Stereoelectronic effects on stability and reactivity of organic molecules: from control of molecular conformations to faster cycloadditions and cyclizations

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Зимняя конференция молодых ученых по органической химии,
January 20, 2015, Krasnovidovo

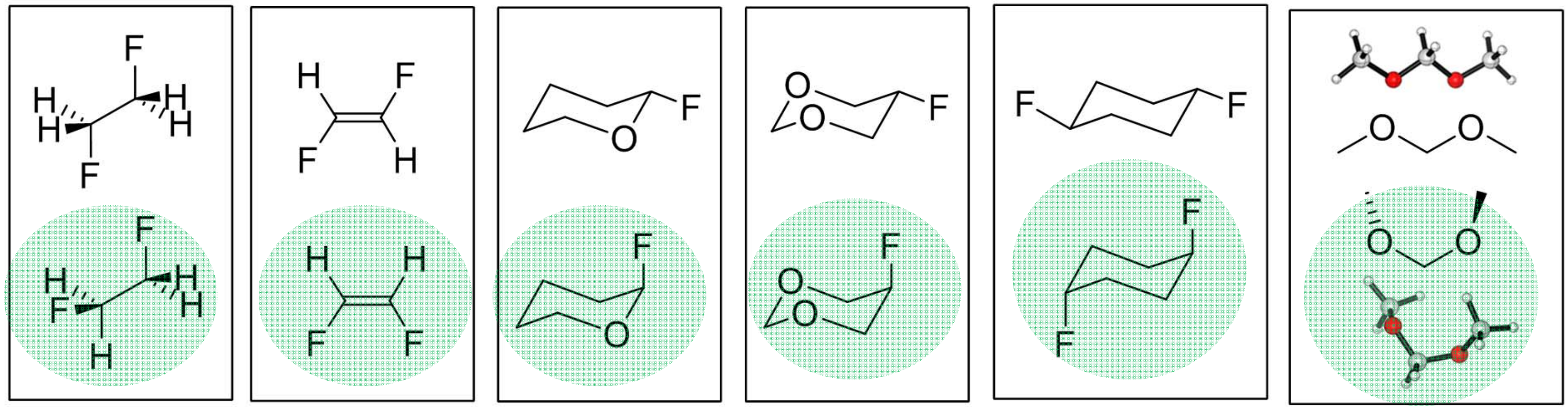
WSOC2015

Importance of delocalization

Introduction

What is the most stable structure/geometry in the following pairs?

Take a second and make your guess:



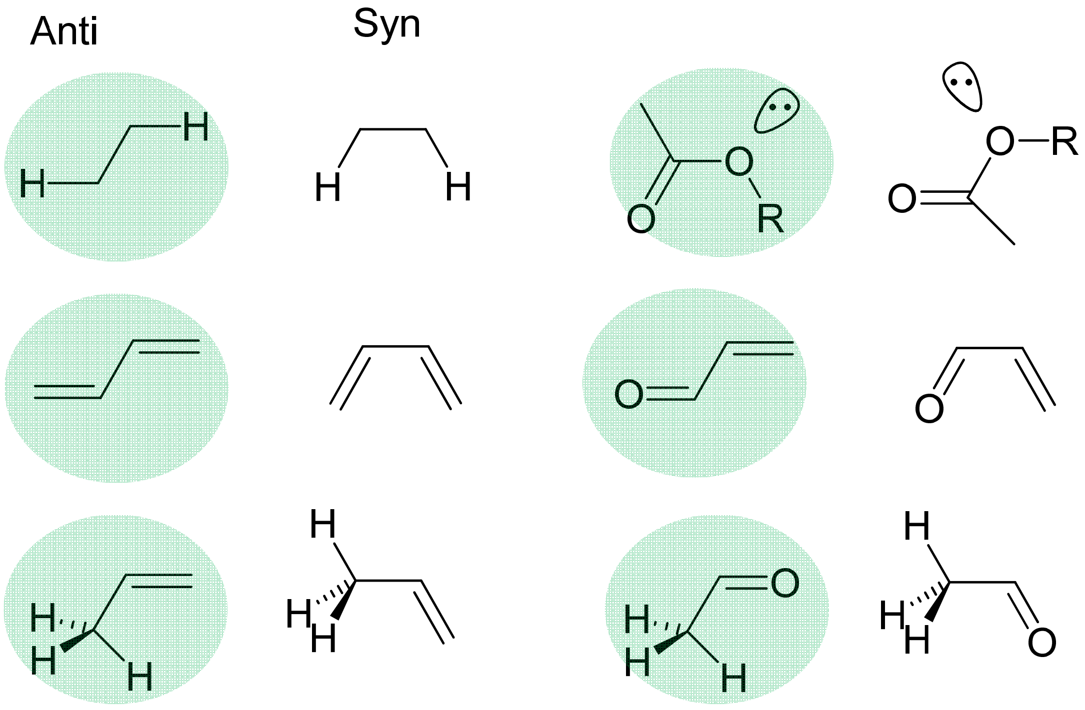
Is there a common theme?

Am I going mad?

From Alabugin, “Stereoelectronic effects”

There is a common underlying effect

It can be expanded to many common functional groups. See if you can spot it



Good News: There are preferred geometries for interactions between molecules, or between parts of a molecule.

These “rules of engagement” are called *stereoelectronic effects*.

From Alabugin, “Stereoelectronic effects”

Stereoelectronic effects

Definition: *Stereoelectronic effects – interactions of electronic orbitals in three dimensions.*

The typical stereoelectronic effect involves an electronic interaction which stabilizes a particular conformation or transition state and is fully expressed only when the correct geometry is achieved.

Caveat:

“stereoelectronic” is not the same as “steric + electronic”!

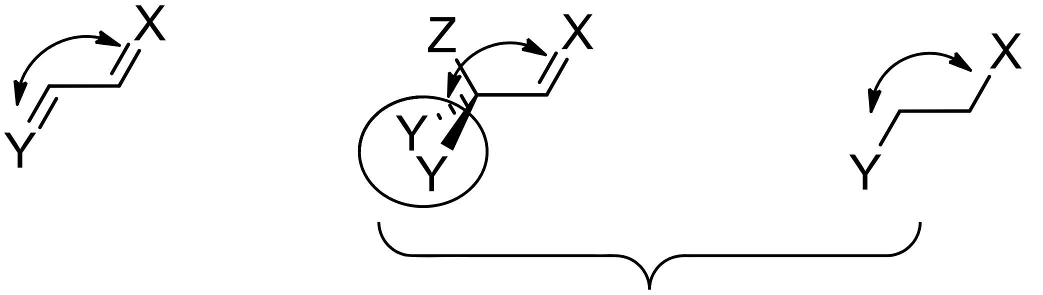
Stereoelectronic effects are **always** stabilizing and reflect increased delocalization at favorable conformations.

From Alabugin, “Stereoelectronic effects”

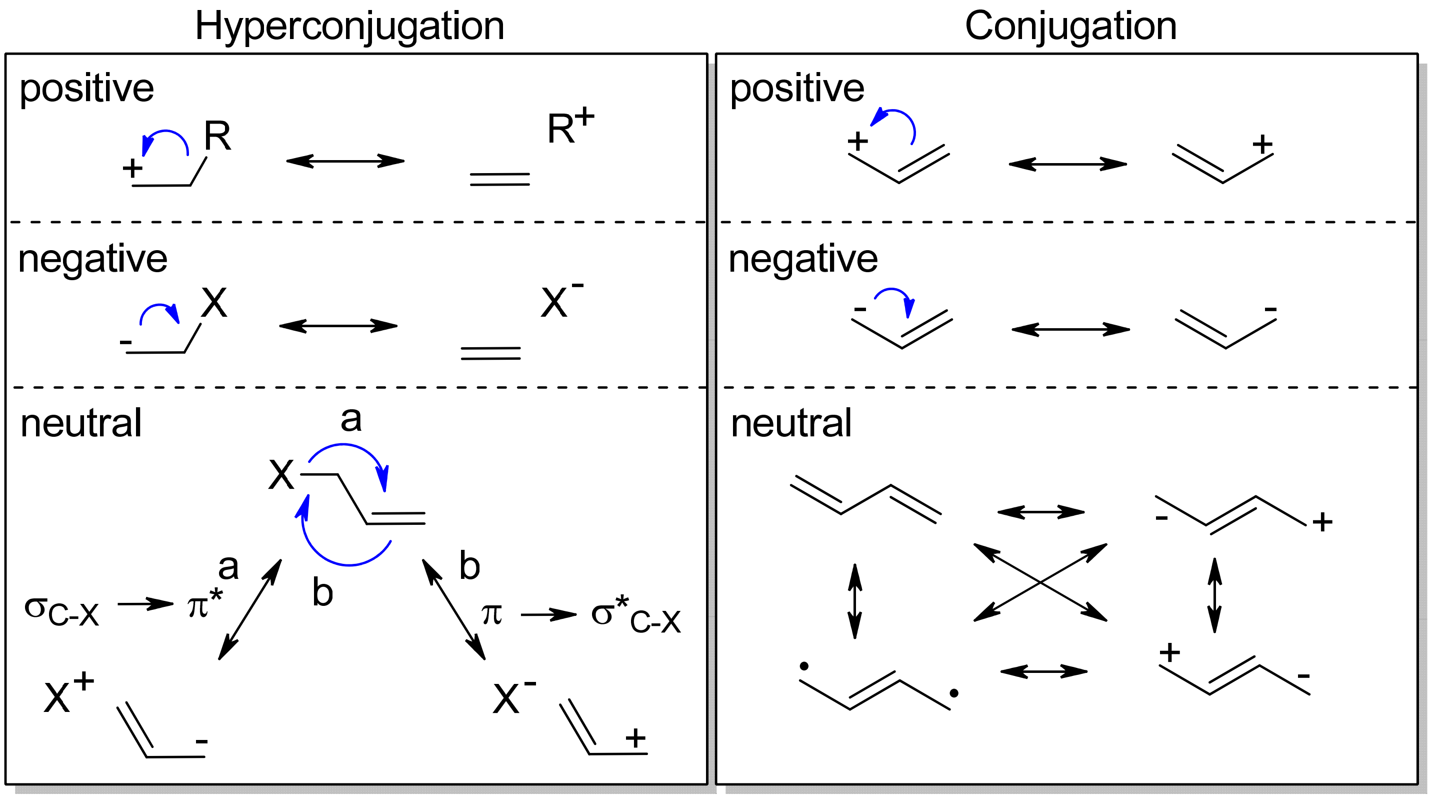
Types of interactions

Types of orbitals

Conjugation **Hyperconjugation** **σ-Conjugation**



Directionality of electron transfer

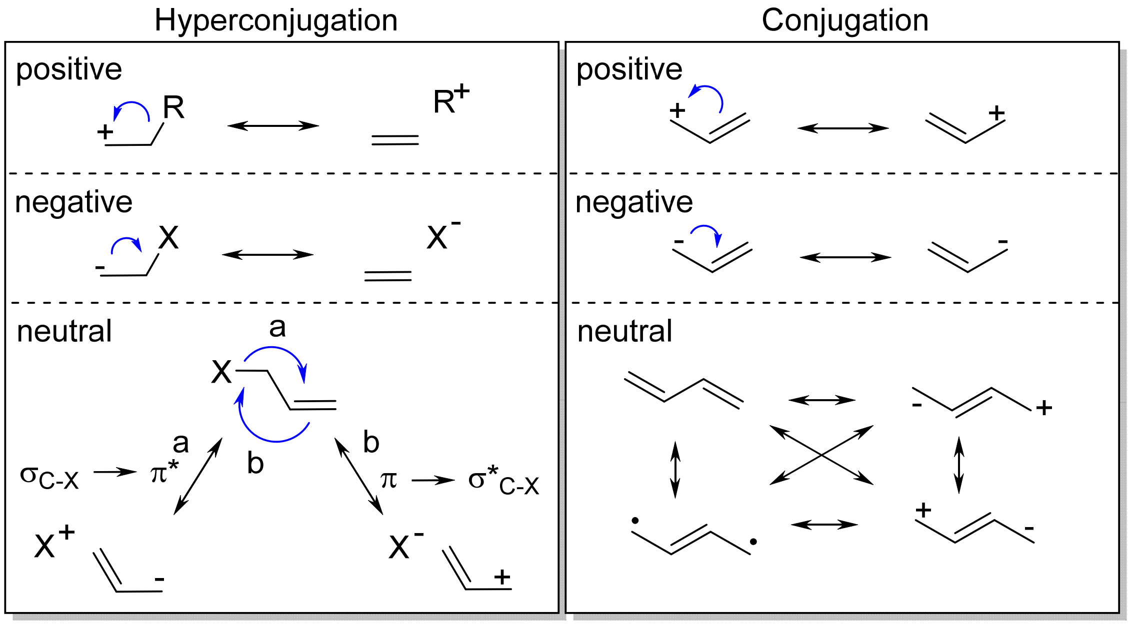


Types of resonance: negative, positive and neutral conjugation and hyperconjugation

Donation of electron density from filled σ-orbitals into π*-orbitals or p-type cationic centers is referred to as positive hyperconjugation.

The interactions between filled π or p-orbitals and adjacent antibonding σ*-orbitals are called negative hyperconjugation.

Both negative and positive hyperconjugation are two-electron stabilizing interactions which build π-bonding between the nominally singly-bonded atoms.



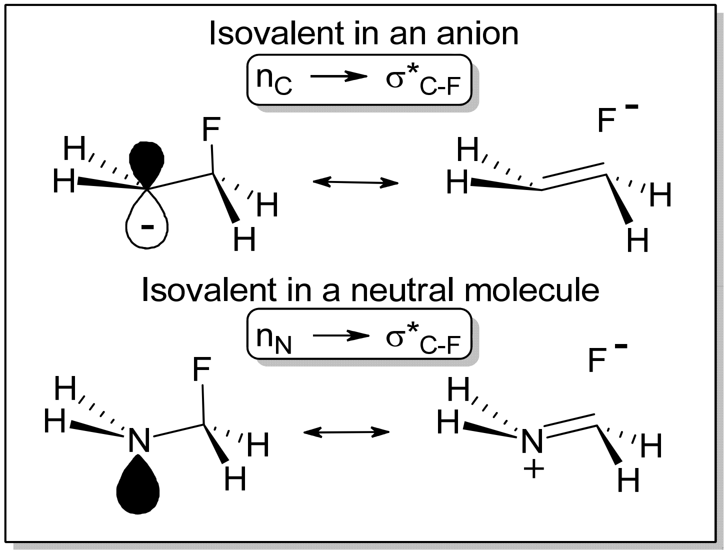
In the absence of dominating unidirectional interactions, hyperconjugation is classified as neutral hyperconjugation. This is the most common conjugative pattern. It blends together the negative and positive hyperconjugation

Analogous classification can be used for conjugative interactions between π-bonds and p-orbitals

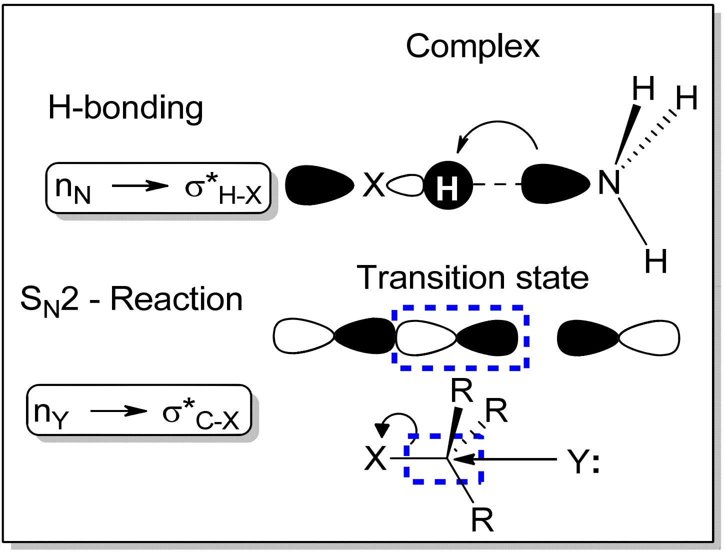
From Alabugin, *Stereoelectronic effects*

Hyperconjugation can be Intra- and Intermolecular

Intramolecular

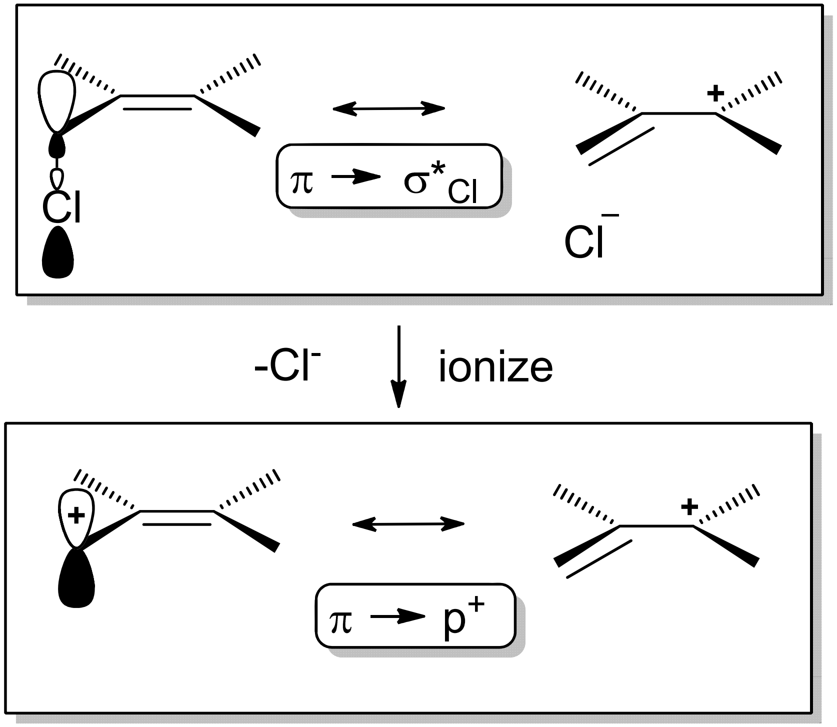


Intermolecular



Intra- and intermolecular negative (hyper)conjugation

Where do we draw the line between these effects?



Hyperconjugation

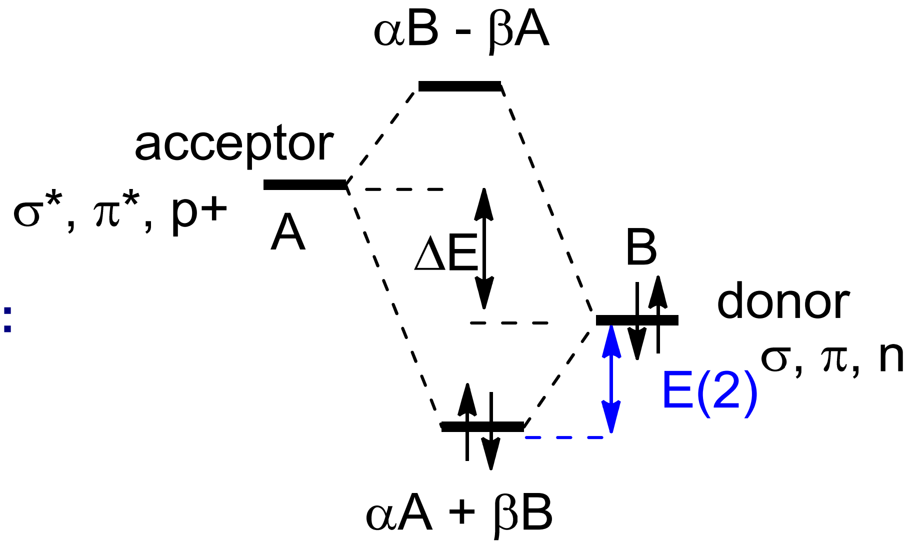
Conjugation

The separation between conjugation and hyperconjugation is based on an arbitrary treatment of σ- and π-orbitals on a different basis. Because the separation is artificial, the lines between effects are often blurred. The separation is especially tricky in the transition states.

Why interactions are stabilizing?

Mixing of empty

and filled orbitals:



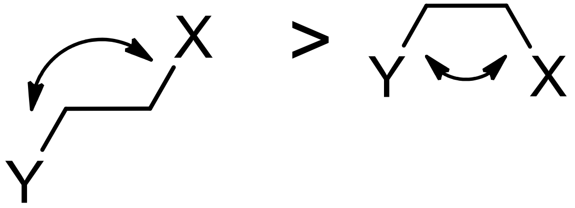
$$E(2) = -n_{\sigma}\frac{\langle \sigma/F/\sigma^{*}\rangle^{2}}{\varepsilon_{\sigma^{*}}-\varepsilon_{\sigma}} = -n_{\sigma}\frac{F_{i,j}^{\;2}}{\Delta E}$$

F_{ij} is the resonance integral for orbitals i and j, ε_{σ} and $\varepsilon_{\sigma*}$ are the energies of the σ and σ* orbitals, and n_{σ} is the population of the donor

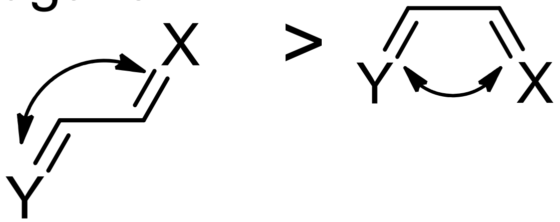
Orbital interaction energies can be calculated using Natural Bond Orbital (NBO) analysis (F. Weinhold and coworkers): http://nbo6.chem.wisc.edu/

How to increase stabilization?
Orbital Overlap and Antiperiplanarity

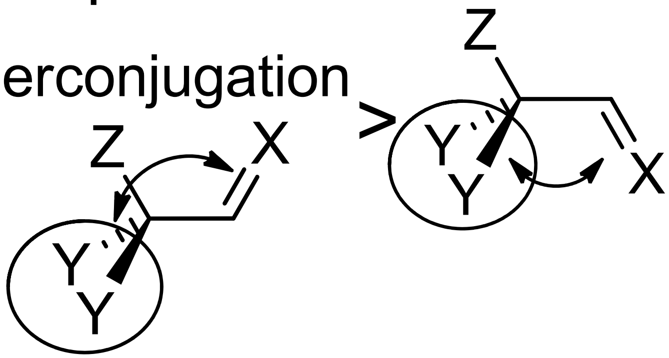
σ-Conjugation



Conjugation



Hyperconjugation

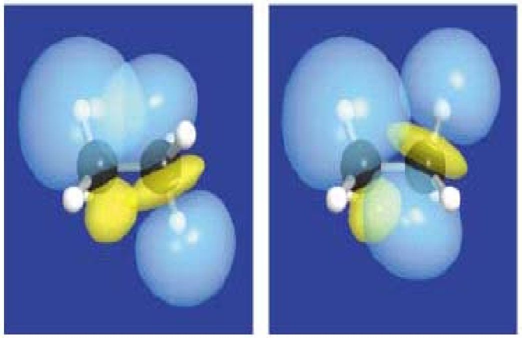


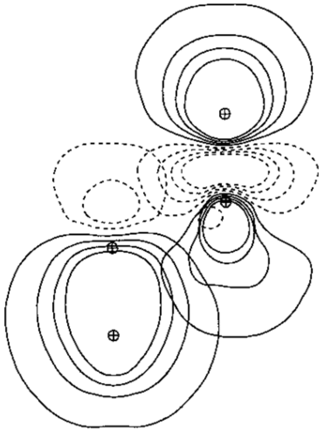
anti syn

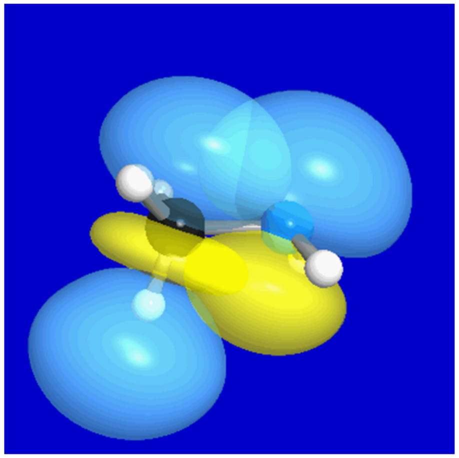
Favorable symmetry for anti-periplanar interactions increases stabilizing orbital overlap:

$$E(2) = -n_\sigma \frac{\langle \sigma/F/\sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{i,j}^{\;2}}{\Delta E}$$

F_{ij} (the resonance integral for orbitals i and j), is proportional to the orbital overlap



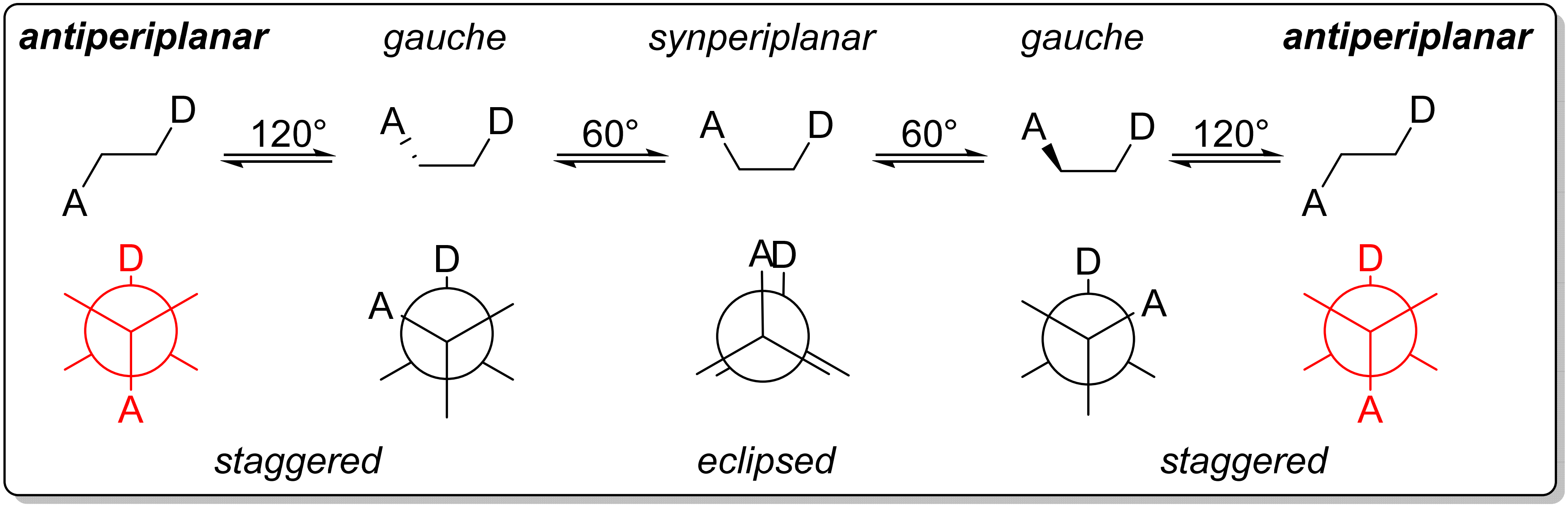




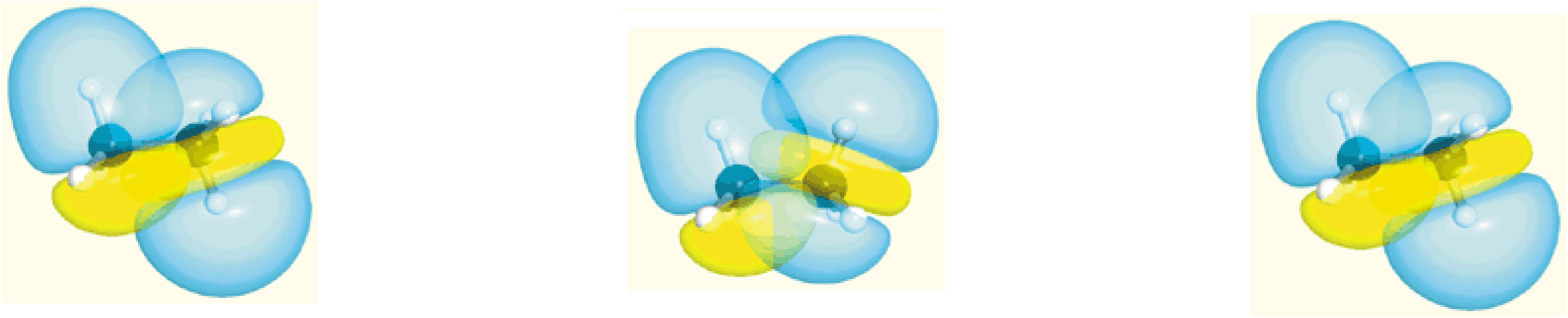
http://nbo6.chem.wisc.edu/

“The main stereoelectronic rule”

"There is a stereoelectronic preference for conformations in which the best donor lone pair or bond is ***antiperiplanar*** *to the best acceptor bond"*



*H's not shown



From Alabugin, “Stereoelectronic effects”

How to increase stabilization?

Additional factors controlling overlap

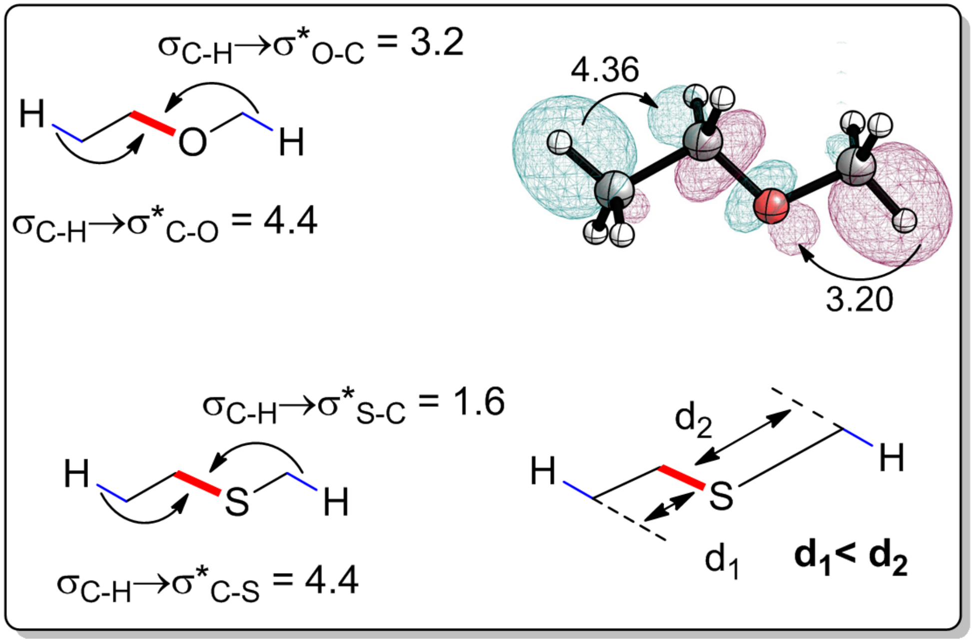
Directionality of interactions:

a) Effect of bond polarization

$$E(2) = -n_{\sigma} \frac{\langle \sigma / F / \sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_{\sigma}} = -n_{\sigma} \frac{\boxed{F_{i,j}^{\ 2}}}{\Delta E}$$

b) Effect of longer or shorter bonds

F_{ij} is the resonance integral for orbitals i and j, <u>is proportional to the orbital overlap</u>



Energies are in kcal/mol

$\sigma^*_{O\text{-}C}$ is a much weaker acceptor than $\sigma^*_{C\text{-}O}$

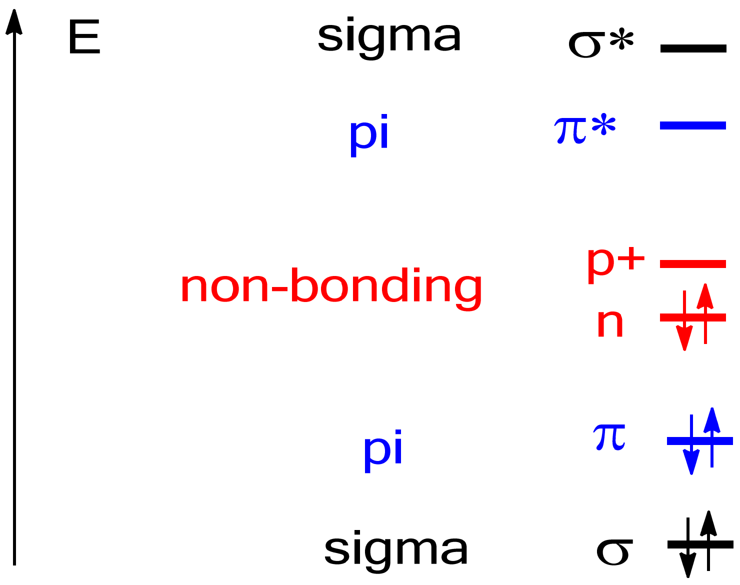
$\sigma^*_{S\text{-}C}$ is a MUCH weaker acceptor than $\sigma^*_{C\text{-}S}$

Alabugin, *J. Org. Chem*. **2000**, 3910

How to increase stabilization?

Decrease energy gap

$$E(2) = -n_\sigma \frac{\langle \sigma/F/\sigma^* \rangle^2}{\varepsilon_{\sigma^*} - \varepsilon_\sigma} = -n_\sigma \frac{F_{i,j}{}^2}{\boxed{\Delta E}}$$



Basis for the HOMO-LUMO approximation in FMO theory (what would happen, by the way, if ΔE is 0?)

Lone pairs are best donors, empty p-orbitals are best acceptors

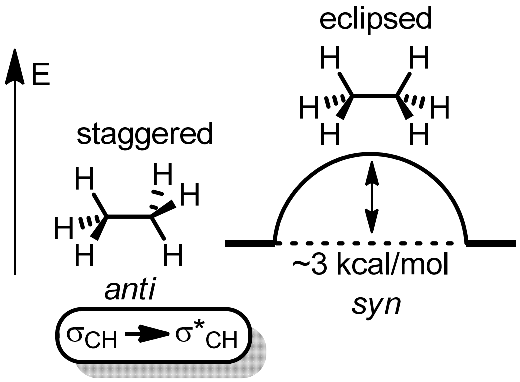
Explains unexpected trend in acceptor ability of C-Hal bonds: σ*C-F < C-Br < C<I

Donor ability: carbanion >> $n_N > n_O > \sigma_{C\text{-}C}, \ \sigma_{C\text{-}H} > \sigma_{C\text{-}X}$

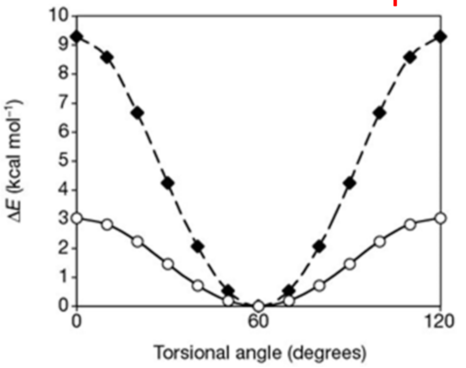
Acceptor ability: carbocation >> $\pi^*_{C=O} > \sigma^*_{C\text{-}Hal} > \sigma^*_{C\text{-}O} > \sigma^*_{C\text{-}N} > \sigma_{C\text{-}C}, \ \sigma_{C\text{-}H}$

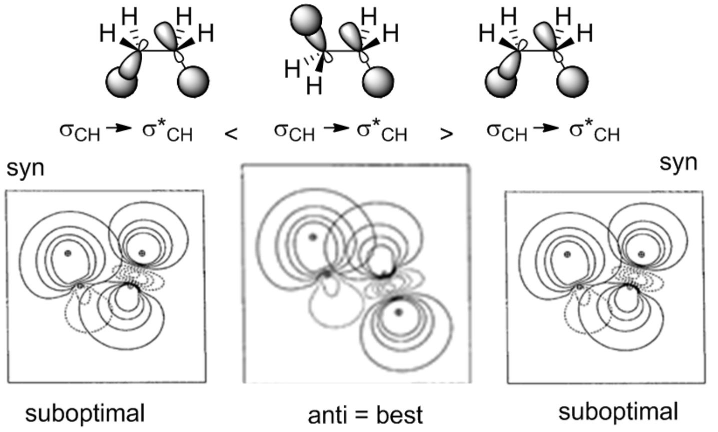
See : Alabugin, Zeidan, JACS, 2002 and Alabugin, Manoharan, JOC, 2004 for more details

Examples of neutral hyperconjugation:
1. Ethane



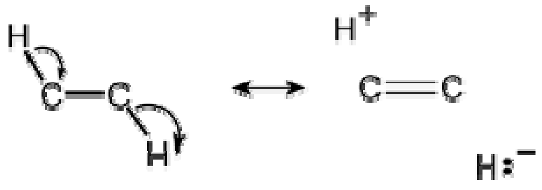
Torsional angle dependencies of energy of real ethane (solid line) and a hypothetical ethane with steric repulsion absent (dashed line):

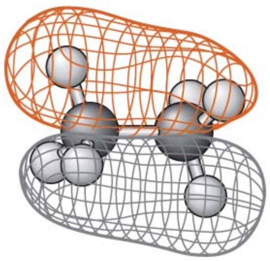


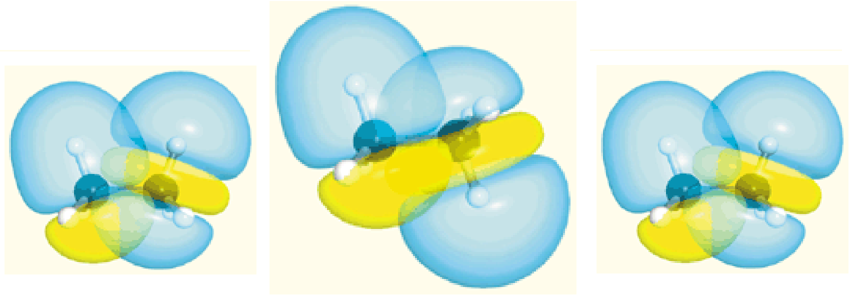


‘Removal of vicinal hyperconjugation interactions yields the eclipsed structure as the preferred conformation, whereas Pauli exchange (steric) and electrostatic (Coulombic) repulsions, have no influence on the preference for a staggered conformation.’

Pophristic, V.; Goodman, L. (2001) Hyperconjugation not steric repulsion leads to the staggered structure of ethane. *Nature, 411*, 565

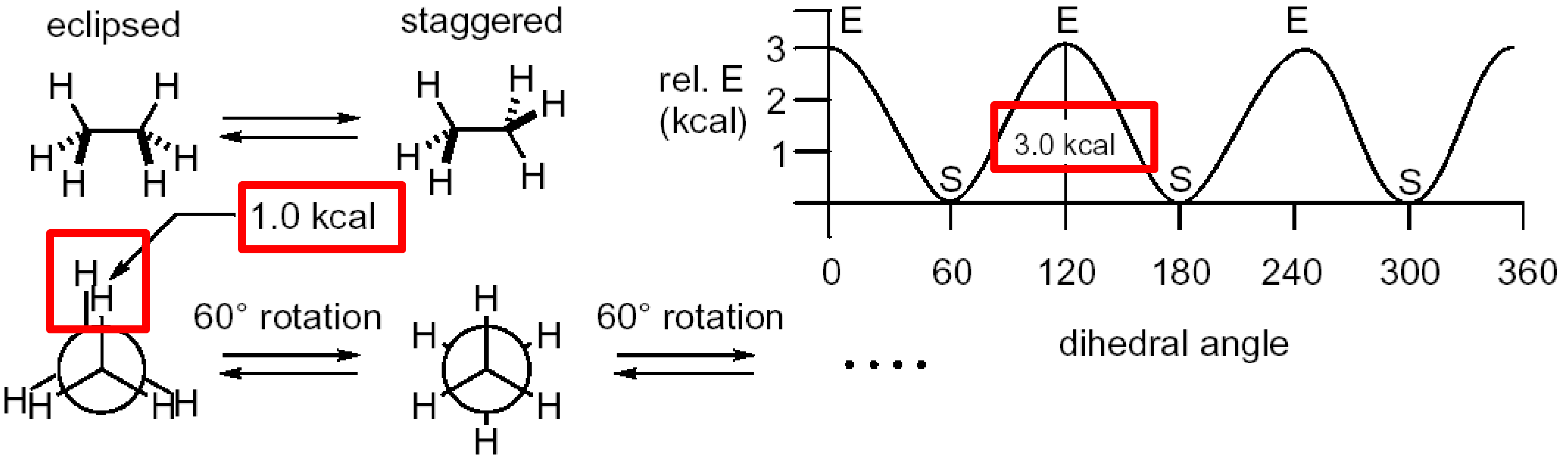




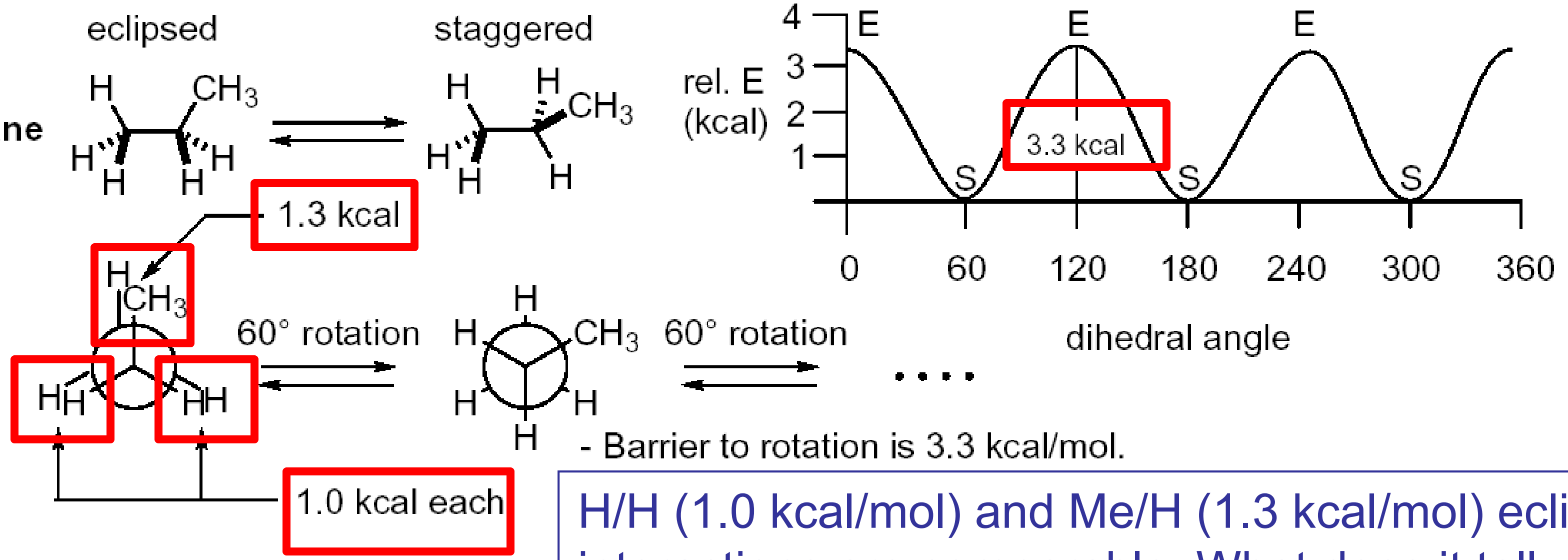


From ethane to propane:
how much steric repulsion do we introduce?

1. Ethane



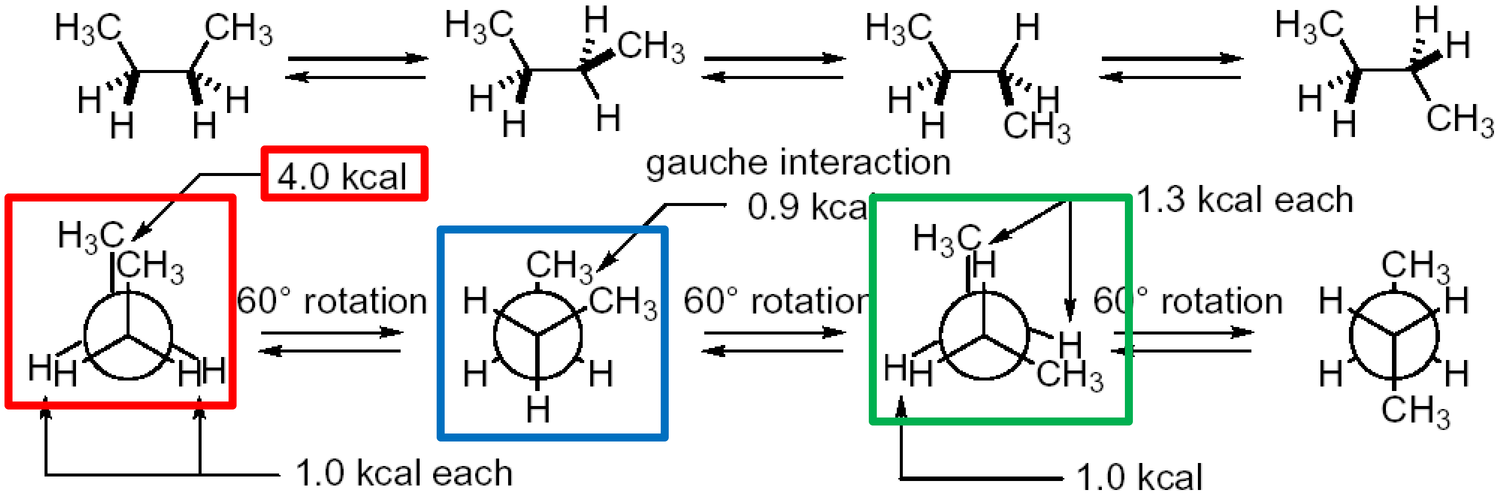
2. Propane

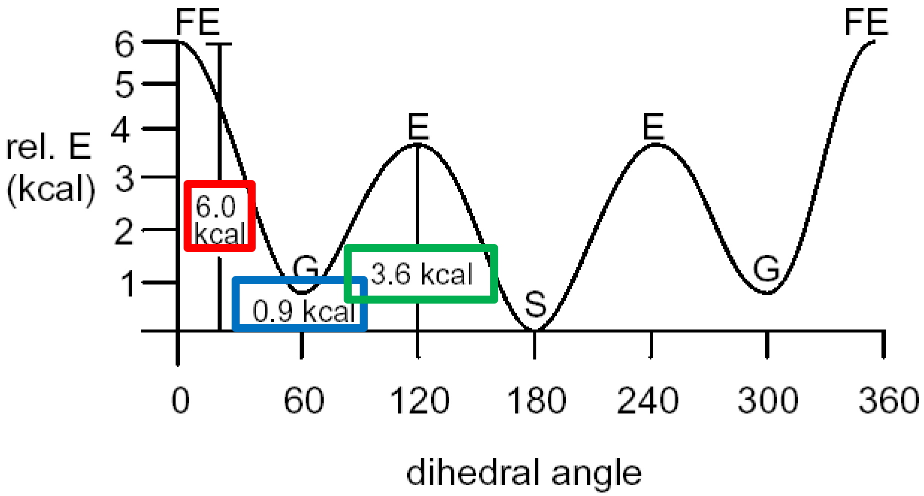


- Barrier to rotation is 3.3 kcal/mol.

H/H (1.0 kcal/mol) and Me/H (1.3 kcal/mol) eclipsing interactions are comparable. What does it tell us about the importance of steric interactions?

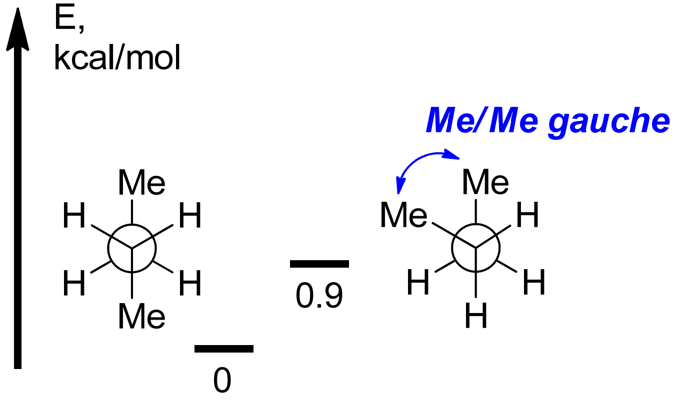
Conformations of simple alkanes revisited. Butane





- Note: the gauche butane interaction and its magnitude (0.9 kcal) are very important and we will discuss it frequently.

Examples of neutral hyperconjugation : 2. Butane



2x $\sigma_{CC} \rightarrow \sigma^*_{CC}$

4x $\sigma_{CH} \rightarrow \sigma^*_{CH}$

$$2\text{x} \begin{cases} \sigma_{CH} \rightarrow \sigma^*_{CC} \\ \sigma_{CC} \rightarrow \sigma^*_{CH} \\ \sigma_{CH} \rightarrow \sigma^*_{CH} \end{cases}$$

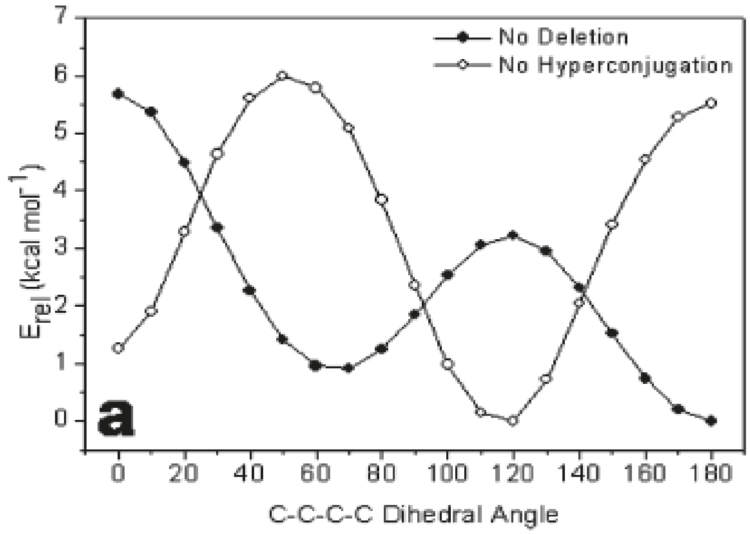
DIfferent mix of hyperconjugative interactions

Where does the 0.9 kcal/mol penalty for the gauche conformation come from?

The anti and the gauche geometries have two different patterns of neutral hyperconjugation:

$2\ \sigma_{CC} \rightarrow \sigma^*_{CC} + 4\ \sigma_{CH} \rightarrow \sigma^*_{CH}$ vs.

$2\sigma_{CC} \rightarrow \sigma^*_{CH} + 2\sigma_{CH} \rightarrow \sigma^*_{CC} + 2\ \sigma_{CH} \rightarrow \sigma^*_{CH}$

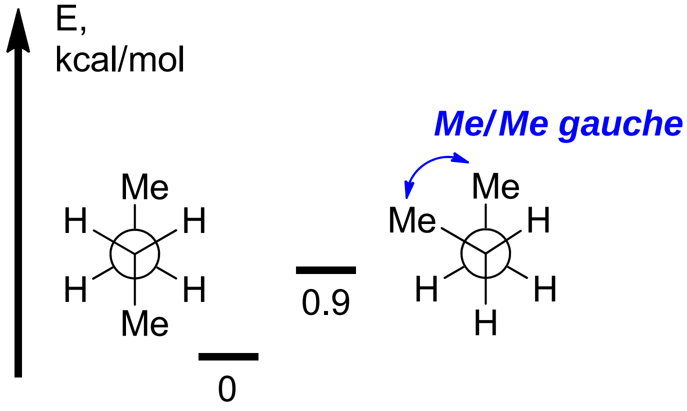


Hyperconjugation has significant effect at the conformational profile.

Can we dissect the individual effects?

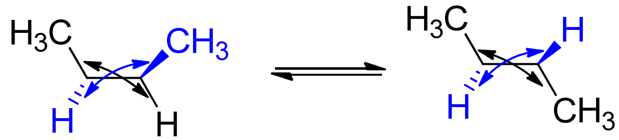
Cormanich and Freitas. A Theoretical View on the Conformer Stabilization of Butane. *JOC,* **2009**, *74*, 8384

Examples of neutral hyperconjugation :
2. Butane – comparing the main effects



$\sigma_{CH} \rightarrow \sigma^*_{CC}$

$\sigma_{CC} \rightarrow \sigma^*_{CH}$



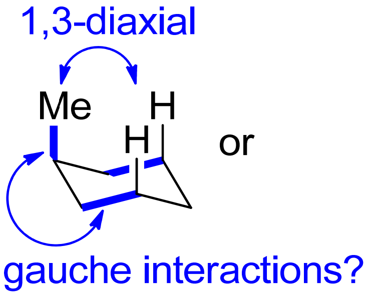
$\sigma_{CC} \rightarrow \sigma^*_{CC}$

$\sigma_{CH} \rightarrow \sigma^*_{CH}$

2 x 3.84 kcal	$\sigma_{CH} \rightarrow \sigma^*_{CC}$		$\sigma_{CC} \rightarrow \sigma^*_{CC}$	2 x 2.34 kcal
2 x 1.60 kcal	$\sigma_{CC} \rightarrow \sigma^*_{CH}$	$\rightleftharpoons$	$\sigma_{CH} \rightarrow \sigma^*_{CH}$	4 x 3.25 kcal
2 x 3.22 kcal	$\sigma_{CH} \rightarrow \sigma^*_{CH}$			
Total:	17.3 kcal *gauche*		17.7 kcal *anti*	

more stabilized by delocalization

The subtle differences between vicinal antiperiplanar interactions can account for ~45% of the difference between the two staggered conformations of butane. Other effects contribute as well.



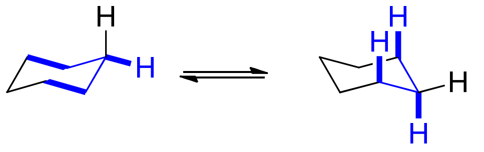
How about 1.8 kcal for the equatorial/axial flip in methylcyclohexane?

Sterics or stereoelectronics?

From Alabugin, “Stereoelectronic effects”

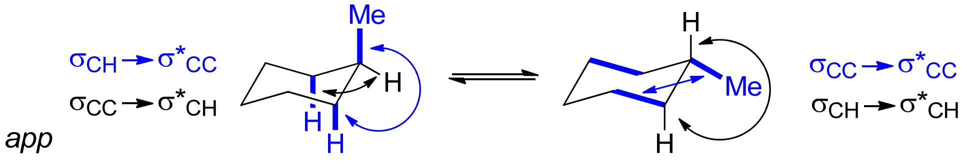
Examples of neutral hyperconjugation :
3. From butane to methylcyclohexane

How about 1.8 kcal for the equatorial/axial flip in methylcyclohexane?
Does hyperconjugation contribute?



C-H bond length, Ang	1.0972	1.1001
$^1J_{C\text{-}H}$, Hz	126	122
	$\sigma_{C\text{-}Heq} \rightarrow \sigma^*_{C\text{-}C}$ $\sigma_{C\text{-}C} \rightarrow \sigma^*_{C\text{-}Heq}$	$\sigma_{C\text{-}Hax} \rightarrow \sigma^*_{C\text{-}Hax}$
ΣE_{del}	14.6 kcal/mol	20.4 kcal/mol

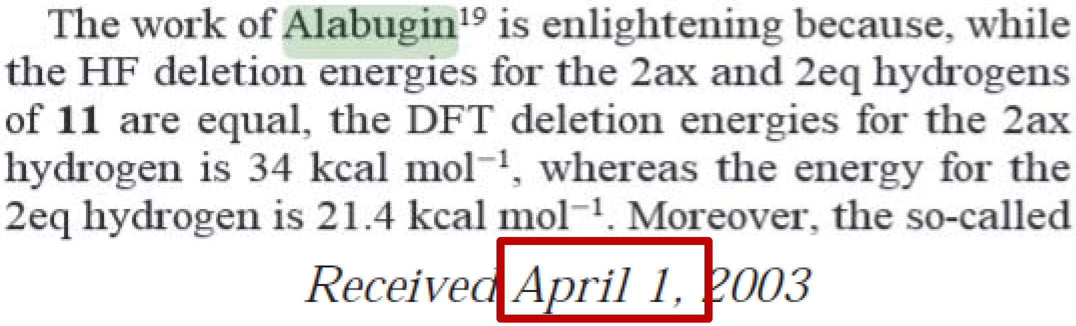
bonds that interact with the C-Me bond are shown in blue



	$\sigma_{CC} \rightarrow \sigma^*_{CH}$		$\sigma_{CC} \rightarrow \sigma^*_{CC}$	
	$\sigma_{CH} \rightarrow \sigma^*_{CC}$		$\sigma_{CC} \rightarrow \sigma^*_{CC}$	
2x	$\sigma_{CC} \rightarrow \sigma^*_{CH}$	$\rightleftharpoons$	$\sigma_{CH} \rightarrow \sigma^*_{CH}$	x2
	$\sigma_{CC} \rightarrow \sigma^*_{CH}$		$\sigma_{CH} \rightarrow \sigma^*_{CH}$	
Total:	22.2 kcal		24.0 kcal	

1.6 kcal in favor of the equatorial conformer

If you ever wanted to know why axial C-H bonds in cyclohexane are longer than the equatorial C-H bonds



The work of Alabugin[19] is enlightening because, while the HF deletion energies for the 2ax and 2eq hydrogens of **11** are equal, the DFT deletion energies for the 2ax hydrogen is 34 kcal mol^{-1}, whereas the energy for the 2eq hydrogen is 21.4 kcal mol^{-1}. Moreover, the so-called

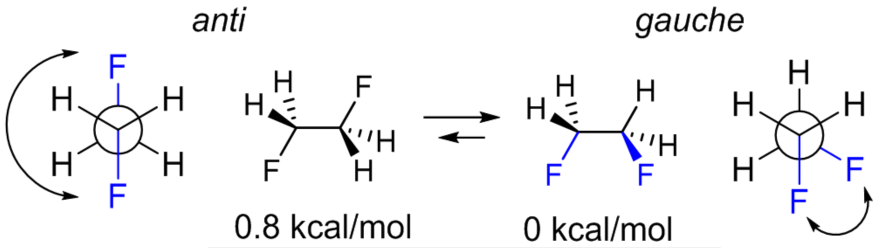
Received April 1, 2003

Alabugin, Stereoelectronic interactions in cyclohexane, 1,3-dioxane, 1,3-oxathiane and 1,3-dithiane: W-effect, σ C-X ↔σ* C-H interactions, anomeric effect - what is really important? *J. Org. Chem*. **2000**, *65*, 3910

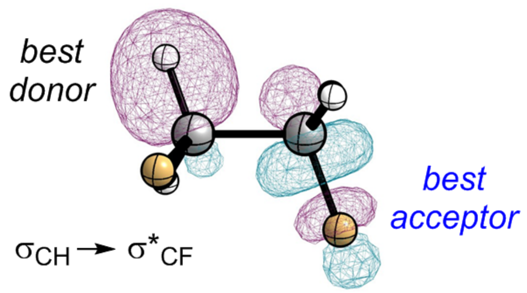
Ribeiro; Rittner, The role of hyperconjugation in the conformational analysis of methylcyclohexane and methyl-heterocyclohexanes. *J. Org. Chem.*, **2003,** *68,* 6780

Examples of neutral hyperconjugation
Add polar bonds = “Gauche effect” and “cis-effect”

Gauche Effect

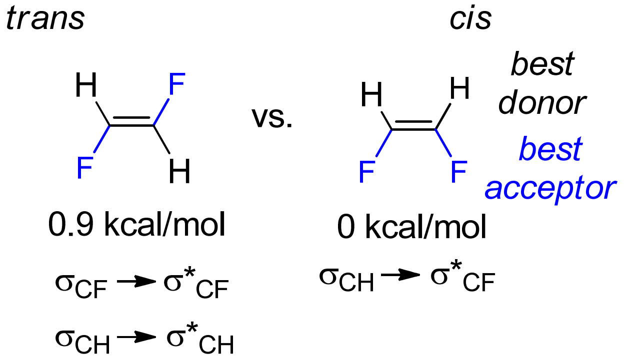


Main Rule is Followed



$\sigma_{CH} \rightarrow \sigma^*_{CF}$

Cis Effect

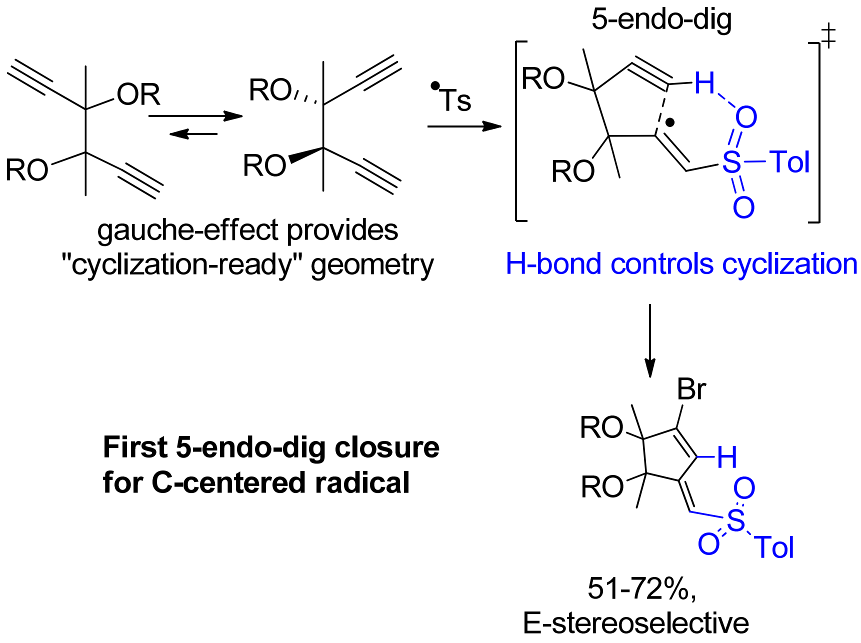


$\sigma_{CF} \rightarrow \sigma^*_{CF}$

$\sigma_{CH} \rightarrow \sigma^*_{CH}$

$\sigma_{CH} \rightarrow \sigma^*_{CF}$

Can be used to control conformations



gauche-effect provides "cyclization-ready" geometry

H-bond controls cyclization

First 5-endo-dig closure for C-centered radical

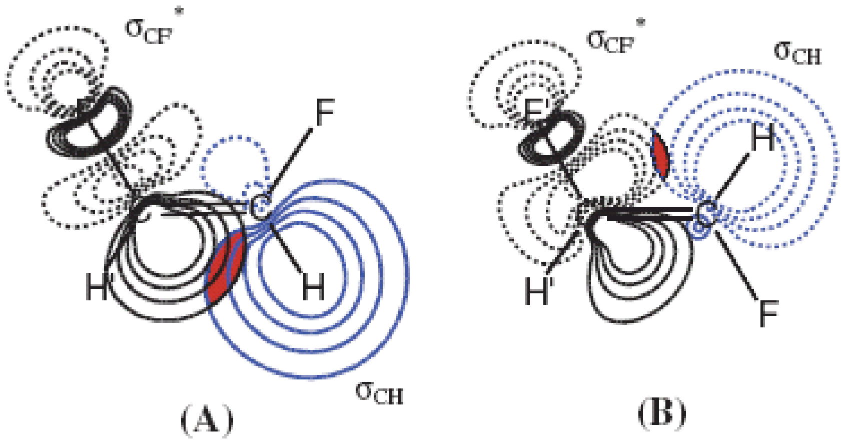
51-72%, E-stereoselective

Alabugin et al. (2008) *JACS*, *130*, 10984

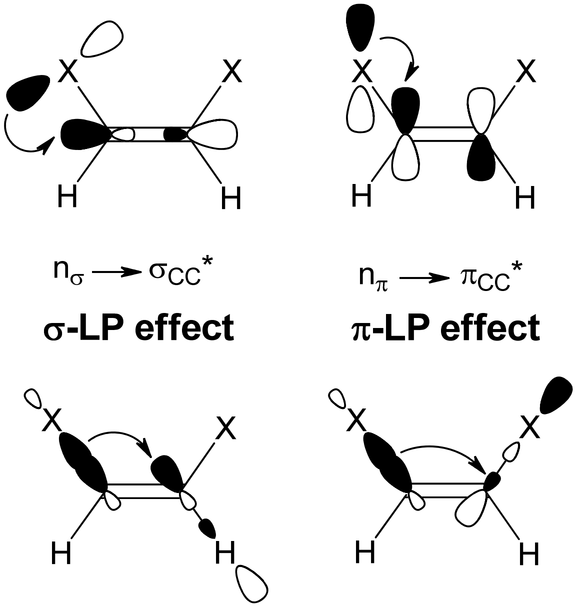
Note the similarities between the two “effects”!

Cis-effect: analysis of orbital interactions

The simplest explanation:



Additional effects analyzed with NBO:



$n_\sigma \rightarrow \sigma_{CC}{}^*$

σ-LP effect

$n_\pi \rightarrow \pi_{CC}{}^*$

π-LP effect

$\sigma_{CX} \rightarrow \sigma_{C'H'}{}^*$

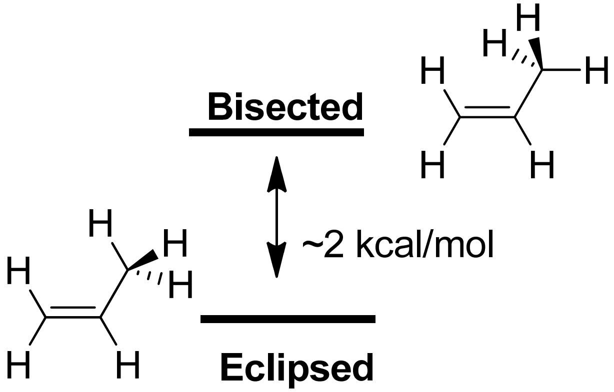
AP effect

$\sigma_{CX} \rightarrow \sigma_{C'X'}{}^*$

SP effect

Yamamoto , Kaneno, Tomoda *Bull. Chem. Soc. Japan.* 2008, 81:1415-1422.

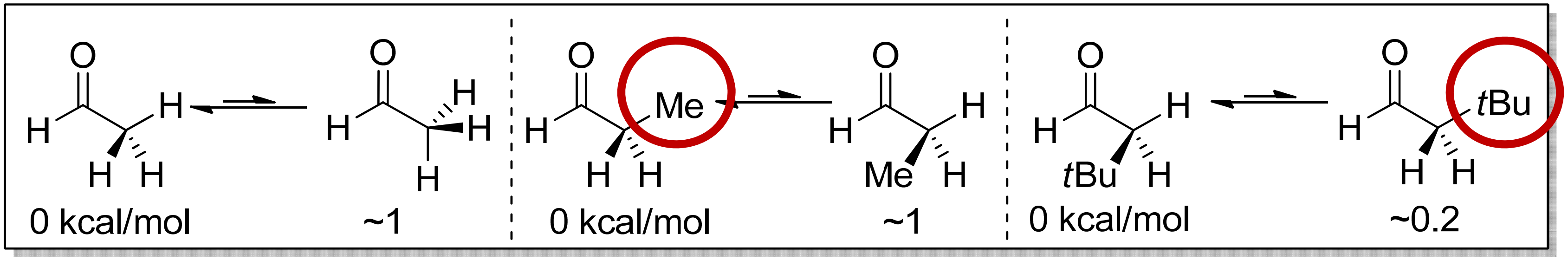
Examples of neutral hyperconjugation
4. Alkenes, aldehydes, ketones



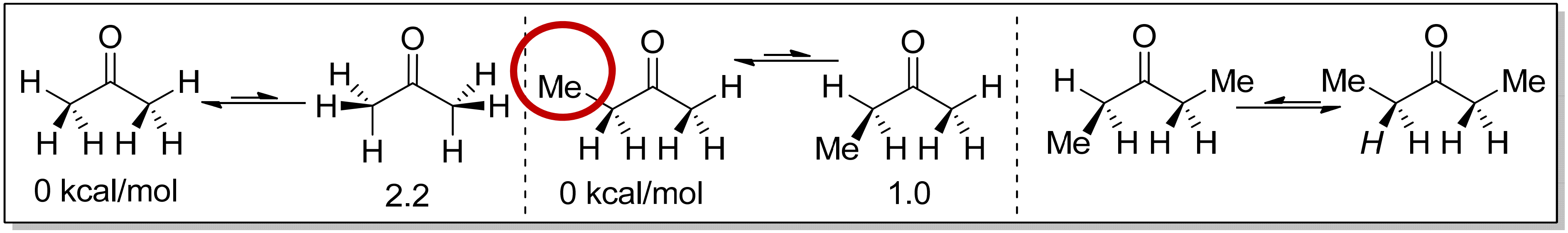
Conformation with one of C-H bonds “eclipsing” alkene σ-C-C bond is preferred

Similar preferences are observed for other π-systems

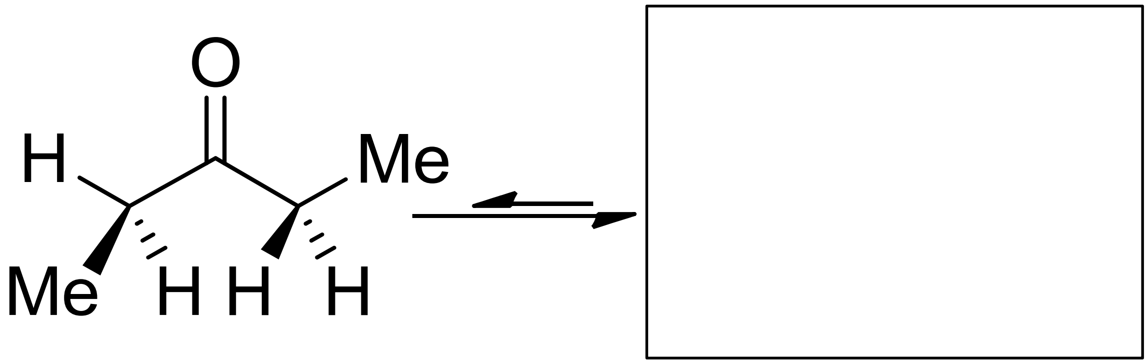
Aldehydes



Ketones



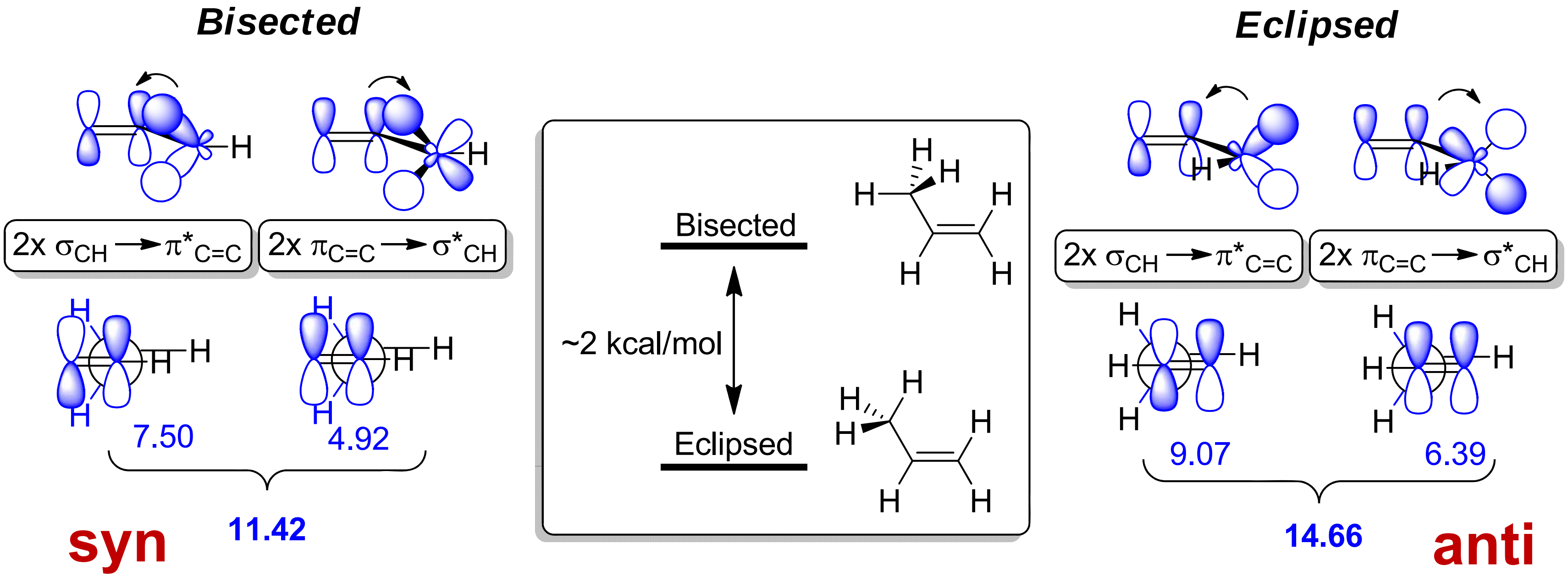
Test yourself: what is the most stable conformation of 3-pentanone?



Doubly eclipsed

Preference for the two C-H bonds to be anti and ~coplanar to the carbonyl π^*

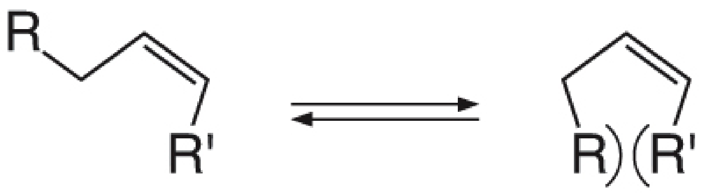
Stereoelectronic basis for the increased stability of the eclipsed conformation in propene



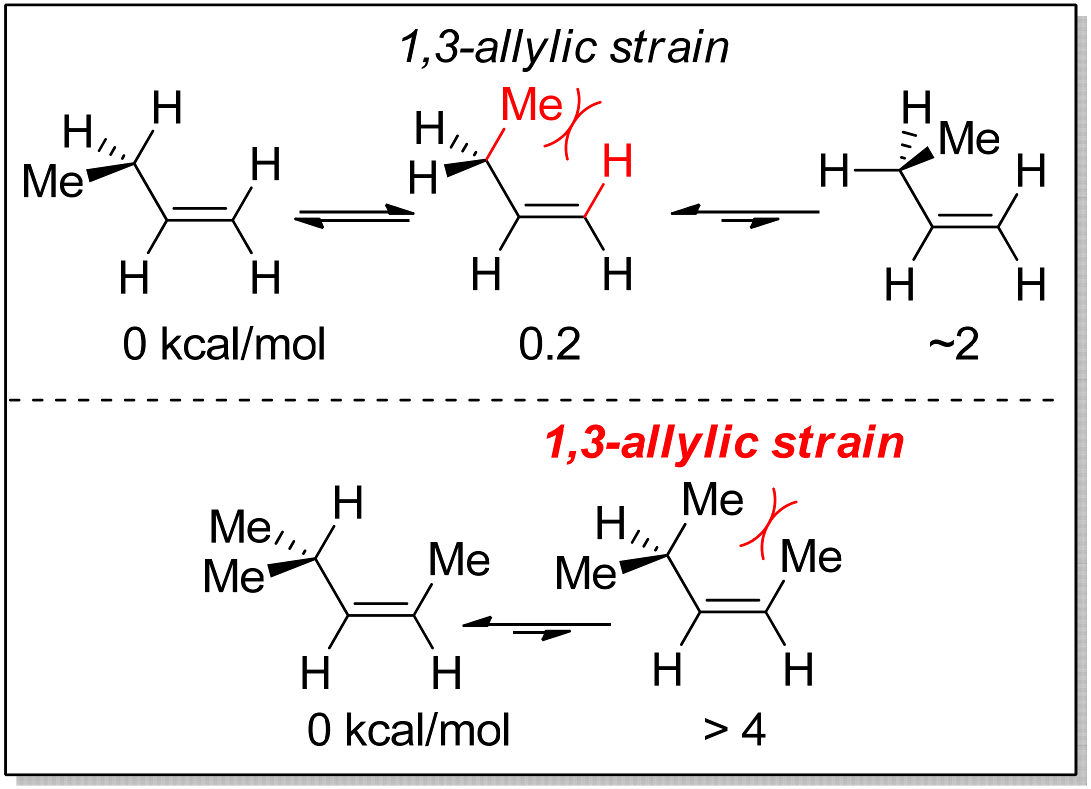
B3LYP/6-31G(d,p) NBO energies for the selected hyperconjugative interactions are shown in blue

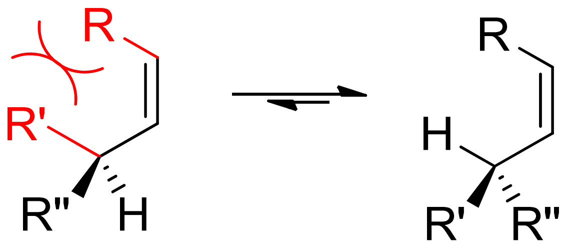
From Alabugin, “Stereoelectronic effects”

1,3-Allylic Strain



In more substituted systems, where several eclipsed conformations are possible, the preference develops for the hydrogen to eclipse the alkene $\sigma_{C\text{-}C}$ bond.



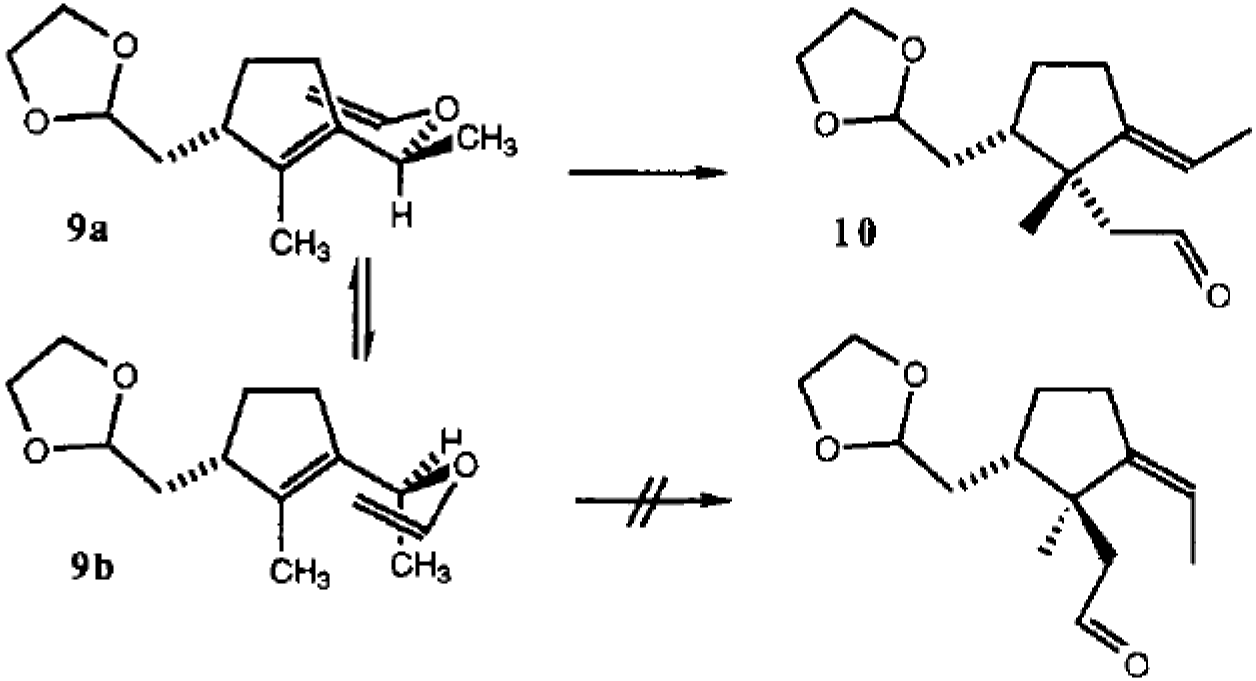


Chiral center is locked in a preferred isomer

↓

pericylic rxns,
cyclizations,
cycloadditions

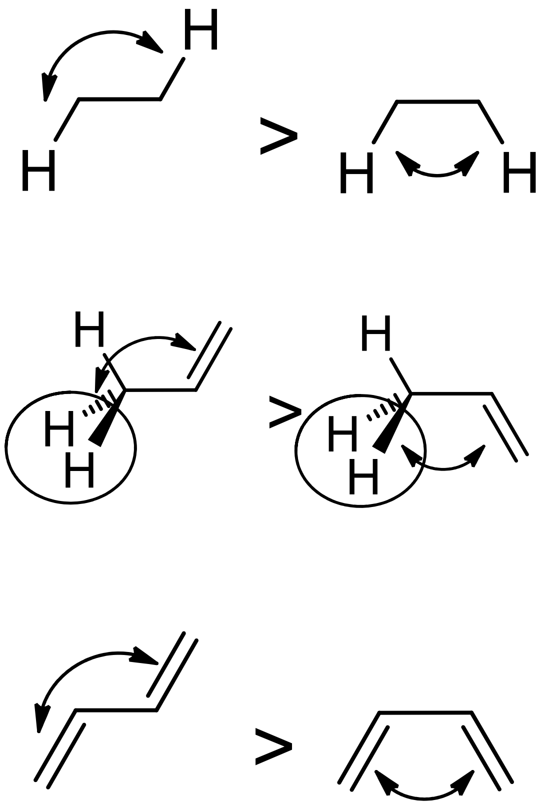
Allylic 1,3-strain in asymmetric synthesis

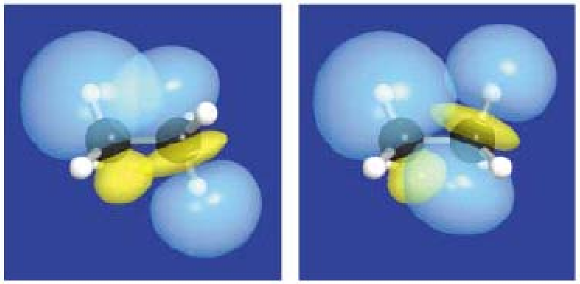


The formation of desired product **10** required an approach of the vinyl ether group at the sterically more hindered a-side. “Surprisingly”, this is the only path which has been observed. Why?

Hoffman, R. "Allylic 1,3-strain as a controlling factor in stereoselective transformations". *Chem. Rev*. **1989,** 89: 1841–1860.

Vicinal conjugation and hyperconjugation display the same stereoelectronic preference for antiperiplanarity

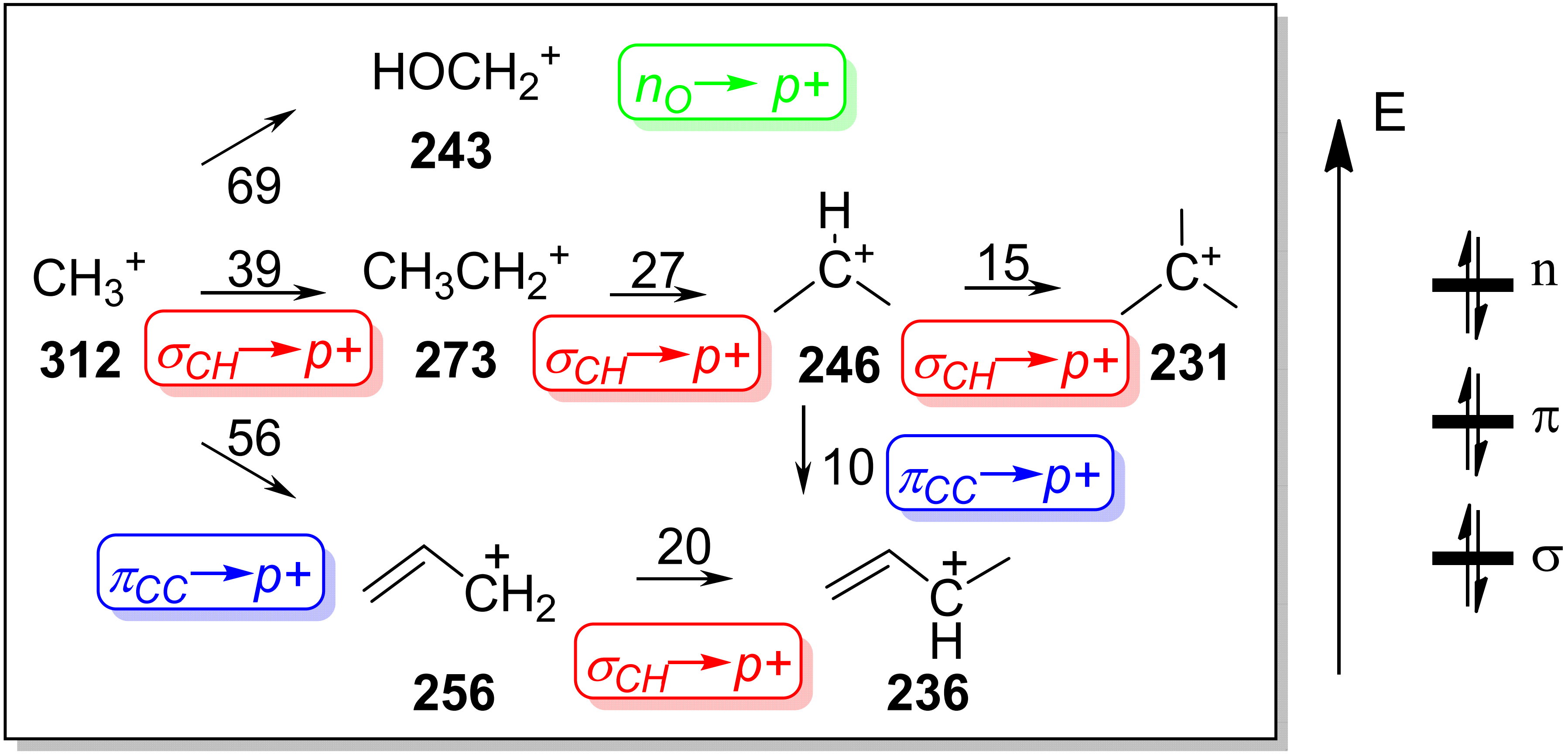




Conjugation and hyperconjugation are conceptually analogous. The same rules apply to these two phenomena.

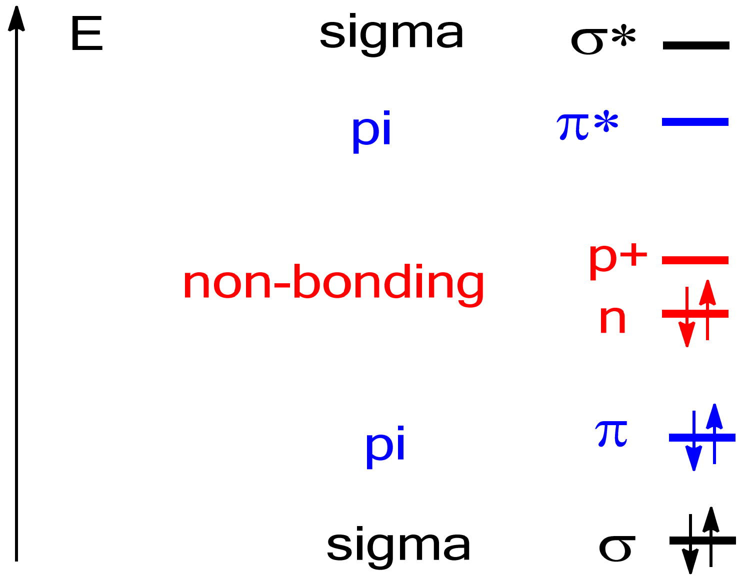
There is no need to be “hyper” about hyperconjugation.

Hyperconjugation: a poor cousin of conjugation?



Absolute (data below the structures) and relative (data near the arrows) gas phase hydride ion affinities for selected carbocations. All energies are in kcal/mol. **Note that hyperconjugative energies for positive hyperconjugation in cations are much larger than they were in neutral hydrocarbons**

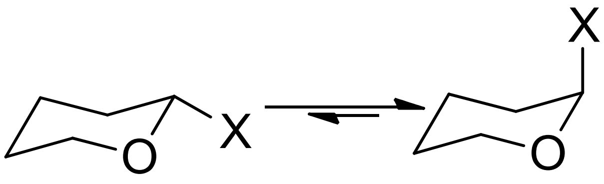
Let's move to stronger donors: Negative hyperconjugation



$$E(2) = -n_{\sigma}\frac{\langle \sigma/F/\sigma^{*}\rangle^{2}}{\varepsilon_{\sigma^{*}}-\varepsilon_{\sigma}} = -n_{\sigma}\frac{F_{i,j}^{\;2}}{\Delta E}$$

Presence of high energy non-bonding donor orbitals (lone pairs) has large consequences for stability and reactivity of molecules with heteroatoms

Negative hyperconjugation: Anomeric effect



M06-2X/6-311G++(d,p)

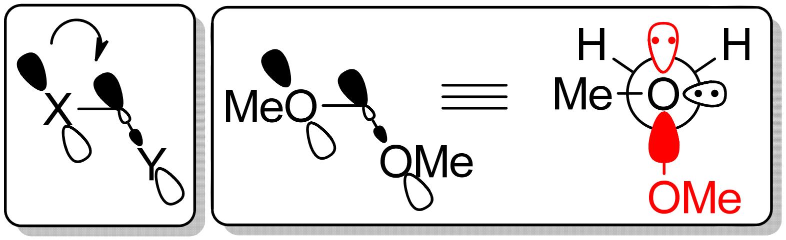
X	ΔE	ΔG
Cl	-3.9	-3.5
F	-3.0	-2.7
OMe	-3.9	-3.6

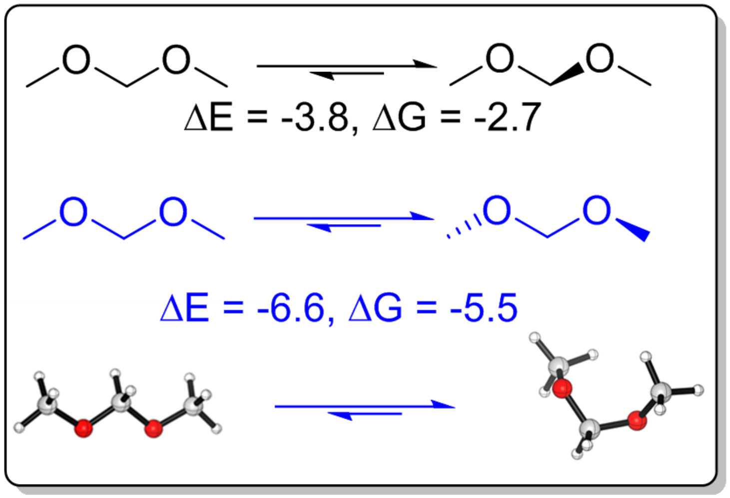
(in kcal/mol)

Acceptors at the anomeric carbon prefer axial position

Generalized anomeric effect: applies to acyclic compounds

Conformational control via $n_X \rightarrow \sigma^*_{CY}$





ΔE = -3.8, ΔG = -2.7

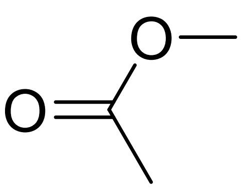
ΔE = -6.6, ΔG = -5.5

Can we apply anomeric effect to something new?

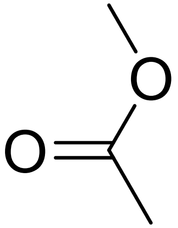
Alabugin, “Stereoelectronic effects”, gas phase M06-2X/6-311G++(d,p) values

Negative hyperconjugation:
Conformations of esters

Which one is more stable?



E-conformer

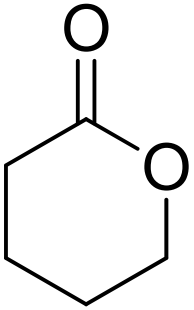


Z-conformer

The strongest effect is $n_O \rightarrow \pi^*$CO but it does not change between the conformers.

We need to look at the 2nd best pair of donor and acceptor

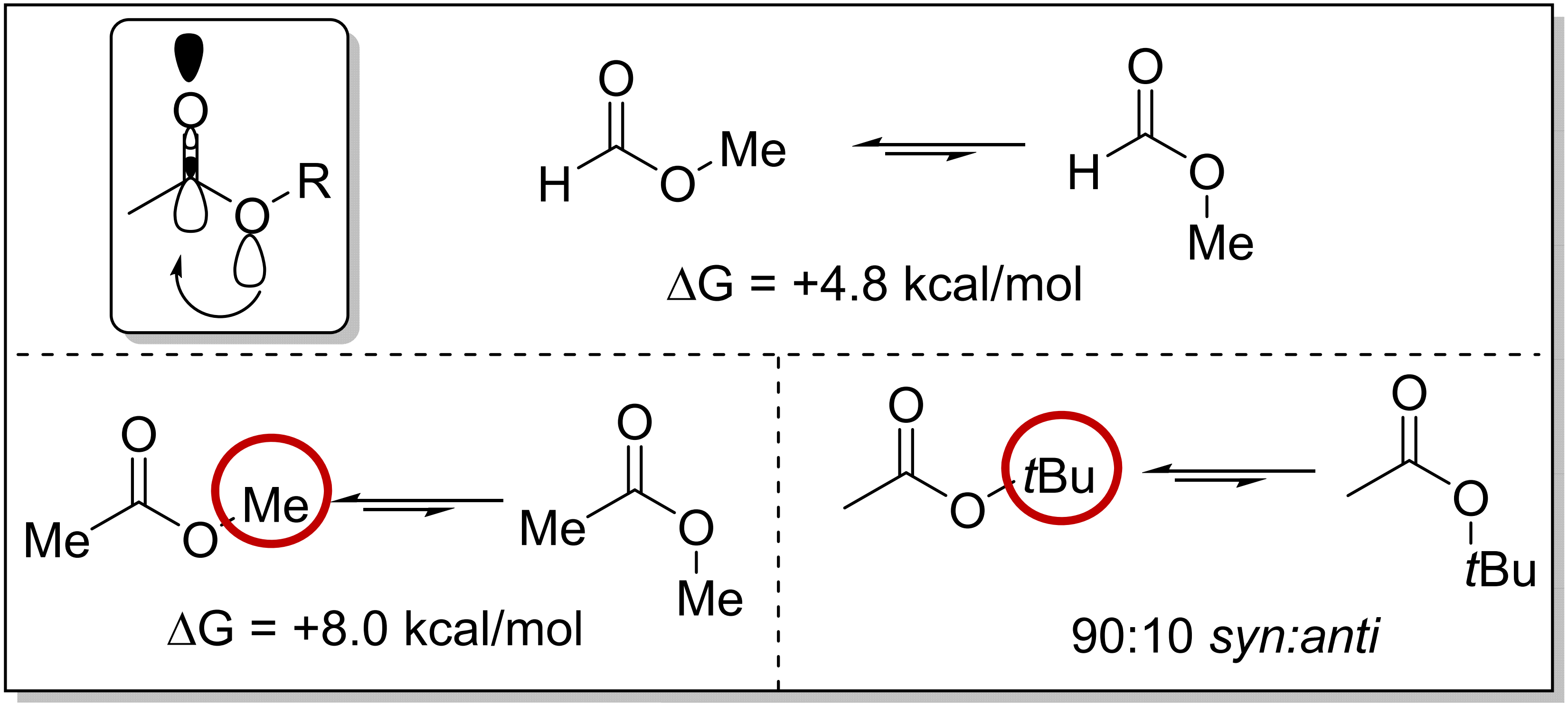
Hint: lactones are more reactive than simple acyclic esters



Methyl, ethyl and isopropyl formate are ~ 99 % “trans”:
Tetrahedron Letters, 1982, 1757–1760

Conformations of esters

The second strongest effect is $n_O \rightarrow \sigma^*$CO



Story #1

D 6093

EurJOC
European Journal of
Organic Chemistry

31/2014
1st November Issue

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Cover Picture
Alexander O. Terent'ev et al.
Synthesis of Nine-Membered Bicyclic Silyl Peroxides

Microreview
Jacky C.-H. Yim and Laurel L. Schafer
Alkyne Hydroamination Catalysts

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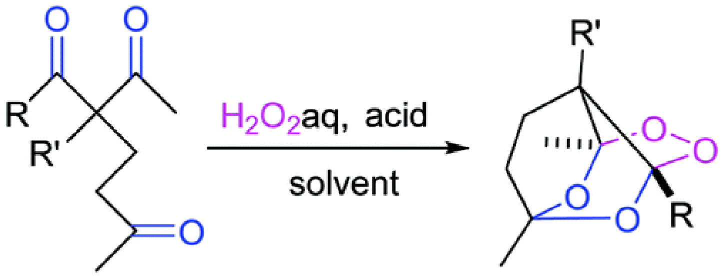
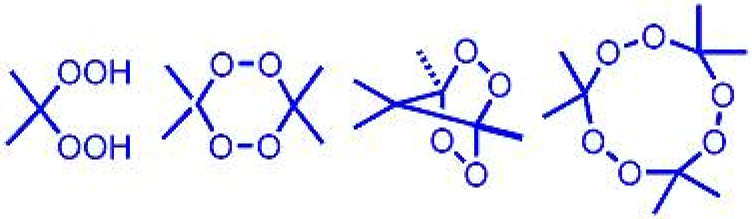
Stable peroxides

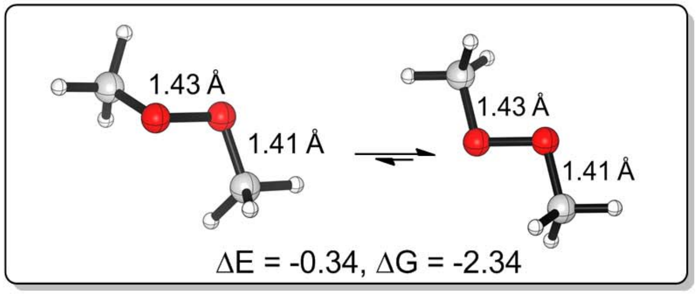


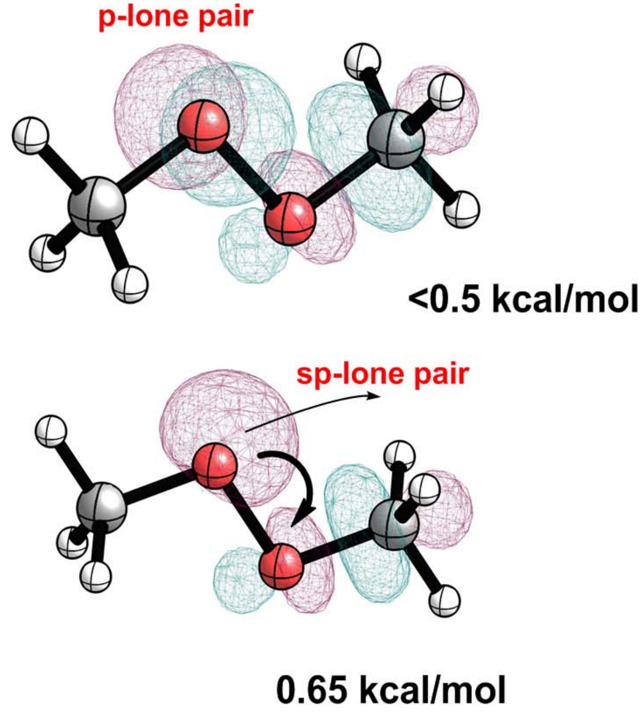
15 Examples; Yield 39-90%

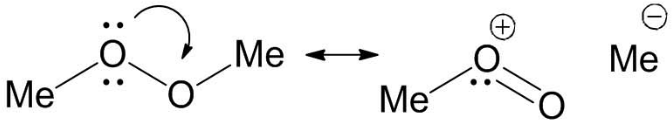


Antitumor, Antiparasitic, Antimicrobial

Can anomeric effect stabilize peroxides?

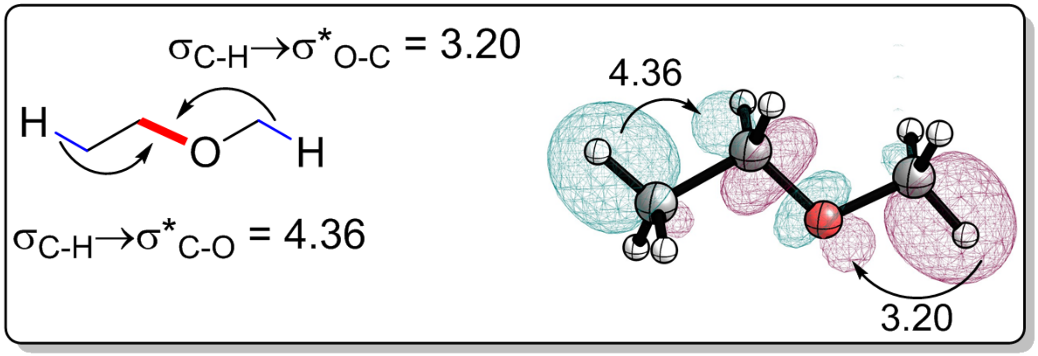






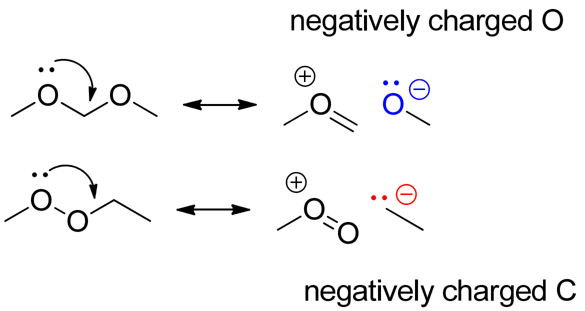
Resonance is inefficient

Anti-conformation is more stable and n→σ*(O-C) interaction are small: anomeric interactions are not important

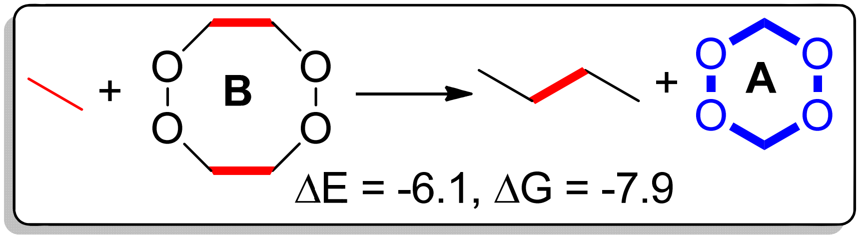


$\sigma^*_{O\text{-}C}$ is a much weaker acceptor than $\sigma^*_{O\text{-}C}$

Alabugin, *J. Org. Chem*. **2000**, 3910



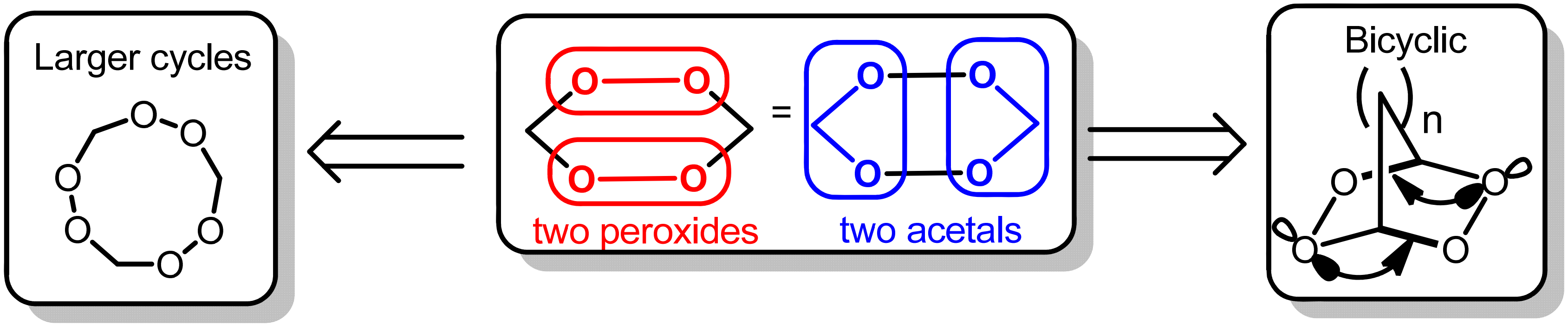
How to activate anomeric effect? Go from mono- to bis-peroxides



ΔE = -6.1, ΔG = -7.9

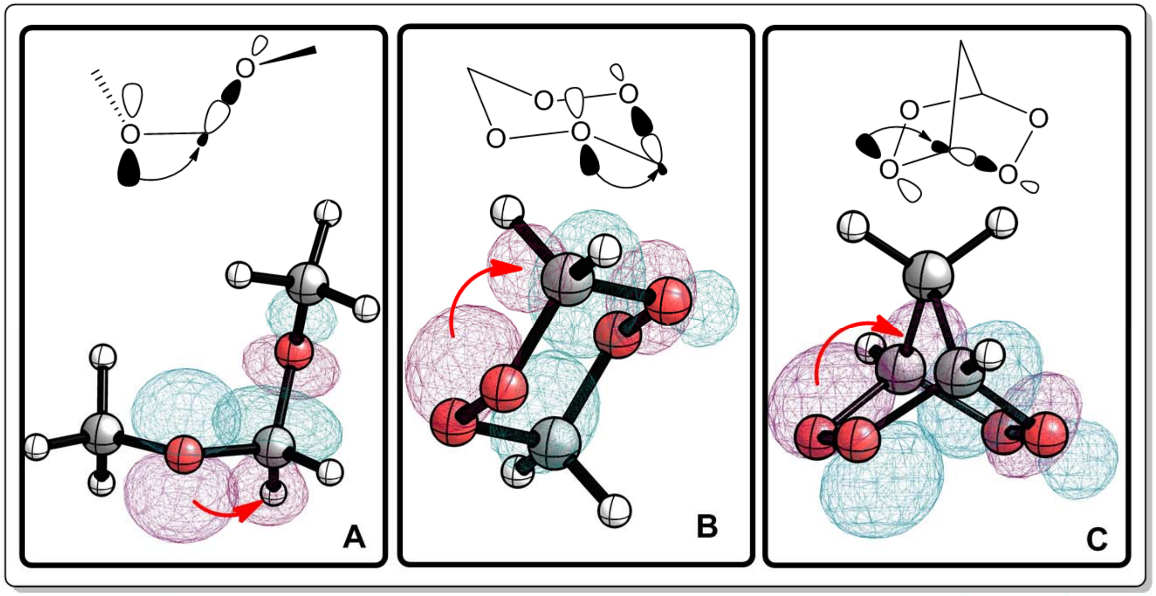
How to stabilize peroxides? Bring two peroxides closer and convert them into acetals!

Two peroxides can stabilize each other when they are separated by a one-atom bridge



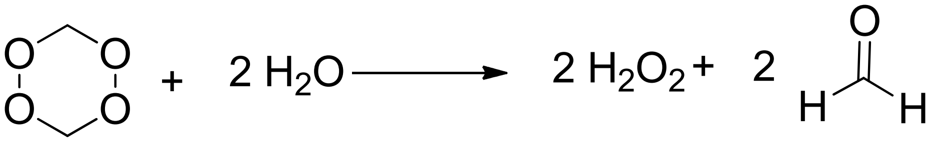
Bis-peroxides masqerade as bis-acetals: strong anomeric interactions

How to stabilize peroxides? Activate anomeric interactions

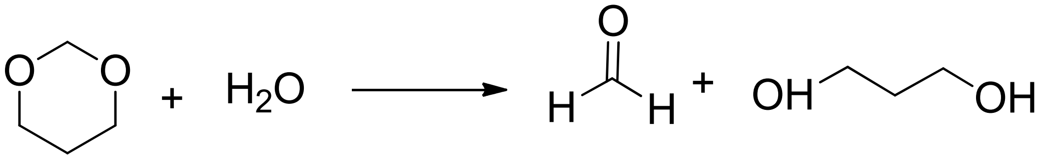


Stabilization energies: 14.1 14.7 16.4 (kcal/mol)

Increase stability to hydrolysis

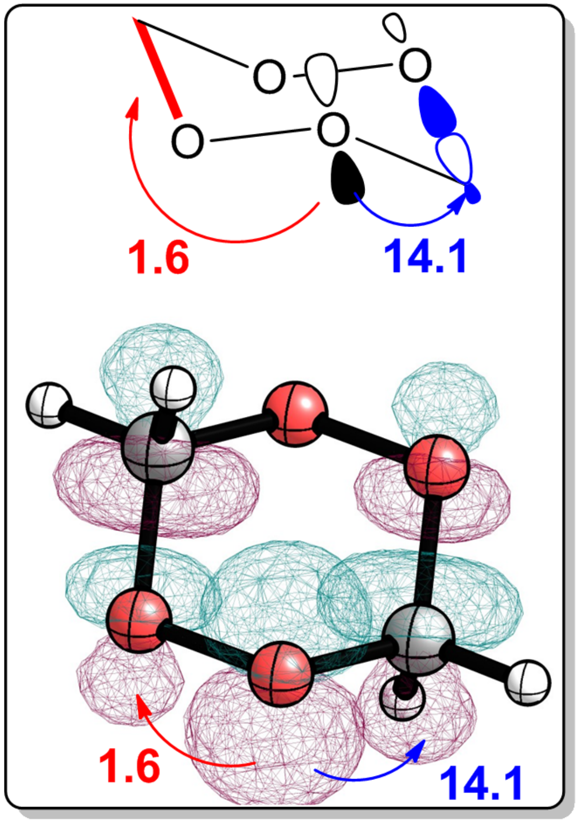


ΔH = 41.5 , ΔG = 25.2 (kcal/mol)



ΔH = 16.5, ΔG = 12.2 (kcal/mol)

Let’s compare acceptor ability of $\sigma^*_{O\text{-}C}$ and $\sigma^*_{O\text{-}C}$ orbitals again

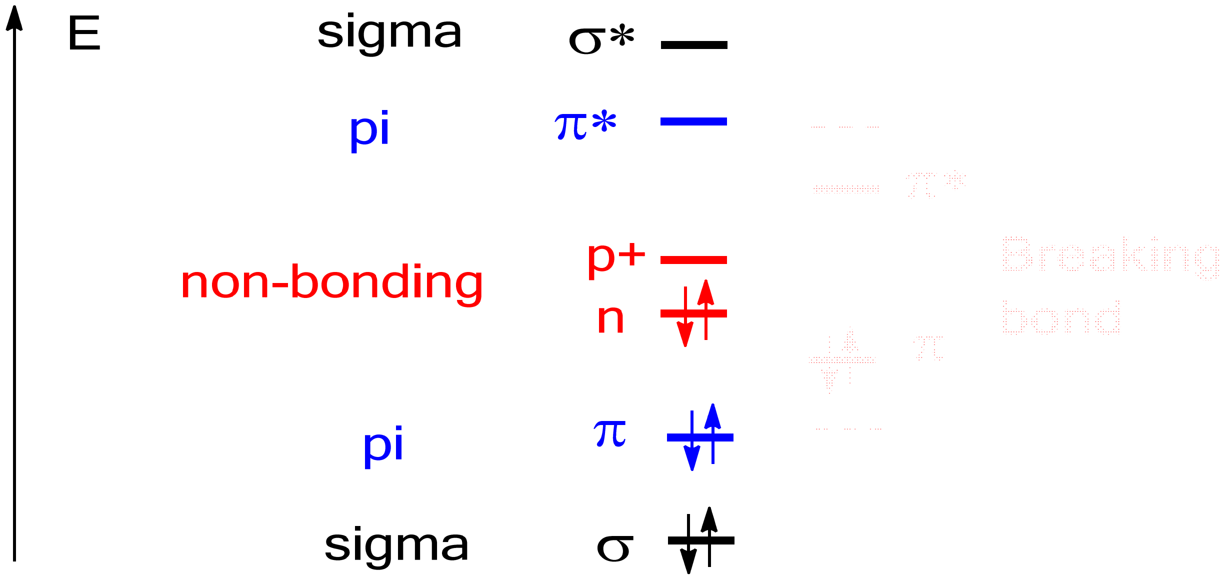


Much stronger $n_O \rightarrow \sigma^*$ CO interactions: greater hyperconjugative stabilization explains why 2nd peroxide in the same molecule can increase stability

Story #2

Hyperconjgation in “click” transition states

What makes a strong donor?
Hierarchy of orbitals:



E

sigma σ^*

pi π^*

π^*

non-bonding p+

n

Breaking bond

π

pi π

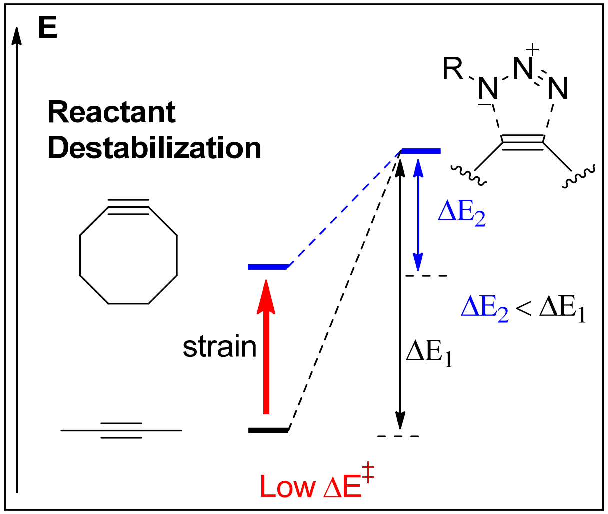
sigma σ

What is missing?

Breaking (or stretched) bonds are strong donors and strong acceptors

New alkynes for Cu-free click chemistry, or molecular matchmaking

- How to achieve alkyne/azide union without the help of copper?

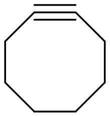


Starting higher on the energy slope

Activation by strain:

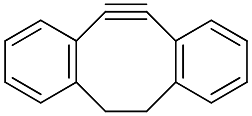
Additional sp^2 atoms

Strain + electronic effects



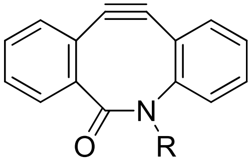
OCT

Bertozzi (2004)



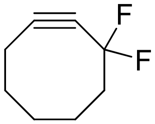
DIBO

Boons (2008)



BARAC

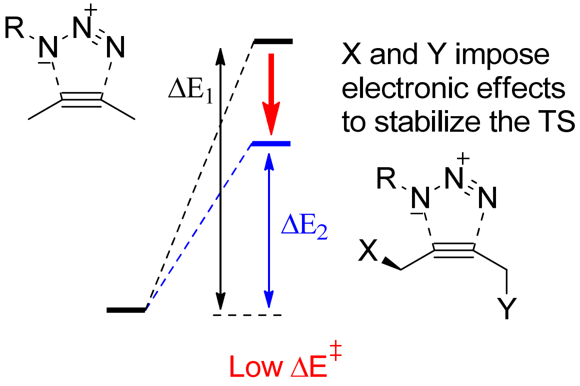
Bertozzi (2010)



DIFO

Bertozzi (2007)

Transition State Stabilization



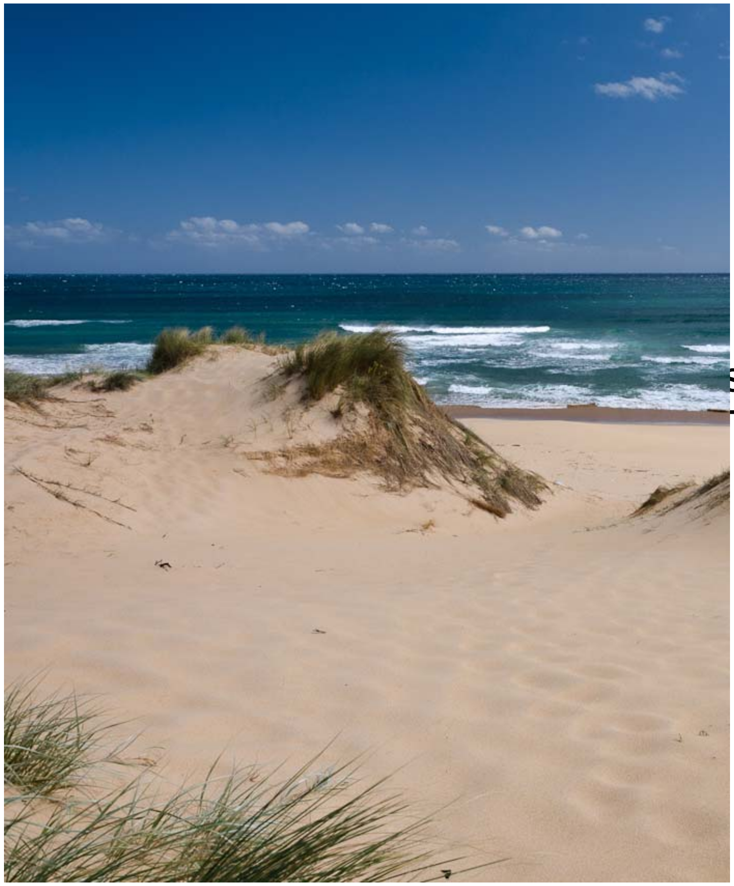
Can we offer an alternative and identify electronic effects for selective Transition State stabilization?

Two Ways Over the “Mountain”

E

Start Higher

Make the Mountain Smaller



E_1

R"

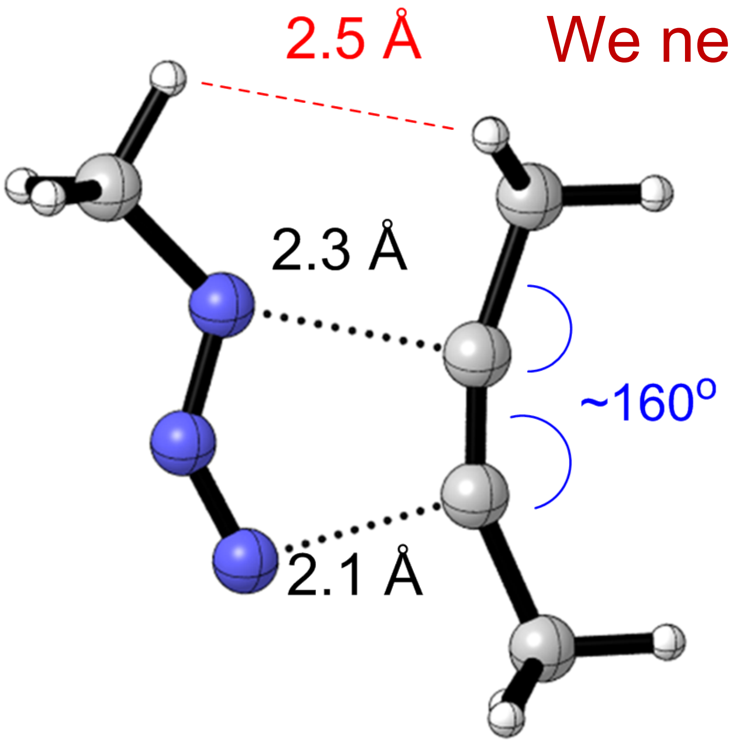
s

TS

B. Gold, N. Shevchenko, N. Bonus, G. B. Dudley, I. V. Alabugin, *J. Org. Chem.* **2012**, *77*, 75.

How to stabilize cycloaddition transition states?

Let’s look at the sources of “molecular discomfort” in the parent TS:



We need to avoid close steric contacts

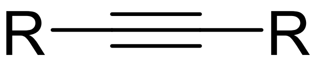
…and alleviate the cost of alkyne bending

How can we make alkynes more flexible?

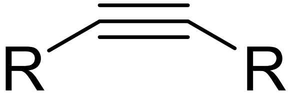
Yoga is not an option!

Bent Alkyne:
Functional Group at the brink of collapse

Linear Alkyne

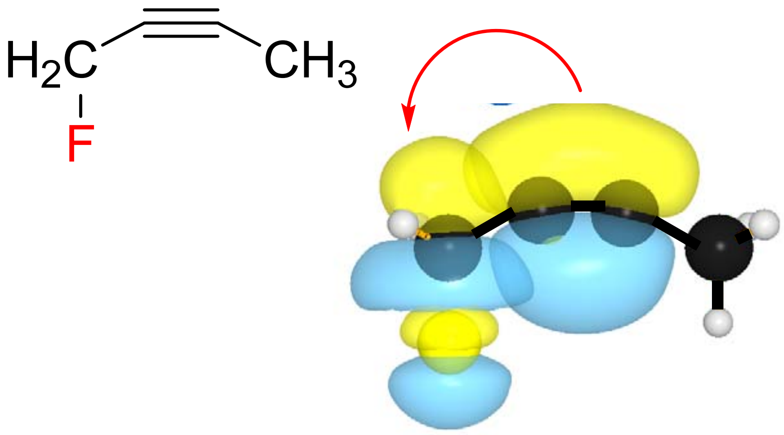


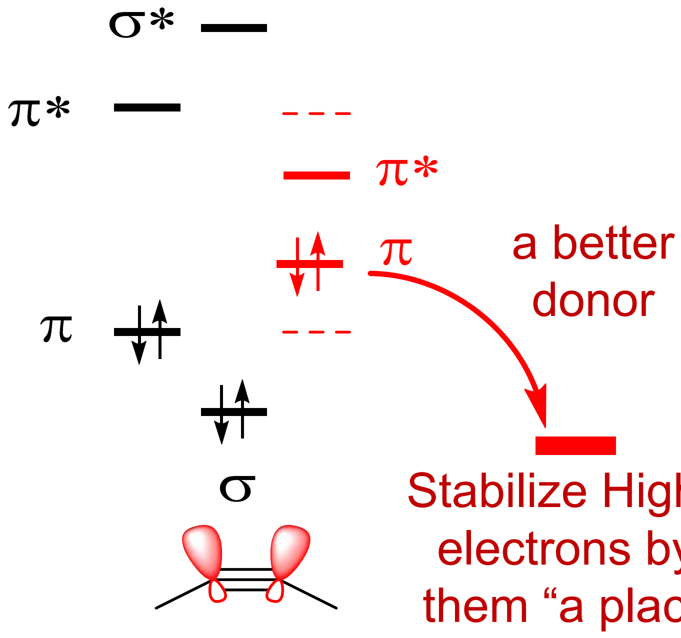
Bent Alkyne



Let's describe the two systems from the molecular orbital point of view

Provide the good donor with a good acceptor

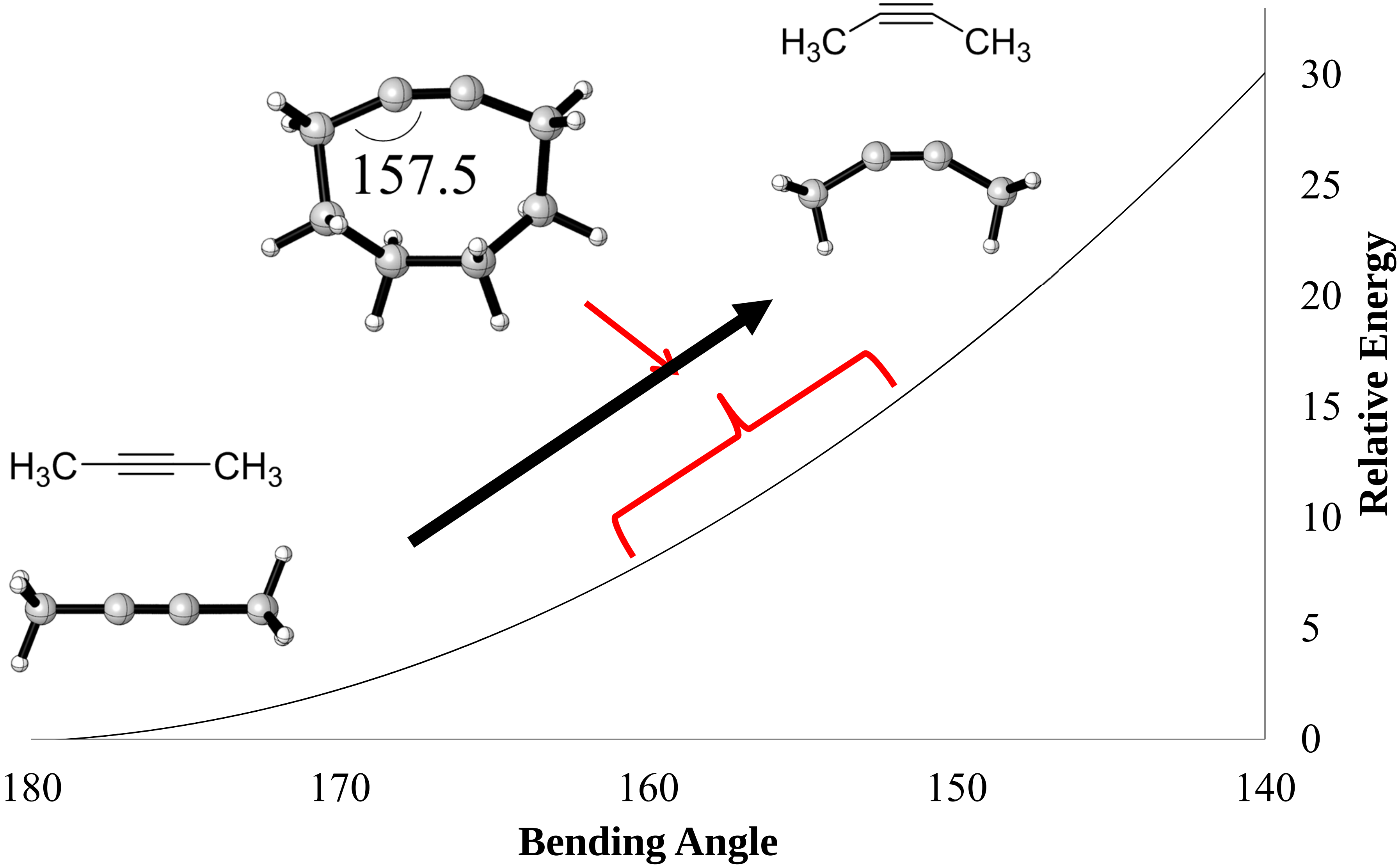




a better donor

Stabilize High Energy electrons by giving them "a place to go"

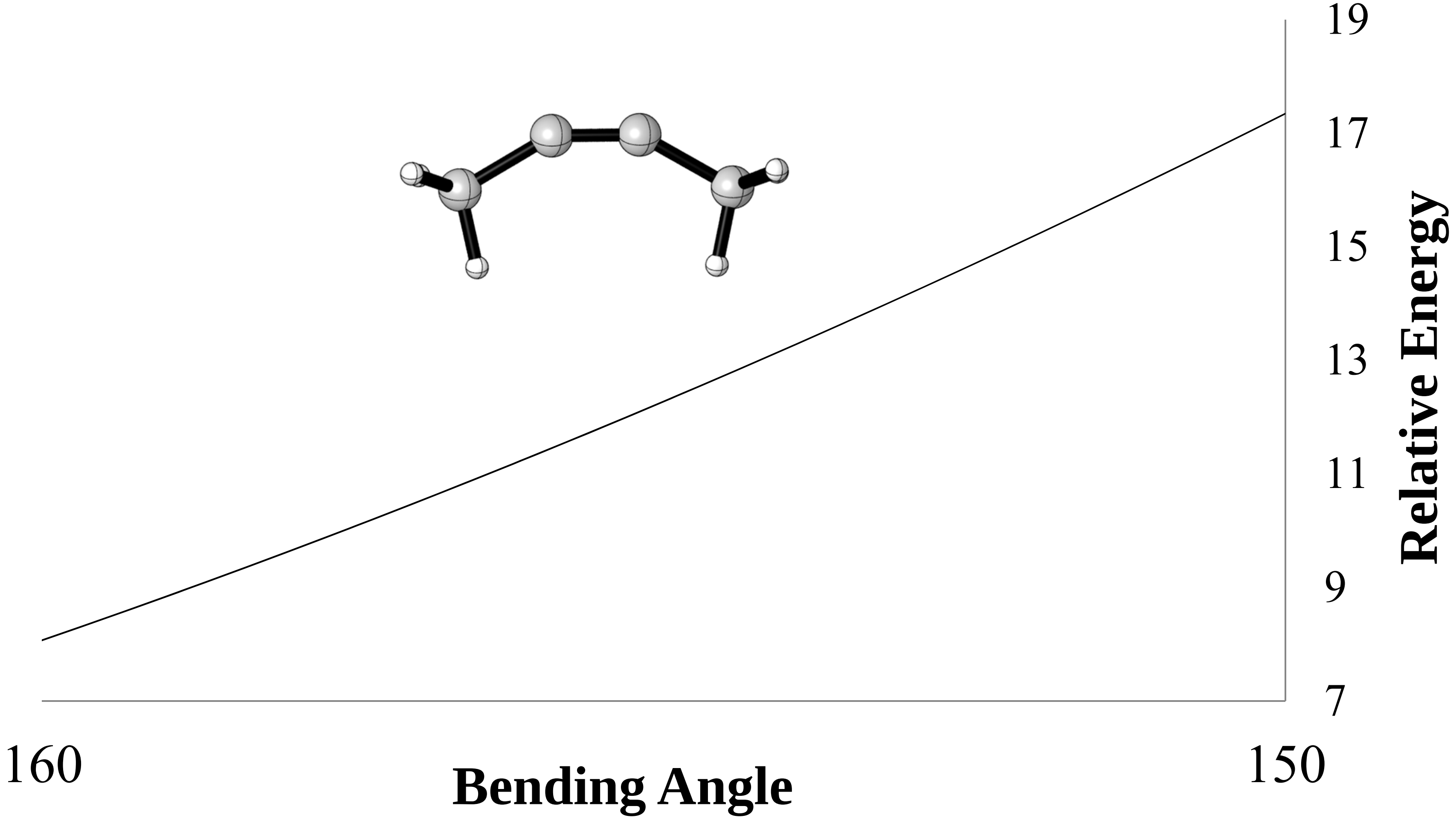
Assistance to Bending



Gold, B. et al. *J. Org. Chem.* **2012**, *77*, 75.

B3LYP/6-31G(d)

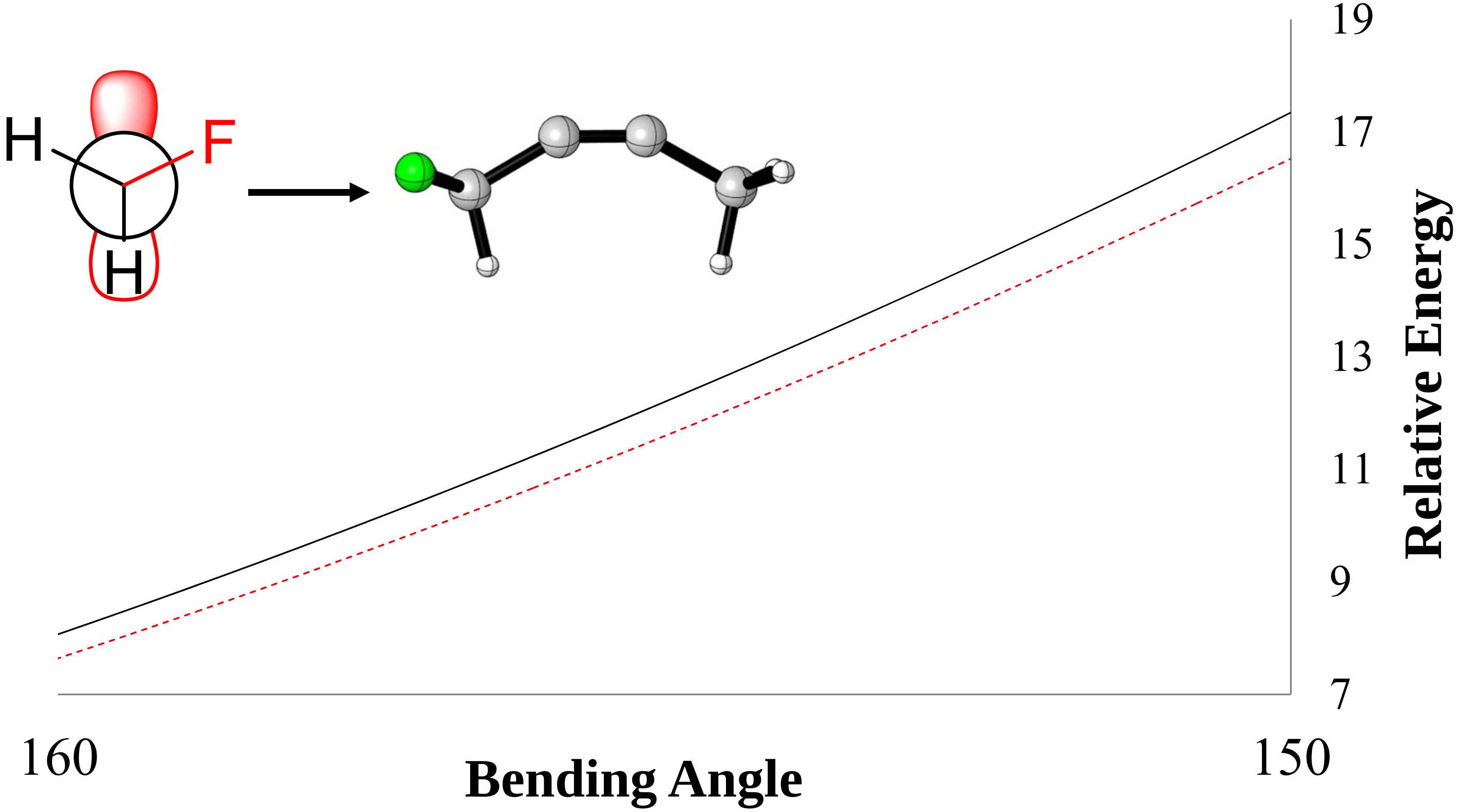
Assistance to Bending



Gold, B. et al. *J. Org. Chem.* **2012**, *77*, 75.

B3LYP/6-31G(d)

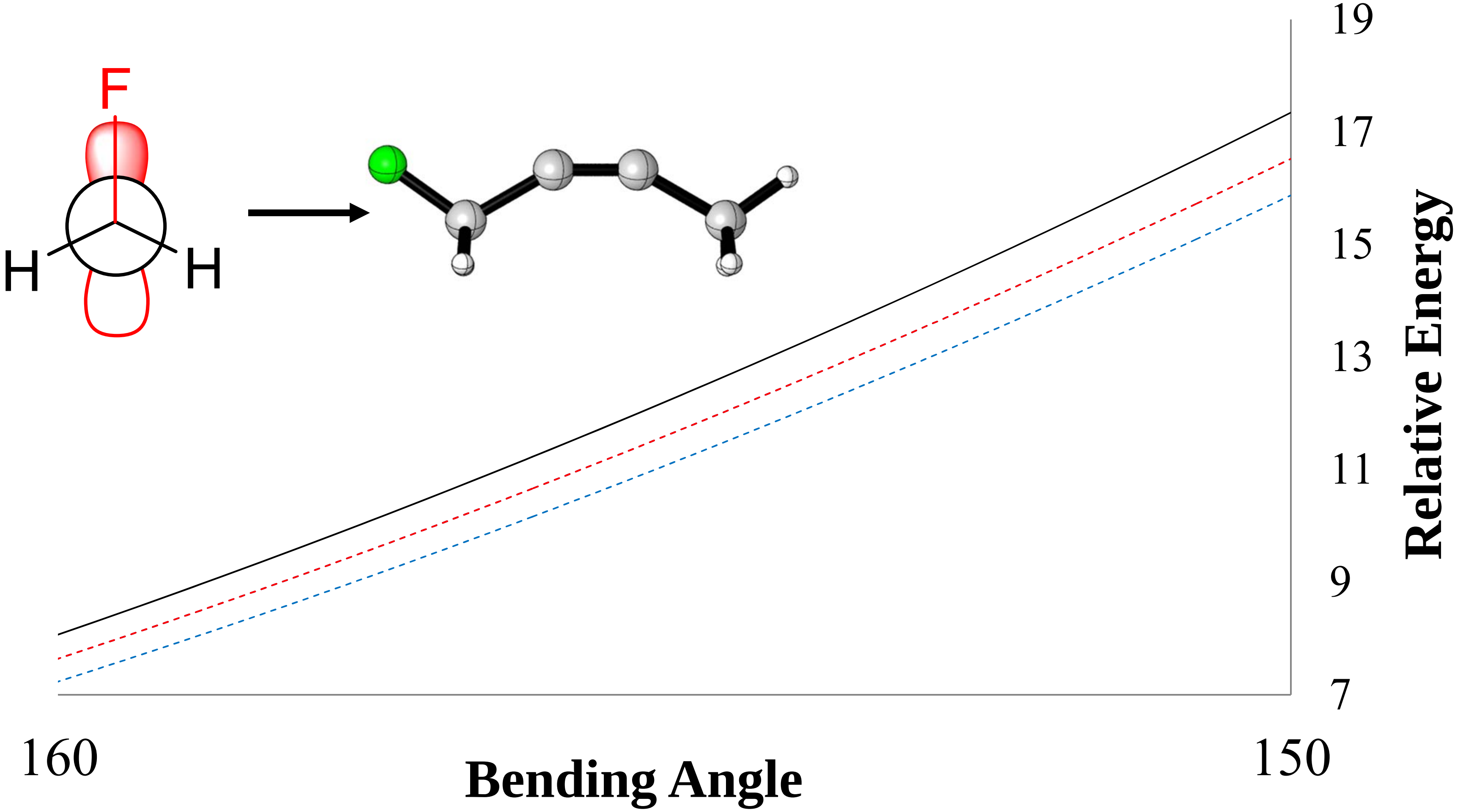
Assistance to Bending



Gold, B. et al. *J. Org. Chem.* **2012**, *77*, 75.

B3LYP/6-31G(d)

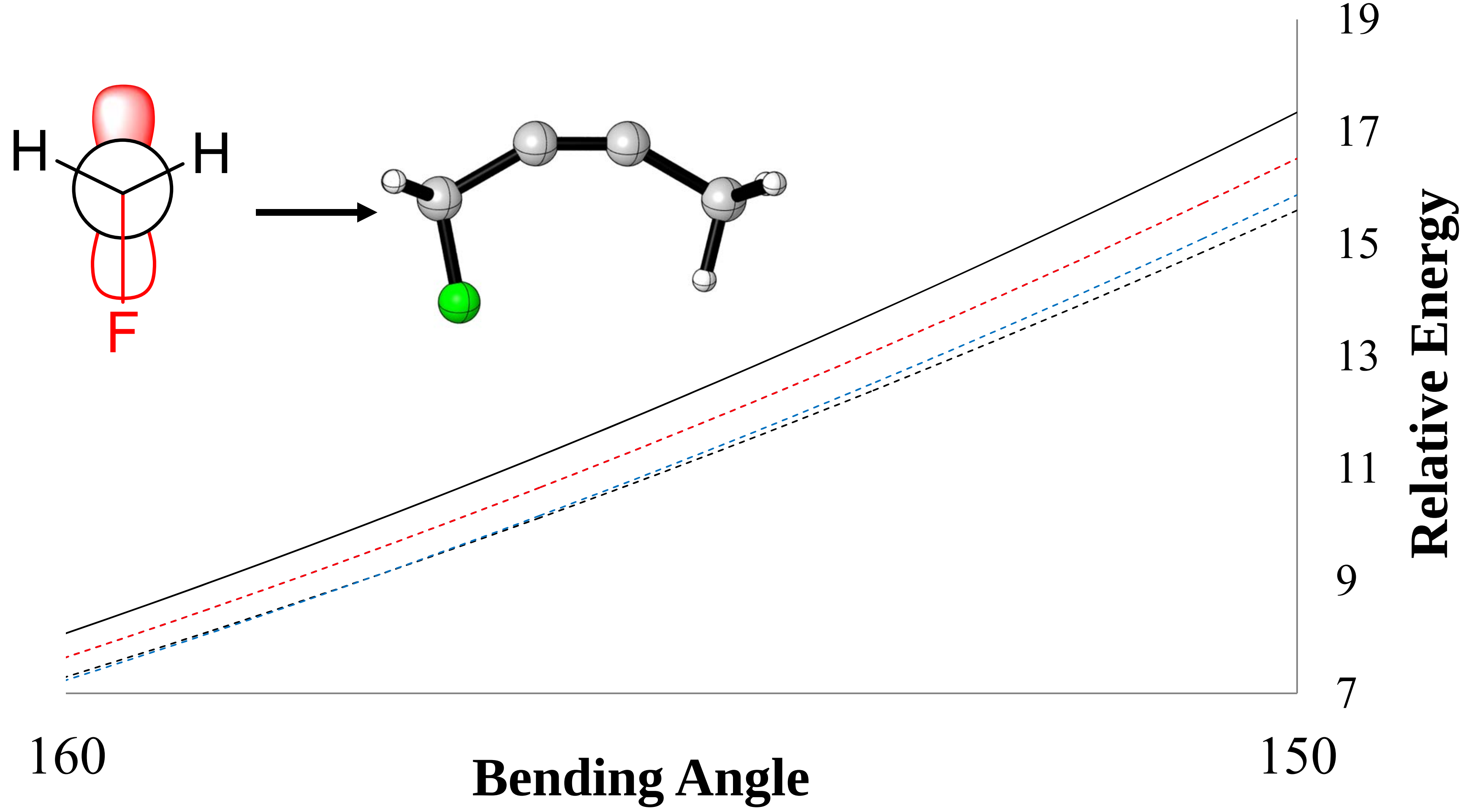
Assistance to Bending



Gold, B. et al. *J. Org. Chem.* **2012**, *77*, 75.

B3LYP/6-31G(d)

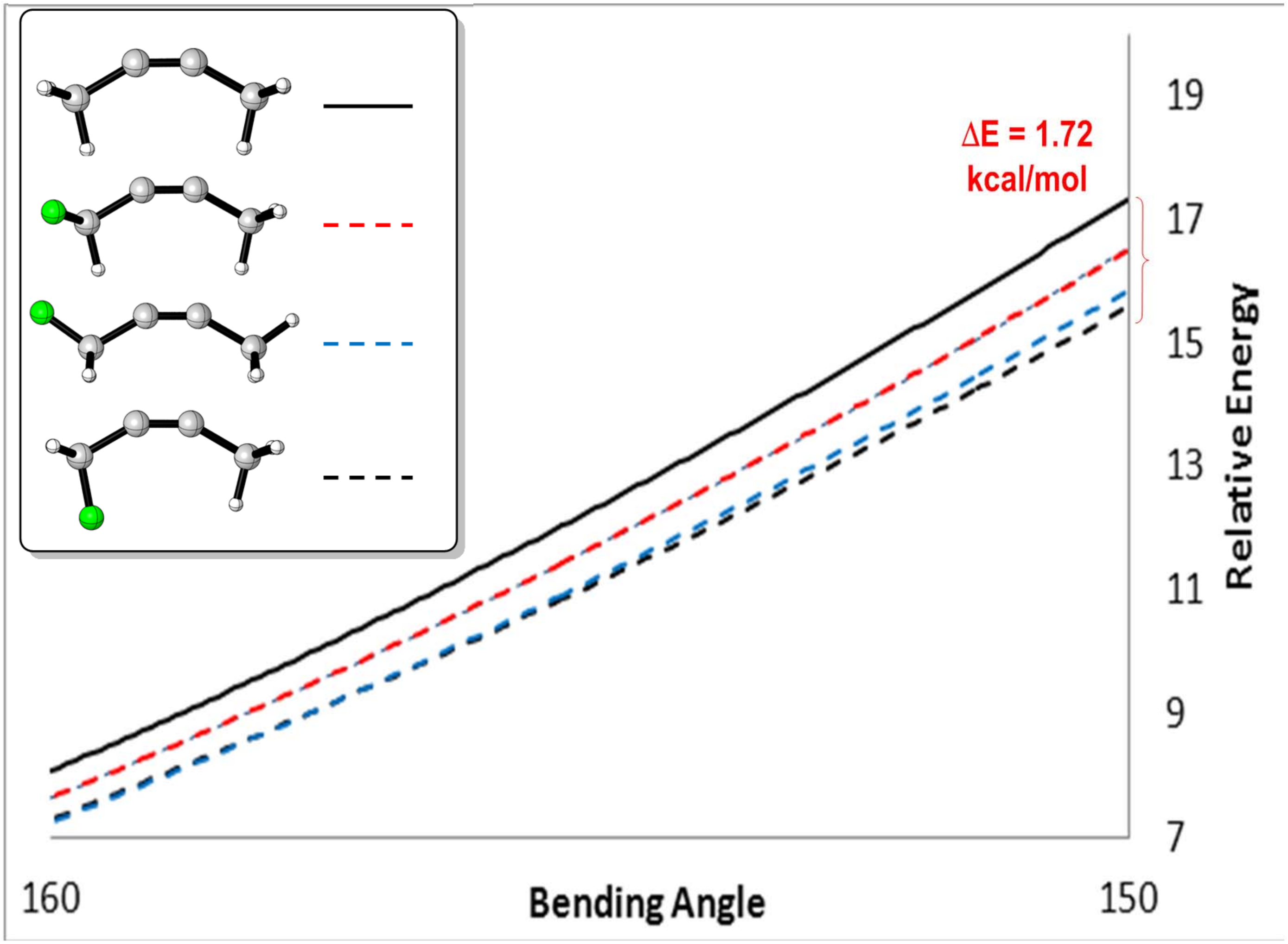
Assistance to Bending



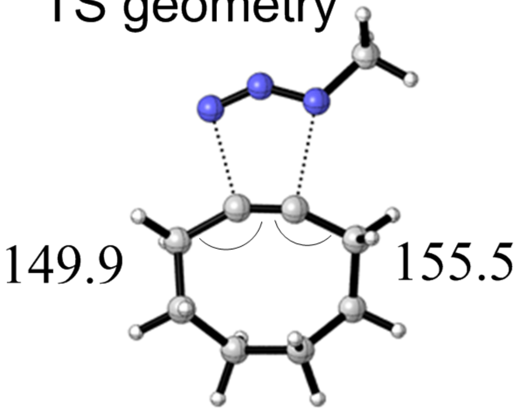
Gold, B. et al. *J. Org. Chem.* **2012**, *77*, 75.

B3LYP/6-31G(d)

An Easier Climb:
Stereoelectronic Assistance to Alkyne Bending



TS geometry

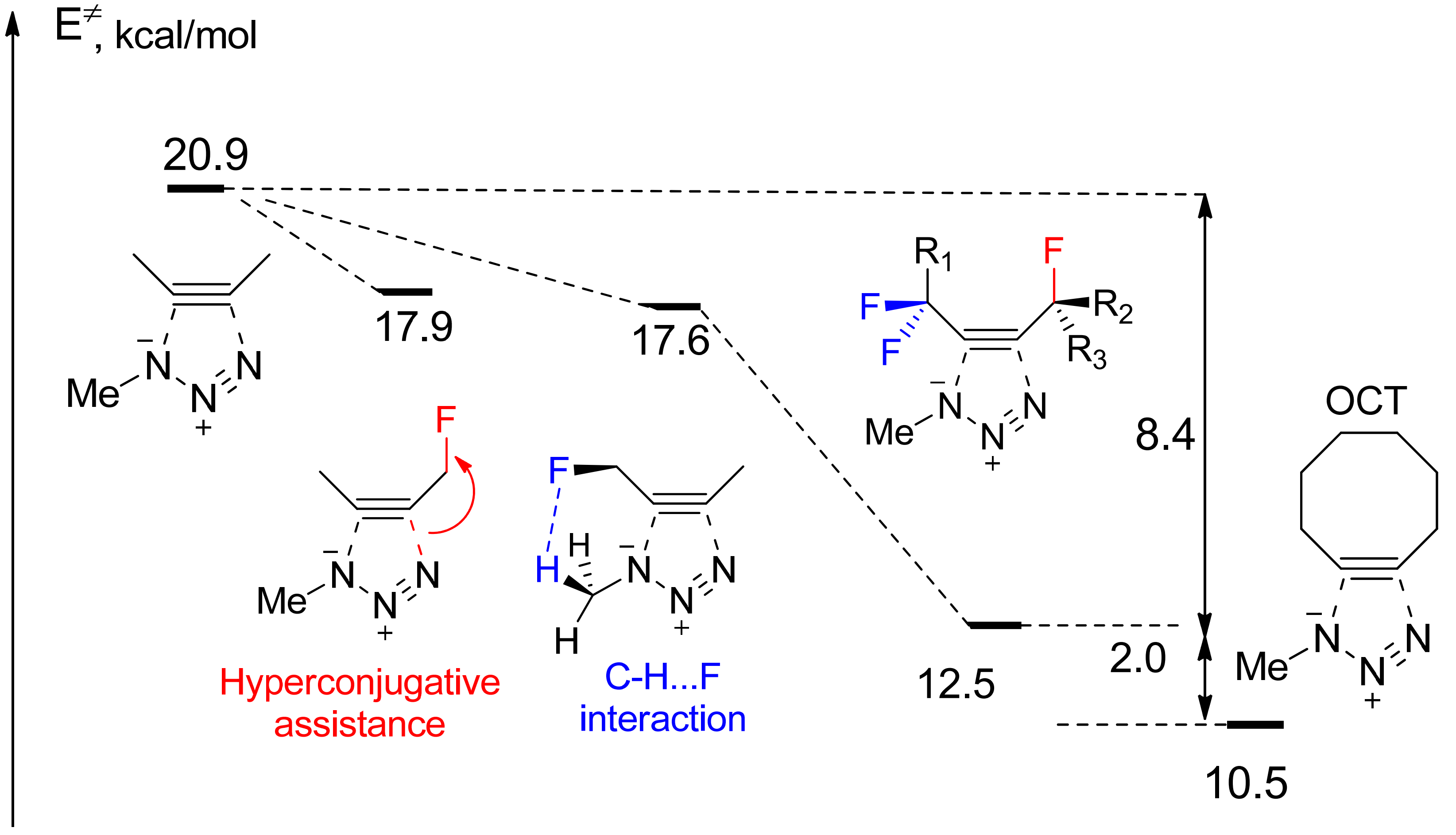


1.7 kcal/mol translates to 20-fold rate increase

Gold, Schevchenko, Bonus, Dudley, Alabugin, *JOC,* **2012**, *77*, 75.

B3LYP/6-31G(d)

Helping two molecules to connect: combining electronic effects for TS stabilization

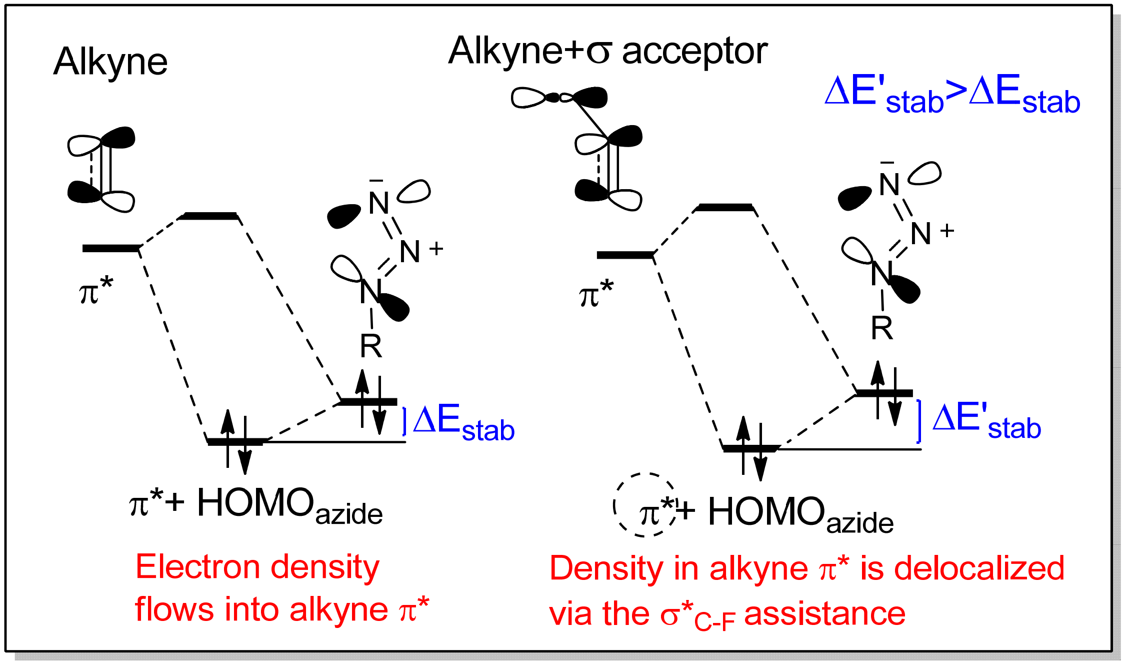


Blend activating effects removes 80% of difference between butyne and cyclooctyne

Gold, Schevchenko, Bonus, Dudley, Alabugin, *JOC*, **2012**, *77*, 75.

Electronic basis for selective TS stabilization:

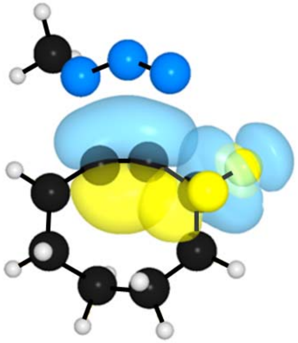
2. Assistance to bond formation:



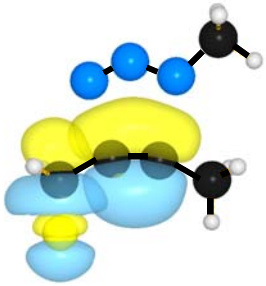
Electron density flows into alkyne π^*

Density in alkyne π^* is delocalized via the $\sigma^*_{C\text{-}F}$ assistance

The increase in the alkyne π^* population due to the C…N bond forming interaction augments the effect of propargylic acceptor on alkyne bending

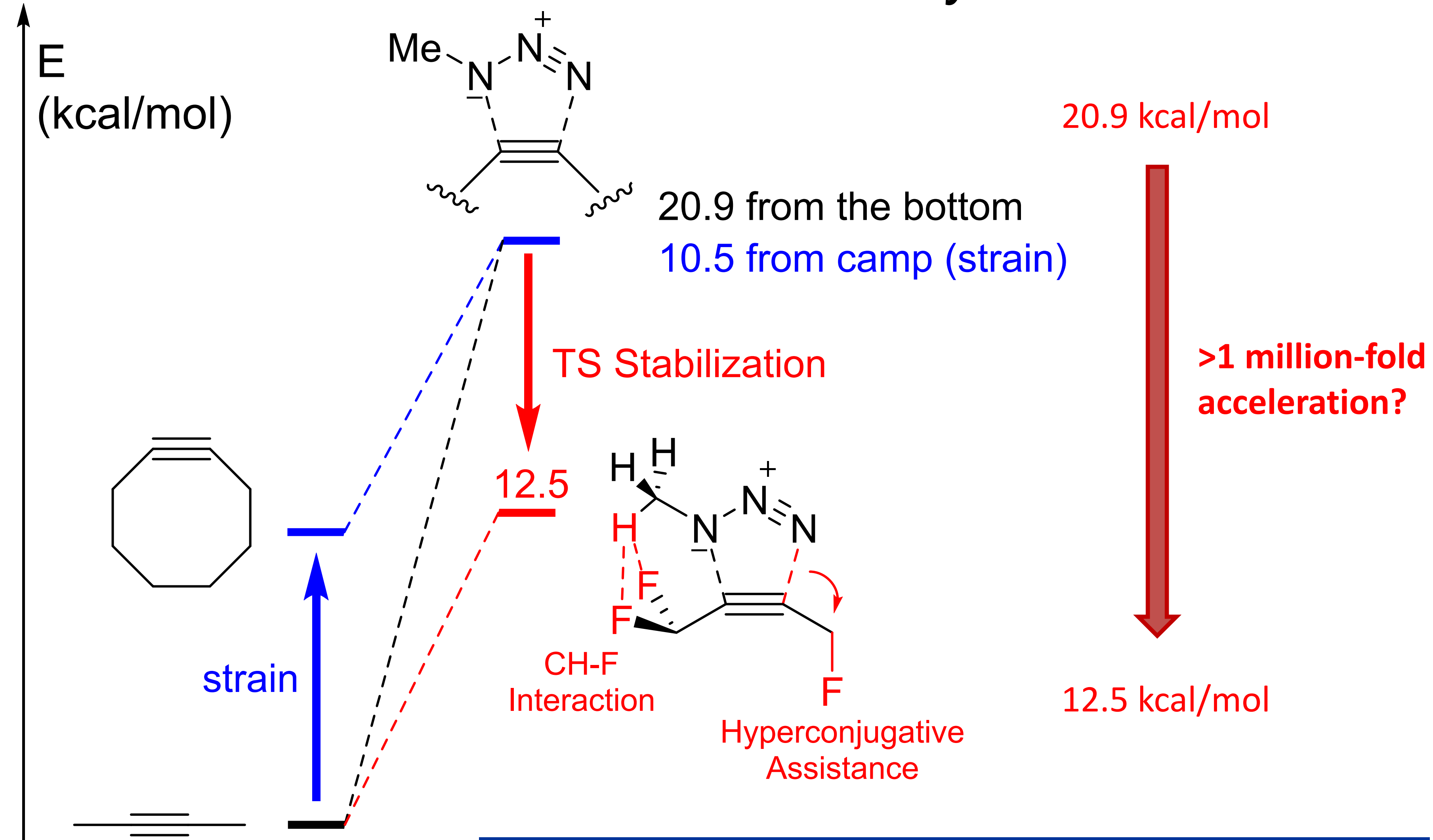


Overlap in DIFO is suboptimal.



Antiperiplanar arrangement is better

Our climb is only ~20% harder than from camp and we haven’t introduced any strain



E (kcal/mol)

20.9 from the bottom

10.5 from camp (strain)

TS Stabilization

12.5

strain

CH-F Interaction

Hyperconjugative Assistance

20.9 kcal/mol

>1 million-fold acceleration?

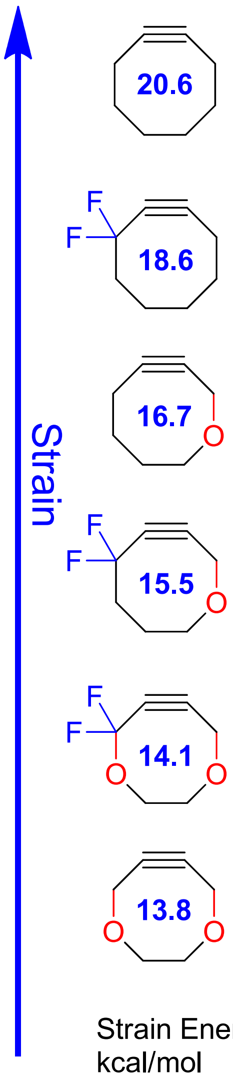
12.5 kcal/mol

Can we design alkynes that surpass cyclooctyne in stability and reactivity?

B3LYP/6-31G(d)

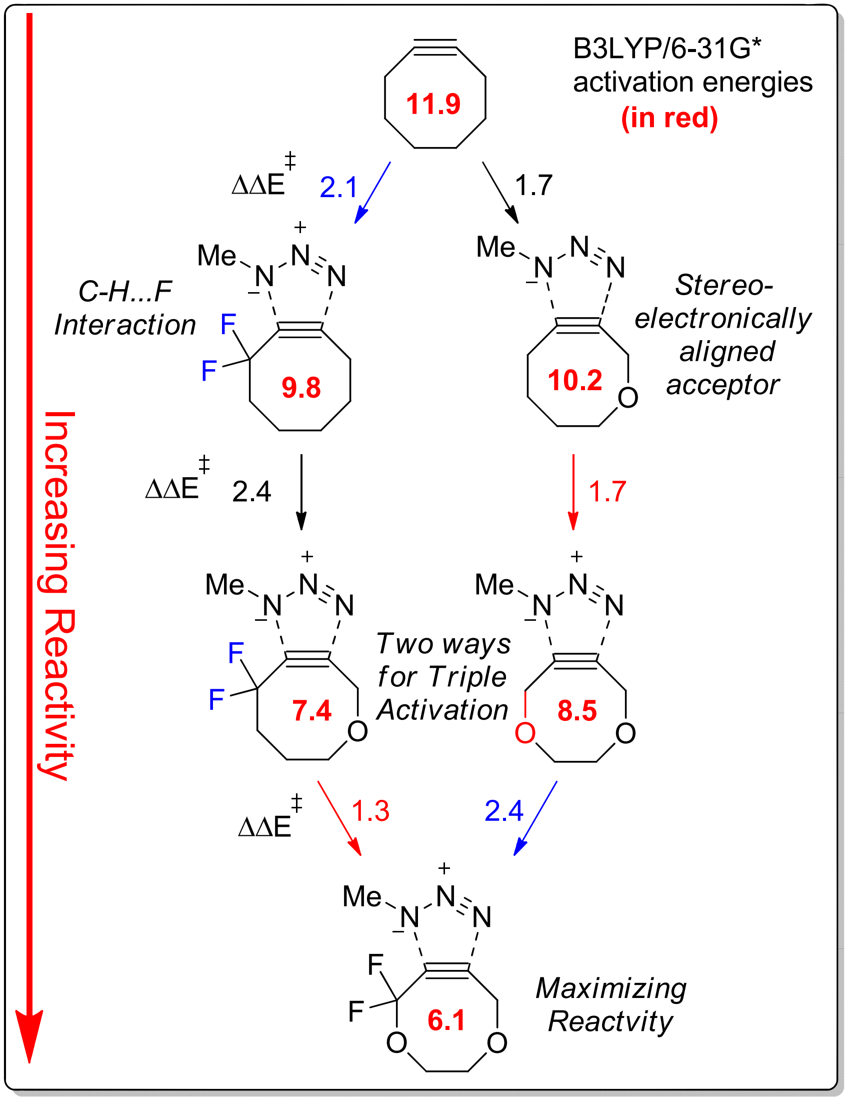
Click reagents with tunable reactivity: combining strain with endocyclic acceptors

Endocyclic acceptors relieve strain... ***...without sacrificing reactivity***



One is better than two

Strain Energy, kcal/mol



B3LYP/6-31G* activation energies **(in red)**

C-H...F Interaction

Stereo-electronically aligned acceptor

Two ways for Triple Activation

Maximizing Reactvity

Increasing Reactivity

11.9 kcal/mol

>10,000-fold acceleration?

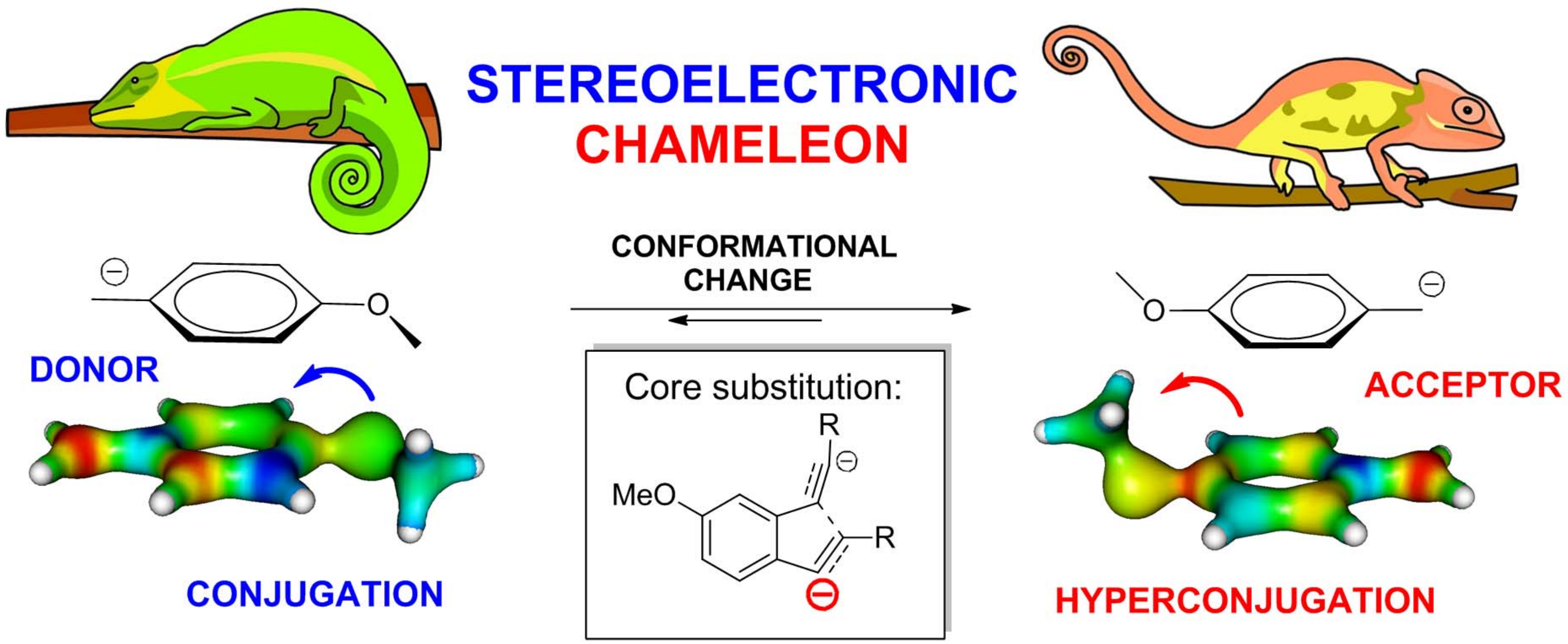
6.1 kcal/mol

B3LYP/6-31G(d), CPCM (H_2O)

J. Am. Chem. Soc. **2013**, *135*, 1558.

Story #3

MeO-group as a stereoelectronic chameleon, or how to take advantage of $\sigma^*_{O\text{-}C}$ acceptor ability to open communication between orthogonal orbitals



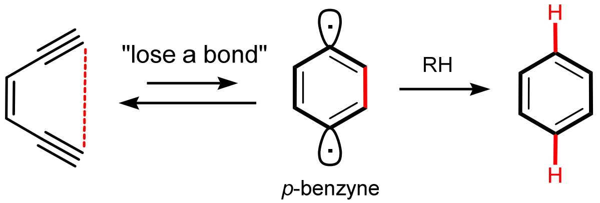
Story #3

Hyperconjugation in the absence of overlap: any hope?

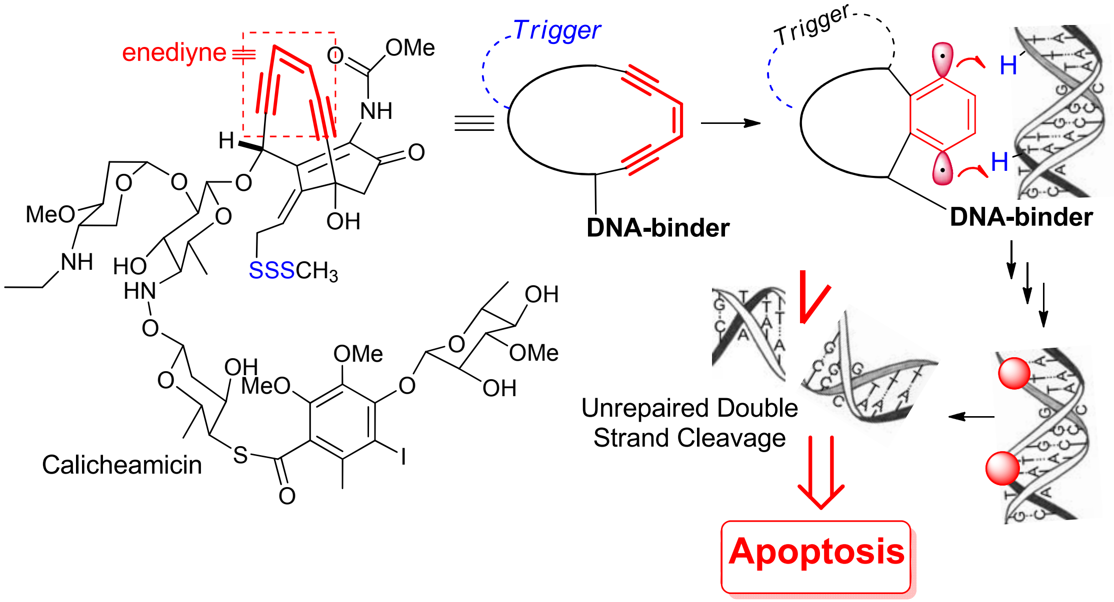
> "… enediynes are the most potent family of anticancer agents discovered ..."
>
> Galm et. al. Chem. Rev. 2005

This chemistry allows double-stranded DNA cleavage only if **both** H-abstractions work perfectly and target the two opposite strands precisely

Bergman cyclization



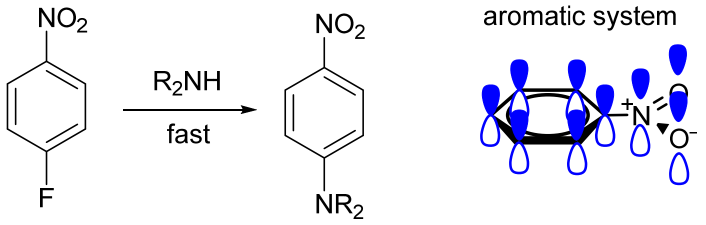
Bergman, R.G. *Acc. Chem. Res.* 1973, 25



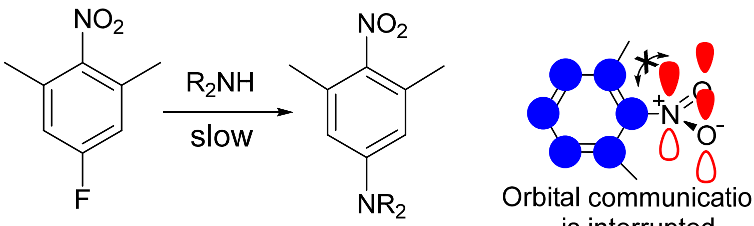
How to control Bergman cyclization?

Substituent control of Bergman cyclization: what options do we have?

Conjugation: sensitive to orbital overlap



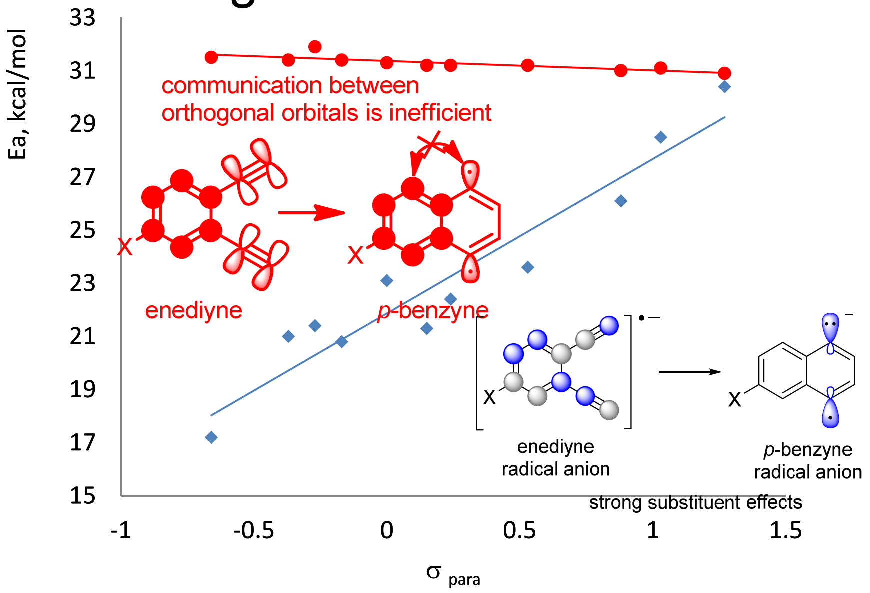
Acceptor activates aromatic system



Orbital communication is interrupted

Steric inhibition of resonance

No communication between orthogonal functionalities

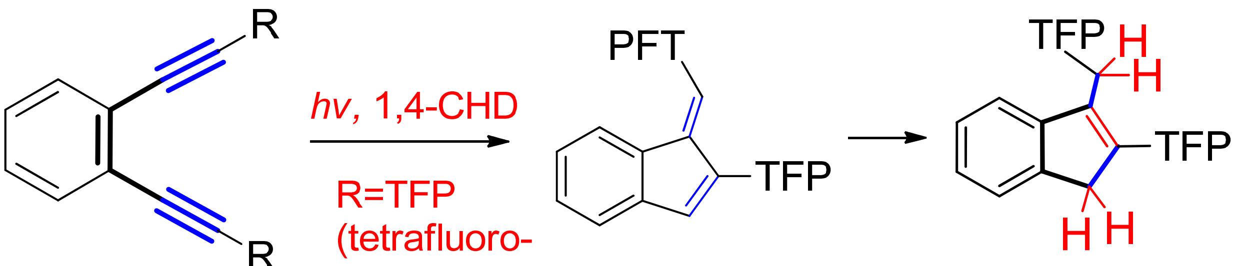


Substituent effects can be activated by electron injection

Alabugin, Manoharan, *JACS*, **2003**, 4495

Mohamed, Peterson, Alabugin, *Chem. Rev.*, **2013**, 7089

C1-C5 cyclization – a way to increase DNA cleaving ability of enediynes

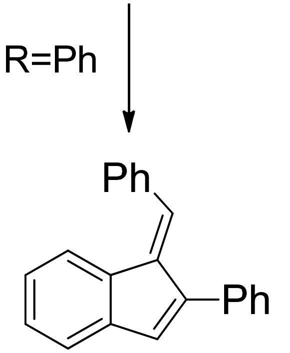


hv, 1,4-CHD

R=TFP (tetrafluoro-pyridinyl)

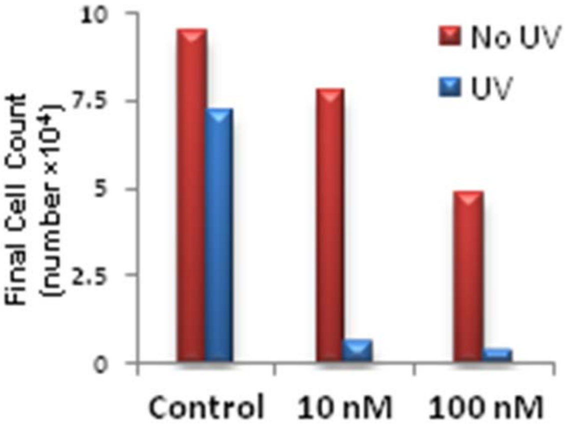
Alabugin, Kovalenko, JACS, **2002**

R=Ph



Whitlock, JOC, **1969**
Reducing agent:
Li, C_6H_{10}

Four "H-abstractions" increase efficiency of localized DNA damage

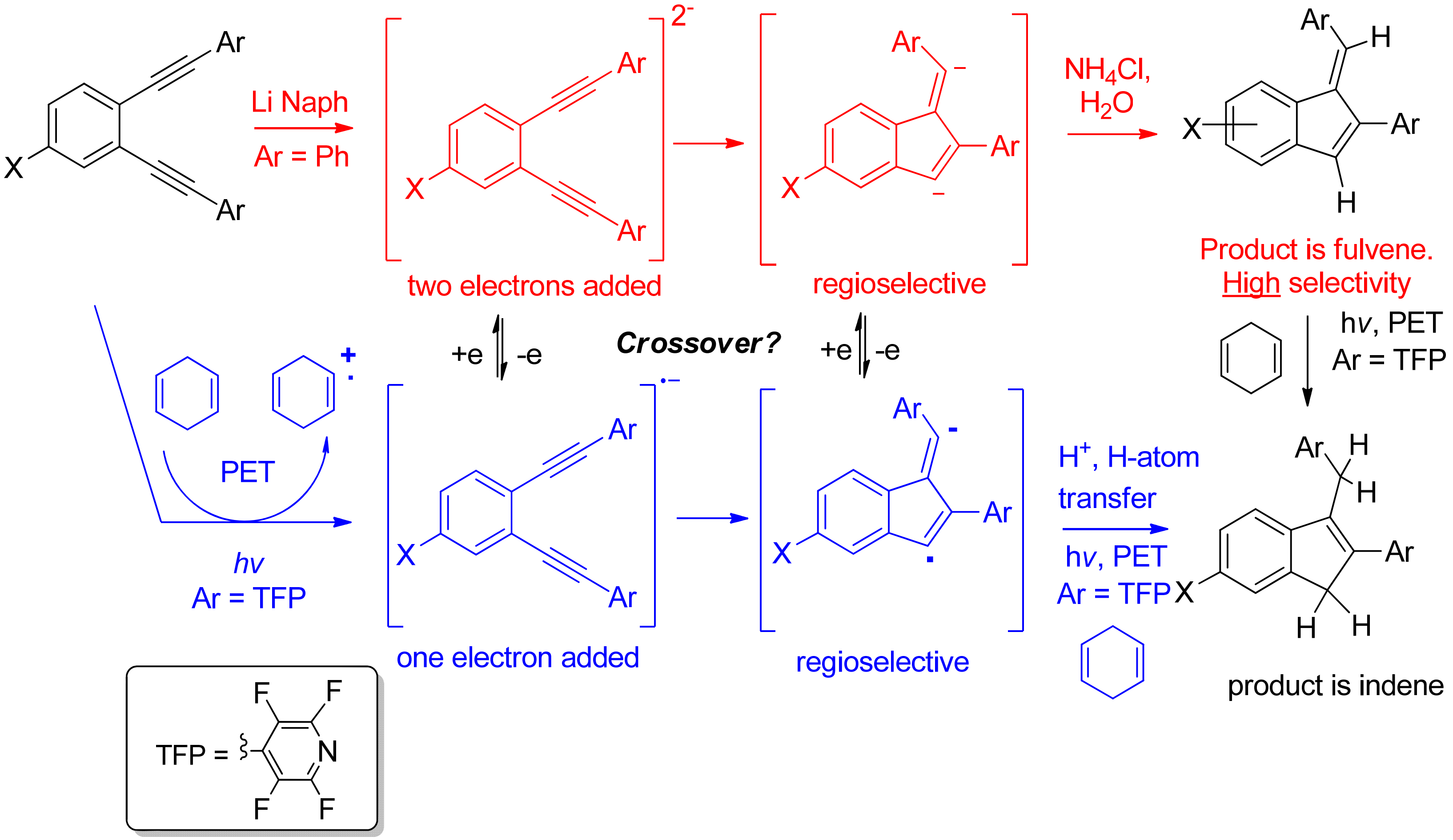


Pronounced phototoxicity against multidrug resistant cancer cells

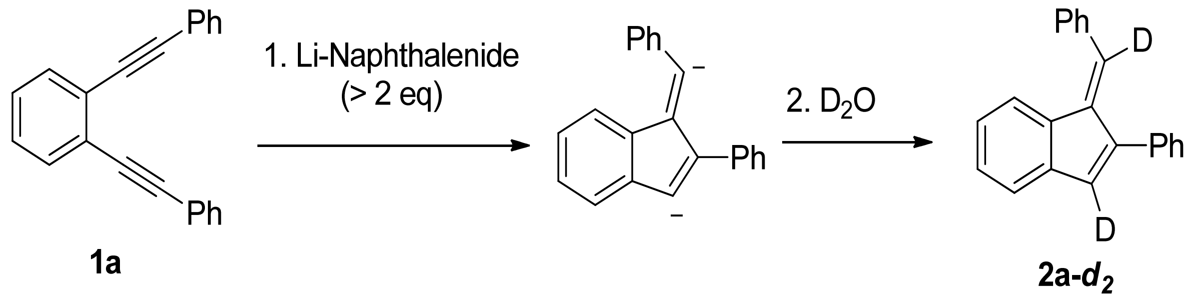
Further details: *ACIE* **2006**, 3666. *PNAS*, **2007**, 13016. Reviews: Applications: *OBC*, **2012**, 3974. Fundamentals: *Chem. Rev*., **2013**, 7089.

Up to 70% of ds DNA cleavage (calicheamicin: ~25 % of ds cleavage)

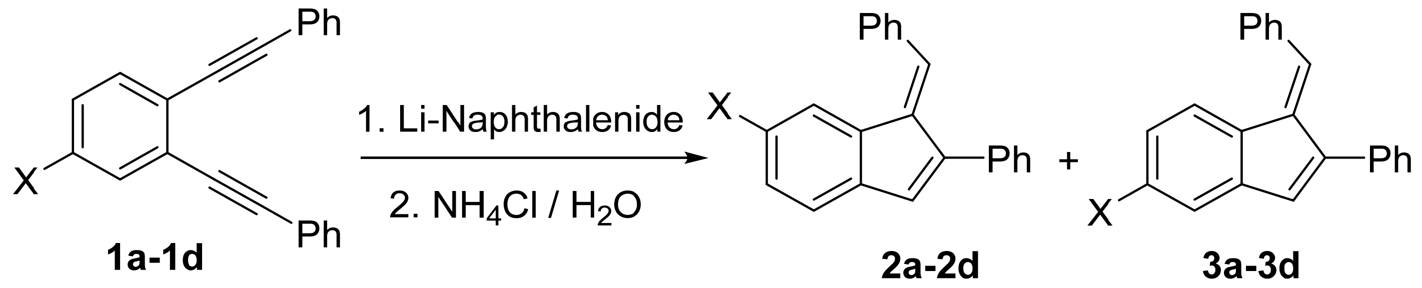
Two reductive paths from enediynes to fulvenes



Enediyne cyclizations induced by Li naphthalenide



The intermediacy of a dianion is consistent with the need for two equivalents of the reducing agent

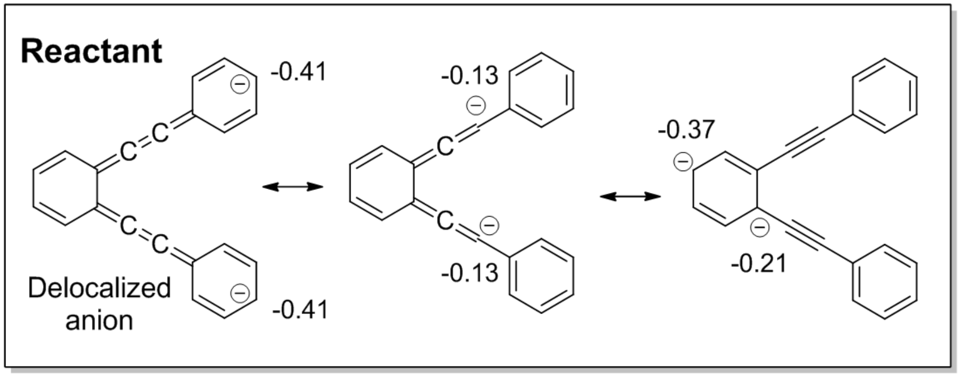


Cyclizations of enediynes with a remote substituent at the benzene core are regioselective

	X =	**2 : 3**	Yield
1a	H	NA	66%
1b	Me	2.2 : 1	74%
1c	F	8.1 : 1	71%
1d	MeO	>19 : 1	38%

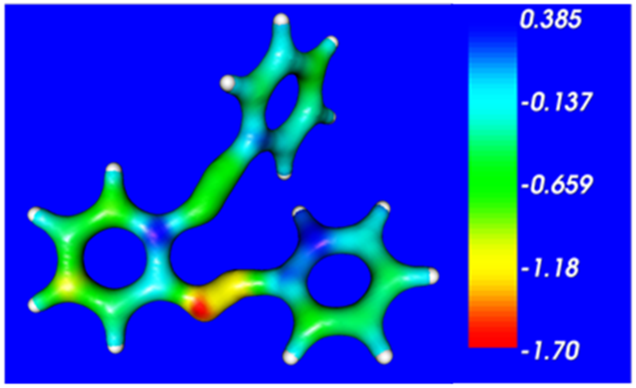
What controls reactivity?

The evolution of electron density distribution along the reaction path



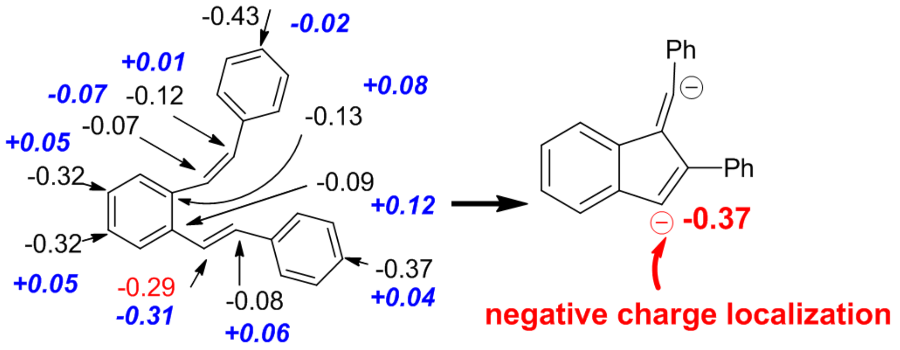
Transition State

MO crossing at the Transition State: the molecule distorts to allow orbital mixing



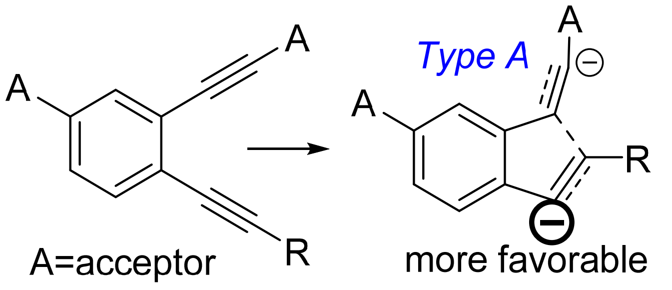
Selected NBO charges (black) and changes in charge in TS relative to the reactant (blue).

Negative and positive values indicate an increase and a decrease in electron density, respectively

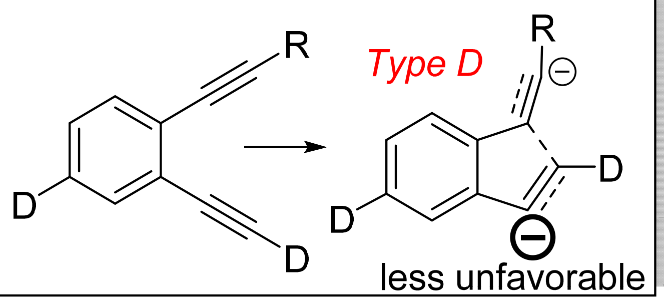


Where to put substituents?

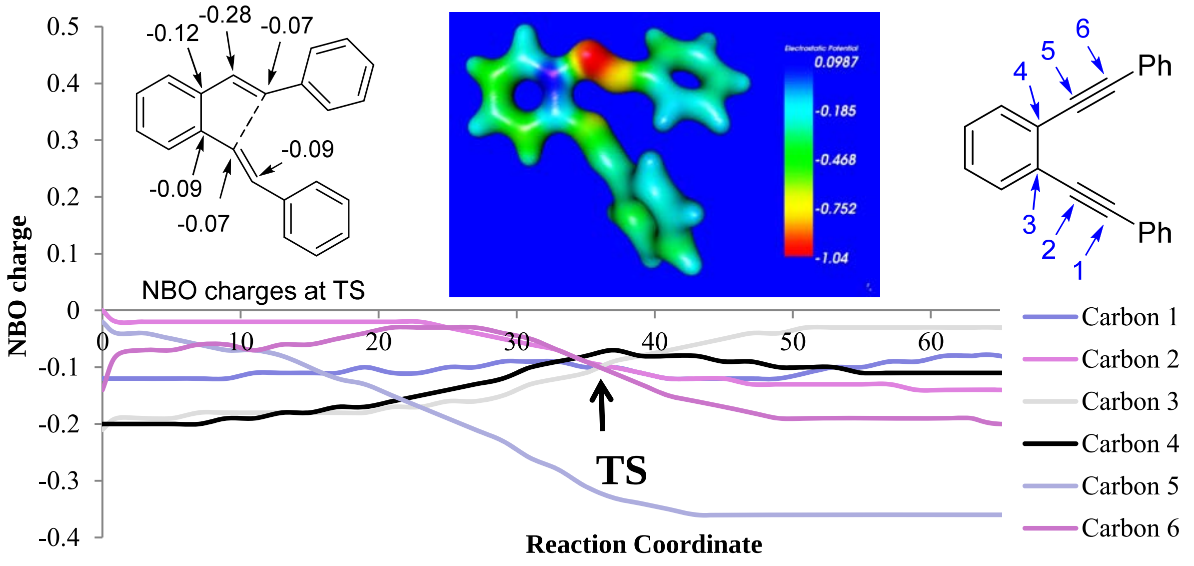
Selective TS stabilization



Selective TS destabilization

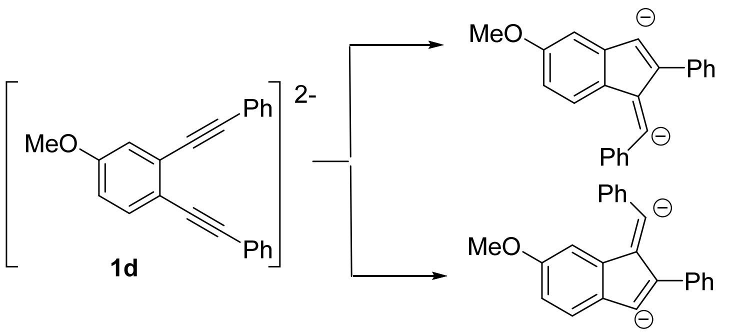


Expected substituent effects associated with the evolution of electron density distribution along the reaction path



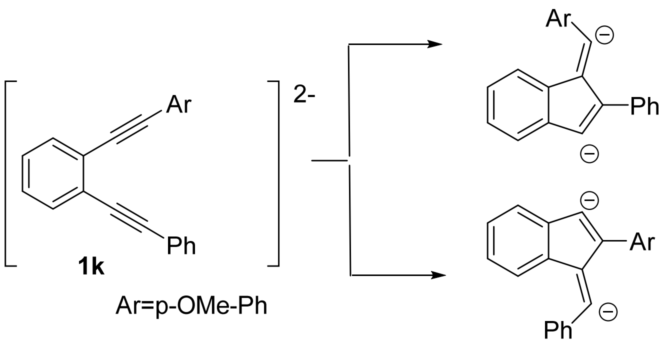
We should place acceptor A para to the developing endocyclic anion in order to provide stabilization in the (non-planar!) TS

MeO: a para-directing anion-stabilizing **acceptor** group?



1d

$\Delta E^\ddagger$	ΔE	experimental ratio:
25.5	-16.7	**1:19**
24.0	-15.6	



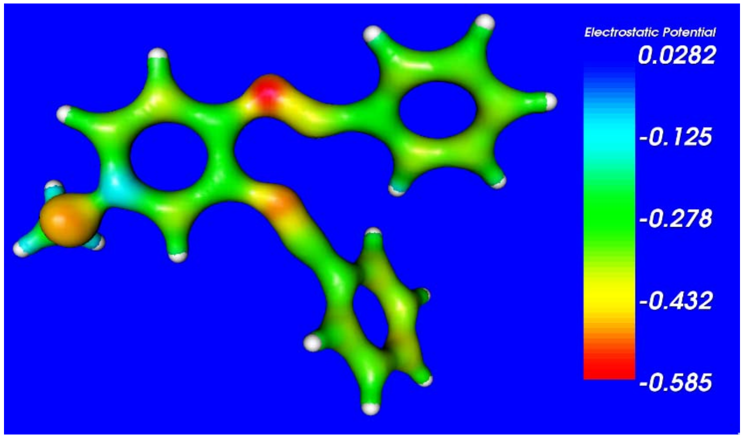
1k

Ar=p-OMe-Ph

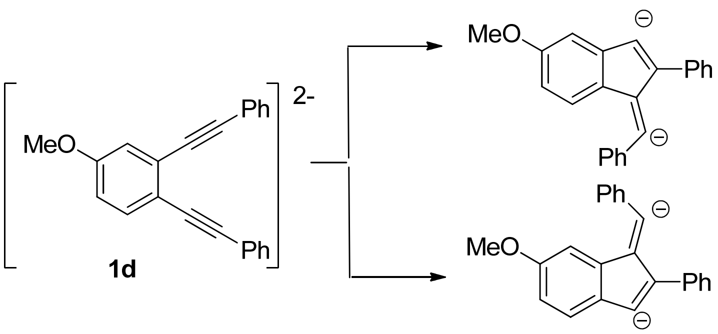
$\Delta E^\ddagger$	ΔE	
25.8	-16.3	**5:1**
26.4	-17.7	

OMe behaves as an acceptor!

Let's examine the preferred TS



MeO-group as a stereoelectronic chameleon



1d

$\Delta E^{\ddagger}$	ΔE	experimental ratio:
25.5	-16.7	**1:19**
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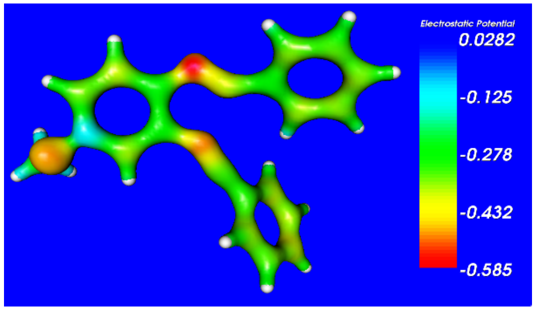
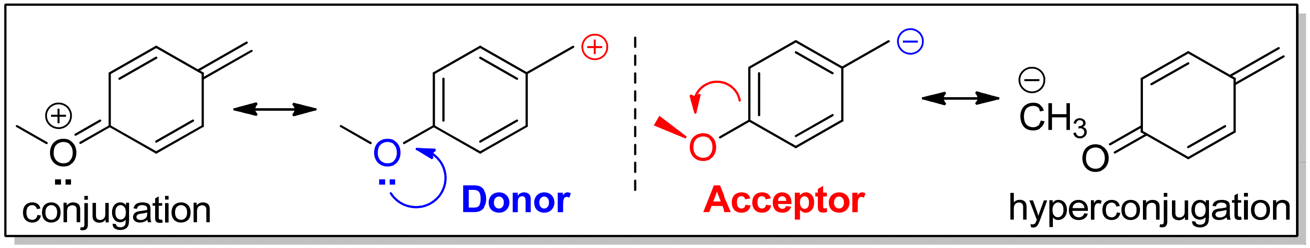
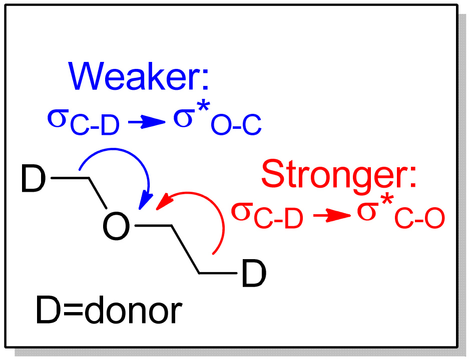
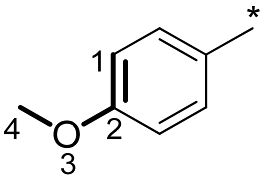


OMe also rotated!

The two faces of the OMe group:



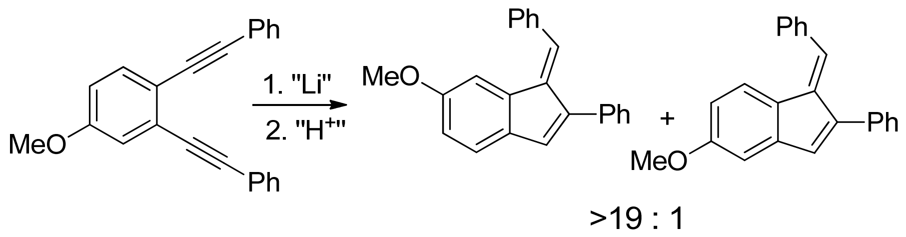




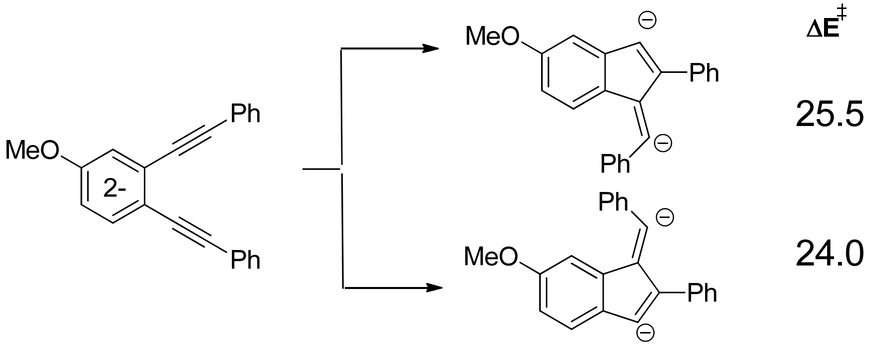
	M06-2X/6-31+G**, kcal/mol		
Ψ(C1,C2,O3,C4)	Cation	Radical	Anion
0°	0	0	1.6
	12.7	3.2	0

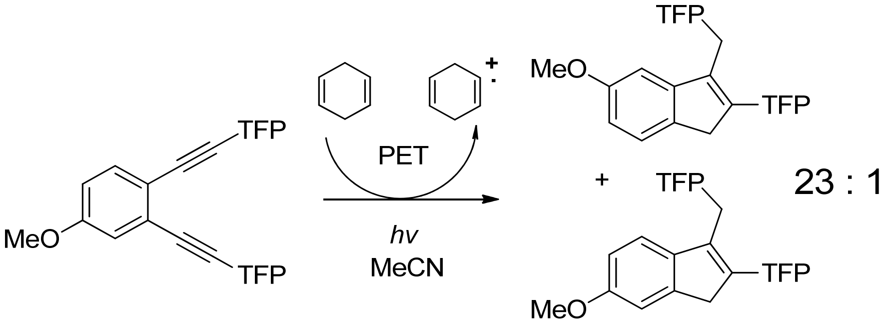
Even the O-C bond can behave as an acceptor when paired with a strong donor

Substituent effects as a probe of diverging mechanistic paths

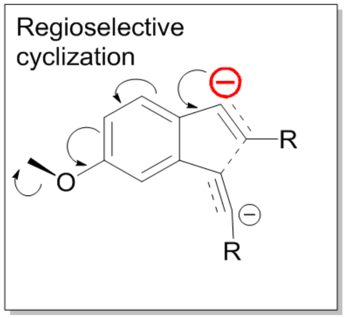


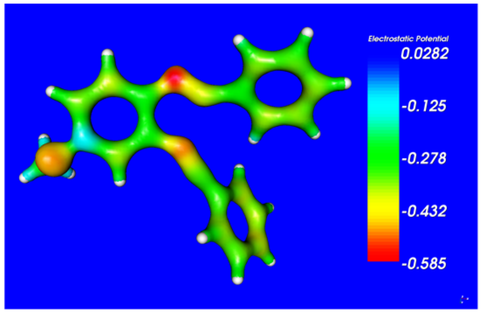
M06-2X/6-31+G** barriers





Selectivity is consistent with reductive cycloaromatization



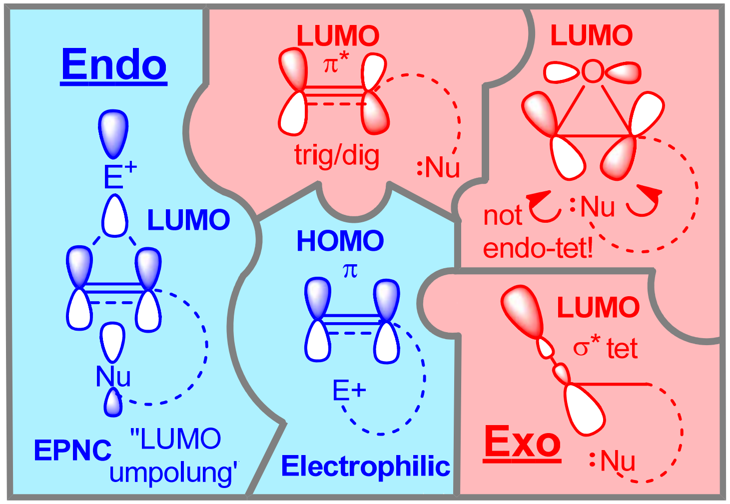


Paul Peterson (practicing his chameleon skills)

Org. Lett. **2013**, 15, 2238

Baldwin rules

and stereoelectronic factors involved in the formation of cyclic structures

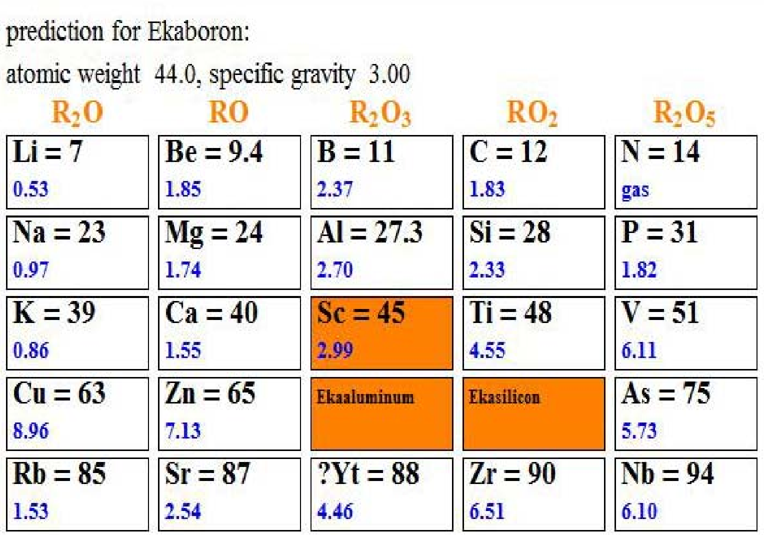


Igor Alabugin,

Florida State University

Predictions in chemistry

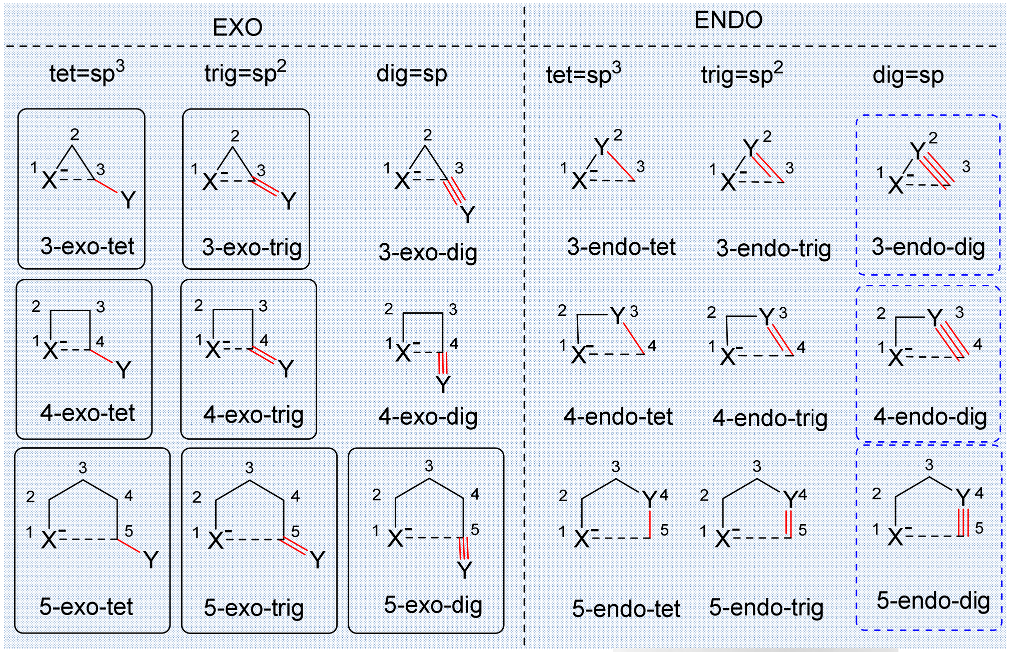
How many do you know?



prediction for Ekaboron:

atomic weight 44.0, specific gravity 3.00

R_2O	RO	R_2O_3	RO_2	R_2O_5
Li = 7 0.53	Be = 9.4 1.85	B = 11 2.37	C = 12 1.83	N = 14 gas
Na = 23 0.97	Mg = 24 1.74	Al = 27.3 2.70	Si = 28 2.33	P = 31 1.82
K = 39 0.86	Ca = 40 1.55	Sc = 45 2.99	Ti = 48 4.55	V = 51 6.11
Cu = 63 8.96	Zn = 65 7.13	Ekaaluminum	Ekasilicon	As = 75 5.73
Rb = 85 1.53	Sr = 87 2.54	?Yt = 88 4.46	Zr = 90 6.51	Nb = 94 6.10



Started with lots of data,
Put them into a table,
Made predictions

?

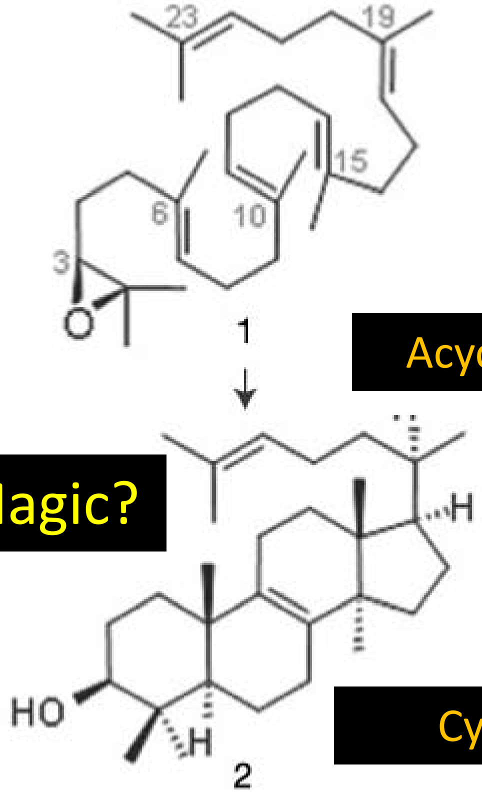
Cycles in chemistry

They are everywhere!

~90% of molecules found in nature possess a carbo- or heterocyclic unit:
R. S. Bon and H. Waldmann, Acc. Chem. Res., 2010, **43**, 1103

Special enzymes:
"cyclases"

Nature makes formation of cycles to look easy

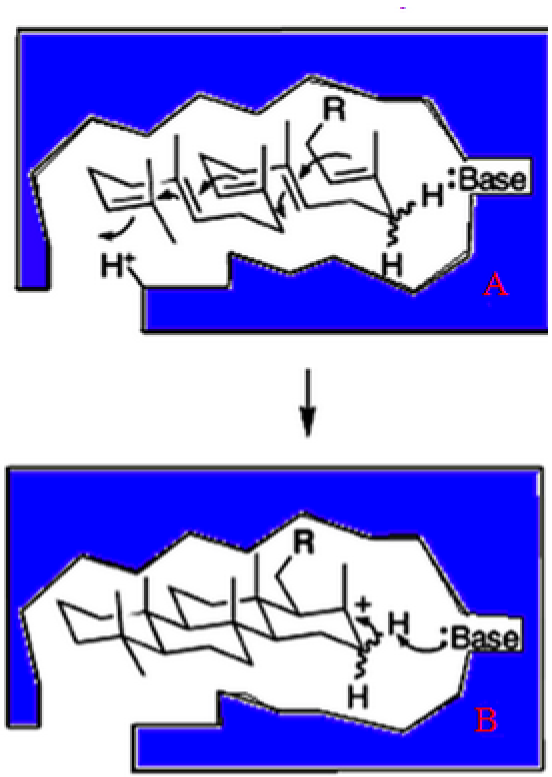


Acyclic

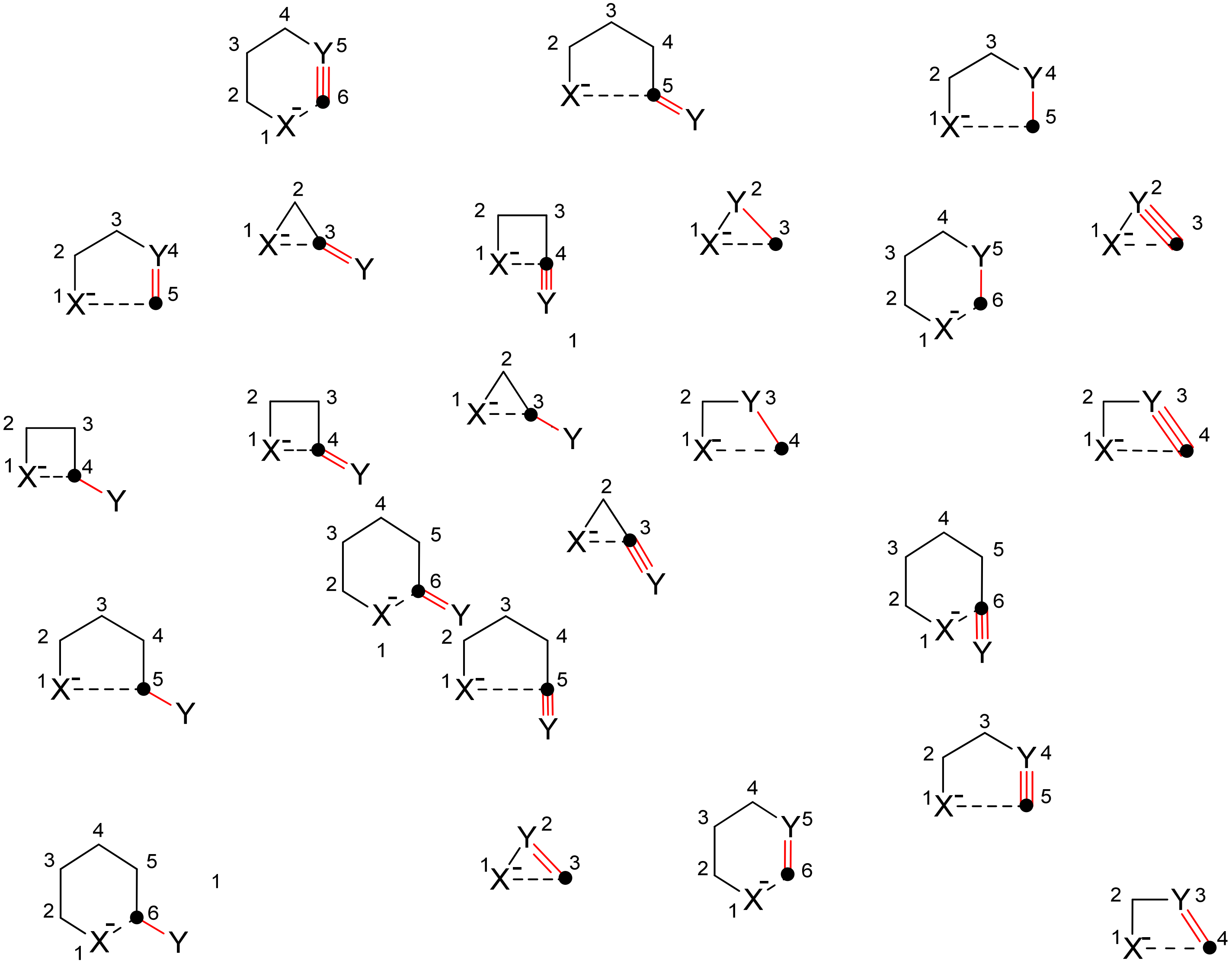
Magic?

Cyclic

Thoma, R. et al. Nature 432, 118-122



The dizzying variety of cyclization patterns



A glimpse of order in cyclization patterns

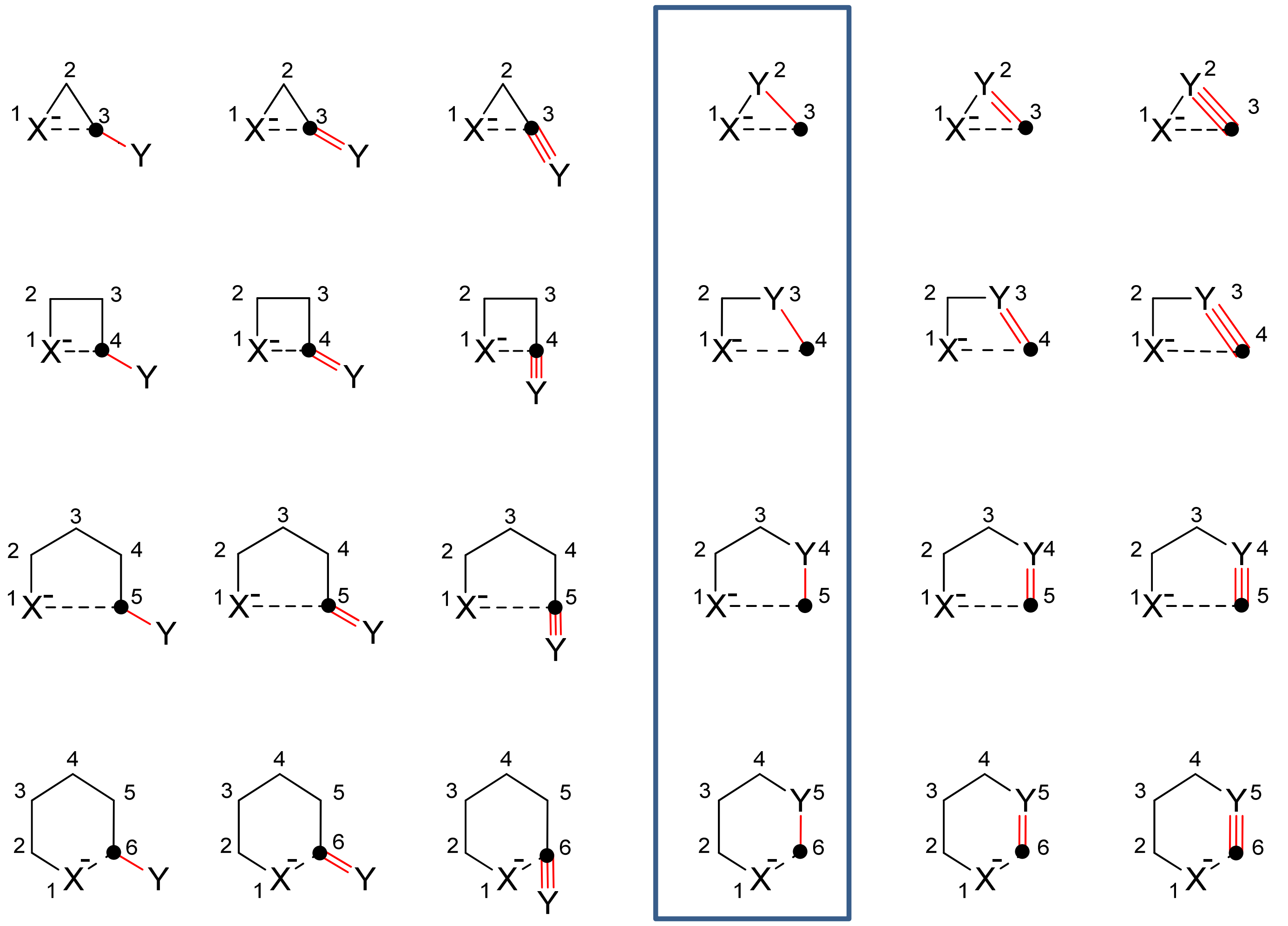
Will not give a cycle

5+1 ways to make a 3-membered cycle

5+1 ways to make a 4-membered cycle

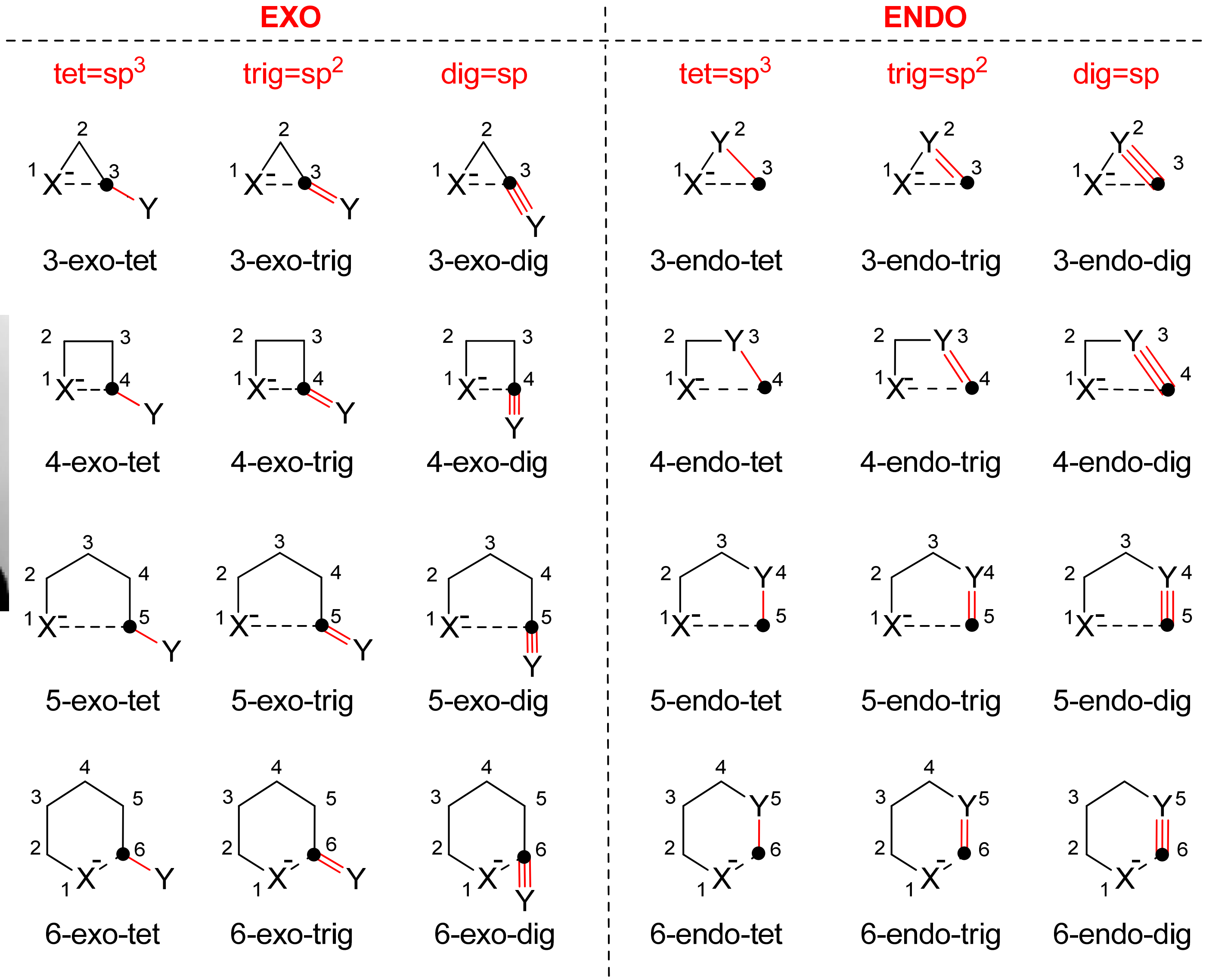
5+1 ways to make a pentagon

5+1 ways to make a hexagon



Order out of chaos

Way to classify cyclizations



3-exo-tet 3-exo-trig 3-exo-dig 3-endo-tet 3-endo-trig 3-endo-dig

4-exo-tet 4-exo-trig 4-exo-dig 4-endo-tet 4-endo-trig 4-endo-dig

5-exo-tet 5-exo-trig 5-exo-dig 5-endo-tet 5-endo-trig 5-endo-dig

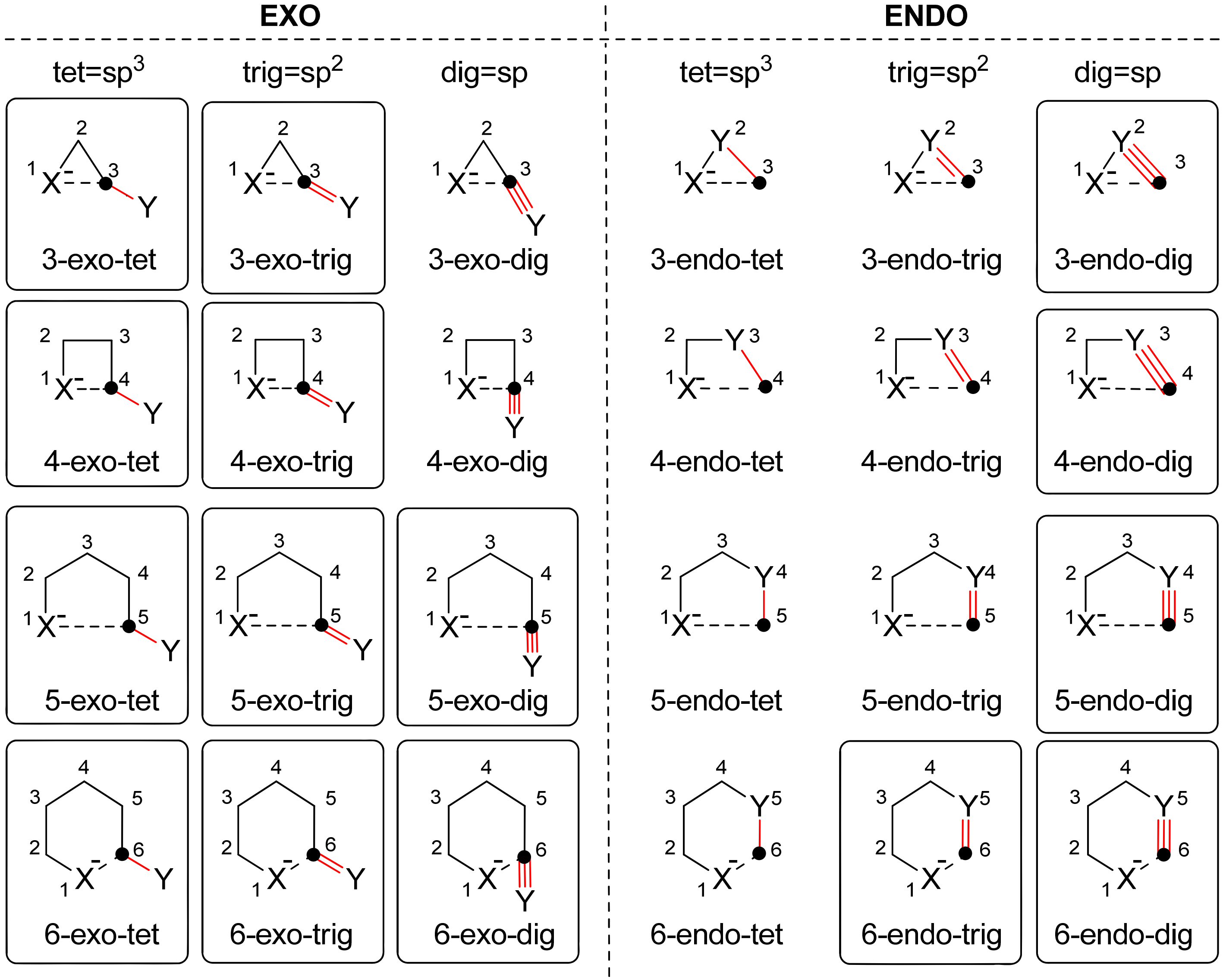
6-exo-tet 6-exo-trig 6-exo-dig 6-endo-tet 6-endo-trig 6-endo-dig

Jack Baldwin,
MIT, Oxford

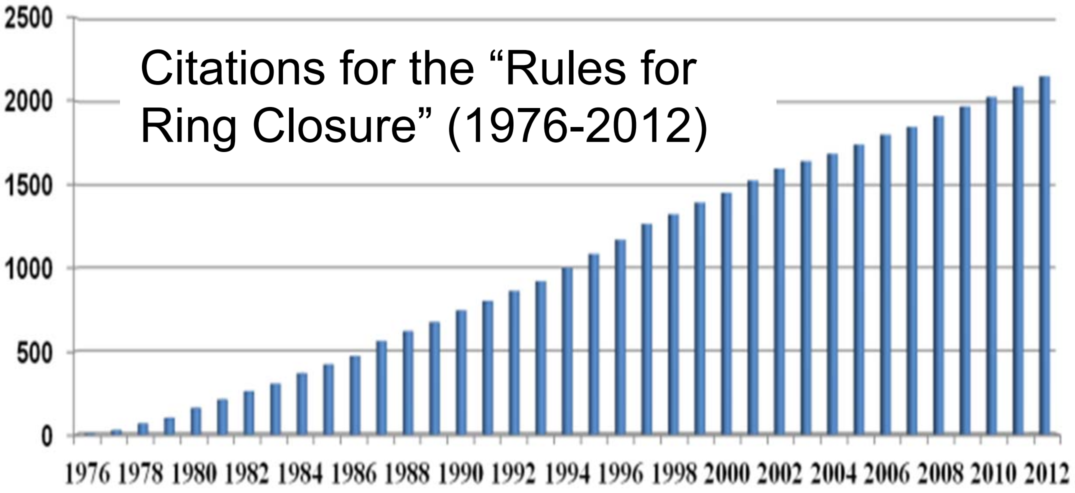
Taking one step further: Baldwin rules

Predictions of Favorable and Unfavorable Reactions

Favorable reactions are boxed

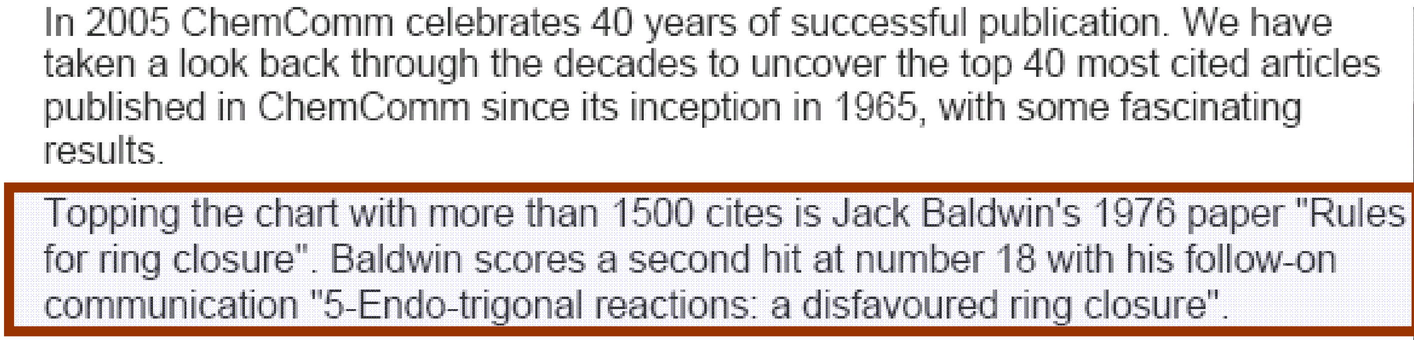


The impact of the Baldwin rules

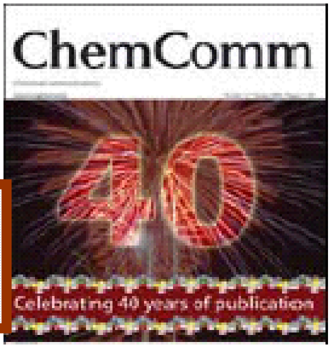

Citations for the “Rules for Ring Closure” (1976-2012)

J. Baldwin, *Chem. Commun.*, **1976**, 734

One of the most successful sets of stereoelectronic guidelines in history (the most cited paper for the first 40 years of *Chem. Comm*.)


In 2005 ChemComm celebrates 40 years of successful publication. We have taken a look back through the decades to uncover the top 40 most cited articles published in ChemComm since its inception in 1965, with some fascinating results.

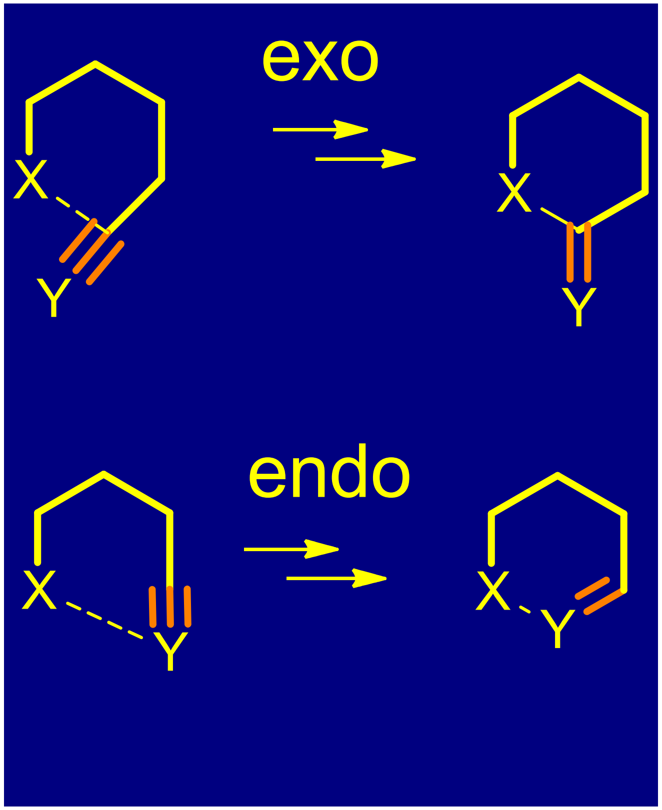
Topping the chart with more than 1500 cites is Jack Baldwin's 1976 paper "Rules for ring closure". Baldwin scores a second hit at number 18 with his follow-on communication "5-Endo-trigonal reactions: a disfavoured ring closure".



Understanding the rules:

Terminology and Nomenclature

Two way for making a cycle



Exo: the breaking bond is outside of the forming cycle

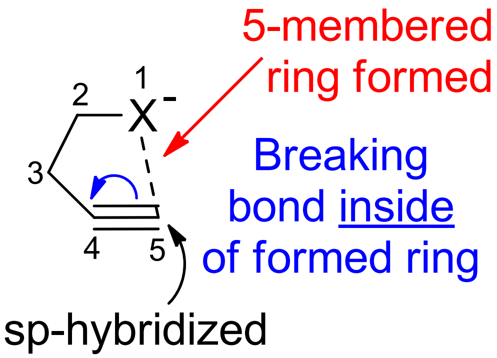
Endo: The breaking bond is inside of the forming cycle

Rules are different for exo- and endo-cyclizations

Are there any other important parameters?

Baldwin’s Nomenclature for Ring Formation

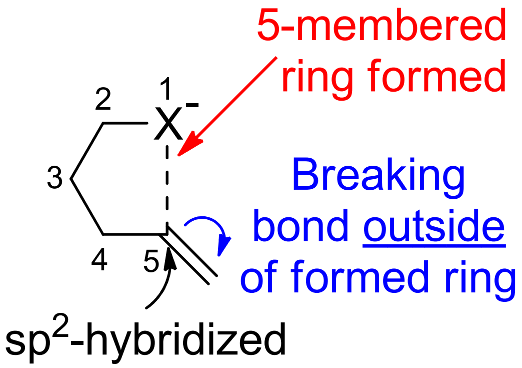
- Three factors:
    - Size of the ring being formed
    - Location of the breaking bond (*endo*, *exo*)
    - Hybridization of the breaking bond (sp^3=tet, sp^2=trig, sp=dig)



5-membered ring formed

Breaking bond inside of formed ring

sp-hybridized



5-membered ring formed

Breaking bond outside of formed ring

sp^2-hybridized

Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

Basis for the rules

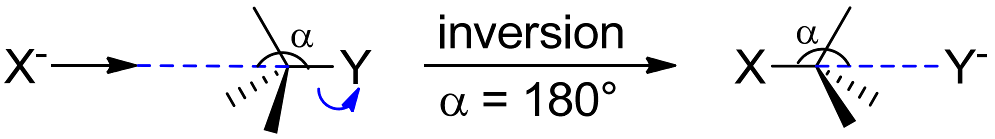
The central hypothesis:

Favored reactions will be those in which length and nature of linking chain enables terminal atoms to achieve required trajectory to form final ring bond

Disfavored reactions would require severe bond angle and distances distortion, so the desired RC will be difficult (if available, alternative pathways will dominate)

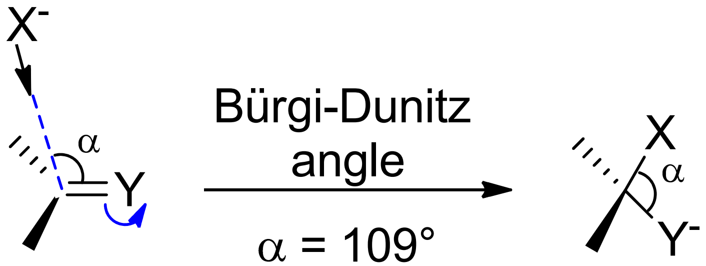
Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734

Reaction trajectories, or how to make and break bonds



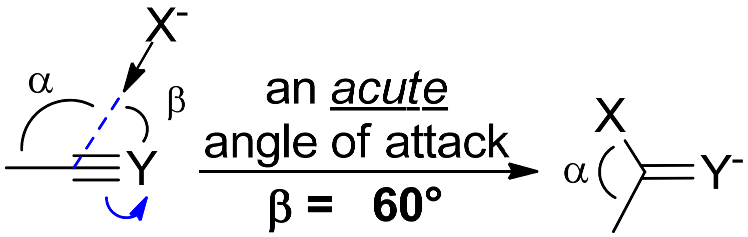
Tetragonal

Jack Dunitz, ETH, Dec. 1, 2014

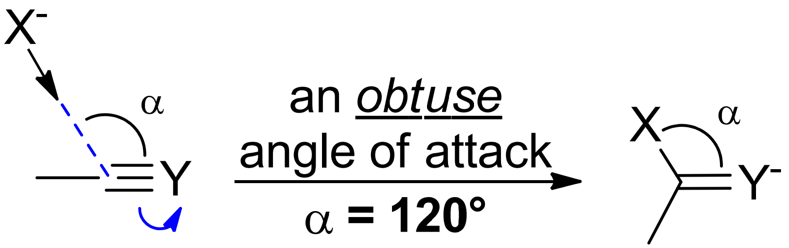


Trigonal

Choose one of the two alternatives for alkynes:



Baldwin's choice

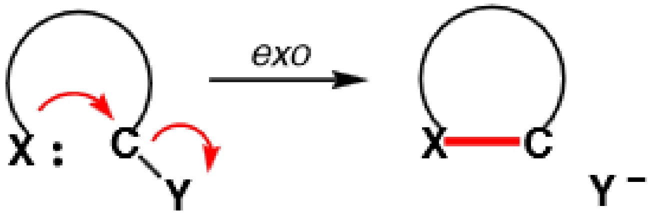


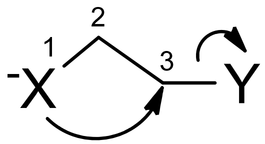
Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

Let’s see where these trajectories will take us

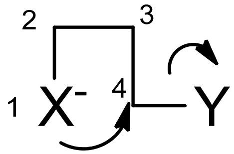
Breaking a single bond: “tetrahedral systems”

<u>all</u> exo-tet cyclizations are **favored**

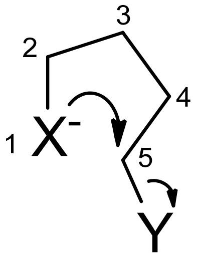




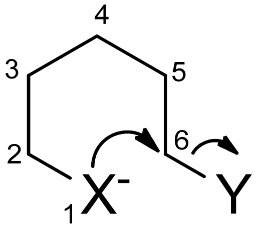
3-exo-Tet



4-exo-Tet

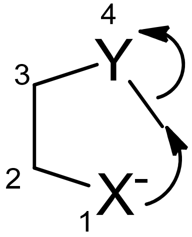


5-exo-Tet

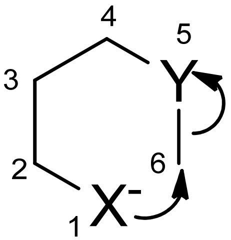


6-exo-Tet

<u>all</u> endo-tet cyclizations are **unfavored** for n less than 7



5-endo-Tet

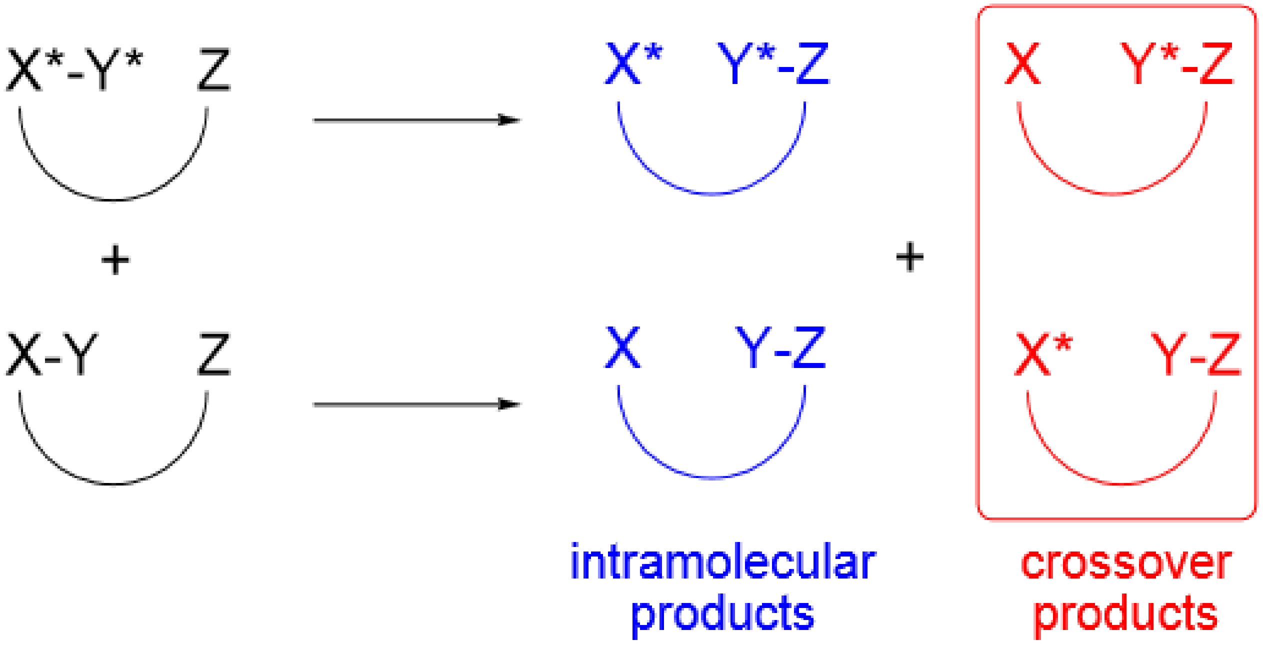


6-endo-Tet

Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

Tet cyclizations: examples

Endo-cyclic restriction test: How large should be the cycle for the endo-tet TS to become possible?

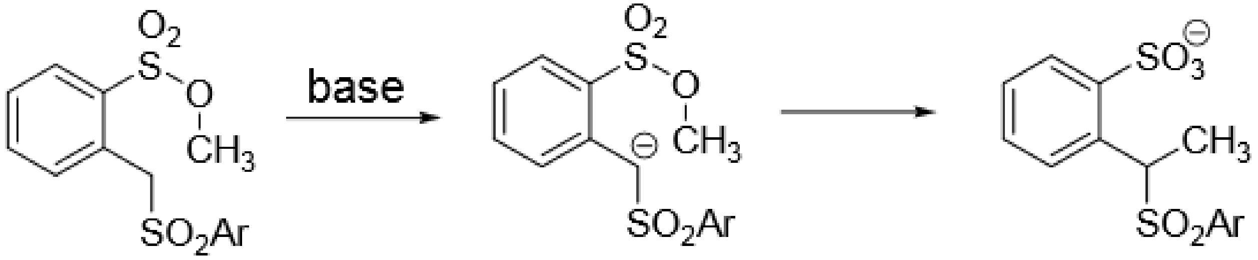


Beak, *Acc Chem Res*, **1992**, *25*, 215

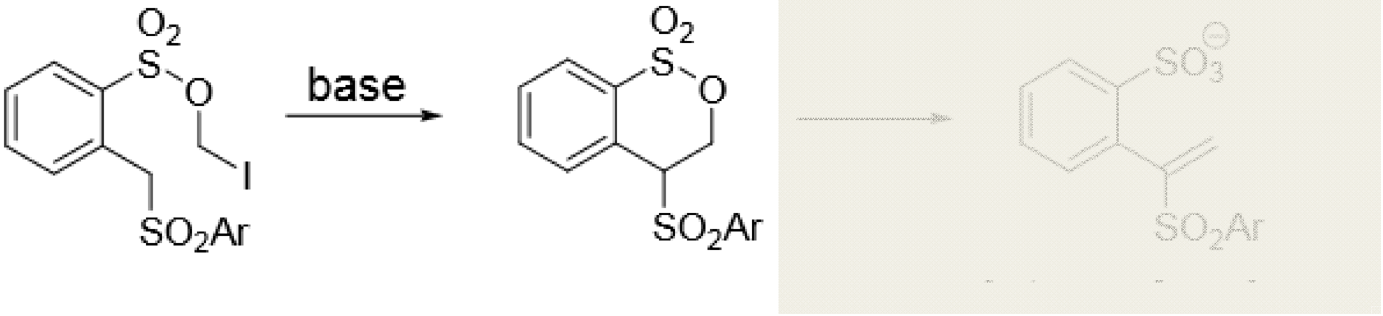
From Evans, CHM206, Harvard
http://isites.harvard.edu/fs/docs/icb.topic776365.files/lecture%206.pdf

Endo-cyclic restriction test, continued

How large should be the cycle for the endo-tet TS to become possible?



Only intermolecular

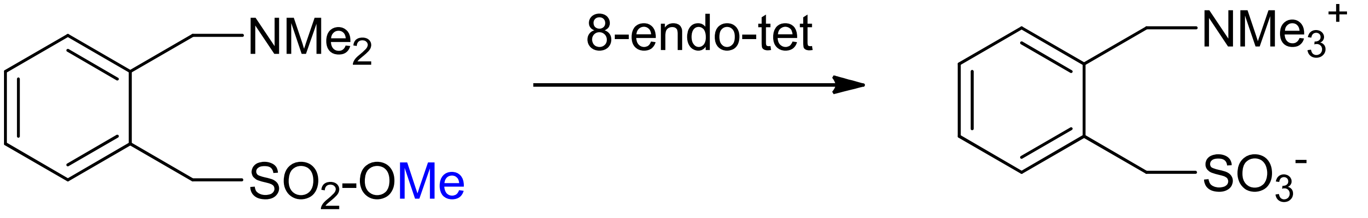


Only intramolecular

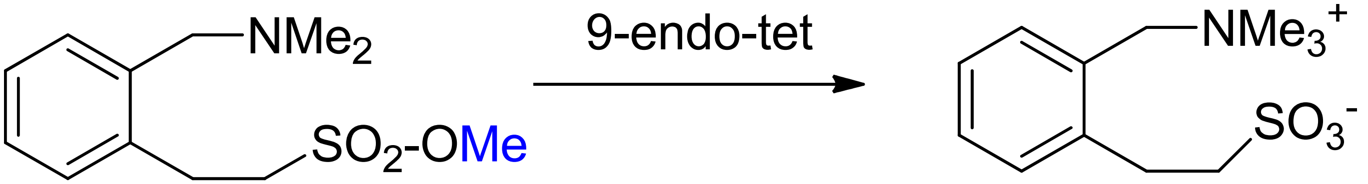
Can you explain why?

Eschenmoser, *Helvetica Chim. Acta* **1970**, *53*, 2059.

Endo-cyclic restriction test, continued



Only intermolecular



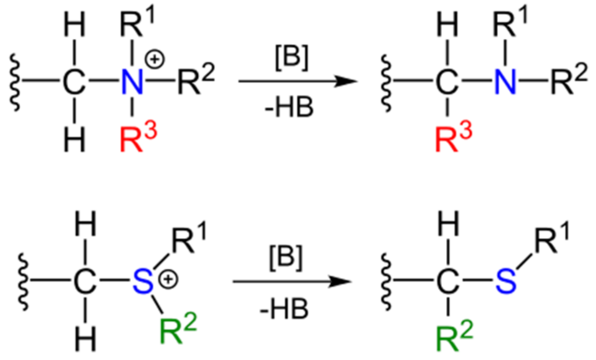
84% intermolecular,
16% intramolecular

Favorable endo cyclization modes required transition state ring sizes of at least nine atoms

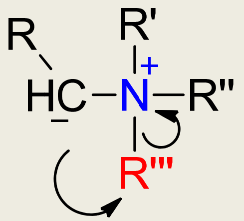
King, *J.C.S. Chem. Comm.*, **1979**, 1140.

Complex mechanisms for simple reactions:

Stevens rearrangements

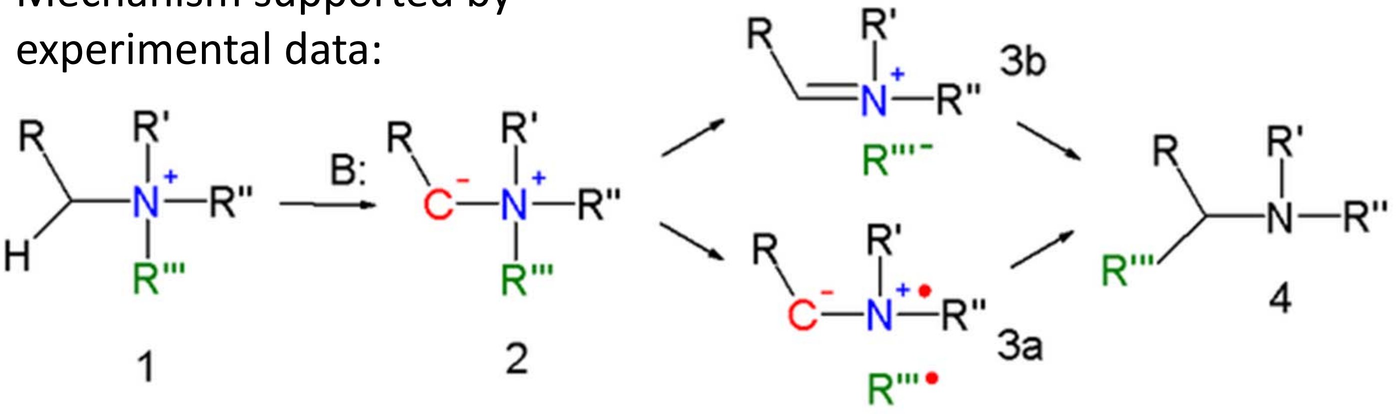


What do you think about this concerted mechanism?



3-endo–tet – fact or fiction?

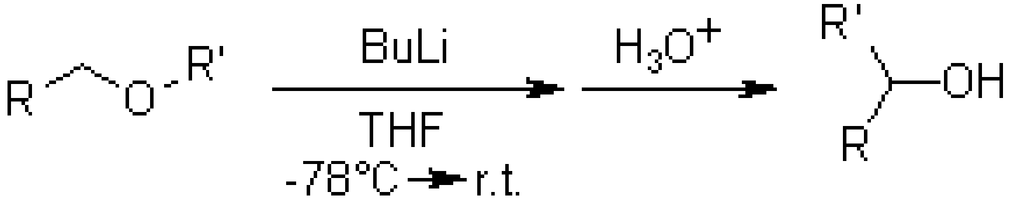
Mechanism supported by experimental data:



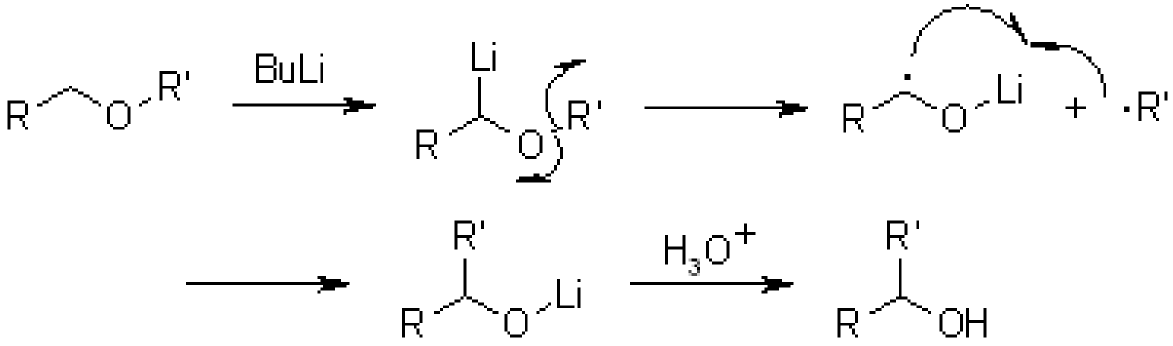
T.S. Stevens *et al.* J. Chem. Soc., **1932**, 1926

Complex mechanisms for simple reactions:

Suggest mechanism for the 1,2-Wittig rearrangement



The [1,2]-Wittig Rearrangement is a carbanion rearrangement that proceeds via a radical dissociation-recombination mechanism. The lithiated intermediate forms a ketyl radical and a carbon radical, which give an alkoxide after fast recombination within the solvent cage

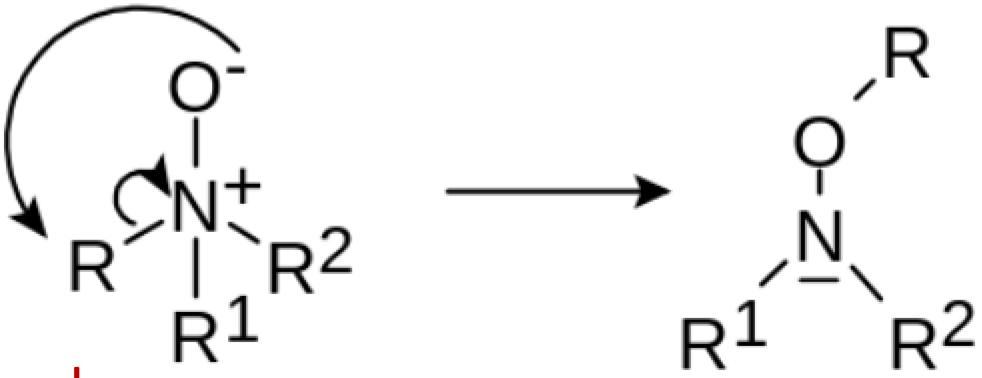


http://www.organic-chemistry.org/namedreactions/1,2-wittig-rearrangement.shtm

Should you always believe Wikipedia?

“In the Meisenheimer rearrangement (after Jakob Meisenheimer) certain N-oxides R1R2R3N+O− rearrange to hydroxylamines R2R3N–O–R1”

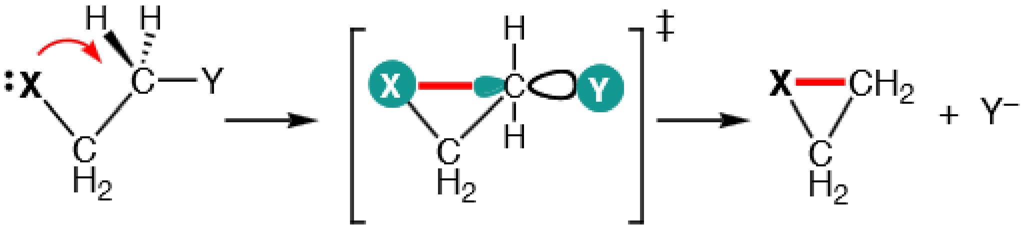
in a 1,2-rearrangement:



Is this a good mechanism?

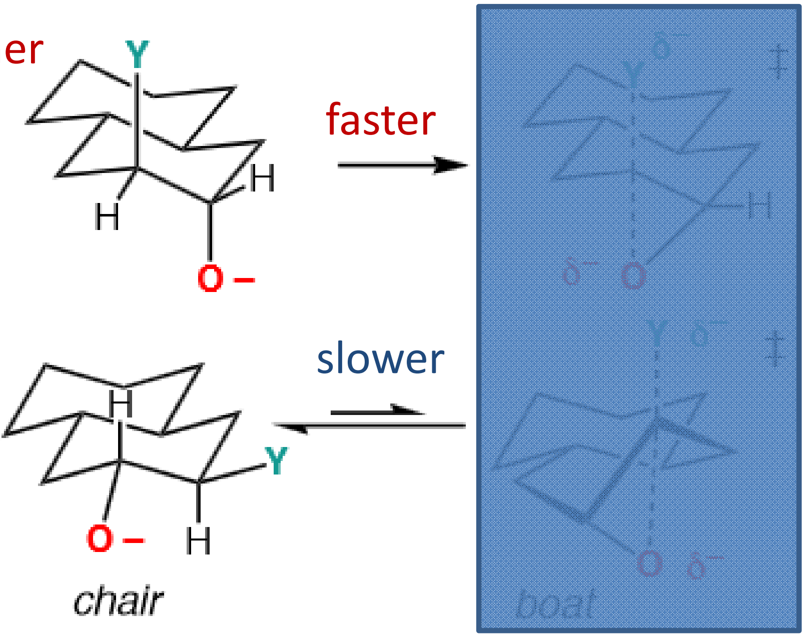
http://en.wikipedia.org/wiki/Amine_oxide

3-exo-tet cyclizations are favored



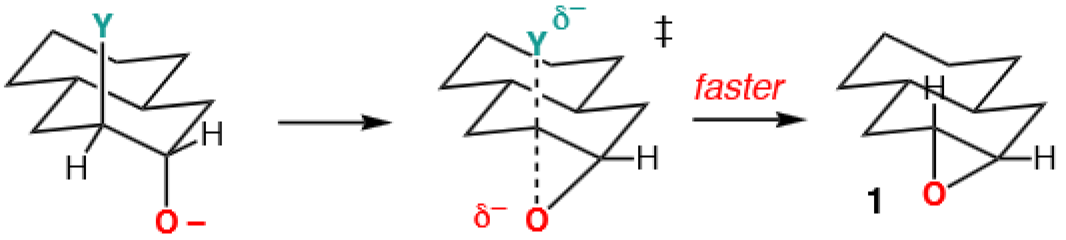
Stereoelectronic restrictions still require antiperiplanar attack of nucleophile at the breaking bond:

Diaxial conformer is optimal:



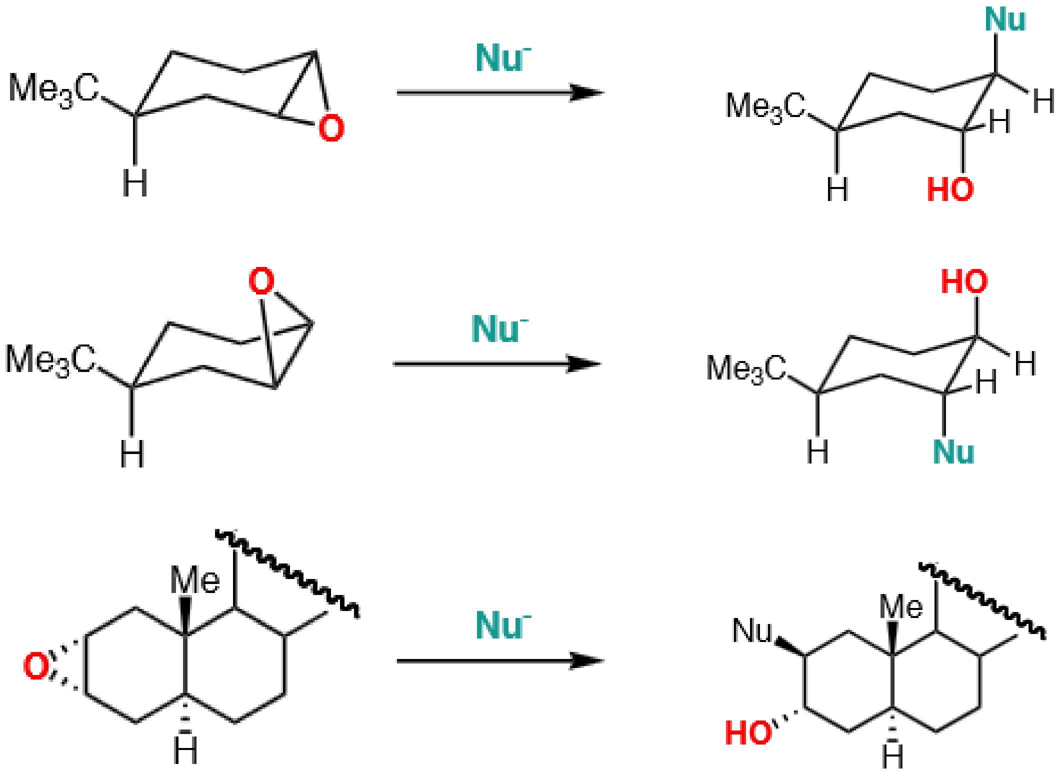
We can use the rules for ring openings too: Epoxide reactions - 3-exo-tet cyclizations in reverse

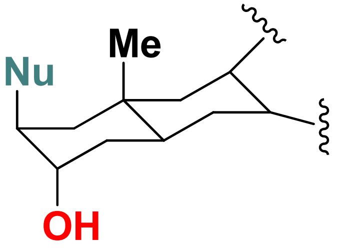
Diaxial arrangement is the best



Let’s use the principle of microscopic reversibility

Which bond will be opened in examples below?

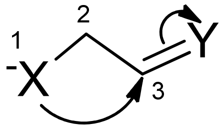




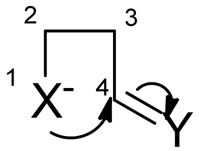
The Fürst-Plattner rule
(the trans-diaxial effect)

Baldwin rules for trigonal systems

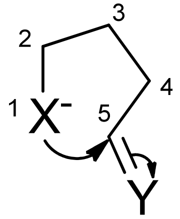
<u>All</u> exo-trig cyclizations are **favorable**



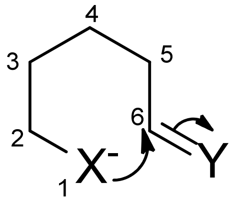
3-exo-Trig



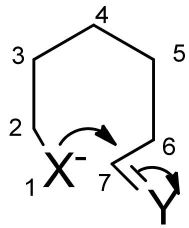
4-exo-Trig



5-exo-Trig

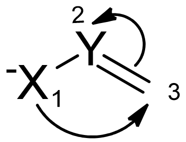


6-exo-Trig

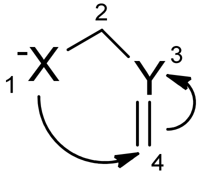


7-exo-Trig

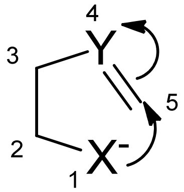
3,4,5-endo trig are **unfavorable**



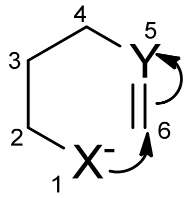
3-endo-Trig



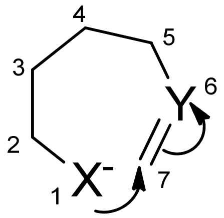
4-endo-Trig



5-endo-Trig



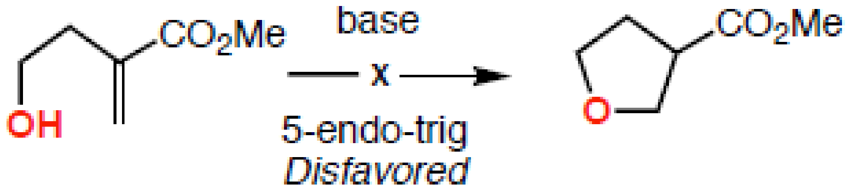
6-endo-Trig



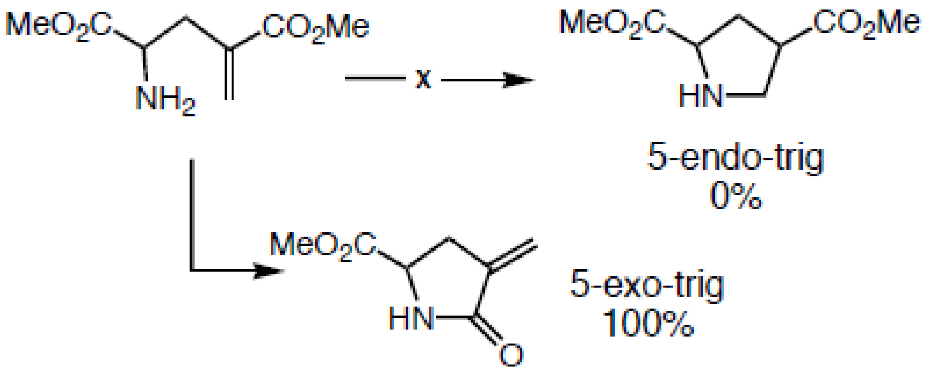
7-endo-Trig

Trigonal systems

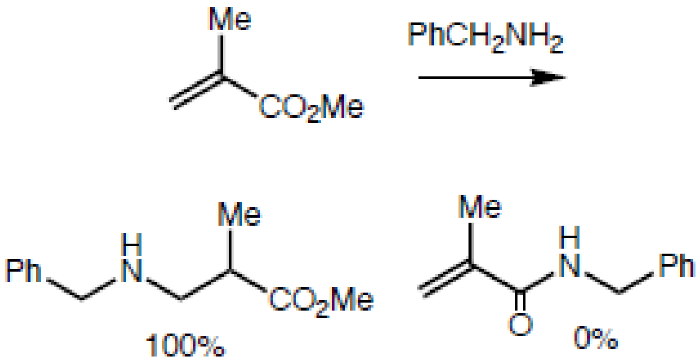
5-endo trig is at the border between favored and unfavored – let's analyse it in more detail



Baldwin, J. Chem. Soc., Chem. Commun., **1976**, 734

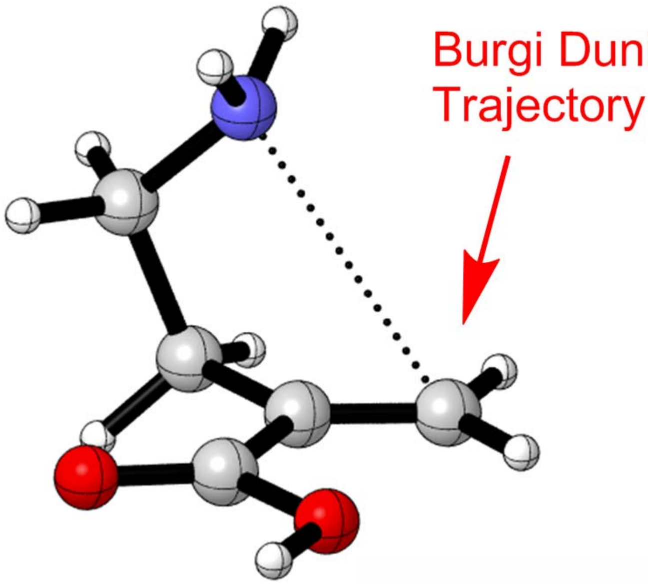


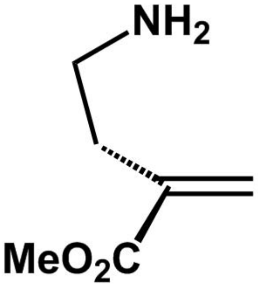
Control experiment:



5-Endo-trigonal reactions: a disfavoured ring closure. Baldwin, J. et al. Chem. Soc., Chem. Commun., **1976**, 736

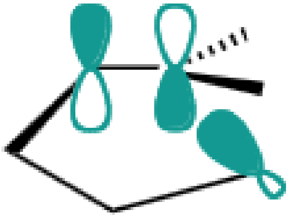
5-endo-trig: geometric restrictions



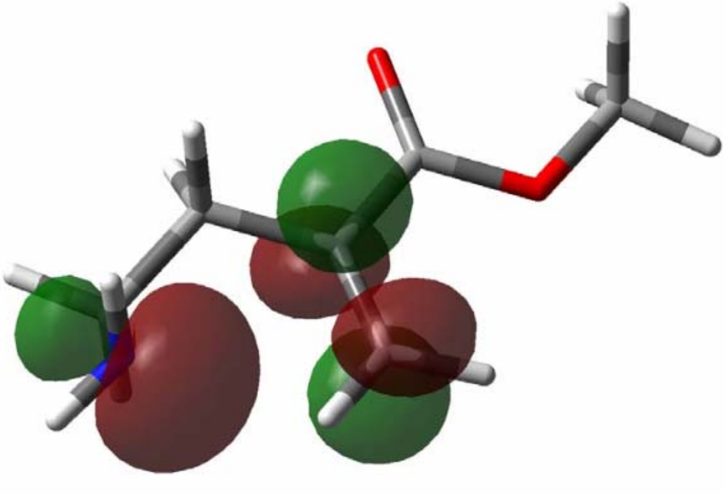


The Burgi-Dunitz angle approach is difficult: the tether is too short.

Nucleophile lone pair can't achieve the right angle of attack



In-plane approach; nucleophile lone pair is orthogonal to π*

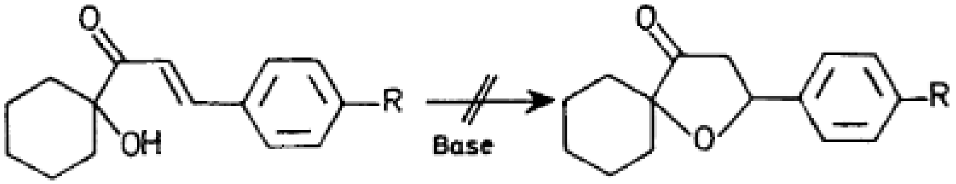


B3LYP/6-31g(d)

Nucleophile lone pair can't make the bond by attacking at the nodal plane

D. A. Evans, J. Johnson, Chem 206 Notes, Harvard

5-endo-trig: additional examples

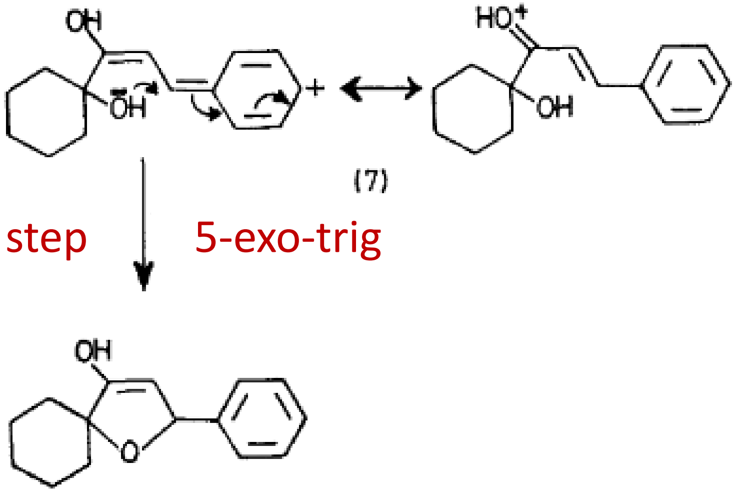


(3) R = H
(4) R = OMe

(5) R = H
(6) R = OMe

5-endo-trig closure is unfavorable…

… but the transformation becomes possible once the mechanism is changed



(7)

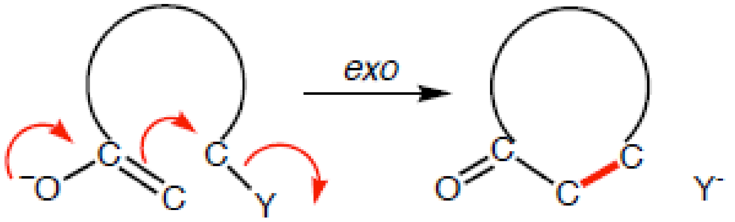
Classify this step

5-exo-trig

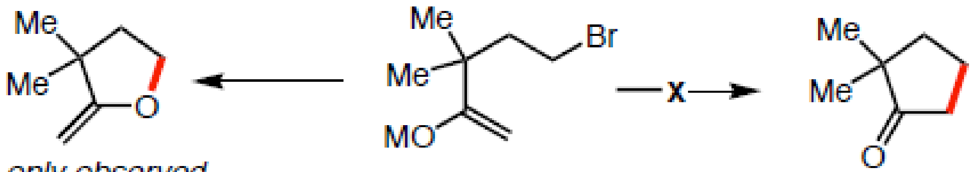
5-Endo-trigonal reactions: a disfavoured ring closure. Baldwin, J. et al. Chem. Soc., Chem. Commun., **1976**, 736

Sometimes one has to consider more than one orbital system: Enolate alkylation

A “hybrid” of exo-tet and endo-trig cyclizations

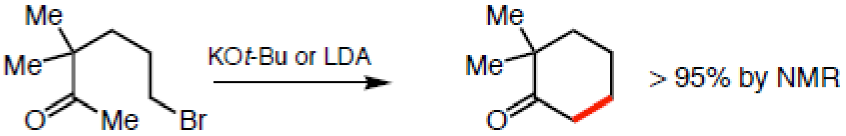


Are enolates always alkylated at carbon?



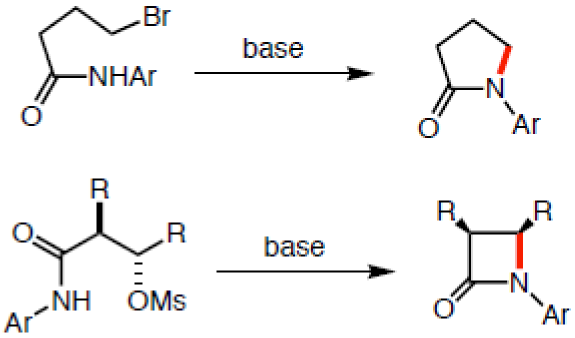
only observed product

Let’s add one more carbon to the tether



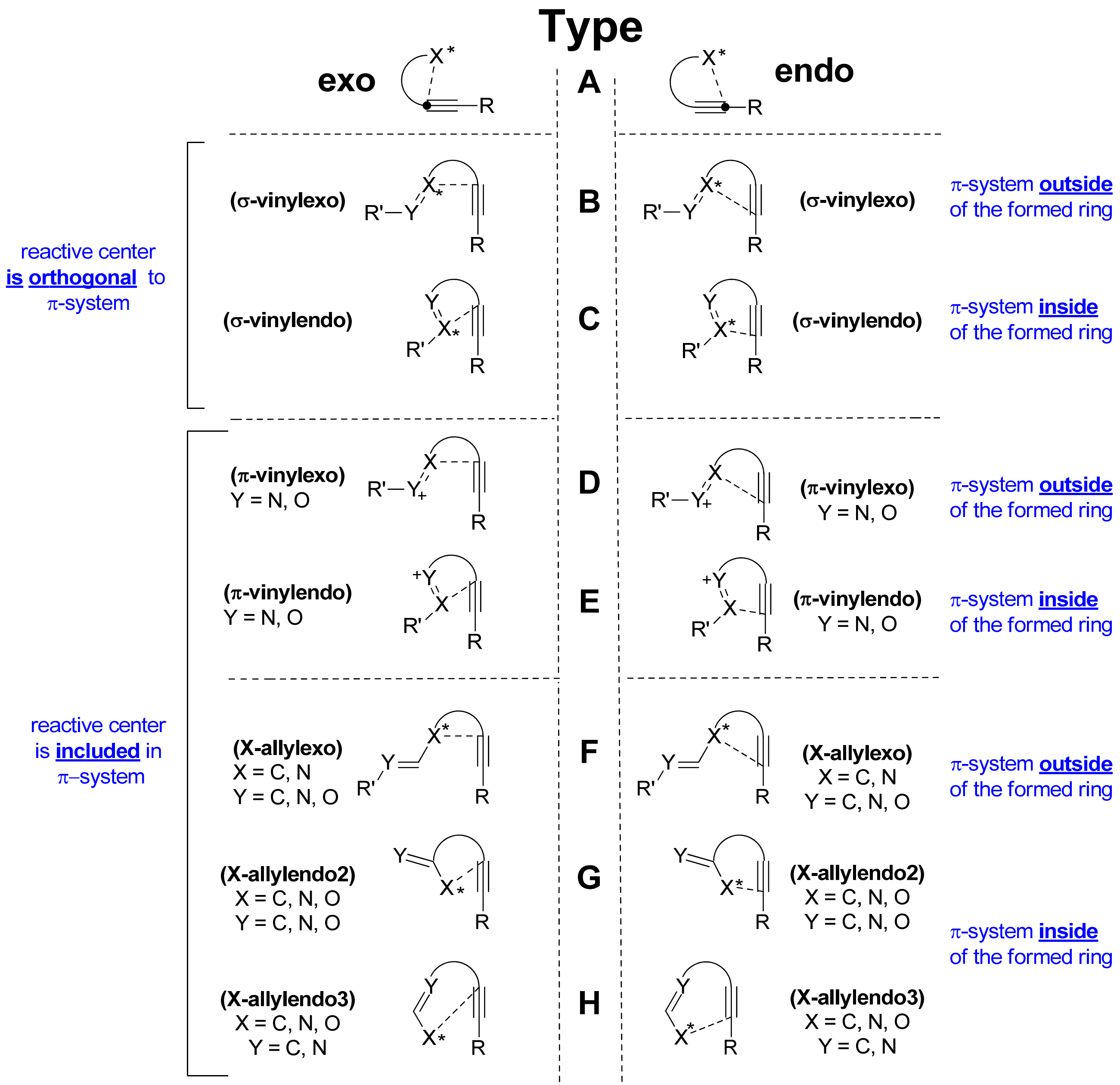
> 95% by NMR

Baldwin, *J. Chem. Soc., Chem. Commun.* **1977**, 233.



Heteroatoms are more “stereoelectronically forgiving”

Full classification of possible ring closure patterns



Type

exo | **A** | **endo**

reactive center **is orthogonal** to π-system

(σ-vinylexo) | **B** | **(σ-vinylexo)** | π-system **outside** of the formed ring

(σ-vinylendo) | **C** | **(σ-vinylendo)** | π-system **inside** of the formed ring

(π-vinylexo) Y = N, O | **D** | **(π-vinylexo)** Y = N, O | π-system **outside** of the formed ring

(π-vinylendo) Y = N, O | **E** | **(π-vinylendo)** Y = N, O | π-system **inside** of the formed ring

reactive center is **included** in π–system

(X-allylexo) X = C, N Y = C, N, O | **F** | **(X-allylexo)** X = C, N Y = C, N, O | π-system **outside** of the formed ring

(X-allylendo2) X = C, N, O Y = C, N, O | **G** | **(X-allylendo2)** X = C, N, O Y = C, N, O

(X-allylendo3) X = C, N, O Y = C, N | **H** | **(X-allylendo3)** X = C, N, O Y = C, N

π-system **inside** of the formed ring

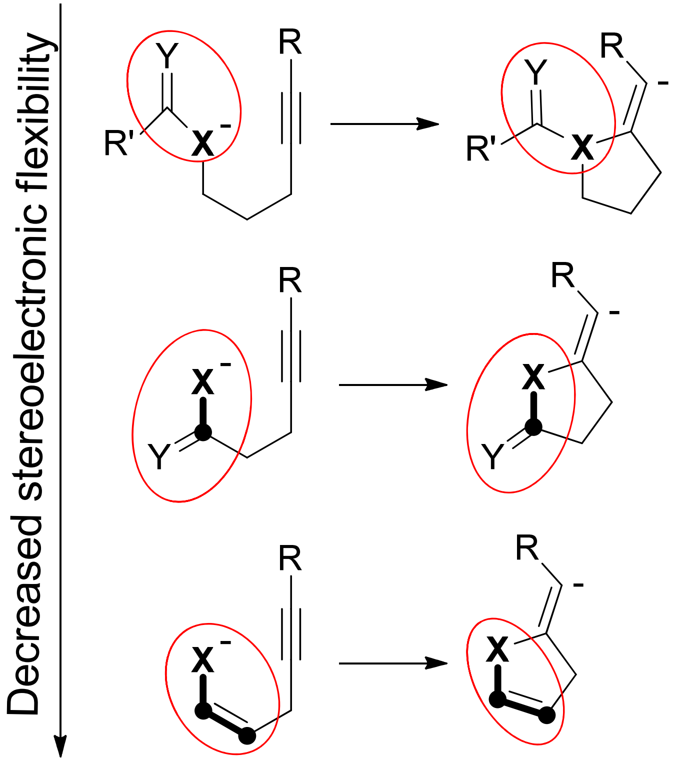
Let’s save detailed discussion for another day.

This is still a not well-understood field and many of these reactions remain unknown

Gilmore, K.; Alabugin, I. V. Cyclizations of Alkynes: Revisiting Baldwin’s Rules for Ring Closure. *Chem. Rev.* **2011**. *111*, 6513–6556

Selected examples:

Differences in stereoelectronic flexibility for the three possible cyclizations of allylic/heteroallylic reagents



sp^2 atoms in the cycle

(X-allylexo)
X = C, N
Y = C, N, O
1

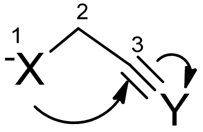
(X-allylendo2)
X = C, N, O
Y = C, N, O
2

(X-allylendo3)
X = C, N, O
Y = C, N
3

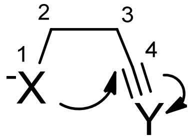
Gilmore, K.; Alabugin, I. V. Cyclizations of Alkynes: Revisiting Baldwin's Rules for Ring Closure. *Chem. Rev.* **2011**. *111*, 6513–6556

Alkynes (digonal systems):
Original Baldwin rules

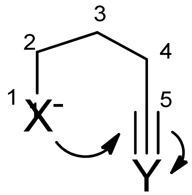
3,4 exo-dig cyclizations are **unfavored**



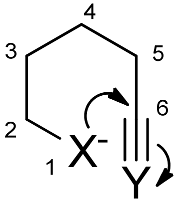
3-exo-Dig



4-exo-Dig

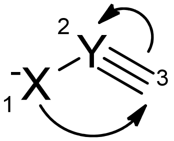


5-exo-Dig

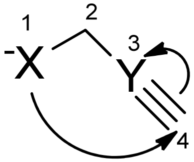


6-exo-Dig

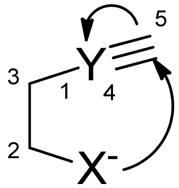
All endo-dig are **favored**



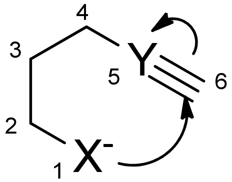
3-endo-Dig



4-endo-Dig



5-endo-Dig

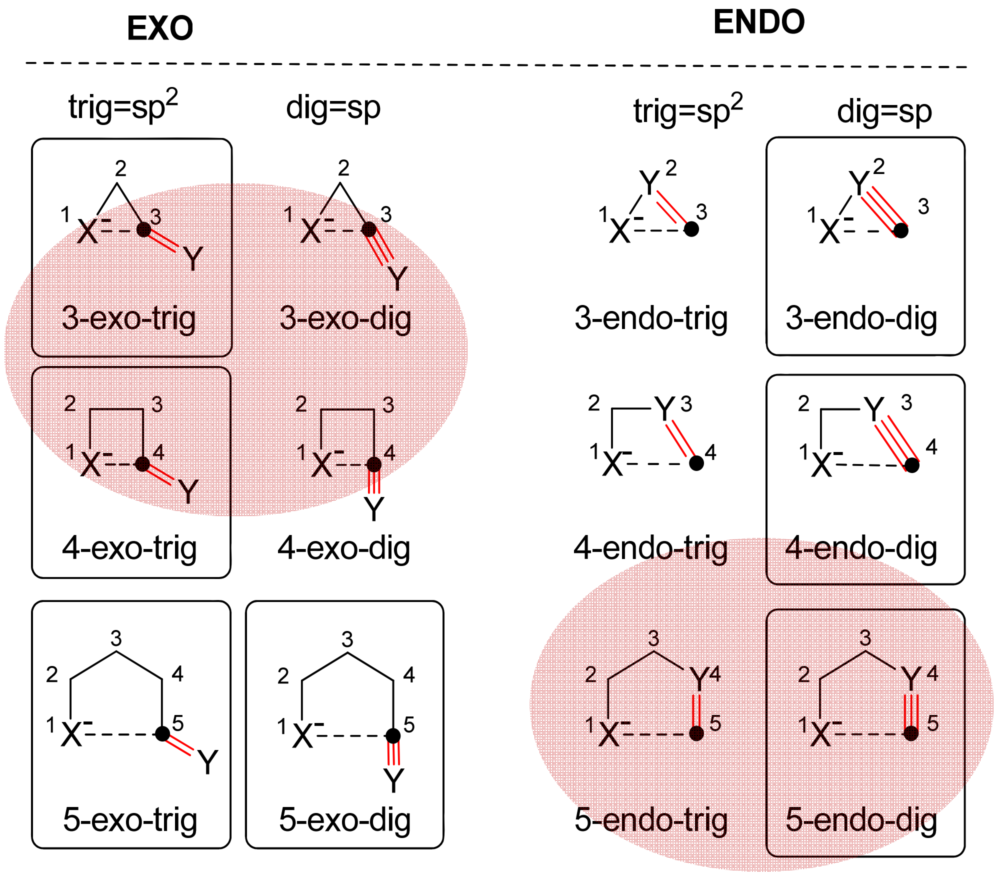


6-endo-Dig

We will have to revisit and reanalyze these predictions very soon

Why Baldwin predictions were surprising?

Boxed reactions were predicted to be favorable



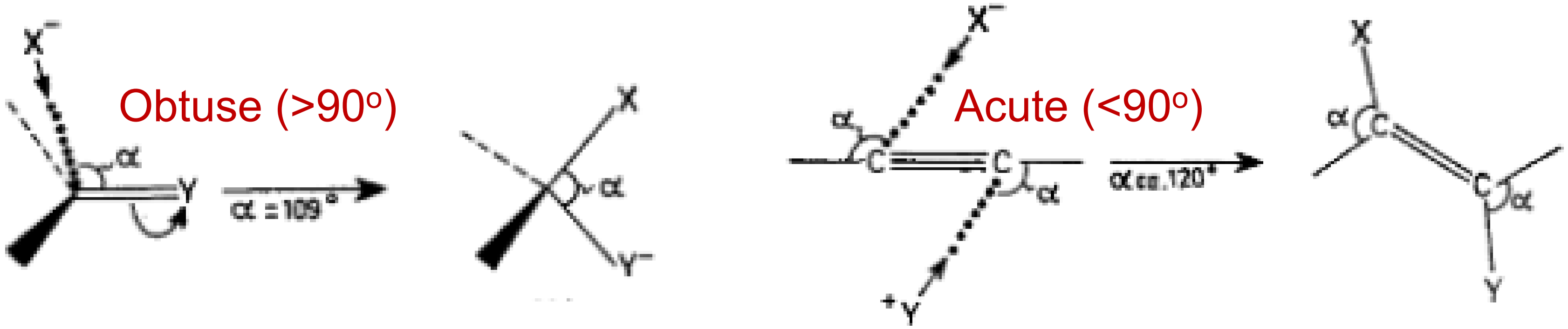
Alkenes and alkynes follow the **opposite** trends

Exo-cyclizations for alkenes and endo-cyclizations for alkynes

Baldwin, J. E. *Chem. Commun.*, **1976**, 734

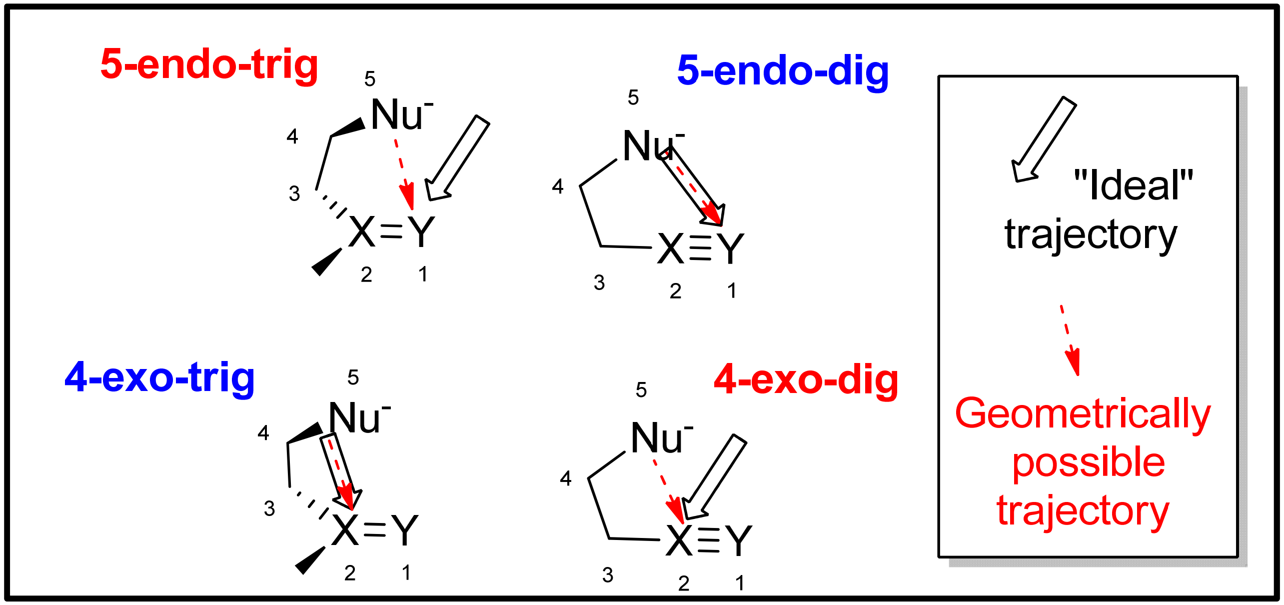
Baldwin Rules: alkynes vs. alkenes

Why rules for alkynes and alkenes are different?

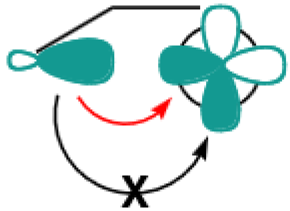


Baldwin, J. E. *Chem. Commun.*, **1976**, 734

Contrasting trajectories = contrasting predictions

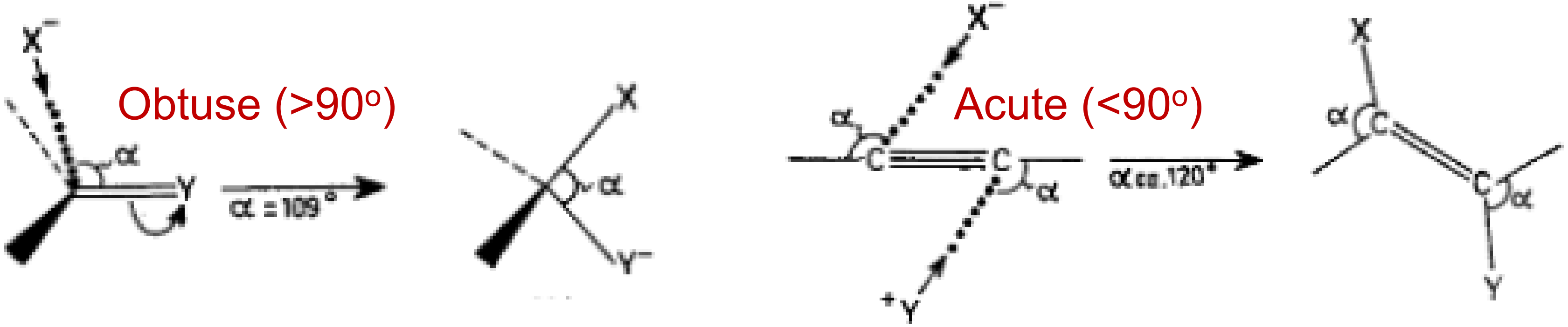


Additional factors: Presence of the 2nd π-system in alkynes



Does it make a difference?

Where does the acute trajectory come from?



Obtuse (>90°)

Acute (<90°)

Baldwin, J. E. *Chem. Commun.*, **1976**, 734

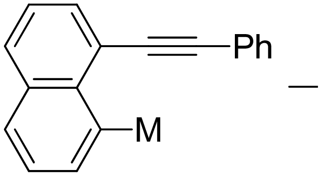
I remember asking myself this question in ca. 1989 when I read the Baldwin's paper for the first time

I could not understand it, so I concluded that I don't know enough (or not smart enough)

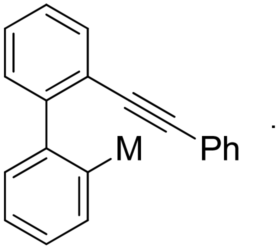
In 2010, I received an invitation to write a Chem. Rev. article on the Baldwin rules. The time had come to finally find the answer!

Let’s reexamine the facts

Experimental evidence available to Baldwin



"parallel"



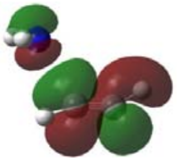
"convergent"

Dessy, R. E.; Kandil, S. A. *J. Org. Chem.* 1965, 3857. Kandil, S. A.; Dessy, R. E. *J. Am. Chem. Soc.* 1966, 3027

Subsequent computational data

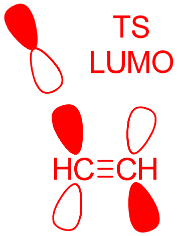
HC≡CH

$+ CH_3^-$



$+ NH_2^-$

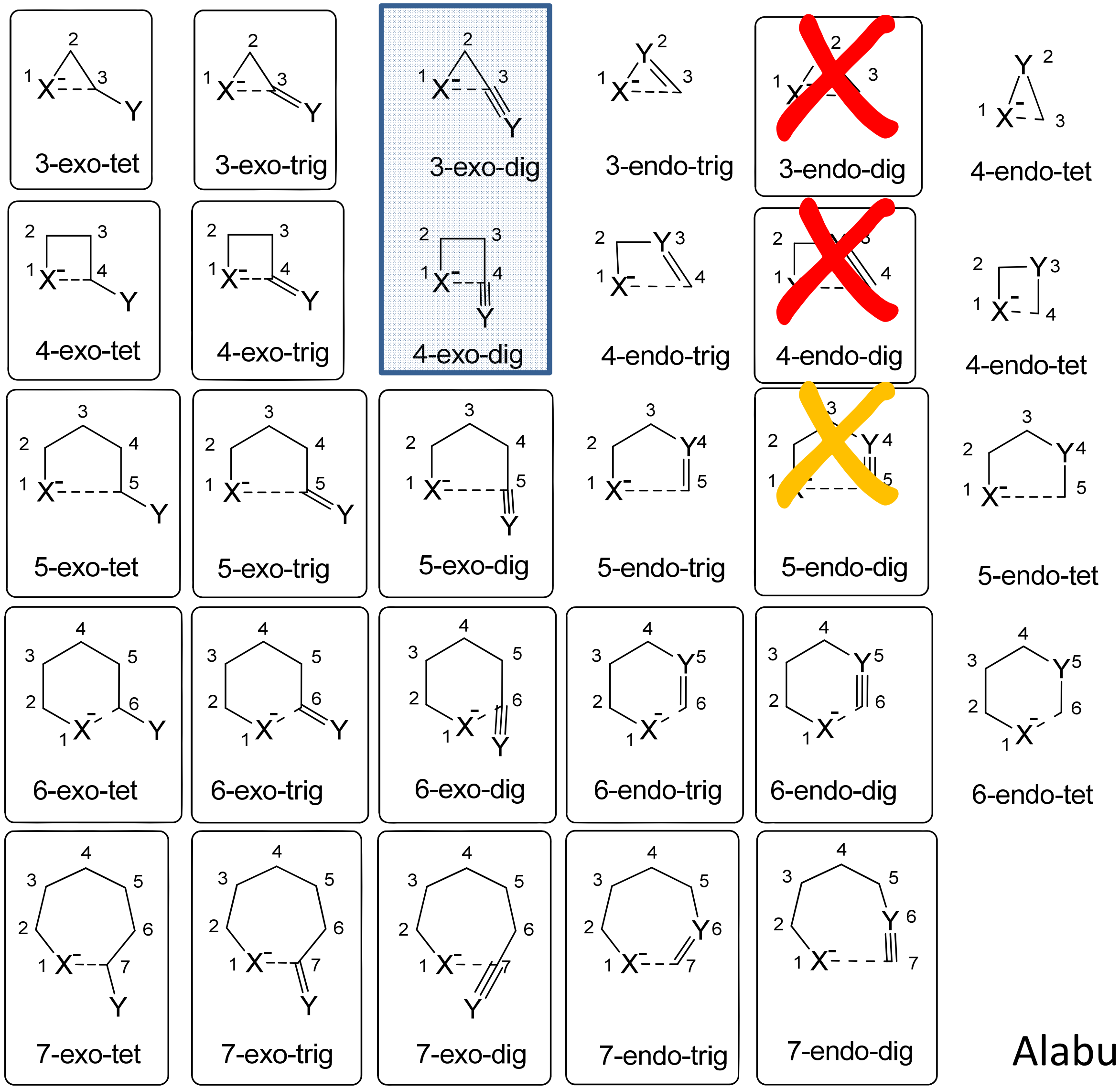
$+ OH^-$



115-130 degree attack angle follows from the LUMO symmetry

Houk, *JACS*, **1979**, 1340. Alabugin, Gilmore *Chem. Rev.* **2011**, 6513

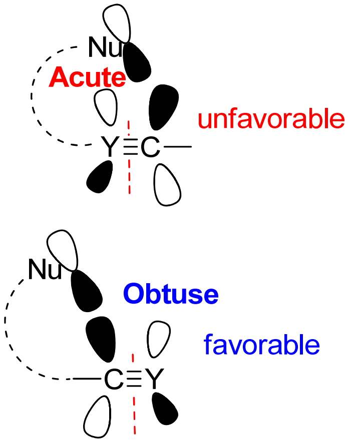
Modified Baldwin rules



Alabugin, Gilmore:
JACS, **2011**, 12608;
Chem. Rev. **2011**, 6513

Redefining the rules for alkyne cyclizations

Kerry Gilmore



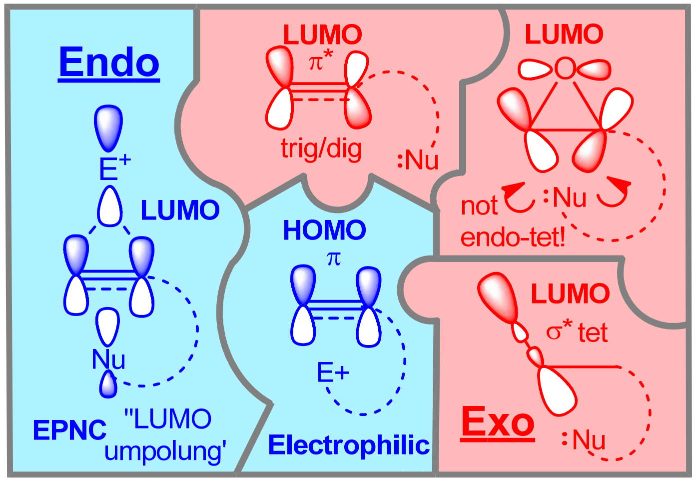
Stereoelectronics suggests exo-selectivity

JACS, **2011**, 12608;
Chem. Rev. **2011**, 6513

"Refined Rules":

Radical/anionic cyclizations prefer exo path

(similar prediction for radical reactions was made by Beckwith decades ago)



"Finding the right path: Baldwin "Rules for Ring Closure" and stereoelectronic control of cyclizations".

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246 (Viewpoint).

What is it good for?

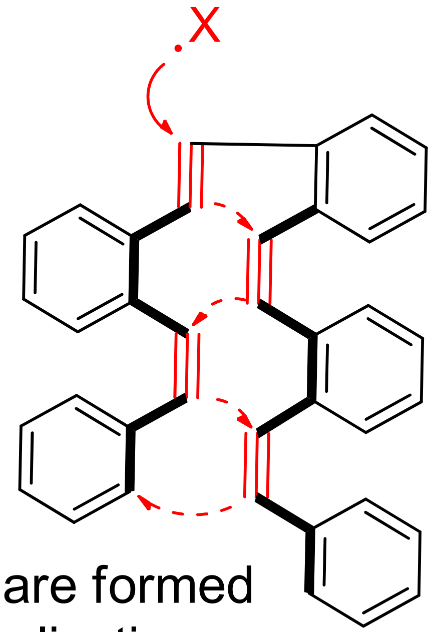
Since alkynes are "carbon-rich", let's make something "carbon-rich"!

Polyaromatics: A perfect test for the cyclization rules

How far can one go with all exo cascades?

Radical cascade:
All Exo

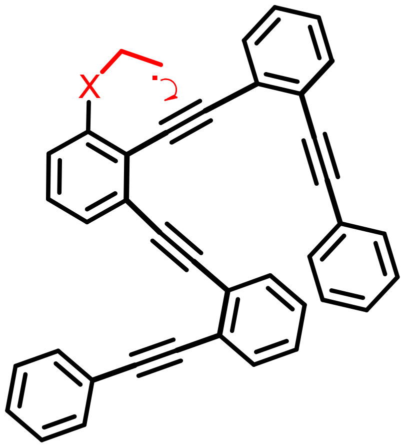
J. Amer. Chem. Soc., **2012,** *134,* 9609



All cycles are formed via **exo**-cyclizations

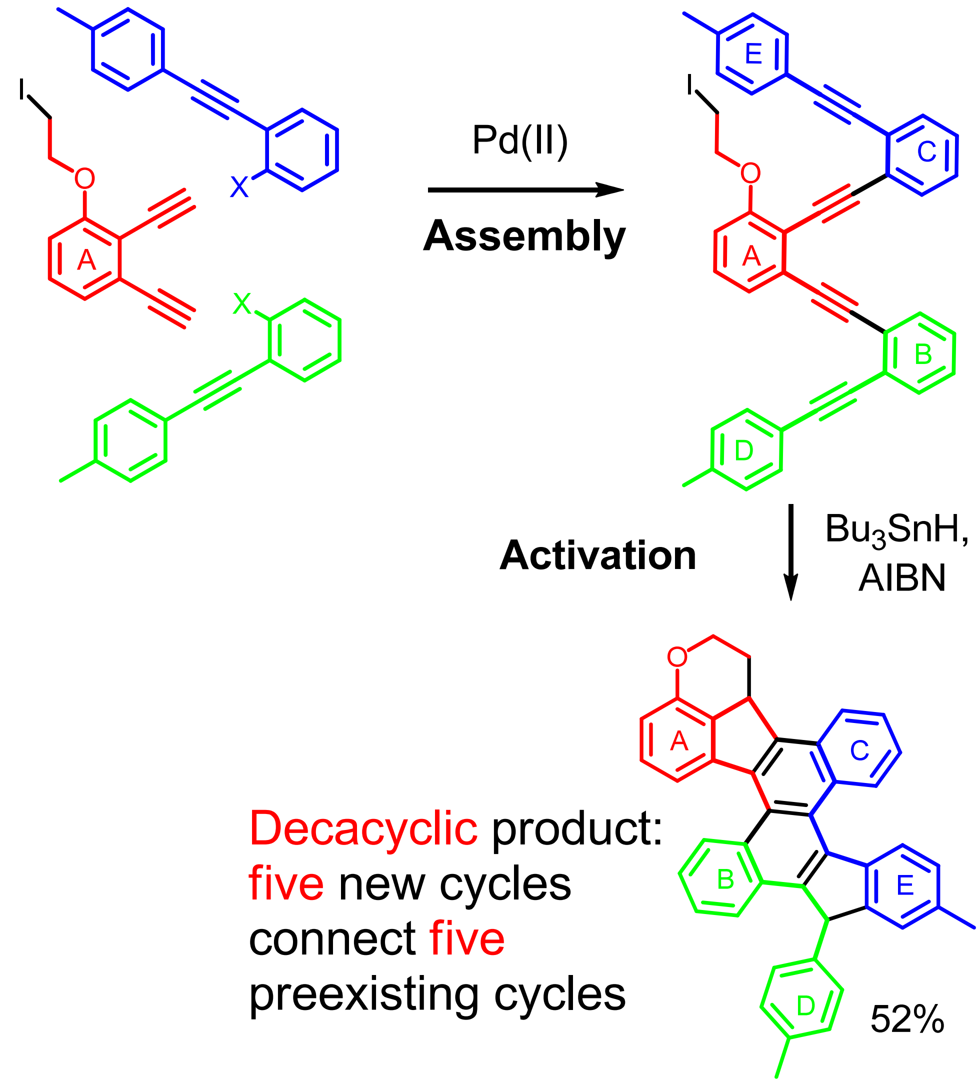
How about making polyacetylene chain between two rows of benzenes with radical "polymerization"?

In search of chemoselectivity: guiding radical processes



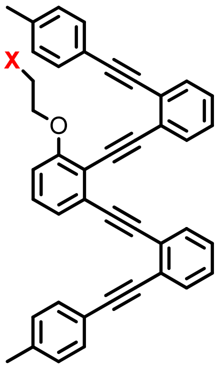
Let’s put radical on a leash...

All aromatic building blocks can be different



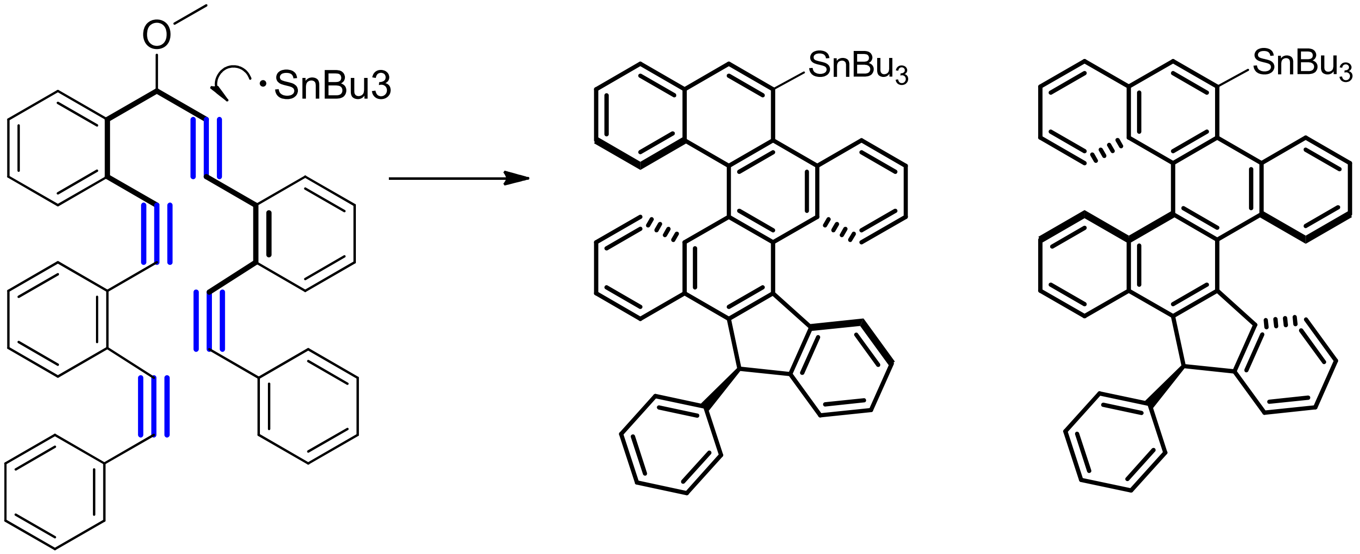
Decacyclic product:
five new cycles
connect five
preexisting cycles

Five new cycles via an “all-exo” cascade



For X=I, >93% yield per step. *Only exo cyclizations!*

Selective initiation of the all-exo-cascade without tethers

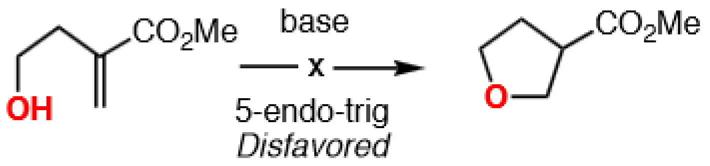


Helicenes

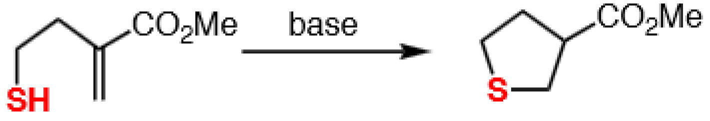
JACS, **2015,** in press, http://dx.doi.org/10.1021/ja510563d

CAVEATS AND VIOLATIONS
Unusual bond lengths

Due to the larger atomic radii and bond distances of heavier atoms, Baldwin stipulated that atoms in the cycle must be “first row elements”.

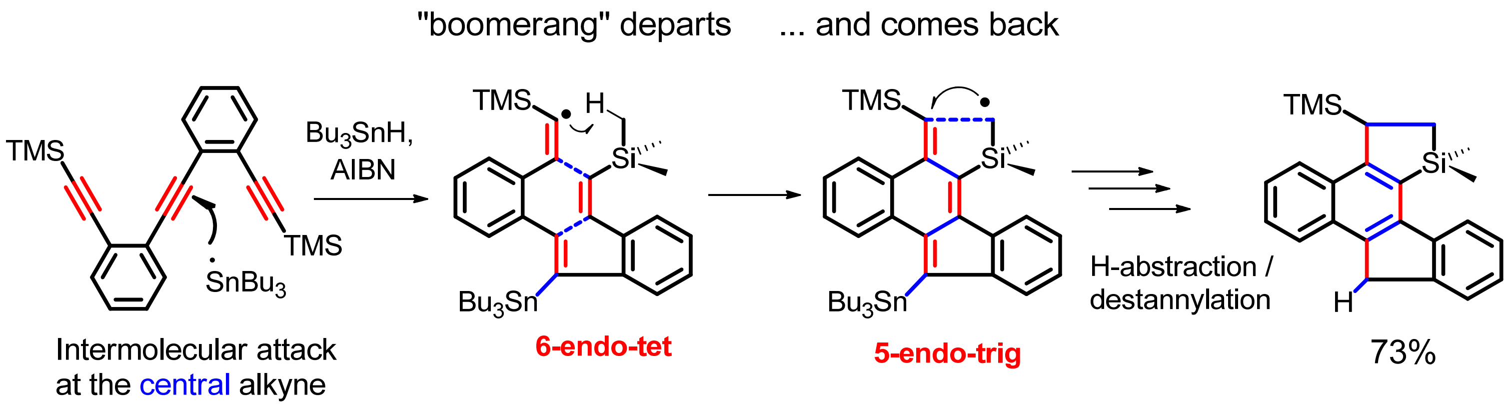


however



A less recognized corollary is that reactions which involve the cleavage and formation of the much shorter bonds to hydrogen often do not follow the rules as well. For example, radical 1,5-hydrogen transfers, which formally proceed via the unfavorable 6-endo-tet transition state, are common

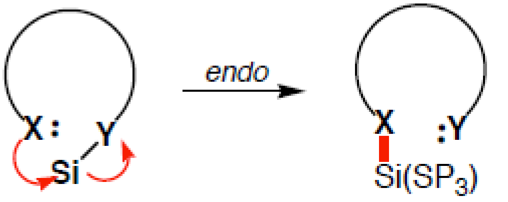
J. Am. Chem. Soc. **2008, *130*, 11535**



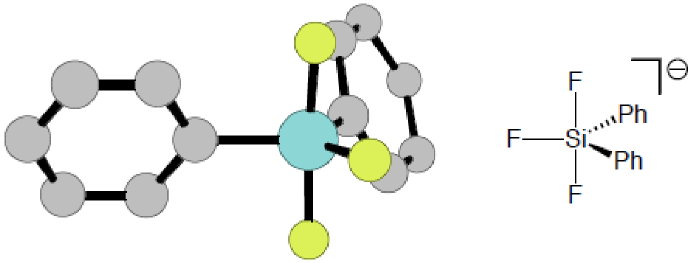
CAVEATS AND VIOLATIONS

Unusual atoms

Endo-Tet cyclization modes are allowed for tetrahedral Silicon



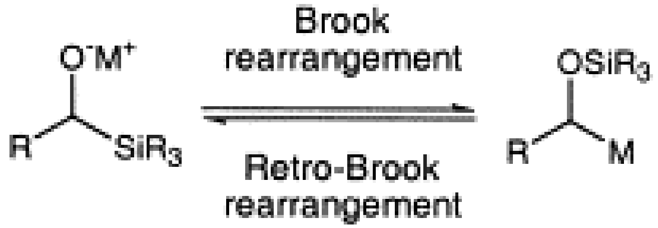
Brook Rearrangements



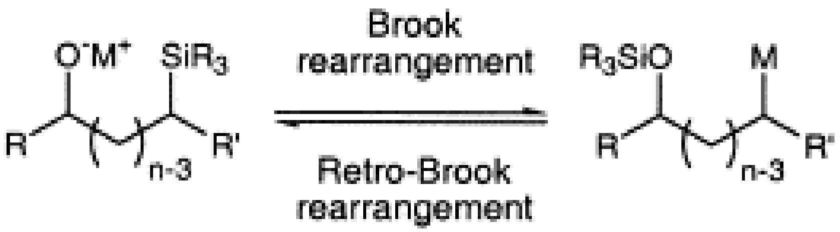
Hypervalent intermediates may be involved (*Inorg. Chem.* **1984**, 1378)

D. A. Evans, J. Johnson, Chem 2006, Harvard

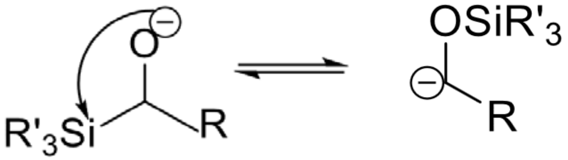
[1,2]-Silyl Migrations



[1,n]-Silyl Migrations



Classify this process:



Formally, 3-endo-tet

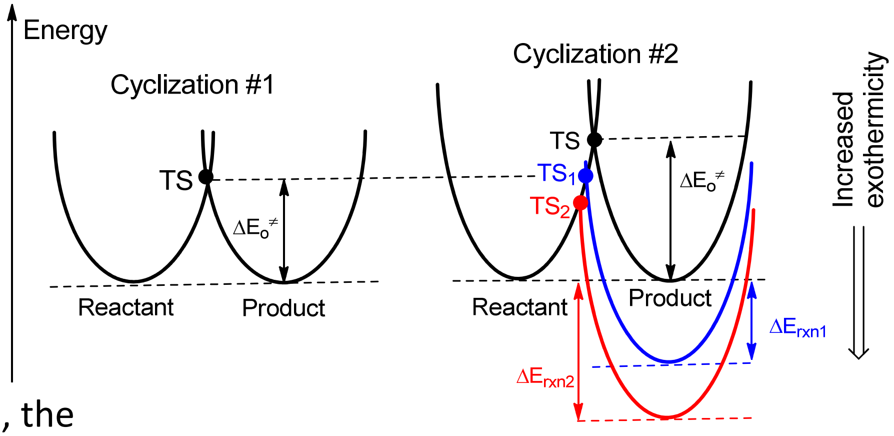
Moser, W. H. "The Brook Rearrangement in Tandem Bond Formation Strategies," Tetrahedron **2001**, 57, 2065

CAVEATS AND VIOLATIONS
Role of thermodynamic factors

1. Baldwin rules are not applicable to transformations that proceed under thermodynamic control
2. In addition, even under kinetic control, thermodynamic factors can modify reactivity in two ways.

2a. Exothermic reactions have early, reactant-like transition states and consequently require less distortion from the reactant geometry to reach the optimal bond-forming trajectories.

2b. Second, thermodynamic contributions directly lower activation barriers of exothermic cyclizations



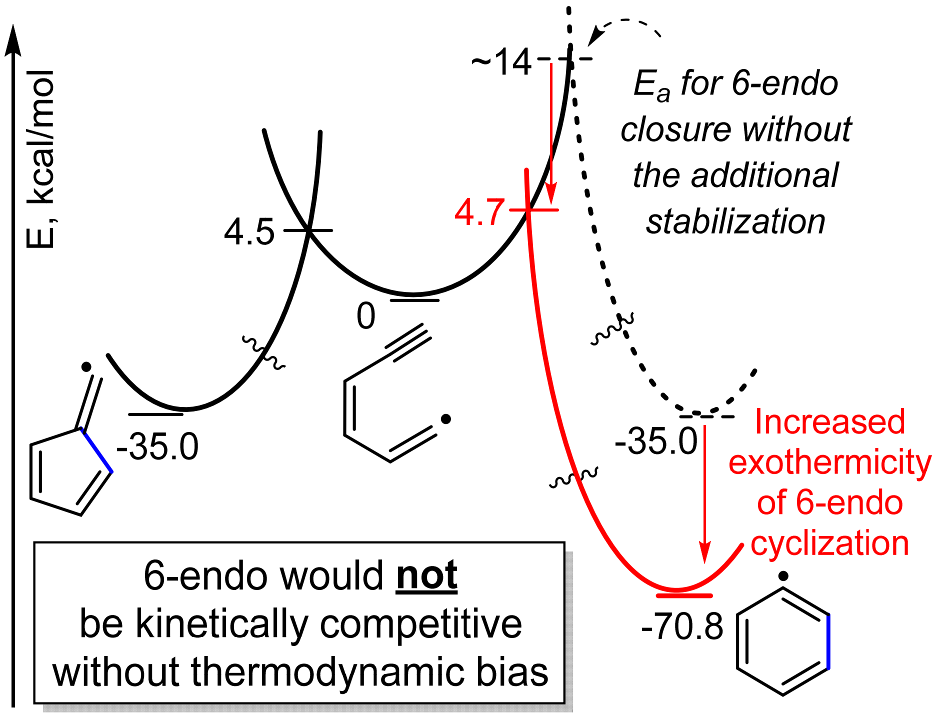
In the absence of a thermodynamic bias, the unfavorable cyclization #2 has a higher barrier

When the thermodynamic driving force for reaction #2 is sufficiently large (red curve), this cyclization becomes more kinetically favorable than the initially favored process #1

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246

CAVEATS AND VIOLATIONS
Role of thermodynamic factors

Example: Effect of aromatic stabilization of the 6-endo-product on the kinetic competition between 5-exo/6-endo-dig closures of conjugated reactants



6-endo would **not** be kinetically competitive without thermodynamic bias

Effects of thermodynamics on kinetics are evaluated using Marcus equation:

$$\Delta E_o^{\neq} = \frac{\Delta E^{\neq} - \frac{1}{2}\Delta E_R + \sqrt{\Delta E^{\neq 2} - \Delta E^{\neq}\Delta E_R}}{2}$$

Alabugin I.V.; Manoharan, M.
J. Am. Chem. Soc. **2005**, 12583

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246

CAVEATS AND VIOLATIONS
Rules for alkynes

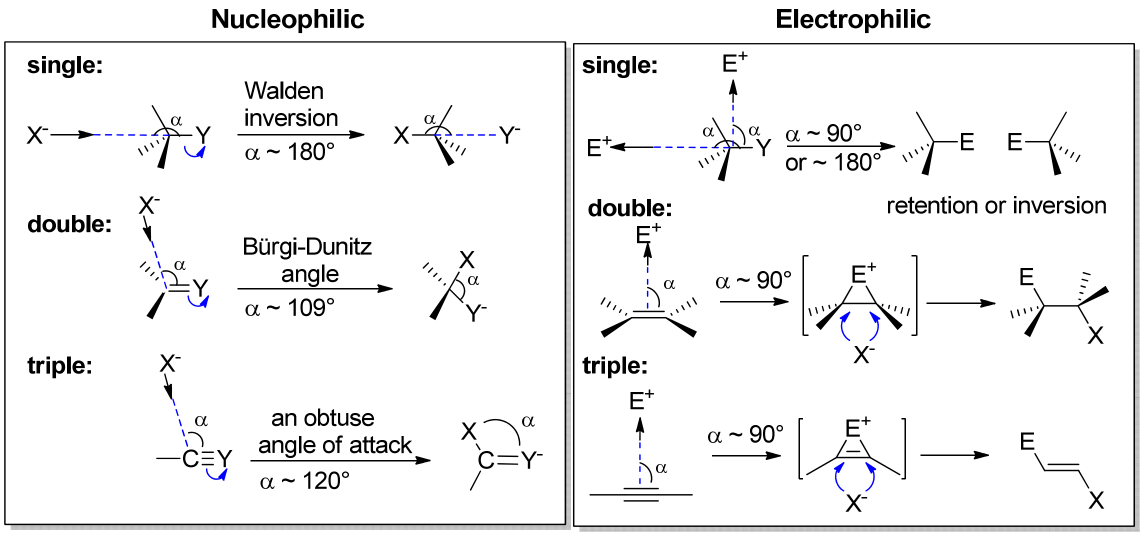
Anionic		3	4	5	6
Dig	endo-	×	×	✓	✓
	exo-	✓	✓	✓✓	✓✓
Radical		3	4	5	6
Dig	endo-	×	×	✓	✓✓
	exo-	✓	✓	✓✓	✓✓

Revised Baldwin rules for nucleophilic and radical cyclizations of alkynes

Alabugin, I. V.; Gilmore, K. *JACS*, **2011**, 12608;
Chem. Rev. **2011**, 6513

CAVEATS AND VIOLATIONS
Rules for cations – very different from anions!

Another potentially controversial aspect of the Baldwin rules is whether their utility extends beyond nucleophilic closures. Although Baldwin stated that this treatment “also applies to homolytic and cationic processes”, one cannot simply “transfer” the guidelines between the different attacking species.

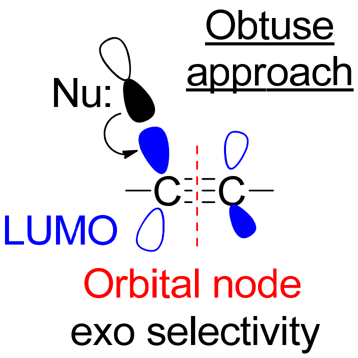


For example, the cationic 1,2-shifts involved in Wagner-Meerwein rearrangements are analogous to the anionic 3-endo-tet process but, whereas cationic processes are ubiquitous, fast, and concerted, their anionic counterparts are clearly unfavorable as illustrated by the non-concerted nature of the [1,2]-Wittig and related anionic rearrangements

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246

Violations can be useful.
LUMO Umpolung: design of endo-selective cyclizations

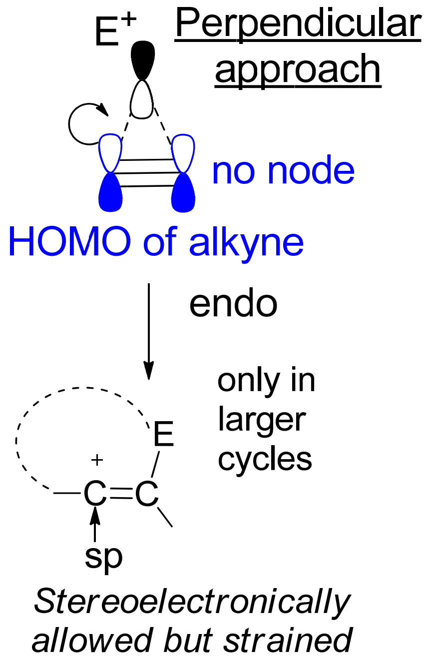
Nucleophilic



Endo cyclizations are disfavored either stereoelectronically (nucleophiles) or thermodynamically (electrophiles).

The solution is to design nucleophilic cyclizations that follow stereoelectronic rules of electrophilic cyclizations.

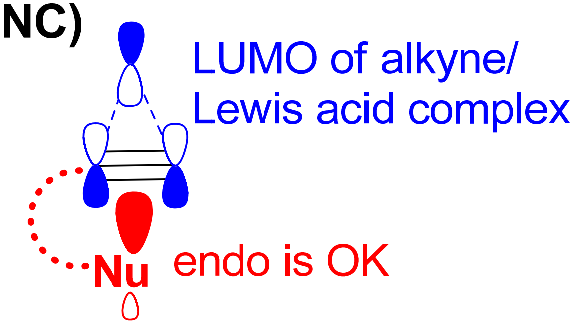
Electrophilic

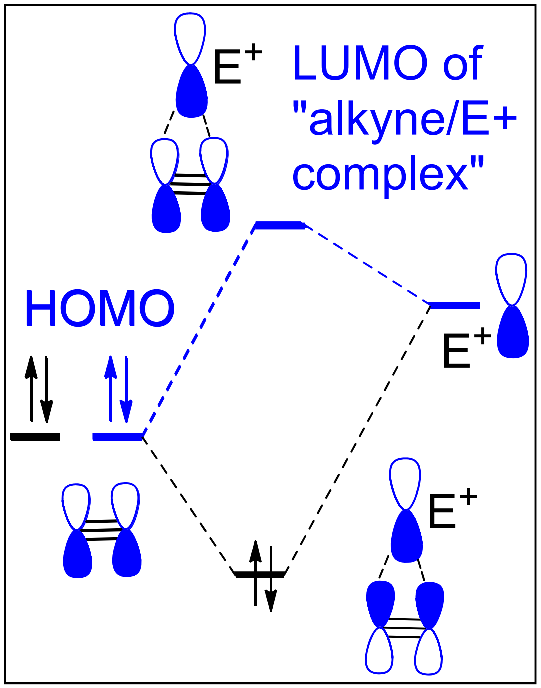


Stereoelectronically allowed but strained

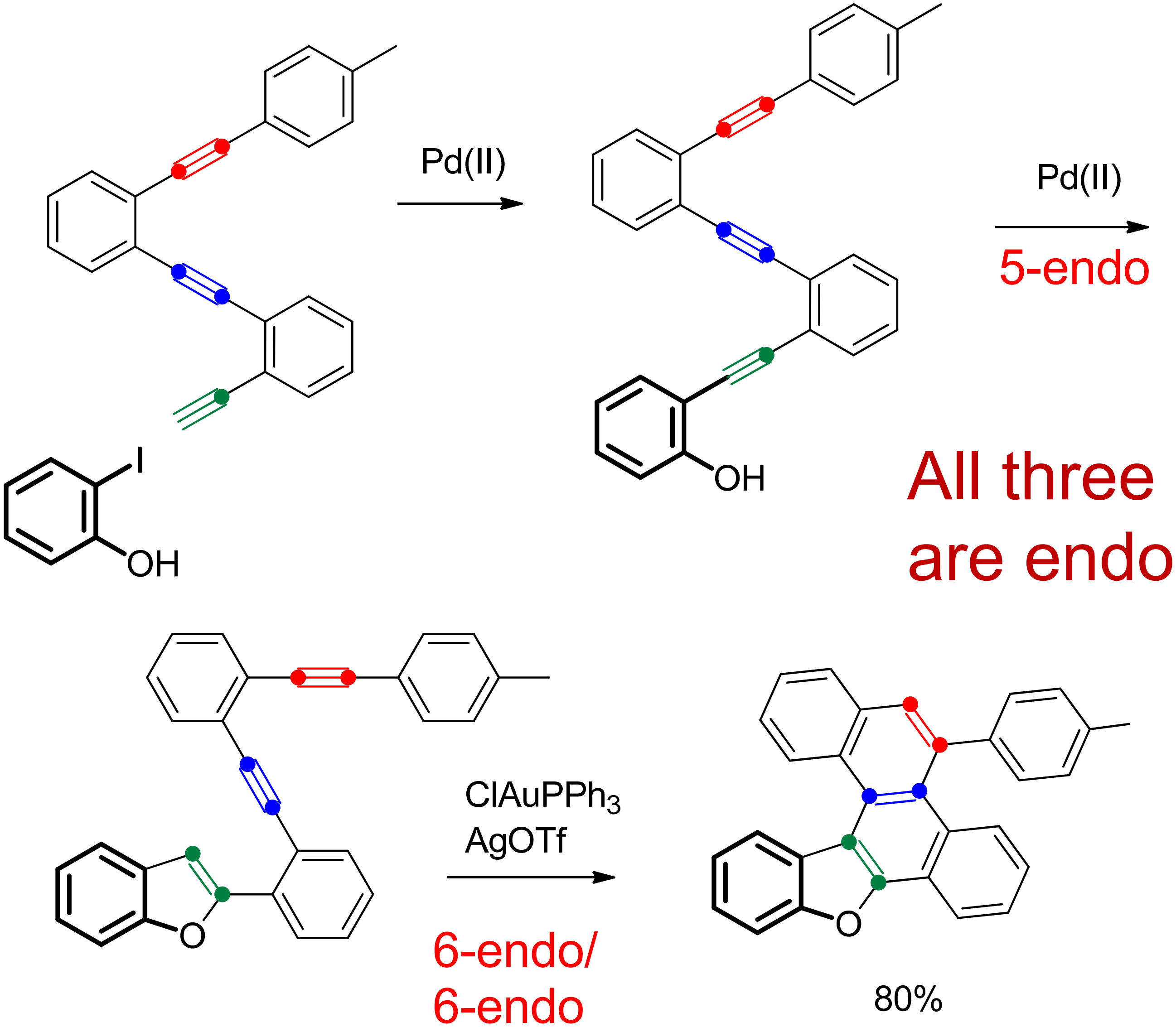
We need to “convert” alkyne HOMO into a LUMO.

Electrophile-Promoted Nucleophilic Closure (EPNC)





“All endo” cascades towards polyaromatics



All three cyclizations are endo-dig!

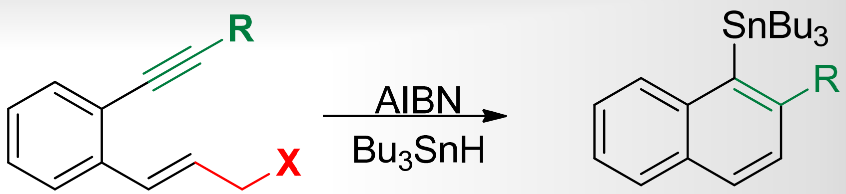
Byers, P. M.; Rashid, J. I.; Mohamed, R. K.; Alabugin, I. V. *Org. Lett.*, **2013**, 6032

Review: Mohamed, Peterson, Alabugin, *Eur. J. Org. Chem.*, **2013**, 2505

Another way to achieve endo-selectivity: couple TWO exo-cyclizations with a fragmentation

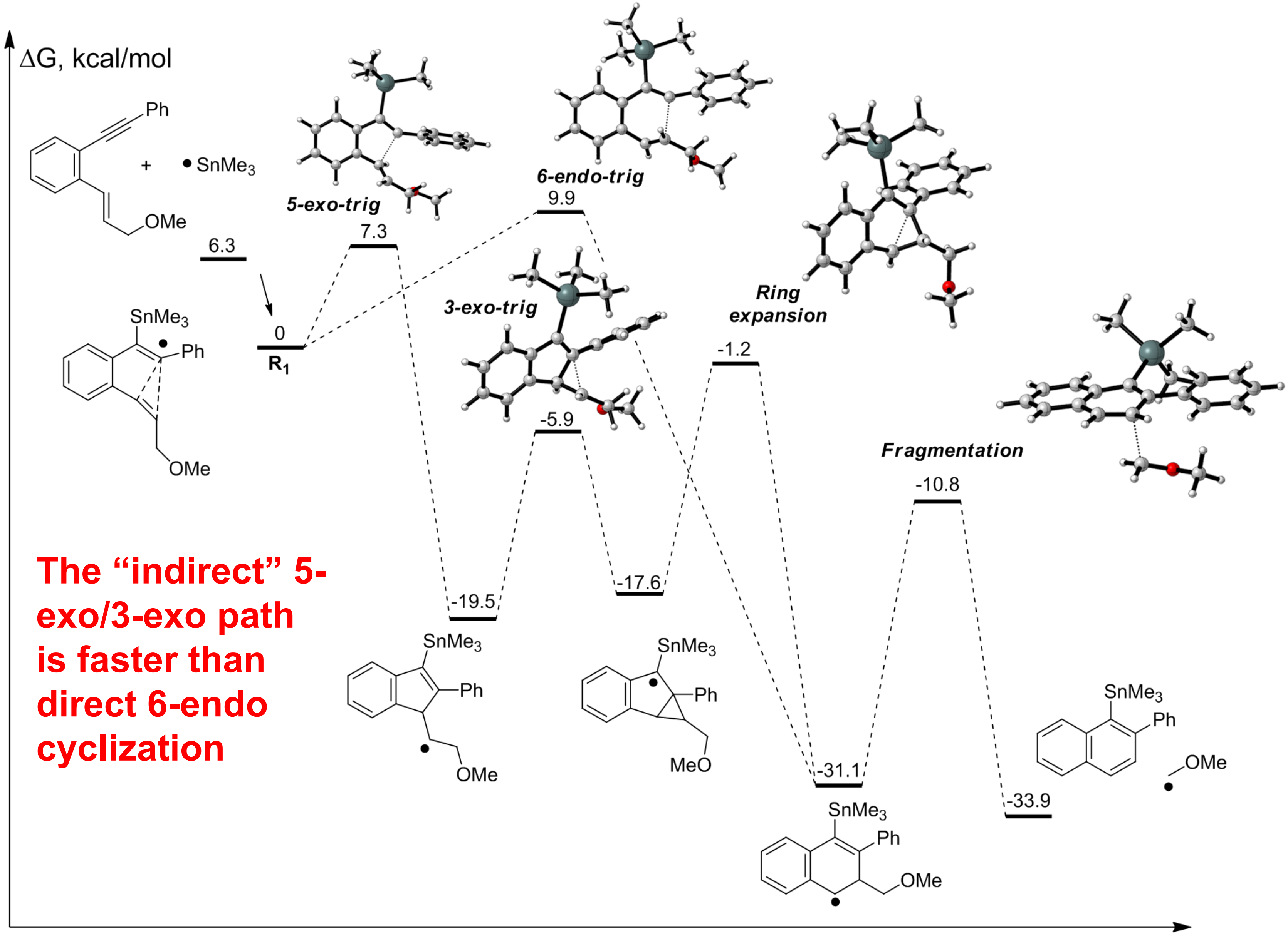
Ring expanding cascades

Why and how did the selectivity change?



It is not that simple!

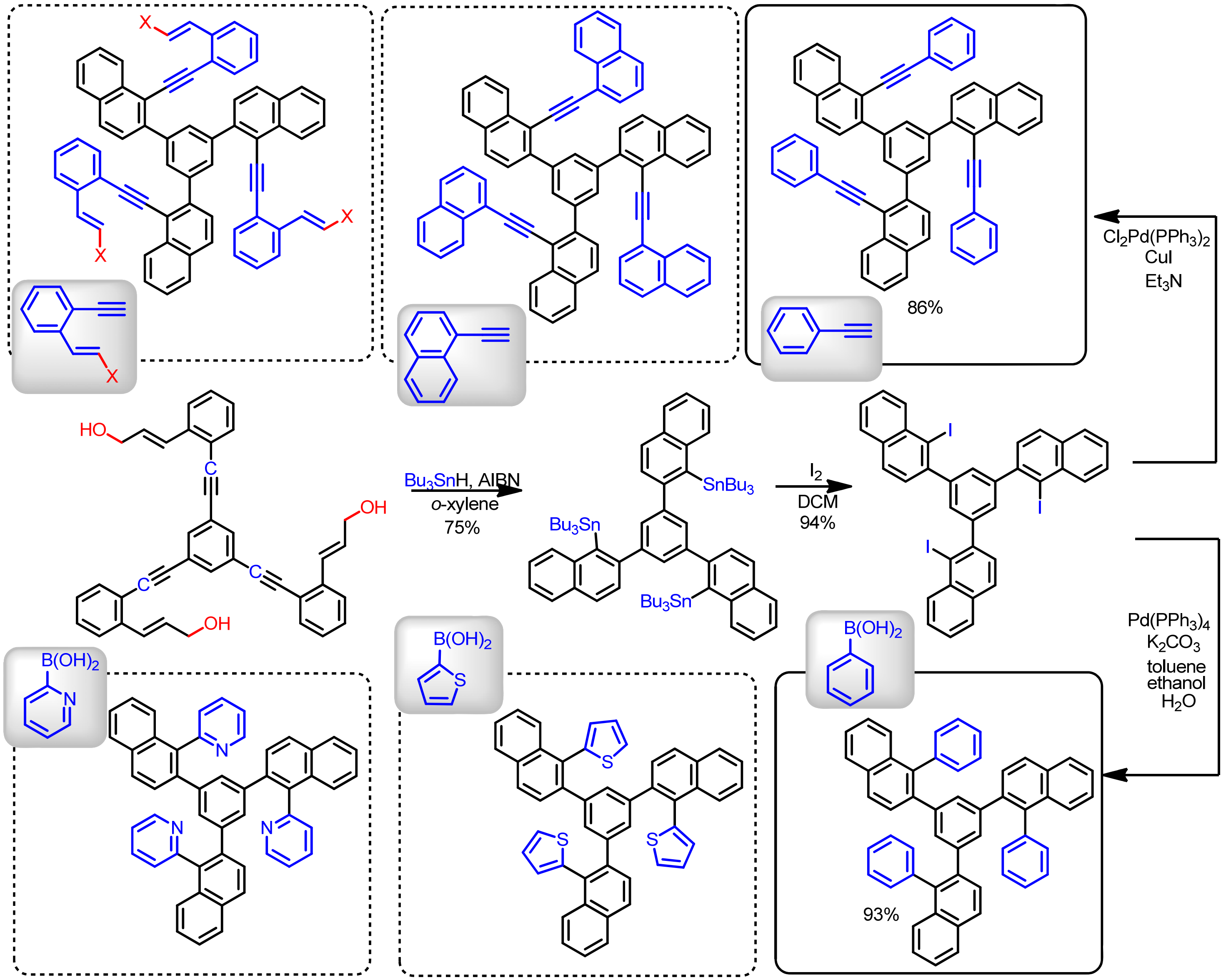
Switch in selectivity: homoallylic expansion



The “indirect” 5-exo/3-exo path is faster than direct 6-endo cyclization

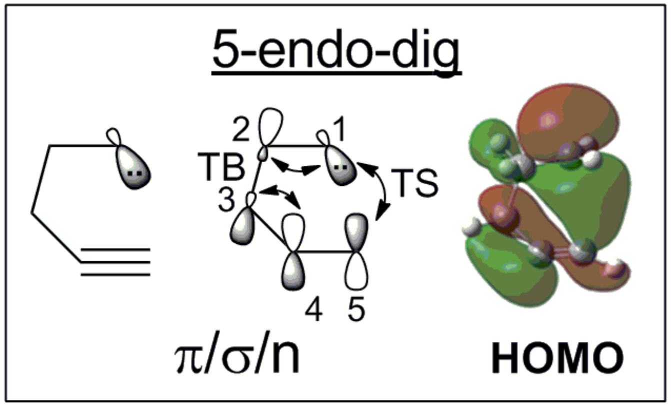
UM062X/LanL2DZ level of theory. Energies in kcal/mol. ΔG’s are calculated at 384K

Modular approach to carbon nanostructures with 3-fold symmetry

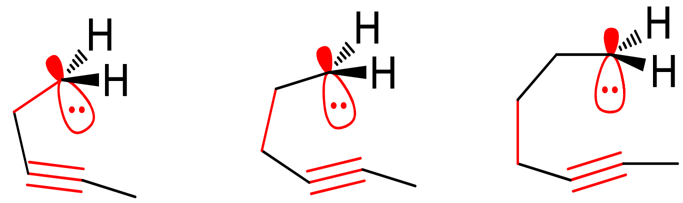


CAVEATS AND VIOLATIONS

Sigmatropic shifts masquerading as endo-cyclizations



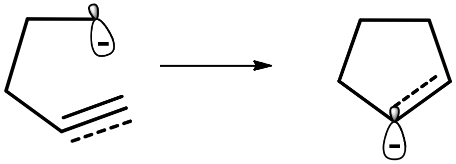
Symmetry-enforced cyclic delocalization: σ-aromaticity

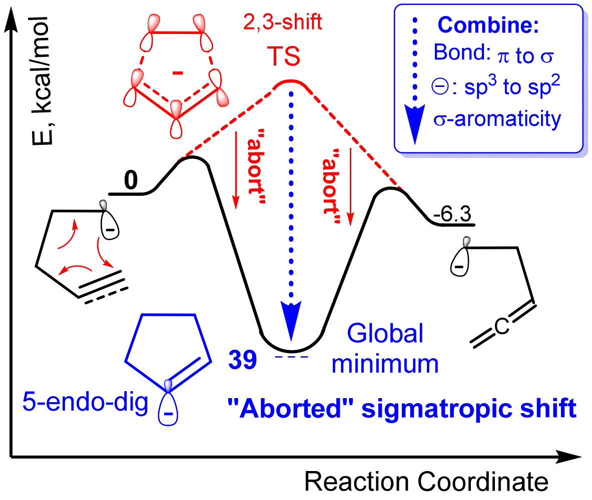


Lone Pair	+21.7	-9.0	+3.1
in-plane π	-1.1	-6.2	-2.6
sigma	+3.3	-5.3	+4.7
NICS(0)$_{MOzz}$	**+23.9 ppm** **(+20.6 ppm)^{a}**	**-20.5 ppm**	**+5.2 ppm**
	antiaromatic	***aromatic***	***non-aromatic***

Gilmore, Manoharan, Wu, Schleyer, Alabugin, *JACS,* **2012**, 10584

Anionic 5-endo cyclizations





Anionic 5-endo cyclizations are "**aborted** [2,3]-sigmatropic shifts" because cyclic intermediate (geometry close to the pericyclic TS) is **more stable** than the rearrangement product

CAVEATS AND VIOLATIONS

Enzyme-catalyzed reactions of epoxides – a violation?

Baldwin mentions cyclic closure onto epoxides only briefly, stating “The rules for opening three-membered rings to form cyclic structures seem to lie between those for tetrahedral and trigonal systems, generally preferring *exo*modes”. This statement led to much misunderstanding and several reports of “anti-Baldwin” reactions

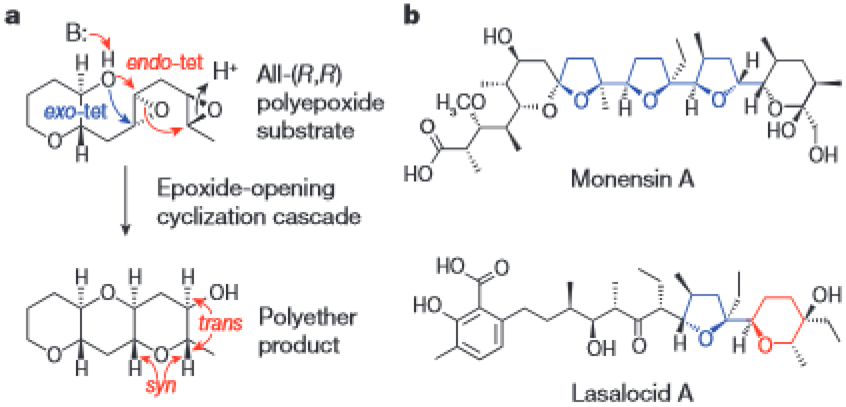
LETTER

doi:10.1038/nature10865

Enzymatic catalysis of anti-Baldwin ring closure in polyether biosynthesis

Kinya Hotta[1]*, Xi Chen[1]*, Robert S. Paton[2], Atsushi Minami[3], Hao Li[1], Kunchithapadam Swaminathan[1], Irimpan I. Mathews[4], Kenji Watanabe[5], Hideaki Oikawa[3], Kendall N. Houk[6] & Chu-Young Kim[1]

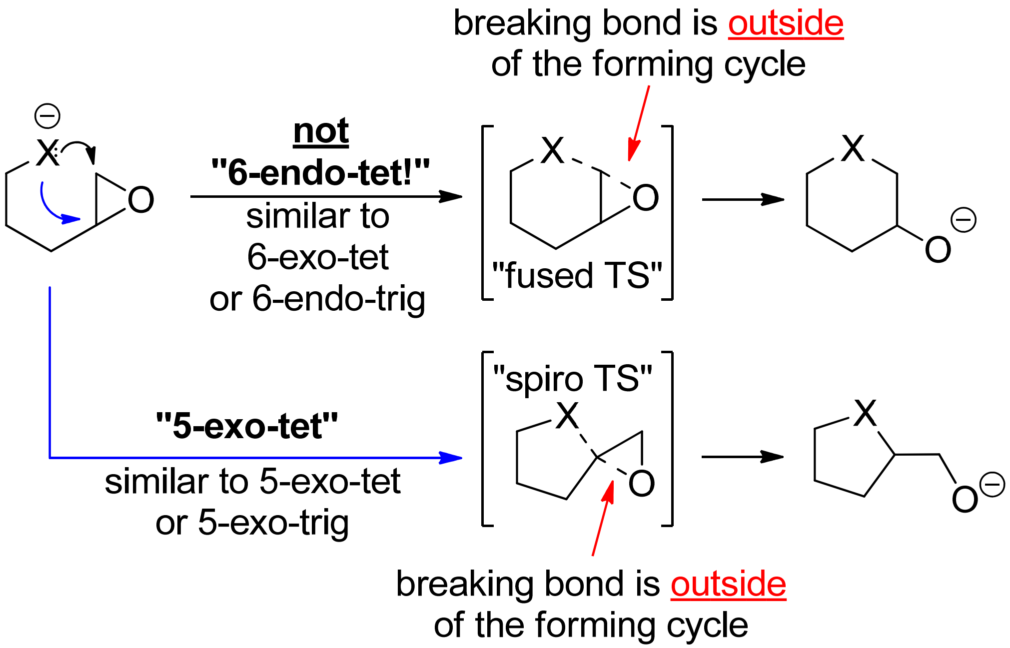
Do you agree with the **endo-tet** classification?



Hotta et al. *Nature,* **2012**, *483*, 355

CAVEATS AND VIOLATIONS

Enzymes DO follow the Baldwin rules



breaking bond is outside of the forming cycle

<u>not</u>
"6-endo-tet!"
similar to
6-exo-tet
or 6-endo-trig

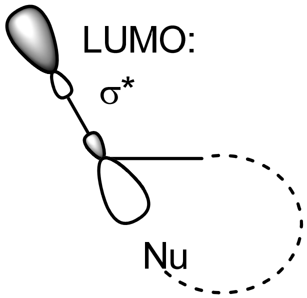
"5-exo-tet"
similar to 5-exo-tet
or 5-exo-trig

breaking bond is outside of the forming cycle

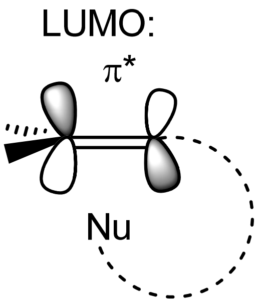
The "anti-Baldwin" enzymatic reactions of epoxides correspond to the favorable 6-exo-tet/6-endo-trig cyclizations. Nature chooses to achieve selective transformations by giving an additional advantage to one of the two favorable processes rather than overruling basic stereoelectronic principles

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246

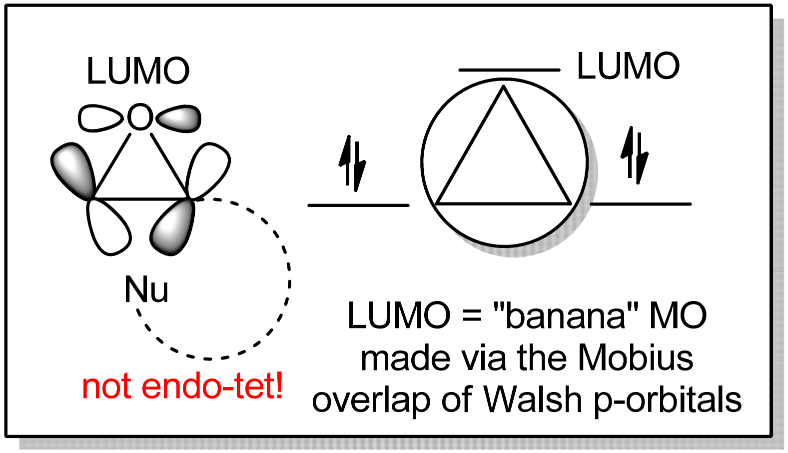
Epoxides: stereoelectronic analysis resolves controversies



n-exo-tet
favorable for n≥3



n-endo-trig
favorable for n≥6



not endo-tet!

LUMO = "banana" MO
made via the Mobius
overlap of Walsh p-orbitals

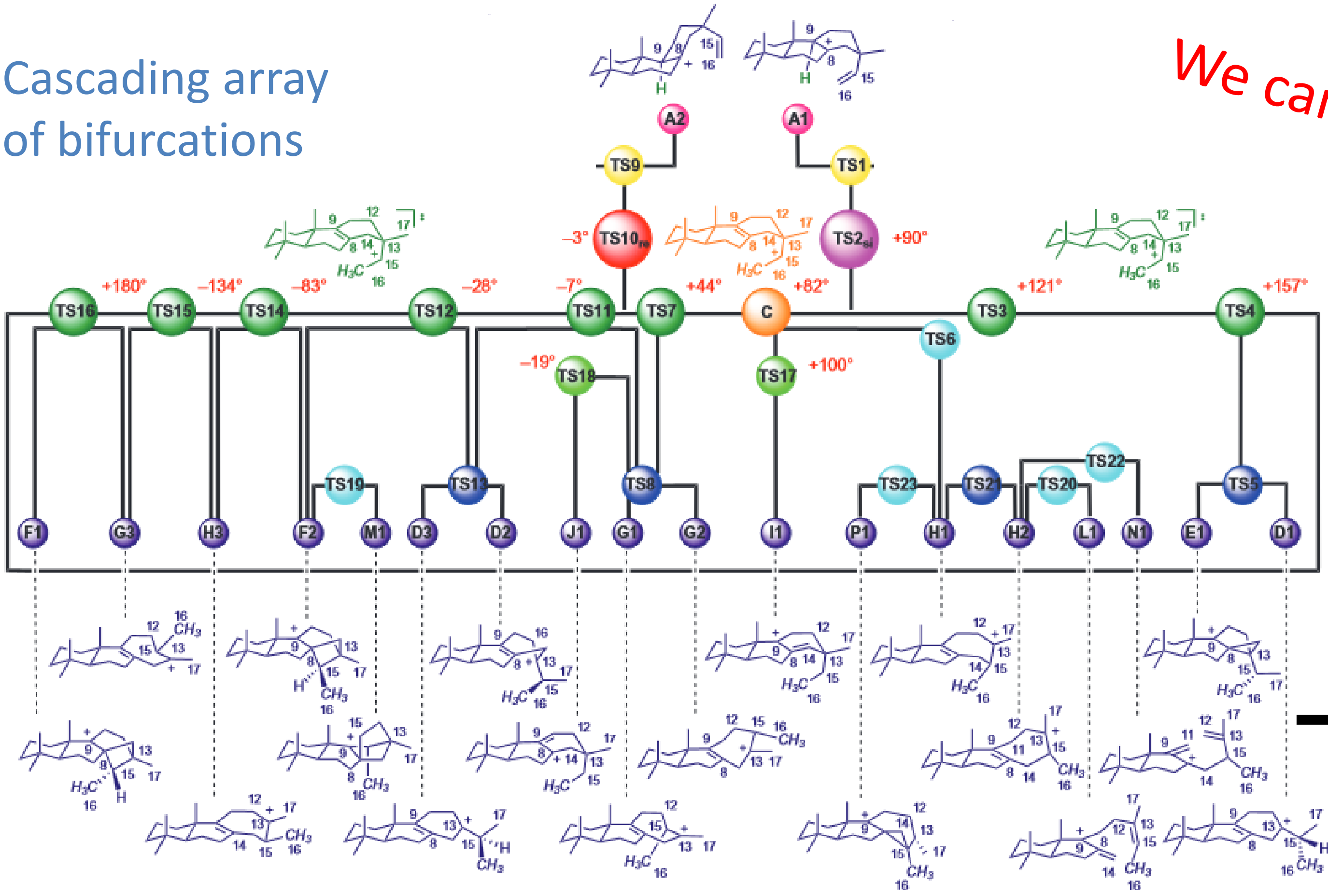
Epoxide cyclizations are indeed a
stereoelectronic hybrid of
exo-tet and endo-trig cyclizations

Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246

CAVEATS AND VIOLATIONS
Formation of multiple products through a single TS

Cascading array
of bifurcations

We can still learn from
Nature

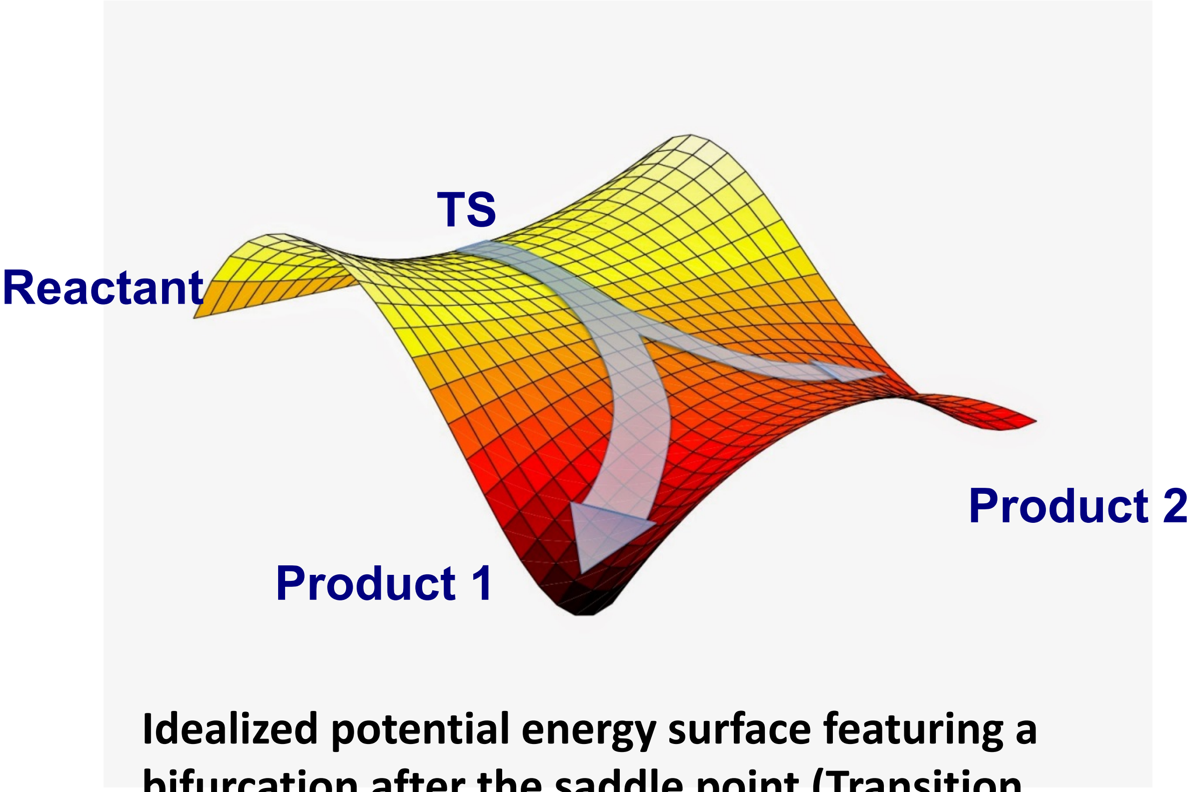


➡ Deprotonation of minima would lead to diterpene products.

Network of pathways that connects the pimar-15-en-8-yl cation (two conformers, A1 and A2) to 18 minima (purple) via only a single intervening minimum (C).

Y. J. Hong, D. J. Tantillo, *Nature Chem*. **2014**, 104

CAVEATS AND VIOLATIONS
Formation of multiple products through a single TS



Idealized potential energy surface featuring a bifurcation after the saddle point (Transition State). The point at which the pathway splits into two is a valley ridge inflection (VRI).

http://www.compchemhighlights.org/2014/04/post-transition-state-dynamics-in.html

Conclusions

Baldwin rules brought order into chaos, providing a set of simple guidelines for the design of cyclization reactions.

Precise control of cyclization steps is crucial for the success of cascade transformations

The rules had stimulated numerous studies aimed at the better understanding of organic structure and reactivity.

Baldwin rules were instrumental for the development of modern understanding of stereoelectronic effects.