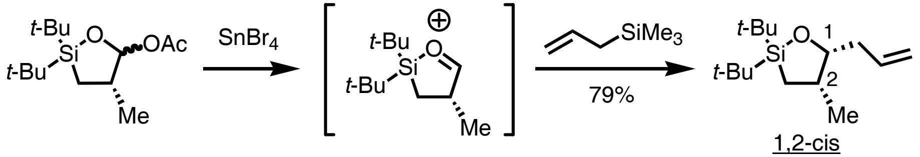
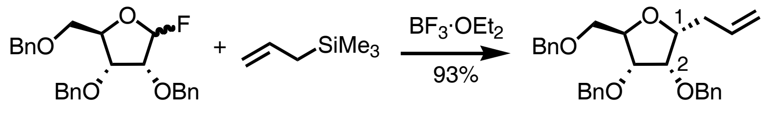
Reactions of Five-membered Ring Acetals



1,2-cis
93 : 7 selectivity

Dr. Jared Shaw

1,2-cis selectivity not unprecedented…

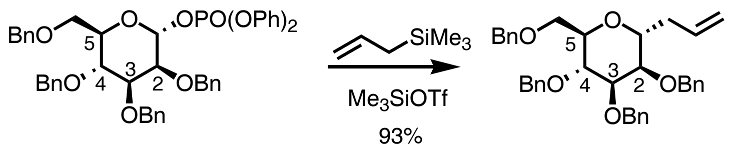


1,2-cis
100 : 0 selectivity

Ishido, Y. *Carbohydr. Res.* **1987**, *171*, 125.

Why are these reactions selective?

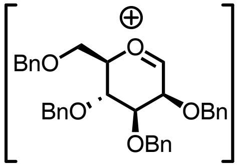
Determining the Structure of the Mannosyl Cation



α-isomer only

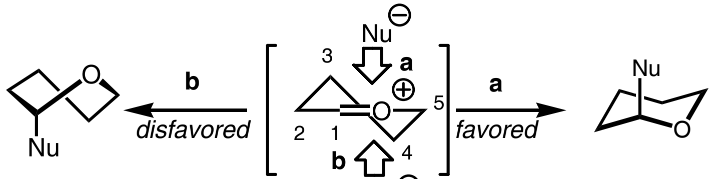
Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545

Oxocarbenium ions are likely intermediates:



How is this selectivity explained?

Stereoelectronic Effects and Reactions of Six-membered Ring Systems

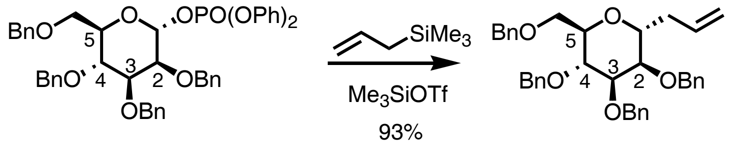


twist-boat

chair

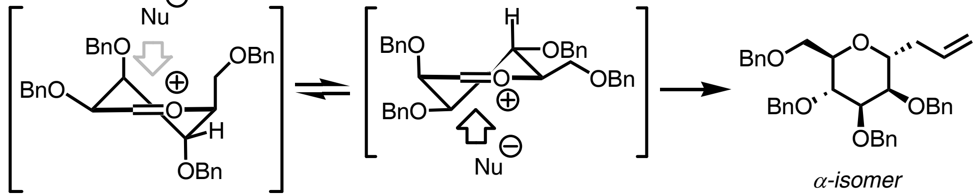
(a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983, pp. 209-221.
(b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

C-Mannosylation Reactions: Insight into the Mannosyl Cation



α-isomer only

Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545



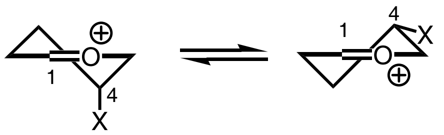
mostly axial

mostly equatorial

α-isomer

Mostly equatorial isomer the major conformer in solution… *or is it?*

C-4 Alkyl versus Alkoxy: Calculations



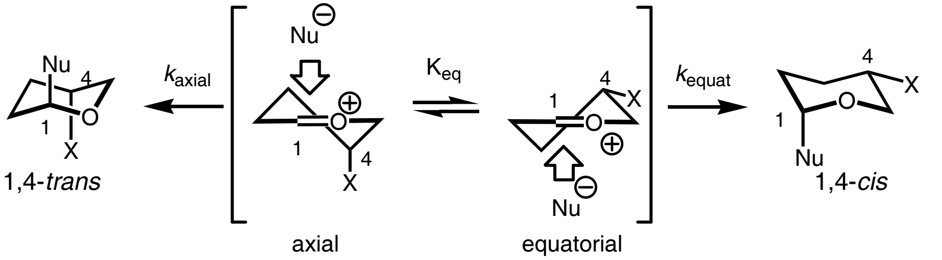
X = Me, ΔG° = –0.7 kcal/mol
X = OH ΔG° = +4.7 kcal/mol

Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859.

Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597.

- Alkoxy groups axial due to electrostatic attraction of oxygen to the cationic carbon

Substituted Oxocarbenium Ions



Because steric interactions are similar in each case…

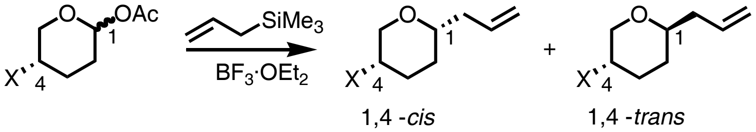
$k_{equat} \approx k_{axial} \Rightarrow$ product ratio $\approx K_{eq}$

(“Winstein–Hollness kinetic scenario”)

Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

X = OR should give opposite product to reaction where X = R

C-4 Substituted Oxocarbenium Ions



X	cis : trans	yield (%)
CH$_2$Bn	93 : 7	77
OBn	1 : 99	75

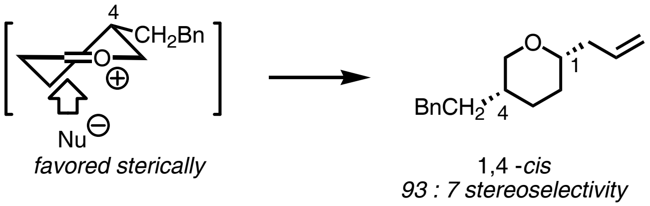
Dr. Jan Romero, Dr. Sarah Tabacco

Control experiments indicate that:

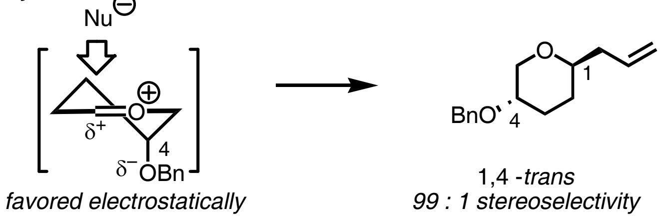
1. Oxocarbenium ions are likely intermediates
2. Ion-pairing effects do not control selectivity

Explanation of Selectivity

Alkyl:



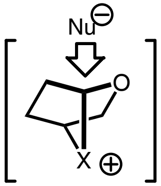
Alkoxy:



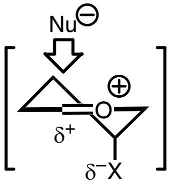
- Selectivity consistent with the calculated conformational preferences

Origin of Selectivity: Anchimeric Assistance or Electrostatic Effects?

Is the heteroatom donating its lone pair to form a bridged structure…

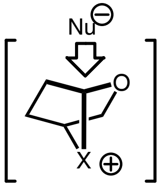


… or do electrostatic effects hold the charged units together?



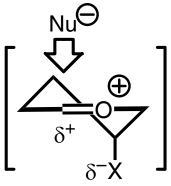
Halogen-Substituted Oxocarbenium Ions

<u>If anchimeric assistance operates:</u>



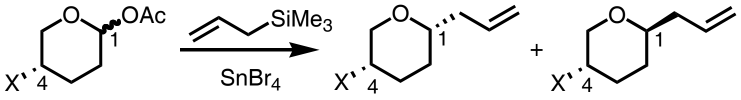
Trans selectivity: I > Br > Cl > F

<u>If electrostatic effects operate:</u>



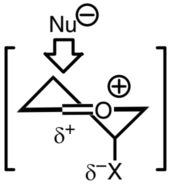
Trans selectivity: F > Cl > Br > I

Results with Halogen Series



1,4 -*cis* 1,4 -*trans*

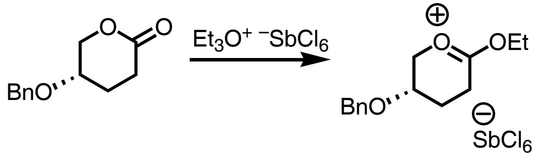
X	*cis* : *trans*	yield (%)
F	4 : 96	45
Cl	14 : 86	90
Br	29 : 71	87
I	72 : 28	90



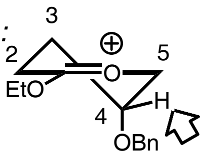
- ■ Data consistent with electrostatic effects, not anchimeric assistance

Dr. Claudia Lucero, Dr. Sarah Tabacco

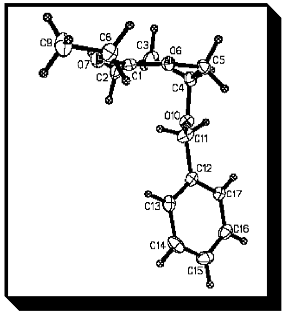
Structural Evidence for Conformational Preferences



In solution:



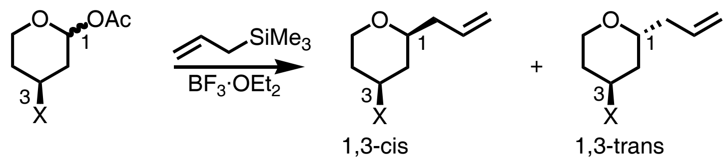
sextet, J = 2.0 Hz
No NOE to C-2 H's



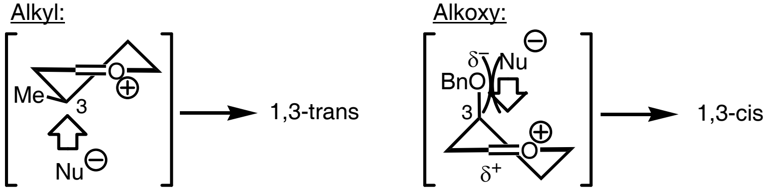
Dr. Steve Chamberland, Dr. Joe Ziller

- ■ Alkoxy-substituted dioxocarbenium ion prefers pseudoaxial conformer

Stereoselective Reactions of Other Alkoxy-Substituted Acetals

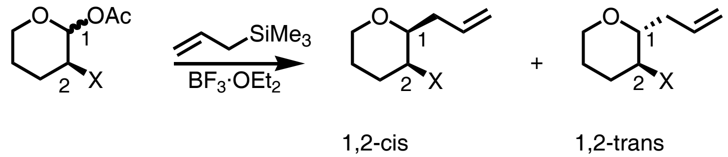


X	cis : trans
Me	1 : 99
OBn	89 : 11

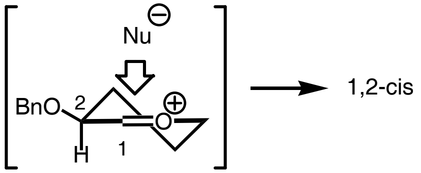


- C-3 alkoxy group favors axial orientation, likely by electrostatic effects

2-Substituted Acetals

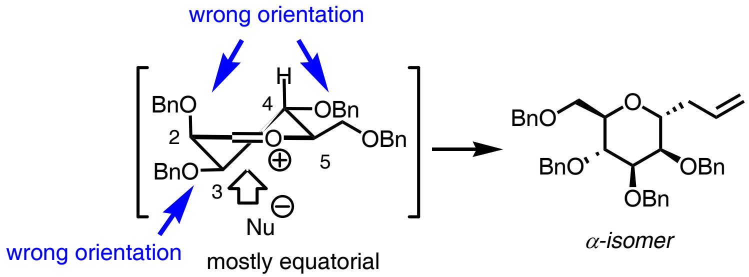


X	cis : trans
Me	52 : 48
OBn	83 : 17



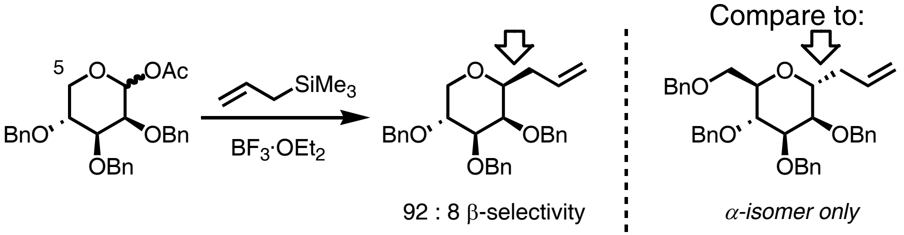
- Equatorial orientation favored by hyperconjugation of $\sigma_{C\text{-}H} \rightarrow \pi^*_{C\text{-}O}$

C-Mannosylation: Why is it Selective?

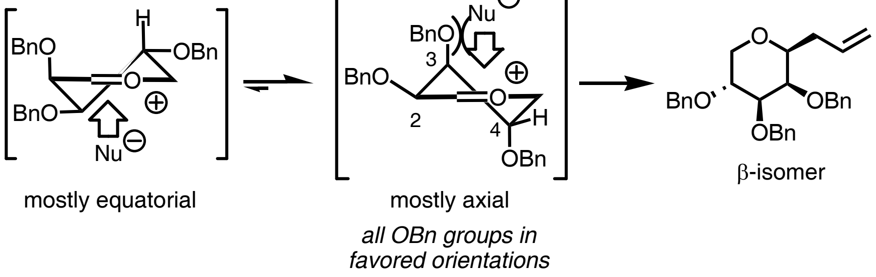


Is selectivity controlled by the C-5 substituent?

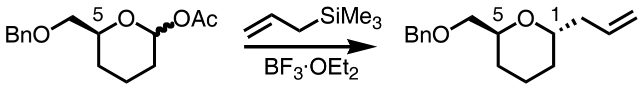
Reactions of Lyxose Derivatives



- With C-5 alkyl missing, the alkoxy groups control selectivity!

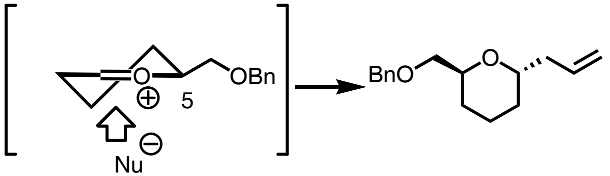


Influence of C-5 Substituent



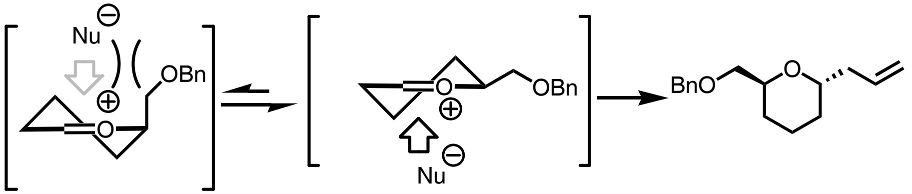
95% α-selectivity

Dr. Claudia Lucero, Mike Yang



But is the preference for equatorial group at C-5 that high?

Curtin-Hammett Scenario



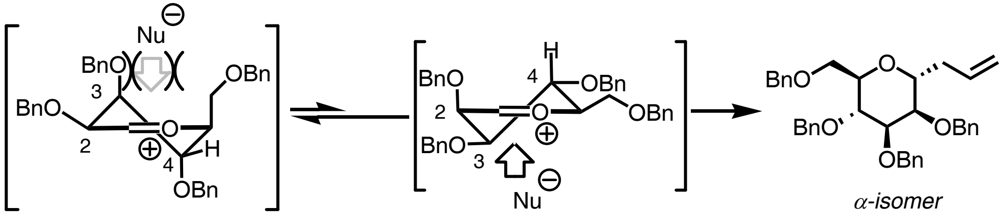
less reactive

more reactive
favored by 0.3 kcal/mol
(B3LYP/6-31G*,corrected
for CH_2Cl_2 solvent)

95% α-selectivity

- C–5 alkoxymethyl group equatorial favored, and reacts faster

Mannosylation Deconvoluted



mostly axial
favored (by 8 kcal/mol)...
but unreactive

mostly equatorial

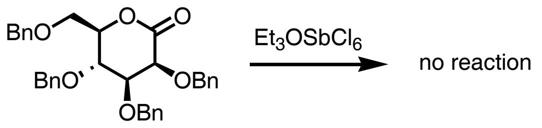
α-isomer

- Product formed from the more reactive, higher-energy conformer

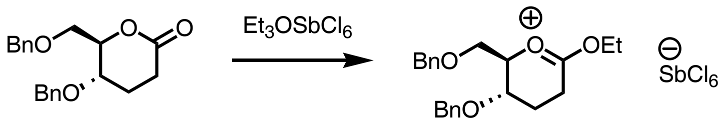
Curtin-Hammett scenario

Can we determine the structure of the mannosyl cation?

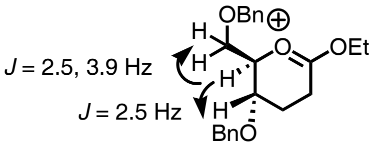
Structural Studies on Mannosyl Cation



Structure of Dideoxymannosyl Cation



Dr. Mike Yang

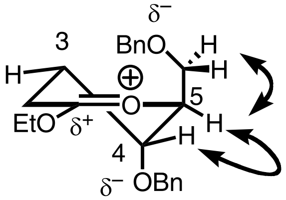


J = 2.5, 3.9 Hz

J = 2.5 Hz

Why are the J-values so small?

Structure of Dideoxymannosyl Cation



J = 2.5, 3.9 Hz ⇐ must be gauche to H-5

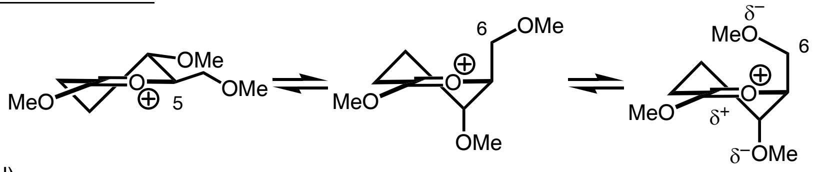
J = 2.5 Hz

also W-coupling between H-5 and H-3 (1.5 Hz)

- C-5 alkoxymethyl group is axial and OBn is pointed over the ring!

Calculations on Dideoxymannosyl Cation

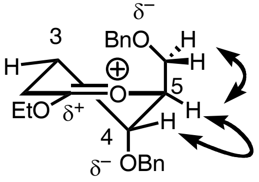
Computational data:



E_{rel} (kcal/mol) (B3LYP/6-31G*,corrected for CH_2Cl_2 solvent) +2.3 + 2.2 0

- The lowest energy structure maximizes electrostatic interactions

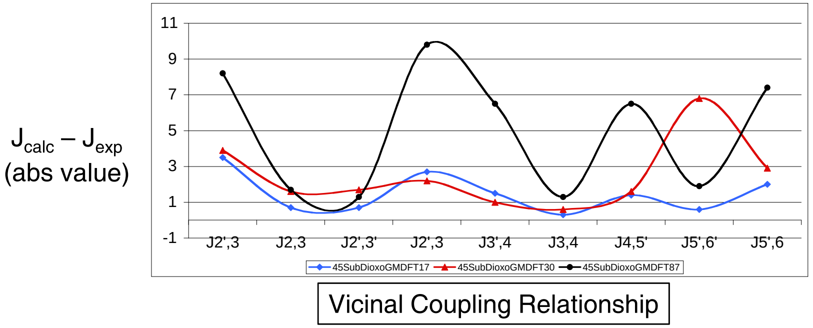
Experimental data:

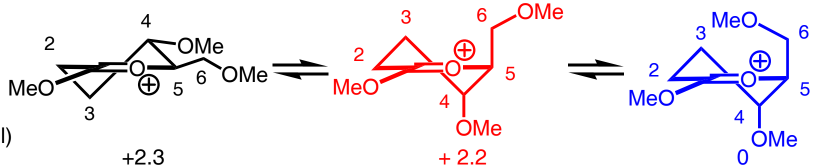


J = 2.5, 3.9 Hz

J = 2.5 Hz

Comparison of Calculated and Experimental Coupling Constants

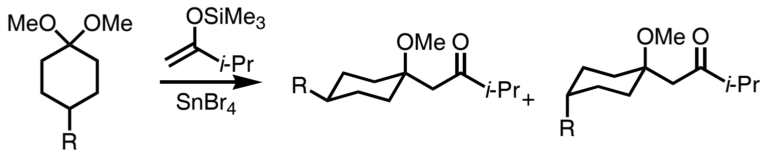




E_{rel} (kcal/mol) +2.3 + 2.2 0

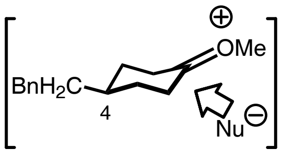
- Lowest energy structure fits the calculated coupling constants best

Electrostatic Effects in Exocyclic Oxocarbenium Ions

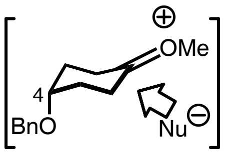


R = CH_2Bn, 96 : 4 dr
R = OBn, 4 : 96 dr

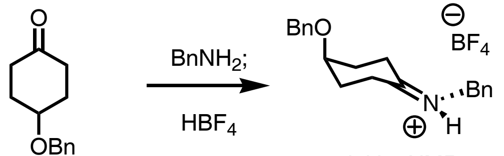
Larger nucleophiles attack equatorially…



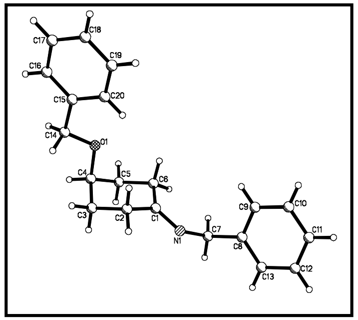
vs.



Structural Studies of Iminium Ions



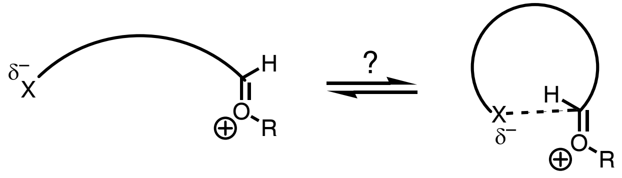
axial by NMR



Josh Dibble, Dr. Joe Ziller

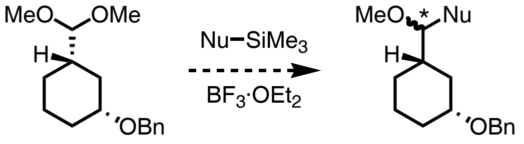
Electrostatic Effects in More Flexible Oxocarbenium Ions

Can electrostatic effects control conformations and reactivities of flexible oxocarbenium ions?

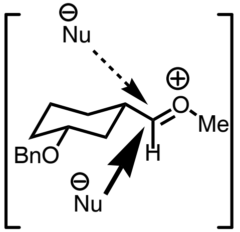


See: Molander, G. A.; Haar, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40-49.

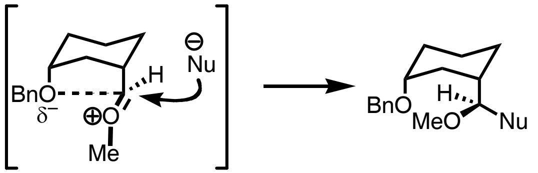
Cis-Cyclohexane Derivatives



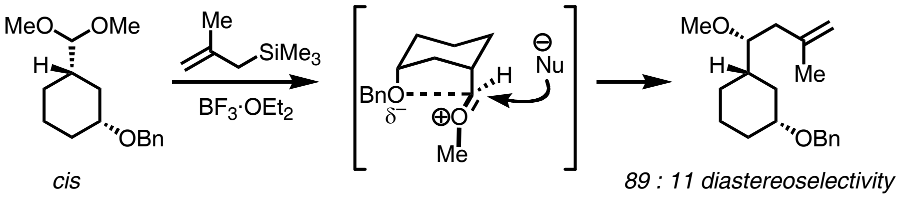
If diequatorial ⇒ unselective



If diaxial ⇒ selective?



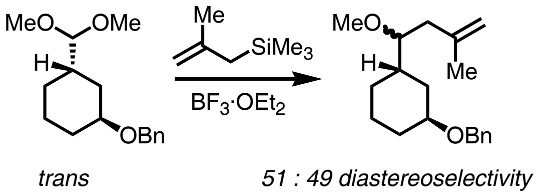
Electrostatic Effects in Acyclic Oxocarbenium Ions



89 : 11 diastereoselectivity

Lisa Barker

Control experiment:



51 : 49 diastereoselectivity

- Electrostatic effects can control selectivities in acyclic systems

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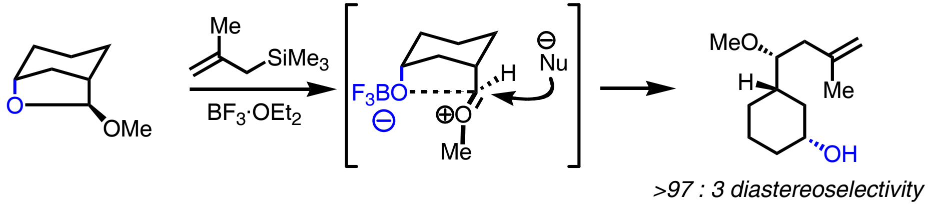
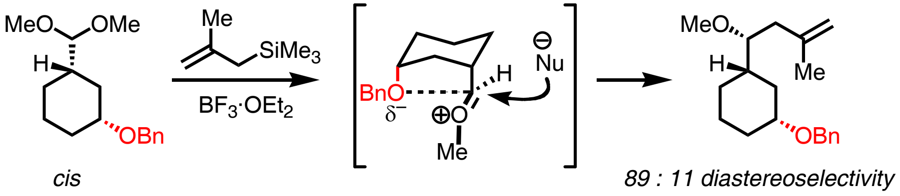
Electrostatic Effects as Function of Substituent



>97 : 3 diastereoselectivity

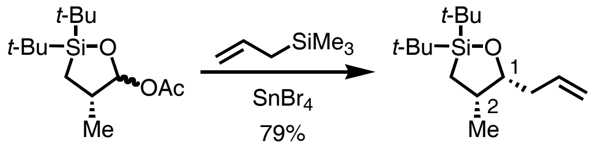
Recall…



89 : 11 diastereoselectivity

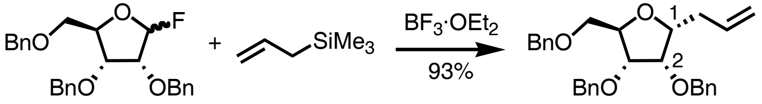
- Maybe "F_3B^-–O" more electron-rich than Bn–O ?

Stereoselective Reactions of Five-membered Ring Systems



1,2-cis
93 : 7 selectivity

Dr. Jared Shaw



1,2-cis
100 : 0 selectivity

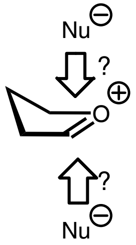
Ishido, Y. *Carbohydr. Res.* **1987**, *171*, 125.

How do we explain these selectivities?

Five-Membered Ring Oxocarbenium Ions

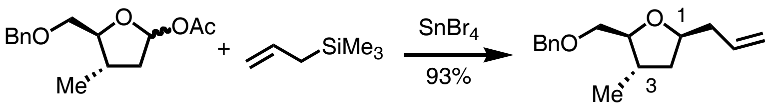
Problem:

No general model to understand the reactions of five-membered ring oxocarbenium ions had been reported!



Once an oxocarbenium ion is formed, which face is attacked?

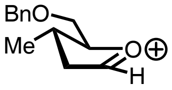
Case Study: *trans*-3,4-Disubstituted Oxocarbenium Ions



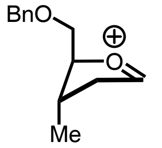
1,3-trans
95 : 5 selectivity

The cationic intermediate could exist in two conformers:

1. Diequatorial conformer

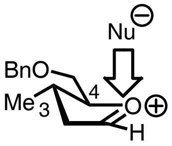


2. Diaxial conformer

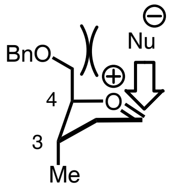


Two Modes of Attack are Consistent with Product Stereochemistry

1. Attack on the diequatorial conformer from "inside" the envelope



2. Attack on the diaxial conformer from "outside" the envelope



"Inside" attack on the diequatorial conformer avoids serious steric interactions

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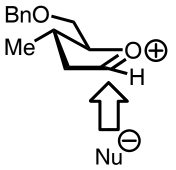
Stereoselectivity Cannot Be Only Steric Effect

Problem:

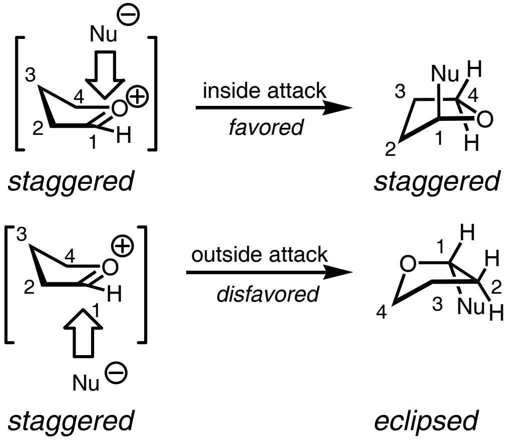
Why is "outside attack" on the diequatorial conformer so disfavored?



This mode of attack only forms 5% of the product!

Stereoelectronic and Torsional Effects

- Analyze five-membered rings like six-membered ones…

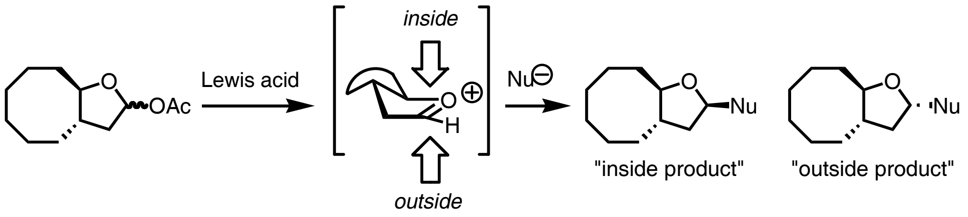


How could we disprove the preference for inside attack?

Bicyclic Oxocarbenium Ions

The idea:

A bicyclic oxocarbenium ion would reside in only one conformer



- Diastereoselectivity would give a quantitative measure of the stereoelectronic preference for inside attack versus outside attack

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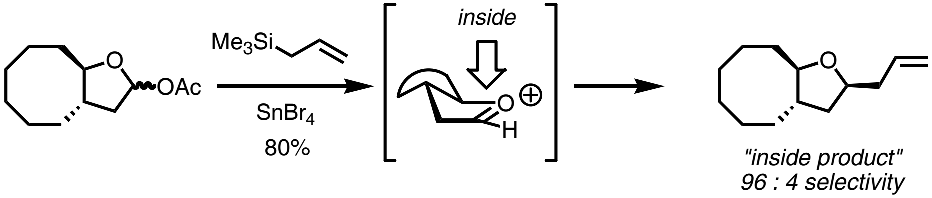
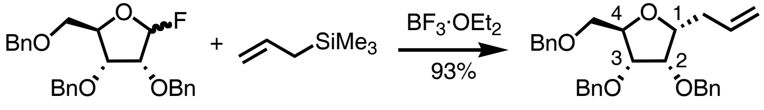
Bicyclic Oxocarbenium Ions



- *Stereoelectronic preference for inside attack is about 1.1 kcal/mol at –78 °C*

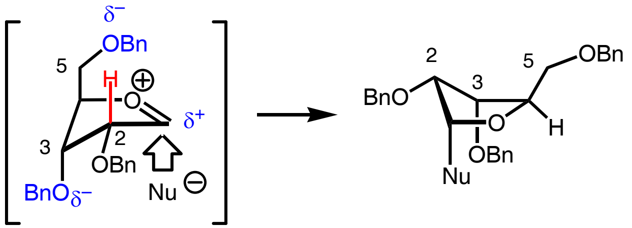
Dr. Deborah Smith, Michelle Tran

Application of the Inside Attack Model: The Ribosyl Cation



100 : 0 selectivity

Ishido, Y. *Carbohydr. Res.* **1987**, *171*, 125.



This structure maximizes electrostatic interactions and hyperconjugation

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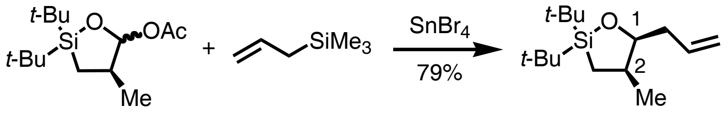
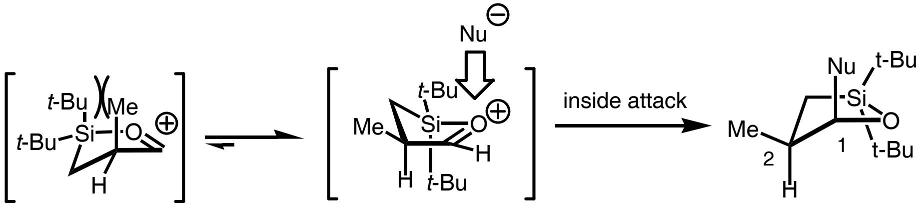
Oxasilacyclopentane Stereochemistry Explained



1,2-cis

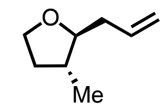
93 : 7 selectivity



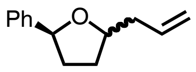
1,2-cis

- Inside attack model is useful in a number of settings

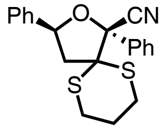
Application of Inside Attack Model



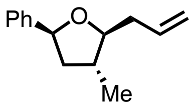
68 : 32 selectivity



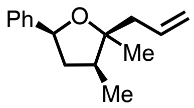
53 : 47 selectivity



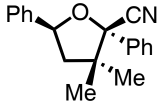
98 : 2 selectivity



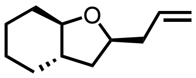
67 : 33 selectivity



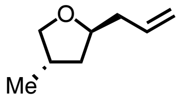
65 : 35 selectivity



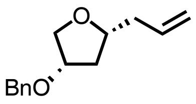
95 : 5 selectivity



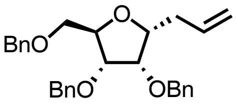
73 : 27 selectivity



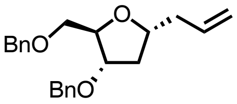
95 : 5 selectivity



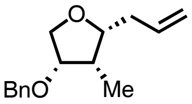
95 : 5 selectivity



>99 : 1 selectivity

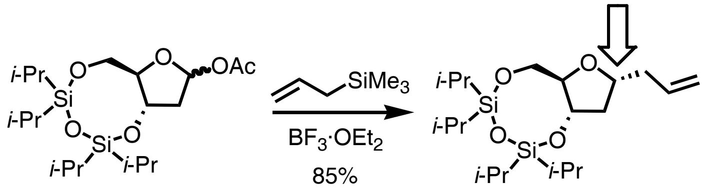


>99 : 1 selectivity



98 : 2 selectivity

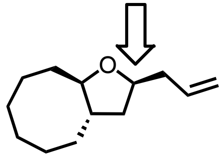
Exception to the Inside Attack Model



85% "outside" product

For hydride additions: Woski, S. A. *Org. Lett.* **1999**, *1*, 1173.

Compare to:



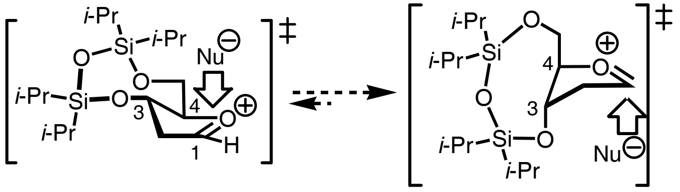
94% "inside" product

Vi Tran

Disiloxane-bridged Oxocarbenium Ion

Two possibilities:

1. Ring is more flexible



favored by electrostatic effects?

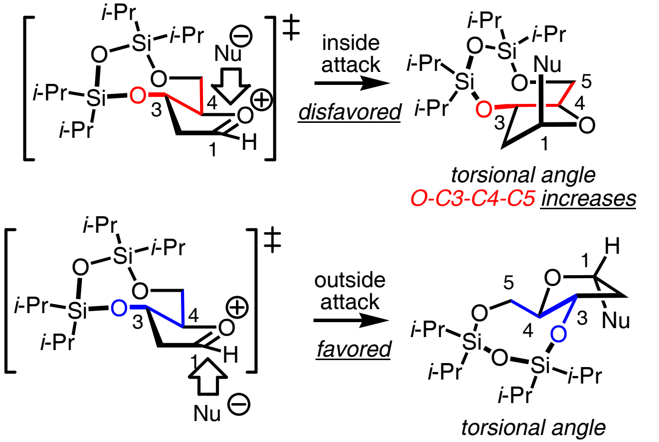
Satisfying… except:

(1) Si–O–Si angle is ~155°
(2) O–Si–O–Si–O linkage is planar

van Boom, J. H. *Acta Cryst.* **1981**, *B37*, 1924

Disiloxane-bridged Oxocarbenium Ion

2. Ring is less flexible

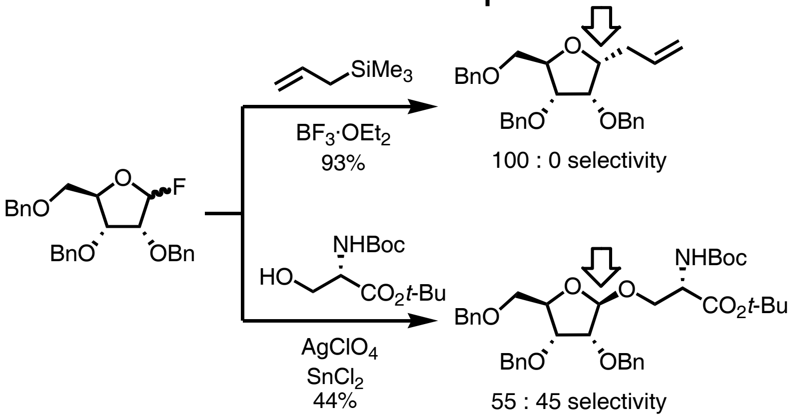


torsional angle
O-C3-C4-C5 increases

torsional angle
O-C3-C4-C5 stays same

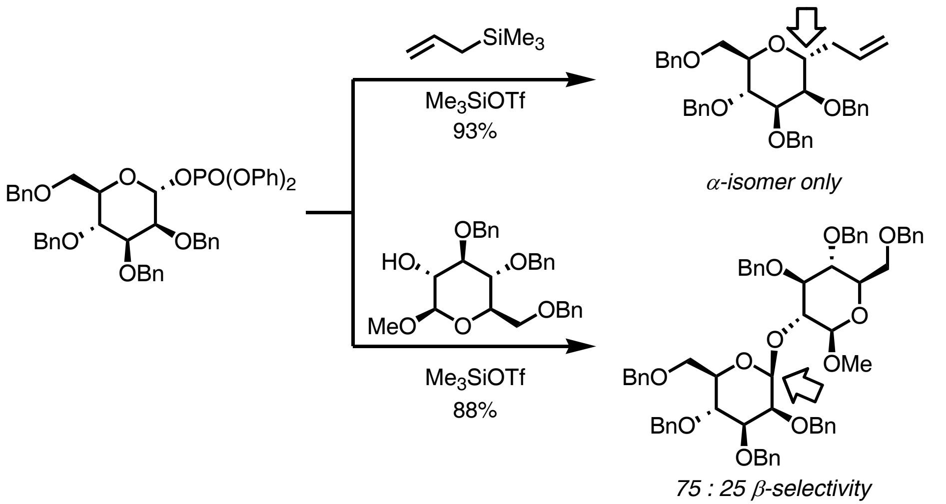
- Rigidity of disiloxane ring may dictate motion of five-membered ring

C-Ribosylation vs. *O*-Ribosylation: Another Exception



Ishido, Y. *Carbohydr. Res.* **1987**, *171*, 125.
Gravier-Pelletier, C.; Le Merrer, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 142.

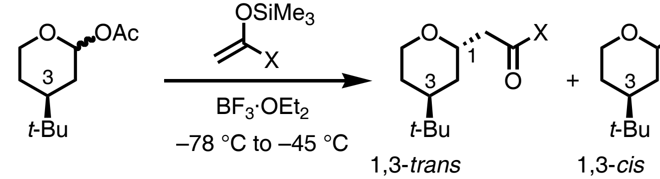
C-Mannosylation vs. *O*-Mannosylation

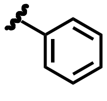
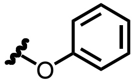
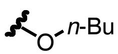


Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545

Why does selectivity depend upon the nucleophile?

Selectivity as Function of Nucleophilicity



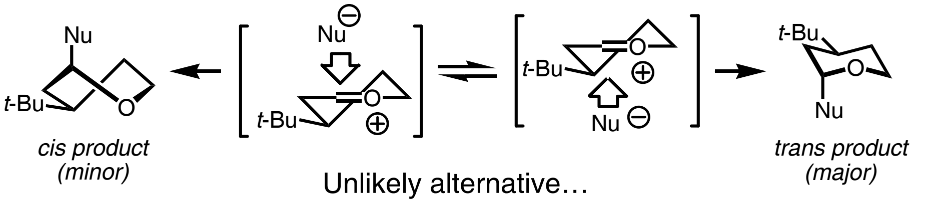
X	*trans : cis*
	98 : 2
	87 : 13
	63 : 37

increasing nucleophilicity

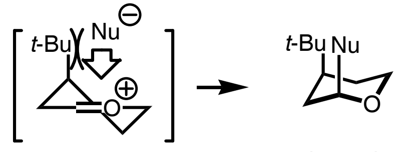
Walter Salamant, Dr. Jen Krumper

Measures of nucleophilicity: Mayr, H. *Acc. Chem. Res.* **2003**, *36*, 66-77.

Origin of Cis Products



Unlikely alternative…



less stable cation *cis product*

<u>cis</u> products likely formed by stereoelectronically disfavored attack

Why does increasing nucleophilicity lead to stereoelectronically disfavored products?

Reactivity-Selectivity Principle

As reactants become more reactive, selectivities decrease

Intuitively appealing… but "constant selectivity" more common
(relative rate is independent of absolute rate)

Mayr, H.; Ofial, A. R. "The Reactivity-Selectivity Principle: An Imperishable Myth in Organic Chemistry," *Angew. Chem. Int. Ed.* **2006**, *45*, 1844.

- Correlation between reactivity and selectivity only predictable as rates approach the diffusion rate limit

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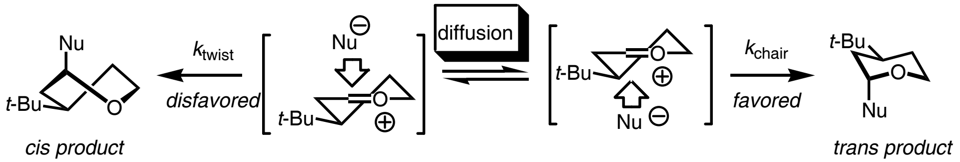
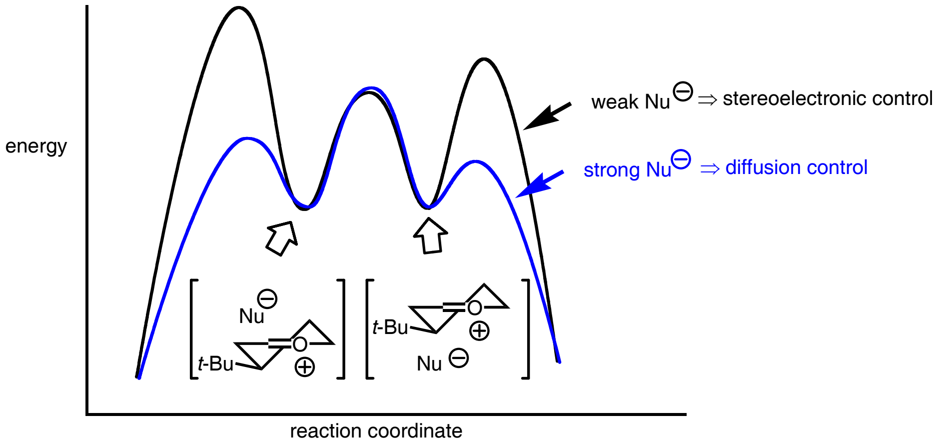
Why is Reaction with a Highly Reactive Nucleophile Unselective?



Stereoelectronic models assume diffusion is fast…
but what if it were not?

For Strong Nucleophiles, Bond Formation Faster than Diffusion



- As rate of nucleophilic attack approaches rate of diffusion⇒ selectivity decreases

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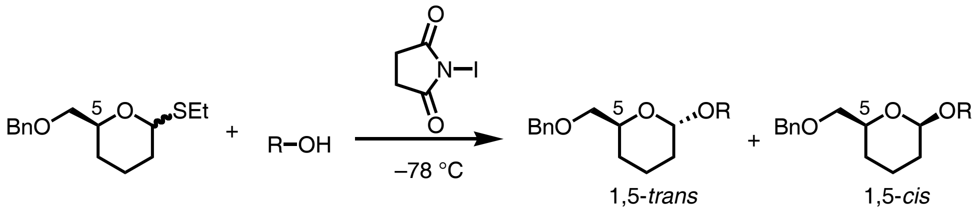
Selectivity as Function of Nucleophilicity: *O*-Glycosylation



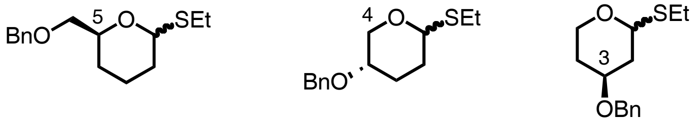
R	*trans : cis*
$F_3C–CH_2$	88 : 12
$F_2CH–CH_2$	82 : 18
$FCH_2–CH_2$	73 : 27
$ClCH_2–CH_2$	66 : 34
$BrCH_2–CH_2$	60 : 40
$HCH_2–CH_2$	48 : 52

increasing nucleophilicity ↓

Correlation between reactivity and selectivity

Matt Beaver

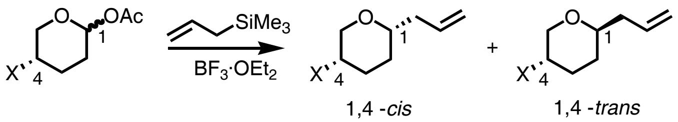
Selectivity as Function of Nucleophilicity: *O*-Glycosylation



- For $F_3C–CH_2OH$, rate below diffusion limit ⇒ stereoelectronic control
- For $H_3C–CH_2OH$, rate near the diffusion limit ⇒ diffusion control
  (see Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888)

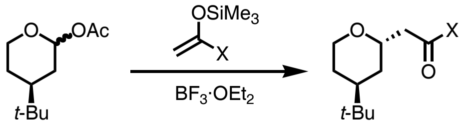
Reactions of Oxocarbenium Ions

- Electrostatic effects influence the conformational preferences of heteroatom-substituted oxocarbenium ions



X	cis : trans
CH_2Bn	93 : 7
OBn	1 : 99

- Stereoelectronic effects determine which face of an oxocarbenium ion is attacked
- Consider interactions of nucleophiles with substituents when analyzing selectivities (Curtin–Hammett Principle)
- Reactions with highly reactive nucleophiles can occur at or near the diffusion rate limit



X = Ph, 98 : 2
X = O*n*-Bu, 63 : 37