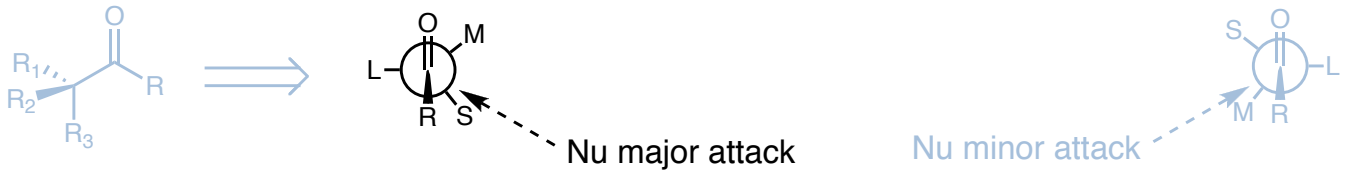
- The energy of σ^*_{CX} falls as the electronegativity of X increases. (Except X= F and strong dipolar stabilization cases)
- The energy of σ^*_{CL} falls as the CL bond weakens
- The HOMO-LUMO gap falls as the number of atoms in S, M or L rises

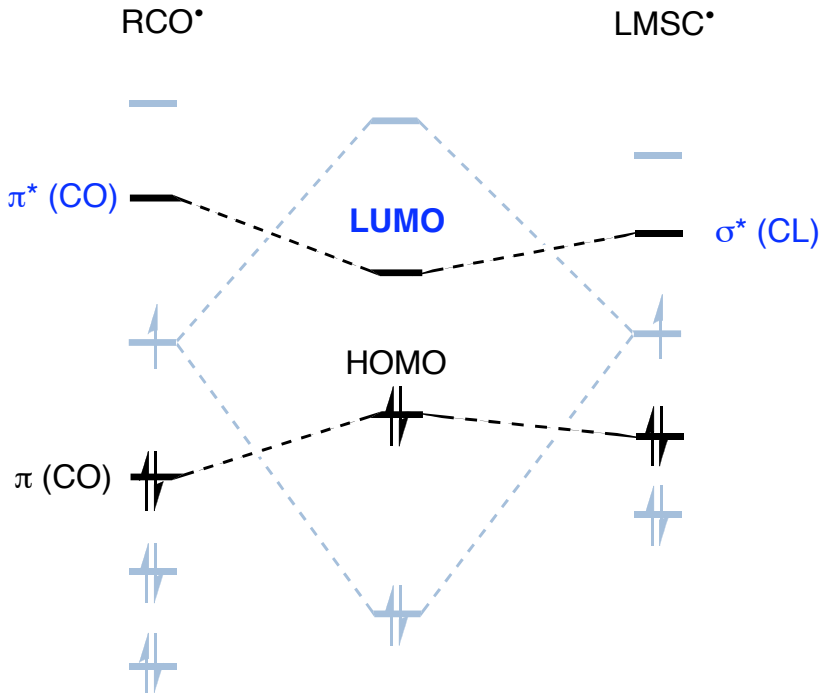
Frontier Orbital Interactions: Stereoselectivity

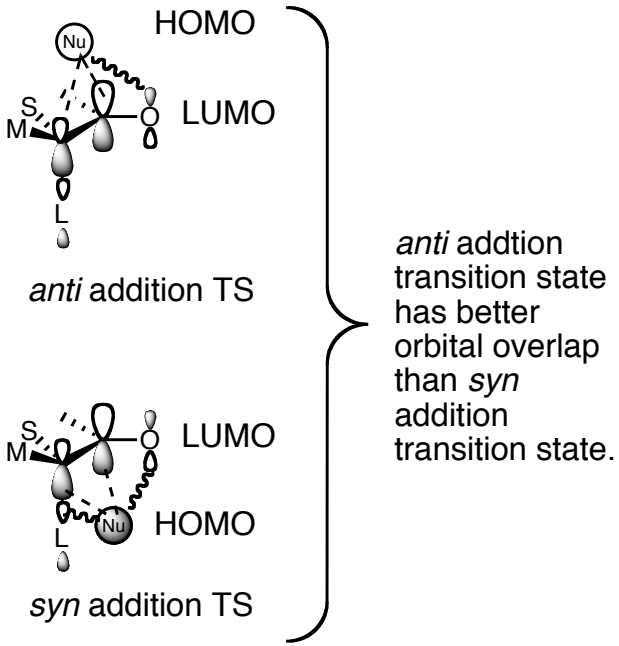
addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

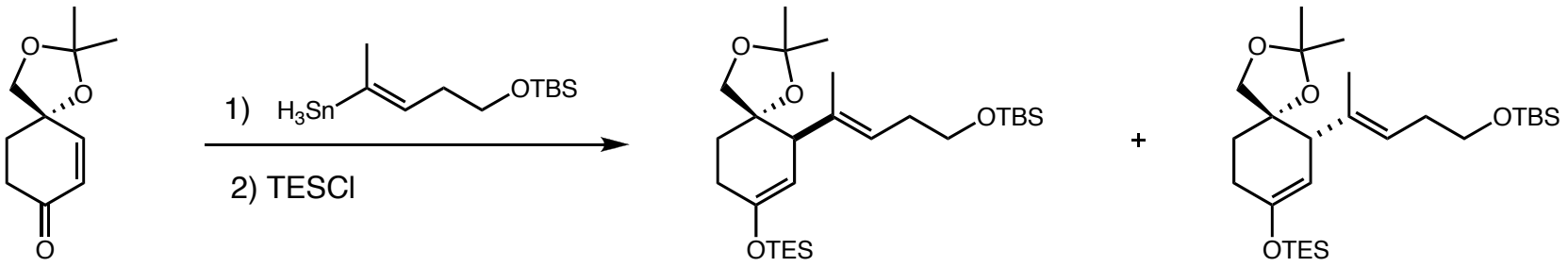
The Felkin model







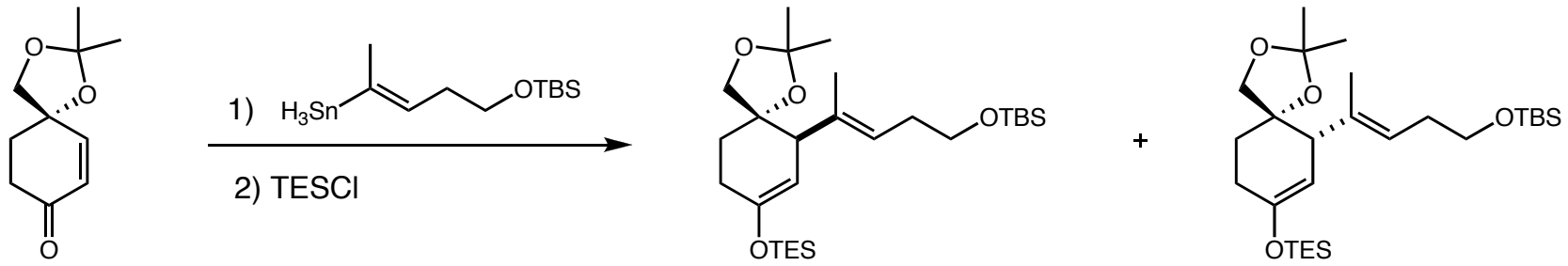
What is the major product of the following reaction?



anti adduct

syn adduct

Taber D. F., *JACS* **1999**, *121*, 5589



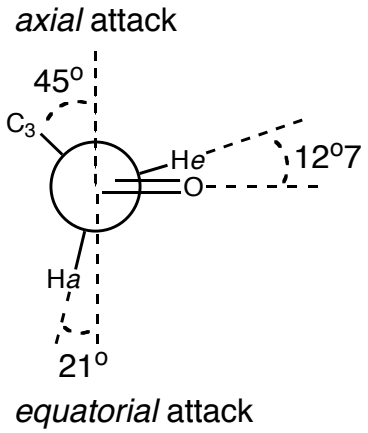
anti adduct : *syn* adduct

96 : **4**

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

Dealing with the cyclic system- the "*flattening rule*"

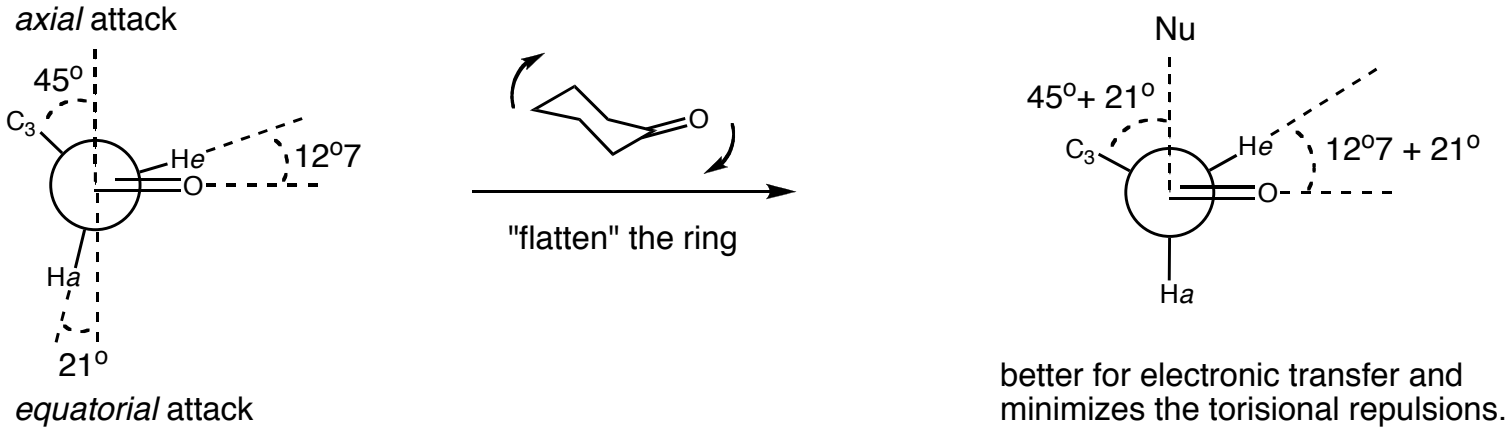


TS in the nucleophilic addition will be strongly stabilized when the C_2–X and C---Nu bonds are antiperiplanar.

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

Dealing with the cyclic system- the "*flattening rule*"



better for electronic transfer and minimizes the torisional repulsions.

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

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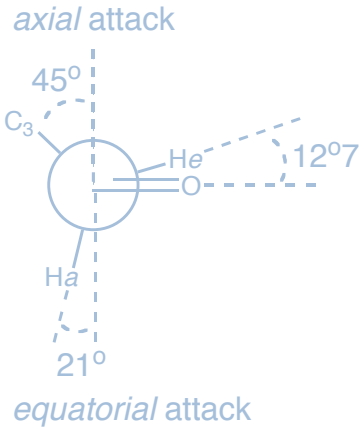
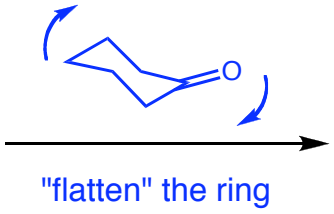
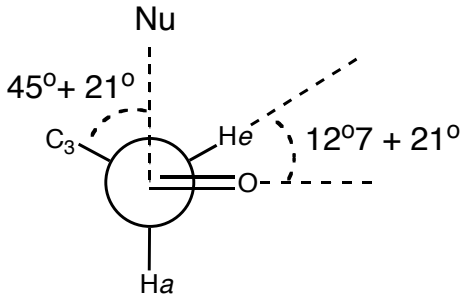




axial attack



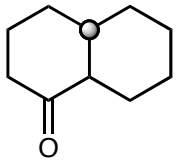
better for electronic transfer and minimizes the torisional repulsions.

*"Axial attack is favored by **flattened** or **flexible rings**"*

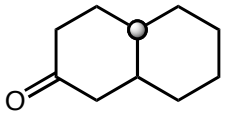
Nguyen. A. T. *et al*, *Tet. Let.* **1976**, *17*, 159

Arrange the following compounds in order of increasing preference for *axial* nucleophilic attack ($LiAlH_4$ for example)?

1)



1



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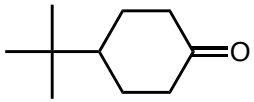
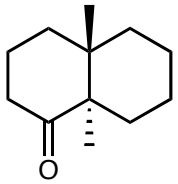


3

2)



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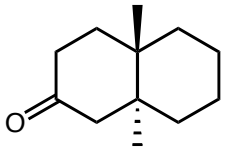

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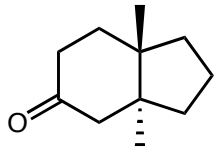

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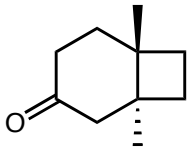
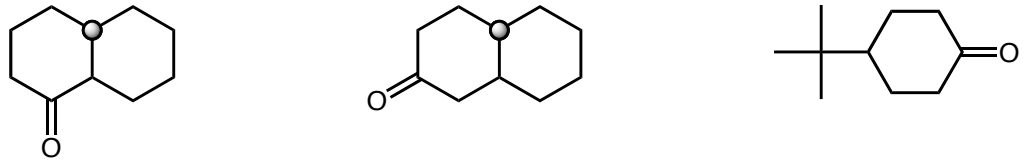


7

Arrange the following compounds in order of increasing preference for *axial* nucleophilic attack ($LiAlH_4$ for example)?

1)



1 < **2** < **3**

2)

4 < **5** < **6** < **7**

The experimentally observed percentageges for *axial* attack

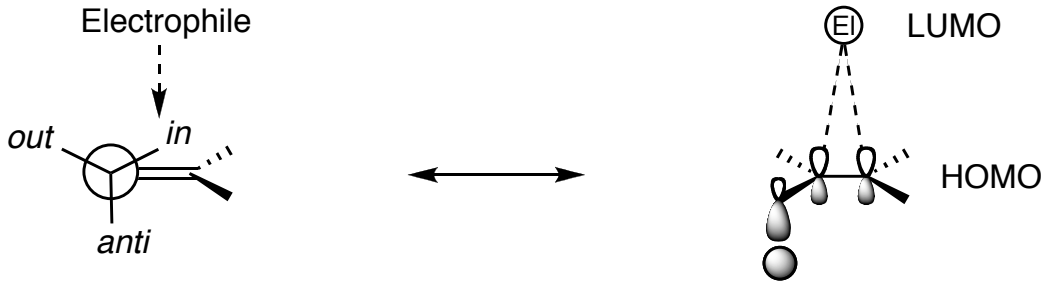
	4	**5**	**6**	**7**
$LiAlH_4$	80	85	89	94
$NaBH_4$	78	88	90	94
MeMgI	12	34	42	56

Casadevall E. *et al*, *Tet. Let.* **1976**, *17*, 2841

Frontier Orbital Interactions: Stereoselectivity

addition reactions - electrophilic additions

Houk model for electrophilic addition to alkenes



Houk K.N. *et al*, *JACS* **1982**, *104*, 7162

Frontier Orbital Interactions: Stereoselectivity

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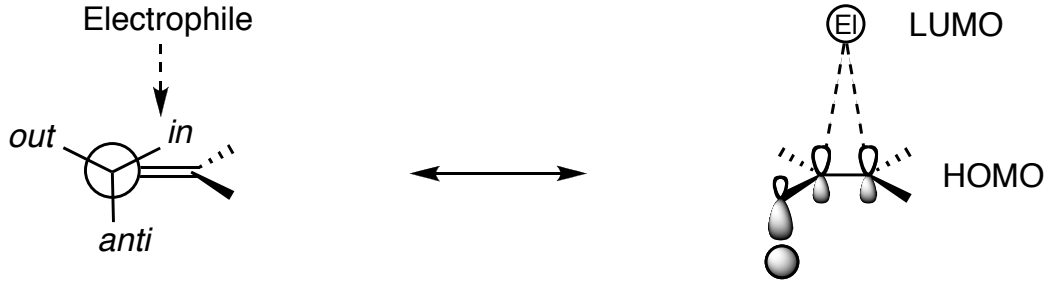
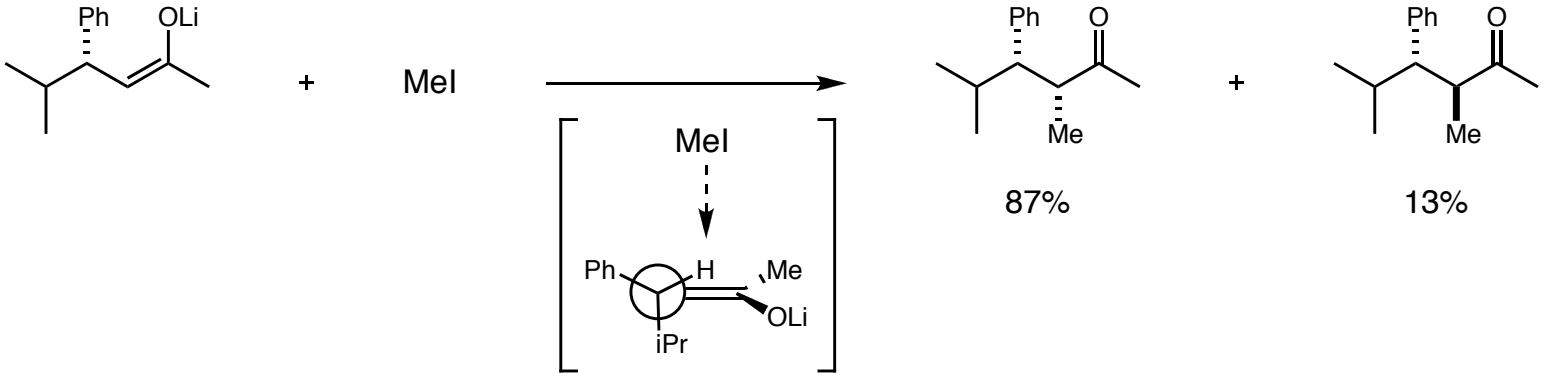


- ED and bulky groups prefer *anti* position
- Small groups prefer *inside* position

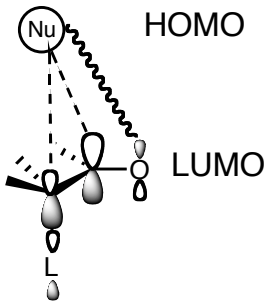


Fleming I., Lewis J.J., *Chem. Soc. Perkin Trans.* 1 **1992**, 3257

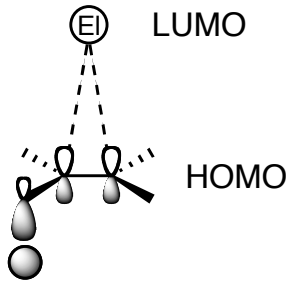
Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

Aldol reaction can be considerred as the combination of nucleophilic and electrophilic addition



The Nu–C–O angle is obstute



The El–C–C angle is acute

Frontier Orbital Interactions: Stereoselectivity

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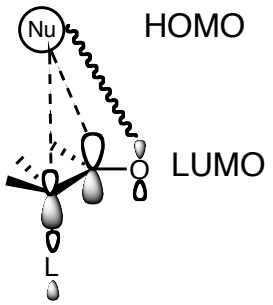
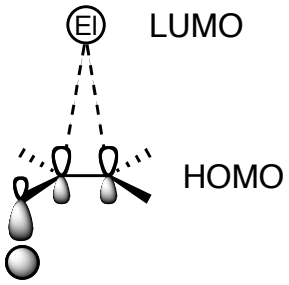
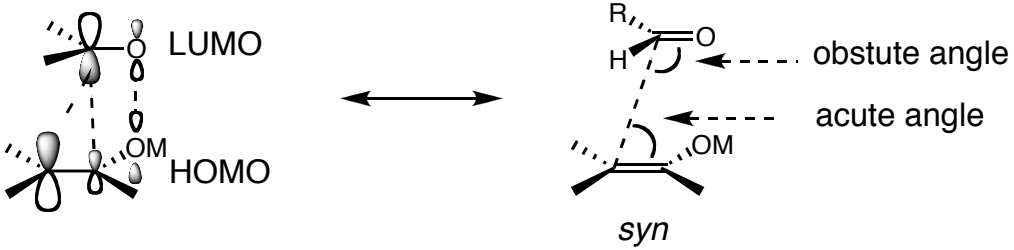


The Nu–C–O angle is obstute



The El–C–C angle is acute



Frontier Orbital Interactions: Stereoselectivity

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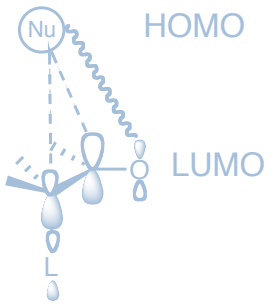

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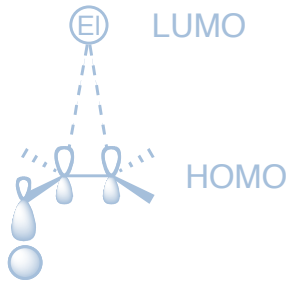

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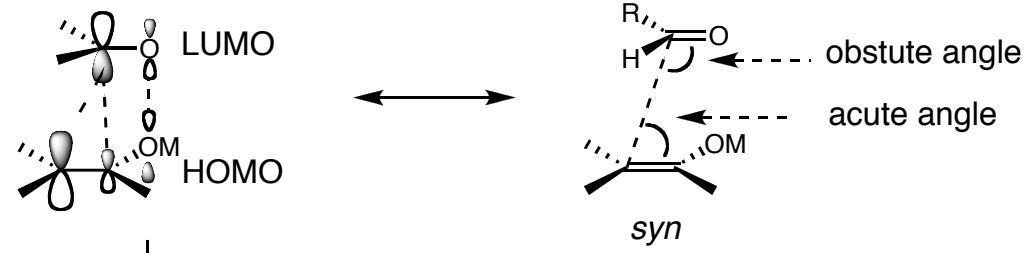
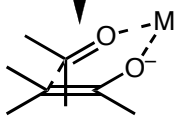
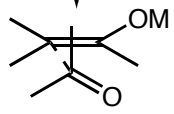




syn–cis



syn-trans

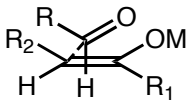
Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

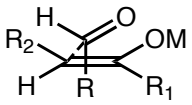
Aldol reaction – Anh's treatment

Step 1. Generate diastereomeric transition state models.

Z–enolate

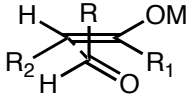


Z_1

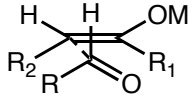


Z_2

E–enolate



E_1



E_2

Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

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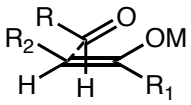
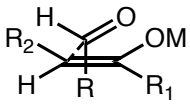
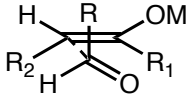


Z_1

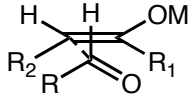


Z_2

E–enolate

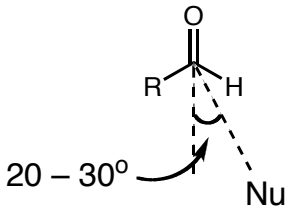


E_1



E_2

Step 2. The calculation modeling addition reaction to aldehyde showed that the bulk of R group forces the incoming nucleophile to approach the aldehyde from the side bearing hydrogen. Thus, rotate (move) the aldehyde in the models to this direction.



Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

Aldol reaction – Anh's treatment

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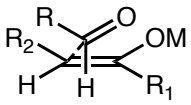
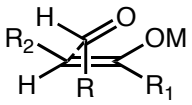
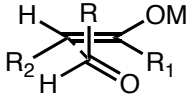


Z_1

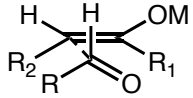


Z_2

E–enolate



E_1



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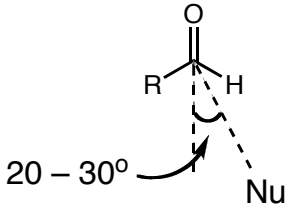
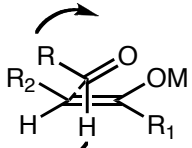
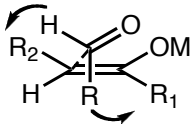


Z–enolate

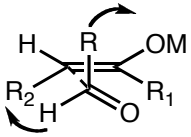


Z_1

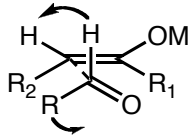


Z_2

E–enolate



E_1



E_2

Step 3. Base on the relative bulk of R_1, R_2 and the change of the intereaction after the movement, decide the best transition state.

With *Z*-enolate: If $R_2 < R_1$, **Z_1** is favorred over **Z_2**; If $R_2 \geq R_1$, **Z_2** is favorred over **Z_1**

With *E*-enolate: If $R_2 < R_1$, **E_1** is favorred over **E_2**; If $R_2 > R_1$, **E_2** is favorred over **E_1**

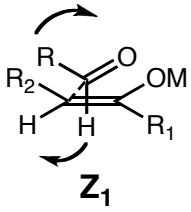
Anh's treatment is quite good for *Z*-enolate aldol addition, but still not clear for the *E*-enolate

Frontier Orbital Interactions: Stereoselectivity

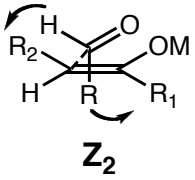
addition reactions - applied to the aldol addition

Aldol reaction – Anh's treatment

Z–enolate

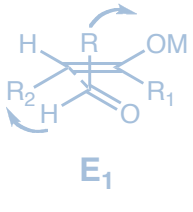


Z1

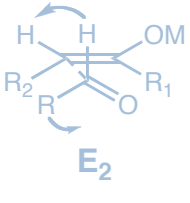


Z2

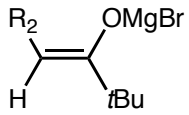
E–enolate



E1



E2



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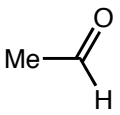

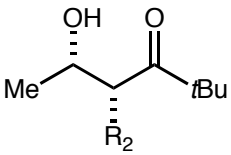

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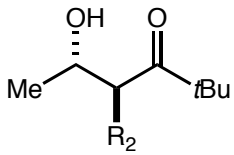
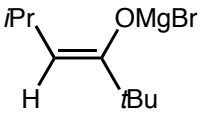


R_2				
Me	100	:	0
*i*Pr	48	:	52
*t*Bu	20	:	80



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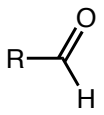

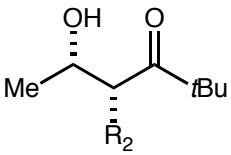

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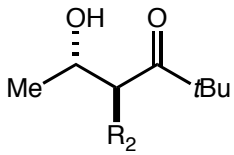


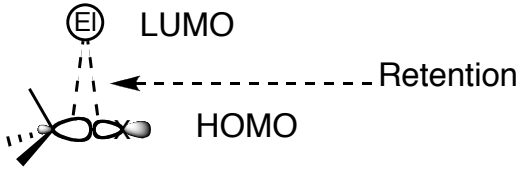
R				
Me	48	:	52
*t*Bu	29	:	71

Felman T., Dubois J.E., *Tet.* **1978**, *34*, 1343

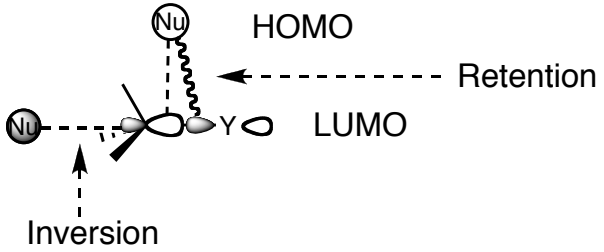
Frontier Orbital Interactions: Stereoselectivity

substitution reactions–retention of configuration

FO intereaction illutrations of bimolecular substitution reaction at saturated centers



Electrophilic substitution FO intereaction



Nucleophilic substitution FO intereaction

For the best FO overlap, normally, S_E2 reactions happen with the retention of configuration while the S_N2 happens with the inversion.

Frontier Orbital Interactions: Stereoselectivity

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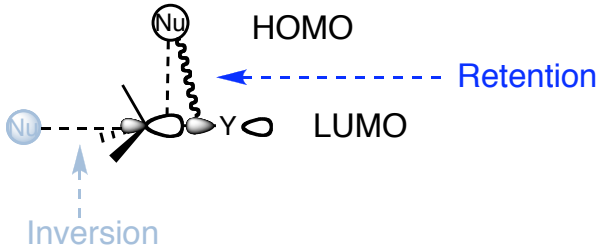

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substitution reactions–retention of configuration

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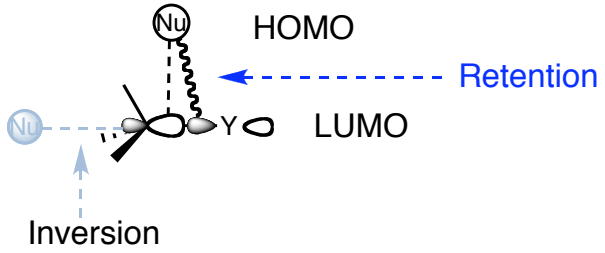


Nucleophilic substitution FO intereaction

For the best FO overlap, normally, S_E2 reactions happen with the retention of configuration while the S_N2 happens with the inversion. The question is if it is possible to obtain *S_N2 reactions with the retention of configuration*.

$$\sigma^*_{CY} = N\left(\varphi_C + \frac{\langle\varphi_C|P|\varphi_Y\rangle}{E_C - E_Y}\,\varphi_Y\right) \Longrightarrow$$

To reduce the contribution of φ_Y, we can rise E_C, lower E_Y, or do both.

- E_C rise when the electronegativity of the reaction center lowerred(Carbon to Silicon for example)
- E_Y lowered when replacing the leaving group by a more electronegative homolog.

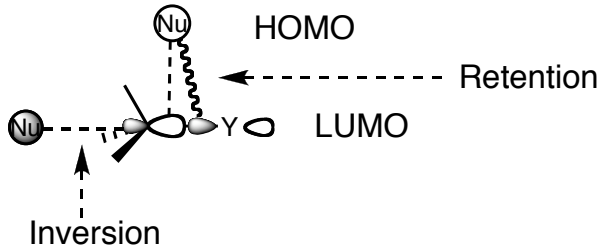
Increasing s character of the hybrid orbitals of the center.

Harder nucleophile induce greater retention of configuration.

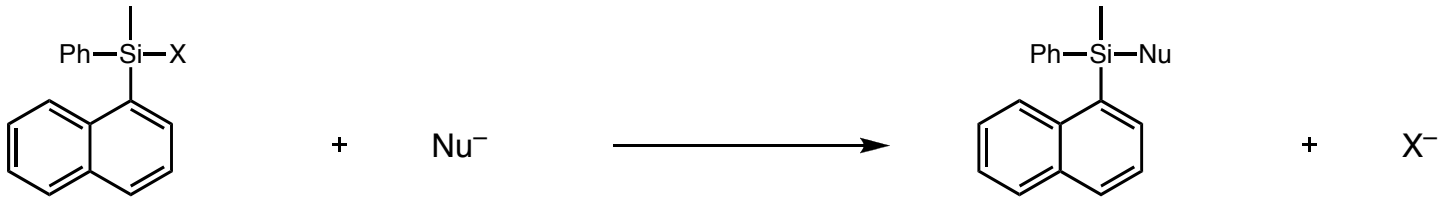
Frontier Orbital Interactions: Stereoselectivity

substitution reactions–retention of configuration

Examples for the retention at the center in S_N2 reactions



Nucleophilic substitution FO intereaction



Nu	X=	H	OMe	SMe	F	Br or Cl
RLi (alkyl or aryl)		*Re*	*Re*	*Re*	*Re*	*In*
Allyllithium		*Re*	*Re*	*In*	*In*	*In*
KOH		*Re*	*Re*		*Re*	*In*

Moreau J.J. *et al*, *Top. Stereochem.* **1984**, *15*, 87

Frontier Orbital Interactions: Stereoselectivity

substitution reactions–retention of configuration

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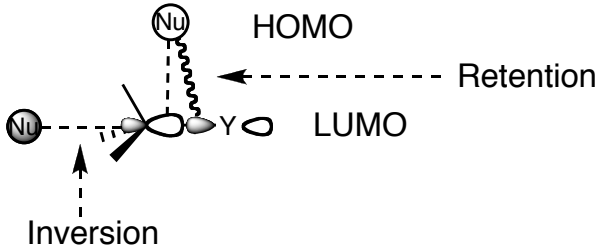
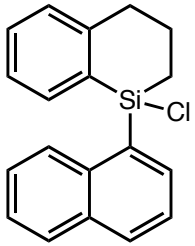
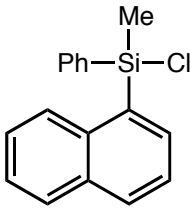


Nucleophilic substitution FO intereaction

Nu		
EtLi	63% *Re*	100% *In*
*n*BuLi	82% *Re*	59% *In*
Allyllithium	86% *Re*	100% *In*
$PhCH_2Li$	99% *Re*	100% *In*

Moreau J.J. *et al*, *Top. Stereochem.* **1984**, *15*, 87

Frontier Orbital Interactions: Stereoselectivity

factors control asymmetric induction

"The preferred trajectory will have the best FO overlap"

- Chelation, when existing, has the strongest influence
- Torisional effects and non-perpendicular attacks are second in importance
- Dipolar and antiperiplanar effects are the next critical factors
- Charge control becomes dominant mostly in compounds containing fluorine of in rigid systems
- Conformational control come to the fore in the absence og hightly polar substituents of in the reactions with vey early or very late TS
- Steric control are included in all systems

Frontier Orbital Interactions: Stereoselectivity

limitations

"The preferred trajectory will have the best FO overlap"

- Easy to use qualitatively and generally gives predictions agreeing with experiment results (80% as the author stated)

- The FO method just considers the HOMO-LUMO intereactions; Thus, the relations between lower orbitals should be taken into account when studying the outcomes of reactions

- *"Best FO overlap"* means statically. The imperfect trajectories may happen if they have enough energy and vaguely resemble ideal geometry

- The HOMO-LUMO interactions just provide information concerning the transition state potential energy, so the kinetic parameter should be considered when examining the reaction