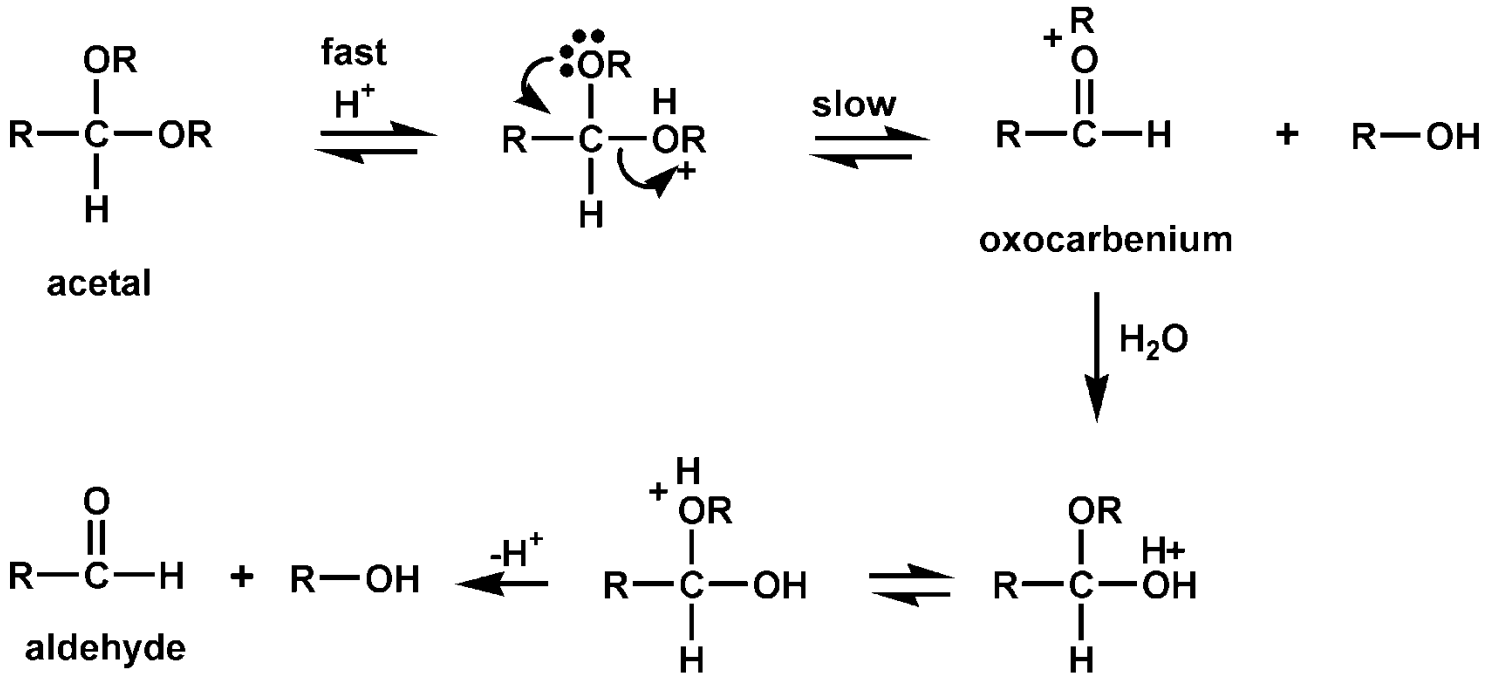
SECTION 4

Stereoelectronic Effects (S.E.)

and Reactivity of Acetals and Related Functions

(2018)

Acetal hydrolysis (mechanism)



E.J. CORDES.

Prog. Phys. Org. Chem. 4, 1-44 (1967).

Conformation of acetals

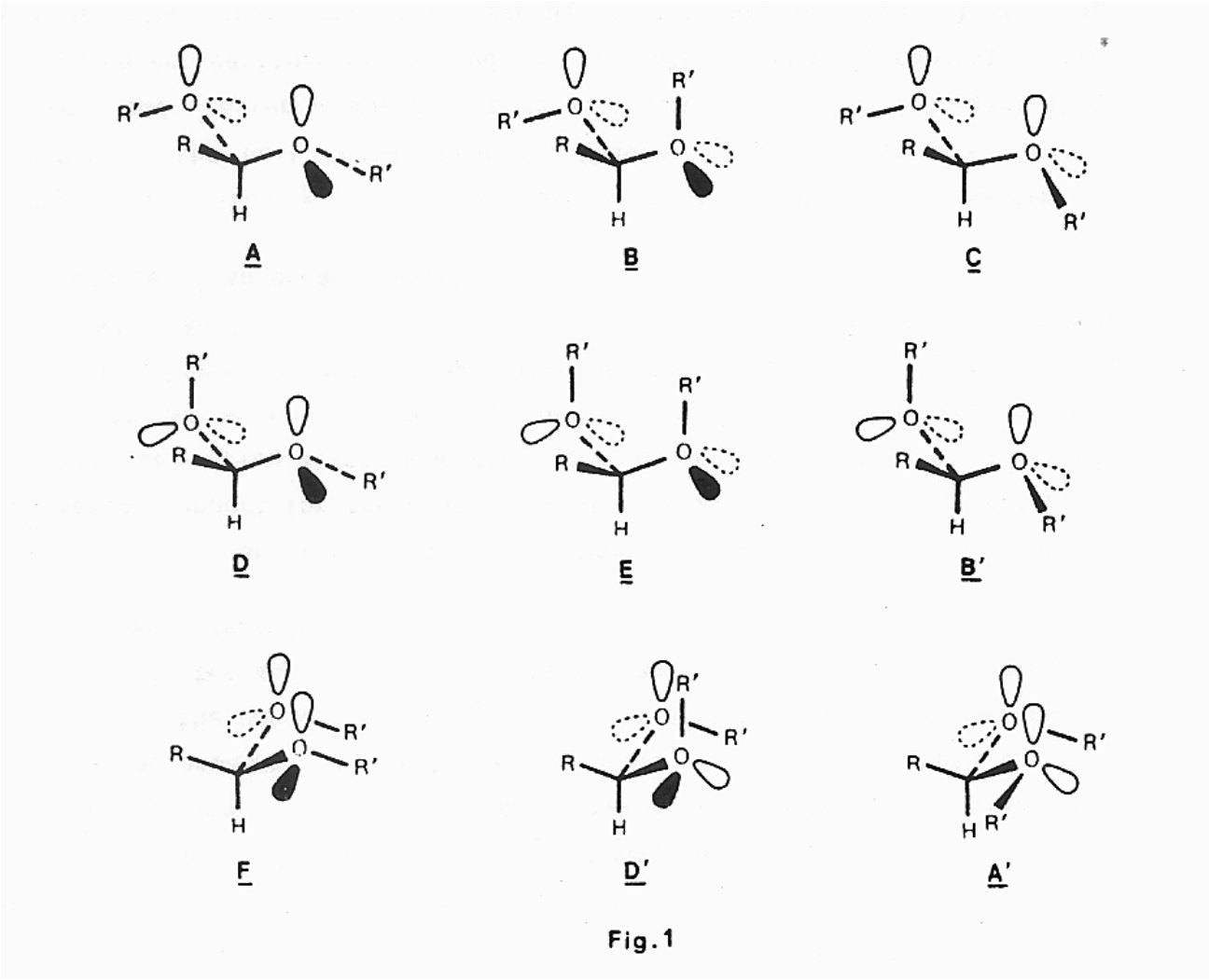
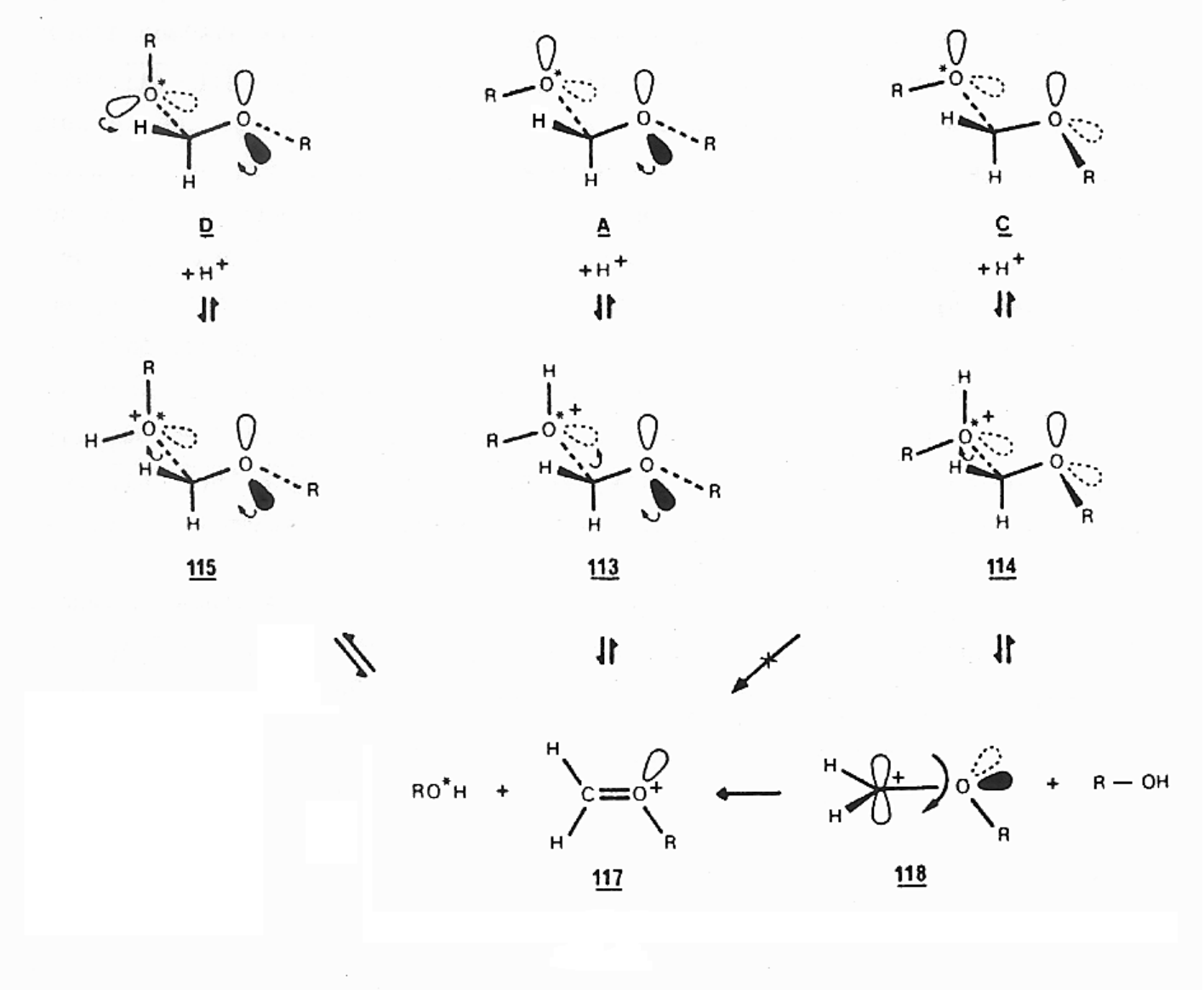
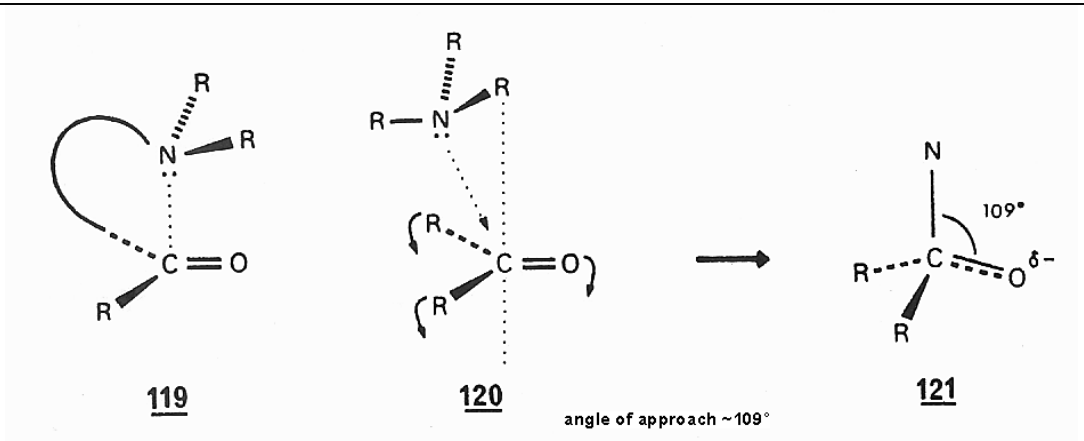


Fig.1

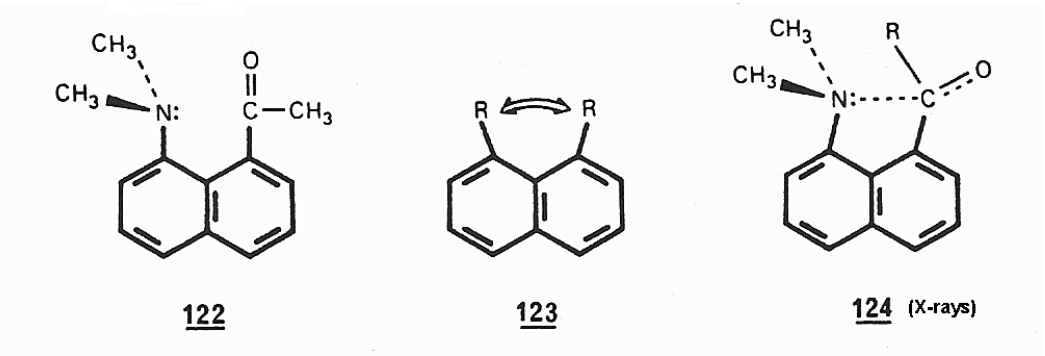
STEREOELECTRONIC EFFECTS and Oxygen Basicity, Bond Length and Preferential Cleavage in Acetal Hydrolysis (theory)



Bürgi-Dunitz Angle of Attack on Carbonyl Group. Evidence from X-Rays Diffraction Analysis



In molecular containing an amino group and a ketone (**119**), X-rays shows the N:---C=O bond too long for a bond but too short for no bonding.
In **120**, the RRC=O unit (**120** to **121**) deviates from coplanarity.

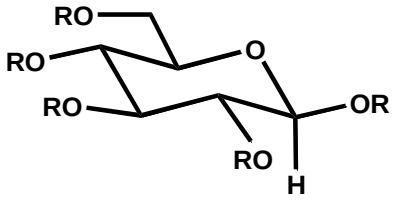


In 1,8-disubstituted naphtalene, both substituents are splayed outward.
In **122**, the C-O bond is splayed outward, but the C-N bond leans inward.

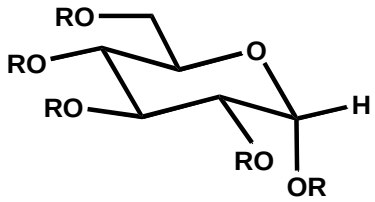
J.D. Dunitz *et al.* *Helv. Chim. Acta* 1978, *61,* 2783.

No Evidence in Favor of Stereoelectronic Control in Acetal Hydrolysis in Early Studies

In 10 anomeric pairs of alkyl glucopyranosides, the β-anomers were hydrolyzed 1.3-3.2 times faster than the α-anomers.

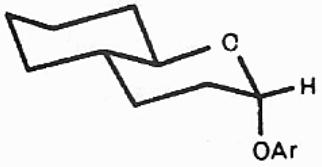


faster than



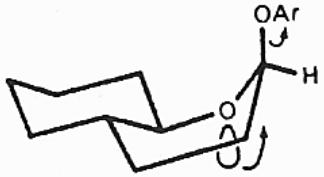
Feather Harris

Also,



127 (1)

128 (~3)



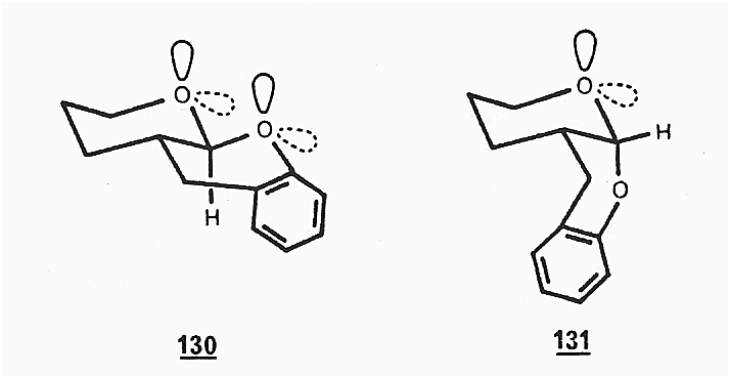
129

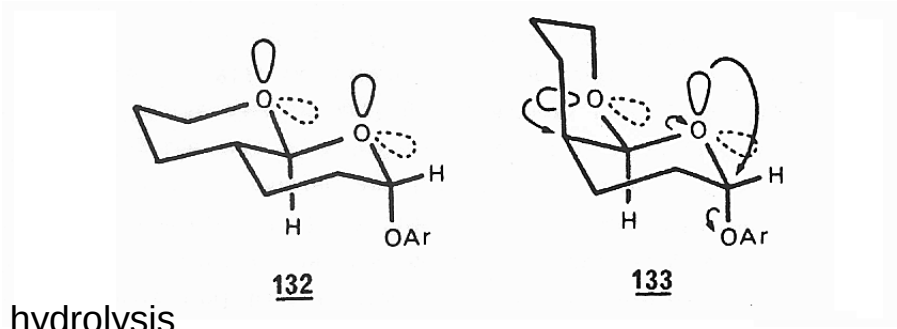
Hydrolysis of *p*-nitrophenoxy **127** is pH-independent in the pH range 7-10.
Spontaneous hydrolysis of **127** is 3.3 times slower than **128**.
It was first concluded that there was no evidence that acetal cleavage is subject to stereoelectronic control.
It was later disclaimed as **128** could hydrolyzed via boat conformer **129**.

Kirby

Evidence of Stereoelectronic Control in Hydrolysis Came with Conformationally Rigid Acetal Compounds

Hydrolysis **131** (0.1 N HCl) is > 3000 faster than **130**

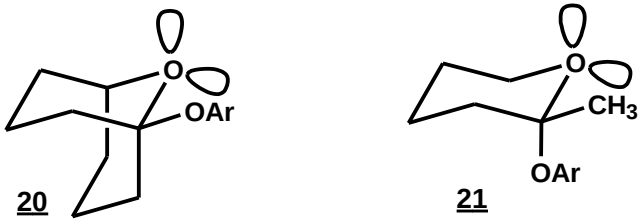




Kirby

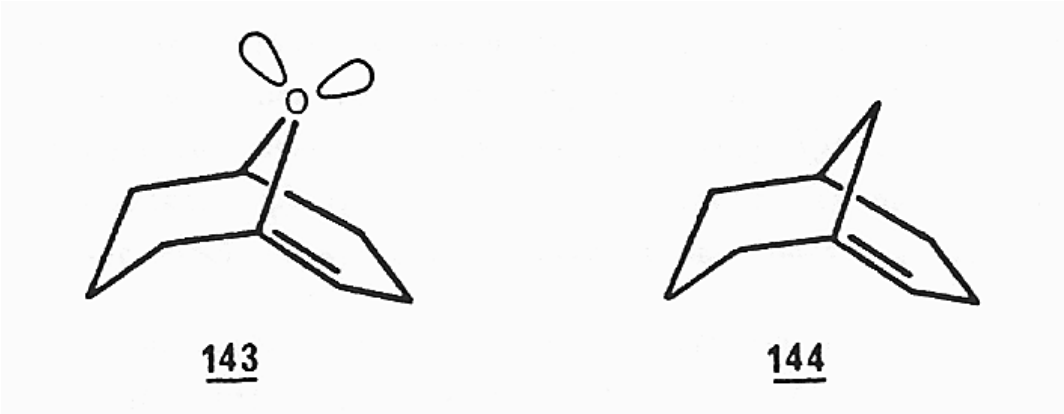
Spontaneous hydrolysis

Relative rate: **1** **~10,000**



Relative rate: **1** **~1.2 x 10^{13}**

Hydration of Enol Ether vs Olefin



143 144

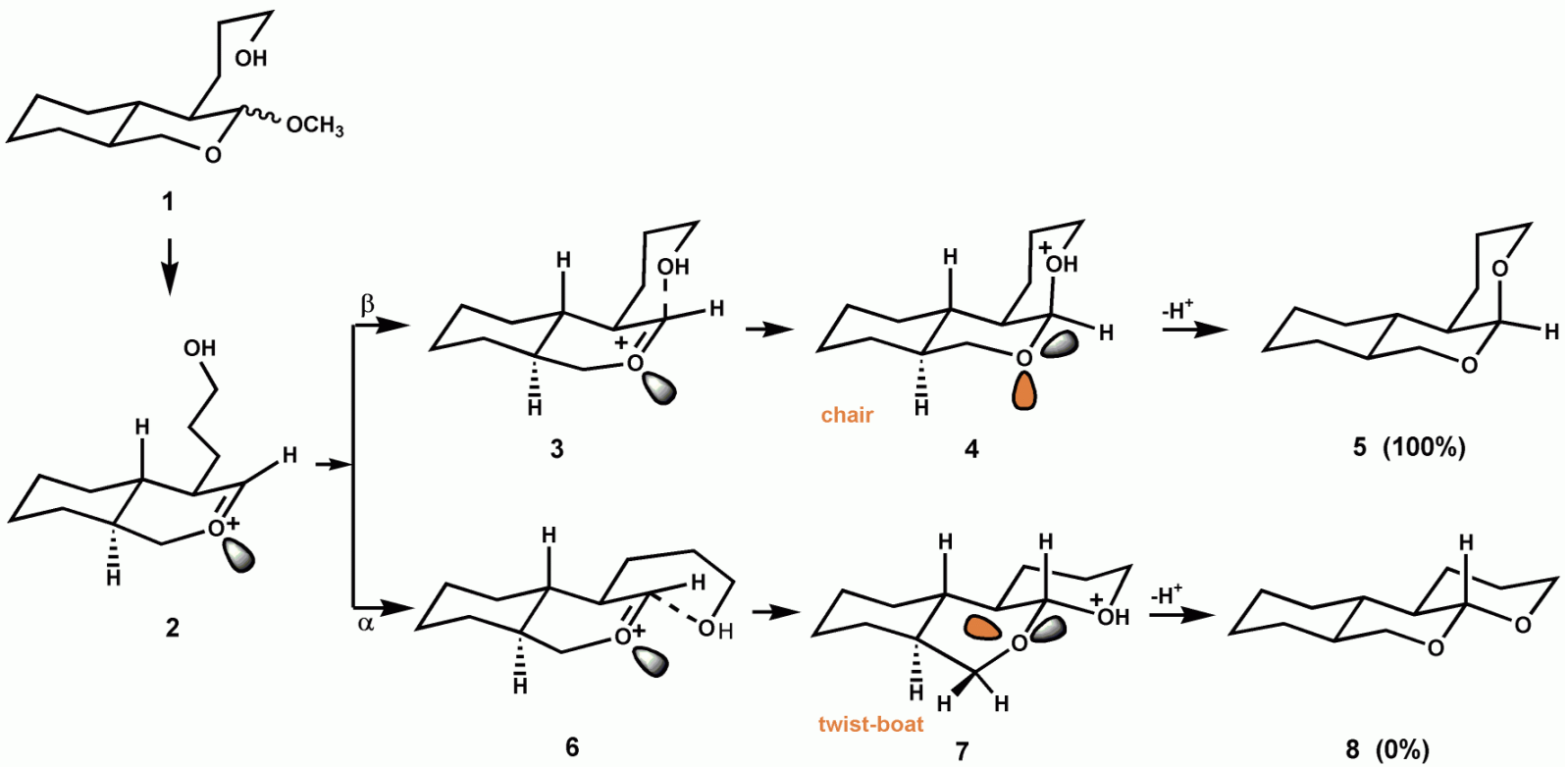
Relative rate: **1** **200**

Kresge-Wiseman

Relative rate: **10^6** **1**

Evidence of Stereoelectronic Control in Acetal Formation

Antiperiplanar Lone Pair Hypothesis



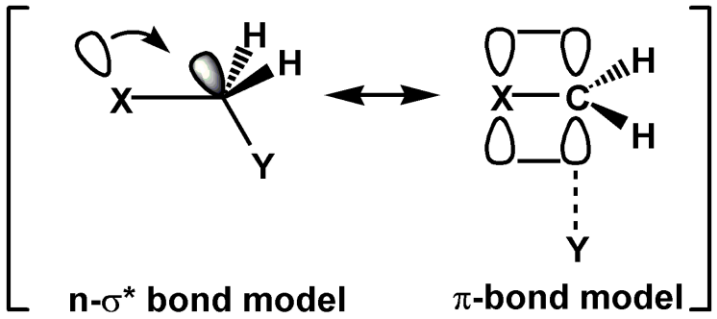
N. BEAULIEU, R.A. DICKINSON, P. DESLONGCHAMPS. *Can. J. Chem.* 58, 2531 (1980).

P. DESLONGCHAMPS, Y.L. DORY and S. LI. *Can. J. Chem.* 72, 2021 (1994).

Strength of the Anomeric Effect as a Function of Leaving Group

Y	E (X = OH)	E (X = NH_2)
NH_2	-0.7	-1.0
OH	-1.0	-1.9
F	-2.0	-3.6
NH_3^+	-3.5	-5.7
OH_2^+	-6.2	-17.3
FH^+	-20.5	-30.6

Energy parameters e_O, e_N for electronic component of anomeric effect due to O, N (kcal/mol)

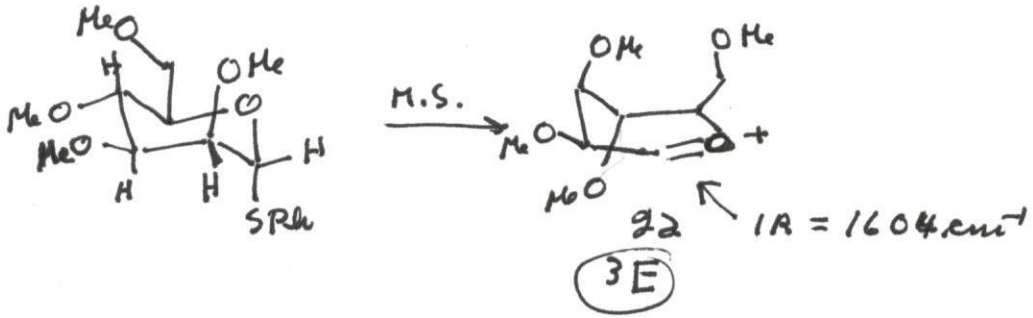


• **F. GREIN and P. DESLONGCHAMPS. Can. J. Chem. 70, 604 (1992).**

• **F. GREIN. *In "The Anomeric Effect and Associated Stereoelectronic Effects"*. Chap. 11 : Anomeric and Reverse Anomeric Effect in Acetals and Related Functions. *Edited by* G.R.J. Thatcher. ACS Symposium Series 539, Washington, D.C., 1993.**

T. J. Boltje et al J. A. C. S. 2018, 140, 6034-6038

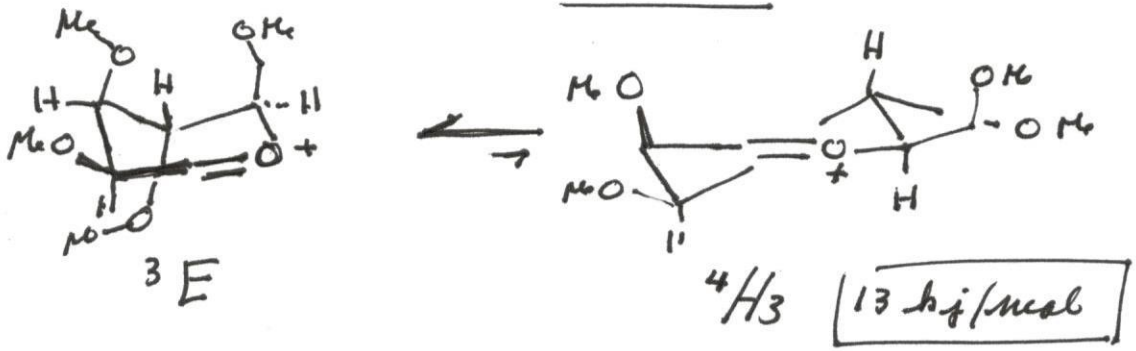
Direct Experimental characterization of Glycosyl cations by infrared ion spectroscopy.



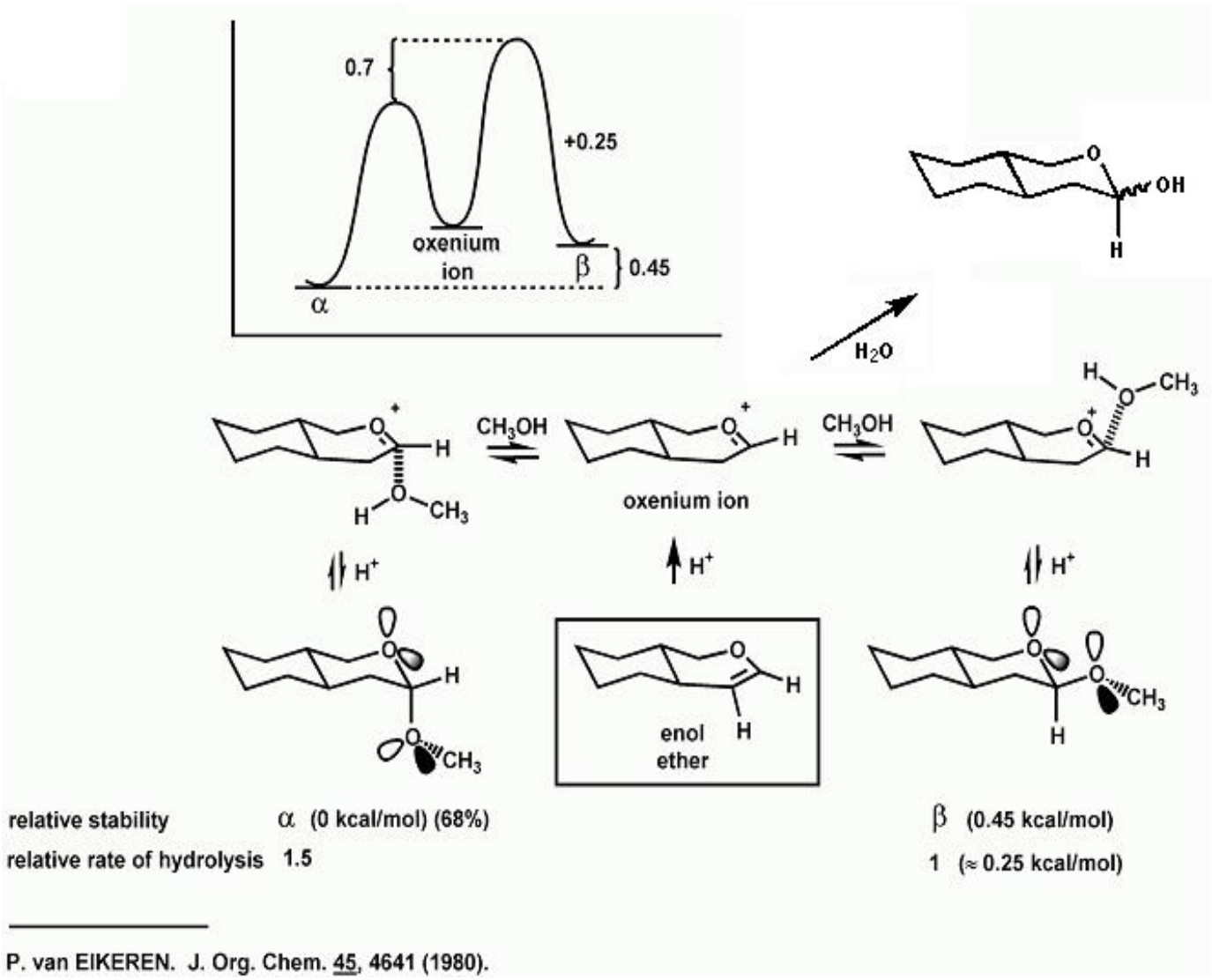
^3E

DFT calculations yielded 2 structures $^3E \rightleftharpoons {}^4H_3$ (13 kJ/mol)

best experimental shows only ^3E.



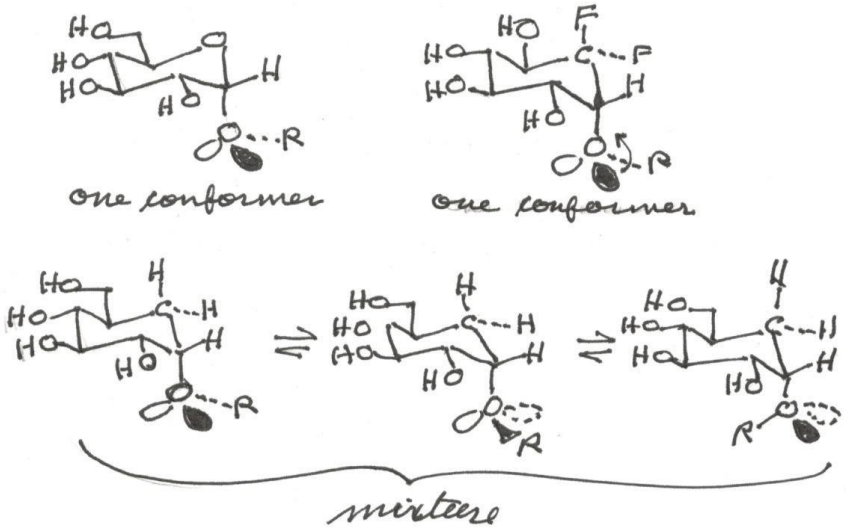
Relative Energy of TS in the Formation of α and β Glycosides Experimental Results



P. van EIKEREN. J. Org. Chem. 45, 4641 (1980).

P. DESLONGCHAMPS, S. LI, Y.L. DORY. Org. Lett. 6, 505 (2004).

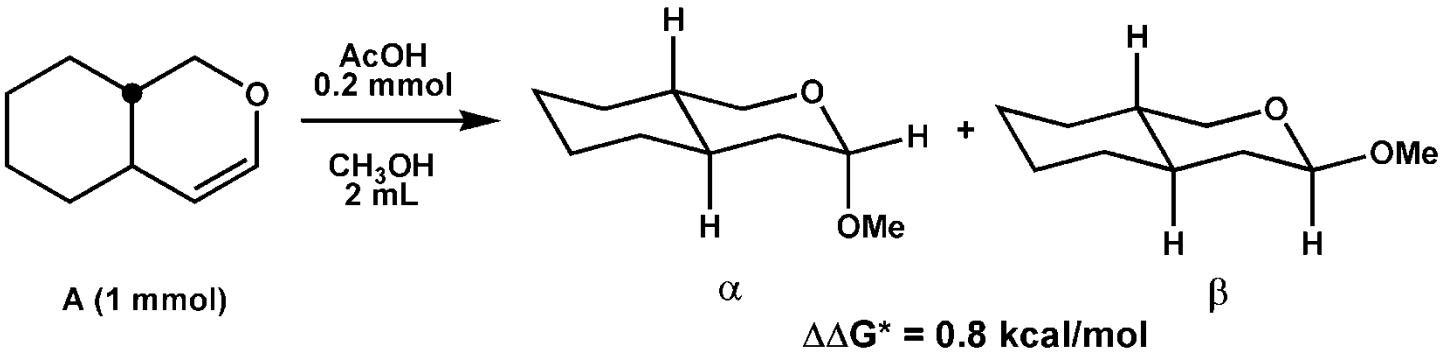
Restoring the exo anomeric effect



gem-difluoro carbohydrate. Restoring the exo anomeric effect

M. SOLLOGOUB et al.
Angew. Chem. Int. Ed.
2014, 53, 9597–9602

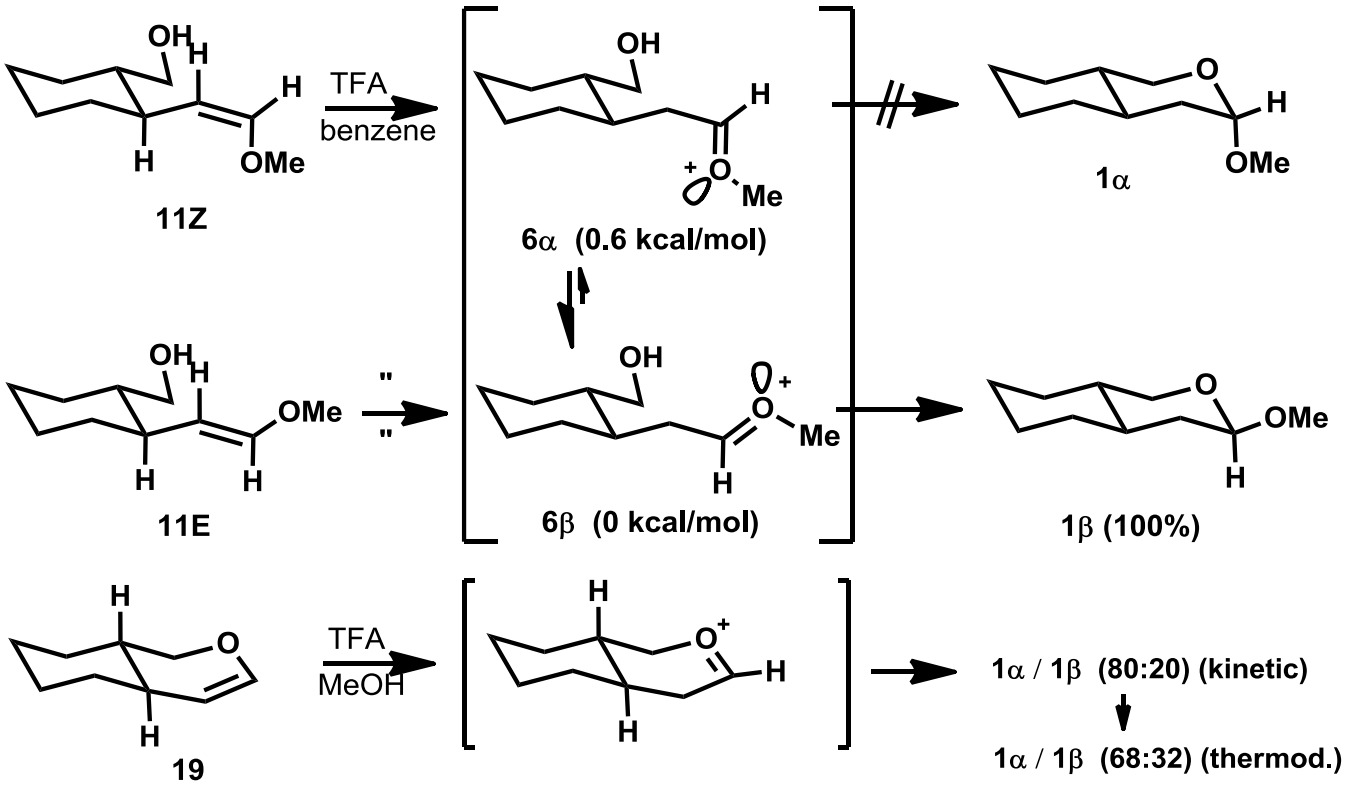
Relative Rate of Formation of α and β Glycosides from Enol Ether



T (h)	A	*alpha*	*beta*
0.5	95	4	1
29	72.5	22	5.5
74	22.8	60.5	16.7
89	18	64	18
115	12.7	67.7	19.6
171	8.1	69.7	22.2

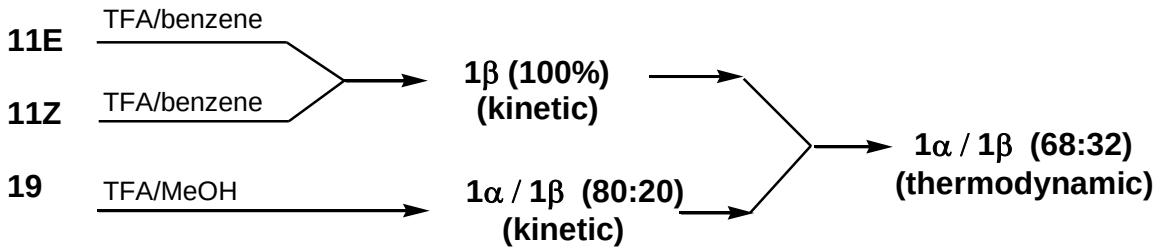
P. Deslongchamps, S. Li, Y.L. Dory. Org. Lett. 2004, *6,* 505-508.

Formation of α and β Glycosides from Enol Ethers



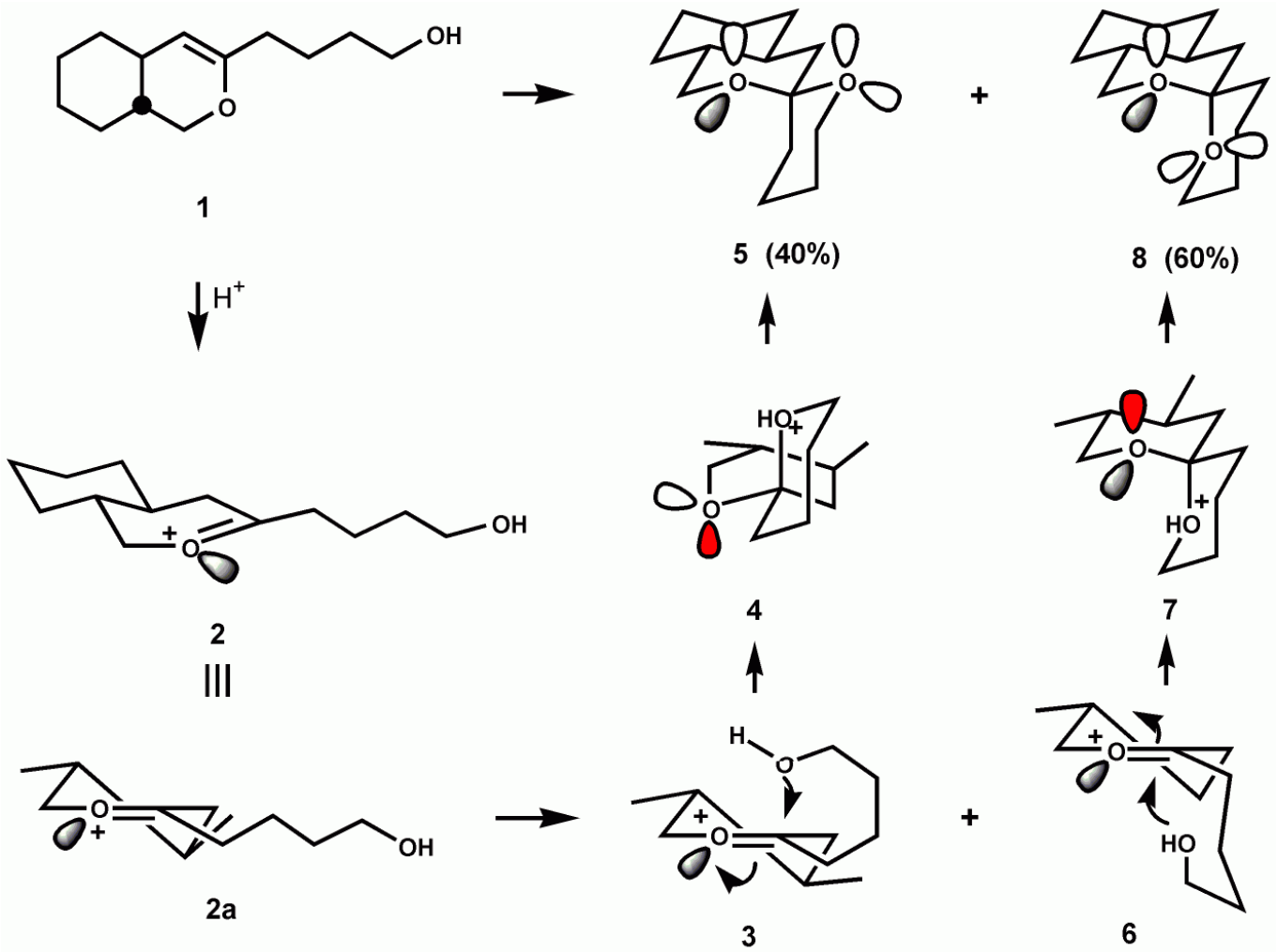
RESUME OF EXPERIMENTAL RESULTS

Intermediates 6β is 0.63 kcal/mol lower than 6α



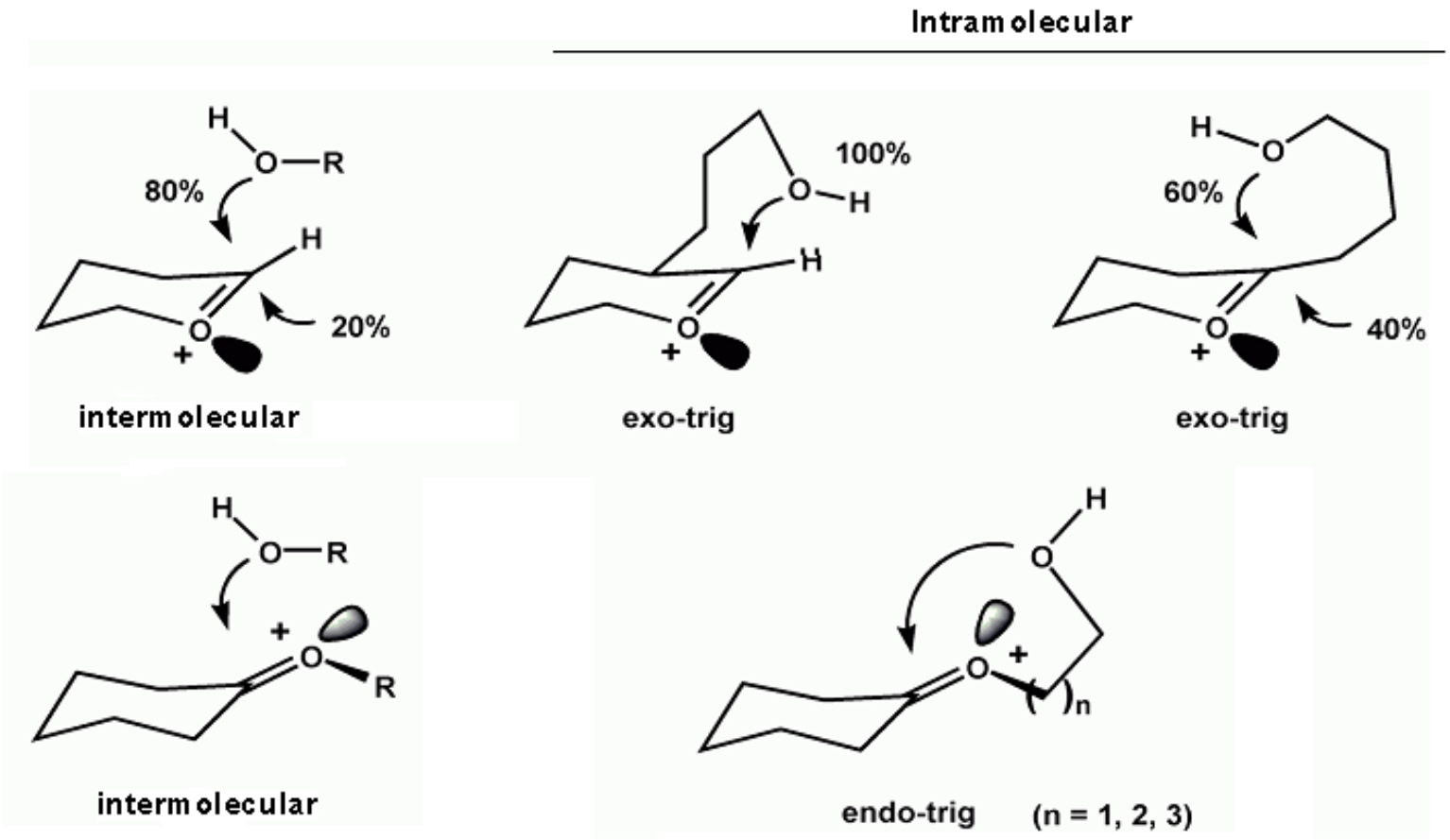
P. Deslongchamps, S. Li, Y.L. Dory. Org. Lett. 2004, *6,* 505-508.

Formation of Spiroketals

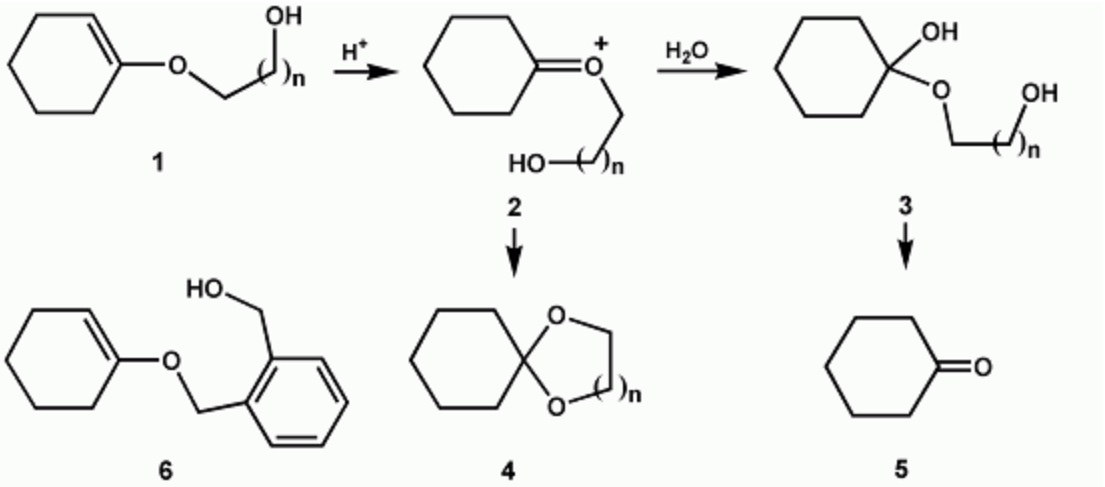


N. POTHIER, S. GOLDSTEIN, and P. DESLONGCHAMPS.
Helv. Chim. Acta *75,* 604 (1992).

Various Cyclization Pathways in Acetal Formation

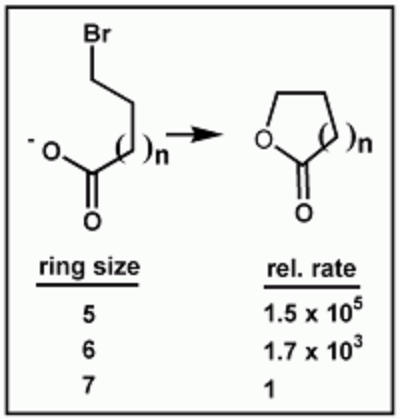


Cyclization Versus Hydrolysis as a Function as a Ring Size



	n	cyclization / hydrolysis ratio	degree of freedom
1	1 (5-membered ring)	57 / 43	(4)
	2 (6-membered ring)	60 / 40	(5)
	3 (7-membered ring)	50 / 50	(6)
6	(7-membered ring)	80 / 20	(5)

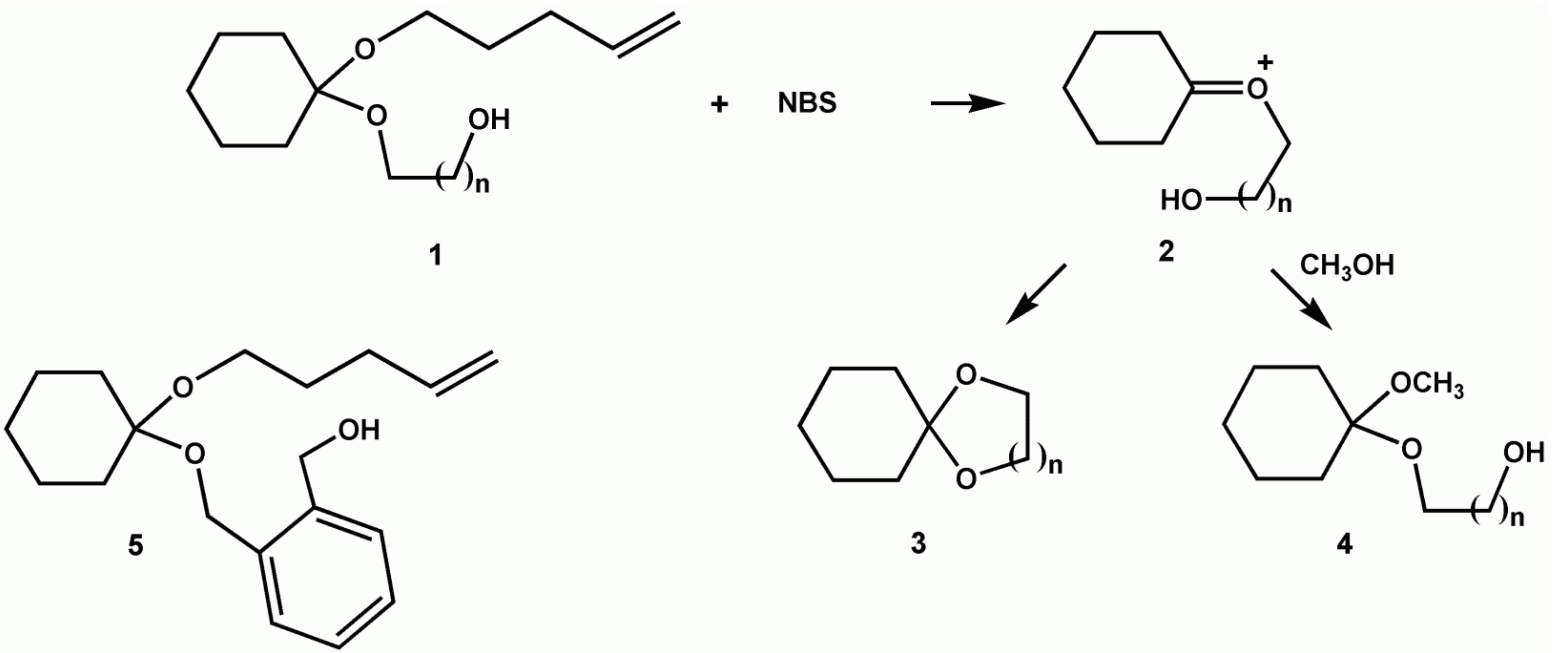
P. DESLONGCHAMPS, Y.L. DORY and S. LI.
Helv. Chim. Acta *79*, 41 (1996).



ring size	rel. rate
5	1.5×10^5
6	1.7×10^3
7	1

G. ILLUMINATI, L. MANDOLINI.
Acc. Chem. Res. *14*, 95 (1981).

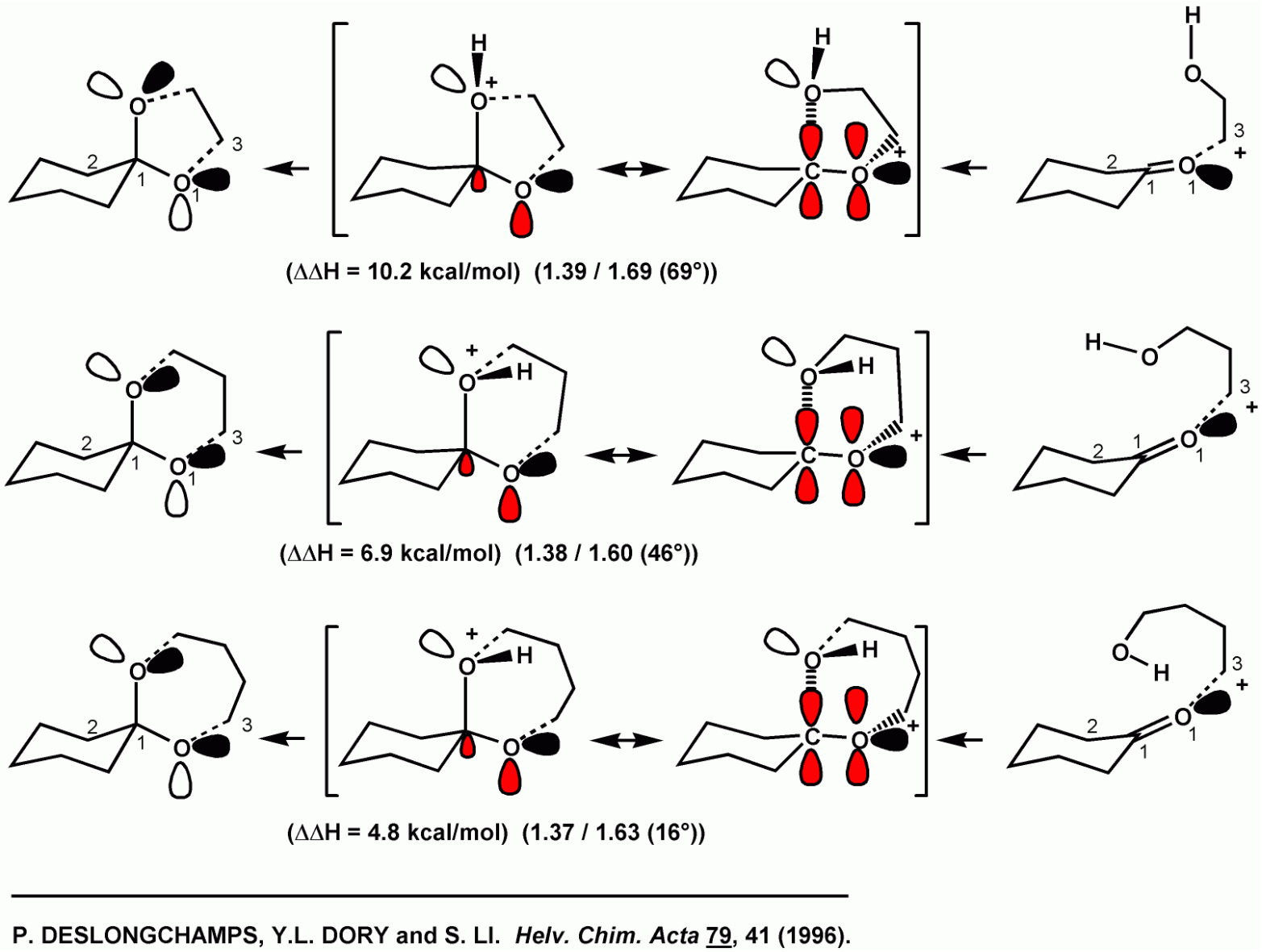
Cyclization Versus Addition of Methanol as a Function of Ring Size



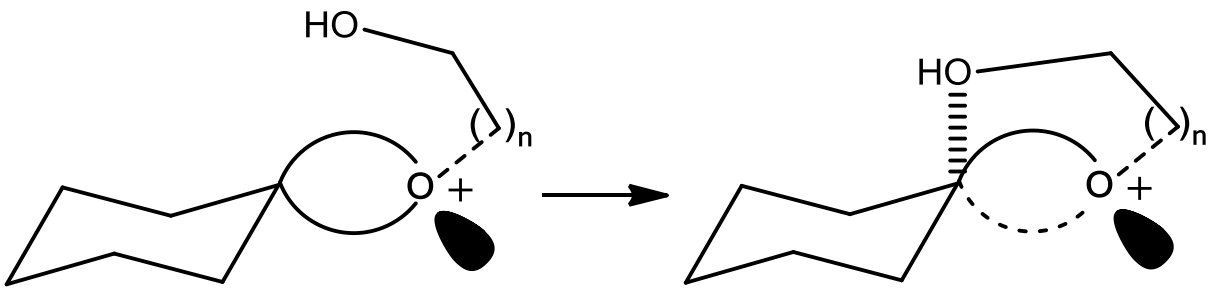
	n	cyclization / addition of CH_3OH
1	1 (5-membered ring)	33 / 66
	2 (6-membered ring)	60 / 40
	3 (7-membered ring)	50 / 50
5	(7-membered ring)	66 / 33

P. DESLONGCHAMPS, Y.L. DORY and S. LI.
Helv. Chim. Acta *79*, 41 (1996).

Molecular Modeling (AM1) of Ketal Formation as a Function of Ring Size

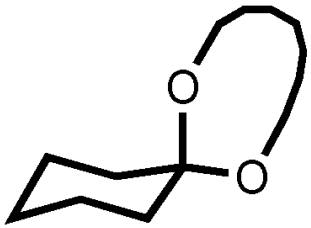


P. DESLONGCHAMPS, Y.L. DORY and S. LI. *Helv. Chim. Acta* 79, 41 (1996).



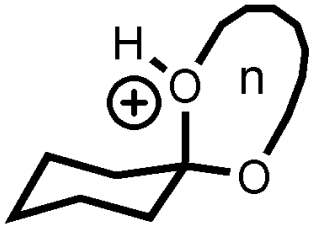
	cycle à 5	cycle à 6	cycle à 7
Δ H	10.2 kcal/mol	6.9 kcal/mol	4.8 kcal/mol
C—O$^+$	1.39 Å	1.38 Å	1.37 Å
C—OH	1.69	1.60	1.63
angle θ	69°	46°	16°
θ distortion	+++	++	+
degré de liberté	4	5	6

DEFINITIONS



depends on
proton affinity

Step 1 ⇌ H⊕



depends on ring size
and decompression
energy

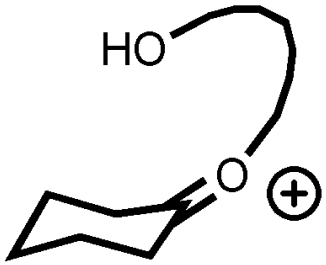
Step 2
ring closure ⇌ bond
cleavage

3 Factors:

(1) Proton Affinity: ΔE (enthalpy) (bond length 1.6 Å) between ketal $+H^+$ and ketal $-H^+$

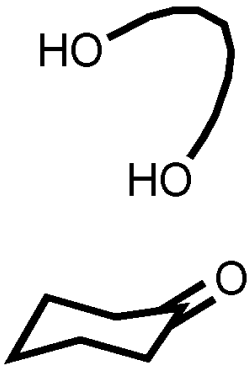
(2) Decompression energy: ΔE (enthalpy) between ketal $-H^+$ and oxocarbenium ion

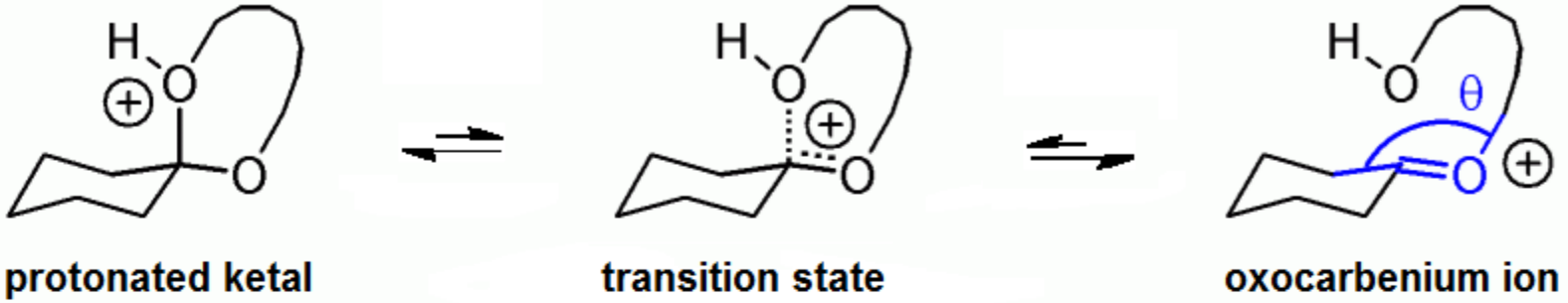
(3) Entropy: (bond cleavage and ring closure)



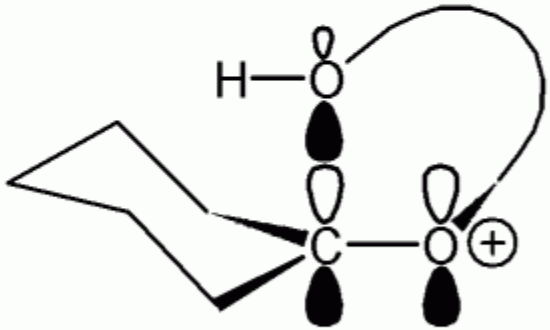
Step 3

H_2O





protonated ketal transition state oxocarbenium ion



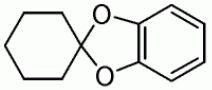
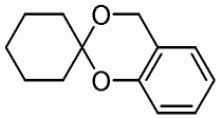
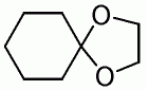
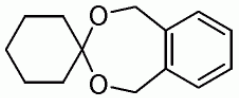
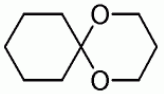
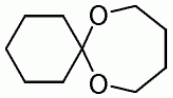
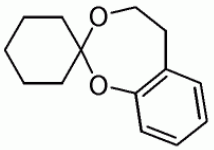
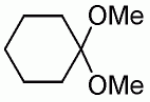
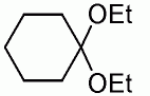
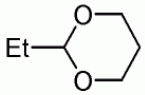
n → σ* interaction

π bonding model

θ Angle = definition at TS
π Bond Model = n-σ*

TS is not found in ketal
(a constraint C-O bond length at 1.6 Å is selected)

Relative Rates of Hydrolysis of a Series of Ketals

Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
1		1	186.11	97°	23.47	4
2		2.1×10^4	193.90 to phenol	39°	10.38	5
			193.85 to alcohol	47°	7.04	
3		5.4×10^5	190.32	70°	10.70	5
4		3.3×10^6	202.41	34°	6.25	6
5		2.1×10^7	196.60	45°	7.45	6
6		1.0×10^8	202.34	16°	6.08	7
7		1.3×10^8	199.56 to phenol	30°	9.62	6
			200.34 to alcohol	24°	5.36	
8		1.5×10^9	195.46	22°	8.48	∞
9		1.3×10^{10}	200.65	21°	7.71	∞
10		5.6×10^2				

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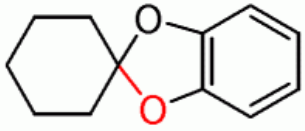
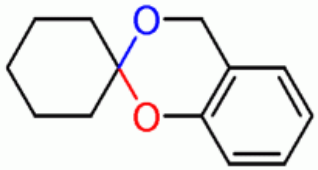
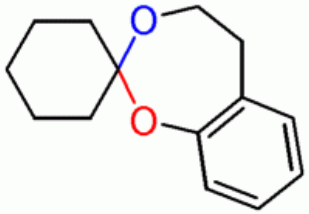
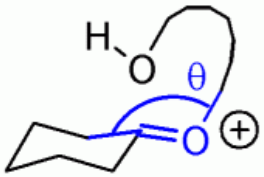
Israel J. of Chem. 2000, *40,* 209-215.

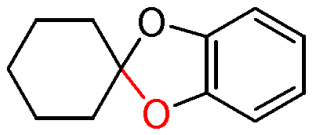
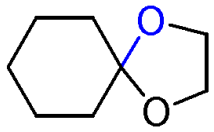
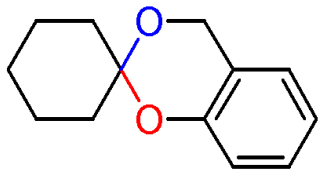
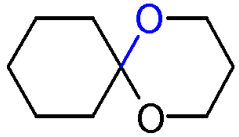
Relative Rate of Hydrolysis of 5-, 6- and 7-Membered Aryl Ketals

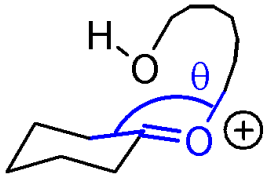
Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
1		1	186.11	97°	23.47	4
2		2.1×10^4	193.90 to phenol	39°	10.38	5
			193.85 to alcohol	47°	7.04	
7		1.3×10^8	199.56 to phenol	30°	9.62	6
			200.34 to alcohol	24°	5.36	



N.B. Proton affinity (basicity) depends on the strength of the anomeric effect

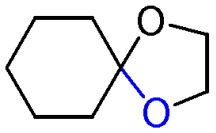
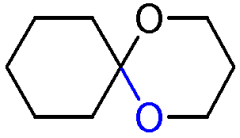
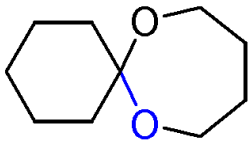
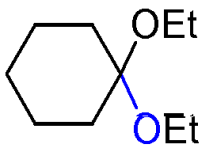
Relative Rate of Hydrolysis of 5- and 6-Membered Ketals

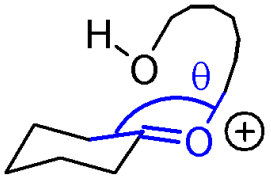
Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
1		1	186.11	97°	23.47	4
3		5.4×10^5	190.32	70°	10.70	5
2		2.1×10^4	193.90 to phenol	39°	10.38	5
			193.85 to alcohol	47°	7.04	
5		2.1×10^7	196.60	45°	7.45	6



N.B. Proton affinity (basicity) depends on the strength of the anomeric effect

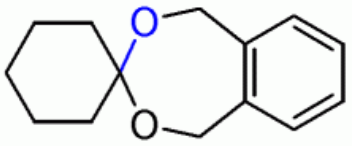
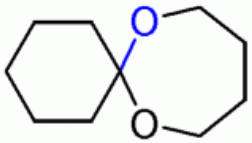
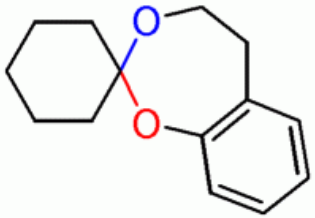
Relative Rate of Hydrolysis of 5- to 7-Membered and Acyclic Ketals

Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
3		5.4×10^5	190.32	70°	10.70	5
5		2.1×10^7	196.60	45°	7.45	6
6		1.0×10^8	202.34	16°	6.08	7
9		1.3×10^{10}	200.65	21°	7.71	∞

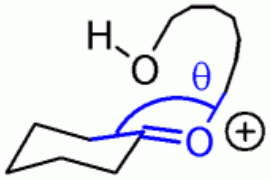


N.B. Proton affinity (basicity) depends on the strength of the anomeric effect

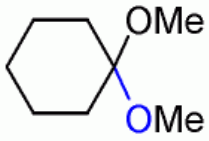
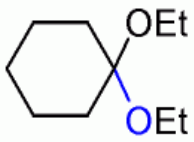
Relative Rate of Hydrolysis of 7-Membered Ketals

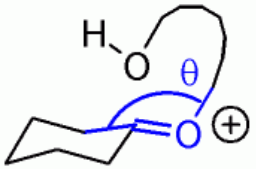
Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
4		3.3×10^6	202.41	34°	6.25	6
6		1.0×10^8	202.34	16°	6.08	7
7		1.3×10^8	199.56 to phenol	30°	9.62	6
			200.34 to alcohol	24°	5.36	

N.B. Proton affinity (basicity) depends on the strength of the anomeric effect



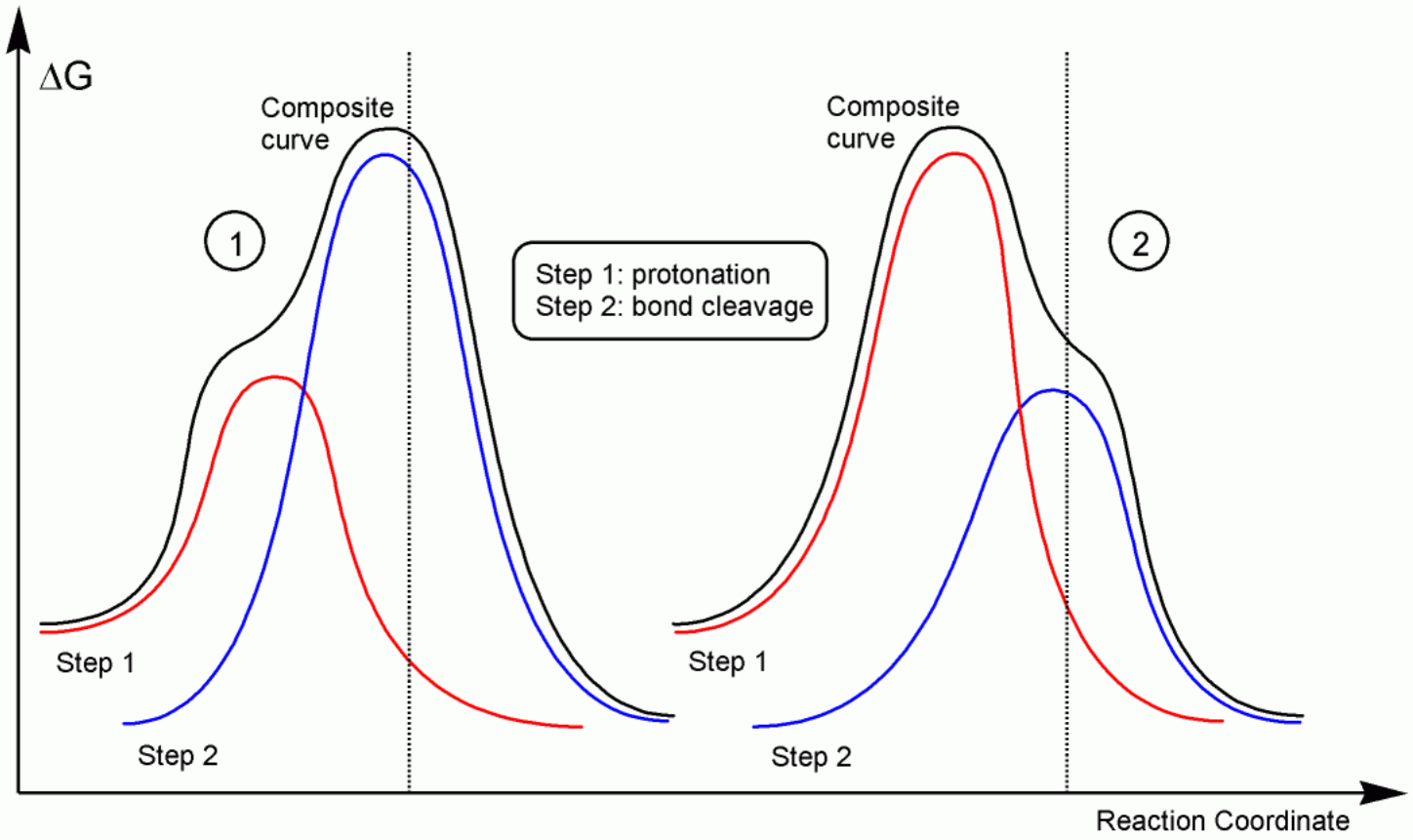
Relative Rate of Hydrolysis of Dimethoxy and Diethoxy Ketals

Ketal	Structure	Relative rate	Proton affinity (Kcal/mol)	θ	Decompression (Kcal/mol)	Free bonds
8		1.5 X 10^9	195.46	22°	8.48	∞
9		1.3 X 10^{10}	200.65	21°	7.71	∞



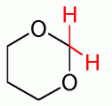
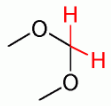
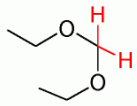
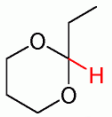
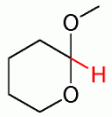
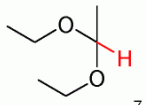
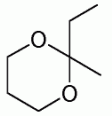
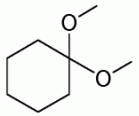
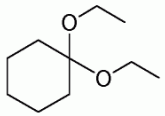
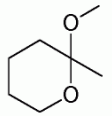
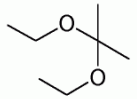
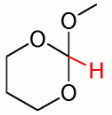
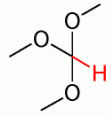
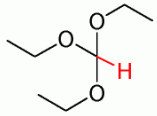
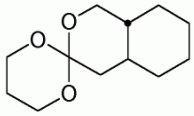
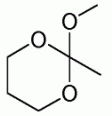
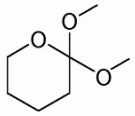
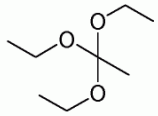
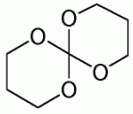
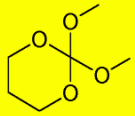
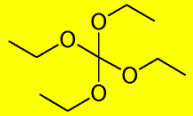
N.B. Proton affinity (basicity) depends on the strength of the anomeric effect

CONCLUSION ON ALKYL AND ARYL KETALS HYDROLYSIS



	1 Alkyl ketals (**3**, **4**, **5**, **6**, **8**, **9**)	2 Aryl ketals (**1**, **2**, **7**)
Protonation	Easy (very basic oxygen atoms)	Difficult (less basic oxygen atoms)
Bond cleavage	Difficult (alcohol as leaving group)	Easy (phenol as leaving group)
Rate controlled	Mostly by bond cleavage	Mostly by protonation

Relative Rates of Hydrolysis

	2 rings	1 ring				acyclic	
		2 O in ring	no O in ring		1 O in ring		
		OMe	OMe	OEt	OMe	OMe	OEt
Acetals		 1				 4.5×10^2	 2.5×10^3
		 1×10^2			 9.3×10^4		 1.5×10^7
Ketals		 3.7×10^6	 2.6×10^8	 2.3×10^9	 2.4×10^9		 4.6×10^{10}
Orthoesters		 6.4×10^8				 2.5×10^9	 1.0×10^{10}
	 4.3×10^8	 8.4×10^9			 4.2×10^{10}		 2.8×10^{11}
Orthocarbonates	 9.6×10^8	 4.2×10^9				 1.7×10^8	 1.0×10^9

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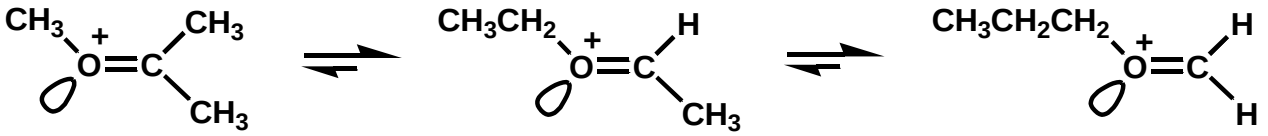
P. Deslongchamps, Y.L. Dory, S. Li.
Tetrahedron *56*, 3533 (2000).

C.A. Bunton, R.H. De Wolfe.
J. Org. Chem. *30*, 1371 (1954).

RELATIVE STABILITY:

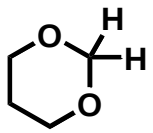
Oxenium Energies (RHF 6-31G*)



0 kcal/mol **5.2 kcal/mol** **19.1 kcal/mol**

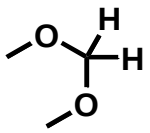
Relative Rates of Acetals of Formaldehyde, Aldehyde, and Ketone

ACETALS

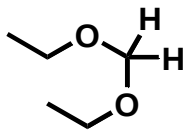


1

reverse of intramol. proc.



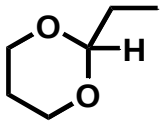
4.2×10^2



2.5×10^3

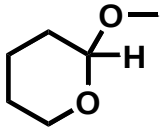
bimolecular processes (entropy)

methoxy less basic than ***ethoxy***

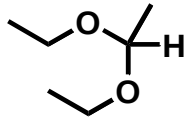


1×10^2

reverse of intramol. proc.



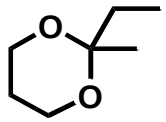
9.3×10^4



1.5×10^7

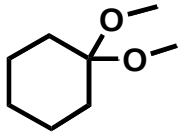
bimolecular processes

methoxy ***ethoxy*** *(2 cleavages) entropy*

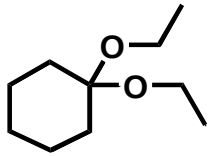


3.7×10^6

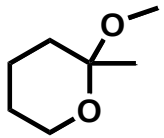
reverse of intramol. proc.



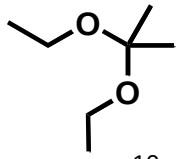
2.6×10^8



2.3×10^9



2.4×10^9



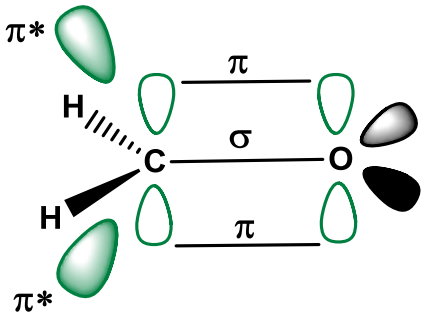
4.6×10^{10}

bimolecular processes

methoxy *(2 cleavages) entropy*	***ethoxy*** *(2 cleavages)*	***methoxy*** *(1 cleavage)*	***ethoxy*** *(2 cleavages)*

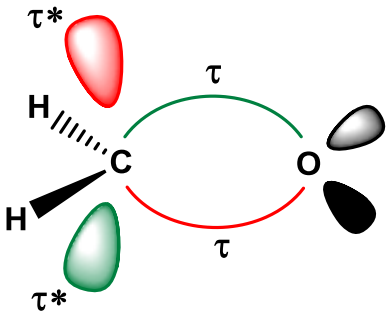
α-π vs τ Bonds in Carbonyl Group and Antibonding Orbitals

σ–π



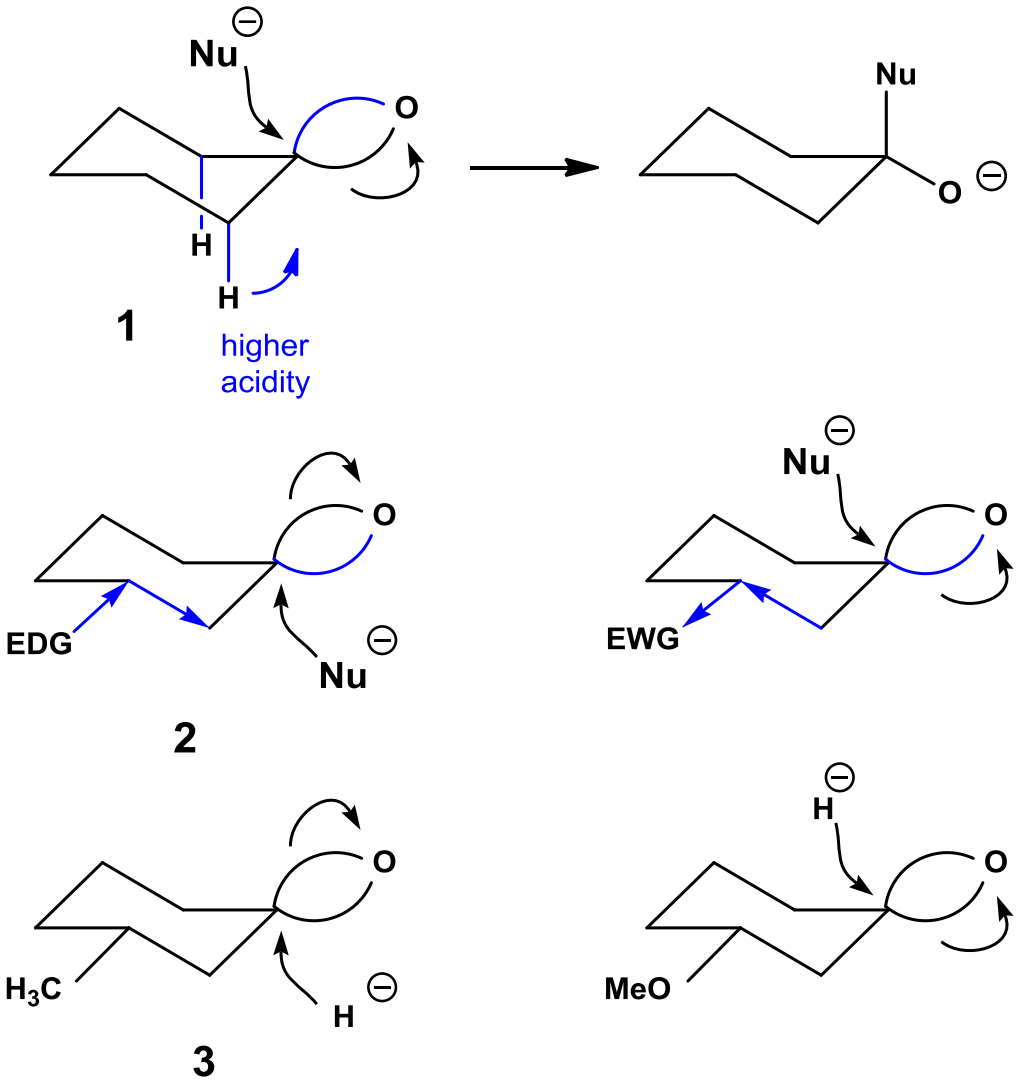
The two antibonding orbitals π* correspond to a single orbital

τ



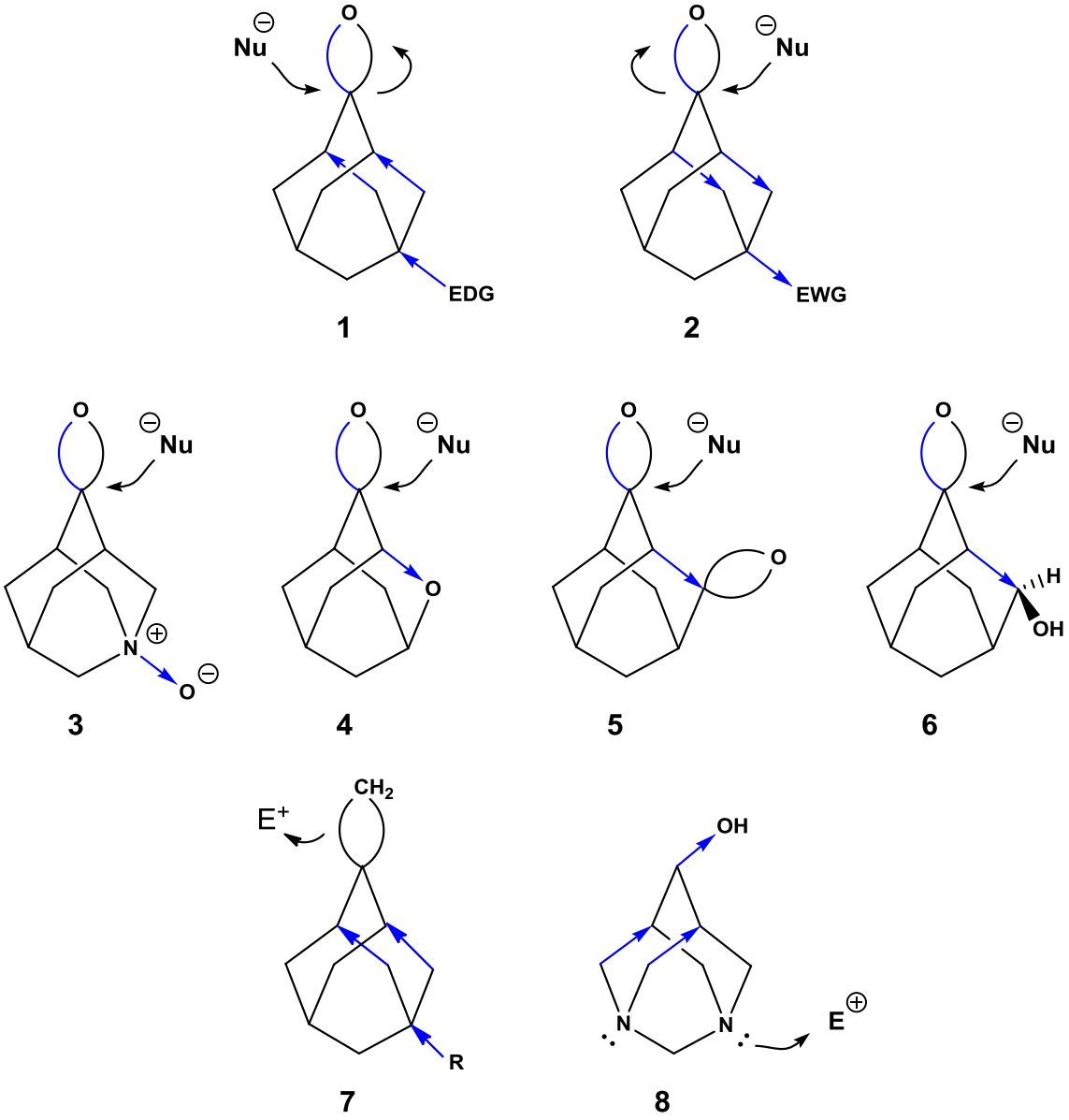
The two antibondiding orbitals τ* correspond to two different orbitals and confer tetrahedral character to carbonyl group

Nucleophilic Addition on Ketone and Hyperconjugation



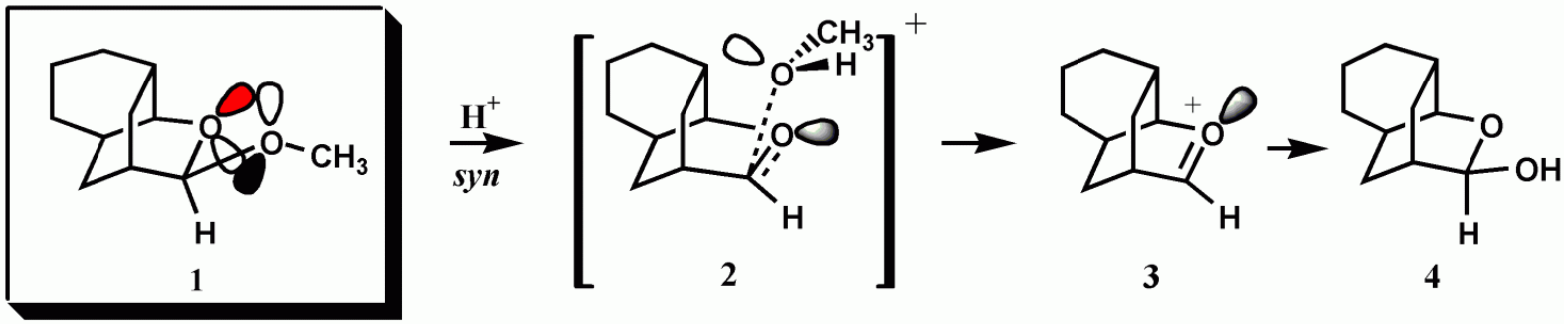
S. Cieplak, B. D. Tait, C. R. Johnson, *J. Am. Chem. Soc.,* 1989, *111*, 8447.
G. Deslongchamps, P. Deslongchamps. *Org. Biomol. Chem.* 2011, *9,* 5321.

Nucleophilic Addition on Adamantanone - Cieplak Effect



M. Kaselj, W. S. Chung, W. J. le Noble, *Chem. Rev.,* 1999, *99*, 1387.
G. Deslongchamps, P. Deslongchamps. *Org. Biomol. Chem.* 2011, *9,* 5321.

Synperiplanar Stereoelectronic Effect and Hydrolysis in Acetal

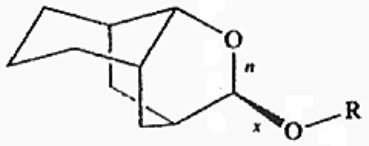


S. LI, A.J. KIRBY, P. DESLONGCHAMPS.

Tetrahedron Lett. 34, 7757-7758 (1993).

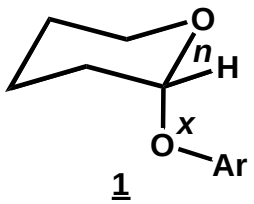
Acetals with Synperiplanar Lone Pairs: Crystal-Structure-Reactivity

Table 1 Geometry at the acetal centre of compounds 3*



3*

R	pK_a of ROH	Bond lengths /Å	
		n	*x*
CH_2CHAr_2	15.5	1.419	1.411(2)
4-Chlorophenyl	9.38	1.410	1.428(2)
4-Cyanophenyl	7.95	1.411	1.432(2)
4-Nitrophenyl	7.14	1.404	1.439(2)



1

***n* = 1.32**
***x* = 1.48**

1: a marked lengthening of *x* and shortening of *n*

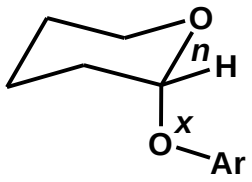
By comparison with

3: no significant change

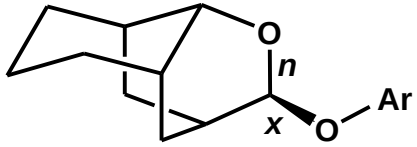
CONCLUSION: The anomeric effect due to the synperiplanar n_O-$c^*_{C\text{-}O}$ overlap in acetal 3 is less efficient than the antiperiplanar one in simple THP acetals 1 in their respective ground state.

P. Deslongchamps, P.G. Jones, S. Li, A.J. Kirby, S Kuusela, Y. Ma.
J. Chem. Soc., Perkin Trans. 2, 1997, 2621-2626.

How About Hydrolysis ?



1

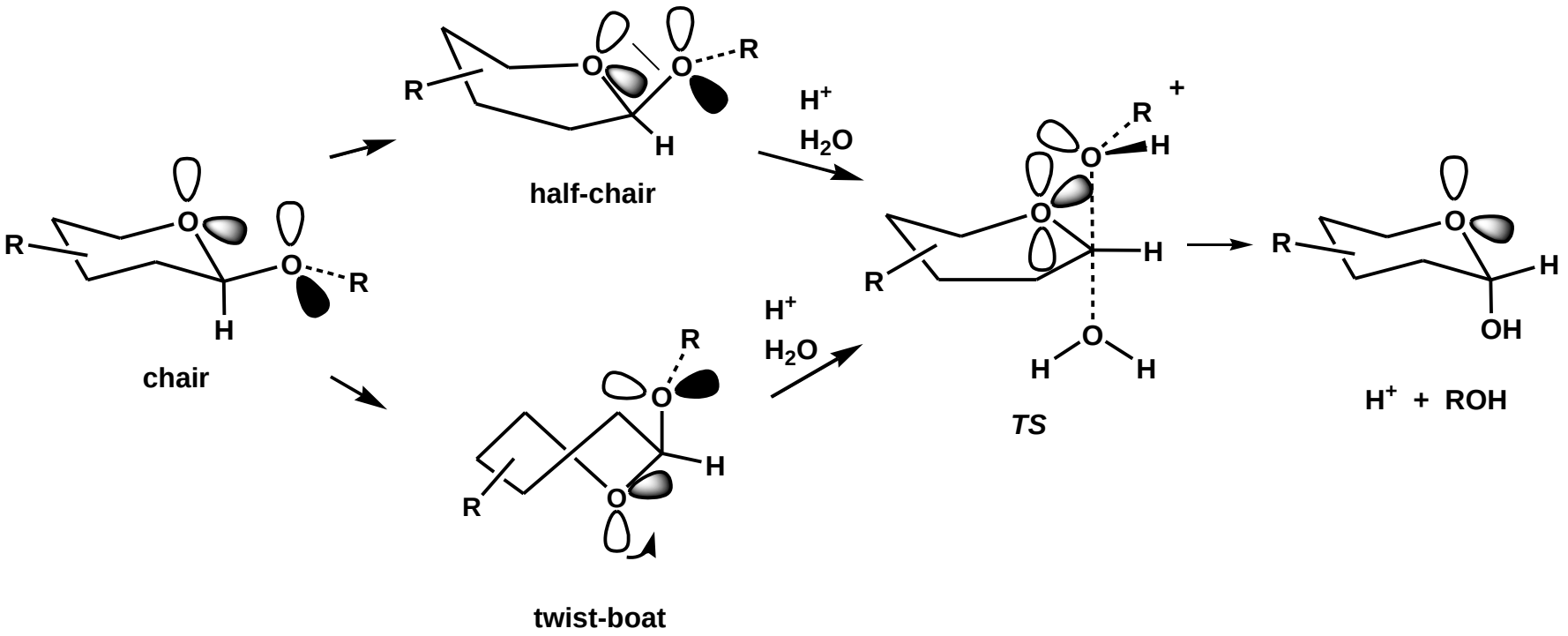


3

In spontaneous hydrolysis, 3 is slightly faster than 1.

1. **The ground state of 3 is in a boat, thus containing more energy than 1 which is in a chair form.**
   3 is thus energetically closer to TS.
2. **TS is late resembling the corresponding cyclic oxenium ion in both reactions.**

Hydrolysis of β-Glycosides via Anti- and Synperiplanar Pathways (σ–π)

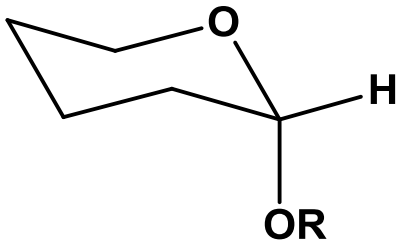


N.B. **The *syn* pathway goes through a half-chair which is higher in energy than the twist-boat.**

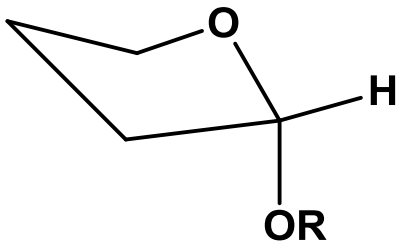
In cyclohexane, half-chair = 10 kcal/mol and twist-boat = 5 kcal/mol.

Synthèse des α et β-glycosides

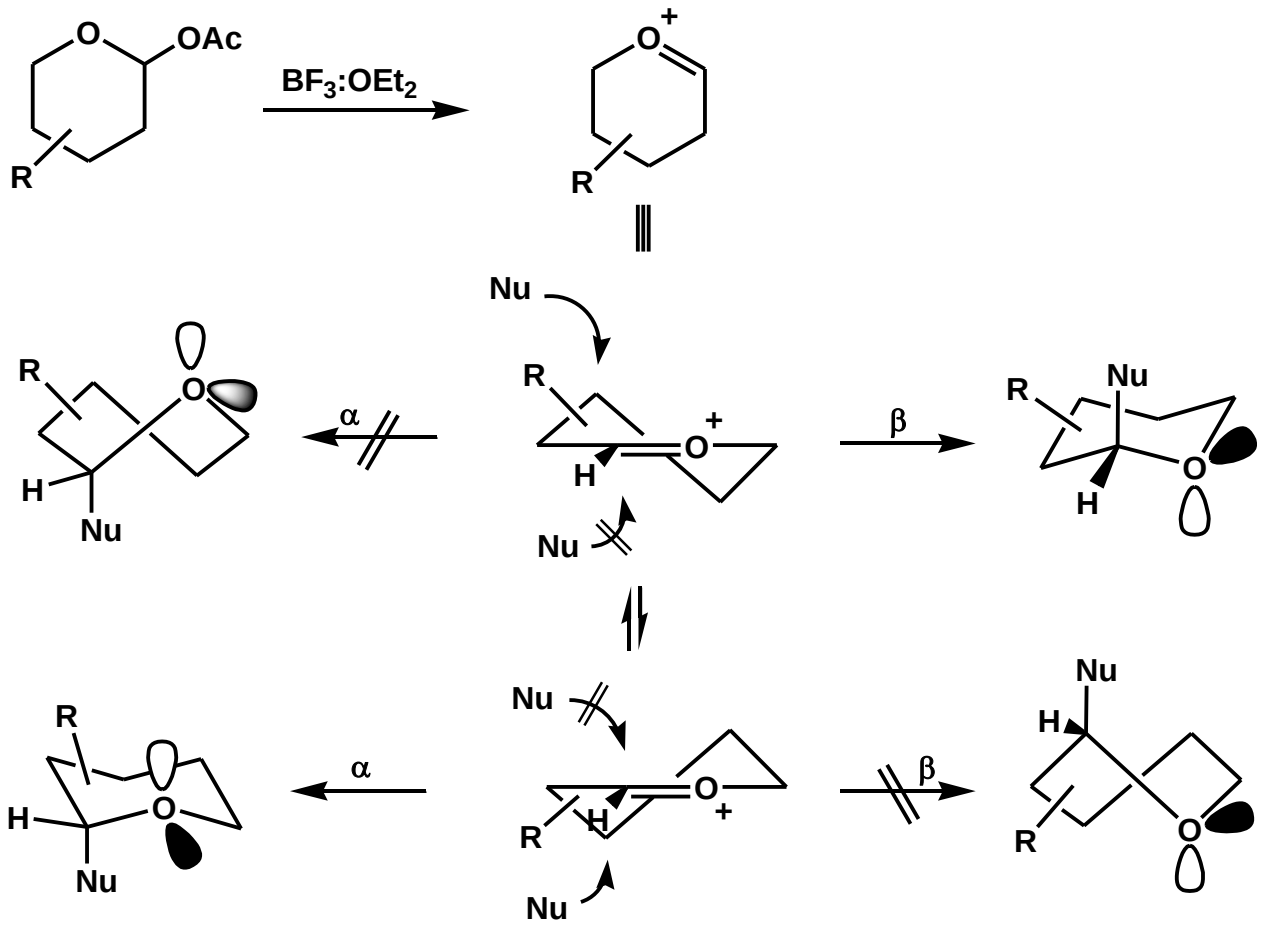
1) Pyranosides



2) Furanosides



Reactivity of Cyclic Oxocarbenium Ion



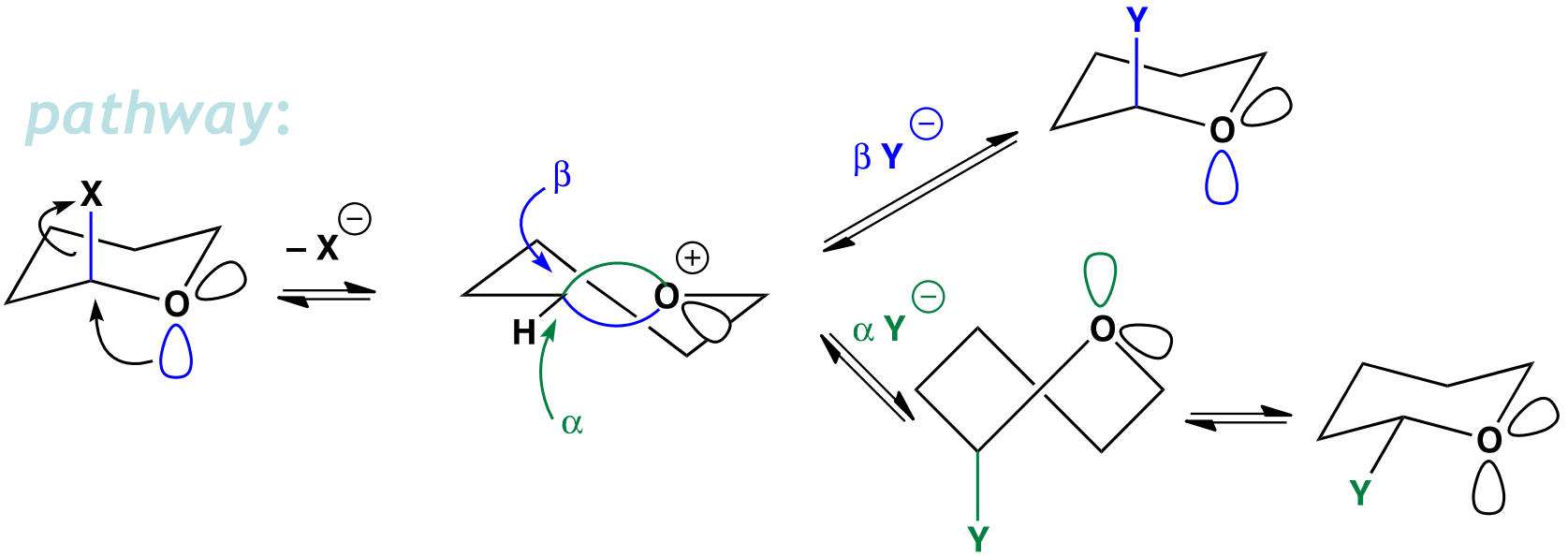
N.B. **(1) True with weak nucleophiles.**

(2) With strong nucleophile, no selectivity due to early transition state (approach the diffusion limit).

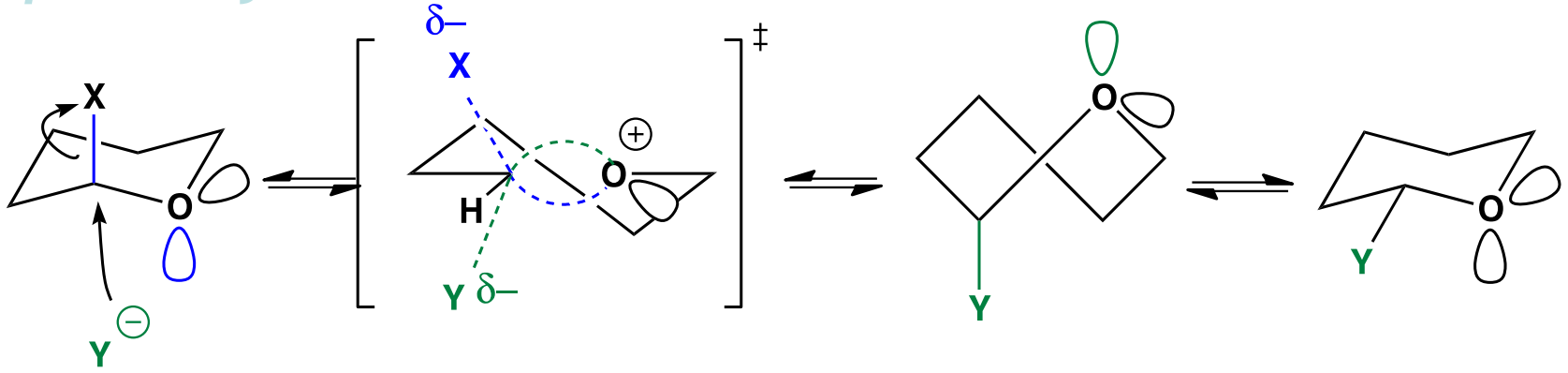
K.O. WOERPEL *et al.* *J. Org. Chem.* 2009, *74,* 8039-50. (Review).

Substitution at Anomeric Center with τ bond

S_N1 pathway:

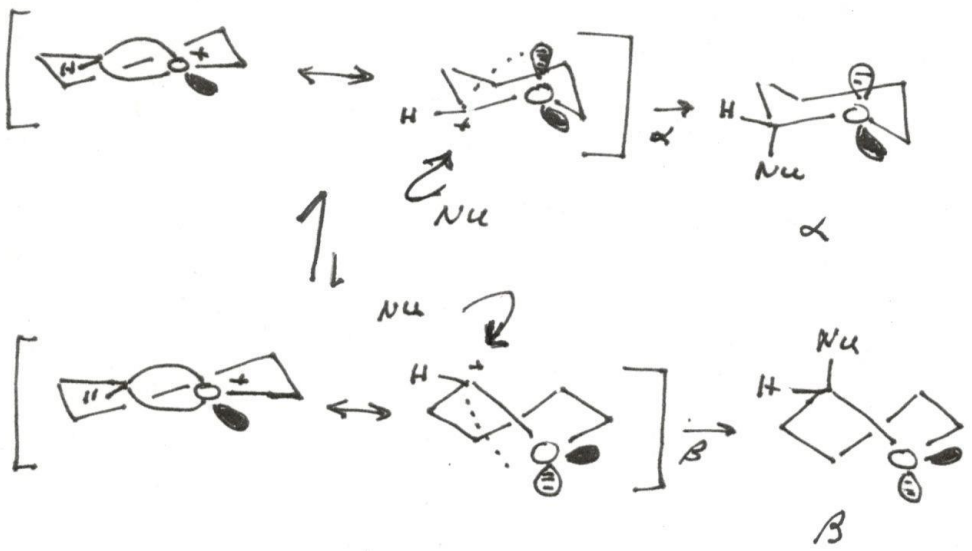


S_N2 pathway:



H. B. Bürgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.,* 1973, *95*, 5065.
G. Deslongchamps, P. Deslongchamps, *Org. Biomol. Chem.* 2011, *9,* 5321.

Use of resonance structure to predict stereoelectronically controlled reaction pathways



In very early TS, at diffusion limit ⇒ no control

in early TS, α TS (chair like) will prevail

in late TS, α TS (" ") will be exclusive.

SN2 reaction of α-D-glucopyranosides

Method: Two KIE values (^{13}C-1 and ^{2}H-1) with measurements for three other glucopyranosyl fluoride isotopologues (^{18}O-5, $^{2}H_2$ and $^{2}H_5$) plus an *ab initio*-computed TS structure produced transition state model TS_1

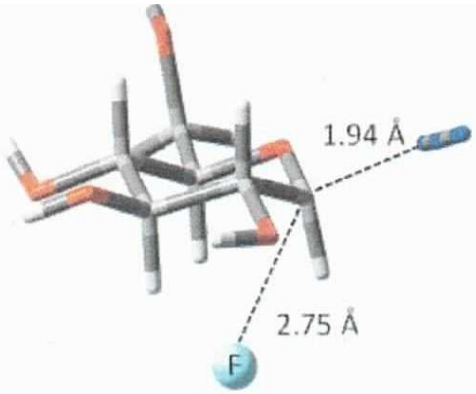
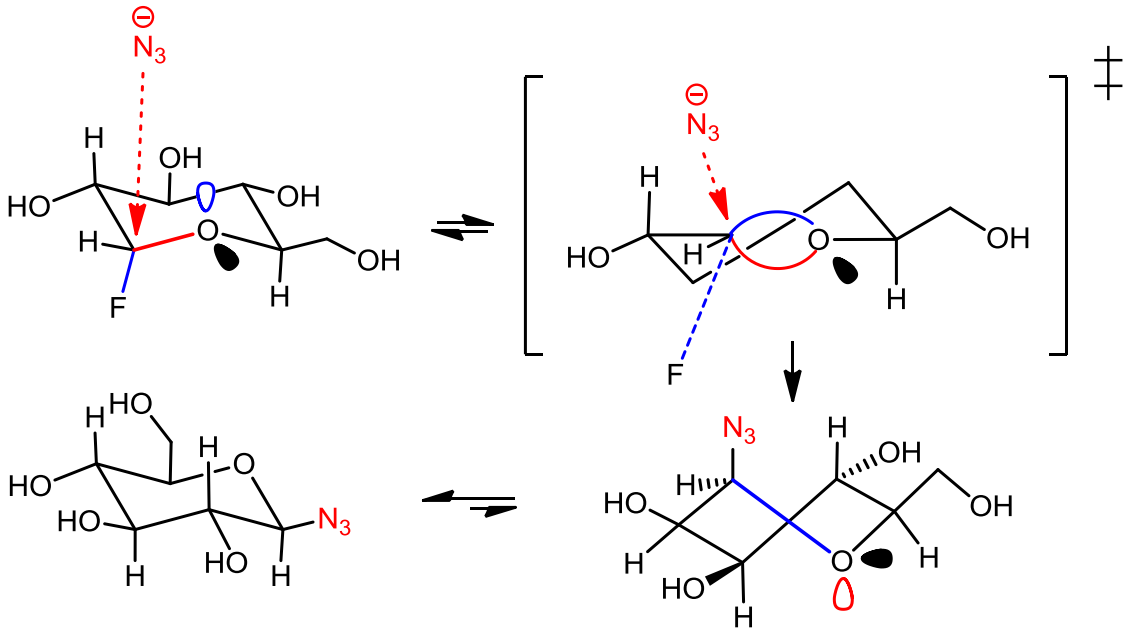


Figure 3. Transition-state model (TS_1) for the reaction of α-glucopyranosyl fluoride with azide ion.

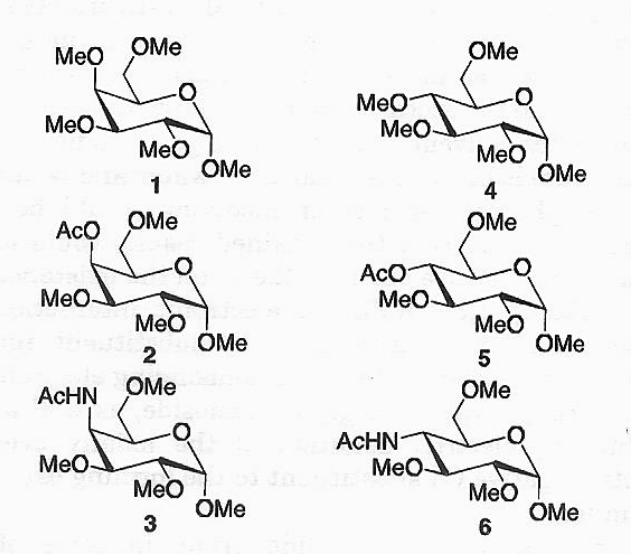
EXPLODED or LOOSE TS

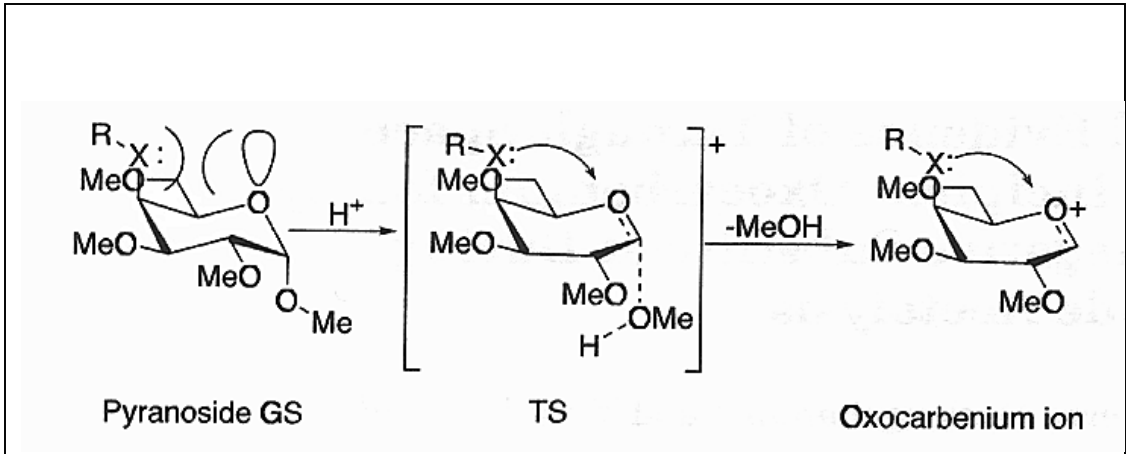


Chan, J.F.*; Sannikova, N.; Tang, A.; Bennett, A.J.* *JACS* 2014, *136*, 12225-12228.

Relative Rate of Acetolysis of Glycopyranosides

(Electrostatic Stabilization by Electron Lone Pairs on Oxocarbenium Ion)





Stabilization of oxocarbenium by axial C_4-X group

Results of relative rates:

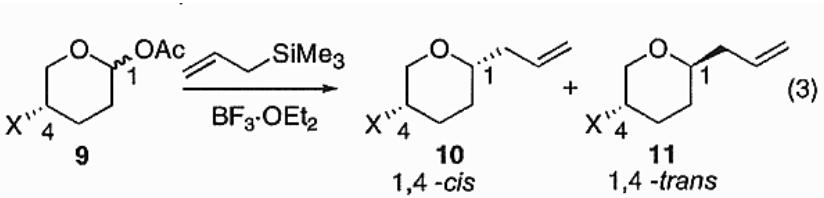
3 (0.5), **4** (1.6), **5** (0.6), **6** (0.5) (similar)

2 is slightly faster (2.4)

1 is much faster (24)

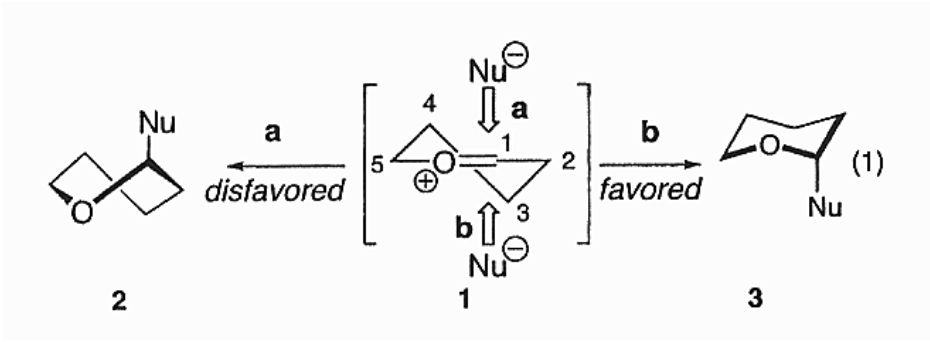
M. Miljkovic, D. Yeagley, P. Deslongchamps, Y.L. Dory. J. Org. Chem. **1997**, *62,* 7597-7604.

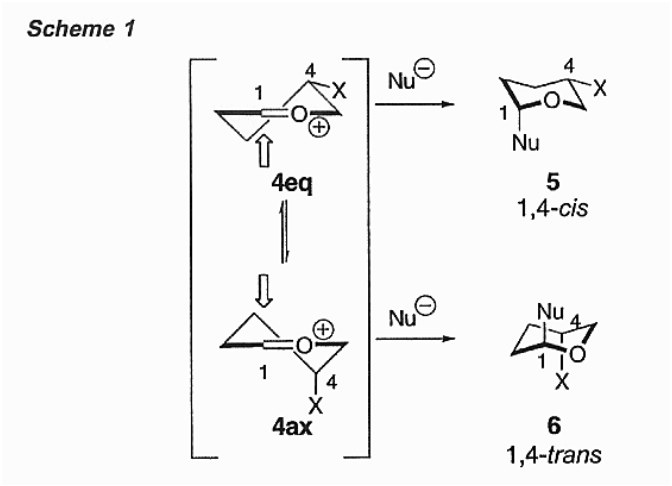
Electrostatic Interaction on 4-Substituted Tetrahydropyran Oxocarbenium Ion



compound	X	cis : trans	yield (%)
a	Me	94 : 6	74
b	CH_2Bn	93 : 7	77
c	OBn	1 : 99	75

explanation





K.A. WOERPEL *et al.* *J.Am.Chem.Soc.* 2003, *125,* 15521-15528.

Electrostatic Interaction on Tetrahydropyran Oxocarbenium Ion Influence on Chemical Reactivity

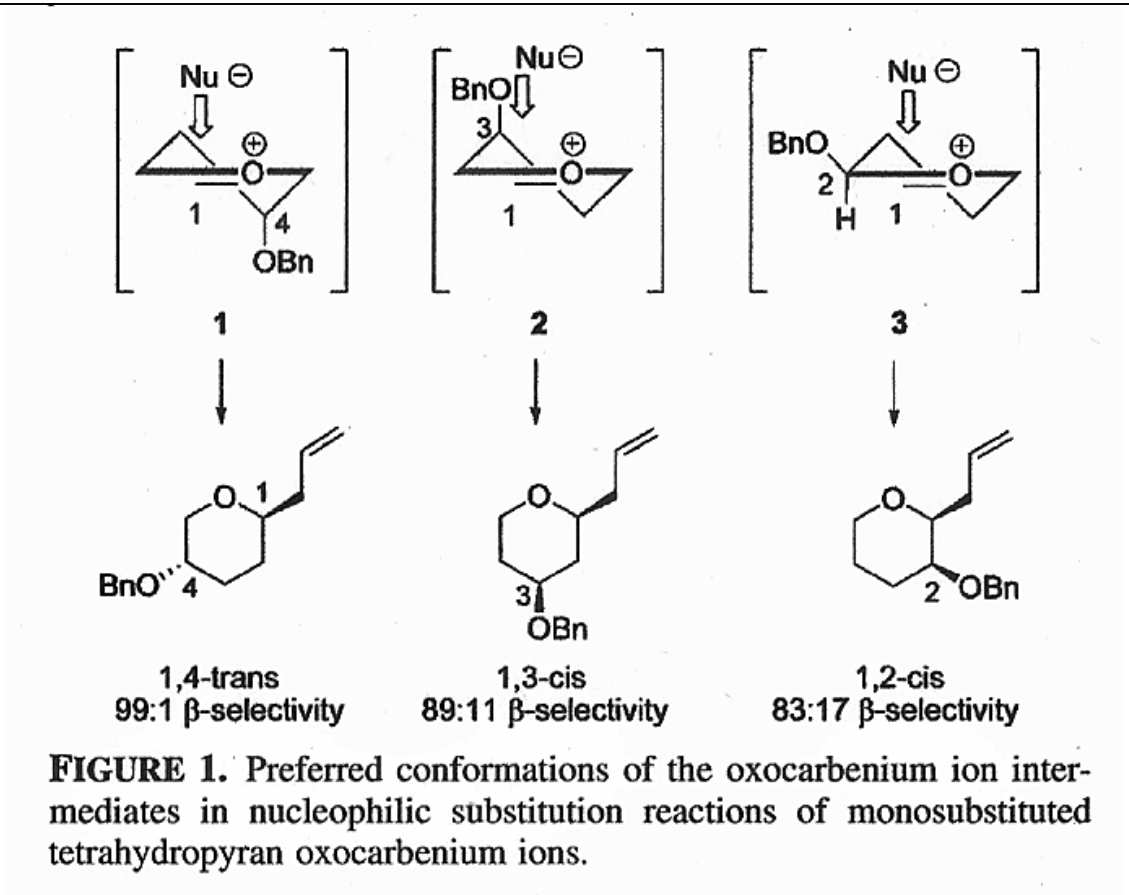


FIGURE 1. Preferred conformations of the oxocarbenium ion intermediates in nucleophilic substitution reactions of monosubstituted tetrahydropyran oxocarbenium ions.

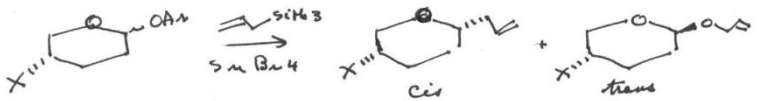
N.B. 3 is stabilized by hyperconjugation from C2-H axial ?

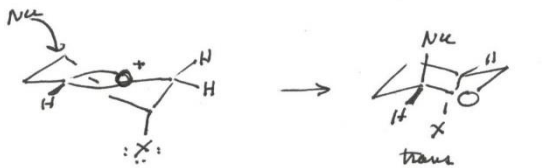
Other explanation next slide…

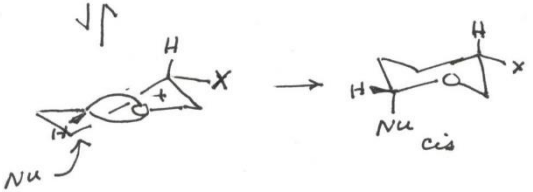
K.A. WOERPEL, M.T. YANG. *J.Org.Chem.* 2009, *74,* 545.

D. M. Smith, K. A. Woerpel Org. Biomol Chem (O.B.C.) 2006, 4, 1195-1201

Electrostatic Stabilization by X (halogen)





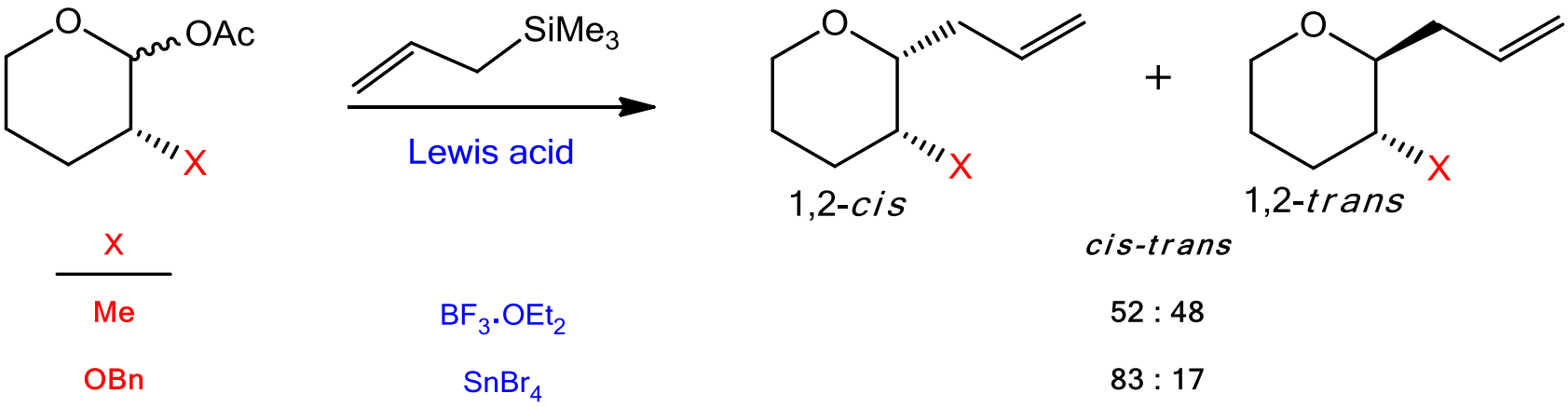


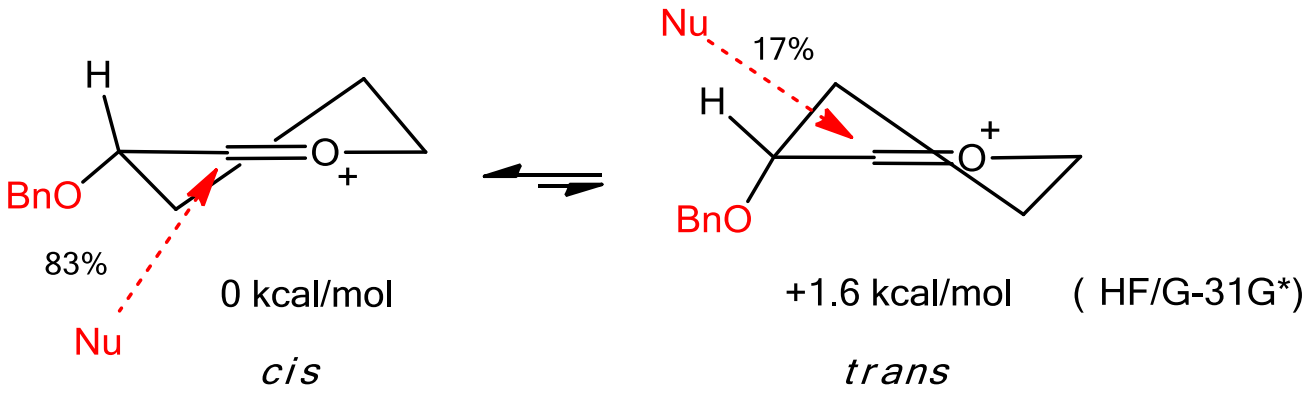
X	cis	trans
F	5	95
Cl	14	86
Br	31	69
I	72	28

So

strong electrostatic stabilization

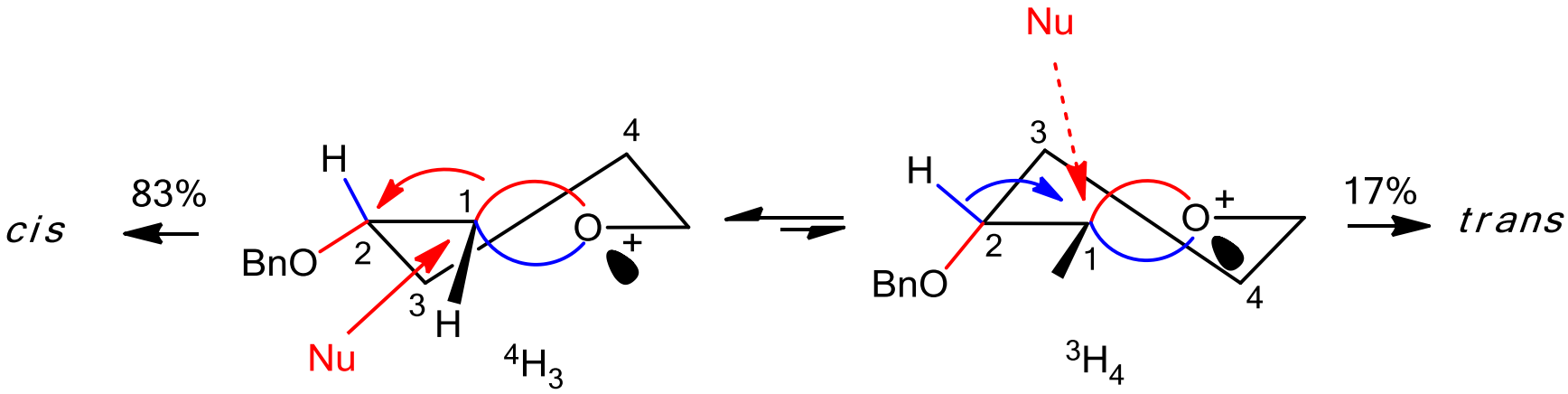
Stabilized by hyperconjugation?



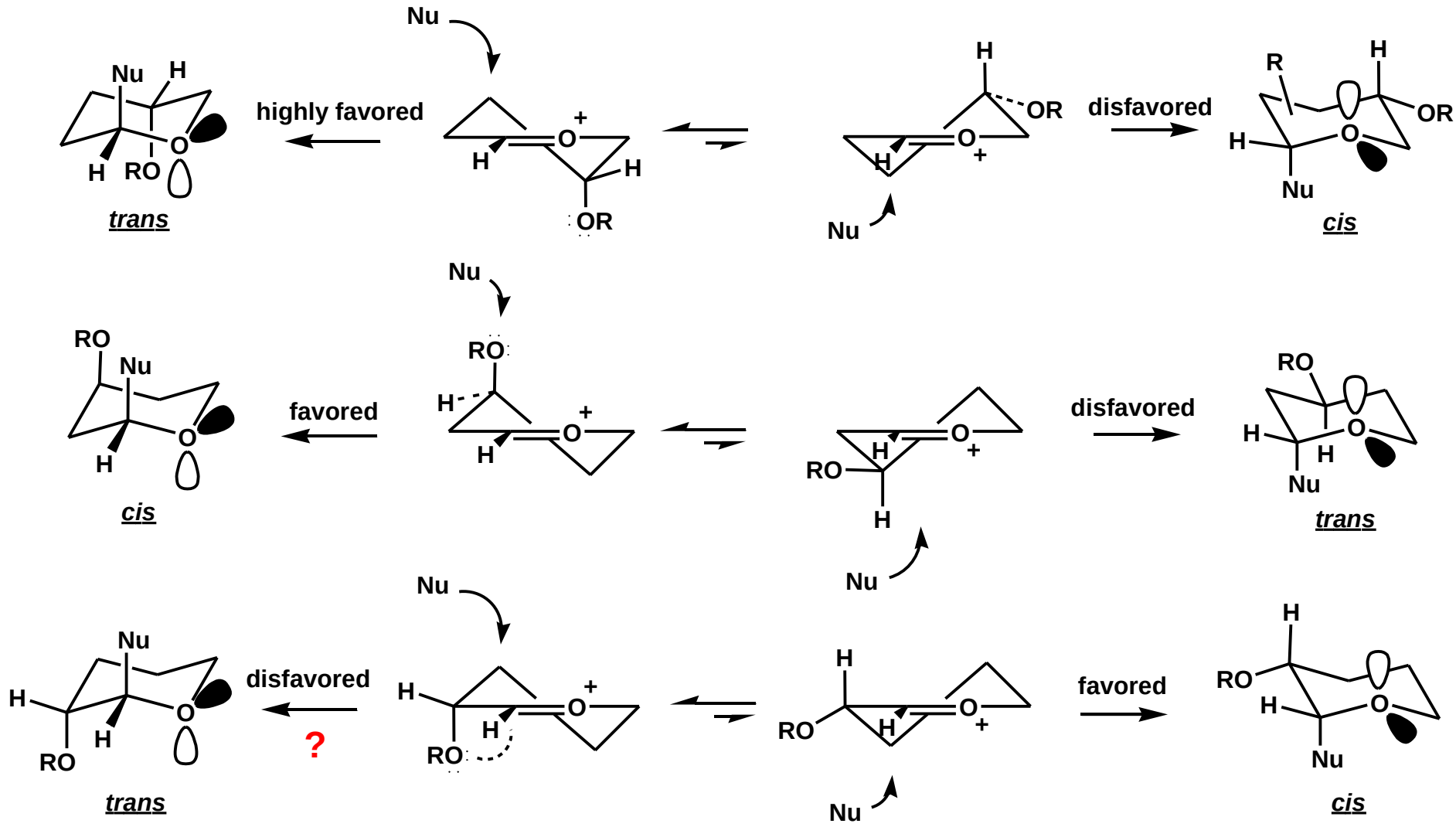


Romeo, J.A.C.; Tabacco, S.A.; Woerpel, K.A. *JACS* **2000**, *122,* 168-169.

BBA Hypothesis and Hyperconjugation

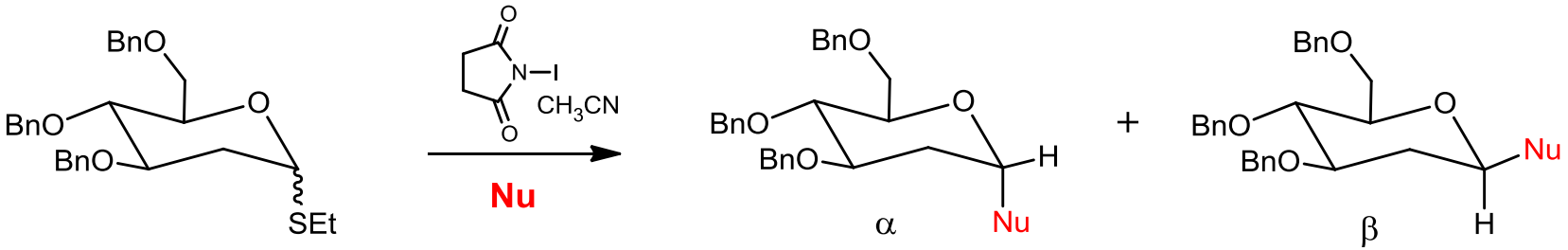


RÉSUMÉ: Relative Stability and Reactivity of Oxocarbenium Ion in the Presence of OR Group



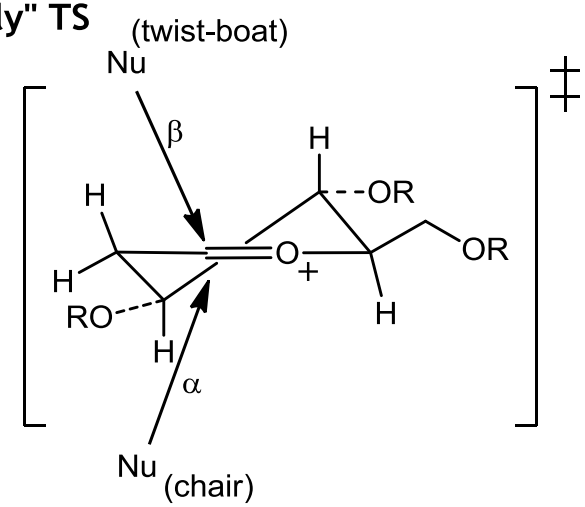
Reverse results when OR is replaced by alkyl group in first two examples (K.O. Woerpel).

Strong vs weak nucleophiles in glycoside formation

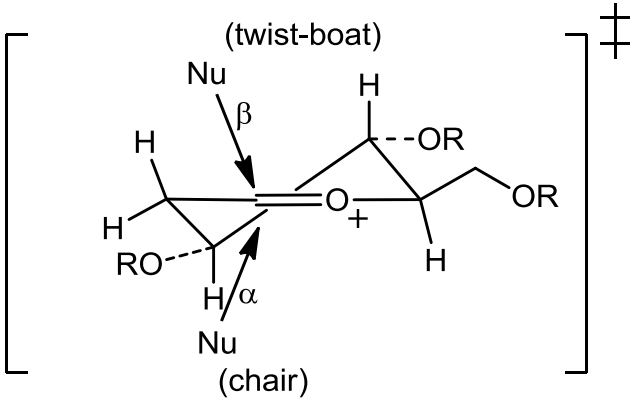


Nu	α : β	
EtOH	50 : 50	(rate of diffusion)
CF_3CH_2OH	83 : 17	
$SiMe_3$, $BF_3.Et_2O$	91 : 9	

"early" TS



"late" TS



Beaver, M.G.; Woerpel, K.A. *J. Org. Chem.* 2010, *75*, 1107-1118.
Yang, M.T.; Woerpel, K.A. *J. Org. Chem.* 2009, *74*, 545-553.

Increasing polarity of solvent stabilizes the oxocarbenium ion

---

Woerpel and co-workers have discovered that stereoselectivity is greater in CH_3CN than in CH_2Cl_2.

"Increasing the polarity of the solvent results in stabilization of the cationic intermediate and subsequently reduces the rate of nucleophilic addition. As the rate of nucleophilic addition is decreased from the diffusion limit regime, greater facial selectivity for the stereoelectronically preferred product would be observed."

Beaver, M.G.; Woerpel, K.A. ***J. Org. Chem.*** **2010,** ***75*****, 1107-1118.**
Shenoy, S.R.; Smith, D.M., Woerpel, K.A. ***J. Am. Chem. Soc.*** **2006,** ***128*****, 8671-8677.**

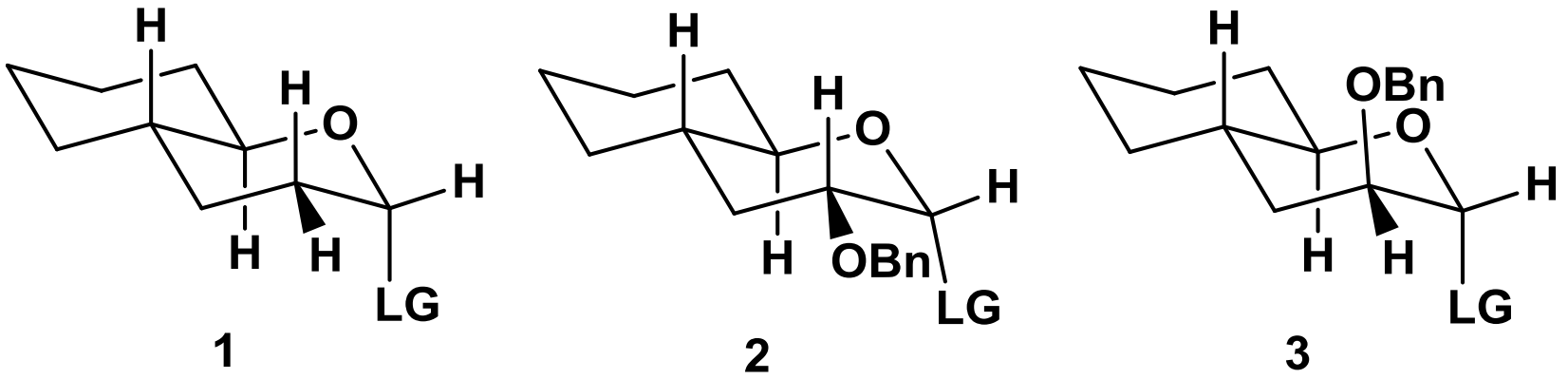
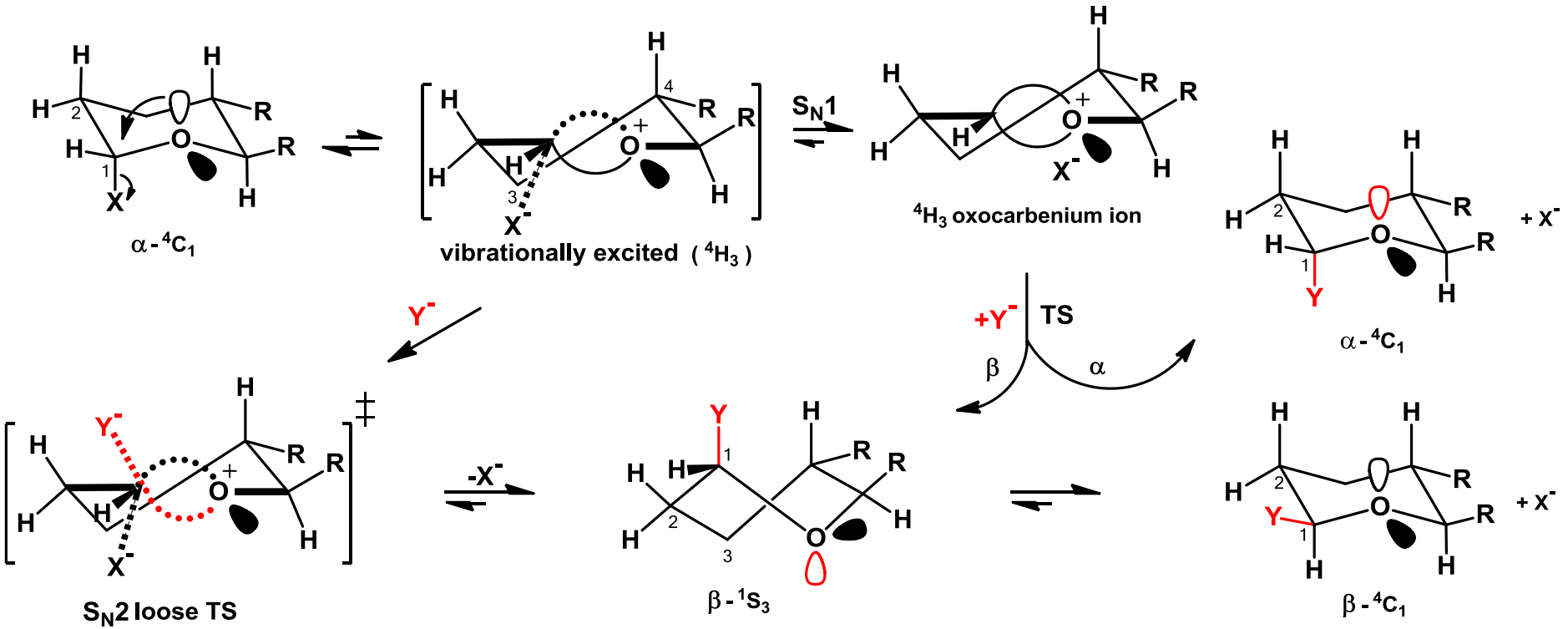
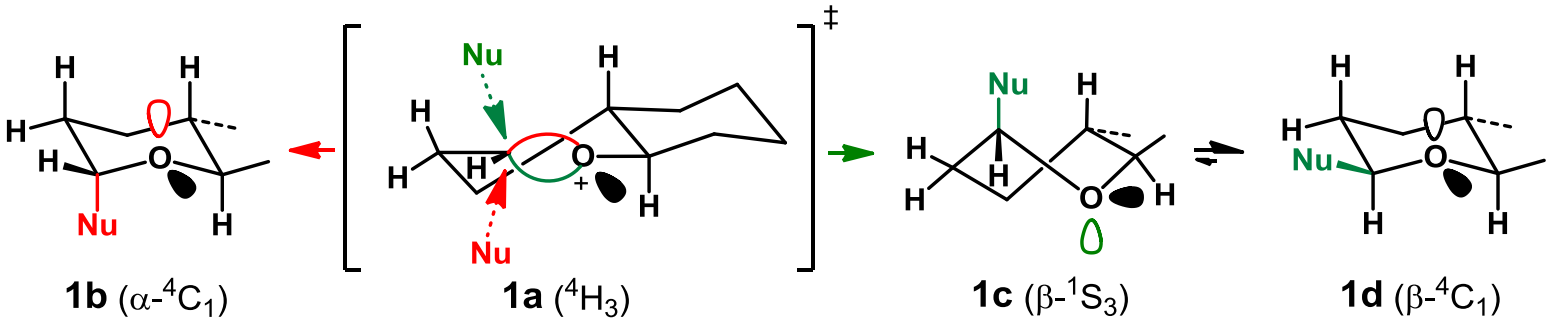


Fig. 6 Bicyclic pyranoside donors **1-3**.

J.-F. Parent, P. Deslongchamps. *Org. Biomol. Chem.* **2016**, *14,* 11183.

S_N1 *vs* S_N2 with τ bonds

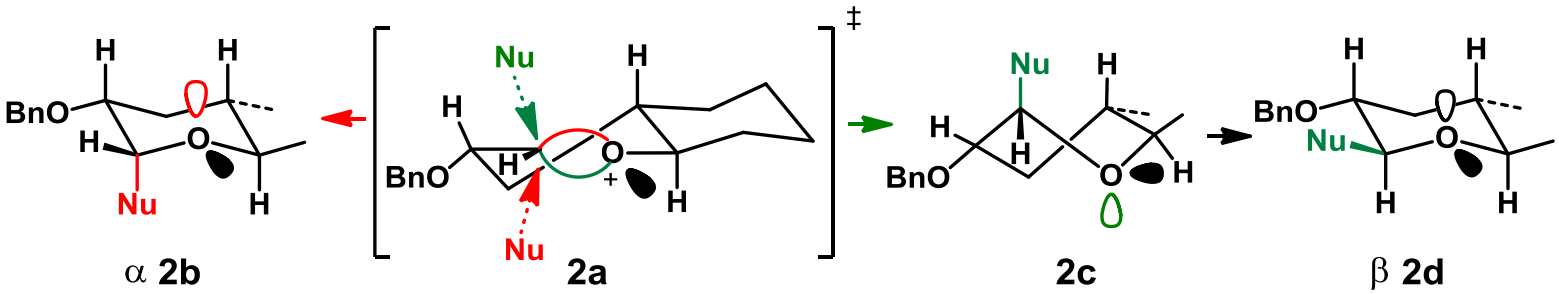




TMS allyl → α only

CF_3CH_2OH → α/β = 95/5

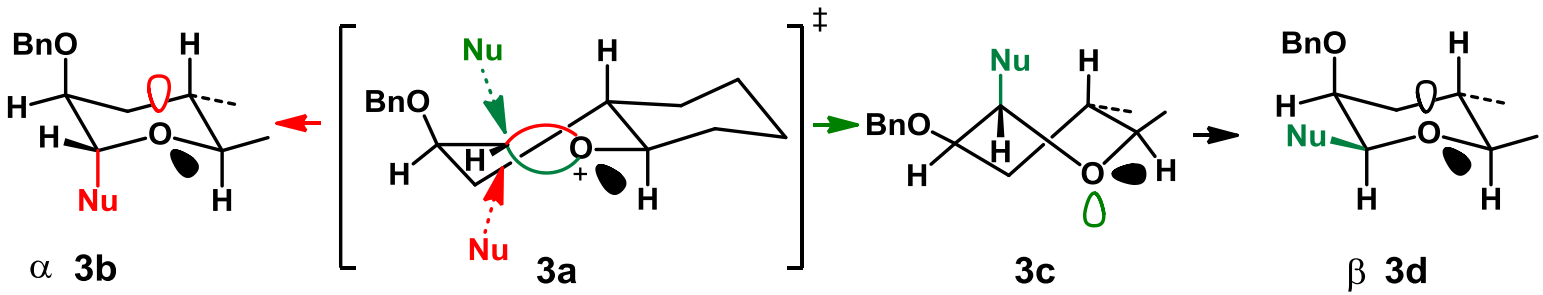
α/β Glycosylation of unsubstituted bicyclic pyranoside.



TMS allyl → α only

CF_3CH_2OH → α only

α/β Glycosylation of equatorial OBn bicyclic pyranoside.

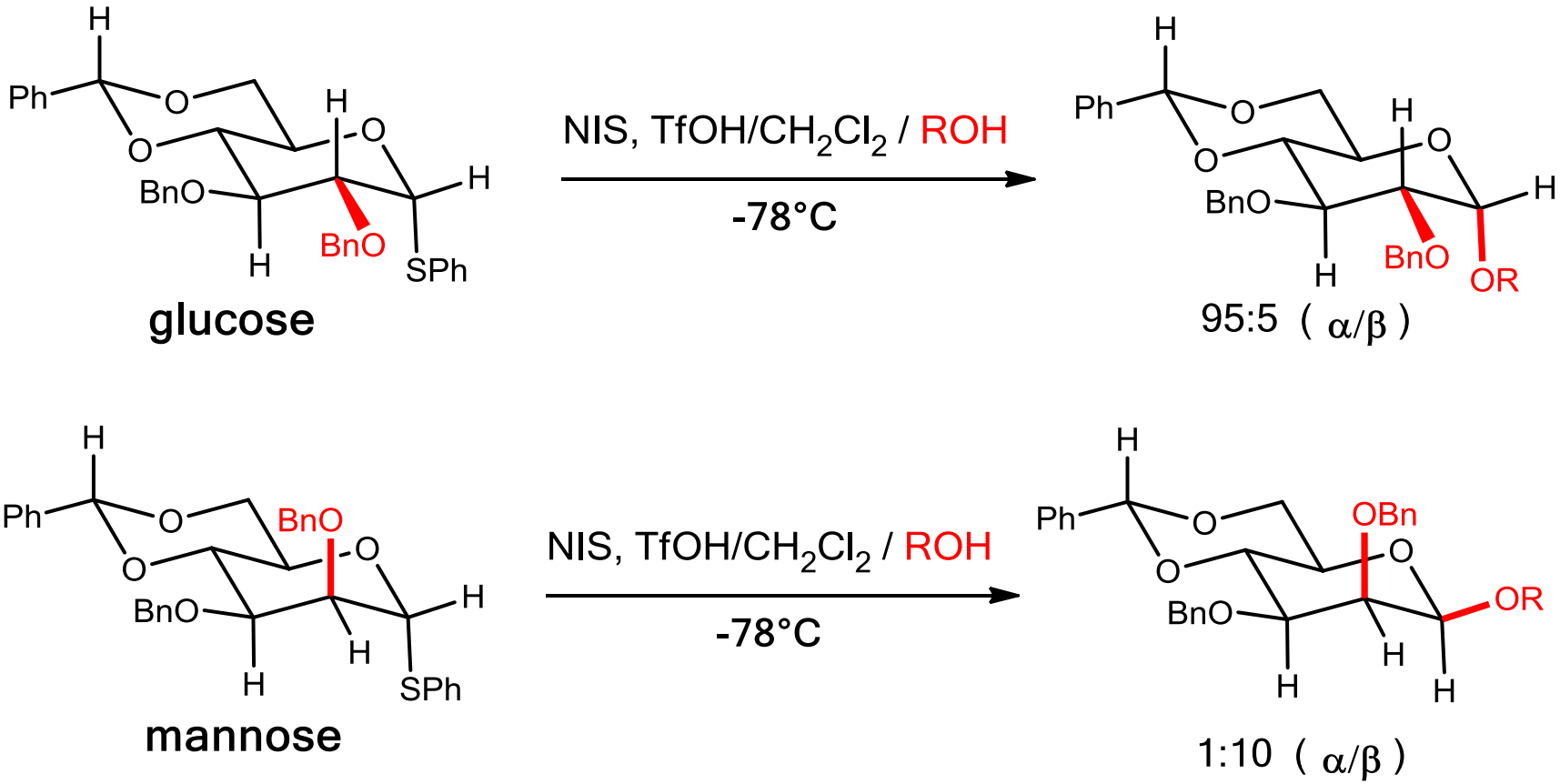


TMS allyl → α/β = 95/5

CF_3CH_2OH → α/β = 78/22

α/β Glycosylation of axial OBn bicyclic pyranoside.

Glucoside/mannoside glycosidation (1,2-*cis*)



D. Crich, S. Sun, *J. Org.Chem.* 1996, *61,* 4506; *Tetrahedron* 1998, *54,* 8321.
D. Crich *et al. Nat. Chem*. 2012, *4,* 663.
M. Bols, M. Pedersen *et al. Org. Lett.* 2014, *16,* 1116.
M. Bols *et al. Chem. Commun.* 2015, *51,* 13283.

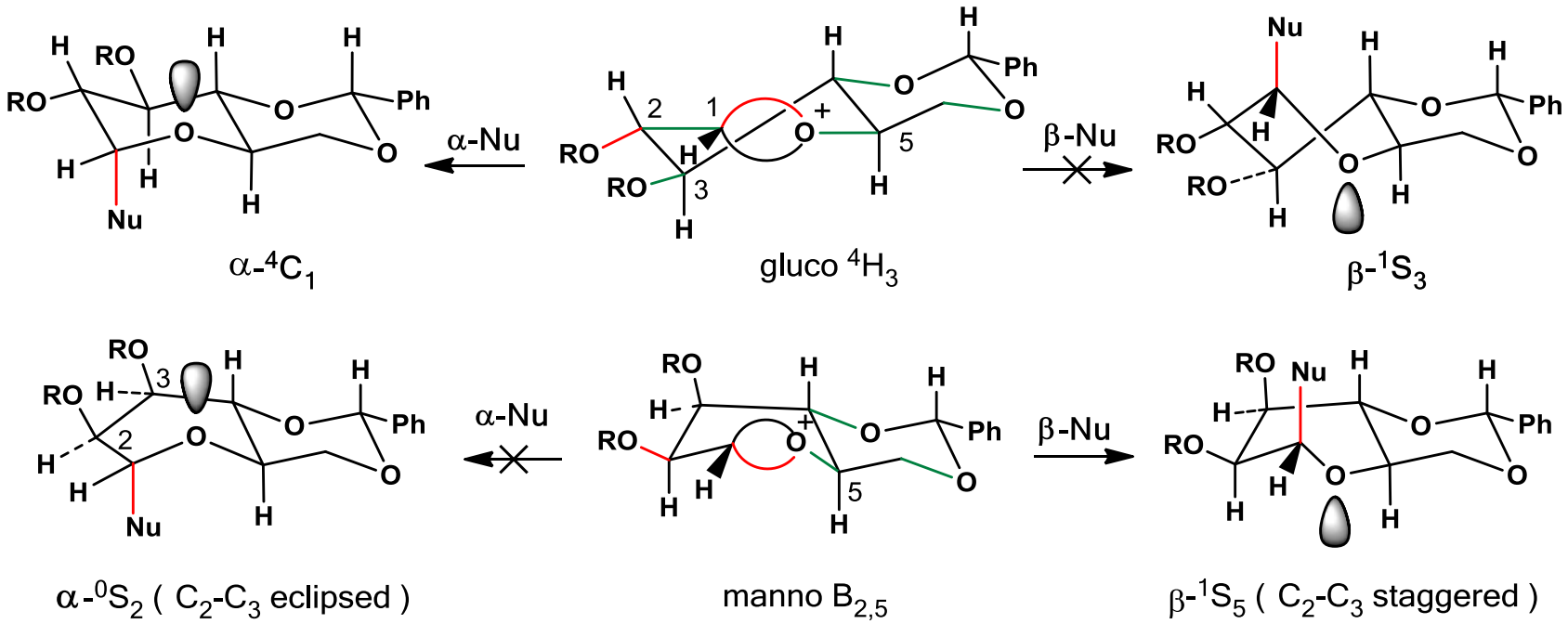


Fig. 12 Glycosylation of 4,6-O-benzyildene of glucose and mannose donors.

D. Crich, S. Sun, *J. Org.Chem.* 1996, *61,* 4506; *Tetrahedron* 1998, *54,* 8321.
D. Crich *et al. Nat. Chem*. 2012, *4,* 663.
M. Bols, M. Pedersen *et al. Org. Lett.* 2014, *16,* 1116.
M. Bols *et al. Chem. Commun.* 2015, *51,* 13283.

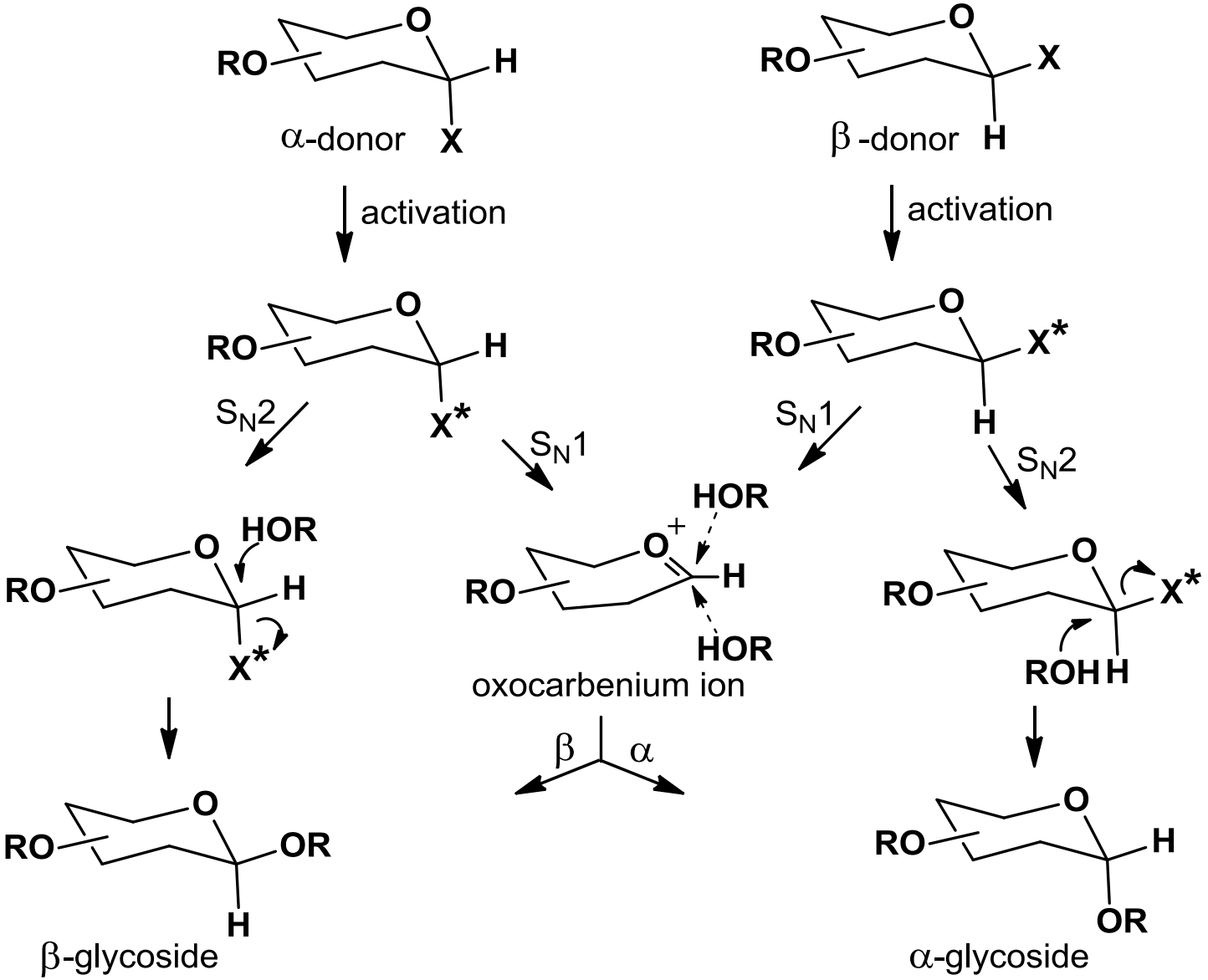


Fig. 1 A general glycosylation mechanism.

FACTORS INFLUENCING THE GLYCOSYLATION STEPS

(1) Conformation of donor ($^4C_1$, $^1C_4$, $^1S_3$, $^0S_2$) and the corresponding oxocarbenium ion (half-chair $^4H_1$ or $^1H_4$) at the transition states (possibility of conformational change).

(2) Inductive effect of exocyclic OR groups at C_3, C_4, C_6 and hyperconjugation stabilizing or destabilizing.

(3) Electrostatic stabilization of oxocarbenium ion by exocyclic OR groups.

(4) S_N1-like (or S_N2-like) process and Bürgi & Dunitz angle of attack.

(5) Polarity of solvent favoring S_N1 or S_N2 process and early or late transition state.

(6) Transient glycosyl donor intermediate (e.g. glycosyl triflate) or contact ion pair (CIP) and solvent-separated ion pair (SSIP).

(7) Steric effects and stereoelectronic effects (antiperiplanar *versus* synperiplanar hypothesis) and reaction trajectory.

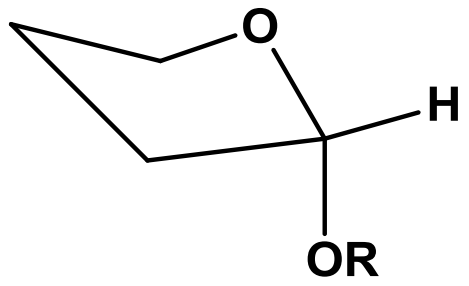
(8) ^{13}C and ^2H primary kinetic isotope effects (KIE).

(9) FMO based *ab initio* calculation.

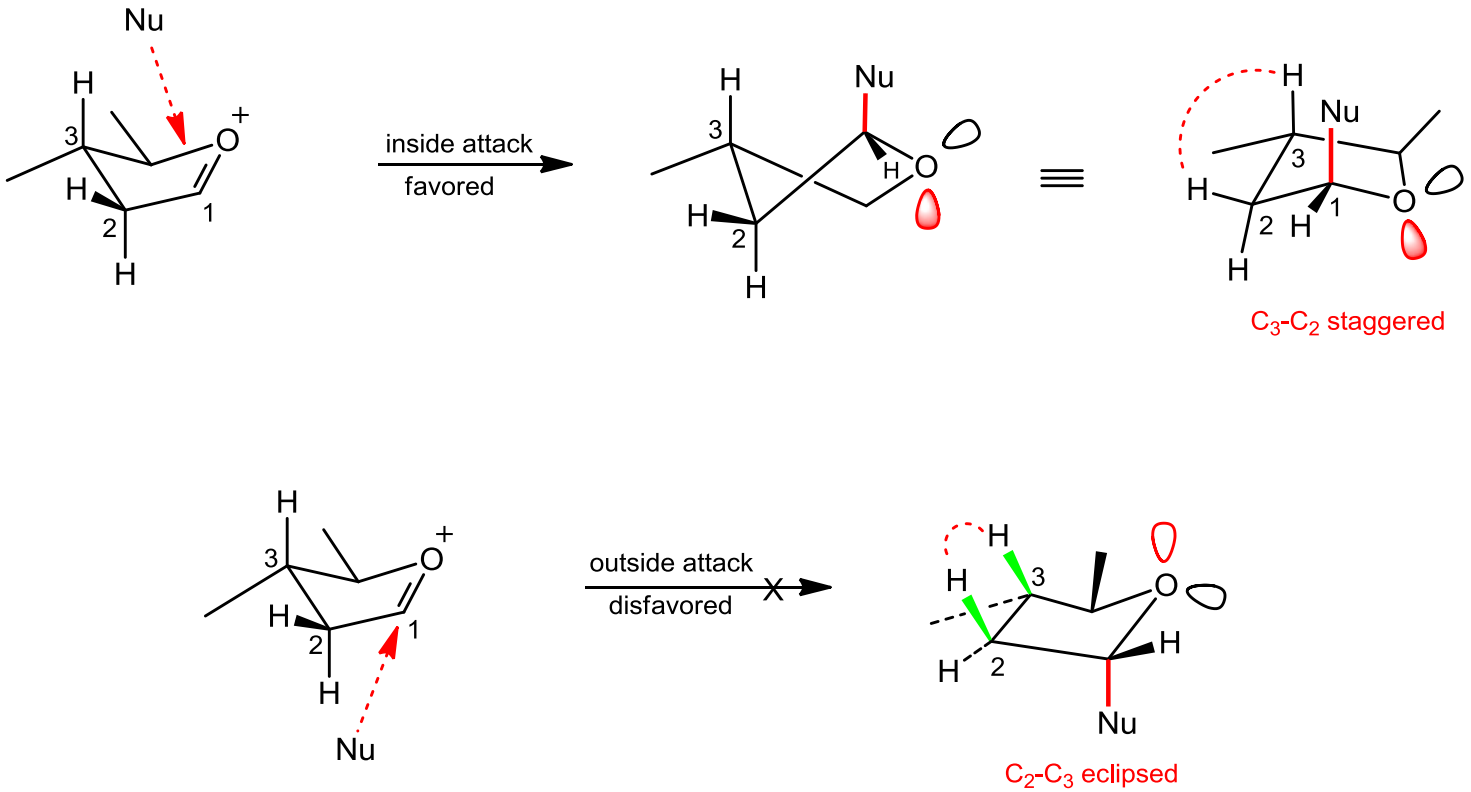
(10) σ–π orbital model.

(11) Bent bond model and the antiperiplanar (BBA) hypothesis.

Synthèse des α et β-glycofuranosides



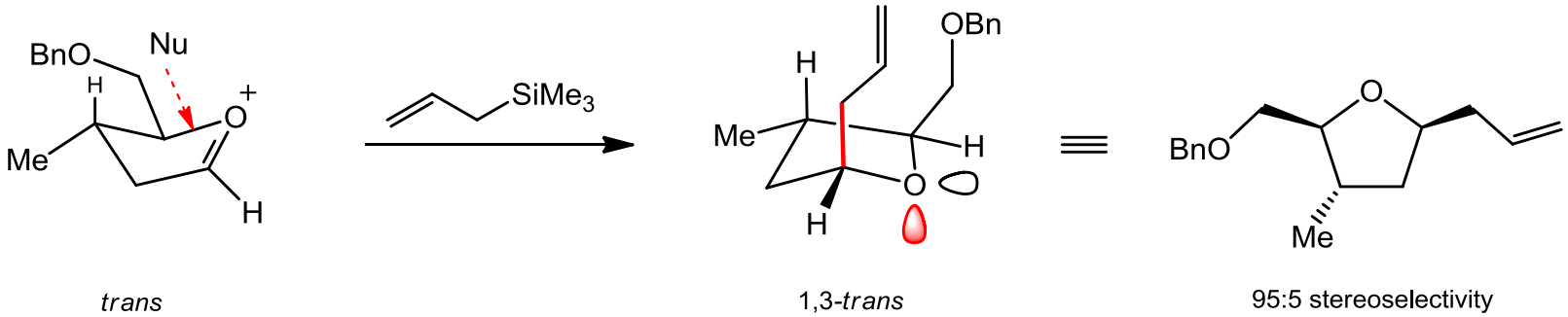
Inside Attack Model of Woerpel



Conclusion: C_2-C_3 eclipsed is too high in energy at transition state, inside atttack is favored

Larsen, C.H., Ridway, B.H., Shaw, J.T., Woerpel, K.A. *JACS* **1999**, *121,* 12208-12209.

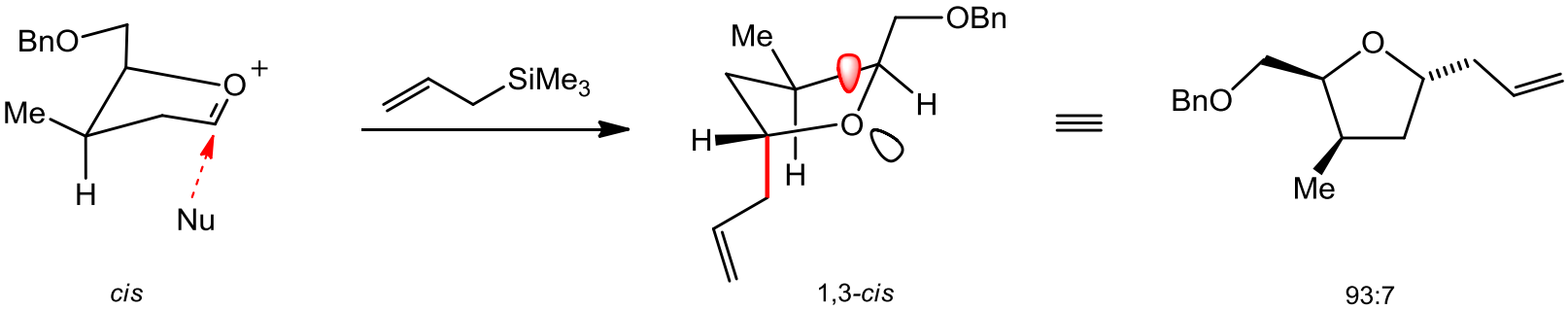
Inside Attack : Experimental Results



trans

1,3-*trans*

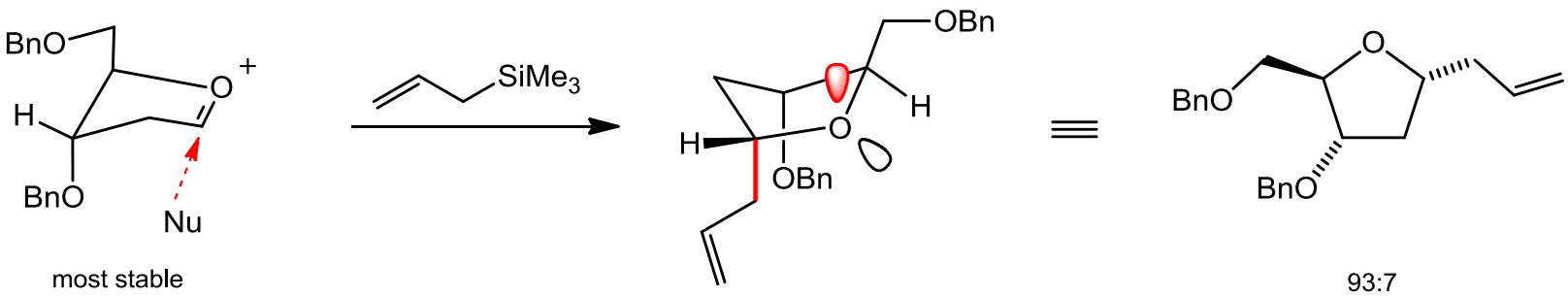
95:5 stereoselectivity



cis

1,3-*cis*

93:7

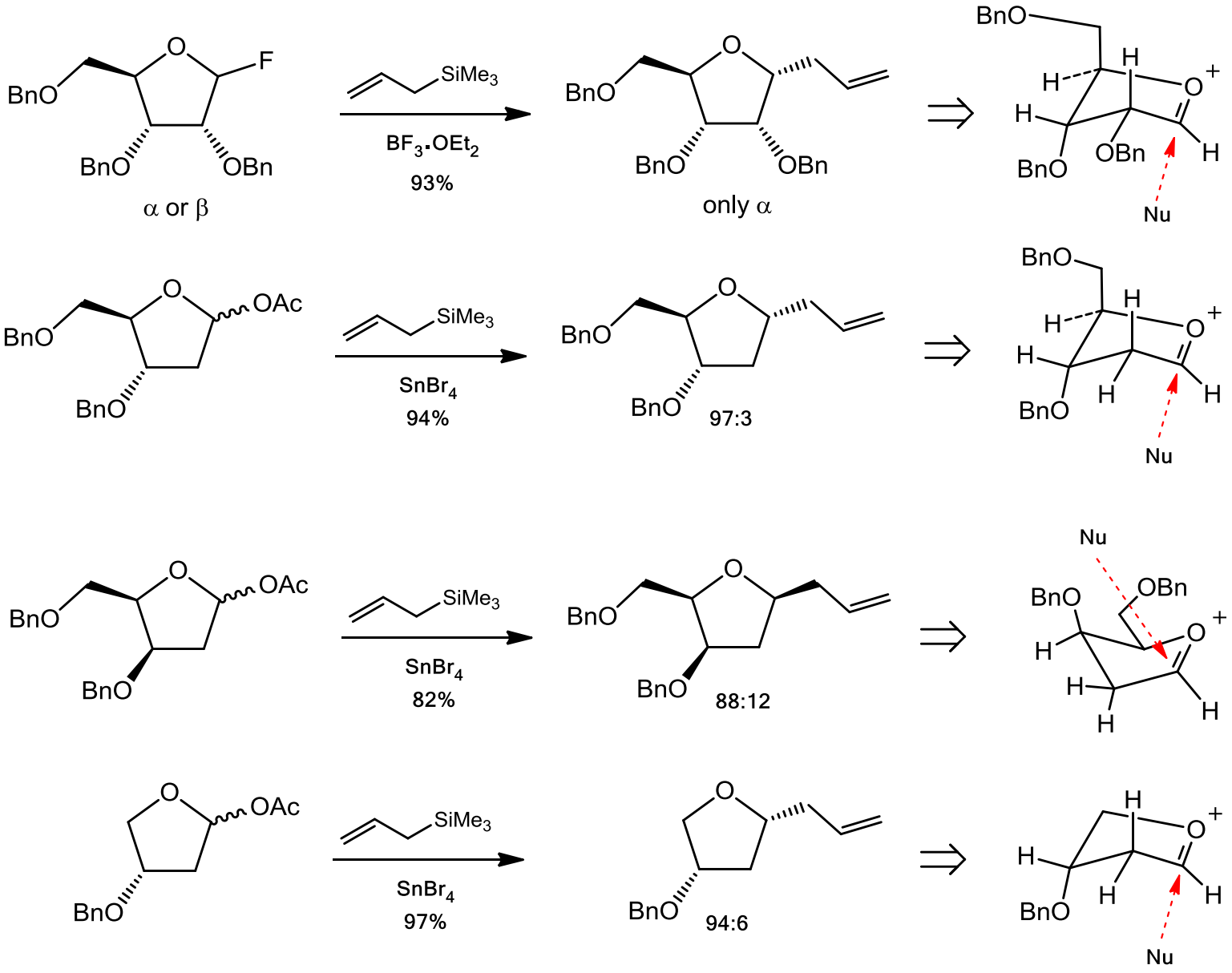


most stable conformation

93:7

Larsen, C.H., Ridway, B.H., Shaw, J.T., Woerpel, K.A. *JACS* **1999**, *121,* 12208-12209.

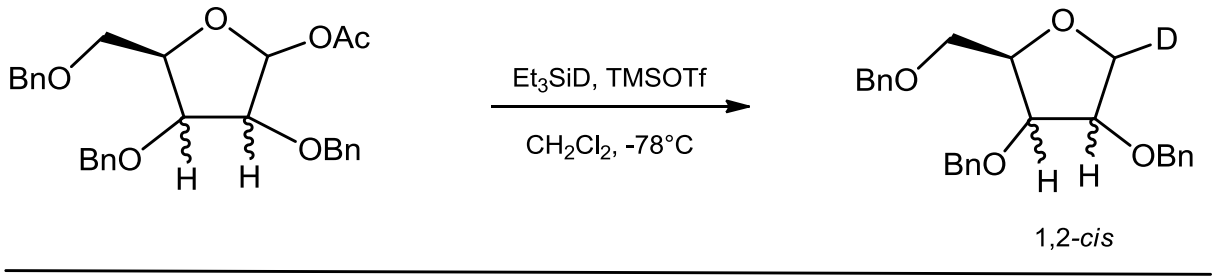
Inside attack in furanosides



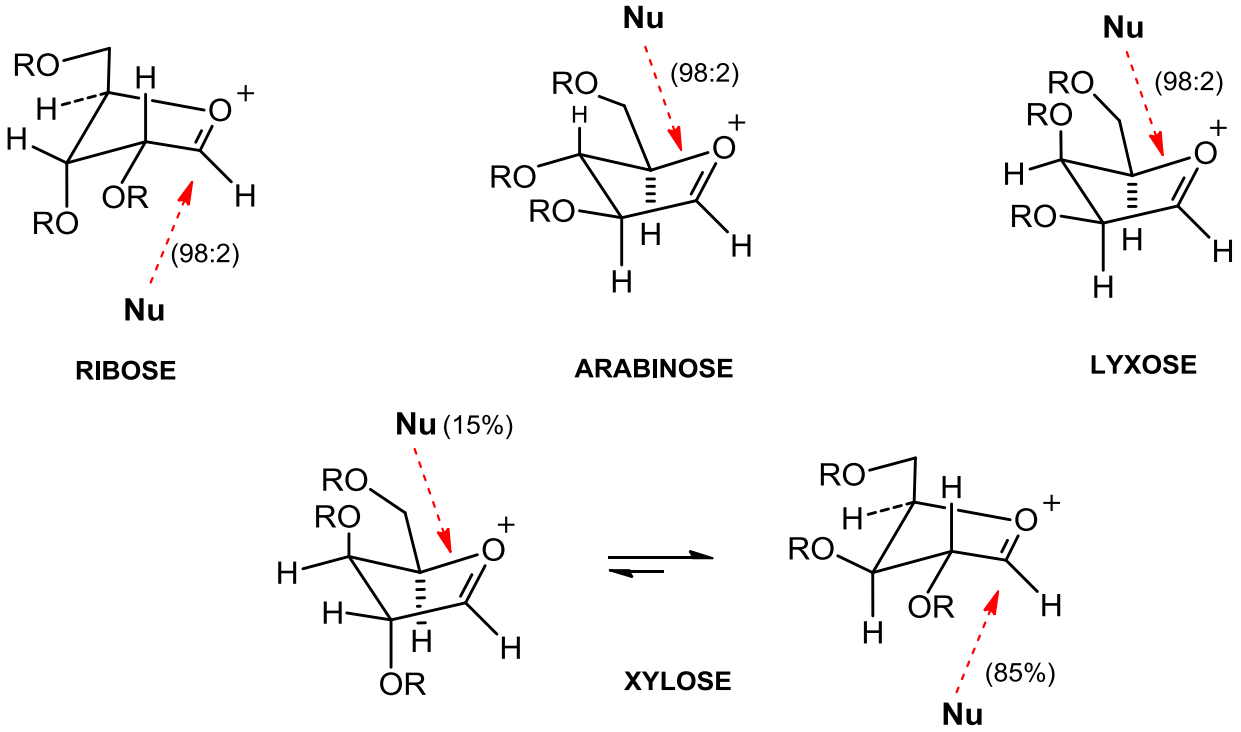
Larsen, C.H.; Ridway, B.H.; Shaw, J.T.; Woerpel. *JACS* **1999**, *121,* 12208-12209.

1,2-*cis* Glycosides from furanose carbohydrates

(*cis* to the OR group at C_2)



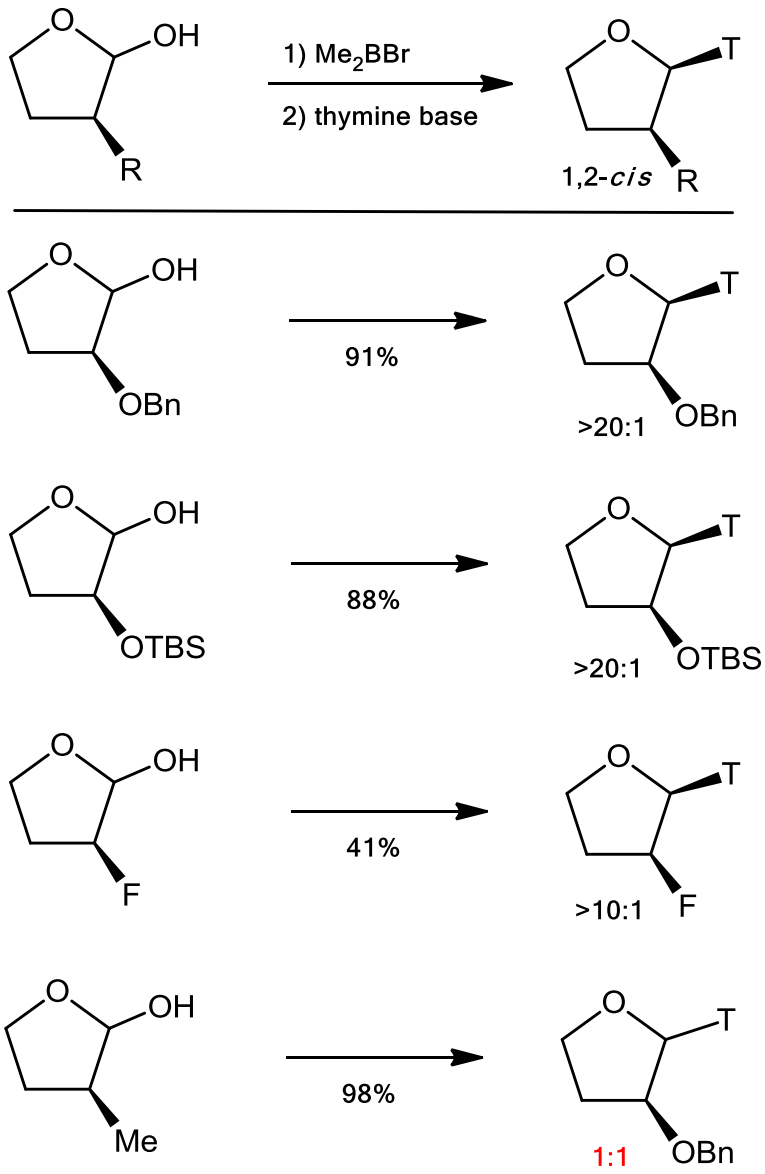
1,2-*cis*

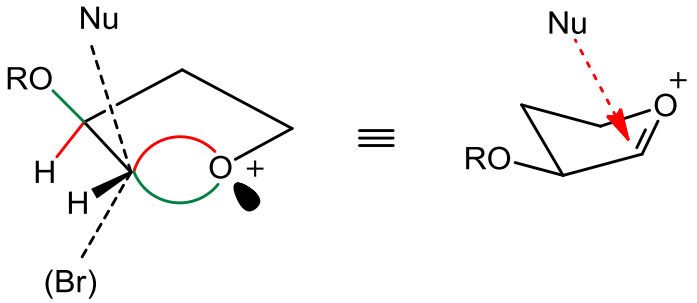


N.B. Most stable furanosyl oxocarbenium

Codée, J.D.C. *Angew. Chem. Int. Ed.* **2014**, *53,* 10381-10385.

1,2-cis-Tetrahydrofuran nucleoside analogues

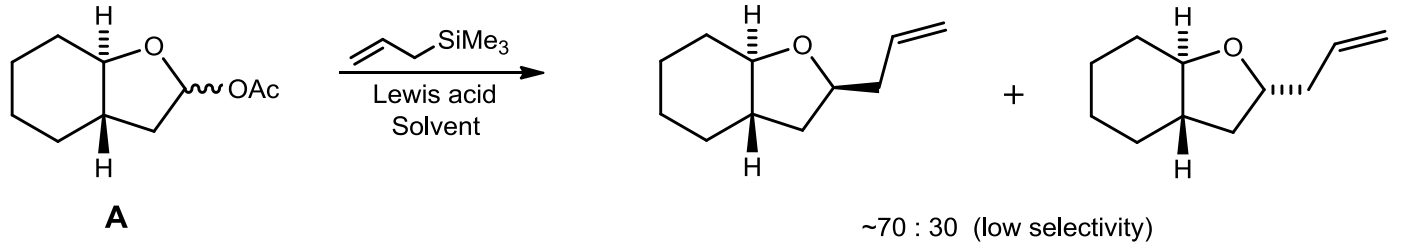




SN_1 or SN_2 (exploded) ?

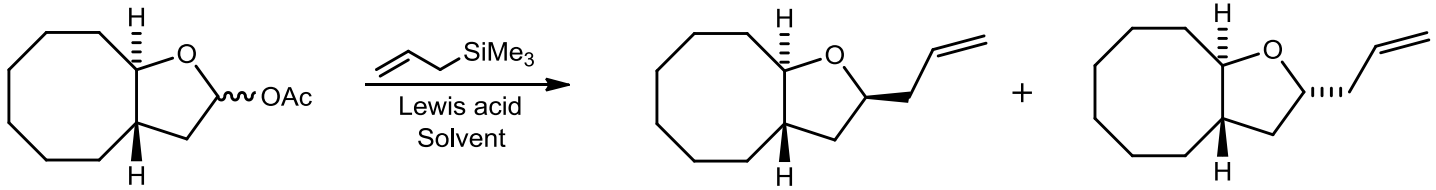
Prévost, M.; St-Jean, O.; Guindon, Y. *JACS* **2010**, *132,* 12433-12439.

Bicyclic 5-membered-ring Oxocarbenium



A

~70 : 30 (low selectivity)



B

~93 : 7 (high selectivity)

(distortion easy in 8-membered ring)

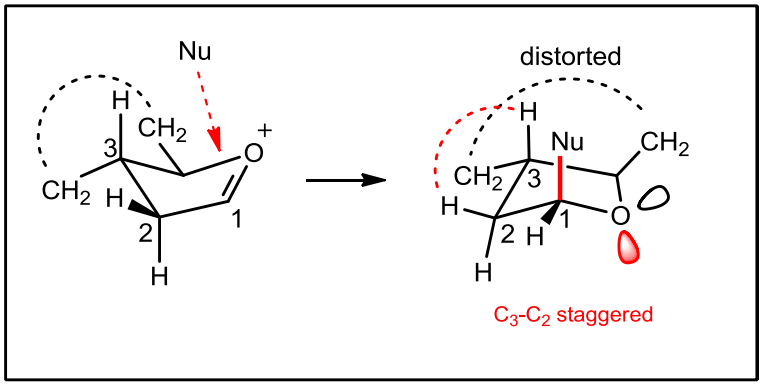
Ratio independent of

1) Lewis acid

BF_3-OEt_2, $SnBr_4$, $TiCl_4$, Me_3SiOTf, Me_2AlCl, $MeAlCl_2$

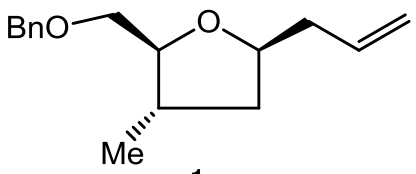
2) Solvent

CH_2Cl_2, $C_6H_5CH_3$, Et_2O, $CHCl_3$, CH_3CN



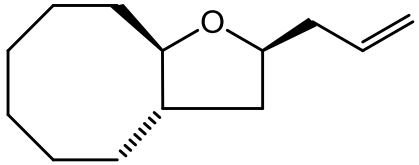
Smith, D.M.; Tran, M.B.; Woerpel, K.A. *JACS* **2003**, *125,* 14149-14152.
Tran, M.B.; Woerpel, K.A. *JOC* **2013**, *78*, 14149-14152.

Bicyclic furanosides



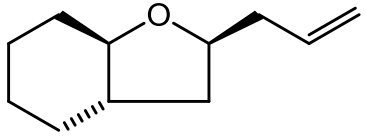
1

95:5 ds



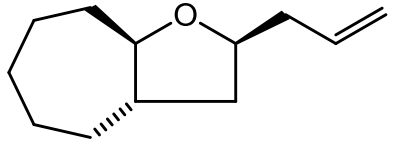
2

93:7 ds



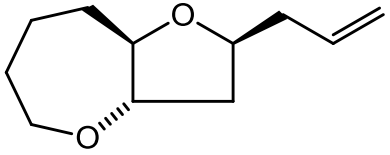
3

73:27 ds



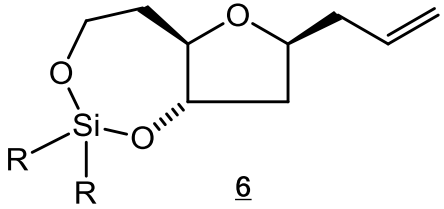
4

92:8 ds



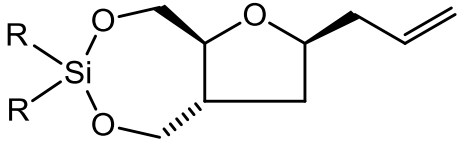
5

60:40 ds



6

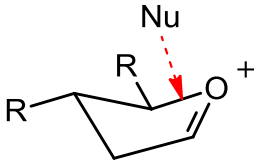
63:37 ds



7

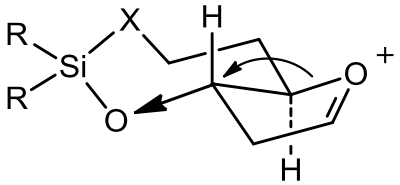
81:15 ds

1, 2 and 4 : inside attack

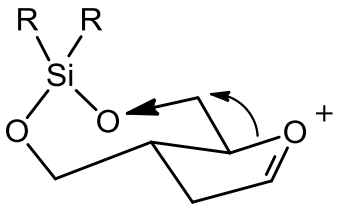


3 : less inside attack due to distortion of 6-membered ring

5 and 6 : earlier TS (more reactive oxocarbenium due to gauche effect (hyperconjugation))



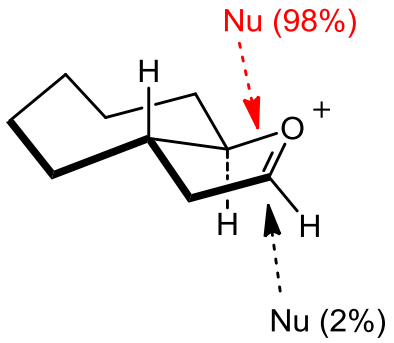
7 : earlier TS (more reactive oxocarbenium) (as in 5 and 6)



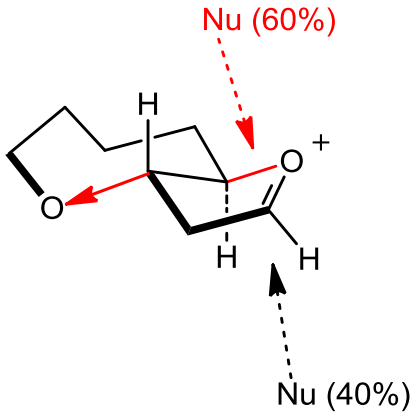
Lavinga, O.; Tran, V.T.; Woerpel, K.A. *Org. Biomol. Chem.* **2014**, *12,* 7083-7091.

Oxygen at C_3 and lost of selectivity

inside attack favored by 1.6 kcal/mol



inside attack favored by 0.2 kcal/mol

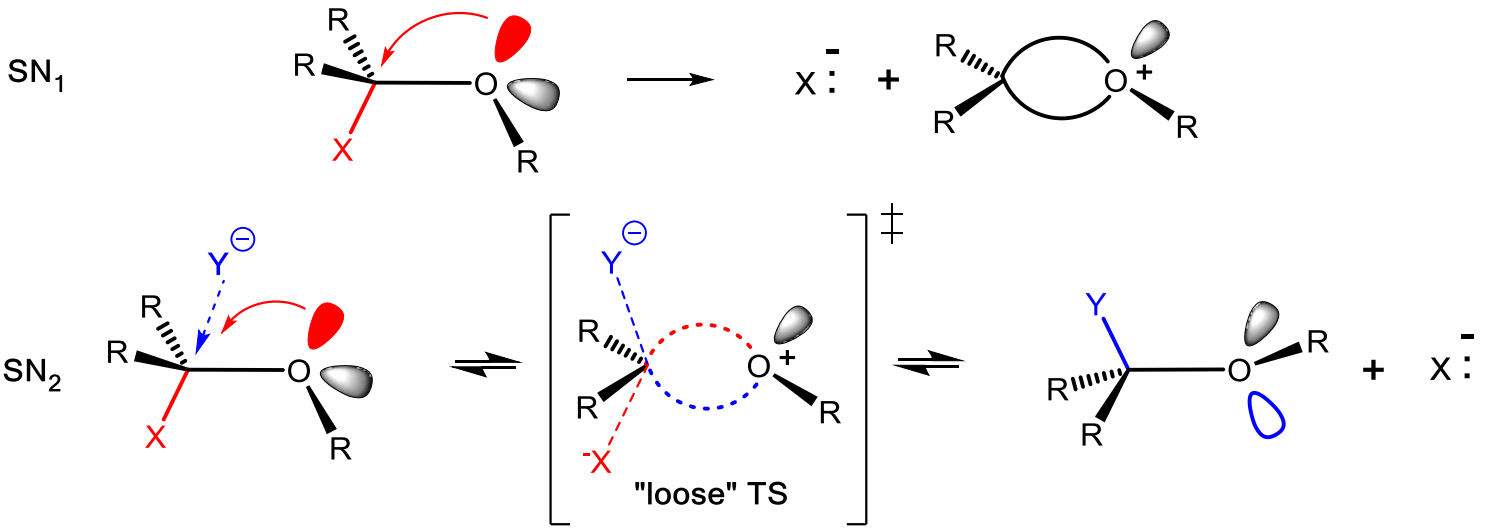


Nu = TMSAllyl

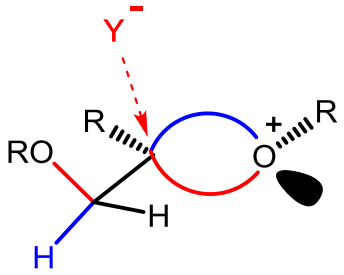
Lavinga, O.; Tran, V.T.; Woerpel, K.A. *Org. Biomol. Chem.* 2014, *12,* 7083-7091.

Key parameters in glycosidation reaction: Summary

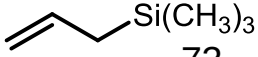
A) Antiperiplanar Hypothesis (Hyperconjugation - Anomeric Effect)



B) Hyperconjugation

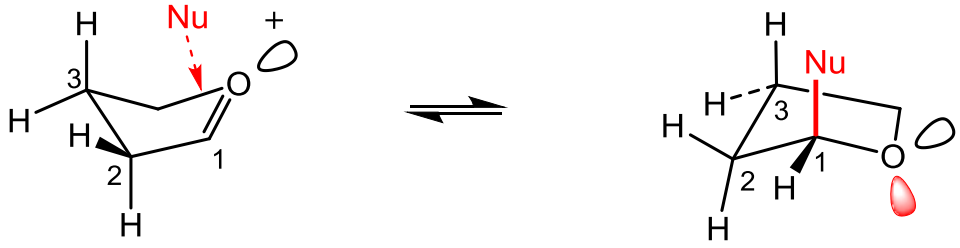


C) Electrostatic stabilization by OR group depending on conformation

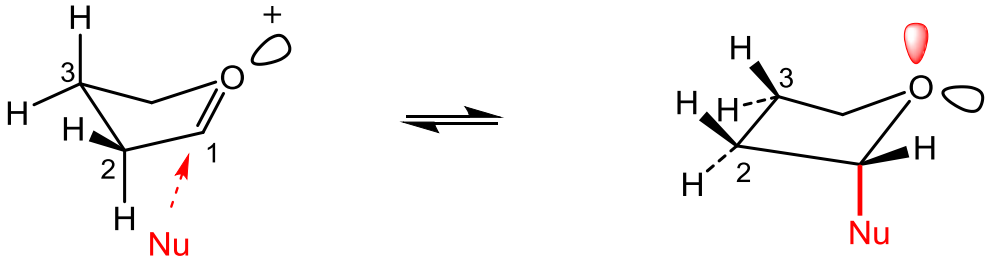
D) Nucleophilicity and position of Transition State ex.: CH_3CH_3OH > CF_3CH_2OH > 

Ring conformation: Summary

5-membered ring

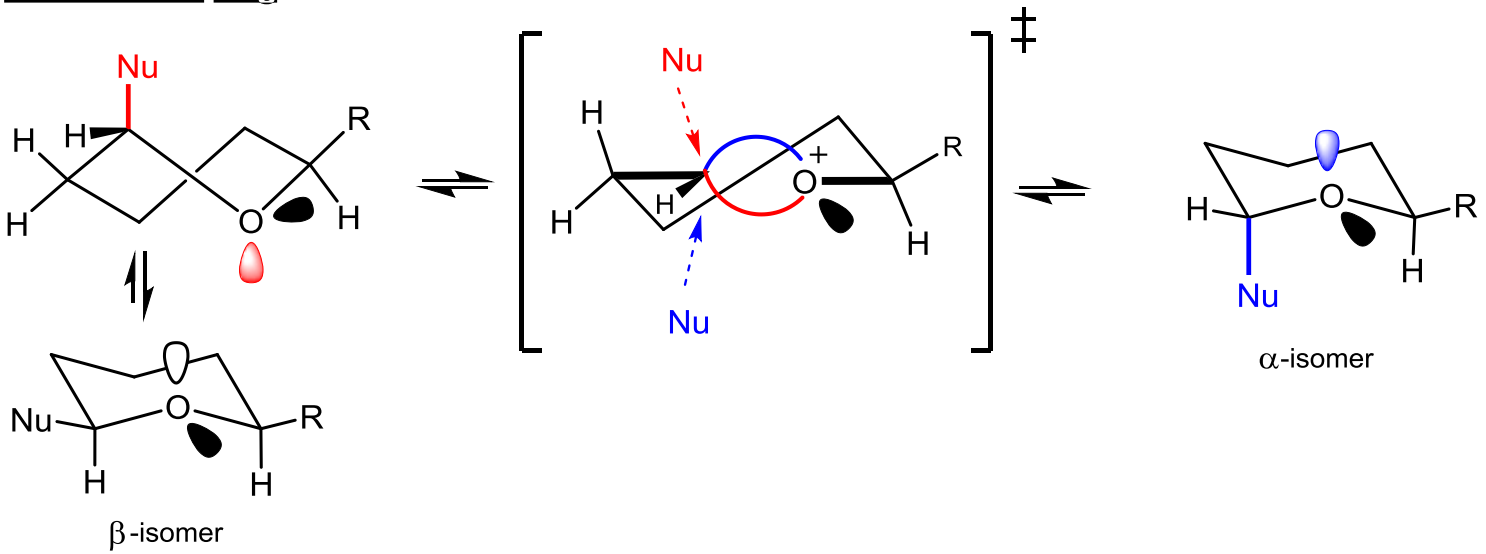


inside attack (staggered) favored



outside attack (eclipsed) disfavored

6-membered ring



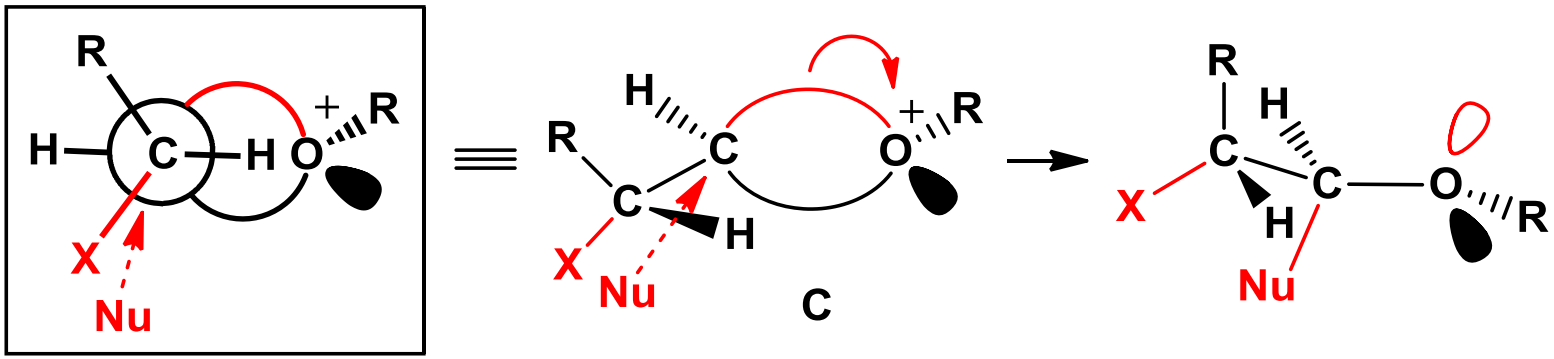
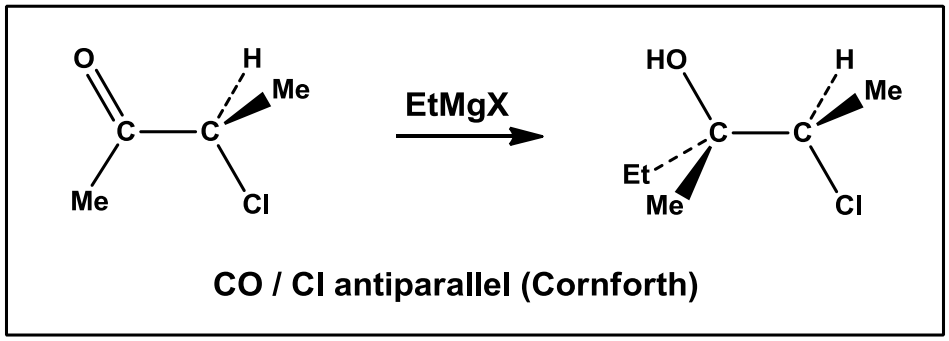
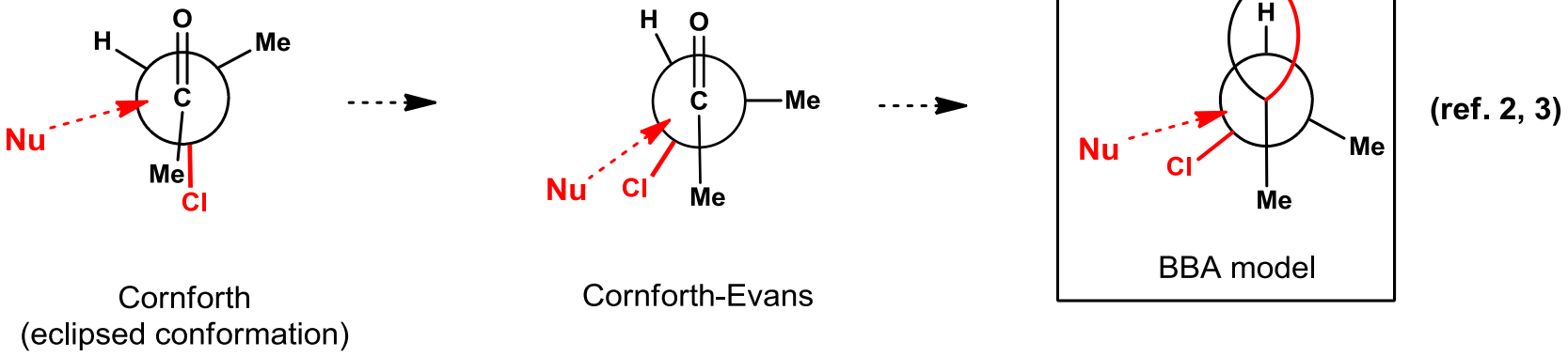


Fig. 3 Stereoelectronically preferred nucleophilic addition.

Cornforth-Evans and BBA Models



(ref. 1)



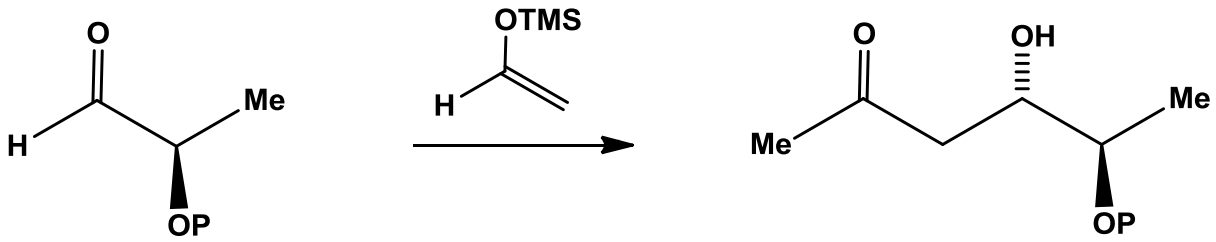
(ref. 2, 3)

(1) J. W. Cornforth, R. H. Cornforth, K. K. Mathew. *J. Chem. Soc.* **1959**, 112-127.

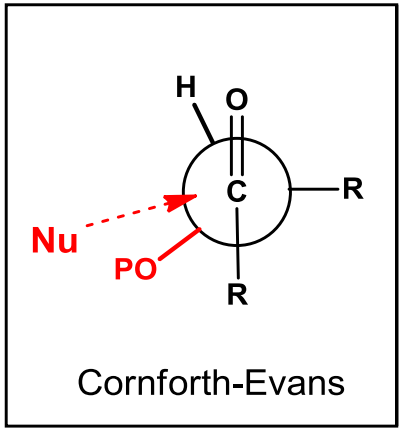
(2) D. E. Evans, S. J. Siska, V. J. Cee. *Angew. Chem. Int. Ed.* **2003**, *42,* 1761-1765.

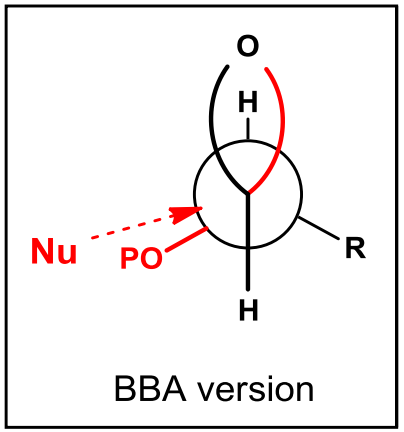
(3) D. E. Evans, V. J. Cee, S. J. Siska. *J. Am. Chem. Soc.* **2006**, *128,* 9433-9441.

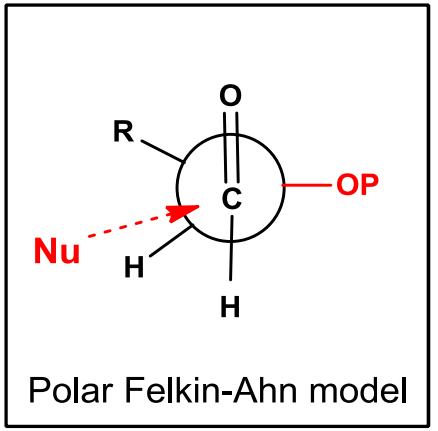
α-Alkoxy-aldehyde (Cornforth-Evans Model)



3,4 *anti* (~80:20)







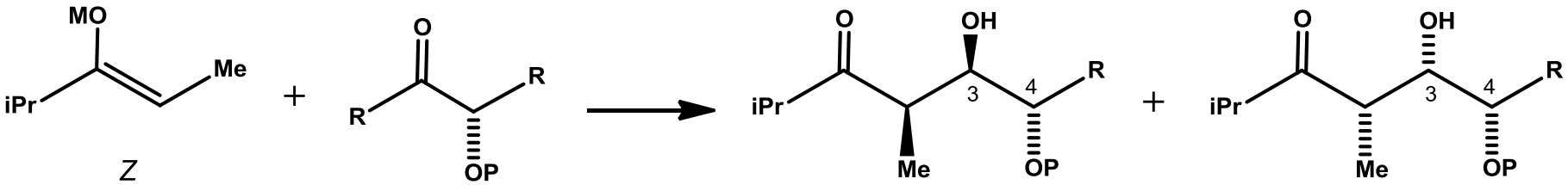
X

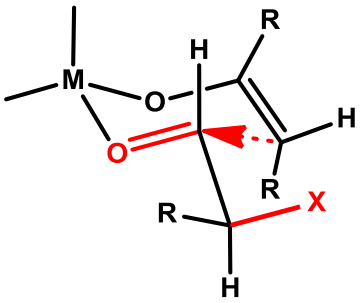
(a) D. E. Evans, S. J. Siska, V. J. Cee. *Angew. Chem. Int. Ed.* **2003**, *42,* 1761-1765.

(b) D. E. Evans, V. J. Cee, S. J. Siska. *J. Am. Chem. Soc.* **2006**, *128,* 9433-9441.

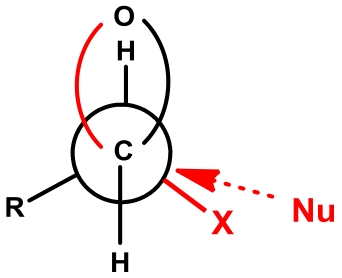
(c) J. W. Cornforth, R. H. Cornforth, K. K. Mathew. *J. Chem. Soc.* **1959**, 112-127.

Z Boron and Lithium Enolates (Chelated Aldol)





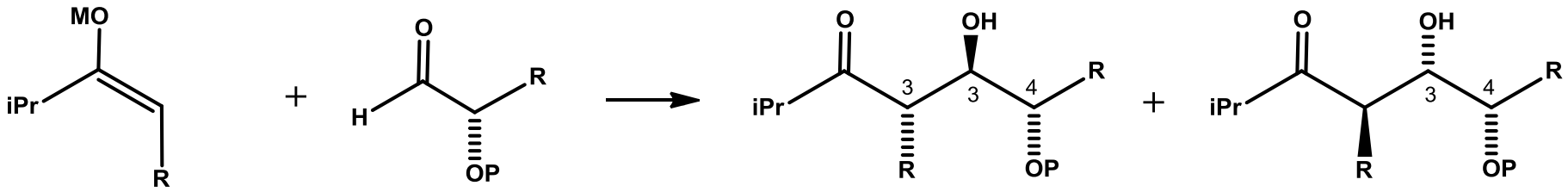
Cornforth-Evans



BBA model

D. E. Evans, S. J. Siska, V. J. Cee. *Angew. Chem. Int. Ed.* **2003**, *42,* 1761-1765.

E Boron Enolates (Chelated Aldol)

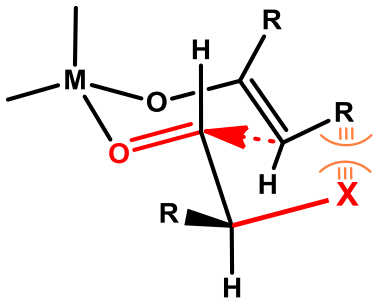


M = $(C\ Hex)_2B$

3,4-*anti*

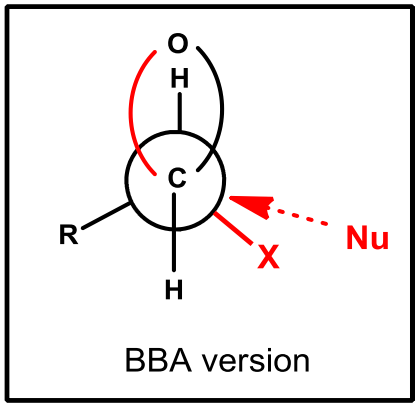
3,4-*syn*

diastereoselectivity poor and often favors the 3,4-*syn* diastereomer



Cornforth-Evans

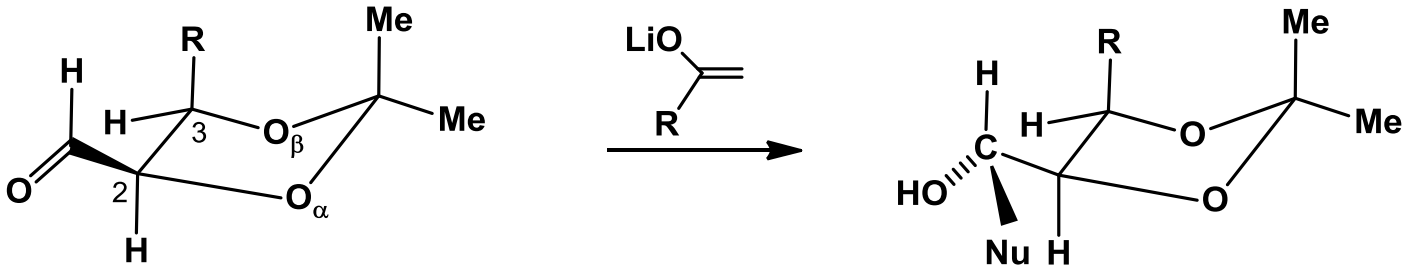
"Enolates TS has a *syn* pentane and the C–X dipole control are not reinforcing"

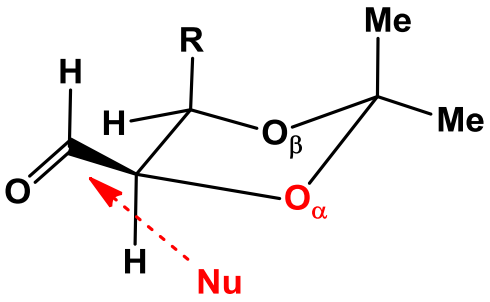


BBA version

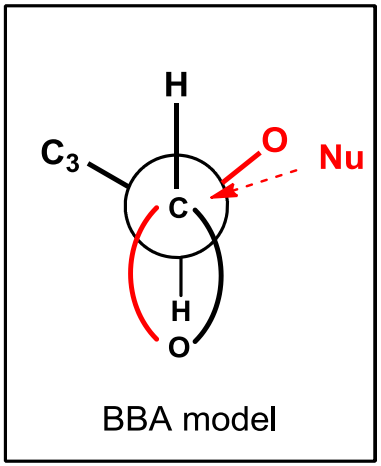
D. E. Evans, S. J. Siska, V. J. Cee. *Angew. Chem. Int. Ed.* **2003**, *42,* 1761-1765.

anti-α,β-Bisalkoxyaldehyde (acetonide)





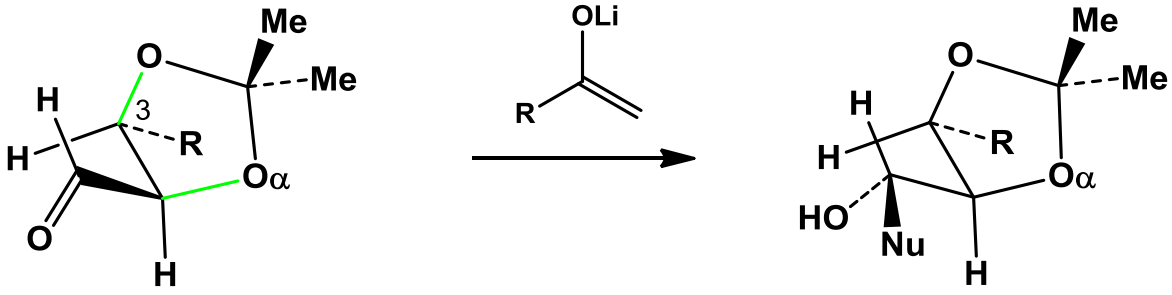
Cornforth-Evans



BBA model

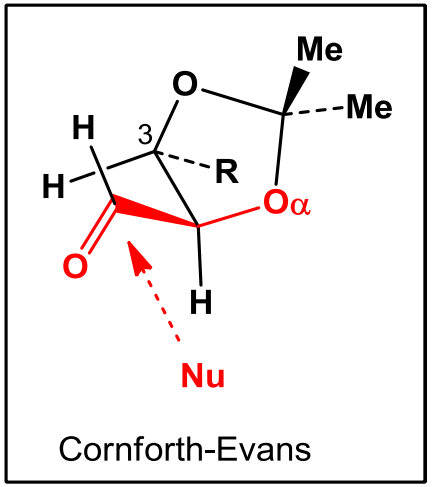
D. E. Evans, V. J. Cee, S. J. Siska. J. Am. Chem. Soc. 2006, 128, 9433-9441.

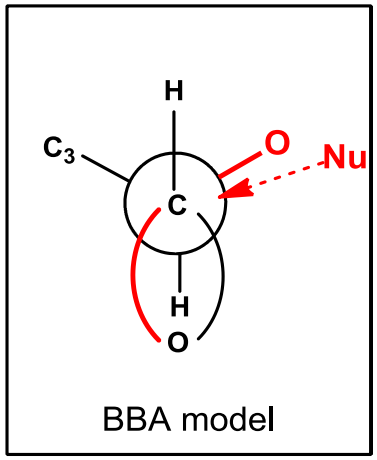
syn-α,β-Bisalkoxyaldehyde (acetonide)



α,β-*syn*

α,β-*anti* (~ 90:10)





D. E. Evans, V. J. Cee, S. J. Siska. *J. Am. Chem. Soc.* **2006**, *128,* 9433-9441.

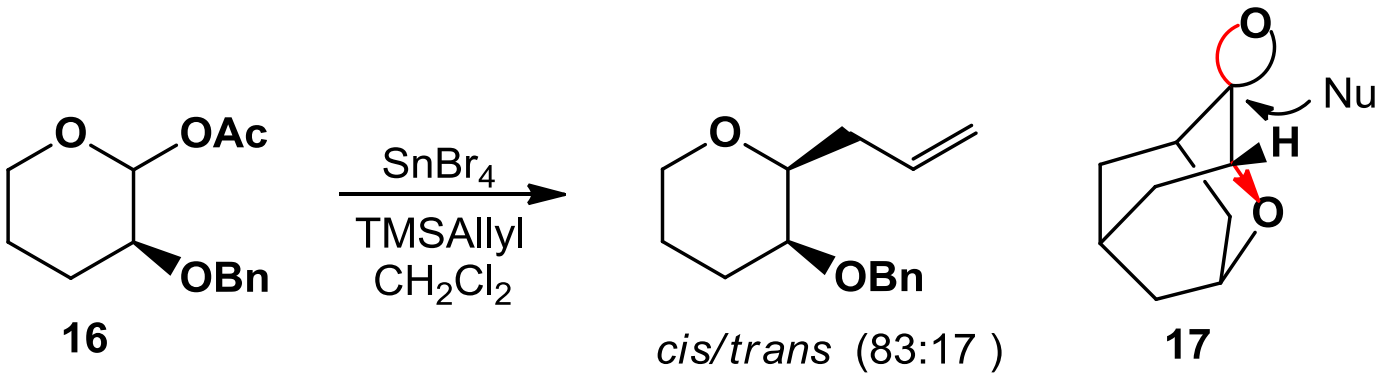
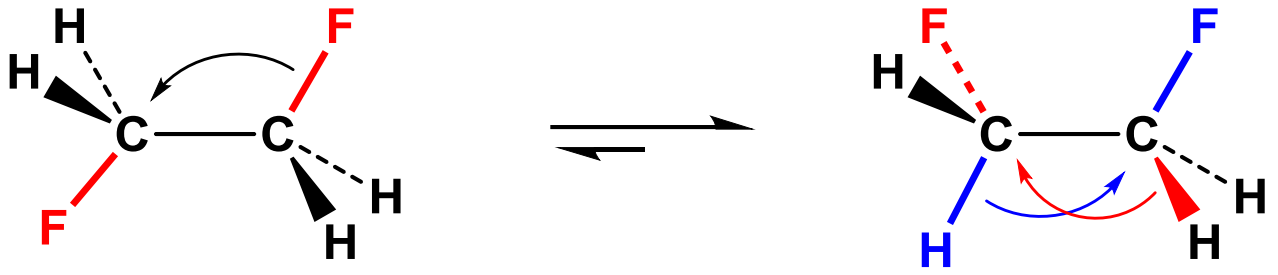


Fig.10 1,2-*Cis* nucleophilic addition on **16** and **17**.

Gauche Effect (Hyperconjugation)



+0.9 kcal/mol
(negative hyperconjugation)

0 kcal/mol
(positive hyperconjugation)

S. Wolfe, *Acc. Chem. Res.* 1972, *5,* 102.
N. C. Craig *et al. J. Am. Chem. Soc.* 1997, *119,* 4789.