Structure and Reactivity

Fall Semester 2008

Supplementary Material

Prof. Jérôme Waser
BCH 4306
021 693 93 88
jerome.waser@epfl.ch

Assistant:

Davinia Fernandez-Gonzalez
BCH 4409
021 693 94 49
davinia.fernandez@epfl.ch

Structure and Reactivity: Prerequired Knowledge

!!! The concepts presented in this summary are required for lecture and examination!!!

1. Important Principles in Organic Chemistry

In general, structures which can stabilize electrons are favored.

1.1 Electronegativity and "Octet" Rule

The electronegativity describes the ability of atoms to attract electrons. The nearest to octet (closed shell) the strongest the electronegativity. The electronegativity is weaker for larger atoms.

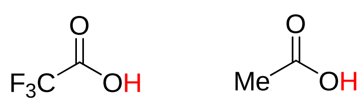
⟹ On chemical structures and during chemical reactions, the electrons go to the more electronegative element.

example:acidity

	Me_3CH		Me_2NH		MeOH		HF
pK_a	53	>	36	>	16	>	3.2
electronegativity	2.5		3.0		3.4		4.0

⟹ The conjugate base is more stable for more electronegative atoms!

Indirect effect: inductive effect



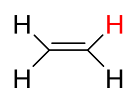
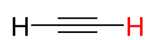
pK_a 0.25 < 4.76

⟹ Transfer of the influence of electronegative atoms through sigma bonds.

Effect of hybridization:

electron in orbitals with more s characters are more stabilized (more probability next to the nucleus)

example: acidity

	Me_3CH		
pK_a	53	50	24
Hybridization	Sp^3	SP^2	SP

1.2 Stabilization through Delocalization: delocalized charges (electrons) are more stable

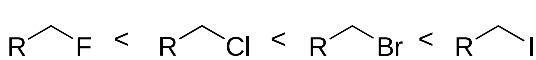
1.2.1 Delocalization onto 1 atom: large atoms are more able to stabilize charges (= polarizable)

examples 1) acidity:

	HF		HCl		HBr		HI
pK_a	3.2	>	-8	>	-9	>	-10
electronegativity	4.0		3.2		3.0		2.7

⟹ Delocalization is more important than electronegativity in this case!

2) leaving group ability in substitution reaction



1.2.2 Delocalization on two atoms: the chemical bond

Important for organic chemistry:

> 1) σ bond is stronger than π bond for C=C bond, but not for C=N and C=O
>
> 2) Delocalization is better between atoms of the same size (orbital overlap)
>
> 3) For strong polar bonds: ionic part can become important and compensate the weaker covalent bonds: prediction is more difficult

examples:

size effects

σ bond:	C-H	C-C	C-N	C-O	C-F	C-F	C-Cl	C-I
energy in Kcal	99	83	70	86	117	117	81	52

π-bonds	C=C	C=N	C=O	C=O	C=S
energy in Kcal	64	77	92	92	49

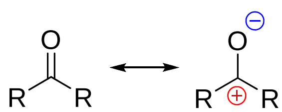
⟹ Important practical consequence: in organic chemistry, losing C=C and making C=O is often favorable!

1.2.3 Delocalization on more than two atoms: resonance structures

Resonance structure = obtained by moving electron without changing position or connectivity of atoms

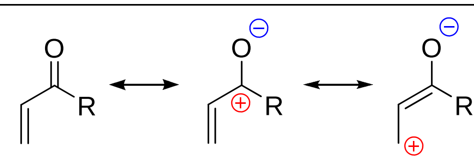
> **Resonance structures are essential to understand structure and reactivity in organic chemistry!**
>
> **good resonance structure** ⟷ octet rule for 1.raw elements, no charges, charges on electronegative atoms, more bonds, "better bonds", aromatic structures
>
> stabilization through resonance (delocalization) is maximal if the **resonance structures are identical**
>
> **"reality" = weighted sums of the resonance structures**

key examples:



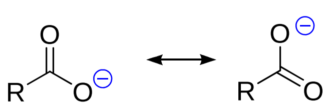
best structure

reactivity of carbonyls



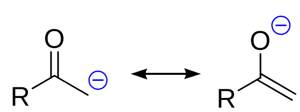
best structure

conjugate reactivity

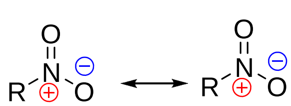


identical structures

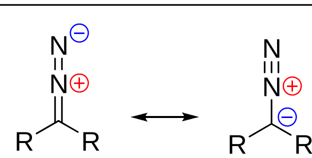
acidity of carboxylic acid



α-acidity of carbonyls and reactivity of enolates



identical structures



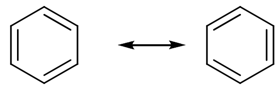
best structure

structure of nitro and diazo compounds

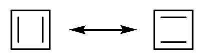
Stabilization of carbocations by neighbouring heteroatoms or bonds

Limitation of resonance structure: descripition of aromaticity

aromatic stabilization: cyclic conjugate π-system with 4n+2 electrons (Hückel's rule)

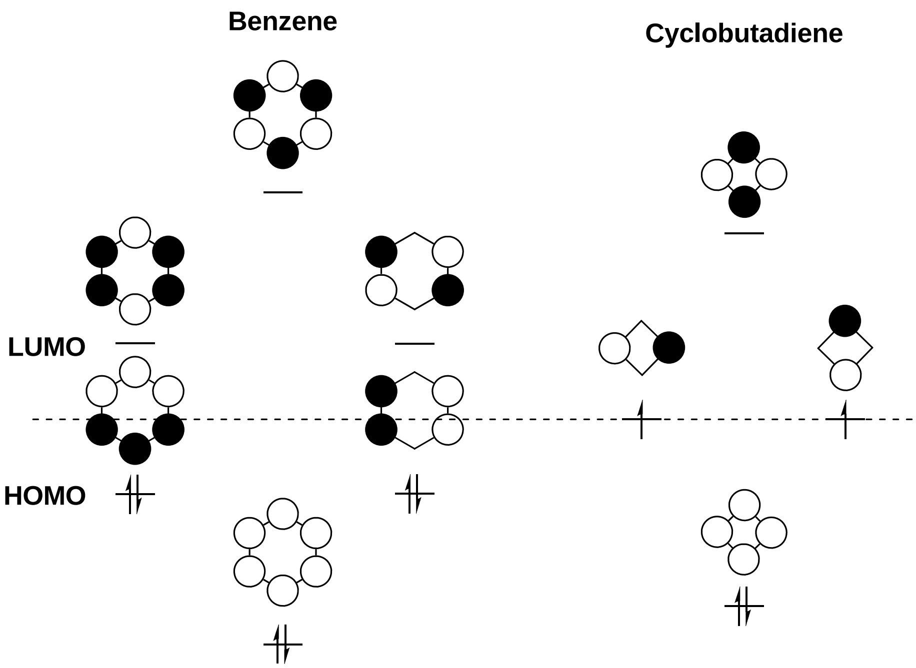


identical structure
stabilized



identical structure?
destabilized!

⟹ Higher level model is needed: orbital theory



Benzene: all electrons stabilized in bonding orbitals

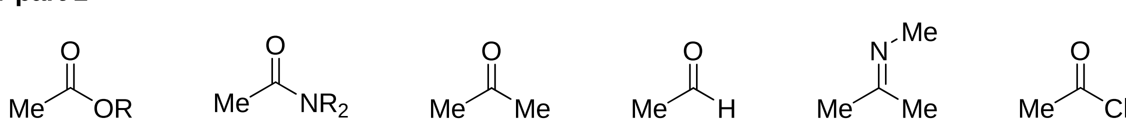
Cyclobutadiene: 2 electrons in non-bonding orbitals, no stabilization

LUMO = Lowest Unoccupied Molecule Orbital

HOMO = Highest Occupied Molecule Orbital

In organic chemistry, many observations can be explained by FMO (Frontier Molecular Orbital, LUMO and HOMO) considerations. This model is more powerful and precise than resonance/Lewis structure considerations, but need more time to apply.

Test for part 1



Classify this carbonyl compounds in order of increasing reactivity towards nucleophile addition.

2. Important Nucleophiles and Electrophiles in Bachelor Level Organic Chemistry

2.1 Nucleophiles

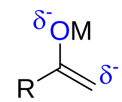
Heteroatoms

neutral:
- ROH (δ⁻ on O) — alcohols
- RNH_2 (δ⁻ on N) — amines
- RSH (δ⁻ on S) — thiols
- PR_3 (δ⁻ on P) — phosphines
- $R_2N{-}NH_2$ (δ⁻ on N) — hydrazines

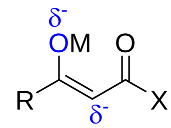
charged:
- $RO^{\ominus}$ — alcoholates
- $RNH^{\ominus}$ — amides
- $RS^{\ominus}$ — thiolates
- $X^{\ominus}$ — halogen anions

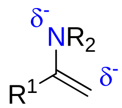
Hydrides (H^-) sources
- $NaBH_4$ (δ⁻ on H) — borohydrides
- $LiAlH_4$ (δ⁻ on H) — aluminium hydrides

C Nucleophiles
- RMgBr (δ⁻ on R) — Grignard
- RLi (δ⁻ on R) — alkyl lithium

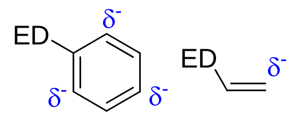

enolates

M = Na, K, Li


stabilized enolates


enamines

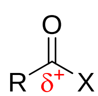
$^{\ominus}CN$ — cyanide

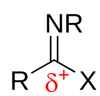

electron-rich aromatic compounds and alkenes

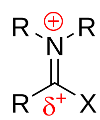
ED = Electron-donating group

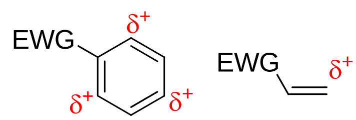
2.2 Electrophiles

- $H^{\oplus}$, $M^{\oplus}$ — proton, metals
- RX — alkyl halogenide


carbonyls


imines


iminiums


electron-poor aromatic compounds and alkenes

EWG = Electron-withdrawing group

2.3 Hard and Soft classification of Nucleophiles (Lewis Bases) and Electrophiles (Lewis Acids)

Hard ⟷ charged, localized electrons, highly electronegative/positive, reaction under charge control

typical hard electrophiles: H^+, Mg^{2+}, RCl, ROTf

typical hard nucleophiles: RMgBr, RLi, RO^-, RNH^-, F^-, O atom of enolates

Soft ⟷ less charged, delocalized electrons, reaction under orbital (HOMO-LUMO) control

typical soft electrophiles: Pd^{2+}, carbonyls, electron-poor double bonds and aromatic compounds

typical soft nucleophiles: C atom of enolates, stabilized enolates, electron-rich double bonds and aromatic compounds, I^-, RNH_2, PR_3

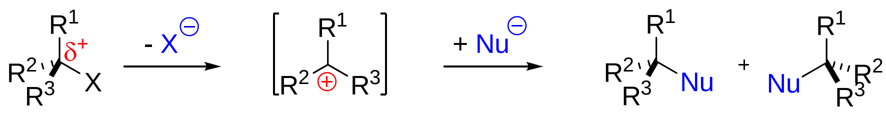
Principle: **Hard-Hard and Soft-Soft interactions are favored!**

⟹ Competition basicity-nucleophilicity: especially hard nucleophiles are usually also strong bases, because proton is hard (hard-hard interaction)

3. Important Classical Reactions in Bachelor Organic Chemistry

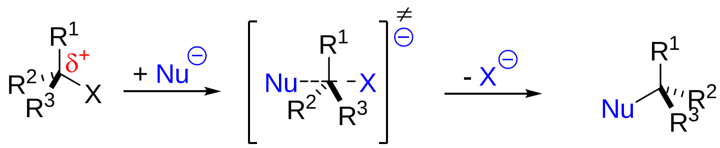
3.1 Substitution Reactions

S_N1



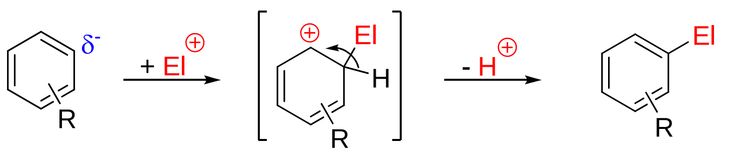
racemization

S_N2



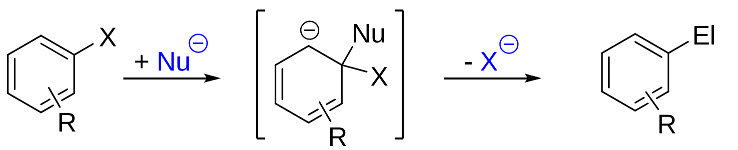
inversion

S_EAr



better for R electron-donating in ortho-para

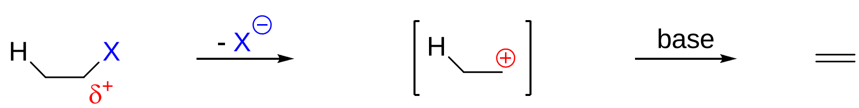
S_NAr



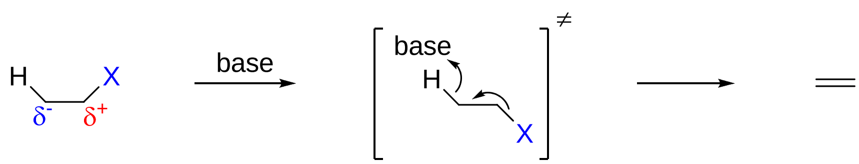
better for R electron-withdrawing in ortho-para

3.2 Elimination Reactions

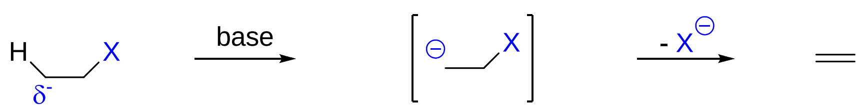
E_1



E_2



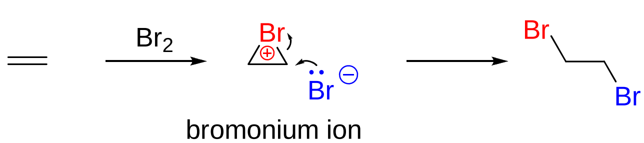
E_{1cb}



3.3 Addition to double bonds

In principle: all mechanisms for elimination are possible in the reverse sense!

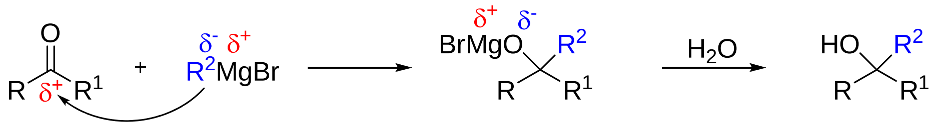
Special case: dibromination



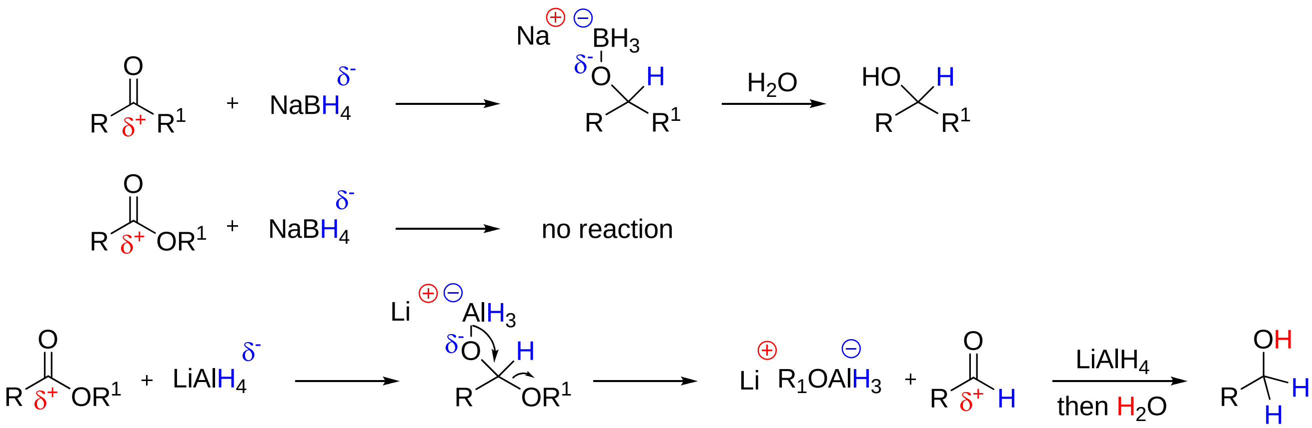
3.4 Chemistry of Carbonyls

3.4.1 Nucleophile Addition

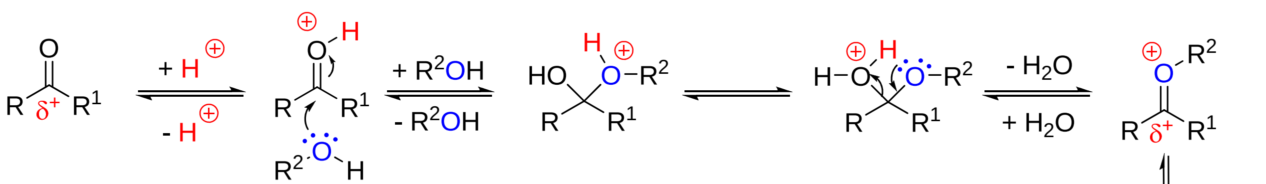
Grignard

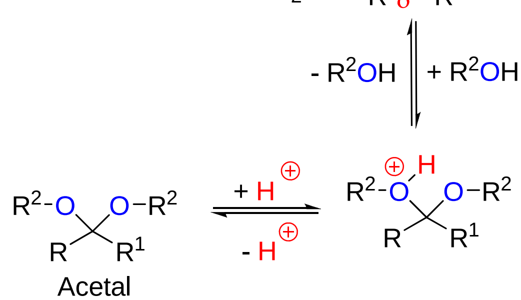


Hydride Reduction



Alcohols: acetal formation under acidic catalysis

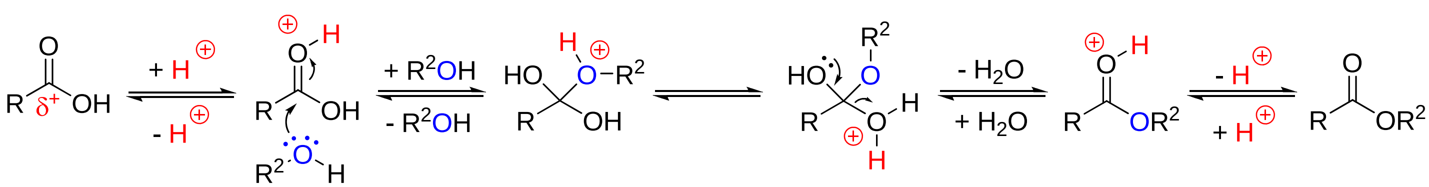




Equilibrium is on the side of the ketone

⟹ It is necessary to remove water to drive reaction!

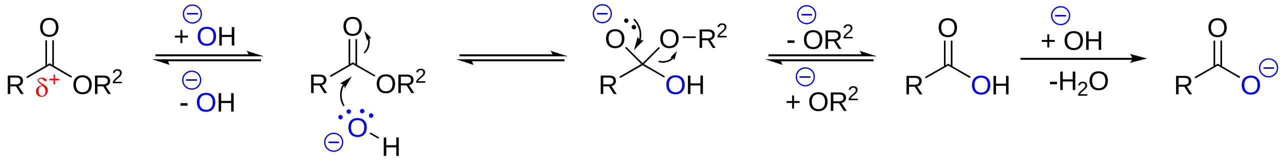
Alcohols: ester formation under acidic catalysis



Equilibrium is nearly 1:1

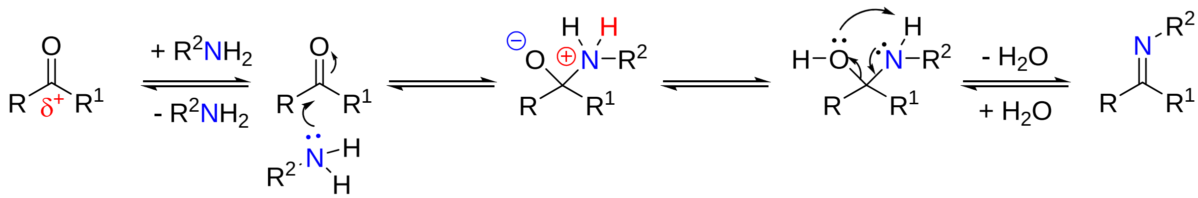
⟹ Use excess alcohol to drive reaction

Ester Hydrolysis



Stability of carboxylate ⟹ completely on the side of product!

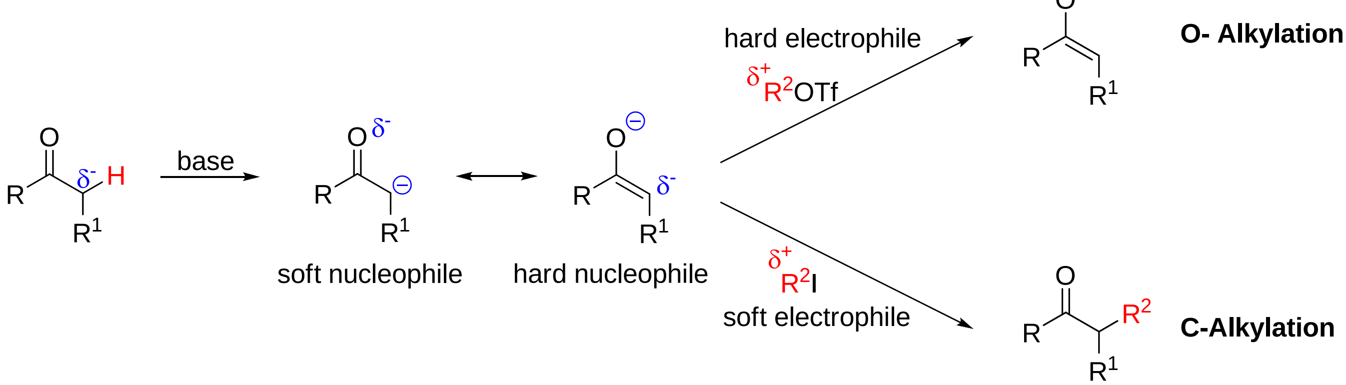
Amine addition and imine formation



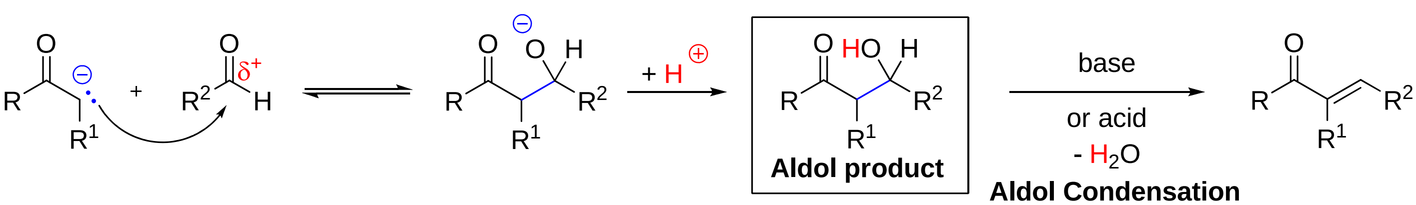
Water removal necessary for ketones, reaction easier with aldehyde

3.4.2 Enolate chemistry

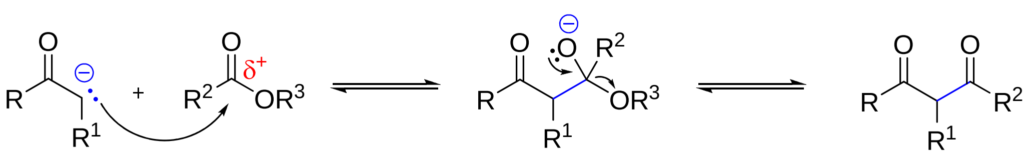
Enolate alkylation



Aldol Reaction

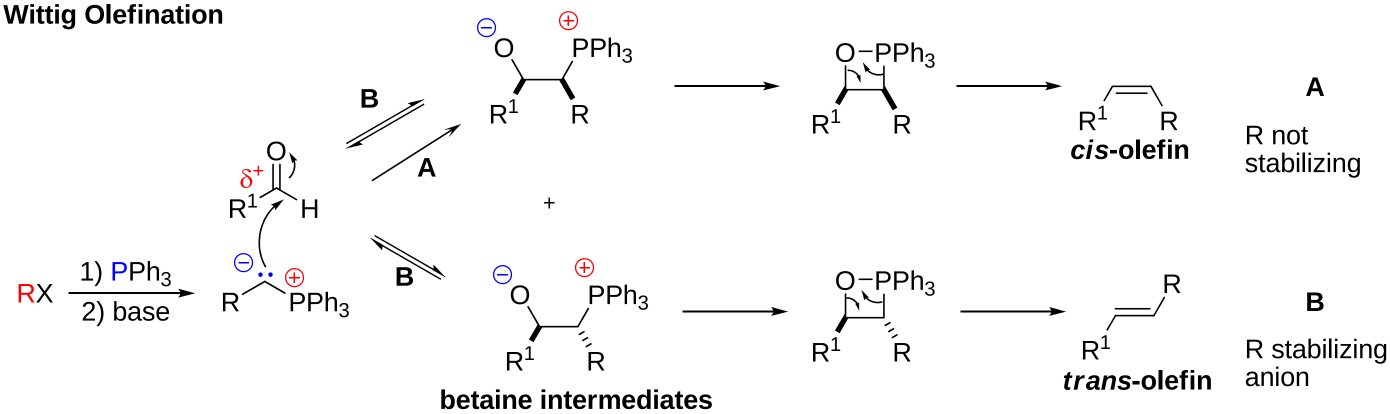


Claisen Condensation



Other related reactions: Knoevenagel condensation, Perkin condensation, Dieckmann condensation.

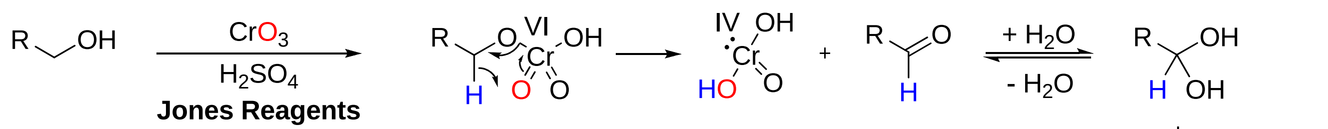
Wittig Olefination



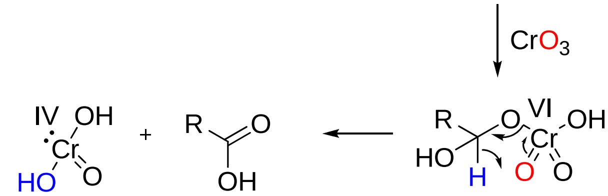
For non-stabilized ylides (**A**), formation of the *cis* betaine is favored and irreversible, leading to *cis* olefin. For stabilized ylides (**B**), an equilibrium lead to formation of the more stable *trans* betaine and finally to *trans* olefin.

3.5 Oxidation Reactions

Chrom(VI)

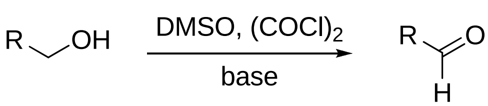


Second oxidation step possible only in presence of water!

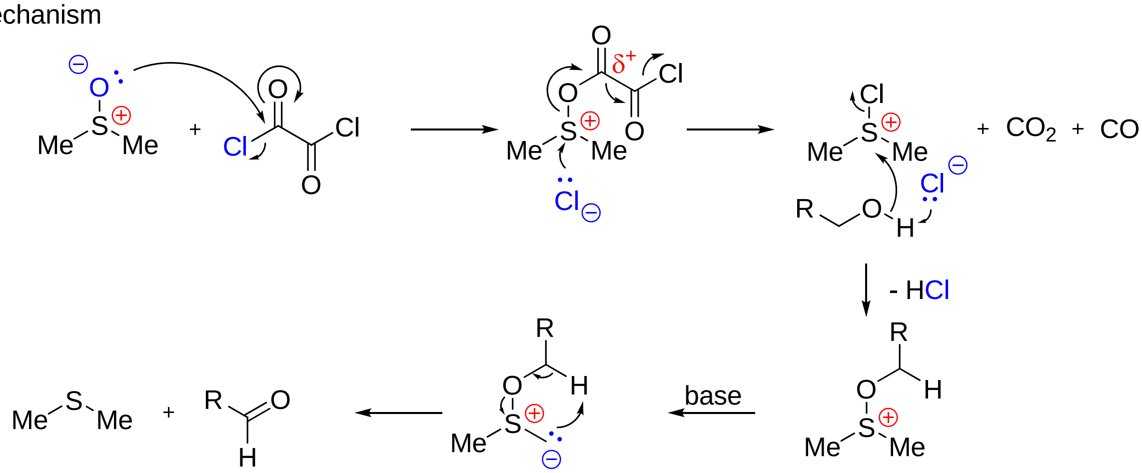


In practice also often used PDC (pyridinium dichromate), PCC (pyridinium chlorochromate)

Moffat-Swern



Mechanism



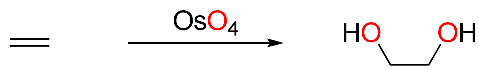
In practice, there are many more methods!

Dihydroxylation, Ozonolysis and Epoxidation

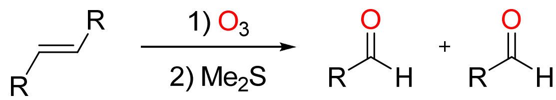
Epoxidation

*m*CPBA = *meta*-chloroperbenzoic acid

Dihydroxylation



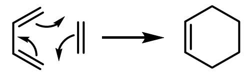
Ozonolysis



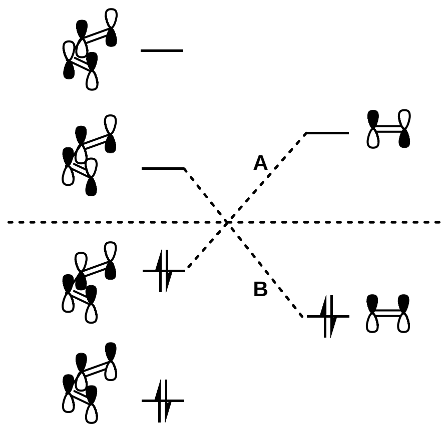
These reactions will be rediscussed in more details in the lecture

2.2.2 Diels Alder Cycloaddition: Introduction

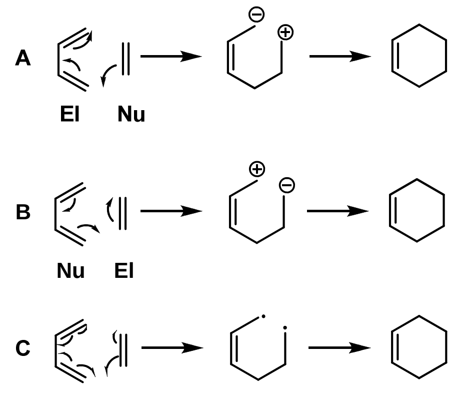
Diels-Alder: Repetition of Key Concepts



Homo-Lumo Interactions



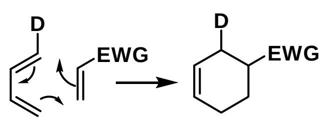
Asynchronous Model



47

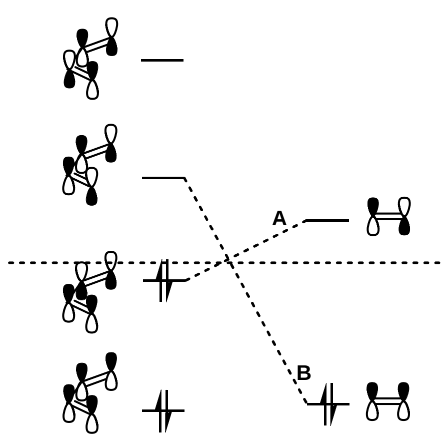
2.2.2 Diels Alder Cycloaddition: Introduction

"Normal Electron-Demand" Diels Alder

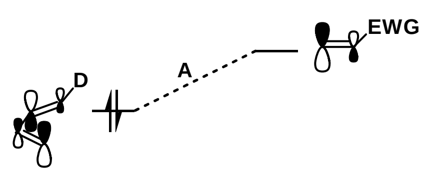


D = OR, NR_2, ...
EWG = COX, NO_2, ...

Homo-Lumo Interactions



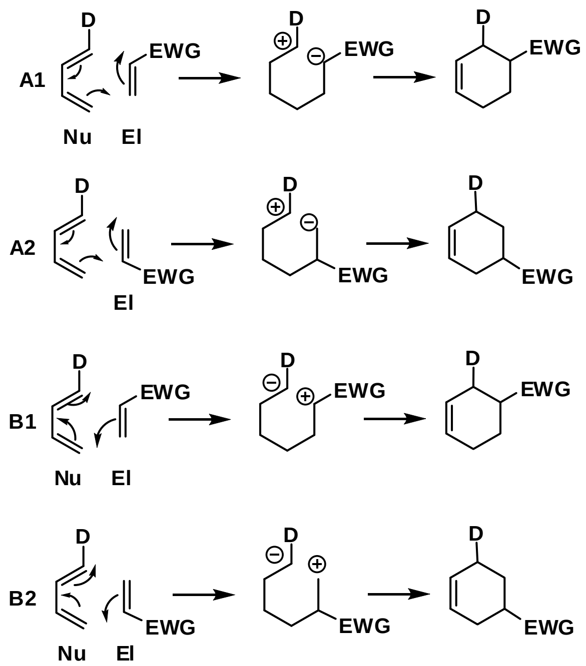
Major Homo-Lumo Interaction:
Including Perturbation of Substituents



48

2.2.2 Diels Alder Cycloaddition : Introduction

Normal Electron-Demand ” Diels Alder: Asynchronous Model



Best stabilization

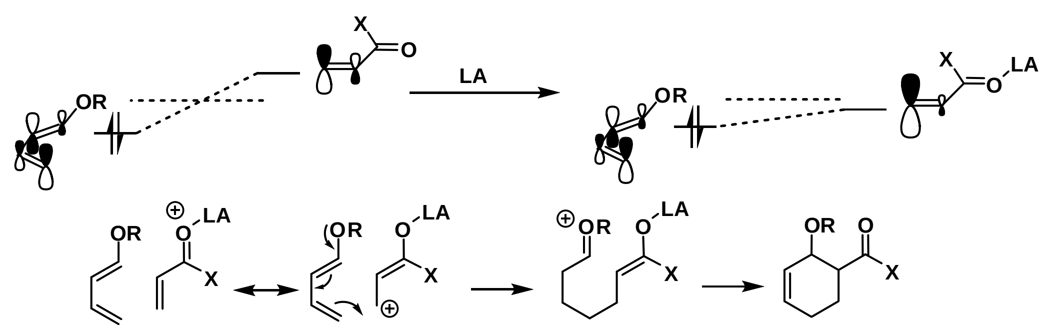
Anion not stabilized

Only destabilization

One destabilization

2.2.2 Diels Alder Cycloaddition : Introduction

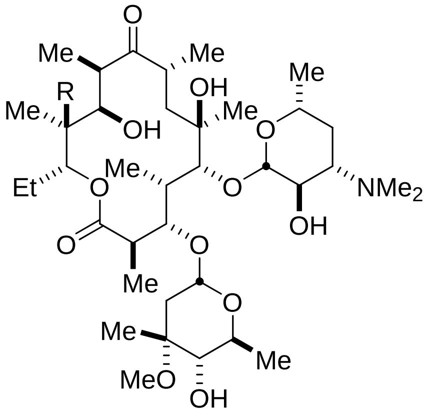
” Normal Electron-Demand ” Diels Alder: Lewis Acid Catalysis



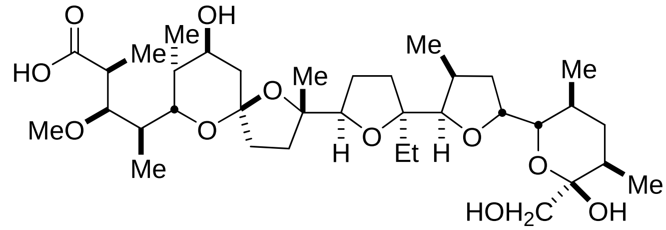
Endo vs Exo Selectivity

A Playground for Carbonyl (Aldol) Chemistry: Polyketide Natural Products

Antibiotic

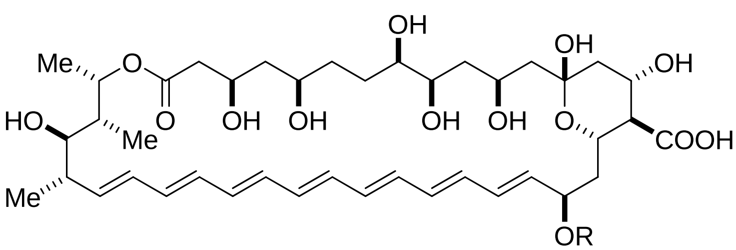


Erythromycin A, R = OH
Erythromycin B, R = H

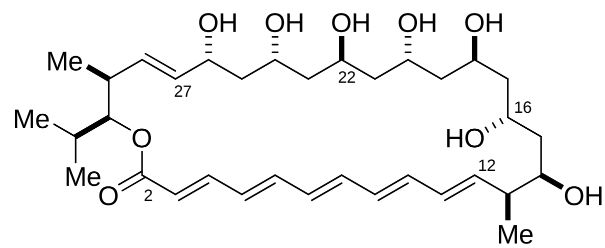


Monensin

Antifungal

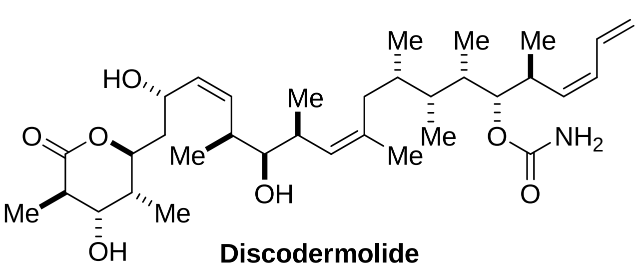


Amphotericin B

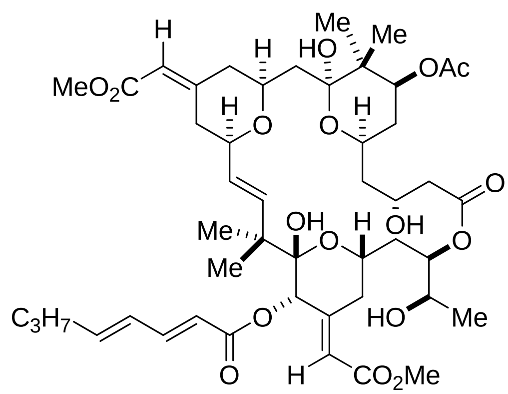


(+)-roxaticin

Anticancer



Discodermolide

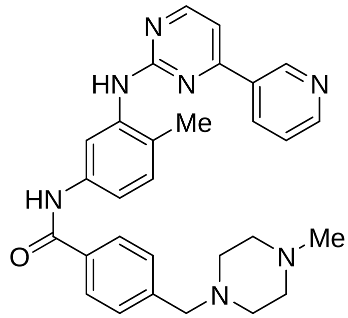


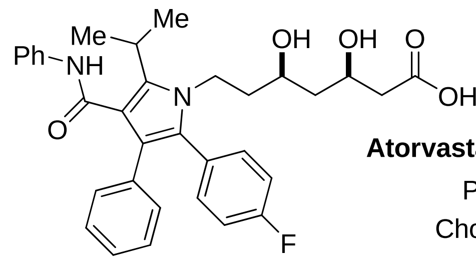
Bryostatin I

Applications of Cross Coupling Reaction: Drugs and Natural Products

Aryl-aryl and aryl-heteroatom cross coupling: synthetic drugs

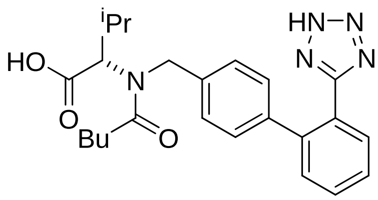
Imatinib (Gleevec®)
Leukemia
Novartis

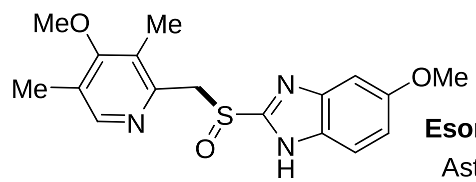




Atorvastatin (Lipitor®)
Pfizer
Cholesterol

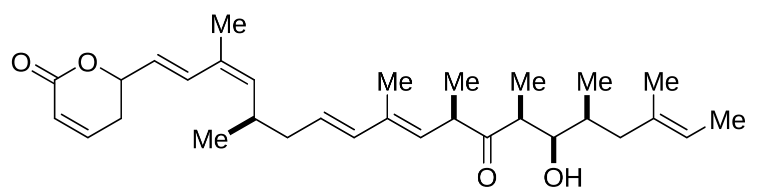
Valsartan (Diovan®)
Novartis
Hypertension



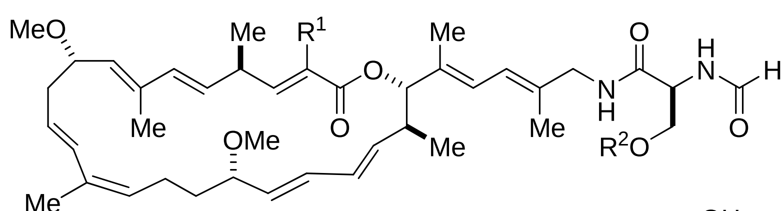


Esomeprazole
AstraZeneca
Gastrointestinal disorders

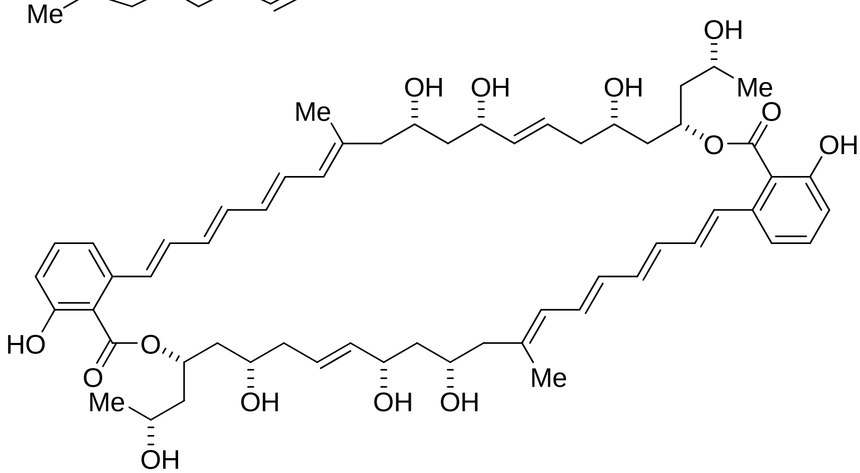
Stereoselective acces to polyene natural products



anguinomycin C
S. Bonazzi, K. Gademann
anticancer



iejimalides
anticancer



Marinomycin A
antibiotic

To synthesize these targets, a combination of cross-coupling and aldol methodology is the winning team!