

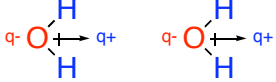

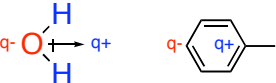
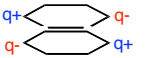
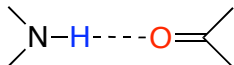


Noncovalent Interactions: Electrostatic Effects

Evans Group Seminar
09/25/2009
Egmont Kattnig

Noncovalent Interactions

		Energy dependence on distance
Charge-charge		$1/r$
Charge-dipole		$1/r^2$
Dipole-dipole		$1/r^3$
Charge-induced dipole		$1/r^4$
Dipole-induced dipole		$1/r^5$
Dispersion		$1/r^6$
Van der Waals repulsion		$1/r^{12}$
Hydrogen bond		

Electrostatic Energy:

Israelachvili, J. *Intermolecular and Surface Forces*, 2nd ed.; Academic Press, London, 1991.

Electrostatic Effect and Bond Energies:

Wiberg, K. B. „The Role of Electrostatic Effects in Organic Chemistry“, *J. Chem. Edu.* **1996**, *73*, 1089.
Wiberg, K. B. „The Interaction of Carbonyl Groups with Substituents“, *Acc. Chem. Res.* **1999**, *32*, 922.
Kemnitz, C. R.; Loewen, M. J. „Amide Resonance Correlates with a Breadth of C-N Rotation Barriers“, *J. Am. Chem. Soc.* **2007**, *129*, 2521.
P. R. Rablan „Is the Acetate Anion Stabilized by Resonance or Electrostatics? A Systematic Structural Comparison“, *J. Am. Chem. Soc.* **2000**, *122*, 357.

Electrostatics and Conformation:

Wiberg, K. B., Wang, Y.-g., Petersson, G. A., Bailey, W. F. „Intramolecular Nonbonded Attractive Interactions: 1-Substituted Propenes“, *J. Chem. Theory Comput.* **2009**, *5*, 1033.
Gooseman, N. E. J.; O'Hagan, D.; Peach, M. J. G.; Slawin, A. M. Z., Tozer, D. J.; Young, R. J. „An Electrostatic Gauche Effect in *b*-Fluoro- and *b*-Hydroxy-*N*-ethylpyridinium Cations“, *Angew. Chem. Int. Ed.* **2007**, *46*, 5904.
Smith, M. D.; Woerpel, K. A. „Electrostatic interactions in cations and their importance in biology and chemistry“, *Org. Bio. Chem.* **2006**, *4*, 1195.

Oxocarbenium Chemistry:

Yang, M. T.; Woerpel, K. A. „The Effect of Electrostatic Interactions on Conformational Equilibria of Multiply Substituted Tetrahydropyran Oxocarbenium Ions“, *J. Org. Chem.* **2009**, *74*, 545.
Lucero, C. G.; Woerpel, K. A. „Stereoselective C-Glycosylation Reactions of Pyranoses: The Conformational Preference and Reaction of the Mannosyl Cation“, *J. Org. Chem.* **2006**, *71*, 2641.

Dipole Controlled Nucleophilic Addition:

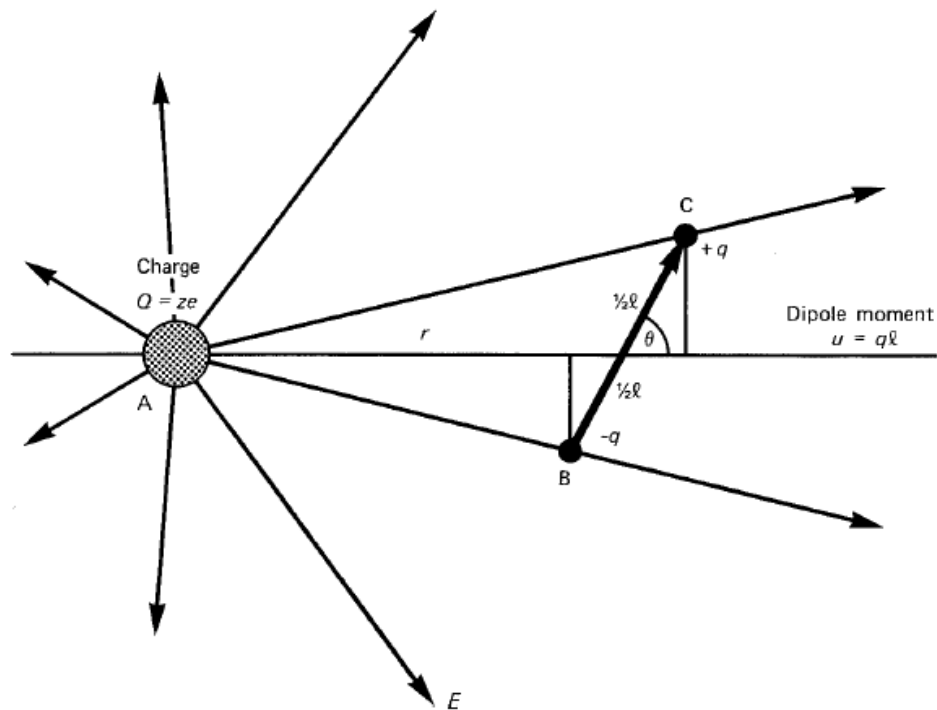
Wipf, P.; Jung, J.-K. „Nucleophilic Additions to 4,4-Disubstituted 2,5-Cyclohexadienones: Can Dipole Effects Control Facial Selectivity?“, *Chem. Rev.* **1999**, *99*, 1469.

Inductive Effect: Polarization of electron density in bonds, caused primarily by electronegativity differences.

Electrostatic Effect: Interaction between atomic charges in various parts of a molecule..
The effect is transmitted through space (i. e. a field effect).

Charge-Charge Interaction: Coulomb Law

Ion-Dipole Interaction:



$$w(r) = -\frac{Qq}{4\pi\epsilon_0\epsilon} \left[\frac{1}{AB} - \frac{1}{AC} \right],$$

$$AB = [(r - \frac{1}{2}l \cos \theta)^2 + (\frac{1}{2}l \sin \theta)^2]^{1/2},$$

$$AC = [(r + \frac{1}{2}l \cos \theta)^2 + (\frac{1}{2}l \sin \theta)^2]^{1/2}.$$

for $r > l$: point-dipol approximation ($l \rightarrow 0$)

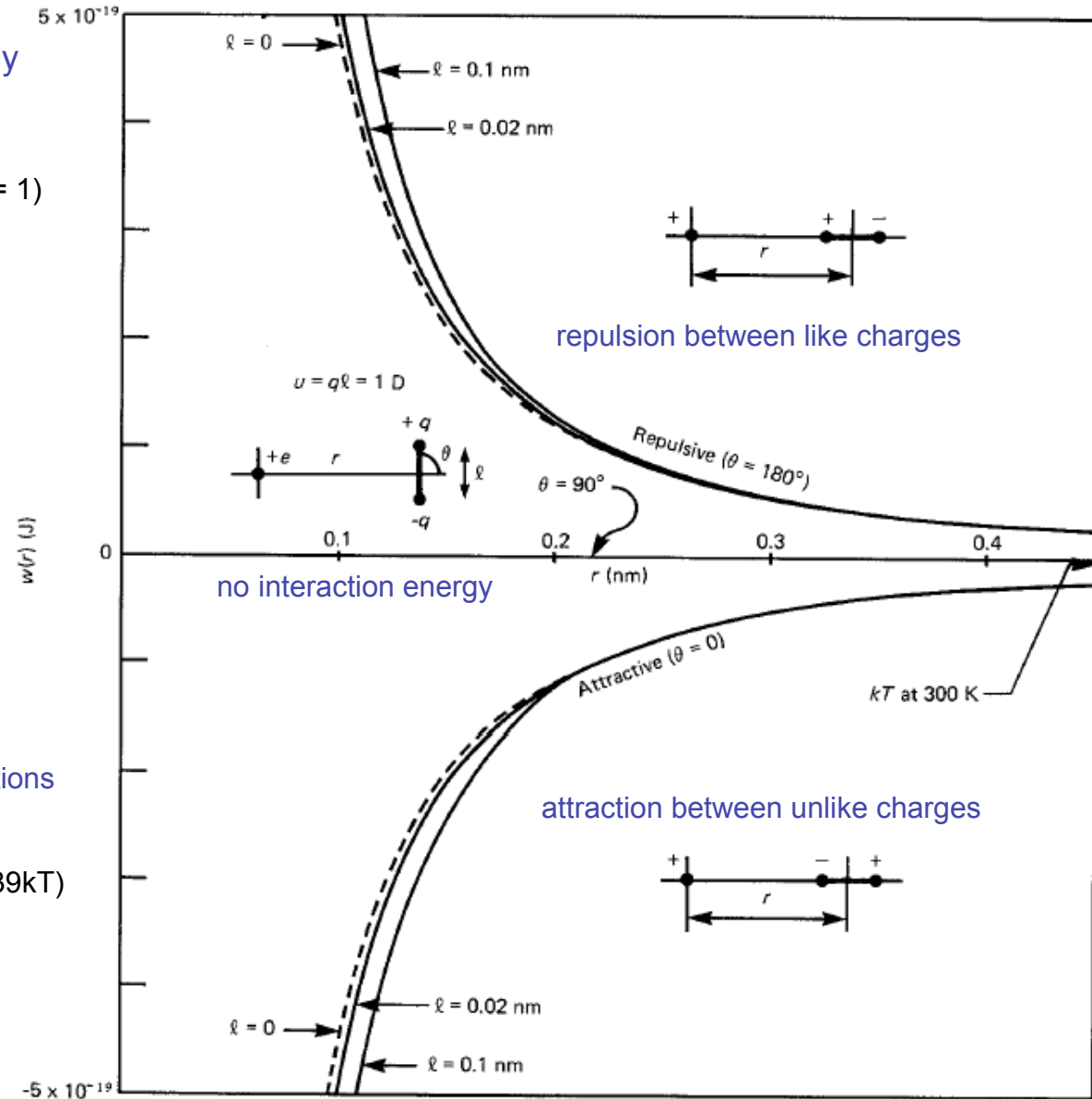
$$w(r, \theta) = -\frac{Qu \cos \theta}{4\pi\epsilon_0\epsilon r^2}$$

Charge-Dipole Interaction Energy

between a unit charge ($Q = e$) and a dipole ($u = ql = 1 \text{ D}$) in vacuum ($\epsilon = 1$)

Solid line: energy for $l = 0.1 \text{ nm}$ and $l = 0.2 \text{ nm}$

dashed line: energy for $l = 0$



Some Examples:

maximal Interaction Energy for cations with a H_2O molecule at 300 K

Na^+ : $w(r, \theta = 0^\circ) = 22.9 \text{ kcal/mol}$ ($39kT$)

Li^+ : 29.8 kcal/mol

Mg^{2+} : 59 kcal/mol

Bond Dissociation Energy (BDE)



Pauling Electronegativities

C	N	O	F
2.55	3.04	3.44	3.98
Si	P	S	Cl
1.90	2.19	2.58	3.16

BDE (kcal/mol)

$\text{H}_3\text{C}-\text{CH}_3$	89	$\text{H}_3\text{C}-\text{SiH}_3$	90	$^-\text{C}-\text{Si}^+$
$\text{H}_3\text{C}-\text{NH}_2$	86	$\text{H}_3\text{C}-\text{PH}_2$	70	
$\text{H}_3\text{C}-\text{OH}$	92	$\text{H}_3\text{C}-\text{SH}$	74	
$\text{H}_3\text{C}-\text{F}$	110	$^+\text{C}-\text{F}^-$		
		$\text{H}_3\text{C}-\text{Cl}$	83	$^+\text{C}-\text{Cl}^-$

Increasing
Electronegativity

π bond strength

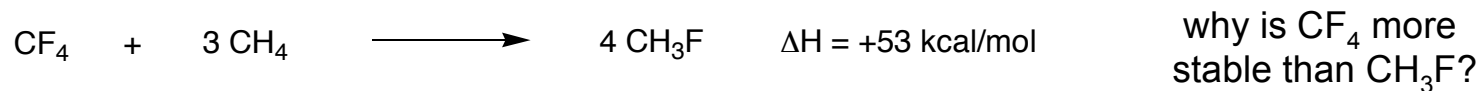
$\text{C}=\text{C}$	64 kcal/mol
$\text{C}=\text{O}$	84 kcal/mol

difference in electronegativity leads to bond polarisation
(charge separation)

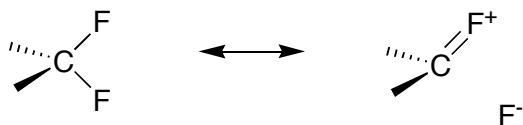
coulombic attraction increases bond strength

bond polarisation affects σ and π bonds

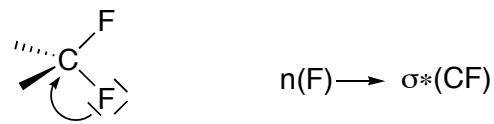
Stabilization in Polyfluorinated Compounds



Valence-Bond Theorie



MO Theorie



F is a poor lone pair donor

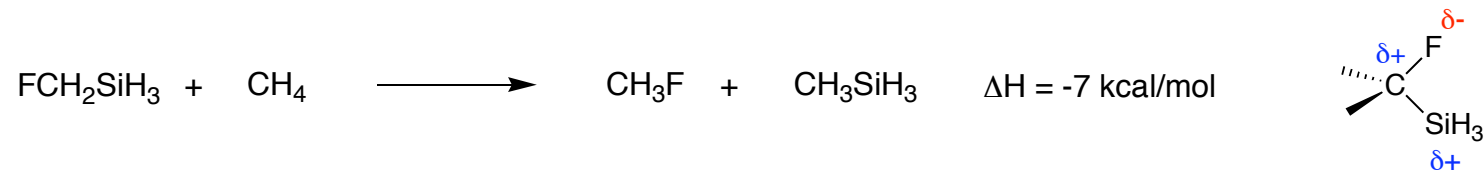
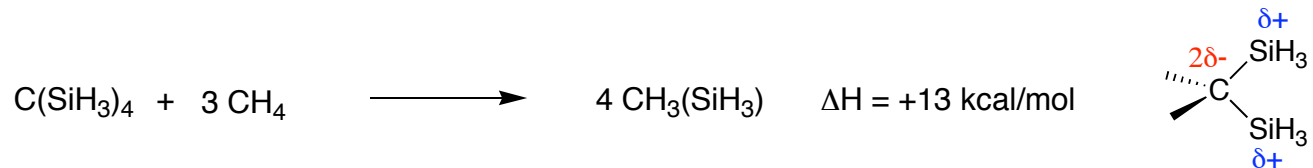
Electrostatic Effect



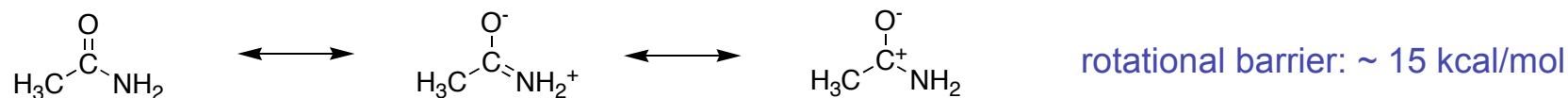
Increased positive charge at carbon leads to stronger electrostatic attraction

Atomic Charges at Fluorine

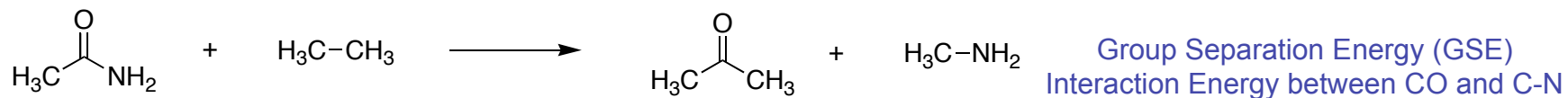
	AIM	NPA	GAPT
CH_3F	-0.743	-0.429	-0.550
CH_2F_2	-0.744	-0.429	-0.576
CHF_3	-0.744	-0.421	-0.576
CF_4	-0.737	-0.405	-0.551



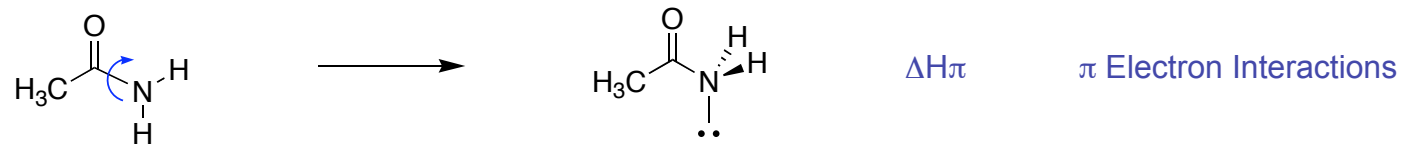
Amide Resonance and CO-X Interactions



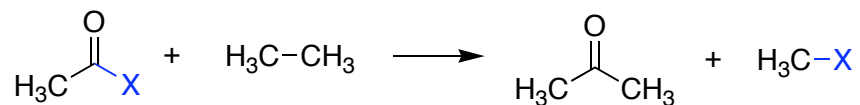
Group Transfer Reaction



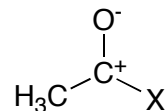
Rotation



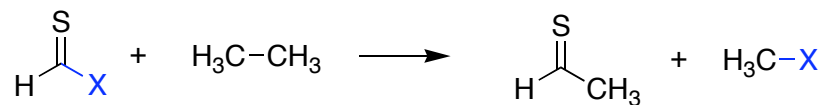
K. B. Wiberg et al. *Acc. Chem. Res.* **1999**, 32, 922.



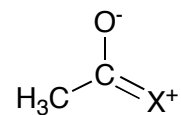
	GSE	ΔH_π	ΔH_σ
F	+16.7	0.0	+16.7
OH	+22.7	+11.5	+11.2
NH ₂	+19.3	+13.9	+5.4
Cl	+6.8	0.0	+6.8



Electrostatic Interactions more important for electronegativ X (F, OH)

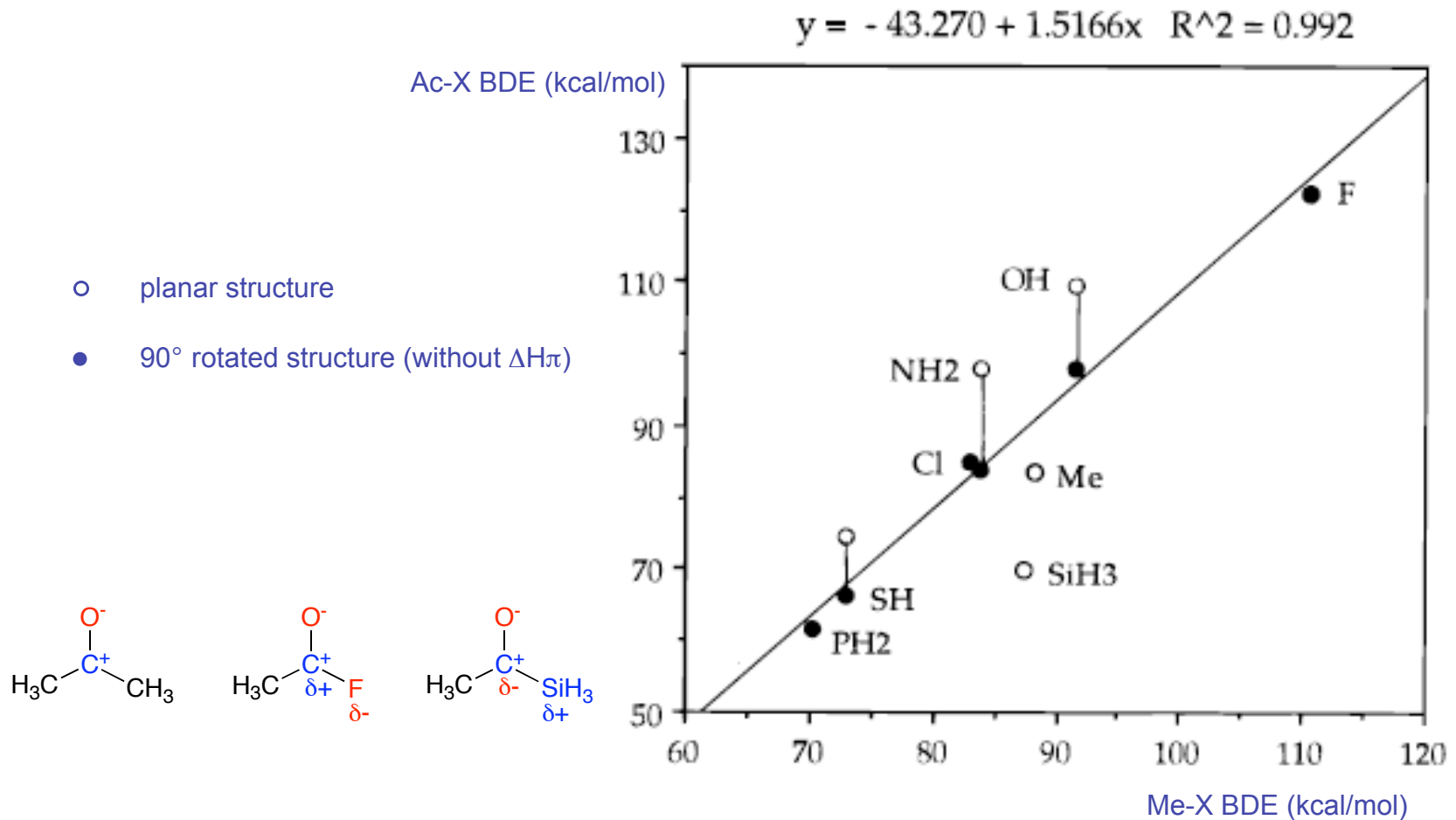


	GSE	ΔH_π	ΔH_σ
F	+4.7	0.0	+4.7
OH	+15.7	+12.3	+3.5
NH ₂	+18.4	+18.0	+0.5
Cl	+0.1	0.0	+0.1



C=S bond less polarized
 π bond contributions more important

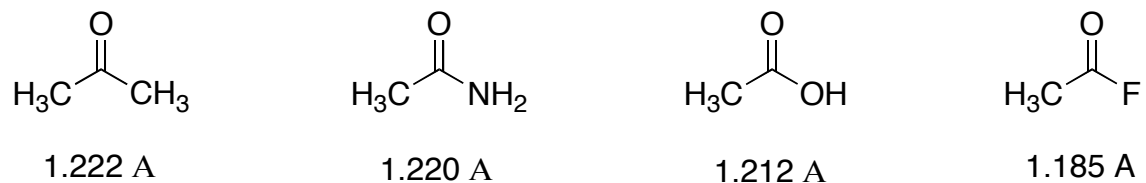
Comparison Ac-X and Me-X Bond Disoziation Energy



Slope of ~1.5: increased positive charge at carbon leads to stronger CO-bond

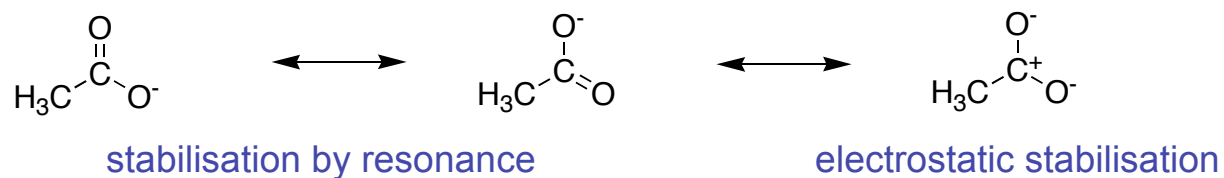
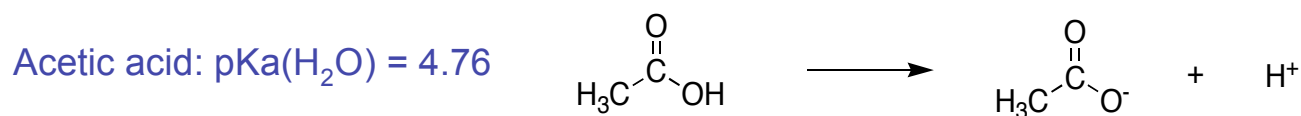
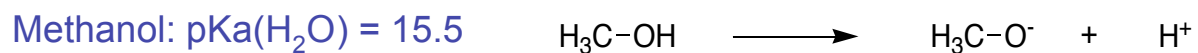
negative charge at carbon destabilizes the compound e.g. CO-Si, CO-CF₃,...

CO-bond length

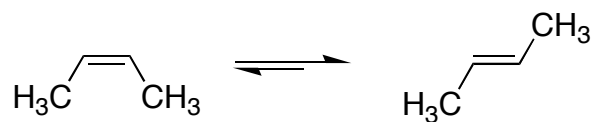


—————→
Increasing Polarisation of Ac-X

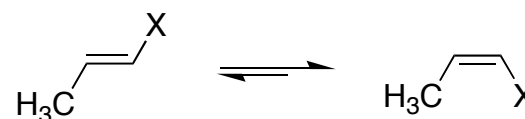
Acidity of Carboxylic Acids



Nonbonded Interactions in 1-substituted Propenes



E favored by 1.1 kcal/mol



Z favored

X = OMe	0.53 kcal/mol
X = Cl	0.68 kcal/mol
X = Br	0.45 kcal/mol

Relative Energies (*E*→*Z*) in kcal/mol

X	HF	B3LYP	MP2	CCSD ^b	CCSD(T) ^b
F	-0.53	-0.56	-0.70	-0.63	-0.65
OMe	-0.56	-0.63	-0.95	-0.76	-0.80
CN	0.09	-0.11	-0.72	-0.37	-0.50
CH ₃	1.56	1.25	1.04	1.13	1.06
Cl	0.01	-0.33	-0.77	-0.49	-0.60
Br	0.18	-0.27	-0.99	-0.63	-0.79
SMe	0.65	-0.26	-0.57	-0.14	-0.35

HF calculations do not include electron correlations (no attractive van der Waals terms)

DFT allows some correction for electron correlation
CCSD(T) gives superior correction for this effect.

calculated Energies independent from used method for X = F, OMe

Energie difference in HF and MP2 calculations for X = Cl, Br, SMe: attractive van der Waals interaction?

calculated C=C-CH₃ angles

X	cis	trans
F	125.24	122.38
Cl	126.78	122.64
Br	127.00	122.63
CN	125.21	123.78
CH ₃	127.22	124.59
OMe	124.54	122.70
SMe	125.14	123.66

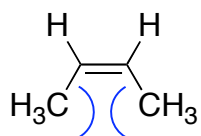
cis-bond angles larger than trans

difference in bond angles increases with size (F→Cl)

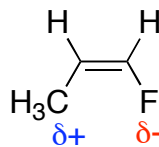
contributions to relative energies (kcal/mol)

X	qq/r	steric	Disp	total
F	-0.553	0.320	-0.221	-0.464
Cl	-0.261	0.391	-0.926	-0.796
Br	-0.036	0.513	-1.028	-0.731
CH ₃	0.003	1.501	-0.792	0.712

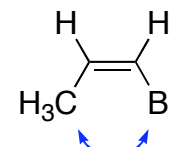
cis preference is combination of Coulombic attraction and dispersion interactions



Steric Repulsion



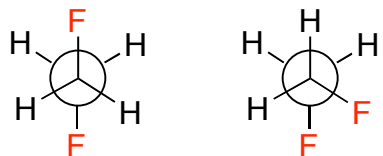
Electrostatic Attraction
(X = F, OMe)



Dispersion
(X = Cl, Br, OMe)

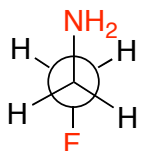
Electrostatic *Gauche* Effect

1,2-Difluoroethan:

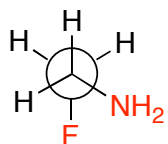


gauche favoured by 0.5-1.0 kcal/mol
 stereoelectronic effect: $\sigma(\text{CH}) \rightarrow \sigma^*(\text{CF})$

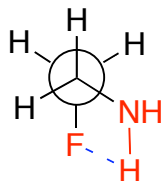
β -Fluoroethylamin



0.0 kcal/mol

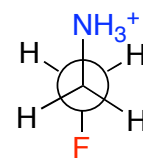


0.9 kcal/mol

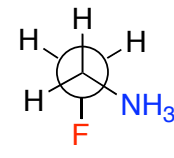


-1.0 kcal/mol

β -Fluoroethylammonium

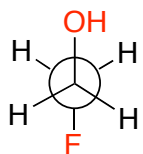


0.0 kcal/mol

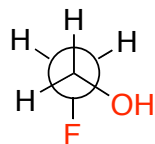


-5.8 kcal/mol

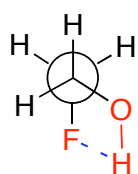
2-Fluoroethanol



0.0 kcal/mol

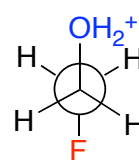


-0.3 kcal/mol

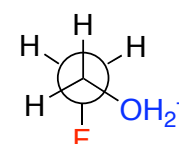


-2.0 kcal/mol

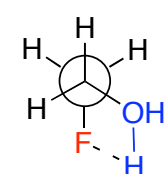
protonated 2-Fluoroethanol



0.0 kcal/mol



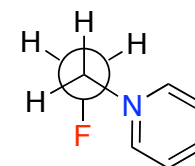
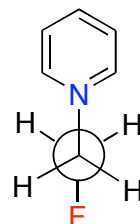
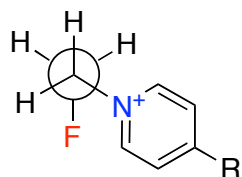
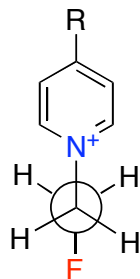
-4.4 kcal/mol



-7.2 kcal/mol

gauche preferred in charged system: electrostatic Attraction

N-(2-fluoroethyl)pyridinium cation



R = H: 0.0 kcal/mol

-3.7 kcal/mol

0.0 kcal/mol

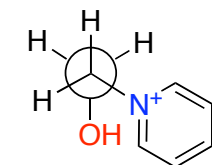
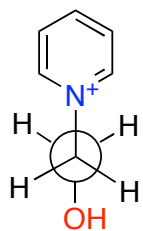
-0.05 kcal/mol

R = NMe₂: 0.0 kcal/mol

-3.1 kcal/mol

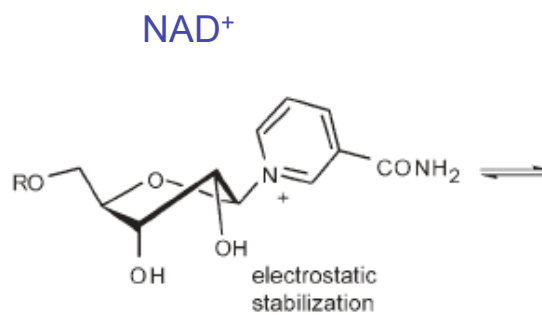
no preference in uncharged system

N-(2-hydroxyethyl)pyridinium cation

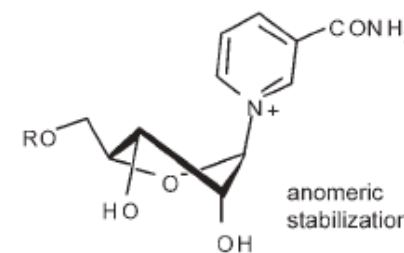


0.0 kcal/mol

-3.7 kcal/mol



C2' endo



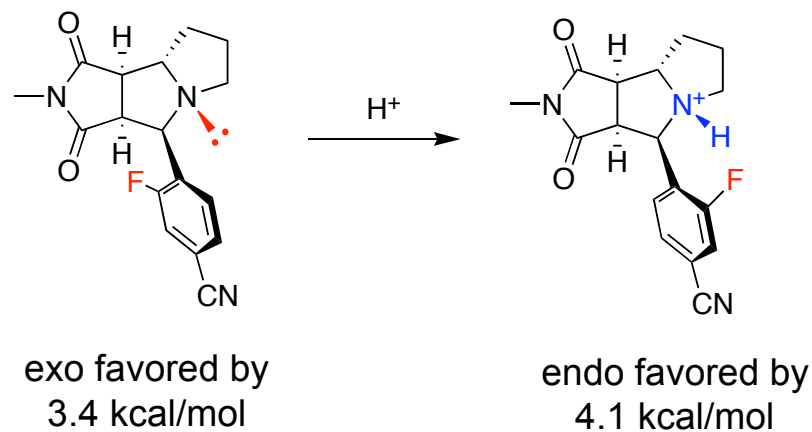
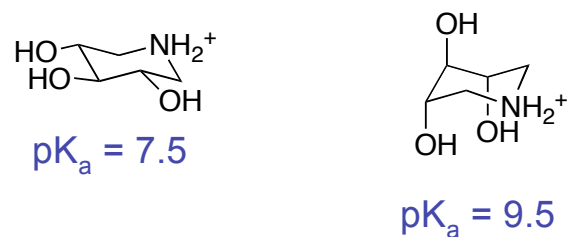
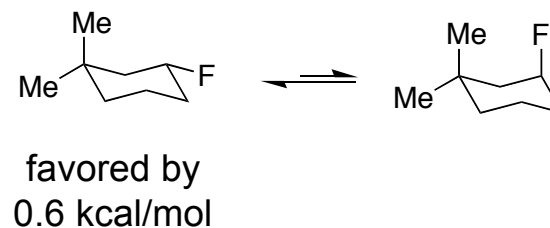
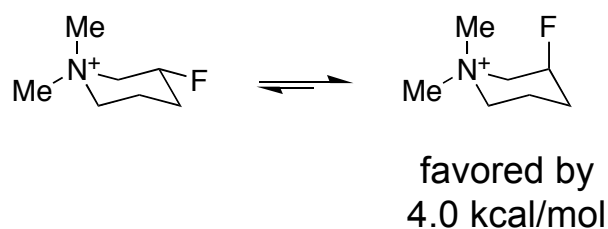
C3' endo

Electrostatic Effects and Conformational Analysis

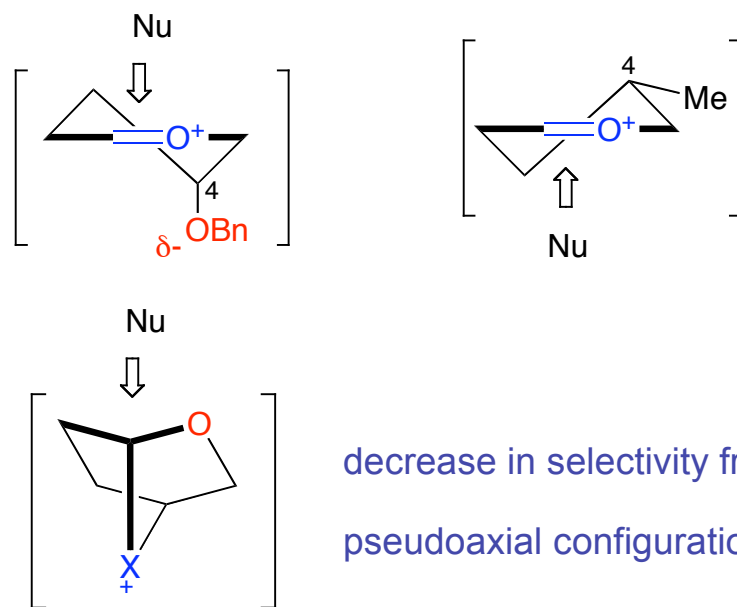
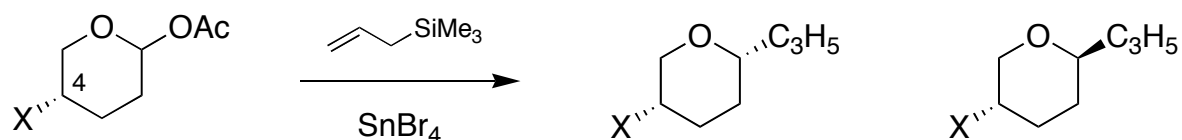


electrostatic stabilization through space

shorter distance between axial-OMe and carbonyl carbon



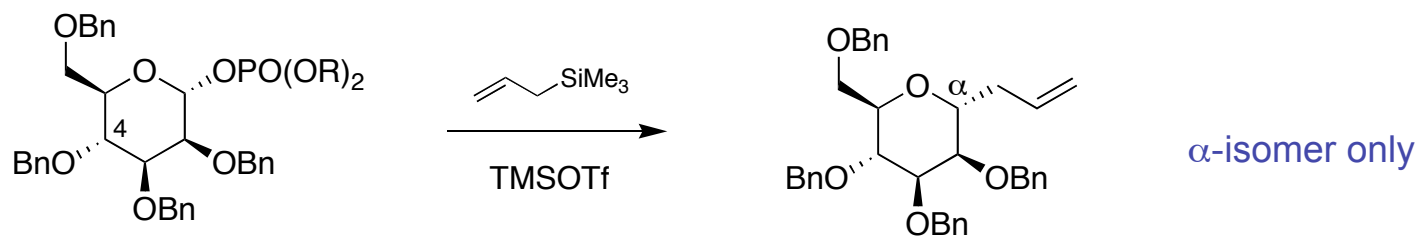
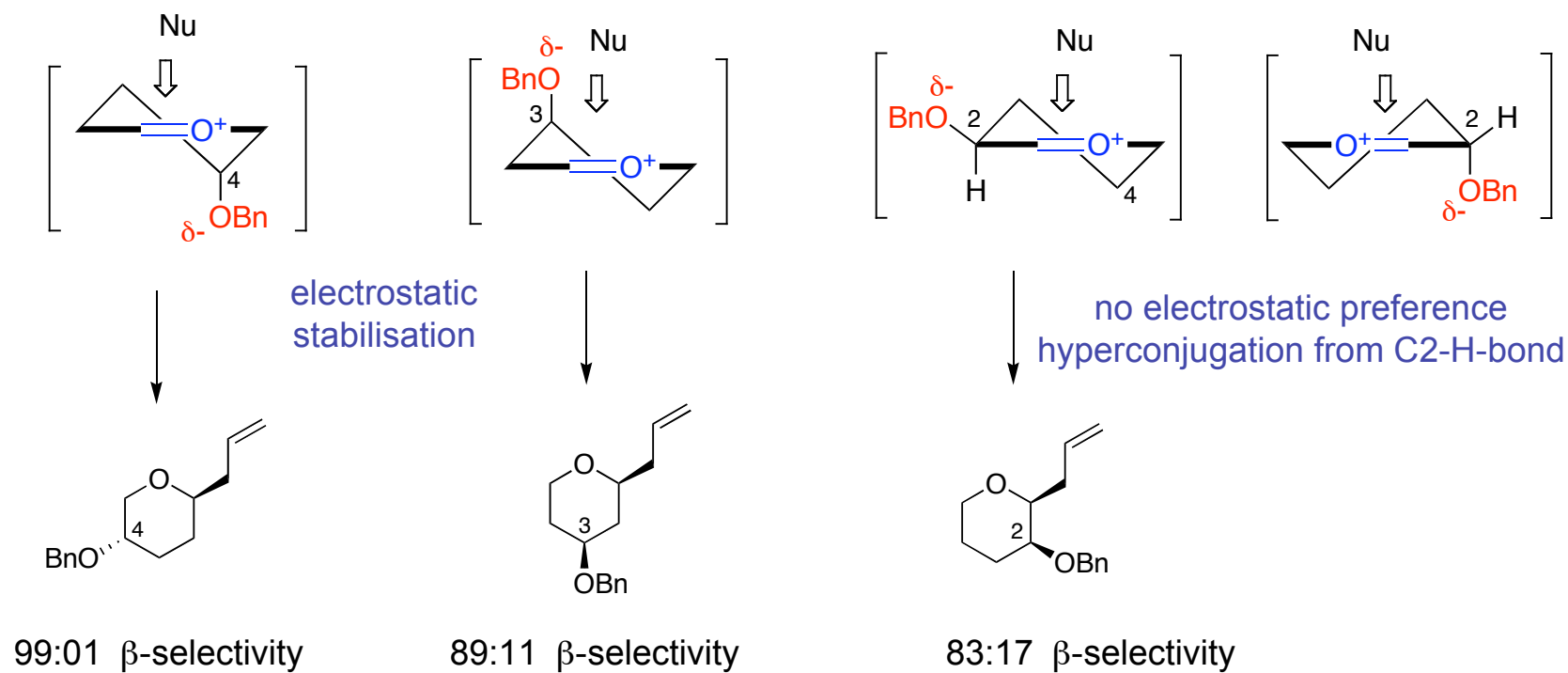
Electrostatic Effects in Oxocarbenium Chemistry



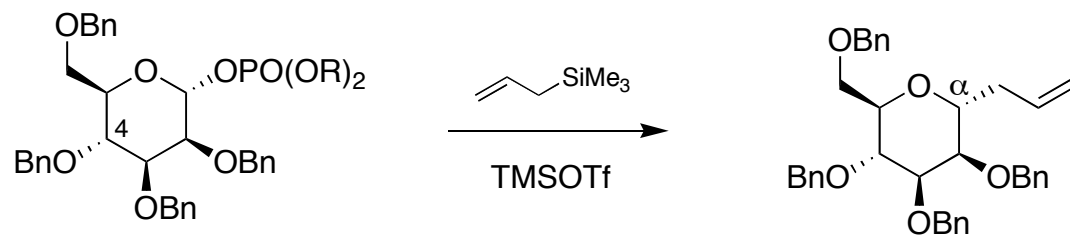
	cis/trans
OBn	01:99
Me	94:06
F	05:95
Cl	14:86
Br	31:69
I	28:72

decrease in selectivity from F to I: no anchimeric assistance
 pseudoaxial configuration favoured by electrostatic interactions

Oxocarbenium Chemistry

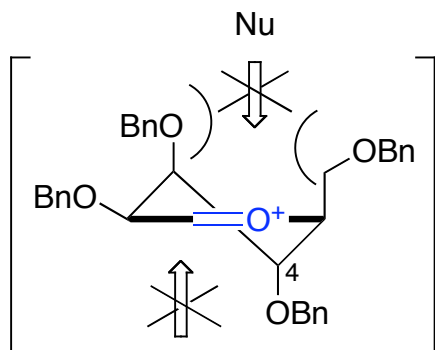


D-Mannosyl Cation



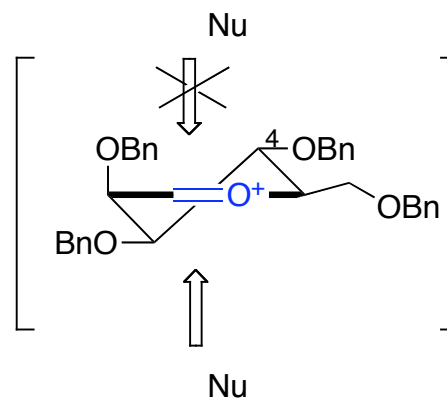
α -isomer only

disfavored because of
syn-pentan interaction



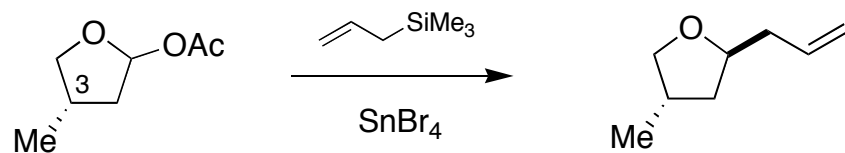
stereoelectronically
disfavored

stereoelectronically
disfavored

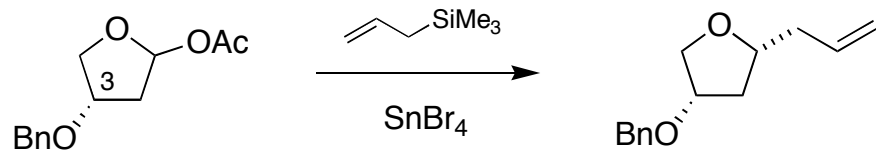


Curtin Hammett scenario possible

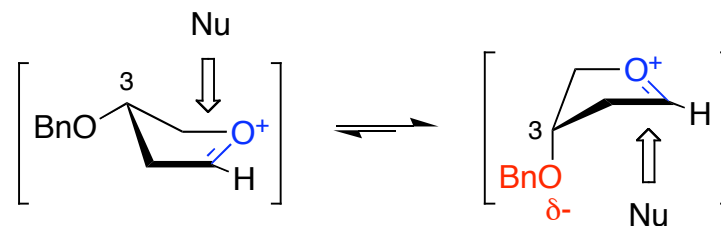
Electrostatic stabilisation of oxocarbenium ions



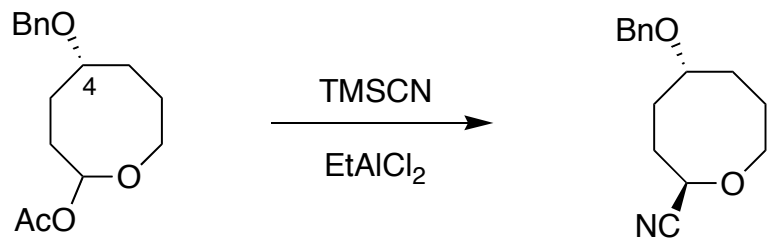
dr = 99:01



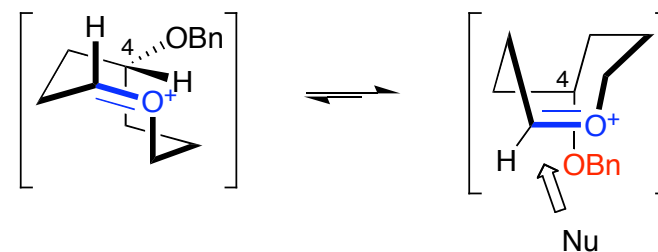
dr = 94:06



inside attack provides staggered product

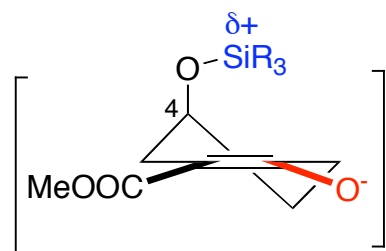
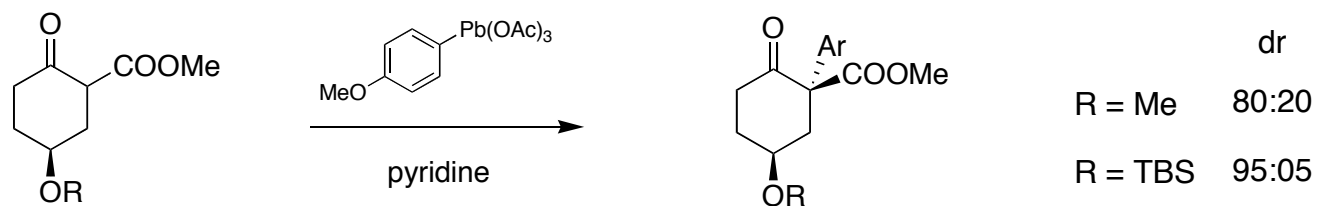


dr = 96:04

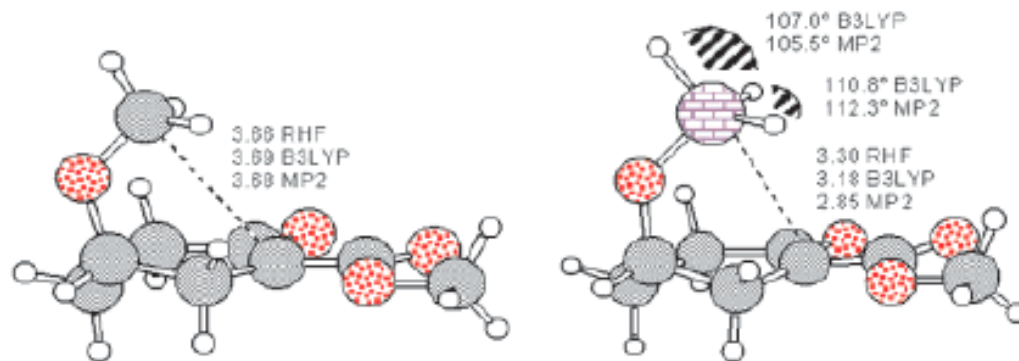


favored by 2.5 kcal/mol

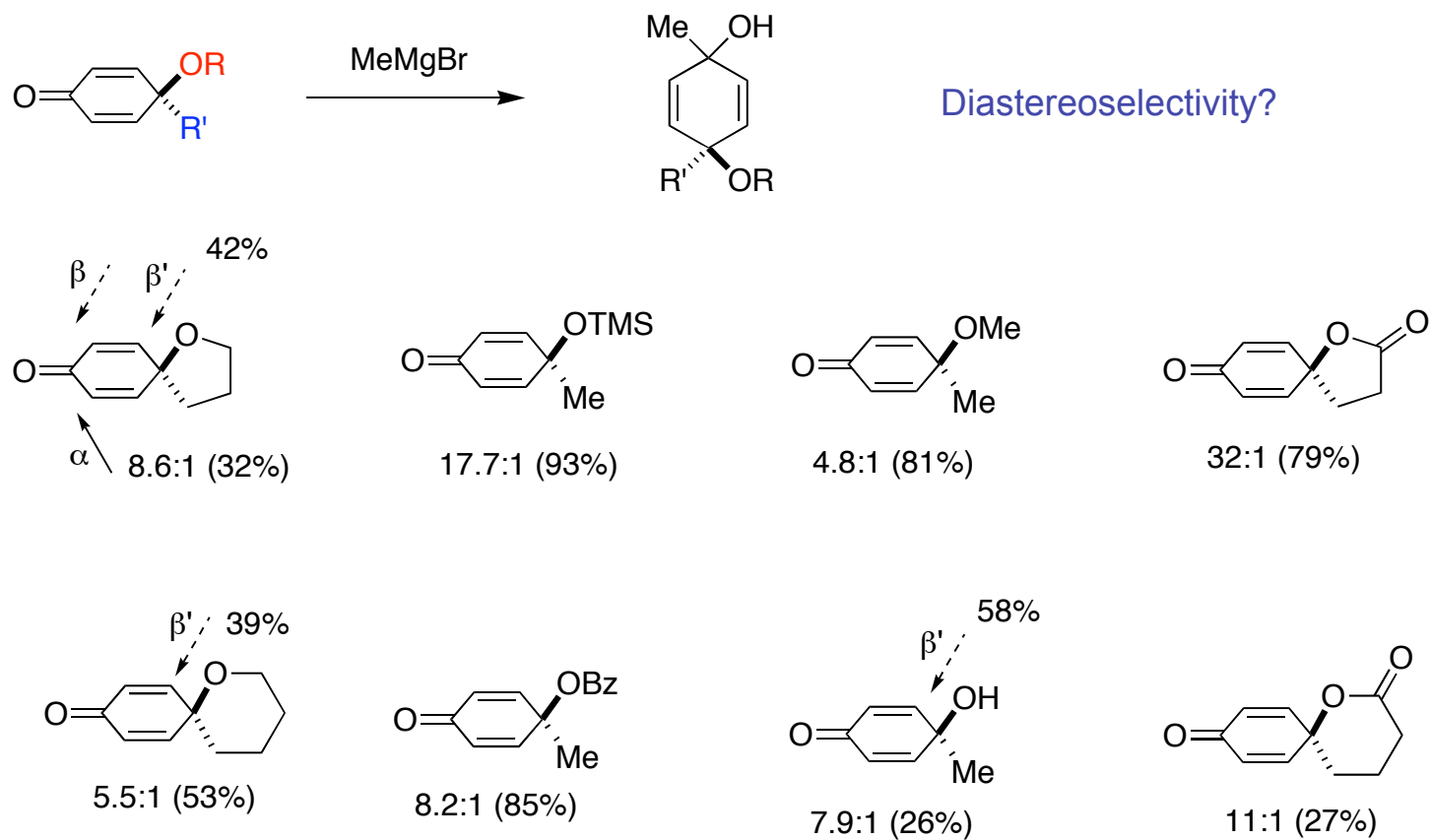
Electrostatic stabilisation of an anionic intermediate

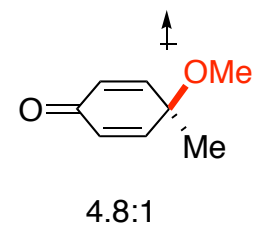
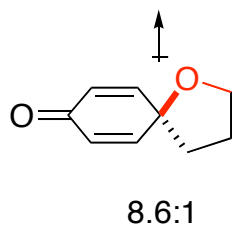
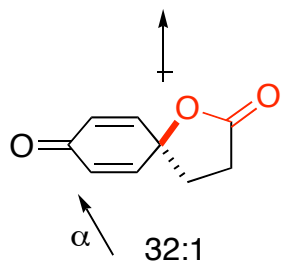


electrostatic interaction between enolate and electropositive silicon stabilizes transition state

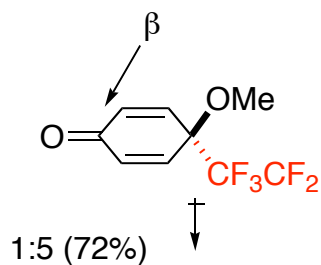


Nucleophilic Additions to 4,4-disubstituted 2,5-Cyclohexadienones





diastereoselectivity correlates with dipole moment



β -selectivity by inverted dipol

dipol-controlled nucleophilic addition

entry	nucleophile	yield (%)	α/β selectivity	solvent
1	MeMgBr	86	4.8:1	THF
2	NaBH ₄ or LiAlH ₄	100	1:1	MeOH or THF
3	HC≡CMgBr	70	1:1	THF
4	H ₉ C ₄ C=CLi	26	1.1:1	THF
5	PhMgBr	83	3.6:1	THF
6	MeLi	87	2.1:1	THF
7	MeLi	77	3.3:1	Et ₂ O
8	BnOCH ₂ Li	84	3:1	THF