Asymmetric Synthesis

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1. Introduction

1.1 Aims and structure of the course

1.1.1 Aims

The scientific aims of the course are the following:

- Become aware of the importance of chirality in organic synthesis and for the bioactivity of organic compounds.
- Analyze and understand stereochemistry elements for fundamental reactions learned in the first two years of study: **Discover the third dimension**.
- Learn about non-catalytic asymmetric synthesis methods in the classical chemistry involving alkenes and carbonyl compounds. Only a few catalytic methods will be presented, as catalytic methods are topic of a dedicated lecture at master level (Catalytic asymmetric reactions in organic synthesis).
- Become able to analyze and rationalize stereochemistry in key diastereoselective steps in multi-step synthesis.

The technical and pedagogical aims of the course are the following:

- Be able to draw and visualize transition states in three dimensions
- Understand important principles in stereochemistry and apply them to new situations.
- Increase independence when acquiring new knowledge.

EPFL curtius in organic chemistry

Bachelor

1ère année : AIMF I: Notions de bases et stéréochimie (Jerome Waser). Fonctions et réactions organiques I : Revue détaillée des réactions de bases en chimie organique (Sandrine Gerber).

2ème année Fonctions et réactions organiques II et III: Revue détaillée des réactions classiques en chimie organique et des modèles pour les comprendre (Jieping Zhu et Nicolai Cramer).

3ème année **Synthèse asymétrique** : Concepts de stéréochimie dans les réactions classiques (Jerome Waser). Chimie Médicinale : Chimie des substances bio-actives (Elena Dubikovskaya). Rétrosynthèse : Concepts de rétro-synthèse et synthèse (Sandrine Gerber)

Master

Bloc organic chemistry : Structure and reactivity : Reactivity concepts in more complex organic chemistry settings (Nicolai Cramer). Total Synthesis of Natural Products (Jieping Zhu). Physical and computational organic chemistry (Clémence Corminboeuf).

Option: Catalytic asymmetric reactions in organic synthesis. (Jerome Waser).

1.1.2 Structure of the course

The core of the course is a blackboard lecture, slides being used only in case of highly complex structures or to summarize less important concepts. There will be one hour of exercise for three hours of course.

- **Lectures note** : The lectures note do not cover all the course, but include all the models and concepts. Examples are given without explanations and solutions. Those will be given during the blackboard lecture or the exercise sessions. Drawing by yourself structures is essential for this lecture. Not all the parts of the lectures notes will be described in depth, as some parts are given as additional information.
- **Exercise sessions** : A lot of exercising is absolutely necessary for this course. In fact, the concepts are usually quite easily understood, but it is often challenging to visualize them in new examples. Participating to exercise sessions actively and working on the exercises constitute the best preparation for the exam. The exercise session will start in the class with the help of the teacher and assistant and should be finished individually. Solutions will be posted on moodle after each class. Old exercises are available on the website of the course.
- **Exam**: Written exam of 2 hours. Five exercises will be given. Solving four of them will give the maximal grade (alternatively 5 can be solved partially).

1.1.3 Bibliography in organic chemistry

To support learning, bibliographic references will be given during the lectures. The exam will be based however only on the lecture notes and exercises. The references may help to understand the courses based on other approaches.

1.1.3.1 Basic knowledge, level lower than the lecture:

- EPFL courses: AIMF, Fonction et réactions organiques I à III
- Peter C. Vollhardt, Neil E Schore, *Organic Chemistry: Structure and Function*, Palgrave Macmillan. (éditions 5-6)
  →One of the best introductory book for organic chemistry.
- Jonathan Clayden, Nick Greeves, Stuart Warren, Peter Wothers, *Organic Chemistry*, 2001, Oxford University Press.

  →More advanced and complete.

1.1.3.2 More advanced books

-General:

- **Francis A. Carey, Richard J. Sundberg, *Advanced Organic Chemistry Part A and B*** (two volumes), Fifth Edition, 2008, Springer.
  + Complete (2500 pages) book and often used, affordable. Good description of reactivity covering the lectures FRO I-III, asymmetric synthesis and structure and reactivity (master).
  - Somewhat repetitive and not focused a lot on stereochemistry, **Bad drawing quality**
- Michael B. Smith and Jerry March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, sixth edition, 2007, John Wiley & Sons.
  + Information is very dense, good for specific questions
  - Not adpated for learning, as too dense
- Lazlo Kürti, Barbara Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, 2005, Elsevier.
  + High quality drawing, good summary of most important reactions
  - No real structure (reactions dictionary). Good for questions on specific reactions.

Stereochemistry:

- Ernest L. Eliel, Samuel H. Wilen, *Stereochemistry of Organic Compounds*, 1994, John Wiley & Sons.
  + Bible of stereochemistry
  - Not synthesis oriented, focus on structure and properties
- **Erick M. Carreira, Lisbet Kvaerno, *Classics in Stereoselective Synthesis***, 2009, Wiley VCH.
  + Focused on stereoselectivity in synthesis, high quality drawing, cover topics of lectures asymmetric synthesis, structure and reactivity and catalytic asymmetric reactions in organic synthesis.
  - Advanced book, only first pages of each chapter OK for bachelor, very good for motivated students wanting to go farther.

Synthesis Strategy :

- K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, 1995, Wiley VCH.
  + Historic collections of total synthesis key for progress in organic chemistry. Detailed description of reactions. Can be read as a novel.
  - Structure based on molecules, not reaction types. It is better to read it once basic knowledge of reactions is acquired.
- K. C. Nicolaou, S. A. Snyder, *Classics in Total Synthesis II*, 2003, Wiley VCH.
  Follow-up of preceding work, slightly less enjoyable.
- Stuart Warren, Paul Wyatt, *Organic Synthesis: The Disconnection Approach*, 2nd edition, 2007, Wiley.
  + Detailed discussion of retrosynthesis. Good support for lecture retrosynthesis.
  - Structure of the book difficult to follow
- E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, 2nd edition, 1995, Wiley.
  + Bible of retrosynthesis. Concepts and numerous examples.
  - Advanced book with concise explanations, difficult to follow before finishing the lecture retrosynthesis

Reaction mechanisms :

- **Reinhardt Brückner, *Organic Mechanisms: Reactions, Stereochemistry and Synthesis*,** 2010, Springer.
  + One of the best books for mechanisms in organic chemistry.
  - No description of multi-step synthesis
- Ian Fleming, *Molecular Orbitals and Organic Chemical Reactions*, 2009, Wiley.
  + Description of structure and reactivity of orbitals, but at a level accessible for organic chemists.
  - Explication of fundamental concepts, not focused on synthesis.
- Kendall N. Houk, Pierre Vogel, *Advanced Organic Chemistry*, 2009, Garland publishing Inc..
  + Quantitative description of physical organic chemistry.
  - Focus on fundamental concepts, not on synthesis.

Information Online :

- **Moodle : http://moodle.epfl.ch/**
- Laboratory of catalysis and organic chemistry (LCSO) : http://lcso.epfl.ch/
- **Evans Lecture** (Google for Evans Chem 206). One of the best courses on the web, available up to 2006. Very good description of reactivity and selectivity.

- **Former asymmetric synthesis lecture of** professeur Vogel
- Several links for organic chemistry resources are available on the LCSO website.

Importance of chapters in lecture notes :

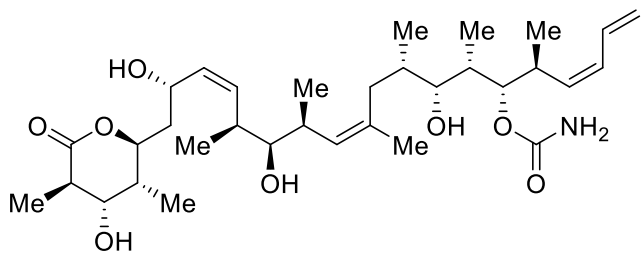
A : essential for success in the lecture

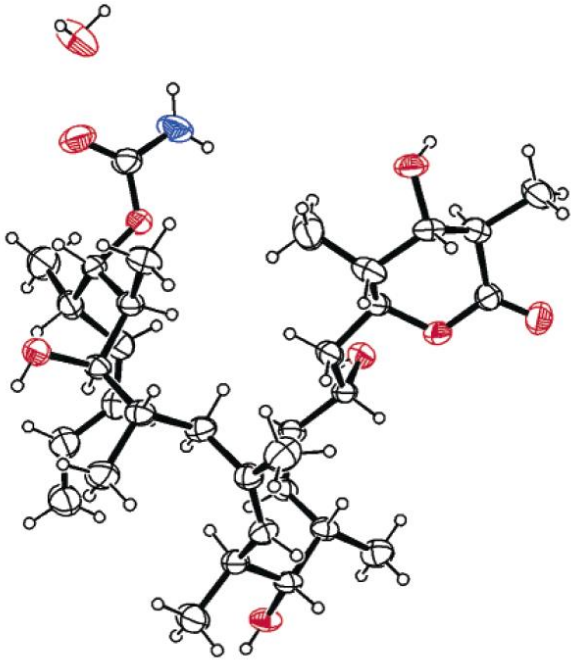
B : important : topic of exam.

C : general information (for linking with other lectures, not exam topic)

D : additional information (more advanced topic usually discussed in master, not exam topic)

1.2 The Discodermolide Challenge (B,C)





13 stereocenters, 2 *cis* alkenes, one conjugated dien

4 alcohols, 1 lactone and 1 carbamate

Background

- Isolated from sponges from the Caribbean Sea (7 mg from 434 g sponges)
- Not produced by the sponge and the producing organism could not be found
- highly cytotoxic (IC_{50} = 3-80 nM, via tubulin polymerization)

⟹ **Job for the chemist**: synthesize 60 g of discodermolide.

Goal: At the end of the lecture, you should be able to understand and rationalize the selectivity in the key steps of the discodermolide synthesis.

1.3 Basic knowledge in organic chemistry required for this course

!!! The basic knowledge presented in this section is required for lecture, exercises and exam!!!

1.3.1 Core principles in organic chemistry (A)

Structures with stabilized electrons are favored.

1.3.1.1 Electronegativity and Octet rule

Electronegativity is correlated to the affinity of nuclei towards electrons. Atoms closer to the octet have a higher electronegativity. Heavy atoms have a lower electronegativity

⟹ On chemical structures and during reactions, the electrons usually "go" towards more electronegative atoms.

example: acidity

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

⟹ conjugated base is more stable for more electronegative atoms

Indirect effect: Inductive effect

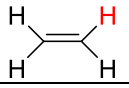
pK_a 0.25 < 4.76

⟹ Induction of electronegativity through sigma bonds

Atom hybridisation effect

The higher the s character, the more stable the electrons (higher probability close to nucleus)

example: acidity

	Me_3CH		
pK_a	53	50	24
Hybridisation	SP^3	SP^2	SP

1.3.1.2 Stabilisation through delocalization: delocalized electrons (charges) are more stable

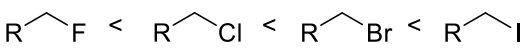
1.3.1.2.1 Delocalization on one atom: Charges on larger atoms are more stable (polarization)

examples 1) acidity:

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

⟹ Delocalization more important than electronegativity in this case!

2) Classification of leaving group ability for substitution reactions



1.3.1.2.2 Delocalization on two bonds: the chemical bond

Important in organic chemistry:

1) σ bond is stronger than π for C=C, but not for C=N and C=O
2) Delocalization in covalent bonds is better for atoms of the same size
3) In polar bonds: favorable electrostatic interactions can (over)compensate for weaker delocalization. Any estimation is difficult in this case.

examples:

						Effect of size		
σ bonds:	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 consequence in organic chemistry: going from C=C to C=O bonds if often favored

1.3.1.2.3 Delocalization in more than two atoms: resonance structures

resonance structures are obtained by moving electrons **without** changing position or connectivity of atoms.

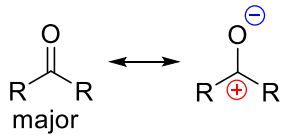
Resonance structures are essential to understand reactivity in organic chemistry!

Good resonance ⟷ Octet respected for 2nd row elements, no charges or charges according to electronegativity, more bonds, more stable bonds, aromatic structures

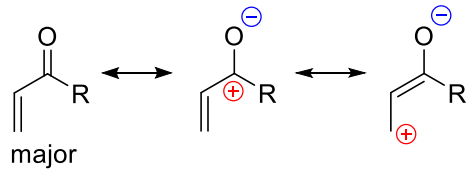
stabilisation effect is maximal for identical structures

"Reality" = Weighted sum of all resonance structures

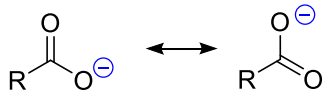
Important examples:



carbonyl reactivity

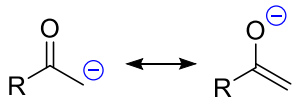


conjugated reactivity

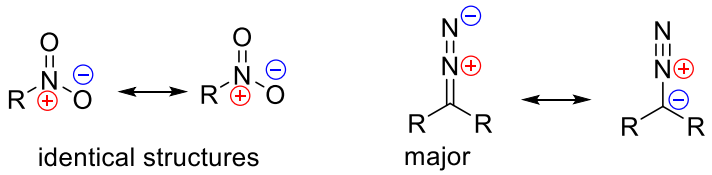


identical structures

acidity of carboxylic acids



acidity in α position of carbonyls and enolate reactivity

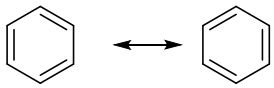


structure of nitro and diazo compounds

carbocation stabilization by sigma bonds or electron pairs

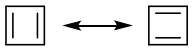
Limitation of resonance structures: aromatic stabilization

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



identical structures

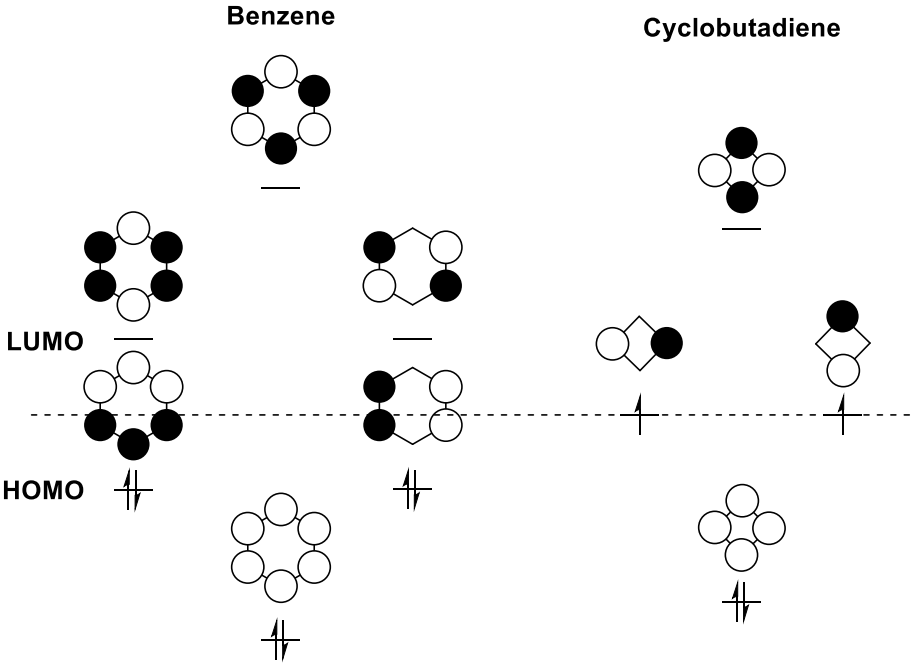
stabilized



identical structures?

destabilized!

⟹ A better model is needed: the orbital model



Benzene: all electrons are stabilized in binding orbitals

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

LUMO = Lowest Unoccupied Molecule Orbital

HOMO = Highest Occupied Molecule Orbital

In organic chemistry, a lot can be explained by the FMO theory (Frontier Molecular Orbital, LUMO and HOMO). This model is more powerful that simple examination of the Lewis structures, but analysis obviously takes more time.

Test

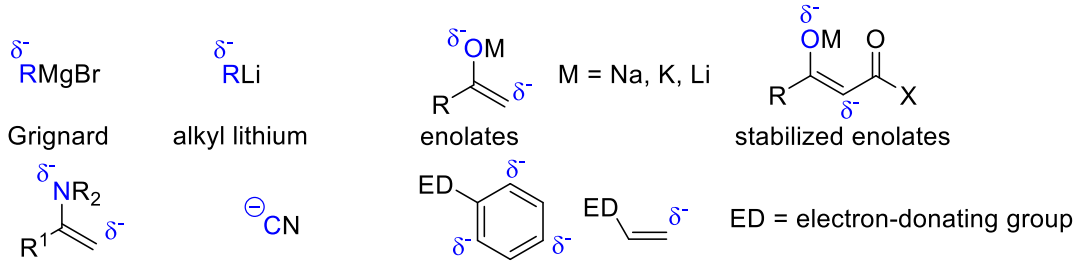
Classify these compounds according to their reactivity for the addition of nucleophiles.

1.3.2. Important nucleophiles and electrophiles in basic organic chemistry (A)

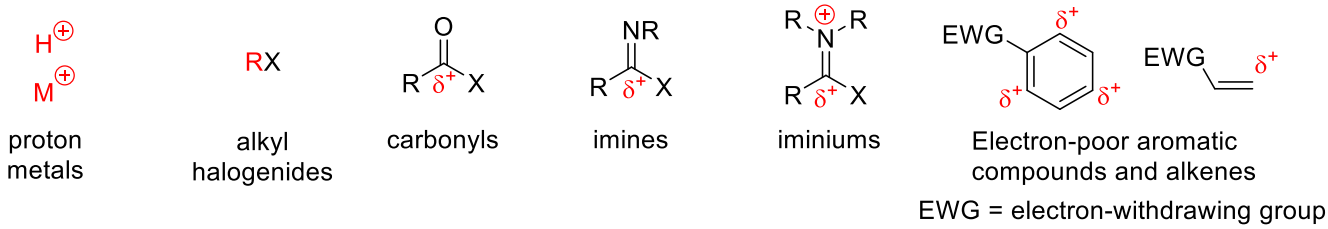
1.3.2.1 Nucleophiles

Heteroatoms	$R\overset{\delta-}{O}H$ alcohols	$R\overset{\delta-}{N}H_2$ amines	$R\overset{\delta-}{S}H$ thiols	$\overset{\delta-}{P}R_3$ phosphines	$R_2N-\overset{\delta-}{N}H_2$ hydrazines	**neutral**
	$RO^{\ominus}$ alcoholates	$R\overset{\ominus}{N}H$ amides	$RS^{\ominus}$ thiolates	$X^{\ominus}$ halogenides		**charged**
Hydride sources (H^-)	$NaB\overset{\delta-}{H}_4$ borohydrides	$LiAl\overset{\delta-}{H}_4$ aluminium hydrides				

C nucleophiles



1.3.2.2 Electrophiles



1.3.2.3 Hard ans soft nucleophiles and electrophiles (Lewis acids and bases)

Hard ⟷ charged, localized electrons, very electronegative/positive, charged controlled reactions

examples of hard electrophiles: H^+, Li^+, Mg^{2+}, Al^{3+}, RCl, ROTf, carbonyls

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

Soft ⟷ less charged, delocalized electrons, orbital-controlled reactions (HOMO-LUMO)

examples of soft electrophiles: Pd^{2+}, carbonyls, Electron-poor aromatic compounds and alkenes

examples of soft nucleophiles: C atom of enolates, stabilized enolates, electron-rich aromatic compounds and alkenes, I^-, RNH_2, PR_3

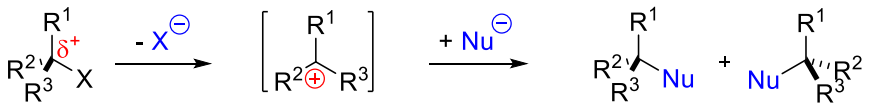
Principle: **soft-soft and hard-hard interactions are favored!**

⟹ Competition basicity-nucleophilicity: in particular hard nucleophiles are also strong bases, as the proton is hard (hard-hard interaction).

1.3.3. Basic reactions in organic chemistry (A)

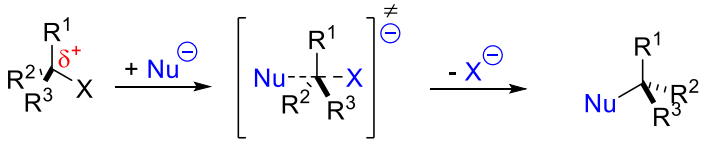
1.3.3.1 Substitution

S_N1



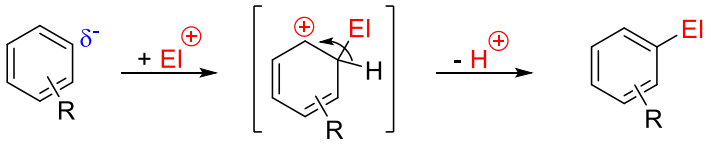
racemisation

S_N2



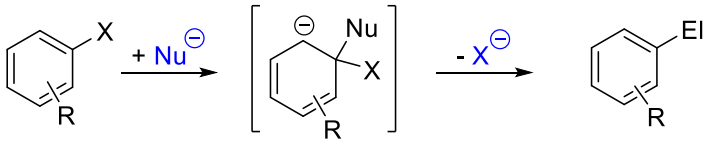
inversion

S_EAr



favored with electron-donating groups in ortho/para positions

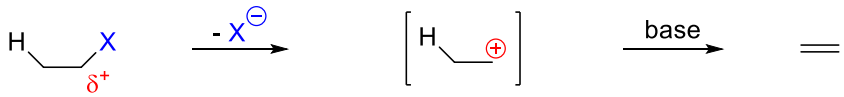
S_NAr



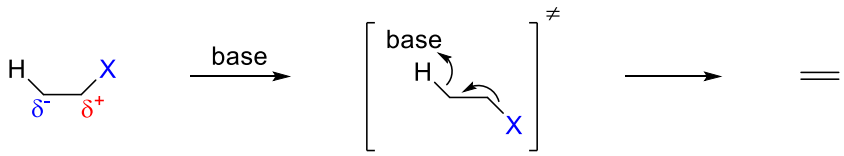
favored with electron-withdrawing groups in ortho/para positions

1.3.3.2 Elimination

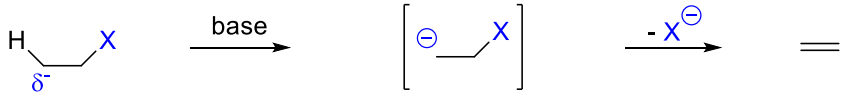
E_1



E_2



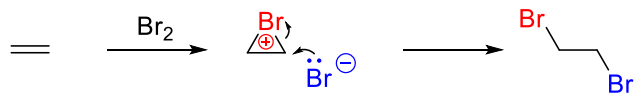
E_{1cb}



1.3.3.3 Addition on double bonds

In principle, all elimination mechanism are possible in reverse sense

Special case: dibromination

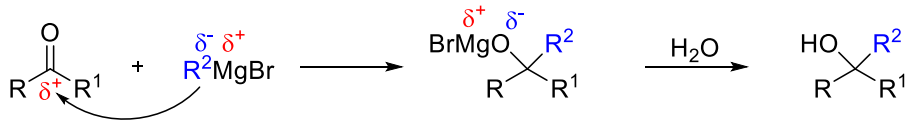


bromonium ion

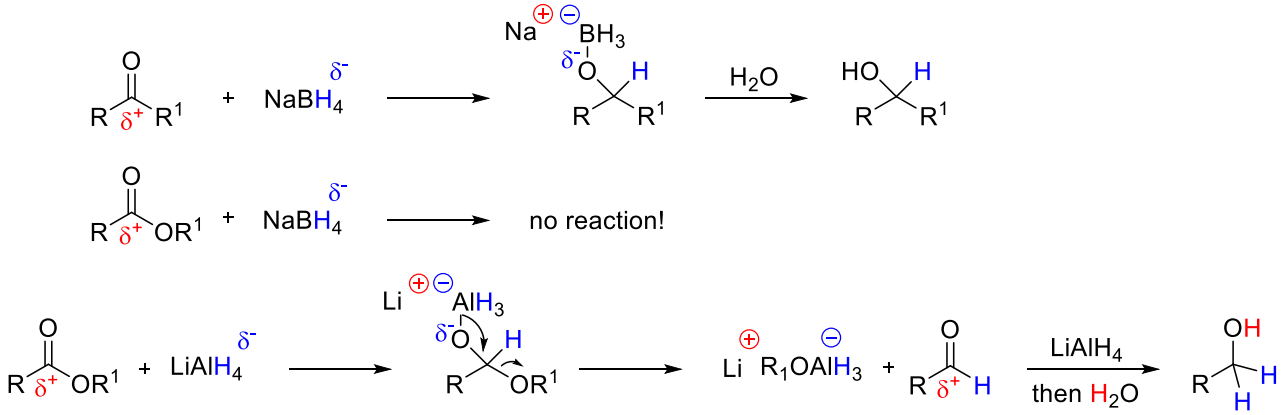
1.3.3.4 Chemistry of carbonyl compounds (A)

1.3.3.4.1 Nucleophilic addition

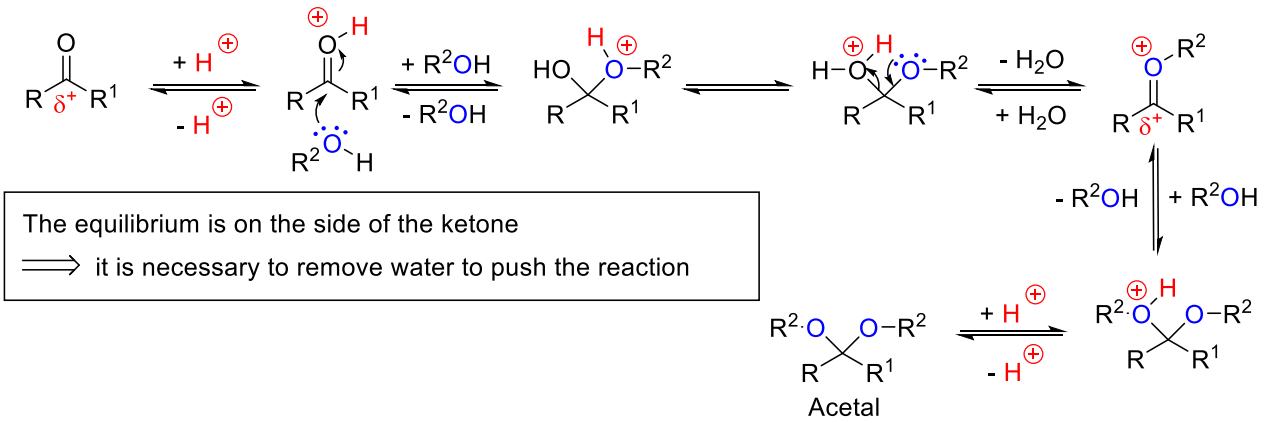
Grignard



Reduction wiht hydrides

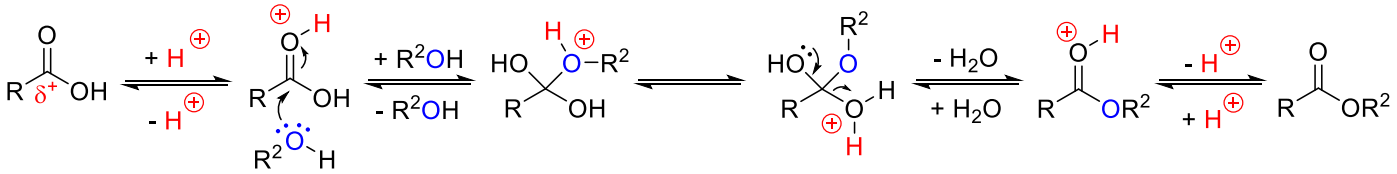


Alcohols: formation of acetals with acid catalyst



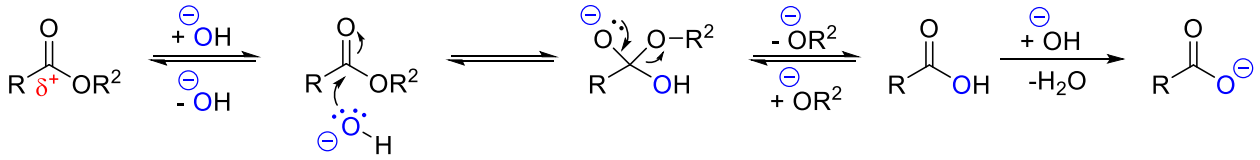
The equilibrium is on the side of the ketone
⟹ it is necessary to remove water to push the reaction

Alcohols: esterification with acid catalyst



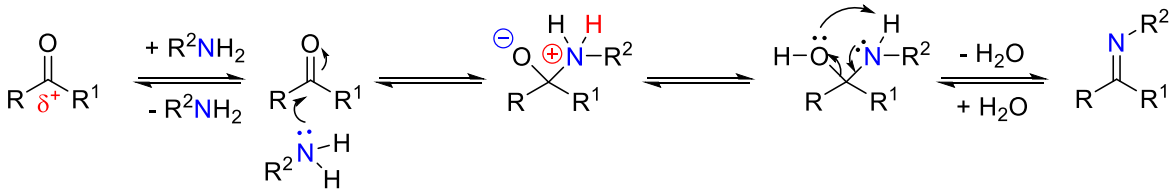
the equilibrium is close to 1:1
⟹ excess alcohol needed to favor reaction

Ester hydrolysis



High carboxylate stability ⟹ complete conversion

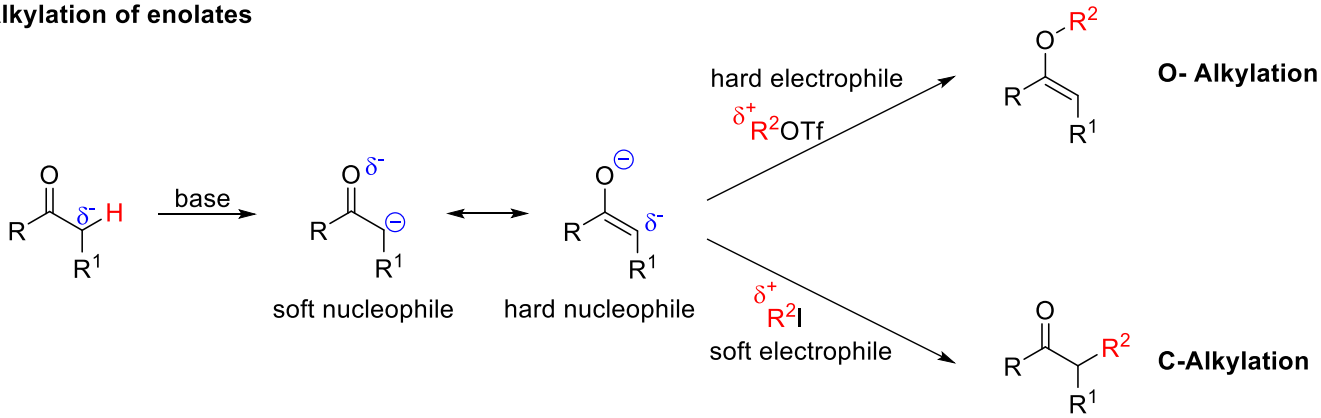
Addition of amines and formation of imines



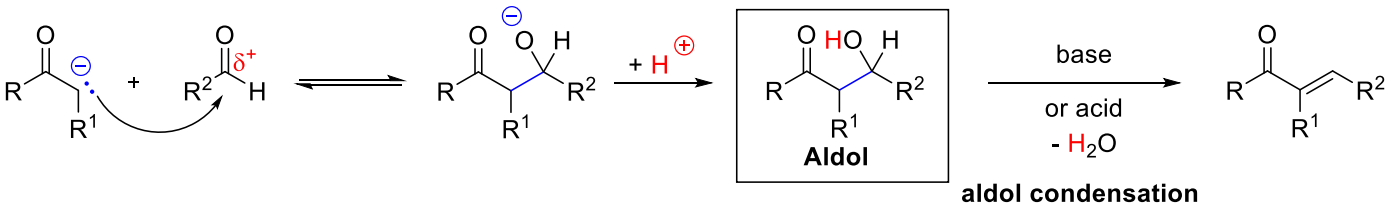
removing water is necessary for ketones, but usually not for aldehydes

1.3.3.4.2 Enolate chemistry

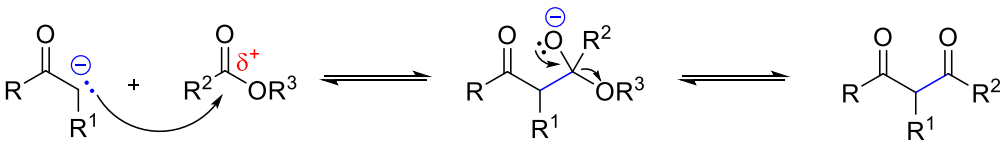
Alkylation of enolates



Aldol reaction

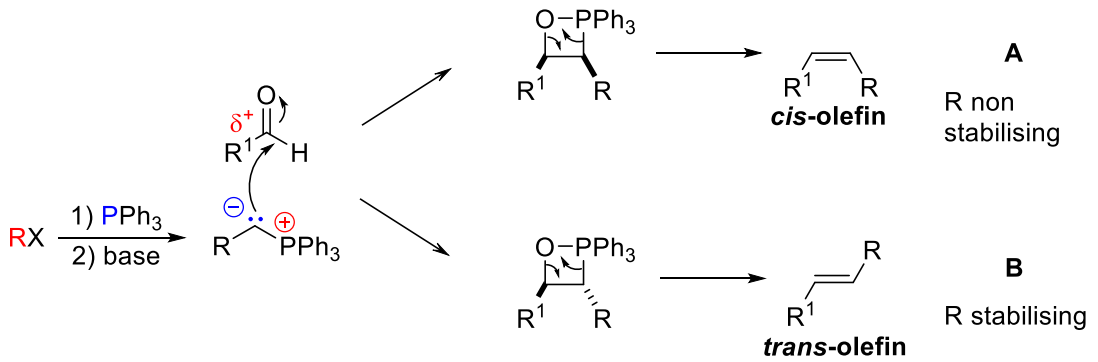


Claisen condensation



Other similar reactions: Knoevenagel condensation, Perkin and Dieckmann.

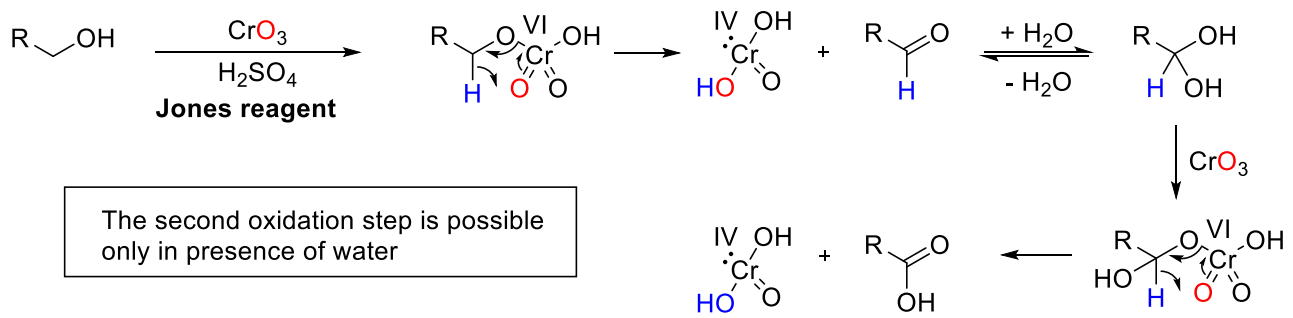
Wittig olefination



For non-stabilized ylides (**A**), the formation of *cis* phosphoxetanes is favored, leading to *cis* olefins. For stabilized ylides (**B**), the formation of *trans* phosphoxetanes is favored, leading to *trans* olefins.

1.3.3.5 Oxidation (B)

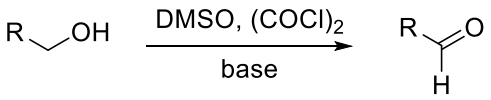
Chrom(VI)



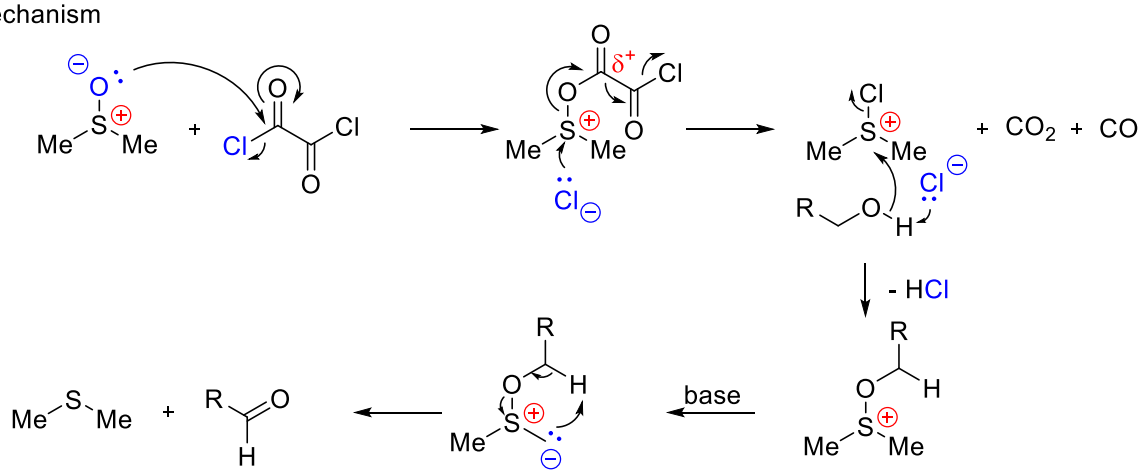
The second oxidation step is possible only in presence of water

Also often used: PDC (pyridinium dichromate), PCC (pyridinium chlorochromate)

Moffat-Swern



Mechanism



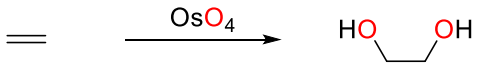
There are also many other oxidation methods!

Dihydroxylation, ozonolysis et epoxidation

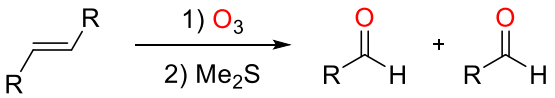
Epoxidation

*m*CPBA = *meta*-chloroperbenzoic acid

Dihydroxylation



Ozonolysis



The first two reactions will be discussed more in details in this course

Bloc I

Concepts of Stereochemistry

2. Chirality and Asymmetric Synthesis

2.1 Definitions and nomenclature (A)

Bibliography: AIMF (chapitre stéréochimie), old course synthèse asymétrique (especially for definitions and historical introduction, Ch. 1 p. 1-44), Carey Sundberg A, Ch. 2.1, p. 119-142.

Definitions

Constitution: connectivity between atoms

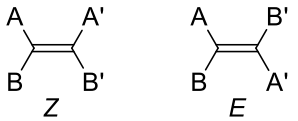
Configuration: same connectivity, but different disposition in space

Conformation: disposition in space in rapid equilibrium at the observed temperature

Stereoisomers: different configurations with the same connectivity

Important cases:

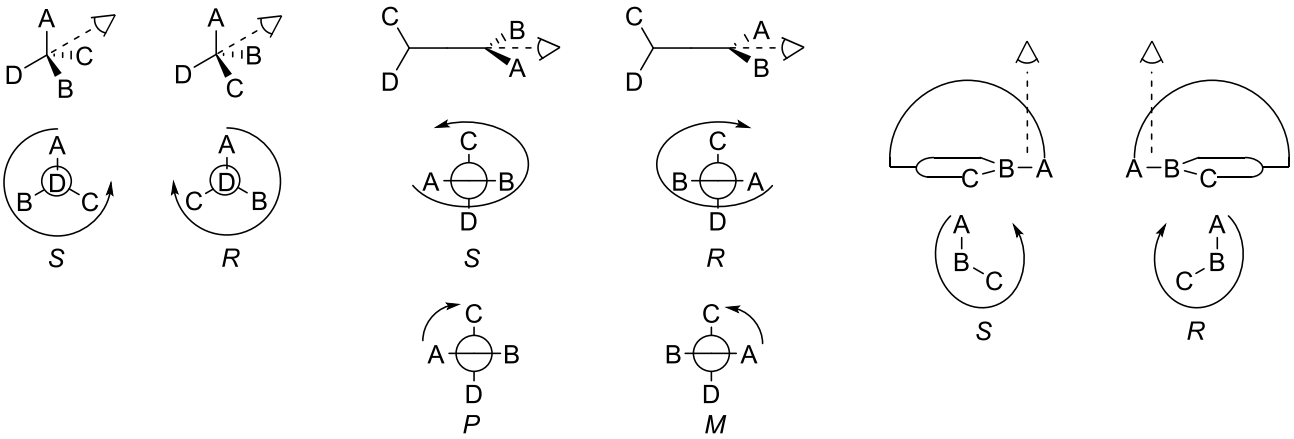
stereoisomers *E* (*trans*) and *Z* (*cis*) of double bonds:



Enantiomers: stereoisomers which are mirror images but not identical = chirality

Chirality elements

Stereocenters (A) **Axis of chirality (B)** **Plan of chirality (C)**



(especially for helices)

Atropoisomers: stereoisomers with an axis of chirality due to hindered rotation.

Priority rules (**CIP, Cahn-Ingold-Prelog**)

1) Atomic number
2) Atomic weight
3) atomic number/weight of substituents compared one to one, if necessary, substituents of substituents
4) multiple bonds correspond to atoms without substitution
5) *R*>*S* and *Z*>*E*

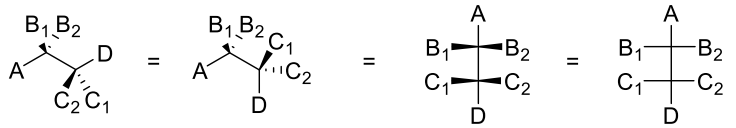
Molecule with identical constitutions and several stereocenters

1) achiral: **meso form**
2) mirror images: **enantiomers**
3) chiral, but not mirror image: **diastereoisomers**

Relation with symmetry

Chiral ⇔ no symmetry plan or centre

Old nomenclature: D and L. According to **Fischer projection (B)**:



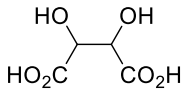
Fischer Projection

A: most oxidized carbon
D: less oxidized carbon

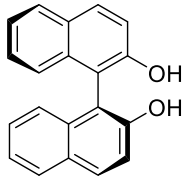
C_1=higher priority: L
C_2=higher priority: D
(At the "lowest" centre)

examples (course):

- centres C-5 and C-17 of discodermolide

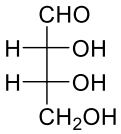


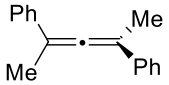
tartaric acid

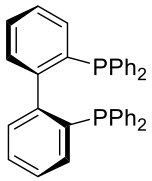


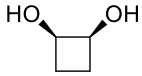
BINOL

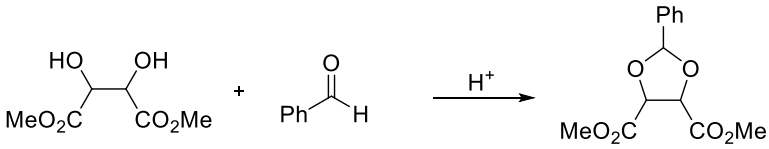
examples (exercises):







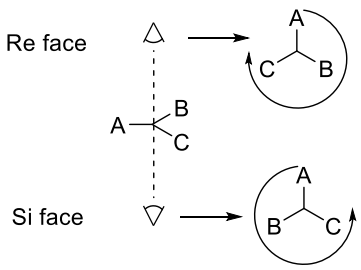




To see also: Question-Answer 13

Nomenclature for "prochirality"

Planar molecule (B)



Atom substitution (C)

The A positions are:

homotope ⇔ exchange of A by a group B gives two identitcal molecules ⇔ permutation of A via rotation axis

enantiotope ⇔ exchange of A by a group B gives two enantiomers ⇔ permutation of A via plan or center of symmetry

diastereotope ⇔ exchange of A by a group B gives two diastereoisomers

2.2 Determination and Importance of Chirality (A)

Definitions

enantiomeric excess (*ee*, %): $100 \cdot \frac{mol(R)-mol(S)}{mol(R)+mol(S)}$

enantiomeric ratio (*er*): mol(*R*):mol(*S*)

relationship between *ee* and *er:* $ee = 100 \cdot \frac{er - 1}{er + 1}$

racemic mixture: *ee* = 0, *er* = 1:1

The concepts (diastereomeric excess) and *dr* (diastereomeric ratio) are defined similarly

For the concept of selectivity, see question-answer 1

2.2.1 *ee* determination

Bibliography: Carey-Sundberg, Ch. 2, Topic 2.1, p1. 208-214.

General issue: many methods of measurement cannot distinguish enantiomers!

1) Optical rotation (A)

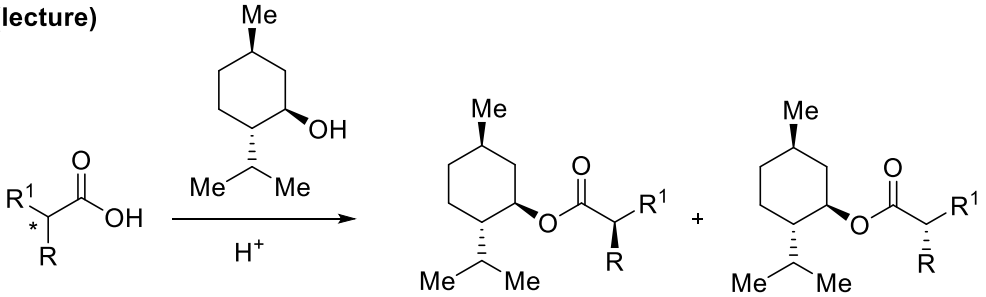
Chiral molecules induce a rotation of circular polarized light. This rotation (**degree of rotation** α) depends on the molecule concentration (c in g/100 mL), the length of solution (l, in dm) and the **specific rotation** of the enantiopure substance ([α]). When the substance is not enantiopure, the measured degree of rotation α_{obs} is directly proportional to the enantiomeric excess. If [α] is known, the enantiomeric excess can therefore be measured, but not very precisely. The absolute value of [α] is the same for both enantiomers, but the sign is opposed.

$$\alpha = \frac{c \cdot l \cdot [\alpha]}{100} \qquad ee = \frac{\alpha_{obs} \cdot 100}{[\alpha]}$$

2) Synthesis of Diastereoisomers (A)

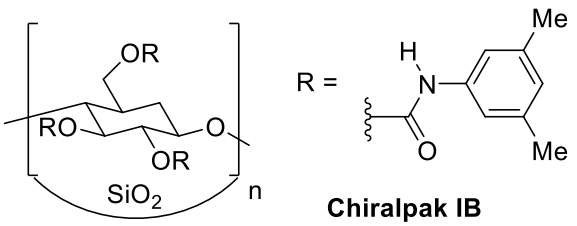
The mixture of enantiomers is modified by a reaction forming diastereoisomers. The diastereoisomers can then be distinguished using classical methods (chromatography, NMR)

example (lecture)



3) Separation by chromatography on chiral phase (B)

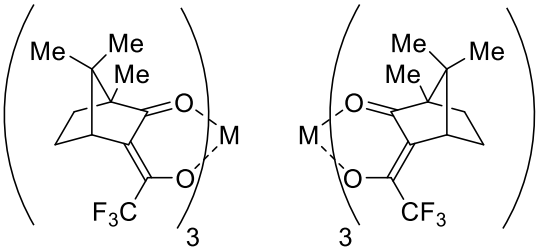
Using a column with chiral phase (especially HPLC, sometimes GC), the enantiomers can be separated and the ee measured. The DAICEL Chiralpak columns are often used in organic chemistry (carbohydrates as chiral phase). This is the preferred method nowadays.



Chiralpak IB

4) NMR-shift (C)

Chiral reagents (especially chiral metal complexes) are added to the mixture of enantiomers prior to NMR measurement. Through coordination ot the substrate, two diastereoisomeric complexes are formed, and separated RMN signals can be measured. This method can be applied only if the chiral metal complex coordinates sufficiently the substrate.



M = Eu, Er, Yb

2.2.2 Determination of absolute configuration (A)

The methods used to measure enantiomeric excess usually do not allow to determine the absolute configuration (eg R or S). There is no direct correlation between absolute configuration (eg *R*, *S*) and the optical rotation sign (+ or -) or the retention time on a chiral column.

1) Transformation in a known substance (A)

The transformation into a known substance followed by comparison of the properties (especially specific rotation) remains even today a method of choice to determine the absolute configuration.

example: lecture: Configuration of glucose.

2) Analogy methods (B)

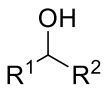
If two similar molecules have been synthesized, comparison (nowadays often by computation) of physical properties can allow a tentative assignment of the absolute configuration. Two classical methods are:

- Octands method (**C**). As interaction between light and molecules is mostly determined by chromophores, the identification of important chromophores and the analysis of their disposition in space allow to predict the sign of optical rotation, or inversely the absolute configuration if the sign of rotation is known.

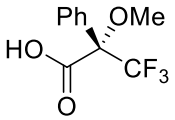
- Synthesis (or *in situ* formation) of diastereoisomers and analysis by RMN (**B**). Data are available for the influence of the absolute configuration on the chemical shifts and allow to deduce the absolute configuration. The Mosher method for chiral alcohols is one of the most often used.

!!! There is no certitude wiht methods proceeding by analogy!!!

example: lecture: Mosher method for alcohols



using



MTPA

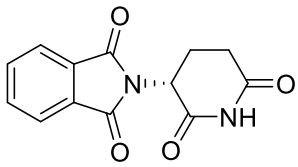
3) X-ray (B)

Standard X-ray methods do not allow to determine the absolute configuration. A special method (anomalous diffraction) is required. She requires high quality crystals and works better with atoms heavier than C, H, N, O.

2.2.3 Importance of chirality (A)

Even if many properites of enantiomers are identical, chirality has a strong influence in biological systems. In fact, biomolecules in human body (amino acids, carbohydrates) are homo-chiral (only one enantiomer is present) and biomolecules are chiral and enantiopure. Therefore, enantiomers of small organic molecules will interact differently with biomolecules in the human body. For examples, enantiomers of drugs have different effects and enantiomers of fragrances different odors. It is essential for the chemist to be able to access compounds with high enantiomeric purity. Examples will be shown in the lecture and can be found in the old lecture notes of Prof. Vogel (p. 14-18).

Example (Lecture):

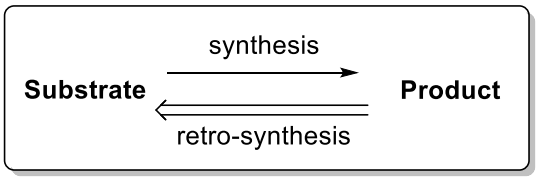


Thalidomide

2.3 Generation of enantiopure compounds (A)

2.3.1 Asymmetric synthesis (A)

Bibliography: Carey-Sundberg A, ch. 2.4-2.6, p. 169-207.



Definitions:

retron:characteristic structure element in product for a particular synthetic method. It is important to know and recognize important retrons.

synthon: characteristic structure element in substrate useful for further transformations.

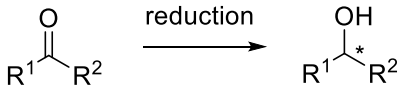
stereoselective reaction: reaction giving a stereoisomer with high selectivity.

stereospecific reaction: reaction that transforms selectively one stereoisomer of the substrate into one stereoisomer of the product.

Generation of stereochemistry:

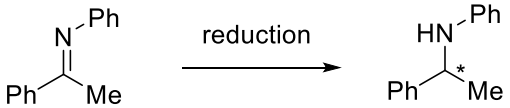
Rule: **Only chirality can generate chirality!**

Example (Lecture)



reduction of ketones

Example (Exercises)

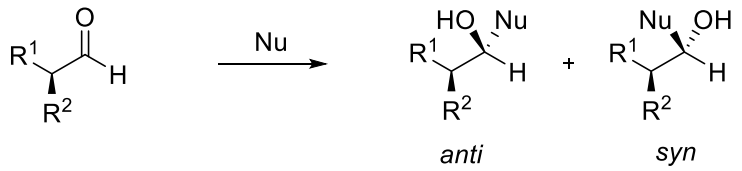


reduction of imines

2.3.1.1.1 Use of chiral substrates (A)

Existing chirality elements in substrates influence the formation of new chirality elements. Selectivity can be determined either by the substrate structure (**substrate control**), the structure of reagents (**reagent control**) or both. The reaction is diastereoselective, as the starting material is already chiral (**relative stereochemistry**). If the starting material is enantiopure, the product is also enantiopure (**absolute stereochemistry**). The analysis of factors influencing selectivity for reactions involving alkenes and carbonyls constitutes the bulk of the lecture.

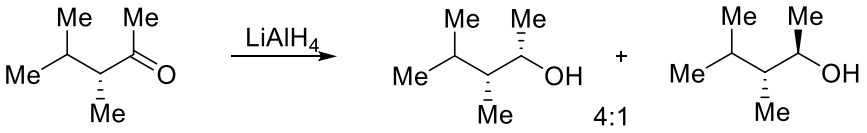
example:



diastereoisomers

!!! *syn* and *anti* are used to describe the relative stereochemistry between R^2 and the nucleophile. These terms are not generally defined, but are always linked to a specific representation/drawing!!!

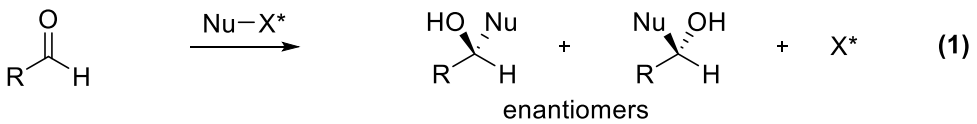
example: lecture



2.3.1.1.2 Use of chiral reagents (A)

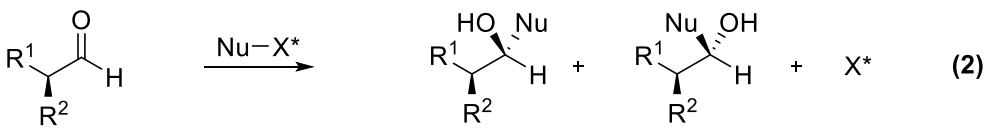
A chiral reagent can induce chirality in the formation of a new chirality element. The element of chirality of the reagent is not incoporated in the product, but determines selectivity in the transition state of the reaction. If the substrate is not chiral, the reaction is enantioselective, as the absolute chirality is determined during the transformation **(1)**. It can be diastereoselective in addition if several chirality elements are formed. When the substrate is chiral, the reaction is diastereoselective and existing chirality elements of substrate are important for selectivity (**double stereocontrol**) **(2)**. When the influences are reinforced, we speak of "**matched** case", in the other case of "**mismatched** case".

Examples:



(1)

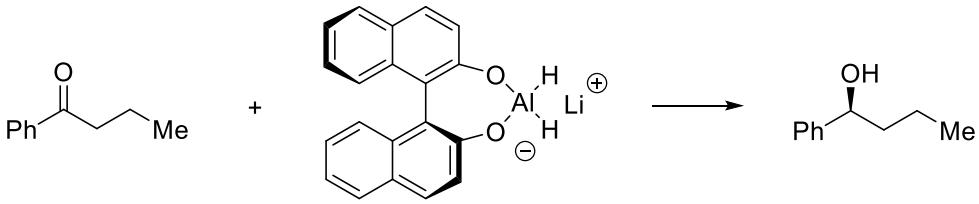
enantiomers



(2)

diastereoisomers

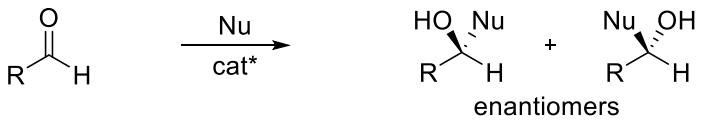
Example (lecture)



2.3.1.1.3 Asymmetric Catalysis (D)

The most elegant method for achieving stereoselectivity is asymmetric catalysis. For this to work, the substrate/reagent needs to react only if bound to the catalyst. This is often more difficult to control and current subject of intensive research. We will see only few key examples, as the lecture "catalytic asymmetric reactions in organic synthesis" in master is focusing on this topic.

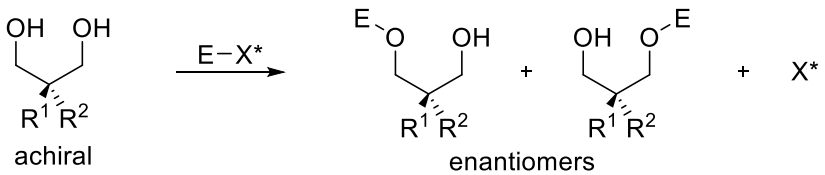
Example:



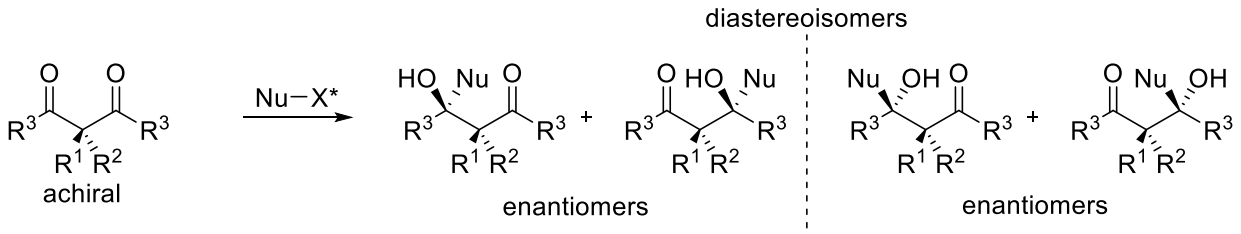
2.3.1.2 Desymmetrization of meso substrates (A)

Meso compounds are special, as they contains "potential chirality elements" which are "cancelled" by high symmetry (plan or point of symmetry). If the symmetry is broken by using a chiral reagent, a chiral molecule can be obtained, even if no new chirality element is formed (the reaction is enantioselective **(1)**). If a new chirality element is formed, the reaction is both enantio- and diastereo-selective **(2)**. The use of meso compounds is attractive, as they can be synthesized easily due to ther high symmetry (bidirectional synthesis is possible).

Examples:



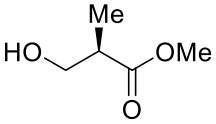
(1)



(2)

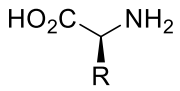
Example (lecture)

Synthesis of Roche Ester

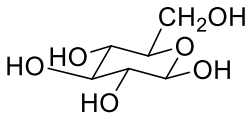


2.3.1.3 The chiral pool (B)

All asymmetric syntheses need a starting element of chirality. The ensemble of all easily accessible chiral compounds constitutes the chiral pool. Most of the chiral pool is of natural origine, but some easy-to-make synthetic compounds are now also included. It is essential to know the molecules of the chiral pool, as they are used intensively as starting materials or as building blocks of chiral reagents and catalysts (review: *Chem. Rev.* **1992**, *92*, 935., Vogel Ch. 4.1, p. 78-79). The most important compound classes in the chiral pool are the amino acids, the carbohydrates, the hydroxylated acids, the terpenes, the alkaloids, the peptides and the enzymes. The reasons for the emergence of homochirality in nature are still not completely understood nowaday.



amino acids
corresponding alcohols

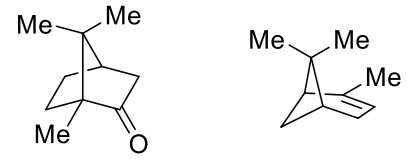


carbohydrates
(Vogel Ch. 2)

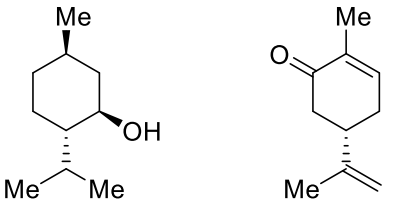
tartaric acid malic acid

mandelic acid lactic acid

hydroxylated acids

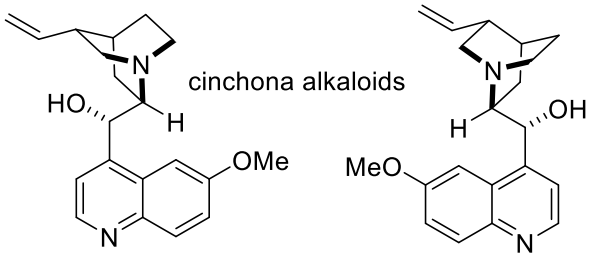


camphor α-pinene

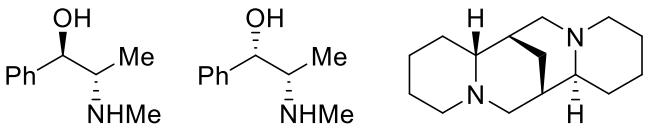


menthol carvone

terpenes



quinidine quinine

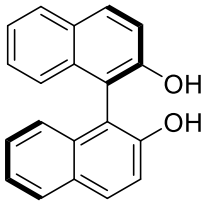


ephedrine pseudoephedrine sparteine

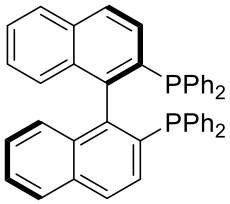
alkaloids

peptides

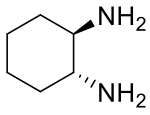
enzymes



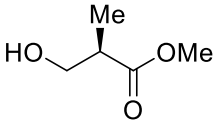
BINOL



BINAP



diamines



Roche ester

Synthetic derivatives

2.3.2 Resolution of racemic mixtures (A)

Bibliography: Carey Sundberg A, Ch. 2.1.8, p. 136-142. Topic 2.1.2 p. 211-215. Vogel, Ch. 3, p. 59-77.

Synthesizing racemic compounds is always easier than asymmetric synthesis. Obtaining the enantiomers from a racemic mixture is therefore an important method, especially if both are valuable. If one of the two enantiomers is not desired, it can often be recycled by racemization to regenerate the racemic mixture.

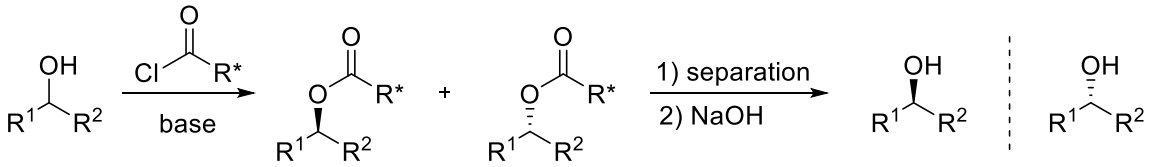
2.3.2.1 Spontaneous separation of enantiomers by crystallization (C)

If a compound crystallizes, separation of enantiomers via crystallization is possible, provided that enantiomerically pure cyrstals are favored over racemic ones. This method was first used by Pasteur to separate the enantiomers of tartaric acid. However, this is a rare case, which cannot be used extensively. More efficient is the initiation of crystallization from an oversaturated racemic mixture by adding a small amount of the desired enantiomer.

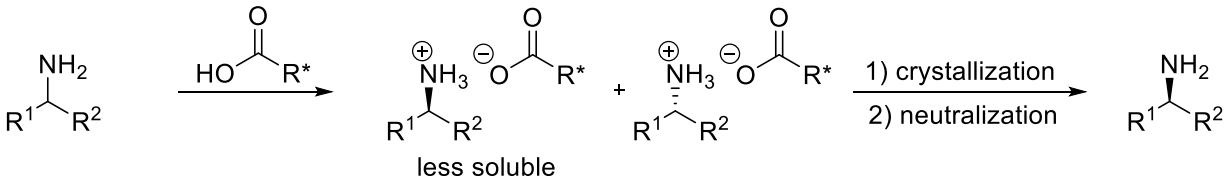
2.3.2.2 Classical resolution via diastereoisomers (A)

By transforming a racemic mixture into a mixture of diastereoisomers, separation becomes easier either by crystallization or column chromatography. Often, three steps are needed (Introduction of an additional element of chirality, separation, removal of the auxiliary).

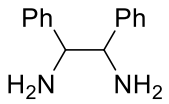
Example: resolution of alcohols via ester formation



It is not always needed to form diastereoisomers by making new covalent bonds. A very efficient method for the separation of acidic or basic molecules (especially amines) is the formation of diastereomeric salts. The solubility of the salts is then different, and a fractional recrystallization becomes possible.



Example (lecture): Resolution of a diamine

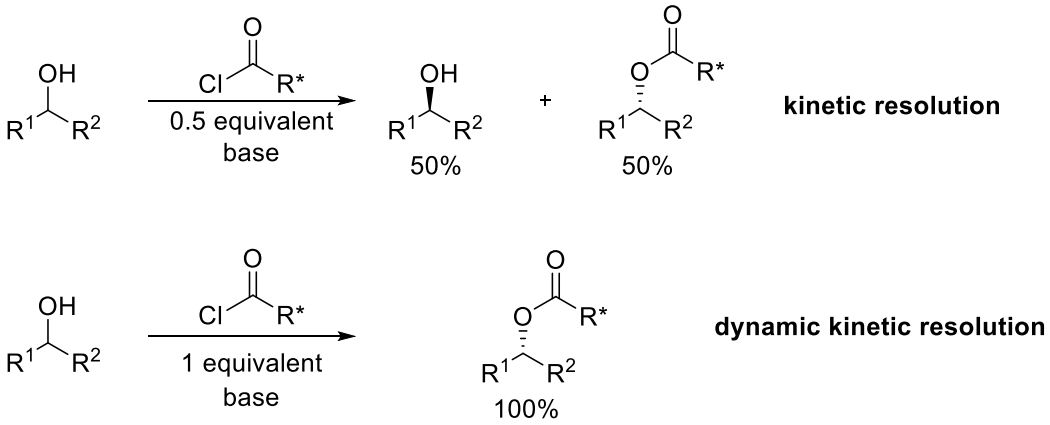


2.3.2.3 Kinetic Resolution (B)

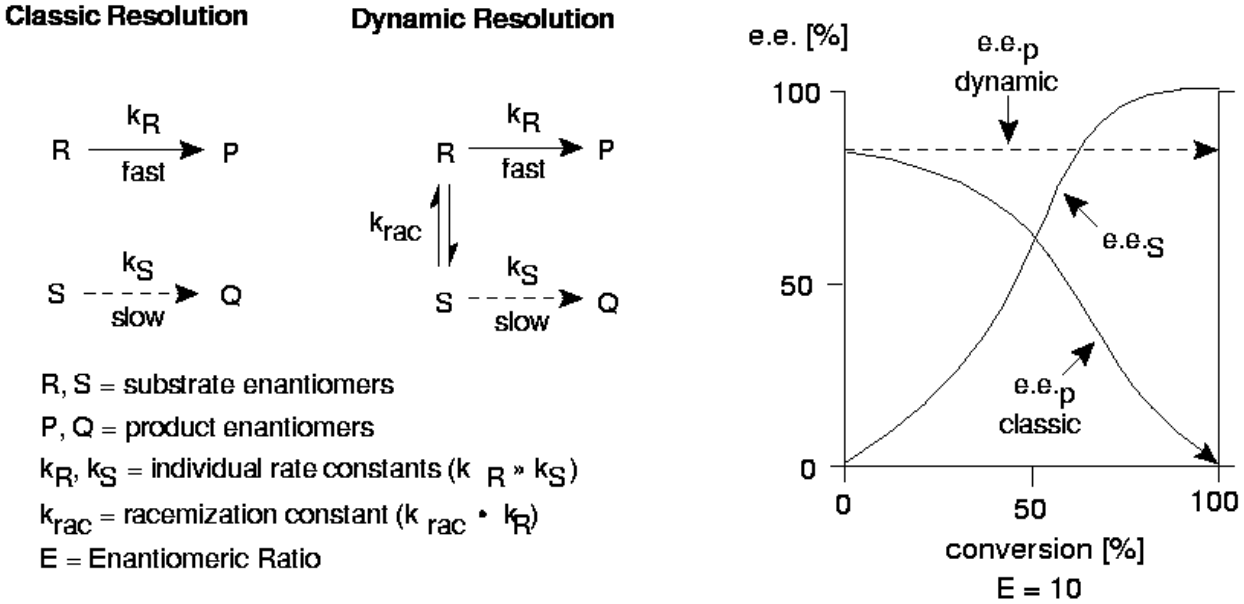
In the kinetic resolution, the different reaction rates of two enantiomers with a chiral reagent are used. If the reaction is stopped prior to full conversion, both substrate and product are enantiomerically enriched. The enriched substrate is therefore obtained without further modification. At the cost of yield, high enantiomeric purity of the starting material can be obtained, even if the selectivity of the reaction is not very good. The best factor to describe the efficiency of a kinetic resolution is the selectivity factor S (sometimes E), which is the ratio of the reaction rates of the enantiomers. A perfect reaction would have S infinite and give 50% of enantiopure starting material and 50% of enantiopure product.

The dynamic kinetic resolution is a special case, in which racemization of the substrate occurs during the reaction. In this case, a theoretical yield of 100% can be obtained. The racemization can either occur spontaneously under the reaction conditions, or be promoted by a catalyst.

Example: Kinetic resolution of alcohols

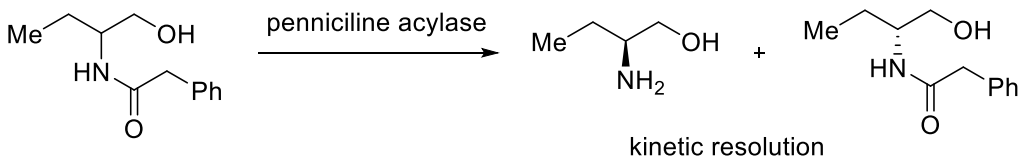


mathematic model (taken from ecsoc2.hcc.ru/ecsoc-2/al001/al001.htm)



The most elegant methods for kinetic resolution make use of chiral catalysts instead of reagents (see lecture catalytic asymmetric reactions in organic synthesis). Enzymes are especially efficient for this type of transformations (see Vogel ch. 3.3, p. 70-72 and Carey Sundberg A, Topic 2.2, p. 215-227).

Example (lecture):



3. Conformational Analysis

Bibliography: Cours fonctions et réactions organiques I, Carey Sundberg A, Ch. 2.2, p.142-167. Evans 206, lectures 4, 5 and 6.

For drawing techniques, see QA 6.

Conformational analysis - the study of different conformations, their relative stability and the necessary energy for their interconversion- was already done in previous courses. In this lecture, the most important elements necessary for analyzing the stereoselectivity of chemical transformations are shortly repeated.

Reminder: **Fondamental relation between equilibrium and energy**

$\Delta G = -RT\ln K$

1.4 Kcal (5.9 KJ) corresponds to a ratio of **10:1**

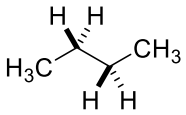
ambiant energy at room temperature: **21 Kcal**

$\Longrightarrow$ Reactions with an activation energy below 21 Kcal occur readily at room temperature.
(all energies are given for mol^{-1})

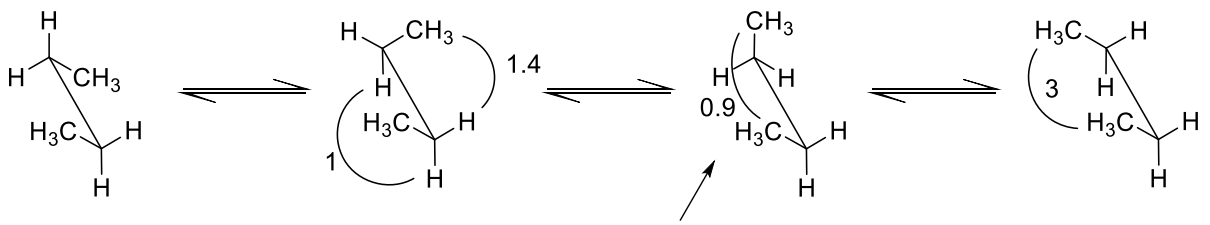
3.1 Alkanes (A)

(Energy values in Kcal/mol, S = small, M = Medium, L = Large)

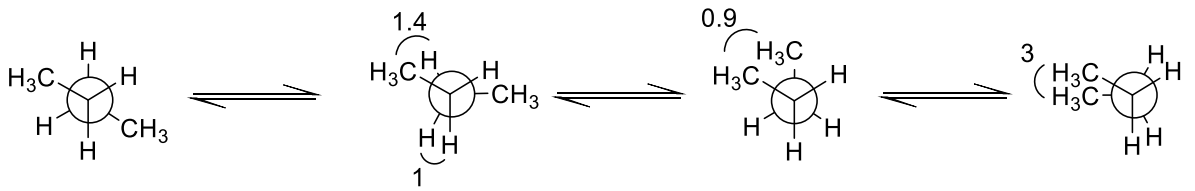
Butane



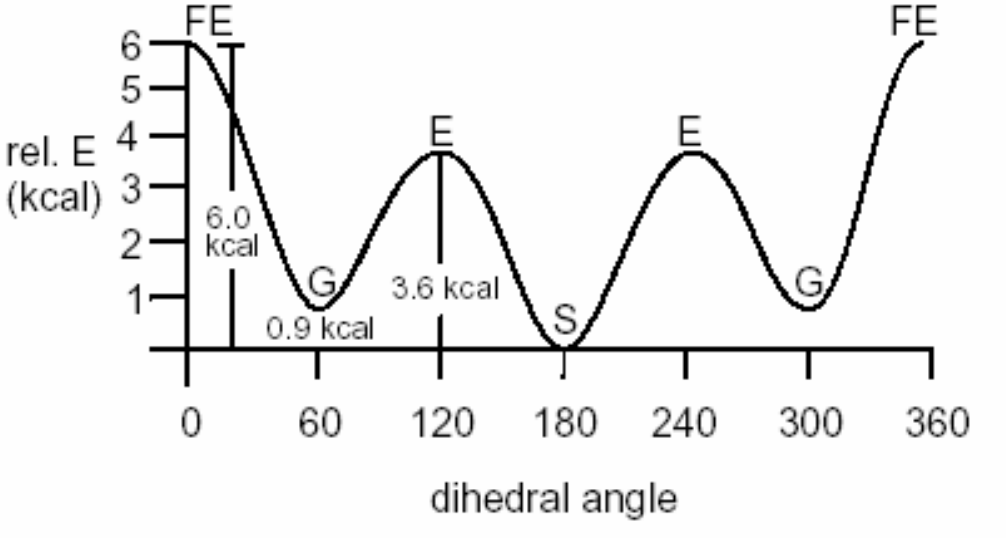
Sägebock projection



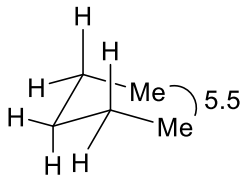
Newman projection



relative energy	**0**	**3.8**	**0.9**	**5**
	staggered antiperiplanar	eclipsed anticlinal	staggered synclinal *gauche conformer*	eclipsed synperiplanar
	global minimum	**local maximum**	**local minimum**	**global maximum**



Special interaction in pentane



Double Gauche Pentane or **Syn Pentane** or **interaction 1,3**

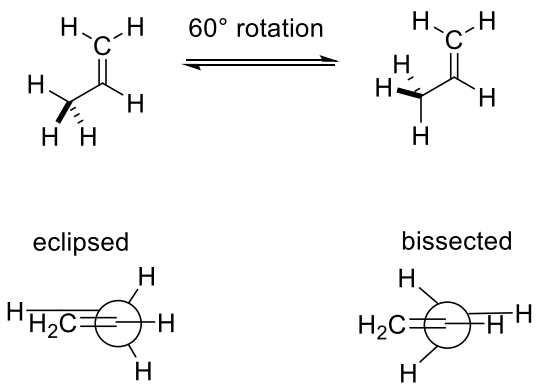
For the conformational analysis of alkanes, the following values should be memorized: eclipsed interaction H-H: 1.0 Kcal, eclipsed interaction Me-Me: 3 Kcal, gauche interaction Me-Me: 0.9 Kcal, double gauche pentane interaction: 5.5 Kcal. These interactions determine the three-dimensional structure of linear alkanes, and therefore their reactivity and bioactivity. These values can be rationalized partially by steric arguments (a more recent rationalization based on orbital interactions has been also proposed, see section 3.4).

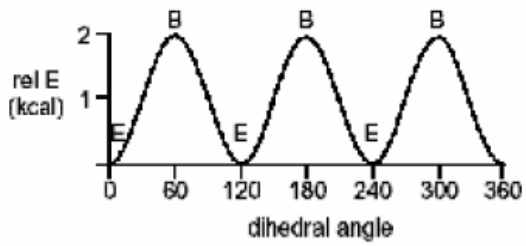
Example (lecture): Conformation of C10-C12 in discodermolide

Example (Exercises): Conformation of 1,2-dichloroethane, Conformation of C16-C20 in discodermolide

3.2 Alkenes: Allylic strain (A)

Propene

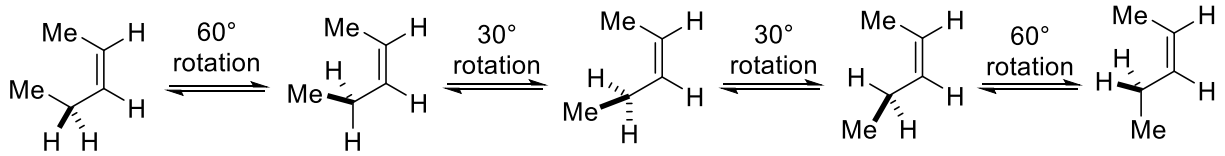


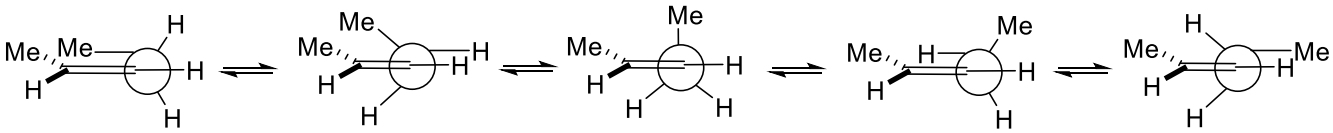


relative energy **0** **2**

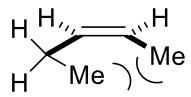
In the case of alkenes, the eclipsed conformation is generally more stable than the bissected one. Steric effects are not sufficient to understand the energy difference. We will rationalize it later based on stereoelectronic effects.

***(2Z)*-Pent-2-ene**

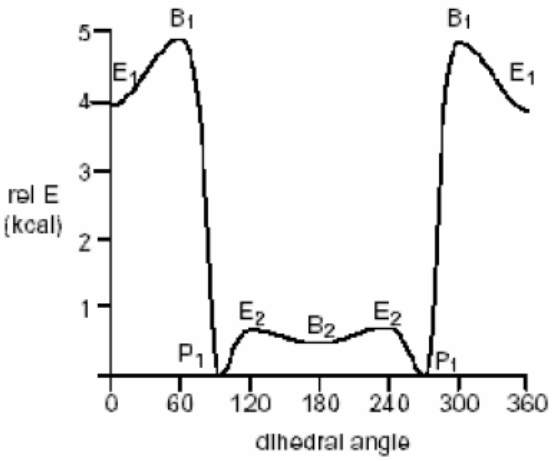


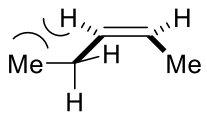


	eclipsed E_1	bissected B_1	perpendicular P_1	eclipsed E_2	bissected B_2
relative energy	**4**	**5**	**0**	**0.7**	**0.6**



1,3 allylic strain

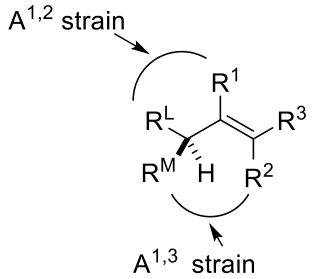


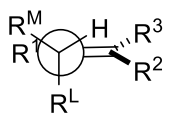


1,2 allylic strain

In case of *(2Z)*-pent-2-ene, the major contribution comes form 1,3-allylic strain (can be compared to double gauche pentane). The E1 and B1 conformations are therefore strongly disfavored. The methyl group also changes the equilibrium between the other conformers, making P1 more stable. The 1,2- allylic strain can be neglected for *(2Z)*-pent-2-ene.

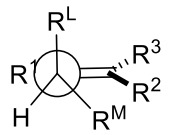
General consideration about allylic strain





$A^{1,3}$ Minimized
- R^L ⊥, in free room
- H in direction of R^2

favorised for $R^2 > R^1$



$A^{1,2}$ Minimized
- R^L ⊥, in free room
- H in direction of R^1

favorised for $R^1 > R^2$

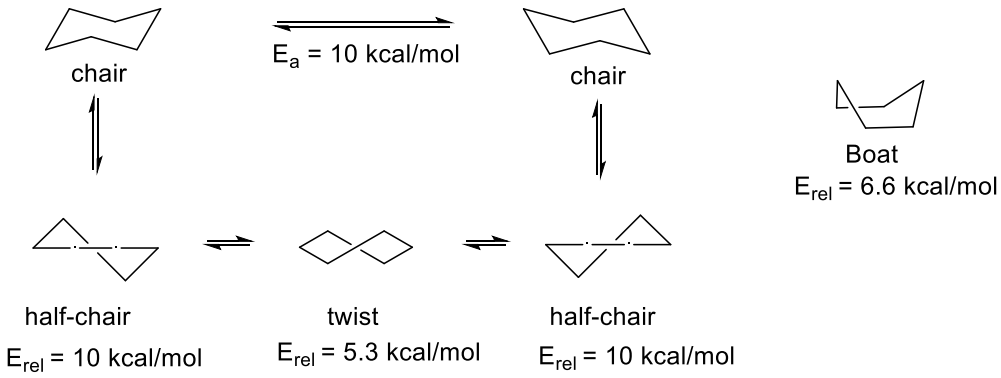
For allylic systems, the conformation wiht the largest substituent (R^L) perpendicular to the alkene is favored. Depending on the size of the substituents on the double bond, either the 1,2- or the 1,3- allylic strain is then minimized by placing the smallest substituent (H). In case of equal size, the 1,3-allylic strain is minimized, but the diffrence is small (Review: *Chem. Rev.* **1989**, *89*, 1841).

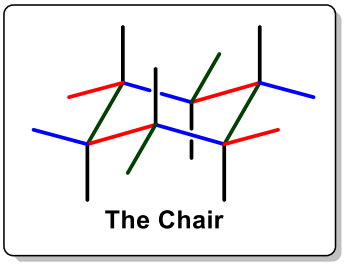
3.3 Cyclic systems (A)

3.3.1 Cyclopentane (C)

The conformation of cyclopentane is important, especially for biochemistry (structure of DNA). At this topic has been already described in previous lectures and will not be intensively used in this course, it will not be repeated here.

3.3.2 Cyclohexane (A)

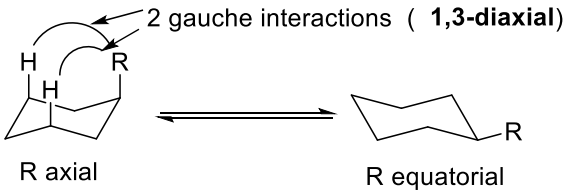




The chair is the most stable conformation of cyclohexane. Chair inversion is a fast process at room temperature. For this course, it is essential to be able to draw correctly the chair with equatorial and axial substituents. This structure is not only important for cyclohexane, but also for transition states containing a cyclic arrangement of 6 atoms.

A Values

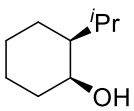
CH_3	1.7
CH_2CH_3	1.7
$CH(CH_3)_2$	2.1
$C(CH_3)_3$	4.7
CN	0.2
C_6H_5	2.8
$Si(CH_3)_3$	2.5
OCH_3	0.6
Cl	0.6



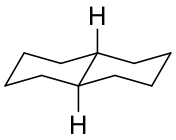
A Value (R) = - ΔG (axial-equatorial)

The A value of a substituent R corresponds to the energy difference between the equatorial and the axial position for R (R = Me, A = 1.7 Kcal/mol). It corresponds to a double gauche interaction. Be careful: A values do not take into account interactions between R substituents when there are several on the cyclohexane.

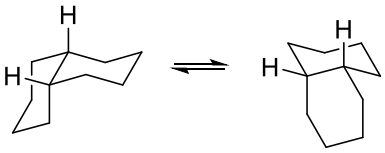
Example (exercises):



Decaline: A special case



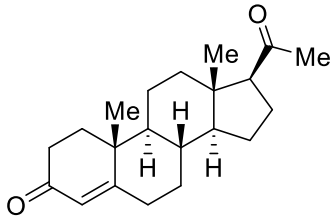
Trans decaline
Rigid



Cis decaline
Flexible

Systems of fused cyclohexanes are important, as they are part of the core of steroids.

Example (lecture): conformation of progesterone



Effect of Heteroatoms

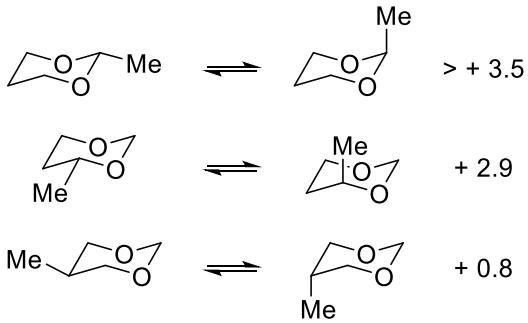
111º

100º

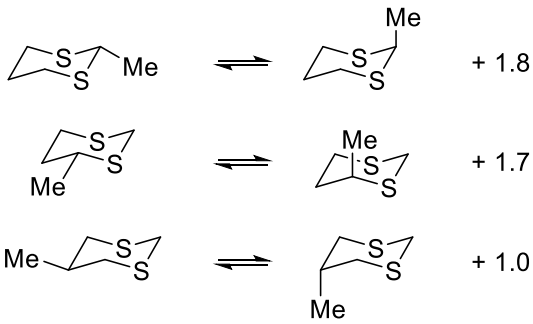
C−C	1.54 Å
C−O	1.42 Å
C−S	1.82 Å

The introduction of heteroatoms diminishes steric effects by replacing a hydrogen with an electron pair and also changes the length and angle of bonds. In particular, the shorter C-O bond reinforces diaxial interactions. In addition, the heteroatoms also changes the energy differences between the different conformers of the six-membered rings.

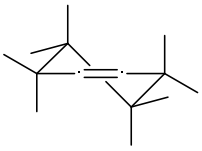
1,3 dioxanes



1,3-dithianes



cyclohexene



The favored conformation of cyclohexene is the half-chair.

3.4 Stereoelectronic effects (A)

Bibliography: Evans 206, lectures 1-3. Cours Fonction et Réaction Organique I. Carey Sundberg A, Ch. 1.1-1.2, p. 1-50; topic 1.1-1.2, p. 78-85.

For a reminder on how to draw orbitals, see QA 4 and 12.

Up to now, conformational analysis has been limited to steric effects. This is not always sufficient. In this section, the electronic effects are described with the help of molecular orbitals. In most cases, it is sufficient to consider , the Frontier Molecular Orbitals (FMO): the HOMO (Highest Occupied Molecule Orbital) and the LUMO (Lowest Unoccupied Molecule Orbital) qualitatively. A qualitative analysis of molcular orbitals from the point of view of energy and geometry allows rationalizing numerous electronic effects in stereochemistry (stereoelectronic effects), not only for structures, but also for reactions. In this section, only illustrative examples not part of later chapters of the lecture will be presented.

3.4.1 General rules for orbital interactions

Rule 1

Stabilization comes form electron delocalization. Consequently, the interaction between empty orbitals is neutral, disfavored between full orbitals and favored between an empty and a full orbital. Only orbitals of the same phase interact positively.

Rule 2

The smaller the energy difference between an empty and a full orbital, the better the interaction/stabilization.

Rule 3

The energy of the orbitals is correlated with their electronegativity, determined by the involved atoms.

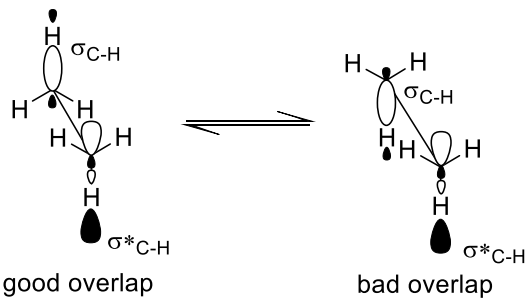
Règle 4 (Stereo)

A geometrical overlap is needed for orbital interactions.

These rules are not strict, but they help organic chemists to analyze rapidly and qualitatively a structure or reaction using orbitals. From rules 1 and 2, it can be deduced that interactions between HOMO and LUMO are strongest, as they are closest in energy. Rule 3 helps us to estimate the relative energy change induced by heteroatoms (O for example). Rule 4 is the most important for this lecture, as she tell us that it is essential to consider both shape and orientation of orbitals.

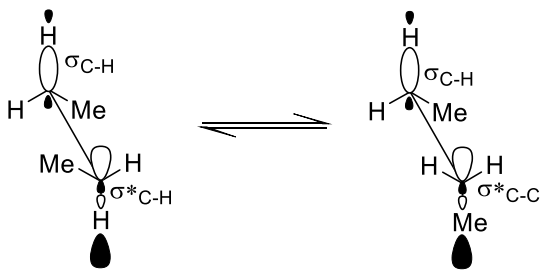
3.4.2 Stereoelectronic effects on structure

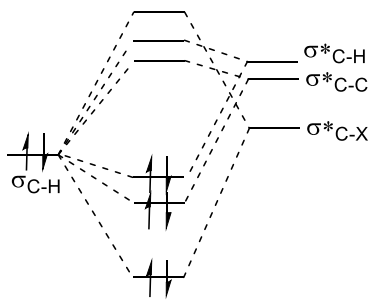
eclipsed H (B)

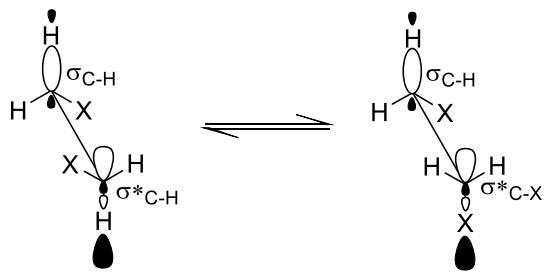


Traditionally, the rotation barrier in ethane has been attributed to sterics. However, calculations have shown that the H are too small to have a real effect. A better explanation is based on an orbital stabilization effect (3x) between the orbital σ_{C-H} (HOMO) and the orbital σ^*_{C-H} (LUMO). The overlap is much better in the antiperiplanar conformation than in the eclipsed one.

Gauche effect (A)



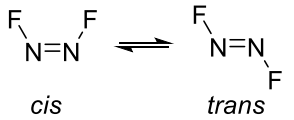




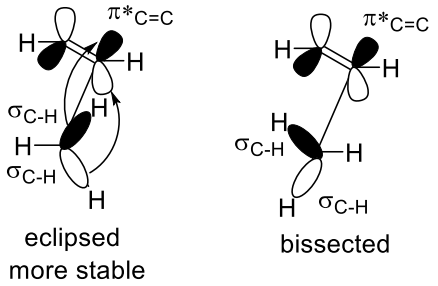
For a methyl group, the electronic stabilization is nearly the same in the antiperiplanar and the gauche conformation. With a more electronegative X group, the interaction with σ^*_{C-X} is stronger in the gauche conformation. Consequently, for small and electronegative X, the gauche conformation becomes more stable!

Example (Exercises): conformation of dichlorethane.

Example (Exercises):

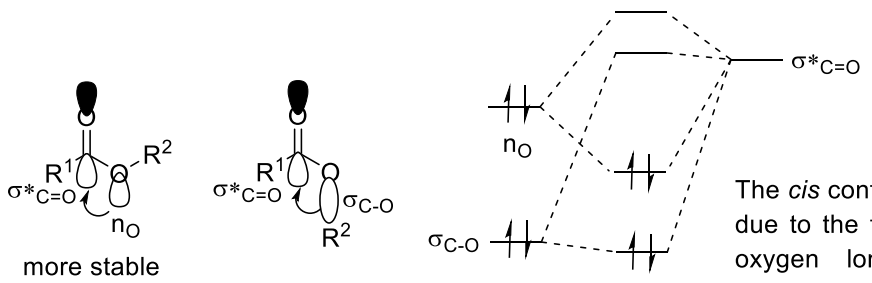


Bissected/eclipsed conformation of alkenes (B)



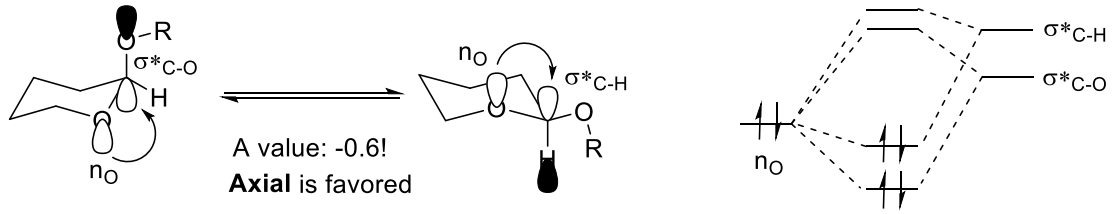
A good overlap between the orbitals σ_{C-H} and $\pi^*_{C=C}$ is possible only in the eclipsed conformation!

Conformation of esters (B)



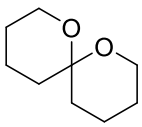
The *cis* conformation of esters is more stable, due to the favorable interaction between the oxygen lone pair and $\sigma^*_{C=O}$. As this conformation does not exist in lactones, those are more reactive than esters.

Structural anomeric effect (A)



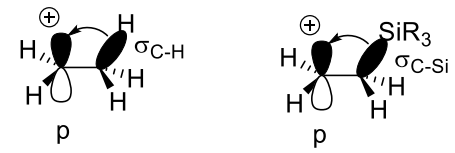
Anomeric effects are very important for cyclic acetals (carbohydrates). In particular, the structural anomeric effect (donation n_O to σ^*_{C-O}) is particularly important and makes the axial position more stable.

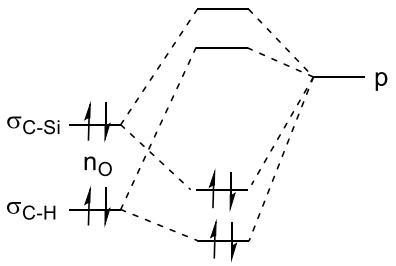
Example (exercises):



conformation of bicyclic acetals

Stabilisation of carbocations: Hyperconjugation (A)



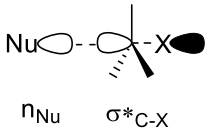


Hyperconjugation (donation by sigma bonds) is especially important for carbocation stabilisation. It explains the relative stability primary carbocation < secondary carbocation < tertiary carbocation. Silicon being more electropositive and polarizable than carbon, the effect is much stronger with Silicon (**beta effect of silicon**).

3.4.3 Stereoelectronic effects on reactions (A)

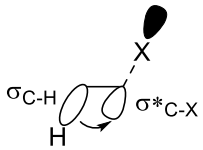
Intermolecular stereoelectronic effects are very important, and allow to rationalize the structure of favorable transition states. By knowing the structure of transition states, it is then possible to analyze the selectivity of reactions. The study of transition states is one fo the main topics of the lecture. In this section, only types of reactions not part of the course are discussed.

S_N^2 Substitution



The favorable interaction between HOMO n_{Nu} of the nucleophile and σ^*_{C-X} (LUMO) of the electrophile rationalizes the 180° angle and the inversion of configuration observed during the S_N^2.

E^2 Elimination



The interaction between σ_{C-H} and σ^*_{C-X} leads to a conformation with H and leaving group *trans*-antiperiplanar. In the case of the Grob fragmentation, one or several bonds are intercalated in an antiperiplanar fashion between proton and leaving group.

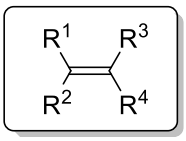
Bloc II

Stereoselective Chemistry of Alkenes

4. Synthesis and Functionalization of Alkenes

Bibliography (repetition): AIMF: Les alcènes, Fonctions et réactions organiques II, Ch. 3.

Retron

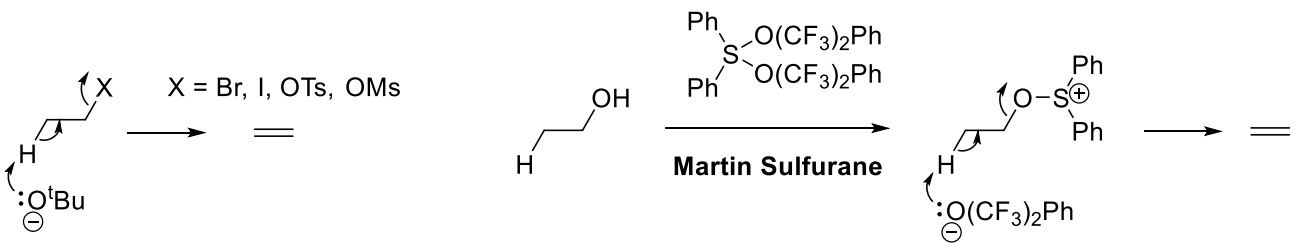


4.1 Stereoselective synthesis of alkenes

4.1.1 Elimination (A)

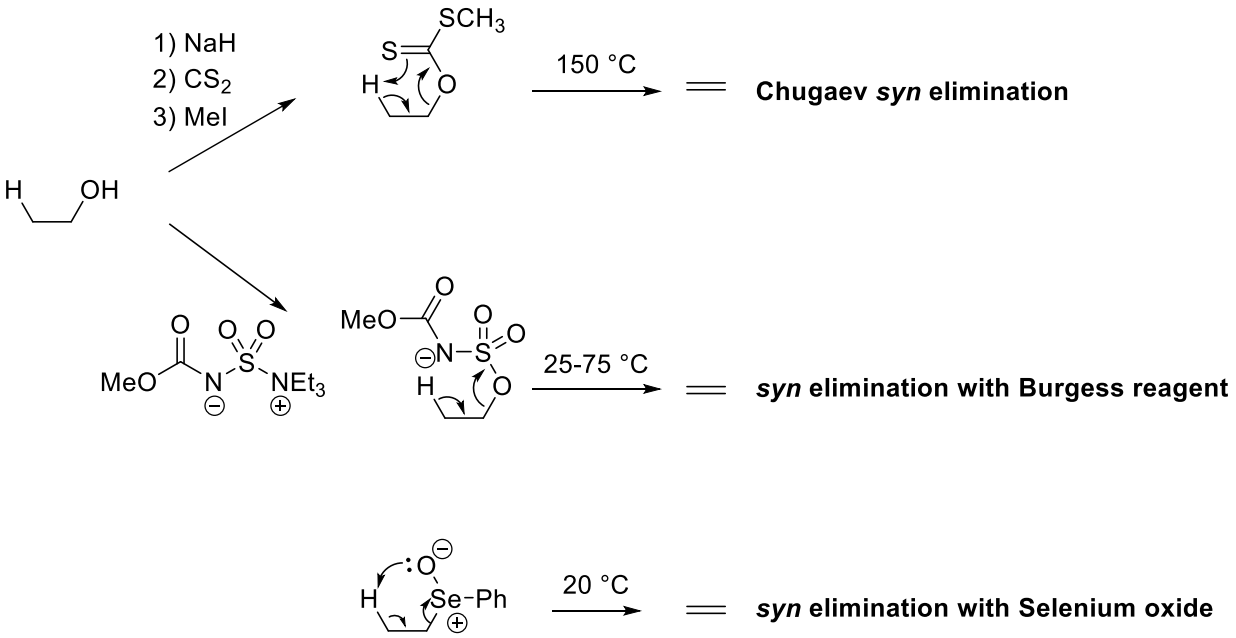
Bibliography: Bruckner, Ch. 4. p. 157-200. Carey Sundberg A: ch. 5.10, p. 546-569; B, ch. 6.6.3, p.596-604. Evans Handout 27A.

E^2, *anti* elimination



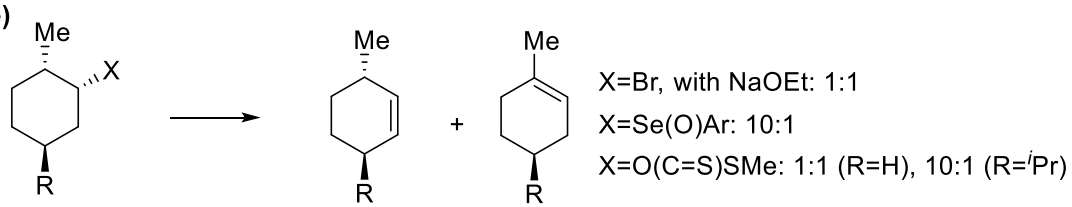
The classical E^2 elimination reactions have already been seen in other courses. For base sensitive molecules, it is good to remember Martin sulfurane as dehydrating agent.

***syn* elimination**

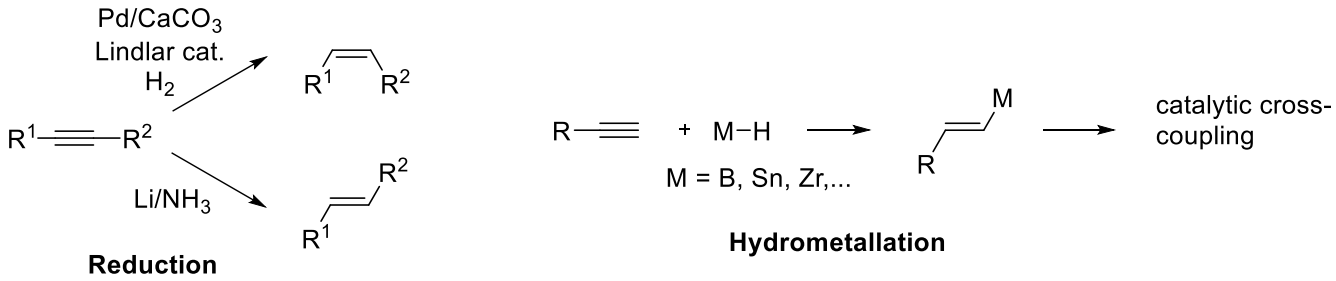


When a *syn* elimination is desired, a cyclic transition state is needed. The classical method is the Chugaev elimination, but several steps are needed to prepare the precursor, as well as high temperature for the reaction. The Burgess reagent and the use of selenium oxides are milder methods often used in total synthesis.

Example (lecture)



4.1.2 From alkynes (B)



Alkynes are interesting starting materials for alkene synthesis. They are easily accessible via addition of acetylides on carbonyls and Sonogashira cross-coupling. They can be selectively reduced to give *cis* alkenes via hydrogenation with Lindlar catalyst or *trans* alkenes in presence of Li/NH_3. The hydrometallation of alkynes give organometallic reagents that can be used in cross coupling reactions (B: Suzuki, Sn: Stille, ...).

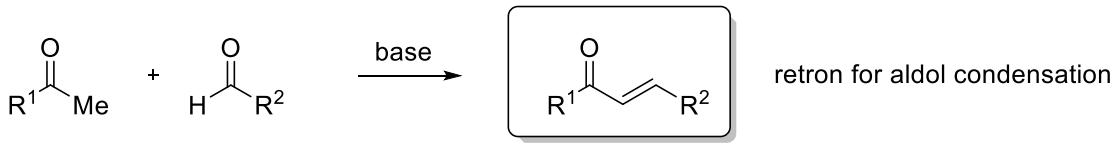
4.1.3 From alkene metathesis (C)

Alkene metathesis is an efficient method for olefin synthesis. The best catalysts are derived from Mo (Schrock) or Ru (Grubbs I et II, Grubbs-Hoveyda). They are used in total synthesis also, in particular for macrocycle formation. However, control over stereoselectivity remains often difficult. This method is discussed extensively in organometallic lectures and will not be treated here.

4.1.4 From carbonyls

4.1.4.1 Aldol condensation (A)

Bibliography: Fonctions et réactions organiques II. Bruckner, Ch. 13.4, p. 565-575.

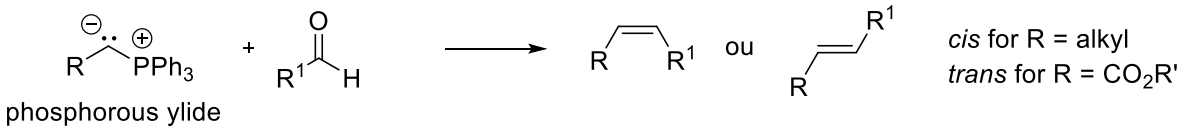


The aldol condensation is the classical method for the synthesis of conjugated olefins. Nevertheless, she is rarely used in complex molecule synthesis, due to the strongly basic conditions and the difficult control over regioselectivity and polymerisation. The intramolecular aldol condensation is easier to control and therefore frequently used.

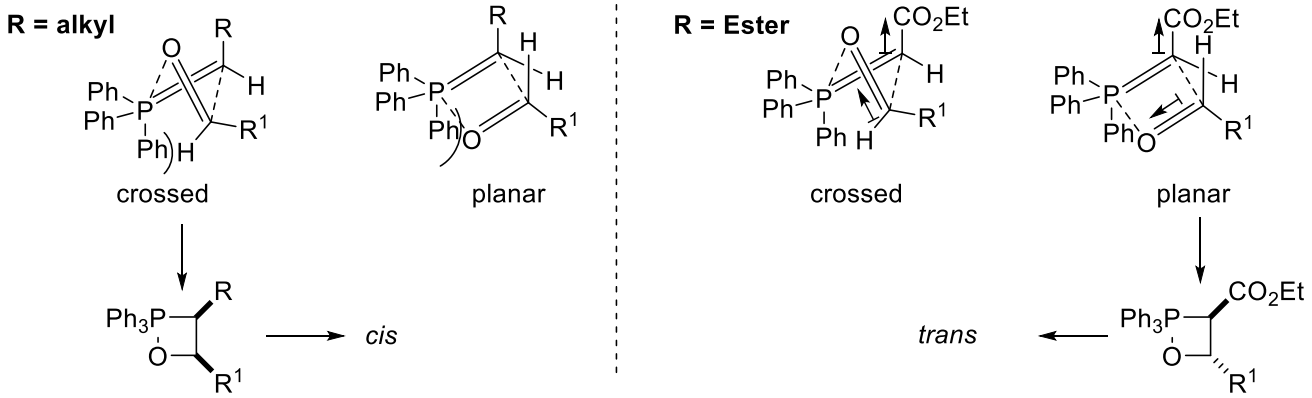
4.1.4.2 Wittig and variations (A)

Bibliography: Bruckner, Ch. 11, p. 457-487. Carey Sundberg B, Ch. 2.4, p. 157-177.

original Wittig

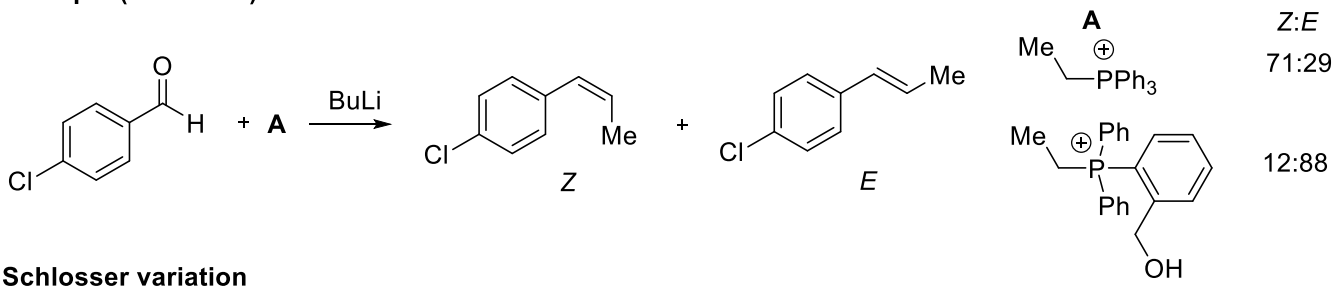


Mechanism

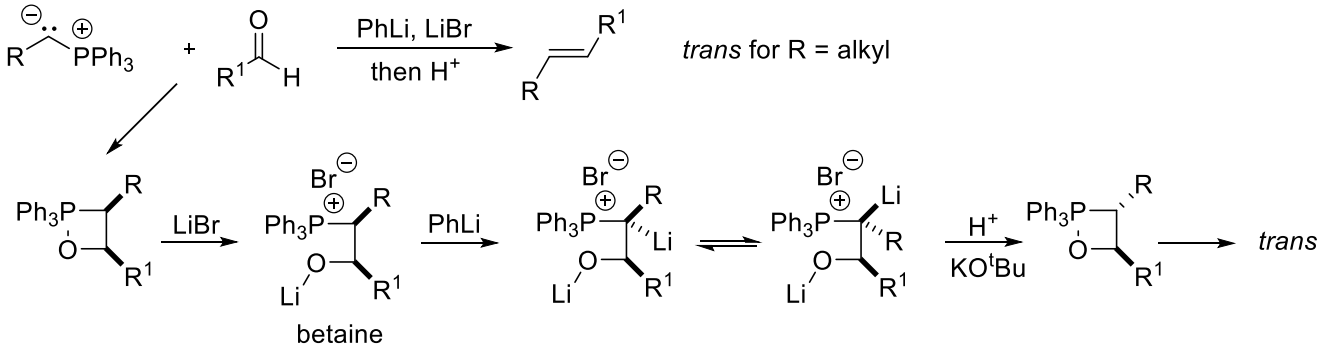


The Wittig reaction allows to access alkenes without stabilizing groups with good *cis* selectivity. Phosphorous ylides stabilized with an ester give *trans* olefins. In the past, a rationalization based on kinetic versus thermodynamic control has been proposed (the *trans* olefin is the thermodynamic product). However, more recent works have shown that both reactions proceed under kinetic control. Steric effects favor the crossed transition state with alkyl groups, whereas dipole effects favor the planar transition state for electron-withdrawing groups.

Example (exercises)



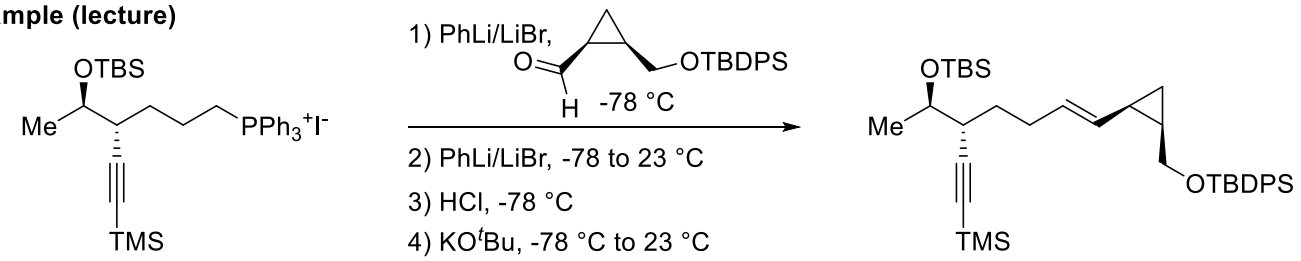
Schlosser variation



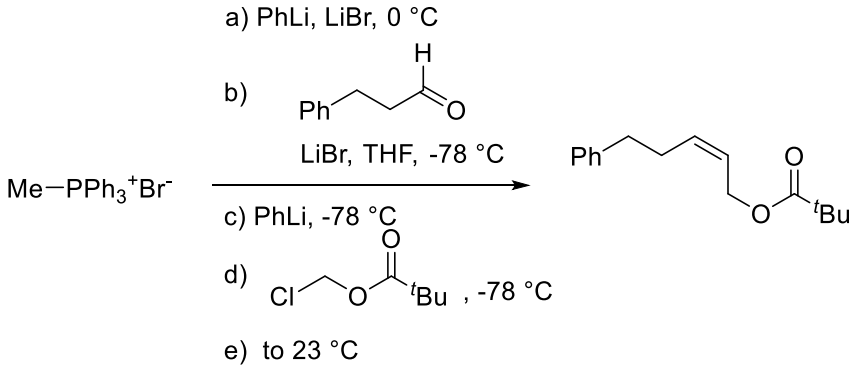
The Schlosser variation (UNIL/EPFL!) makes use of the stabilization of the betaine intermediate with lithium salts. The stabilization of the betaine prevents the elimination of phosphorous oxide and allows a second deprotonation with PhLi. The formed organolithium epimerizes at room temperature to give the more stable *trans* intermediate. The organolithium is then protonated and the strong lithium oxygen bond broken by adding KO^{t}Bu, leading to the elimination of phosphine oxide.

The Wittig reaction and the Schlosser variation allow the stereoselective synthesis of olefins, but they still require strong basic conditions, which are often not compatibe with sensitive compounds.

Example (lecture)

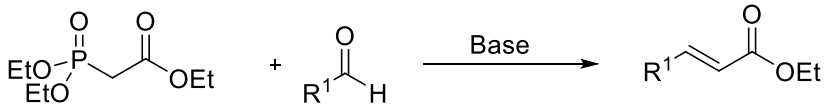


Example (exercises)



Milder variations

Horner-Wadsworth-Emmons (HWE)



base:

Classical: NaH

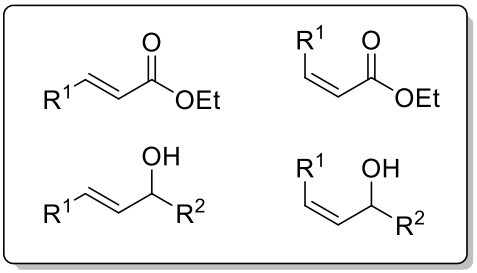
Roush-Masamune: LiCl, DBU

Paterson: BaOH

***Cis* selective variations**

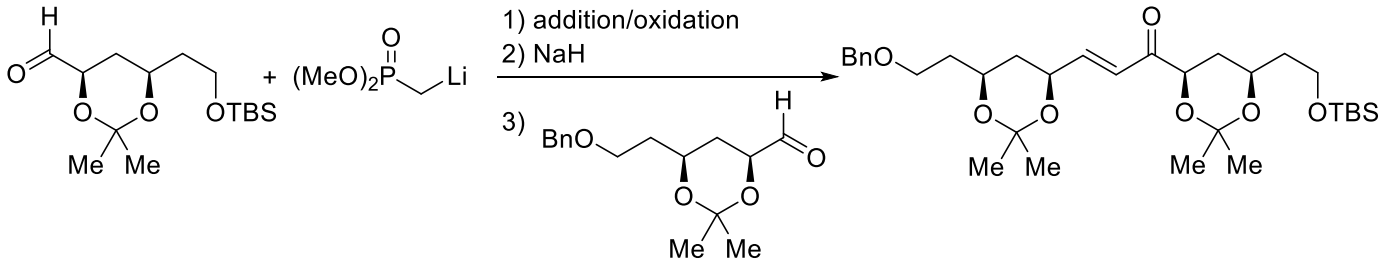
Still-Gennari **Ando**

Retrons for HWE and variations



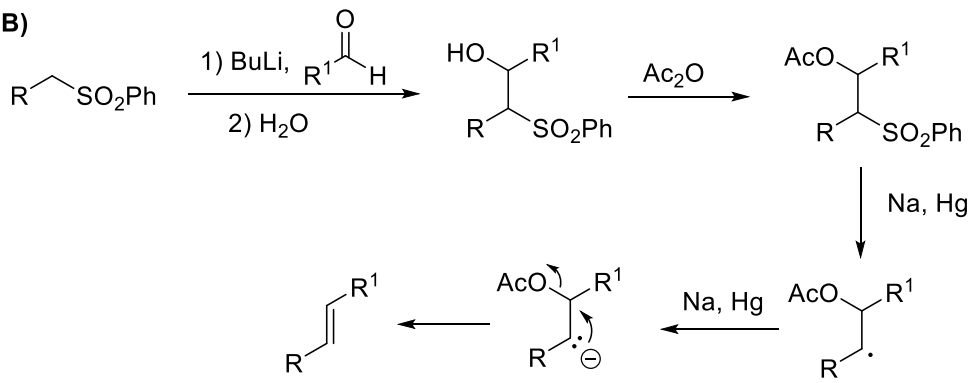
The HWE reaction gives good *trans* selectivity and proceeds under milder conditions than the Wittig reaction. *cis* olefins can be synthesized using the variations of Still-Gennari or Ando. These methods are frequently used for olefin synthesis in complex molecules. The obtained esters can be easily reduced, leading to allylic alcohols.

Example (lecture)



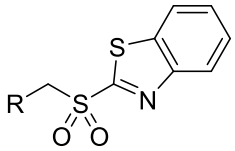
4.1.4.3 Julia and Variations (A)

Julia-Lythgoe (B)

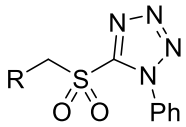


The advantage of the Julia-Lythgoe reaction is a good *trans* selectivity, which is determined by a *trans* elimination in the last step. However, this method requires several steps, including one using sodium mercury amalgam. Therefore, this reaction is only rarely used nowaday.

Julia-Julia (Julia square)

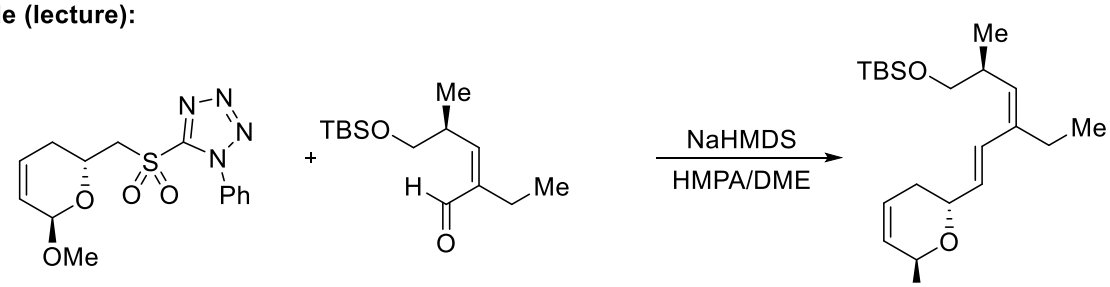


Julia-Kociensky

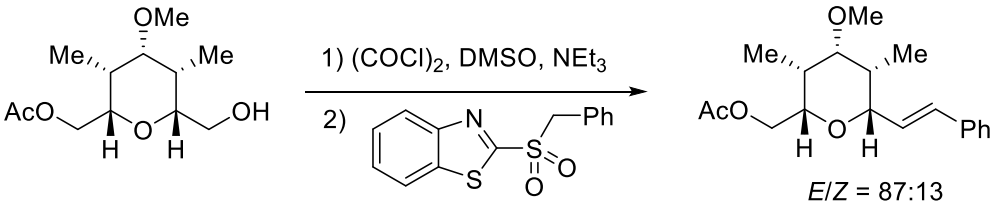


An important progress was realized with the development of variations proceeding in a single step, like the Julia modification (brother of the first) and the Julia-Kociensky variation. The method of Julia-Kociensky is one of the best methods to obtain *trans* olefins in non-stablized systems. As the conditions are milder than for the Schlosser-Wittig, it is often used for more complex and sensitive compounds.

Example (lecture):



Example (exercises):



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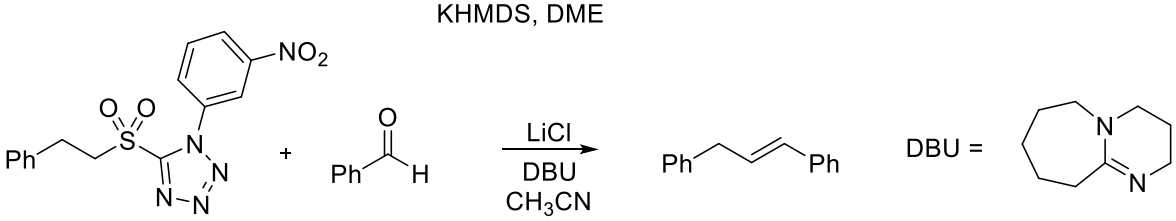
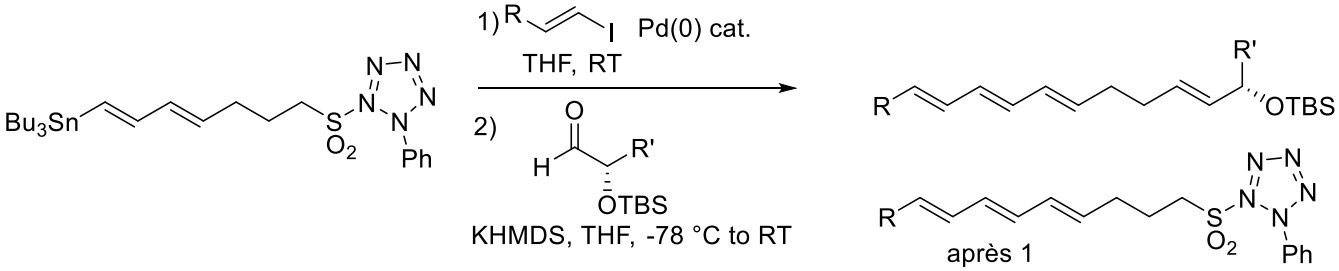
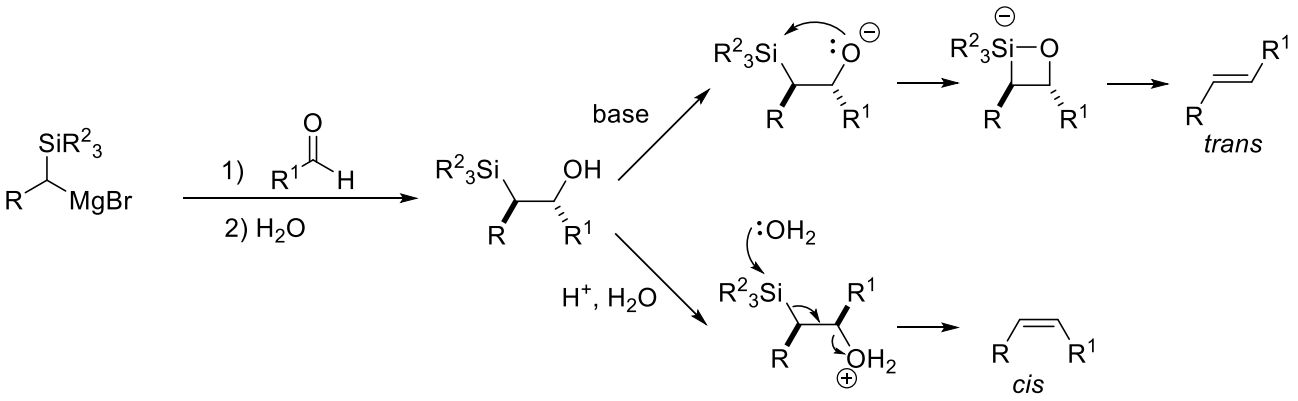




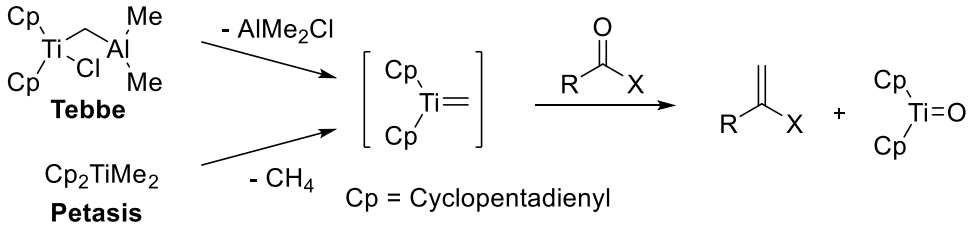
4.1.4.4 Peterson Olefination (B)



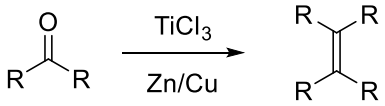
The Peterson method is interesting, as it is stereodivergent. The obtained *anti* intermediate gives the *trans* olefin in presence of base via the formation of a silaoxetane and the *cis* olefin in presence of acid and water via a *trans* elimination. If the diastereoselectivity in the first step is not good, the diastereoisomers can be separated and converted to the desired alkene geometry by chosing the conditions in the second step.

4.1.4.5 Methods with transition metals (C)

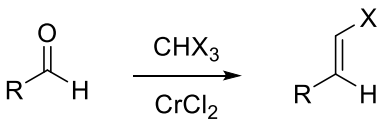
Methylenylation of carbonyls



McMurry



Takai



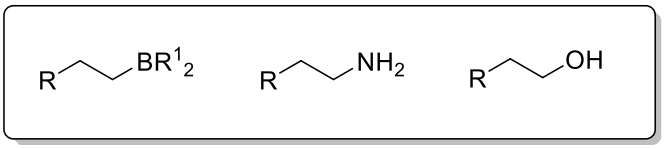
The transition metals give access to different reactivity. The reagents of Tebbe and Petasis lead to methylenation of carbonyls. In contrast to the Wittig reaction, these methods also work with esters and amides. The reaction of McMurry is a good method for the synthesis of tetrasubstituted olefins and the reaction of Takai allows the synthesis of halogenated *trans* olefins.

4.2 Stereoselective reductions of alkenes

4.2.1 Hydroboration

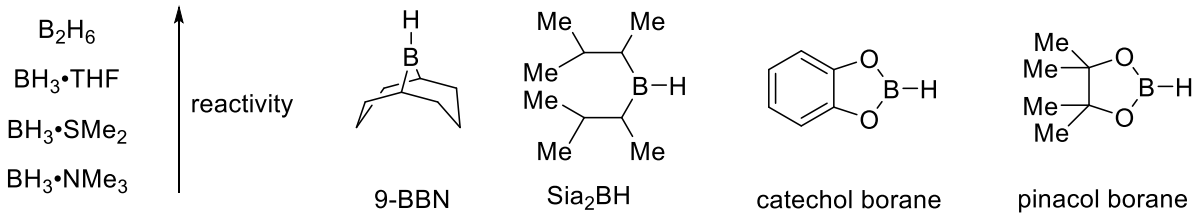
Bibliography: Fonctions et réactions organiques II, Bruckner ch. 3.3.3-3.4.5, p. 118-136. Evans Lecture 8, Carey Sundberg A, Ch. 5.7, p. 521-531; B, Ch. 4.5, p. 337-353. Carreira Ch. 7, p. 215-235.

Retrons:



4.2.1.1 Important boron reagents and general mechanism (A)

Reagents

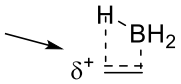


boranes **Alkylboranes** **Alkoxyboranes**

The structure of the used boron reagent will have a strong influence on selectivity. The smallest borane, BH_3, is very reactive and dimerizes spontaneously. It can be stabilized with Lewis bases such as THF, SMe_2 and NMe_3. Alkyl boranes are larger and less reactive. They are themselves synthesized by hydroboration of the corresponding olefins. Alkoxyboranes are the least reactive and usually require a catalyst to react.

Mechanism and regioselectivity

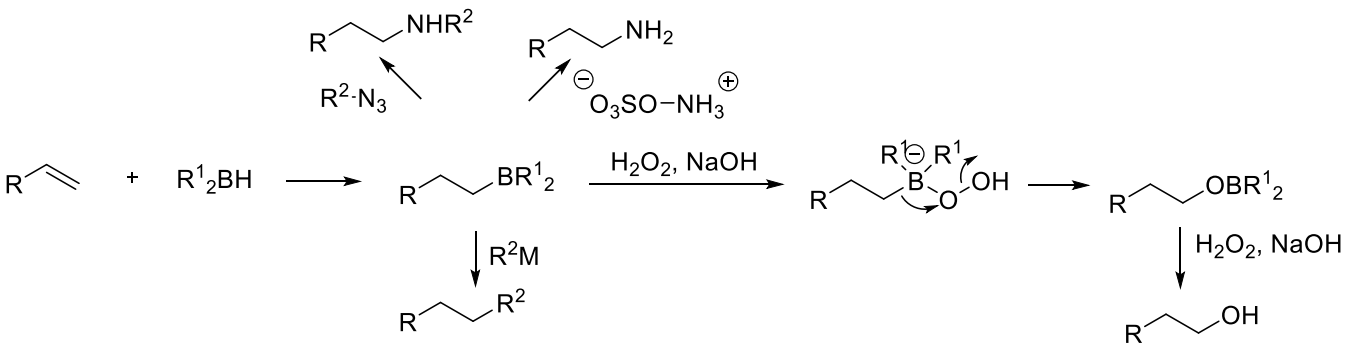
partial positive charge



tertiary carbocation > secondary carbocation > primary carbocation

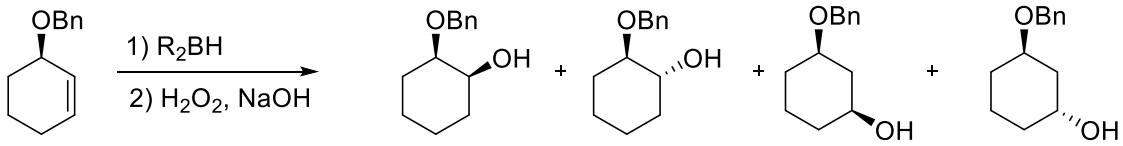
The hydroboration is concerted, but strongly asynchronous. The formation of the B-C bond preceeds the one of the C-H bond, leading to the formation of a partial positive charge in the transition state. The stabilization of this charge is essential for regioselectivity.

Fonctionalisation of organoboranes (B)



Organoboron reagents are very useful intermediates in organic synthesis. The most classical transformation is oxidation to give alcohols. Other imporant transformations are metal-catalyzed cross-couplings and amine formation via reaction with azides or NH_2OSO_3H.

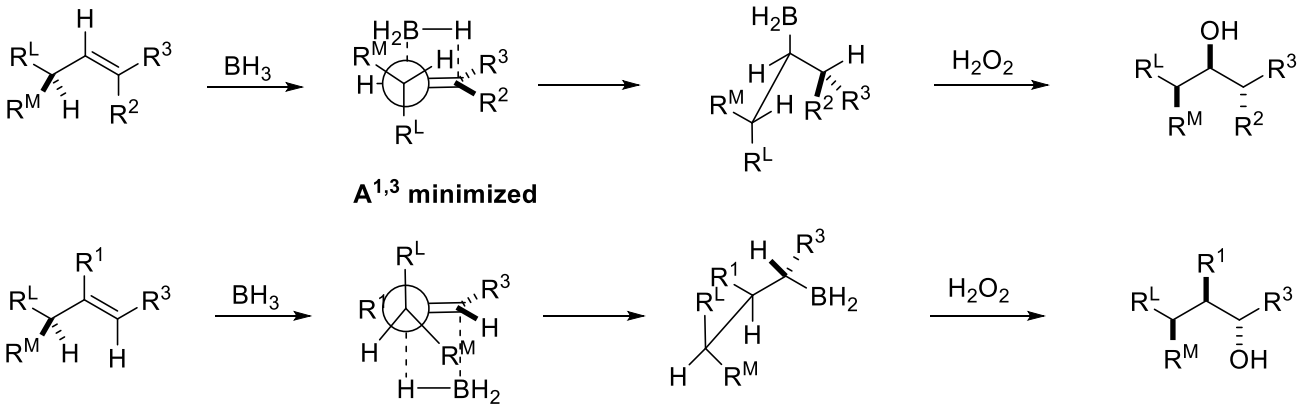
Example (lecture):



R = H	10%	81%	5%	5%
R = 9-BBN	0%	68%	19%	13%

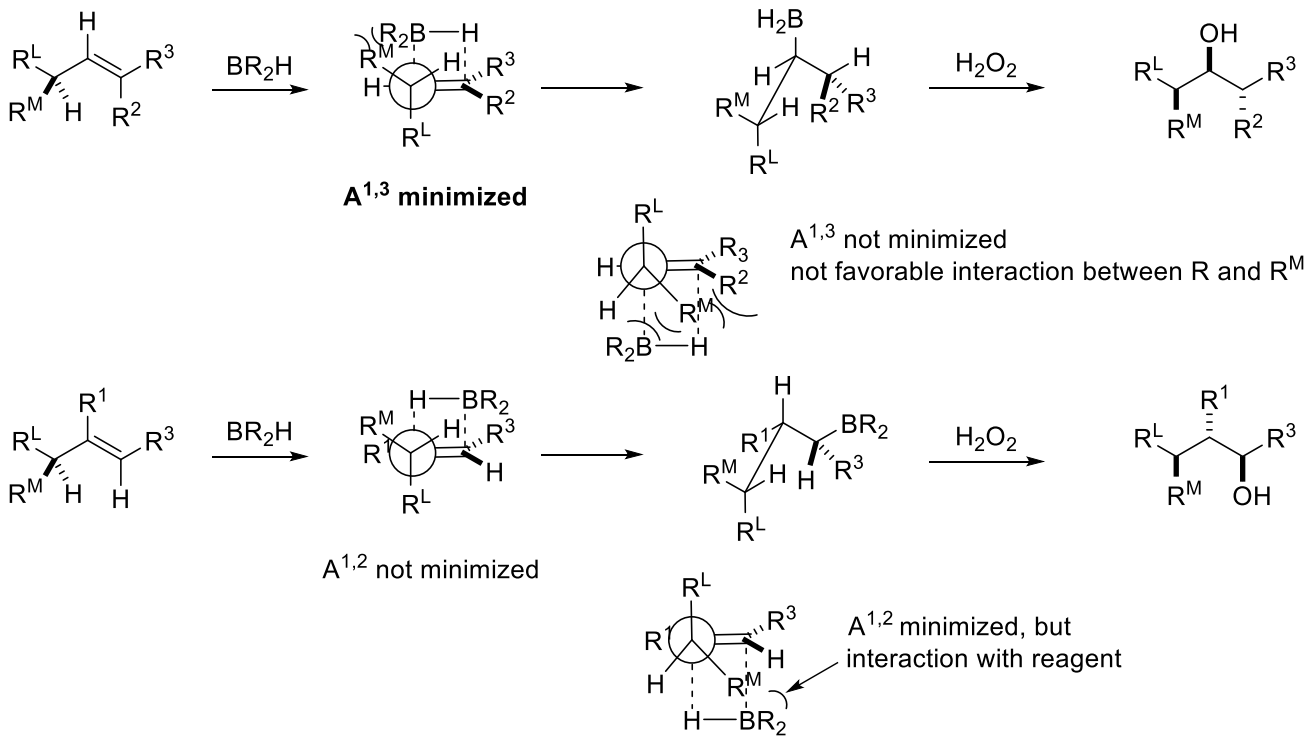
4.2.1.2 Stereoselectivity (A)

Diastereoselectivity with small boranes



The observed diastereoselectivity can be rationalized by minimizing steric effects in the transition states. In dependence on the alkene substitution, either $A^{1,3}$ or $A^{1,2}$ allylic strain dominates and needs to be minimized. The regioselectivity is determined by stabilization of the partial charge in the transition state, so that the hydrogen atom ends on the most substituted center.

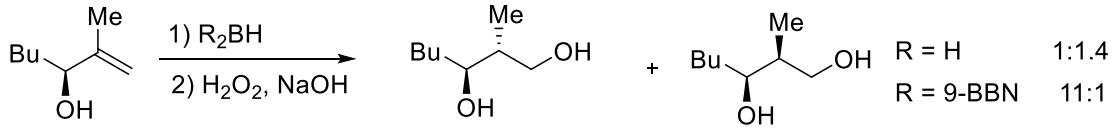
Diastereoselectivity with large boranes



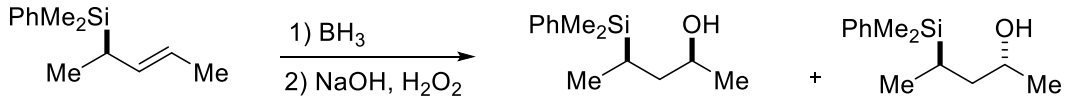
When boranes grow larger, interaction between reagent and substrate in the transition state becomes more important (reagent control). For olefins in which the $A^{1,3}$ strain dominates, there is not much difference on both faces for reagent-substrate interactions. The selectivity can be even reinforced. In case of substrates in which the $A^{1,2}$ strain dominates, steric interactions between reagent and substrates are weaker when the $A^{1,2}$ strain is not minimized. It is therefore possible to invert selectivity in this case.

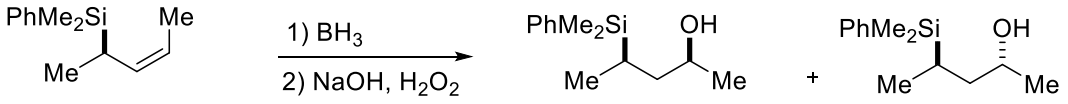
Examples (lecture):

1)

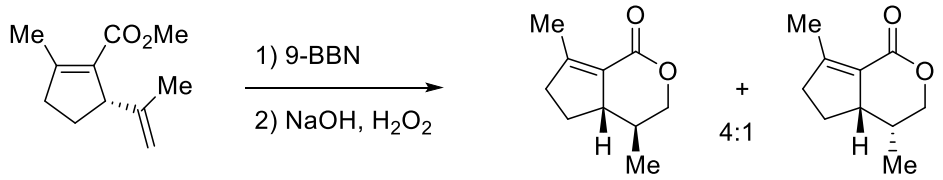


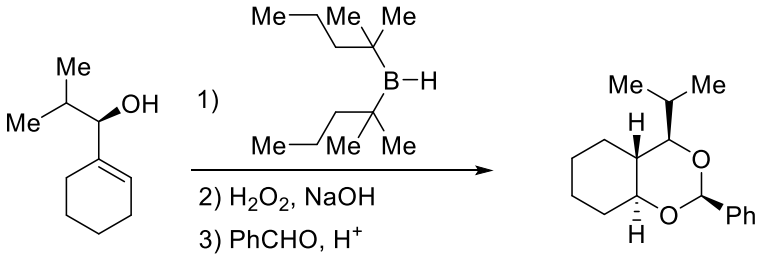
2)

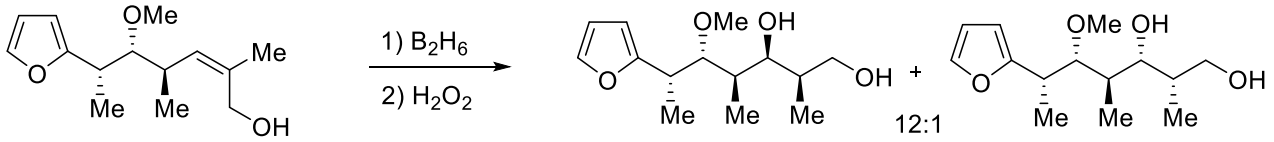


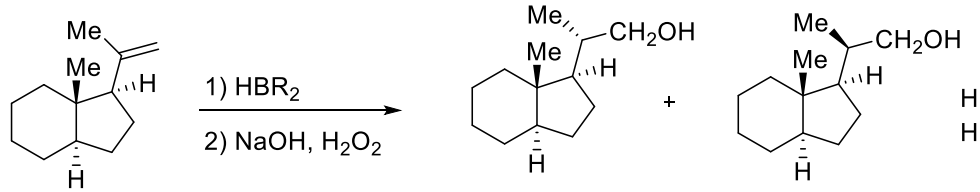


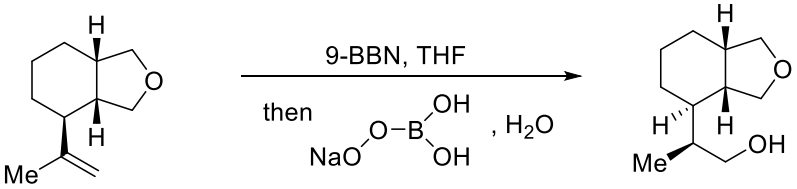
Examples (exercises):



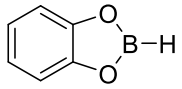






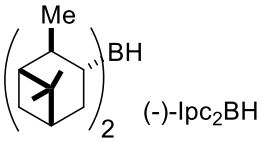


Enantioselective reactions (D)



, Rh cat., chiral biphosphine

asymmetric catalysis



(-)-Ipc_2BH

chiral reagent

For asymmetric synthesis starting from non-chiral olefins, several methods have been developed. An important reagent is (-)-Ipc_2BH, obtained via hydroboration of (+)-α-pinene and introduced by Brown. The analysis of selectivity is difficult due to the complexity of the reagent. Catalytic asymmetric methods have also been developed with rhodium catalysts making use of the lower reactivity of alkoxy boranes. In this case, the selectivity is induced by chiral ligands (oftent biphosphines like BINAP, see lecture catalytic asymmetric reactions in organic synthesis). In case of catalytic methods, other regioselectivities can be obtained.

4.2.2 Other hydrometallations (C)

Bibliography: Carey Sundberg B, Ch. 4.6, p. 353-358.

Reagents reacting directly with olefins: $HAlR_2$, $(Cp)_2HZrCl$.

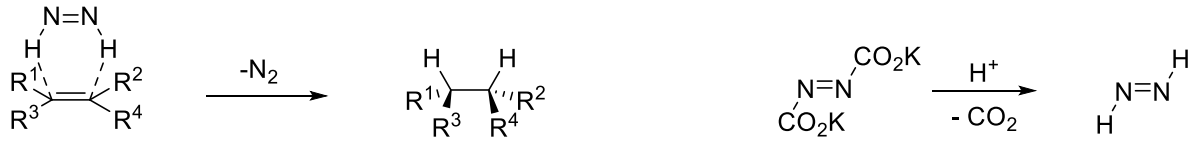
Reagents requiring catalysts: $HSiR_3$, $HSnR_3$.

Hydrometallations are not limited to boranes. Direct reactions are possible with organoaluminium and organozirconium reagents. Silanes and stannanes are less reactive and require the use of a catalyst, such as palladium.

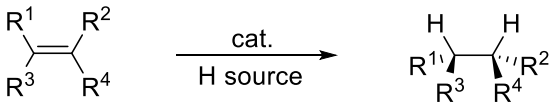
4.2.3 Hydrogenation (C)

Bibliography: Carey Sundberg, B, Ch.5.1, p. 367-390. Carreira Ch. 8, p. 235-263.

reduction with diimide



The reduction of olefins with diimide is an excellent method for *cis* hydrogenation not requiring transition metal catalysts. Diimide is unstable and can be generated *in situ* from the corresponding dicarboxylate in presence of acid.



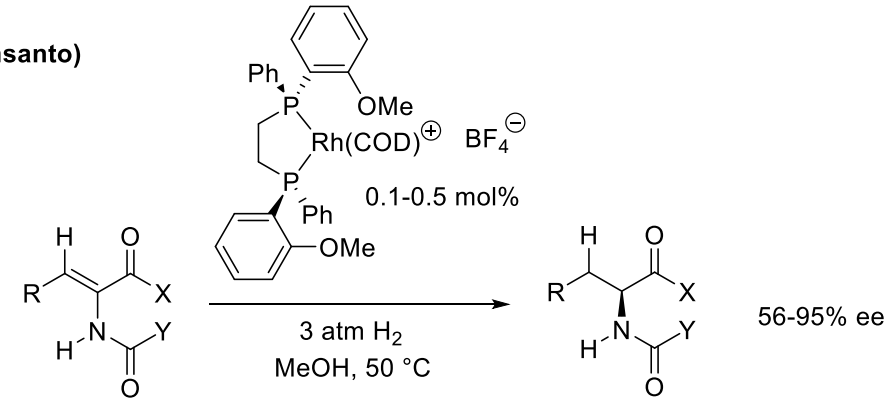
important catalysts: Pd, Ru, Rh, Ir, Pt, Ra-Ni

Hydrogen sources: H_2, ^iPrOH, HCO_2^-

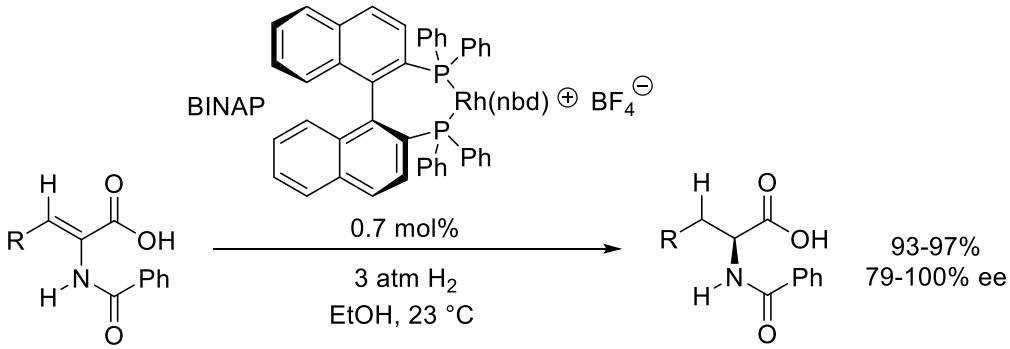
The majority of hydrogenation methods uses transition metal catalysts with hydrogen sources, such as H_2, formate salts or alcohols (hydrogen transfer).These reactions are discussed in details in inorganic chemistry lectures.The conformation analysis made for boranes also remains valid for catalytic transformations!

Asymmetric Hydrogenation (D)

Knowles method (Monsanto)



Noyori method



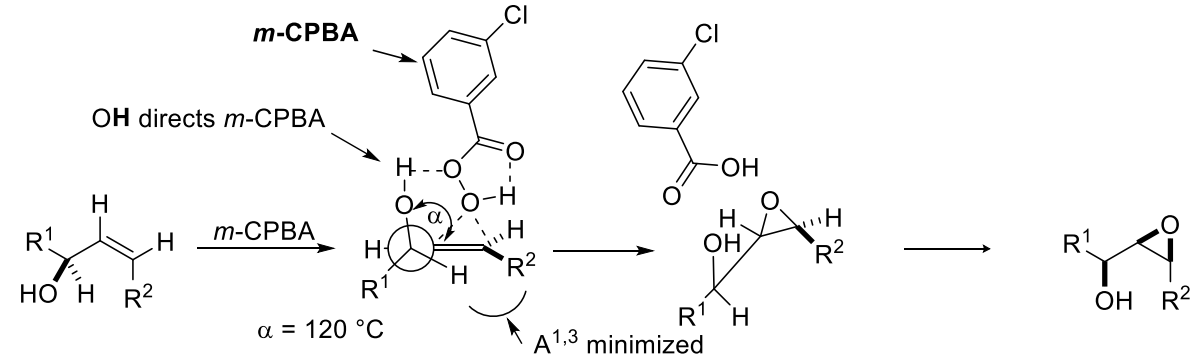
Asymmetric hydrogenation using metal catalysts and chiral ligands is very important in organic and industrial chemistry. These reactions will be discussed in details in the lecture catalytic asymmetric reactions in organic synthesis. The two pioneering examples are: The method of Knowles with phosphines chiral on phosphorus and the method of Noyori, who discovered BINAP as a privileged ligand.

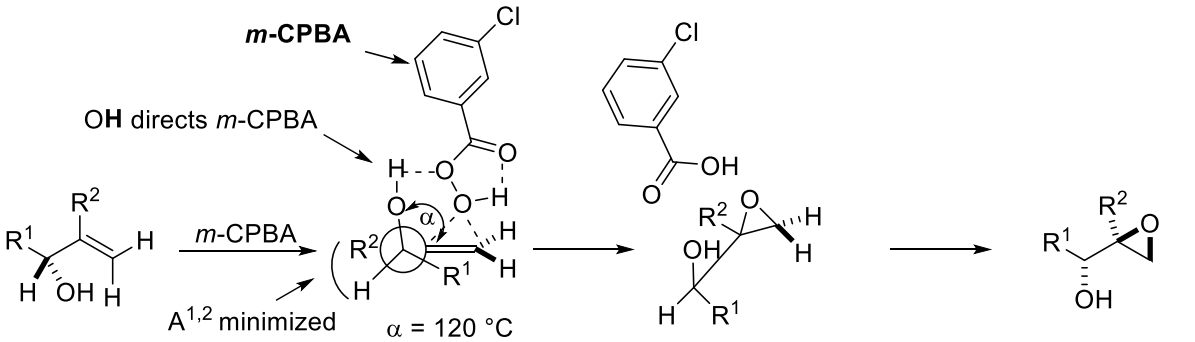
4.3 Alkene Oxidation

4.3.1 Epoxidation

Bibliography: Fonctions et réactions organiques II, Carey Sundberg A, Ch. 5.5.1, p. 503-511; B, Ch. 12.2.2, p. 1091-1104. Evans lecture 9D. Carreira, Ch.9.2-9.3, p.264-277. Bruckner, Ch. 3.4.6, p. 136-142.

4.3.1.1 Directed epoxidation with *m*-CPBA (A)

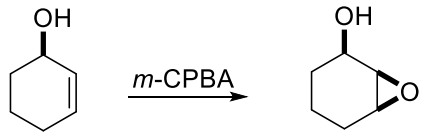




m-CPBA (*meta*-chloroperbenzoic acid) is an electron-poor peracid. It reacts rapidly with electron-rich olefins. The intramolecular hydrogen bond makes it more soluble in organic solvents and less acid than the corresponding carboxylic acid.

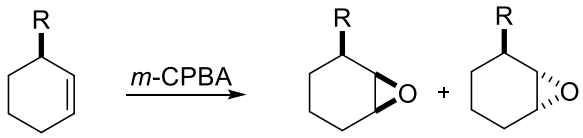
The reaction is **directed** by hydrogen bond donors, like alcohols or amides, and these substrates react faster and with higher selectivity than other olefins. This effect is partially due to entropy (pseudo unimolecular reaction) and partially to the activation of the peracid through hydrogen bonding, which makes it more electrophilic. The transition state is concerted, but asynchronous, with electron transfer from alkene to peracid preceeding the nuclophilic attack of the oxygen atom. Therefore, a favorable interaction determines the transition state, in contrast to the non-favorable interactions discussed in the previous section. Still, steric interactions are minimized according to the substitution pattern of the olefin.

Prediction is easier for cyclic substrates



Directed reaction ⇔ Substrate bound to reagent to control trajectory of attack

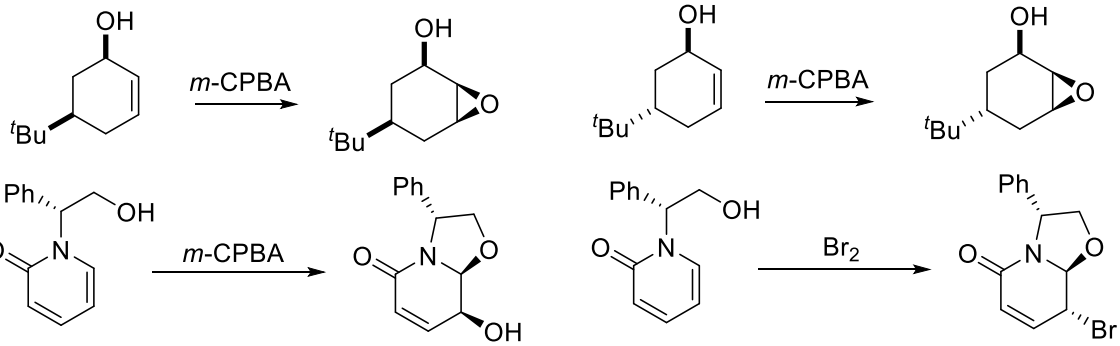
Example (lecture):



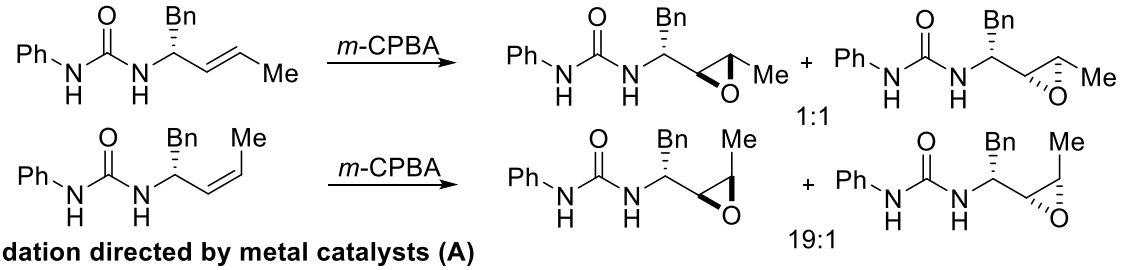
R=OH: 92:8

R=OAc: 37:63, 20x slowlier

Examples (exercises):

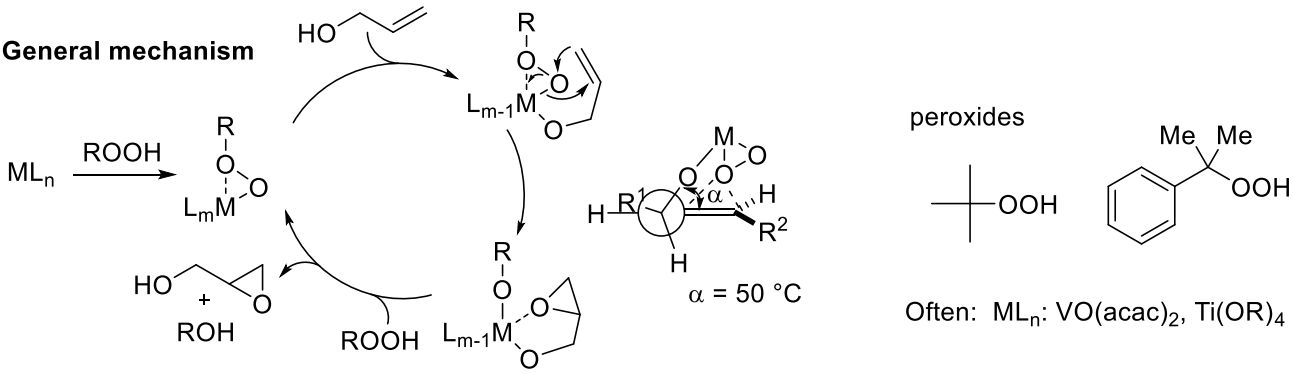


Example (exercises):



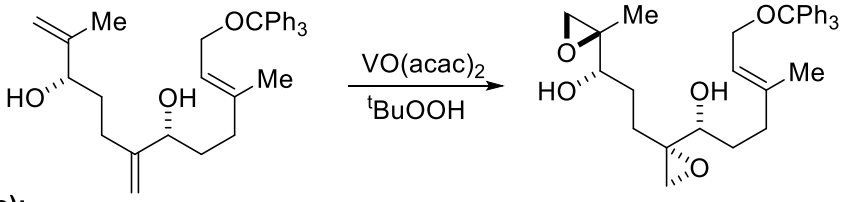
4.3.1.2 Epoxidation directed by metal catalysts (A)

General mechanism

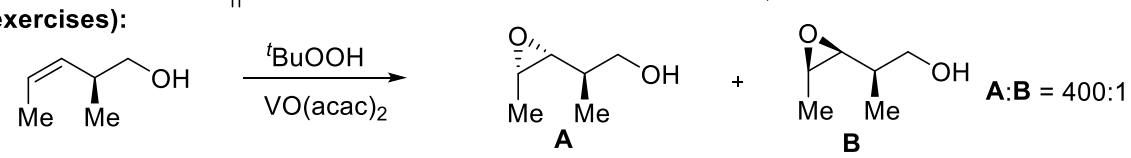


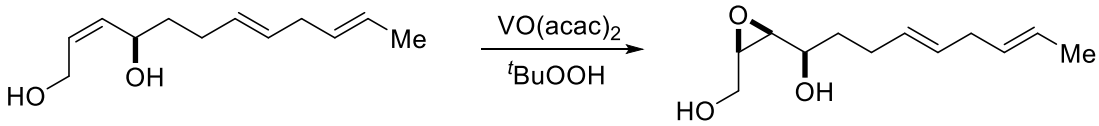
Metal catalysts, especially vanadium and titanium, are able to activate simple hydroperoxides for the epoxidation of olefins. In contrast to peracids, no reaction is occuring between hydroperoxides and alkenes in the absence of catalyst. This reaction are in principle always directed: epoxidation occurs only if the substrate is bound to the metal. Transition state analysis is similar, but the exact angle between alcohol and olefin can lead to different selectivity when compared to *m*-CPBA.

Example (lecture):



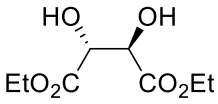
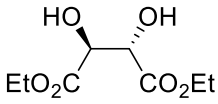
Examples (exercises):

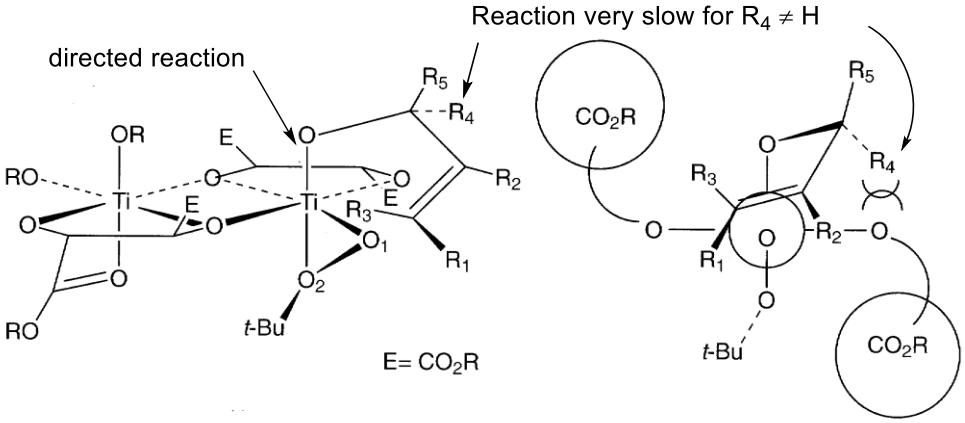




Sharpless catalytic asymmetric epoxidation (B)

conditions: 5 mol% $Ti(O^iPr)_4$, 5 mol% DET, ^{t}BuOOH, molecular sieves, CH_2Cl_2, -20 °C

L-(+)-DET = diethyltartrate  D-(-)-DET = diethyltartrate 



Sharpless asymmetric epoxidation

1) Only for allylic alcohols

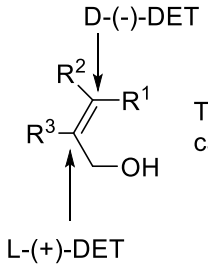
2) The peroxide reacts only when bound to titanium, no direct reaction

3) Selectivity is determined by the position of the ester groups on the ligand, not substrate conformation (excellent reagent control)

4) Achiral substrates give very good enantioselectivity.

5) For substrates bearing a chiral center, one enantiomer only can bind efficiently to the catalyst for steric reasons. The other enantiomer reacts only very slowly. This allows an efficient kinetic resolution of racemic mixtures.

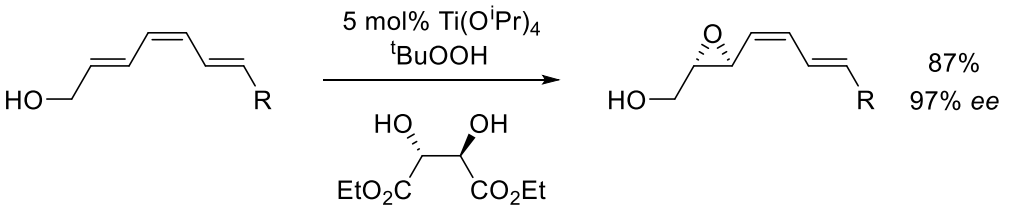
mnemotechnic model



The Sharpless epoxidation is often used in synthesis, as its selectivity can be easily predicted, which facilitates greatly planification.

The weak point of the Sharpless epoxidation is its limitation to allylic alcohols. In the lecture catalytic asymmetric reactions in organic synthesis, other asymmetric epoxidation methods will be discussed, in particular those of Jacobsen and Shi.

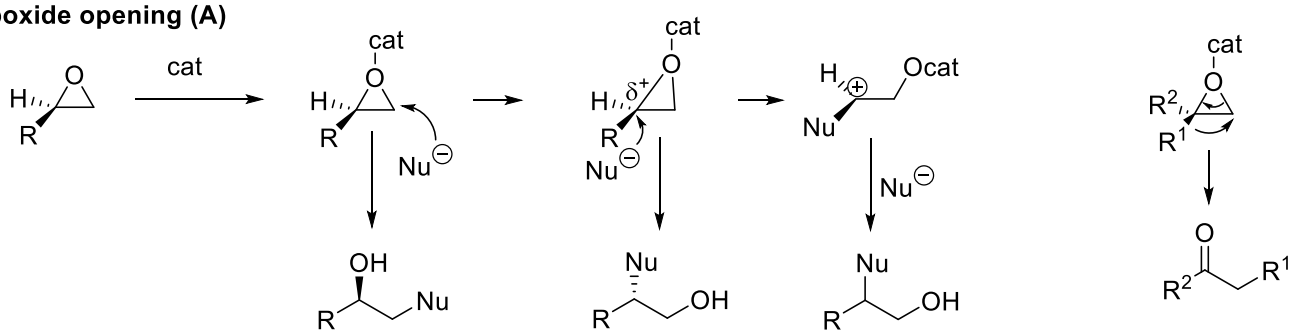
Example (lecture):



4.3.1.3 Epoxide opening and rule of Fürst-Plattner

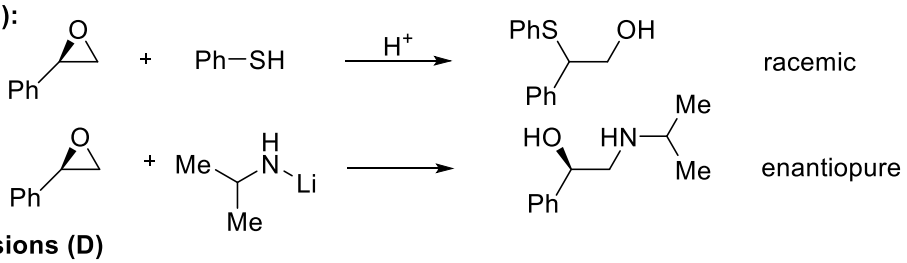
Bibliography: Fonctions et réactions organiques II. Carey Sundberg A, Ch. 5.5.2, p.511-515; B, Ch. 12.2.3, p.1104-116. Carreira, Ch. 9.4.

Epoxide opening (A)

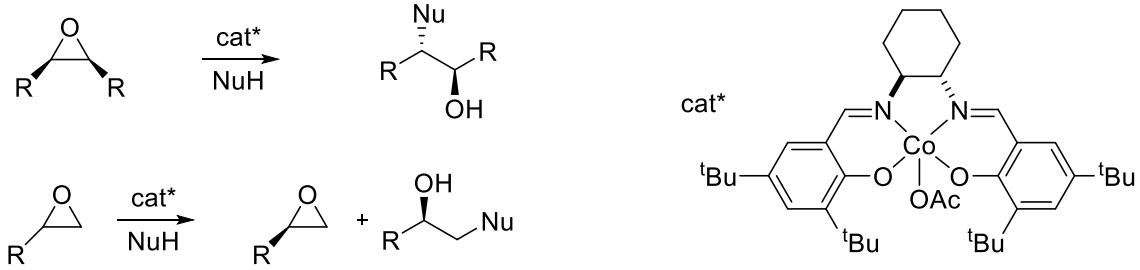


Epoxide opening is important for the stereoselective synthesis of organic compounds bearing two adjacent functional groups. In general, a catalyst (Lewis or Brønsted acid) is necessary for activation. Depending on substrate structure, catalyst strength and nucleophile properties, ring-opening occurs at the more or the less sterically encumbered position, either via stereoinversion or loss of stereochemistry. If there is no nucleophile, a 1,2- shift to give the carbonyl group can occur.

Example (lecture):

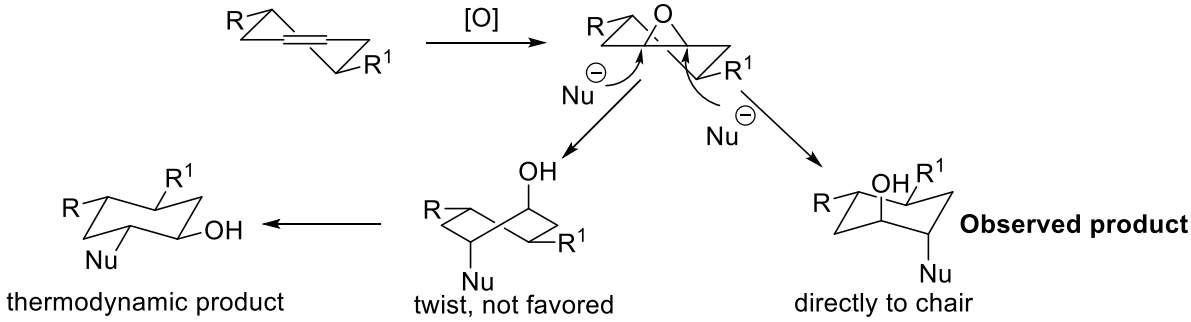


Asymmetric versions (D)



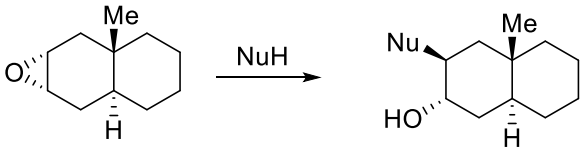
There are two main methods for asymmetric epoxide ring-opening: the desymmetrization of meso-epoxides and the kinetic resolution. An important catalyst is the Co-Salen developed by Jacobsen. These reactions will be discussed in the course catalytic asymmetric reactions in organic synthesis.

Fürst-Plattner rule (A)

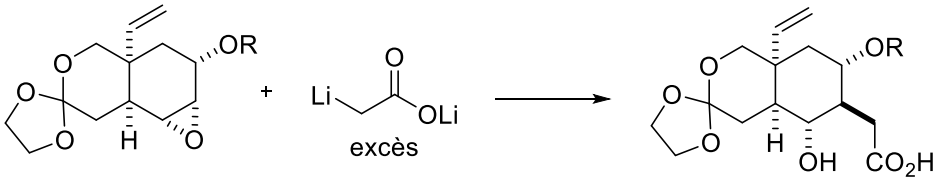


The Fürst-Plattner rule is an example of kinetic stereocontrol. Due to the 180° attack of the nucleophile, the product with two substituents in axial positions is obtained. Microreversibility: The formation of the epoxide is possible only if the two groups are in position axial!

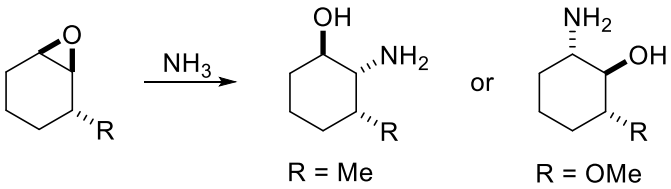
Example (lecture):



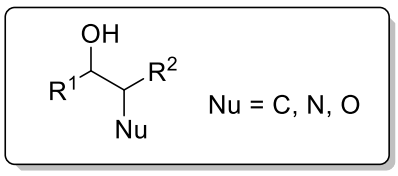
Example (exercises):



Forr R = H
For R = PG (protecting group)
no reaction



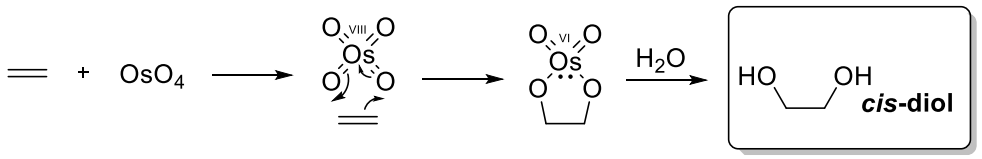
Retron for the sequence epoxidation / ring-opening (B)



4.3.2 Dihydroxylation

Bibliography: Bruckner, Ch. 17.3.2, p. 758-766. Carey Sundberg B, Ch. 12.2.1, p. 1074-1091 (in part). Carreira Ch. 9.7-9.8, p. 291-300.

General mechanism (B)

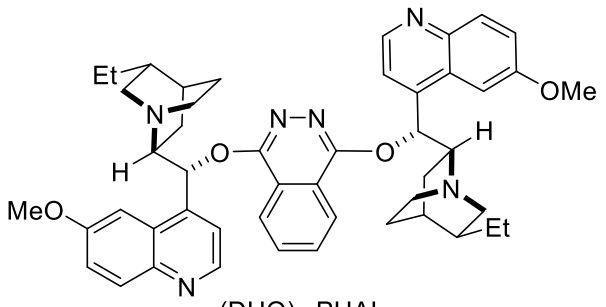


retron for dihydroxylation

The major issue with the original dihydroxylation protocol was the stoichiometric quantity of expensive and toxic OsO_4. A first progress was the use of catalytic osmium with a stoichiometric oxidant, such as NMO (*N*-Methylmorpholine-*N*-oxide).

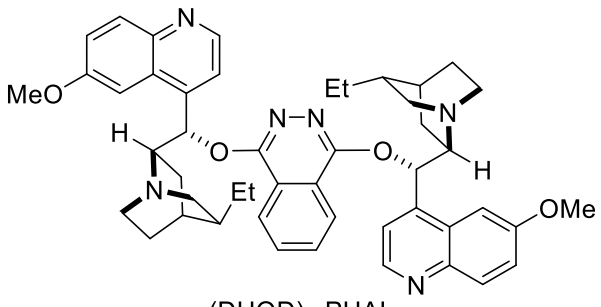
The analysis of diastereoselectivity of dihydroxylations is complex, as both steric and electronic effects need to be considered. Several models have been proposed, but will not be discussed in this course (see Carreira for a detailed discussion).

Sharpless asymmetric dihydroxylation AD-mix α and β. (D)



$(DHQ)_2$-PHAL

AD-mix α



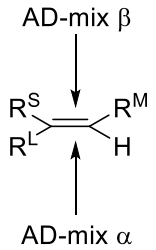
$(DHQD)_2$-PHAL

AD-mix β

5 mol% $K_2OsO_4(OH)_4$ (catalyst)
$K_3Fe(CN)_6$ (oxidant)
Cinchona derivative (chiral ligand)
inorganic base

} **AD-mix**

Mnemotechnic model



The Sharpless dihydroxylation is the most used method for the asymmetric synthesis of diols

The complex AD-mix system has been optimized over several years. Instead of stoichiometric osmium(VIII), it uses only 5 mol% of osmium(VI) salt, which is much less toxic. The oxidant is Fe(III). The best ligands are dimers derived from cinchona alkaloids (chiral pool). This reaction will be discussed in the lecture catalytic asymmetric reaction in organic synthesis.

Bloc III

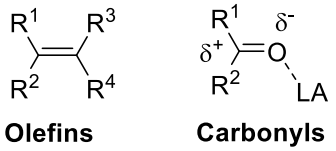
Stereoselective Chemistry of Carbonyl Compounds

5. Additions on carbonyl compounds

5.1 Concept and models: Felkin-Anh and Baldwin rules (A)

Bibliography: Fonctions et réactions organiques II. Bruckner, Ch. 10.3, p. 405-422. Carey Sundberg A: Ch. 7, p.629-638. Evans, lectures 19-21A. Vogel Ch. 5., p.128-132. Carreira Ch. 2.1-2.2, p. 19-25.

Comparison with olefins



- Steric: only electron pairs on oxygen
- C=O is electrophilic: only addition of nucleophiles
- C=O is polarized, no problem of regioselectivity
- Easy activation of C=O with Lewis or Bronsted acids

5.1.1 Model hystory

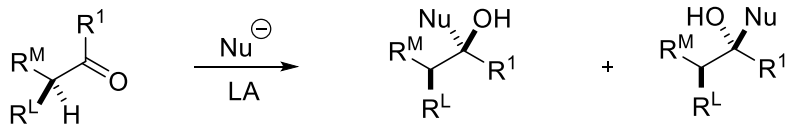
What is a model for the stereoselectivity of a reaction

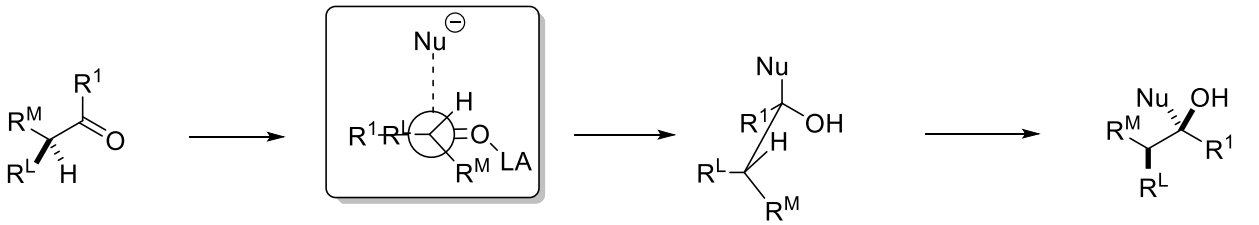
It is a representation of the transition state of the reaction which allows to rationalize selectivity

A model does not correspond always to "reality", but it allows to plan synthesis (even with often some bad "surprizes"). Of course, chemists always try to propose models taking into account the whole information available, and new knowledge constantly allows to improve models to explain observed exceptions. The organic chemist is pragmatic and will use the simplest model allowing him to explain rapidly the results. The history of models for the addition onto carbonyl compounds is representative of this way of proceeding.

Step 1: Cram 1952 (C)

Empirical observation out of many experiments:

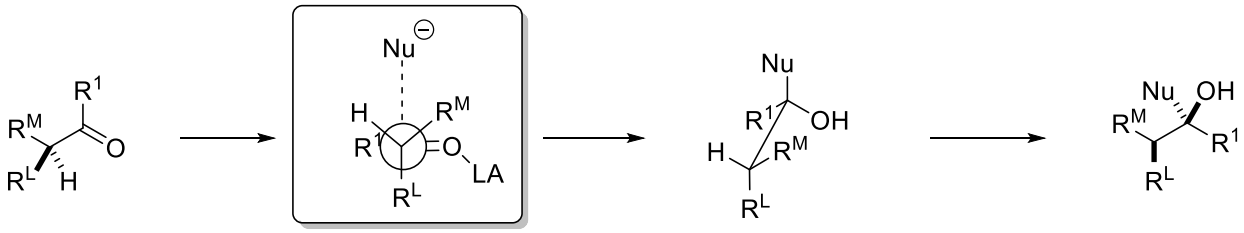




Cram model: Place R^L in eclipsed conformation with the group R^1 on the carbonyl, The nucleophile attacks on the side of the smallest substituent. Cram model allows a correct prediction, but it is not fully "satisfying": The considered conformation is not sterically favored (interaction R^1-R^L in the transition state) and the conformation obtained after reaction is also partially eclipsed.

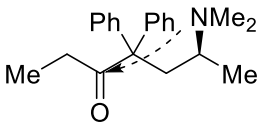
Theoretical work of Houk for transition states: Transition states leading directly to staggered conformations are strongly favored.

Step 2: Felkin (C)

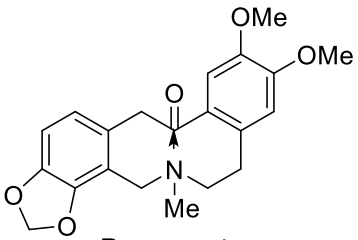


Felkin model: Felkin model takes into account Houk's principle of maximizing staggered conformations. R^L is now ⊥ to C=O, the smallest group (H) is placed on the side of R^1. The nucleophile attacks opposite to R^L. This model corresponds to the one for addition to alkenes with minimization of $A^{1,2}$ strain. However, the model cannot explain the good selectivities observed with aldehydes, which have a very weak $A^{1,2}$ strain.

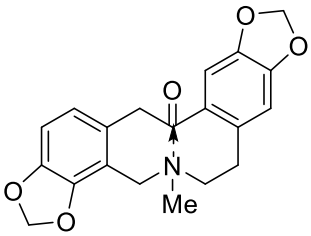
Crystallography work of Bürgi-Dunitz (B):



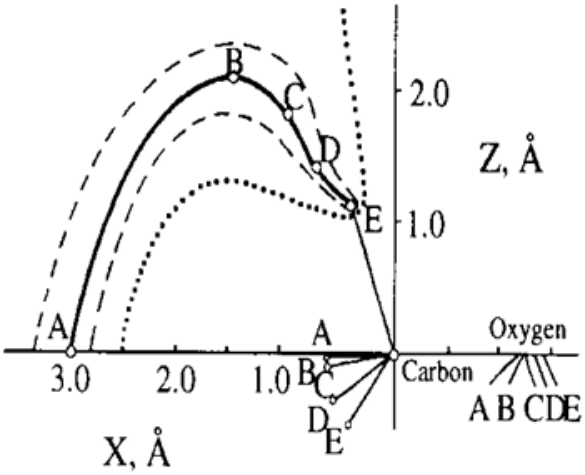
A: methadone

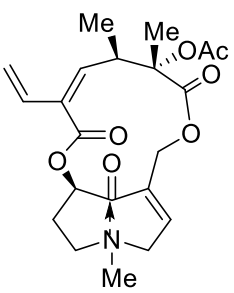


B: cryptopine

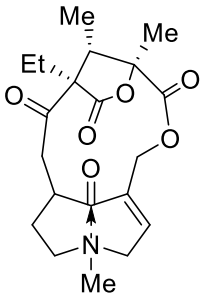


C: protopine



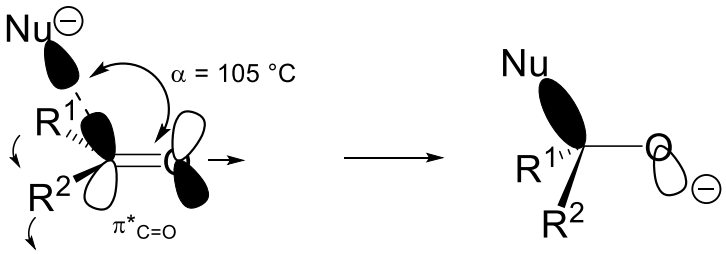


D: clivorine



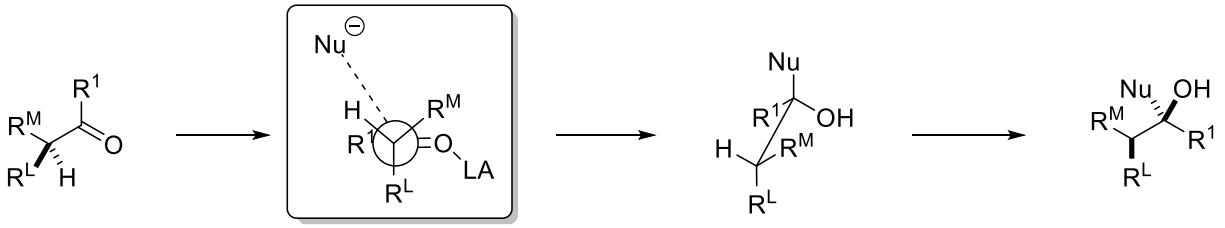
E: retusamine

Bürgi and Dunitz have studied at ETHZ the crystal structure of compounds containing a nucleophile (amine) and a carbonyl in close proximity in the same molecule. They observed an interesting trend: Starting from a certain distance (< 2.0 Å), the amines are oriented along a fix angle of 105 °C in relation to the C=O plan. They proposed that the crystalline structures can be considered as "pictures" of the transition state for addition of nucleophiles onto carbonyls, and that intermolecular reactions will also occur along the same angle, now known a the Bürgi-Dunitz trajectory.



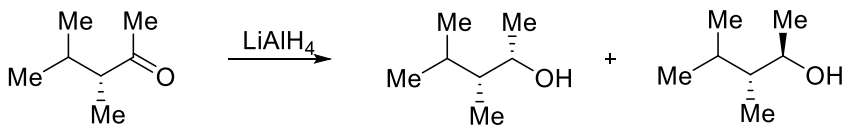
The Bürgi-Dunitz trajectory can be explained by the geometry of the LUMO of the carbonyl, $\pi^*_{C=O}$, which is inclined 105 °C relative to the C=O plan. It is an important example of stereocontrol. During the reaction, the hybridation changes from Sp^2 to Sp^3 and the π bond is removed. These changes are also visible in the crystal structures!

Step 3: Felkin-Anh (A)



Felkin-Anh model: Anh improved Felkin model by taking the discovery of Bürgi-Dunitz into account. As for Felkin, the R^L group is placed ⊥ to C=O and the nucleophile attacks the opposite face. However, the angle of attack is now 105 °C and the smallest group is placed on the trajectory. The steric interaction between nucleophile and substrate is now minimized. This model explains well why aldehydes give also high selectivity. One expects that larger nucleophiles should lead to higher selectivity, which is indeed observed. The Felkin-Anh model is still considered noawaday as one of the most powerful.

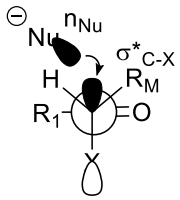
Example (lecture):



Polar groups: When polar groups are present in the susbtrate, a Felkin-Anh analysis based on the substituent size only fails to predict the observed selectivity.

Step 4: polar Felkin-Anh (A)

Electron-withdrawing group behaves as R^L

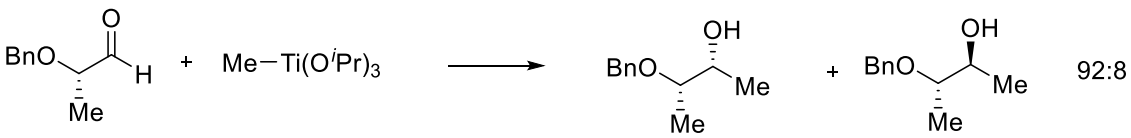


Favorable interaction between n_{Nu} and σ^*_{C-X}

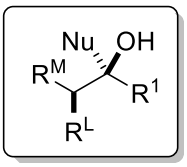
X = OR, F, Cl, Br, I, ...

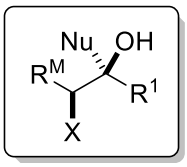
The electron-withdrawing group is now ⊥ à C=O, even if it is not the largest. One good rationalization is that there is a favorable interaction between the HOMO of the nucleophile and the σ^*_{C-X} orbital. This model works well for a large number of reactions.

Example (lecture):



Important retrons for addition to carbonyl compounds according to Felkin-Anh (**B**)





Nu = C, H

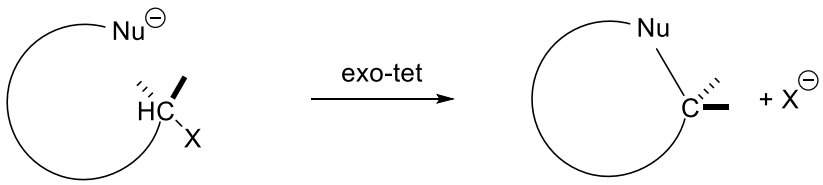
X = OR, halogens

The retrons for stereoselective addition to carbonyl compounds contain an alcohol adjacent to a stereocenter. The most frequently used nucleophiles are derived from C or H (reduction), as addition of O or N nucleophiles are in general reversible and not favored thermodynamically (see AIMF and Fonctions et réactions organiques II).The products obtained by polar Felkin-Anh are especially interesting, for example selectively protected diols.

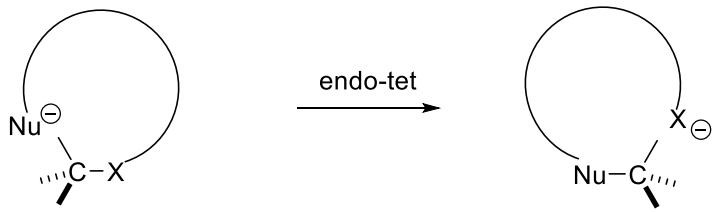
5.1.2 Baldwin rules (Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.) (**B**)

Baldwin has generalized the concept of stereocontrol for intramolecular additions by considering the hybridation of the electrophile (trig = trigonal, sp2, addition or tet = tetragonal, sp2, substitution). He further differentiates exo cases (leaving group or double bond outside the ring) from endo cases (leaving group or double bond inside the ring).

Substitution (tet = tetragonal)

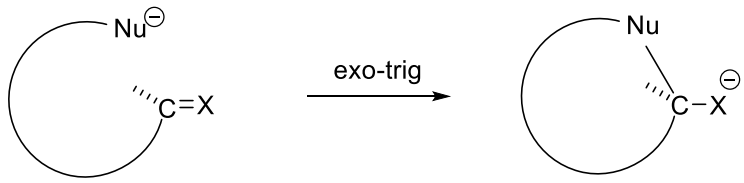


3- to 7-exo-tet all favored

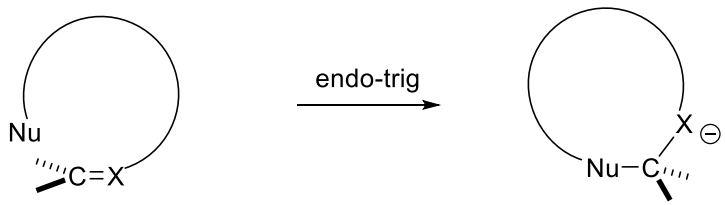


5- to 6-endo-tet not favored

Addition (trig = trigonal)



3- to 7-exo-trig all favored



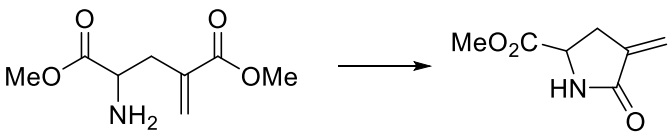
3- to 5-endo-trig not favored

6- to 7-endo-trig favored

Universal and simplified version of the rules

cyclization is easy ⇔ orbital overlap is optimal

Example (lecture):

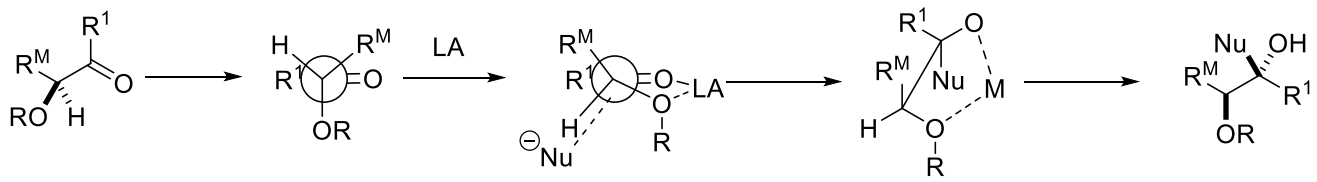


5.2. Reaction not following the Felkin-Anh model

5.2.1 Chelation control (A)

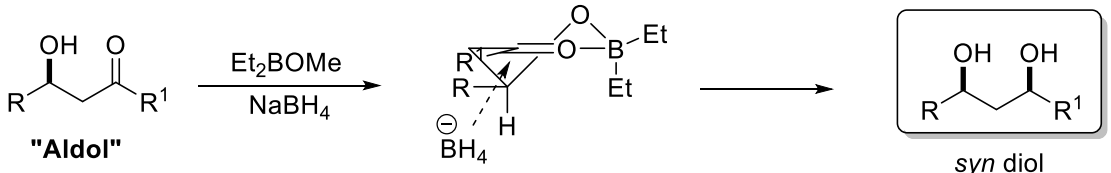
Bibliography: Bruckner, Ch. 10.3, p. 403-422. Carreira, Ch. 2.3-2.4, p. 25-37.

1,2-Chelation



One of the limitations of the Felkin-Anh model is that it doesn't consider multiple interactions between the Lewis acid and the substrate. When the Lewis acid can coordinate a group in α position to the carbonyl, a 5 atom chelate is formed and the reaction does not follow the Felkin-Anh model. The polar group is now forced in the C=O plan and the nucleophile attacks on the side of the smallest substituent (H). The obtained stereochemistry is opposed to the one predicted by the polar Felkin-Anh model!

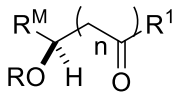
1,3 Chelation



R pseudo-equatorial
axial attack (Fürst-Plattner)

Chirality induction from the β position of the carbonyl is more difficult to analyze. When chelation is possible, an excellent selectivity can be observed. An important example is the reduction of aldol products with $NaBH_4$ in presence of Et_2BOMe to give *syn* diols (**Prasad reduction**). The transition state contains a 6-atom chelate with a half-chair conformation. The largest group(s) are in pseudo-equatorial positions. The hydride attacks in axial position to access directly a chair conformation (Fürst-Plattner rule).

Factors favorizing chelation



- **R is small:**

  good: R = Me, Bn, $MeOCH_2$ (MOM), $BnOCH_2$ (BOM)

  bad: R = ^{t}Bu, $SiMe_3$, $SiMe_2{}^t$Bu (TBDMS or TBS), Si^iPr_3 (TIPS)

- **Non coordinating solvents:**

  Toluene, CH_2Cl_2 >> Et_2O > THF >> DMF, EtOH, H_2O

- **size of chelate:**

  5 (n = 0) > 6 (n = 1) > 7 (n = 2) >others

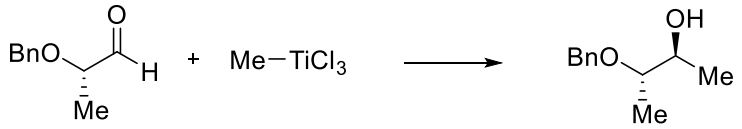
- **Strong Lewis acid, with at least two free coordination sites:**

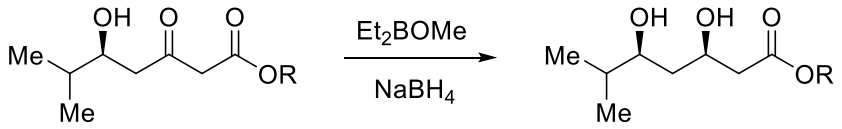
  good: MgX_2, ZnX_2, LiX, $TiCl_4$, $SnCl_4$, $SnCl_2$, LnX_3, $AlCl_3$,...

  bad: Na^+, K^+ (weak Lewis acid), BF_3 (only one coordination site), LiX

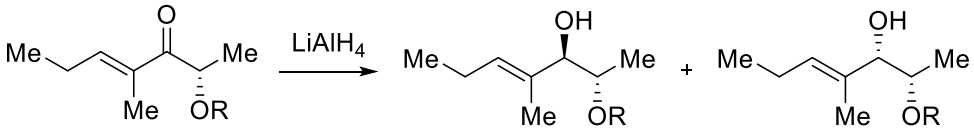
Importance of X: Depending on the strength of the M-X bond, the dissociation of X can be easy and one supplementary coordination site becomes available. F^-, R^- usually do not dissociate, Cl^- and OAc^- can dissociate and Br^-, I^-, OTf^- dissociate easily. Therefore, BF_3 cannot form chelates, but BBu_2OTf can.

Examples (lecture):

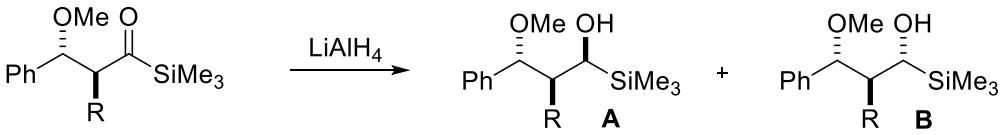
1) 

2) 

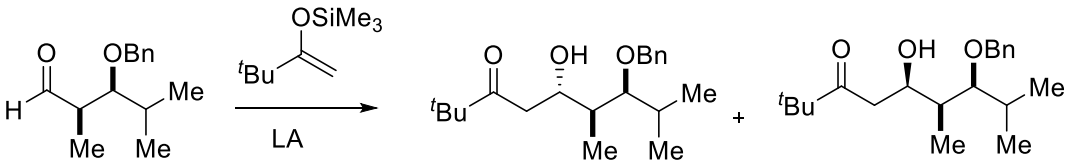
Examples (exercises):



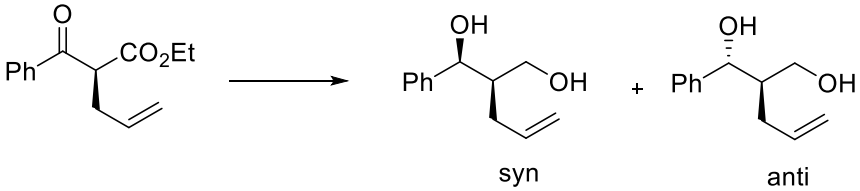
R = Bn, in Et_2O: 98:2
R = Si^tBuPh_2: 5:95



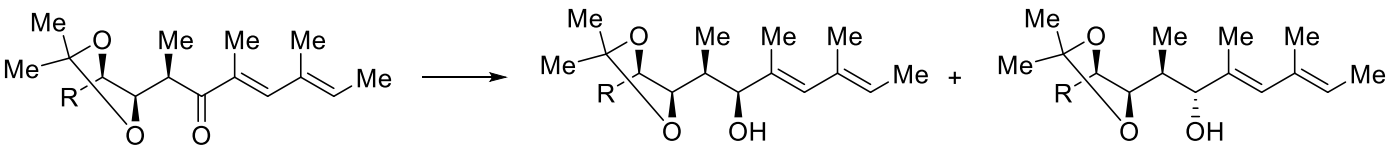
R	
Et	**A:B** = 45:55
Ph	**A:B** = 96:4



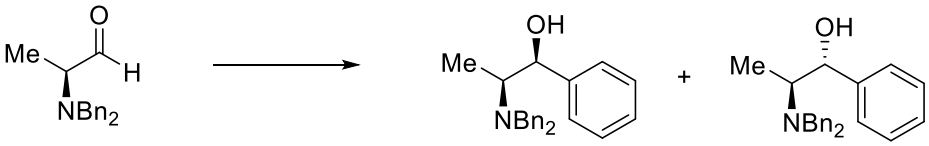
LA = BF_3: 5:95
LA = $MeAlCl_2$: 99:1



$Zn(BH_4)_2$, Et_2O	100:0
$LiAlH_4$, THF	0:100

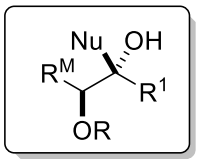


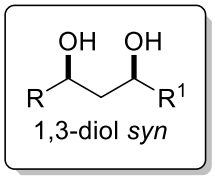
A: with $NaBH_4$, $CeCl_3$, MeOH: 40:60
B: with $LiAlH_4$, LiI, Et_2O: 98:2



	syn	*anti*
with PhMgBr, Et_2O:	3	97
with $PhB(OH)_2$, Et_2Zn, toluene:	95	5

Retrons for chelation controlled addition to carbonyls (B)





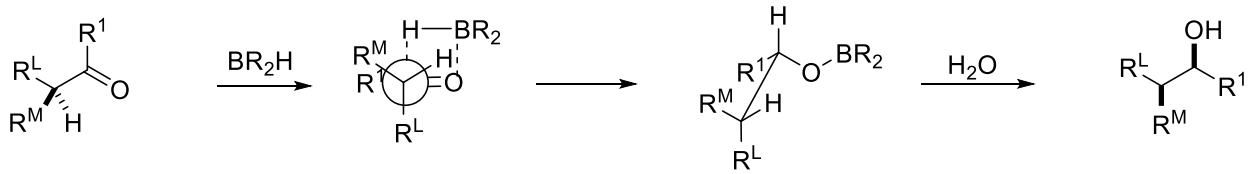
The reactions occuring via 1,2-chelation gives access to diols with opposite chemistry when compared to polar Felkin-Anh. The reduction with 1,3-chelation gives access to *syn* 1,3-diols, which are often found in natural products, such as discodermolide.

5.2.2 Directed additions

A second important weak point of the Felkin-Anh model: attractive interactions between substrates and reagents are not considered. Such directed reactions are frequent, however.

5.2.2.1 Carbonyl directed reactions (A)

Reduction with boranes (A)



Boranes are special reagents, as they are at the same time reductant and Lewis acid. Selectivity can be rationalized using a model similar to the hydroboration of olefins: The R^L group is ⊥ to C=O, and the interactions substrate-reagent are minimized (H on the side of C=O). When the reagent is very small, (BH_3), the $A^{1,2}$ strain can again lead to an inversion of selectivity.

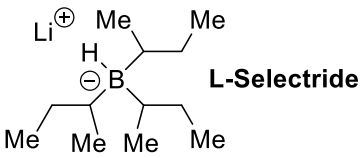
It is therefore needed to separate reducing agents in two classes depending on their coordinating ability:

Bibliography: Bruckner, Ch. 10.2-10.4, p. 403-426. Carey Sundberg B, Ch. 5.3, p. 396-425.

non coordinating:

MBH_4

$LiHBEt_3$
Superhydride



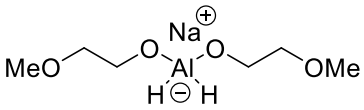
L-Selectride

Boron

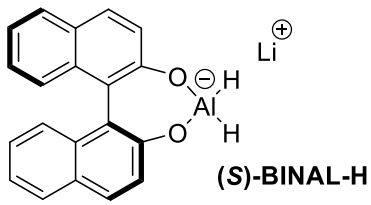
R_4SiH

Silicon

$LiAlH_4$



Red-Al



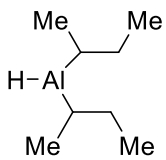
(*S*)-BINAL-H

Aluminium

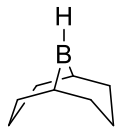
Non coordinating reductants are usually salts, most often hydride derivatives of boron or aluminium (alkyl silanes are an exception, as they are coordinatively saturated in their neutral form, they are very weak reducing agents, requiring the use of strong Lewis acids). The selectivity can be explained either by the Felkin-Anh model, or by the chelate model, depending on the cation used in the salt. The reagents given above are the most frequently used. (*S*)-BINAL-H is an interesting reagent for the stereoselective reduction of ketones.

coordinating:

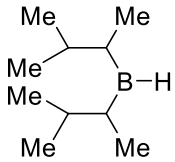
BH_3 AlH_3



DIBAL (DIBAL-H)



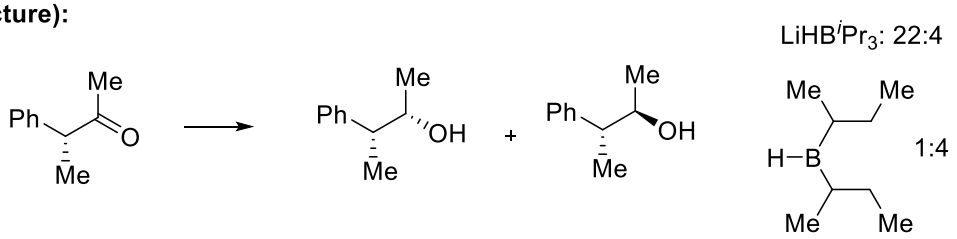
9-BBN



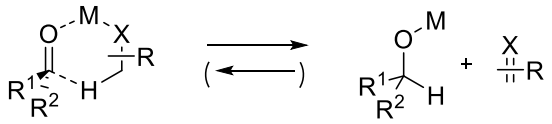
Sia_2BH

These reagents, such as boranes and alanes, are at the same time Lewis acids and reducing agents. The selectivity can then be explained using similar models as for the hydroboration of olefins.

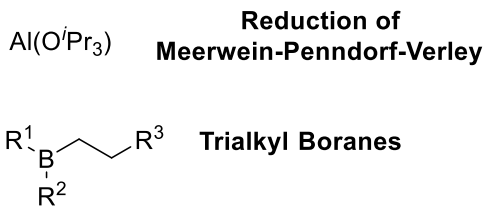
Example (lecture):



Special case: reduction via β elimination (B)

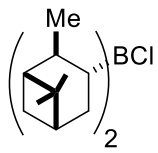


Important Reductants

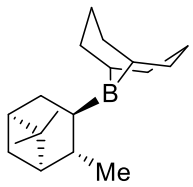


Reducing agents are not limited to compounds containing a metal hydride bond. An interesting case are reagents containing a hydrogen in β position to a metal. These reductions proceed via a 6-atom transition state (chair or boat). During the reduction, a new olefin or carbonyl is formed. They are called transfer hydrogenations and are often reversible. The most important example is the reduction of Meerwein-Penndorf-Verley using aluminium alkoxides. The reaction is fully reversible and can be pushed towards reduction with an excess of alcohol or towards oxidation with an excess of acetone (**Oppenhauer oxidation**). Trialkyl boranes can also follow this mechanism.

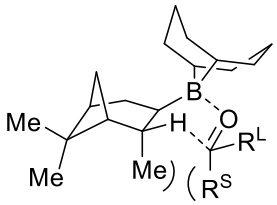
Chiral alkyl boranes (B)



DIP-Chloride



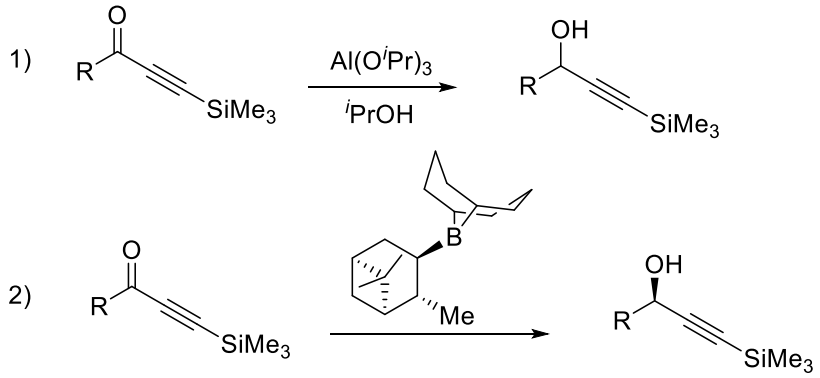
Alpine borane



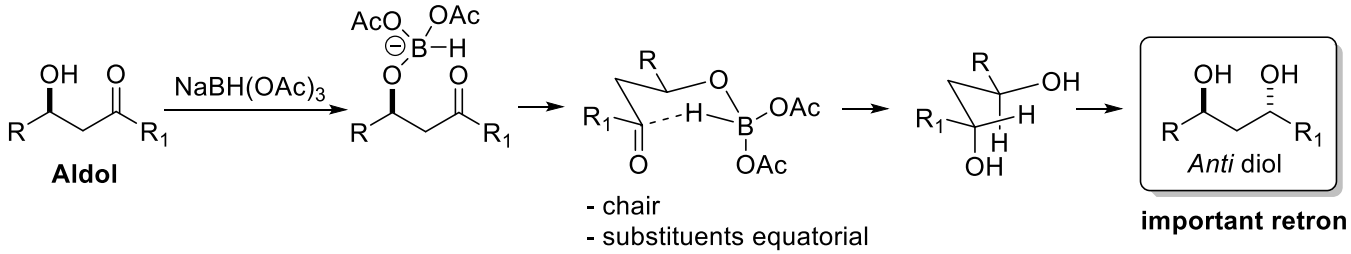
Transition state for Alpine borane

Chiral alkyl boranes give good selectivity for the asymmetric reduction of carbonyls. For Alpine borane, a boat transition state has been proposed, with the smallest group on the carbonyl placed in pseudo-axial position to avoid interaction with the methyl group.

Examples (lecture:

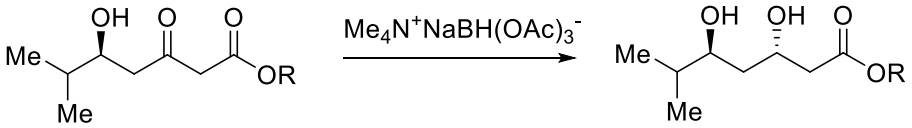


5.2.2.2 Directed addition with other groups than carbonyls (A)

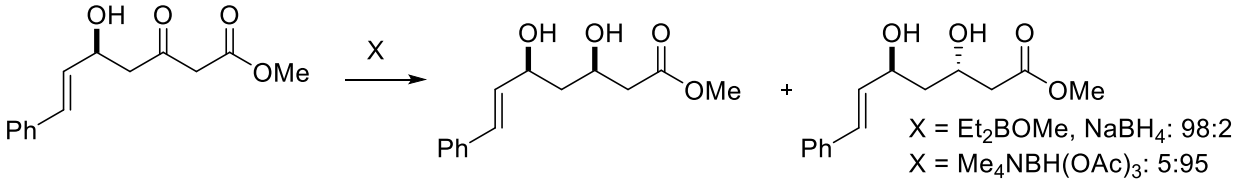


Other groups than carbonyls can direct reductions. Only one important example will be discussed: The reduction of aldol products with $NaBH(OAc)_3$ (**Evans**) to give *anti* diols. Because of the electron-withdrawing acetate group, $NaBH(OAc)_3$ is a weak reductant. It is only after ligand exchange with the alcohol that an intramolecular reduction becomes possible. The chair transition state has the R and R^1 groups in equatorial position. This method is important, because it gives opposite selectivity (*anti*) when compared to reduction proceeding via 1,3-chelation (*syn*). From the aldol product, it is therefore possible to access selectiviely either the 1,3- *syn* or the 1,3- *anti* diol.

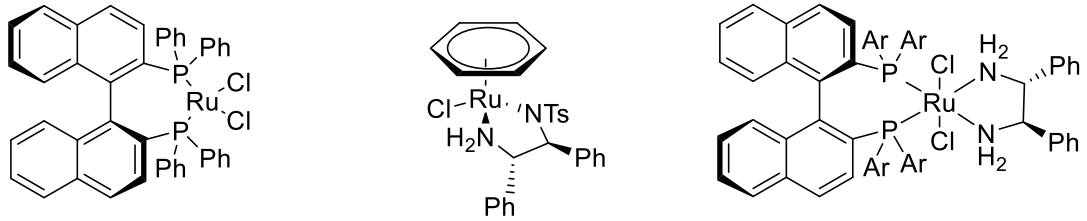
Example (lecture):



Example (exercises):



5.2.2.3 Catalytic asymmetric reduction of carbonyl compounds (D)



with H_2

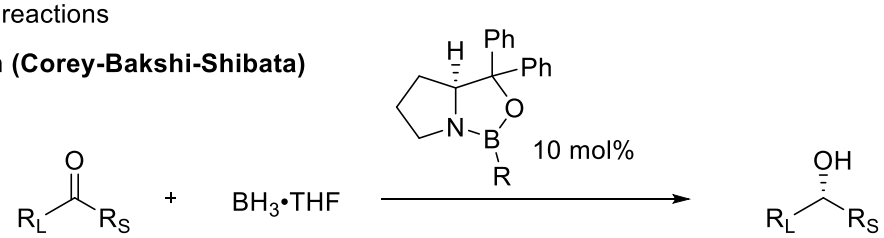
Noyori I, only for directed reactions

with ^{i}PrOH

with H_2

Noyori II, more general

CBS reduction (Corey-Bakshi-Shibata)



Modern organic chemistry has developed numerous catalytic asymmetric methods for carbonyl reduction. These methods are discussed in the lecture catalytic asymmetric reactions in organic synthesis.The Noyori hydrogenation and the CBS reduction are now considered as classical asymmetric reduction methods and should be known by all organic chemists. The chiral ligands are BINAP and chiral diamines for Noyori and prolinol for CBS.

5.2.2.4 Reactions with other nucleophiles (B)

Bibliography: Bruckner, Ch. 10.1, p. 397-403; Ch. 10.5, p.426-443.

The majority of other interesting nucleophiles are carbon derived. Classical organometallic reagents (Mg, Li, Na, K) usually follow either the Felkin-Anh or the chelate model. The introduced models can therefore be used, but with care, as aggregates can be formed, which makes analysis more complex. Other organometallic reagents (Zn, Sn, B, Si, ...) are usually less reactive and requires a catalyst.

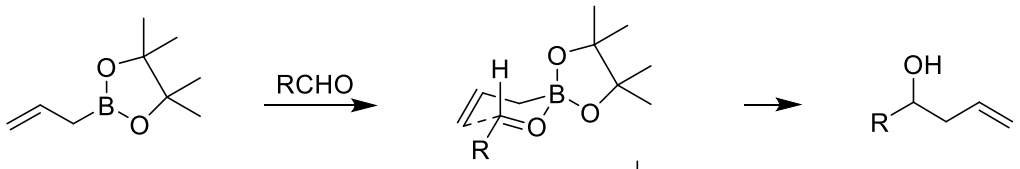
Two very important classes of carbon nucleophiles follow a directed pathway involving coordination of the carbonyl: allyl reagents and enolates. These methods are very important in organic chemistry and will be discussed in the next sections.

5.3 Allylation of carbonyl compounds

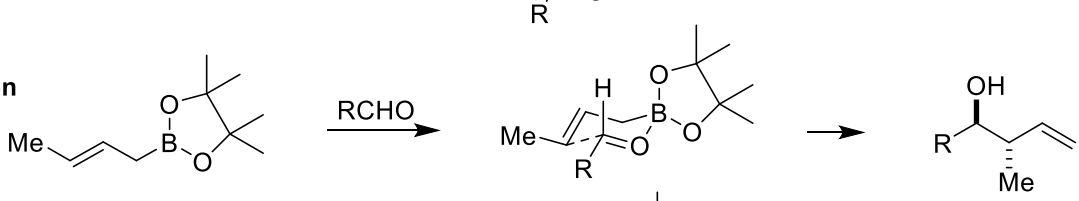
Bibliography: Carey Sundberg, B, Ch. 9.1.5, p. 797-809. Carreira: Ch. 5, p.153-187.

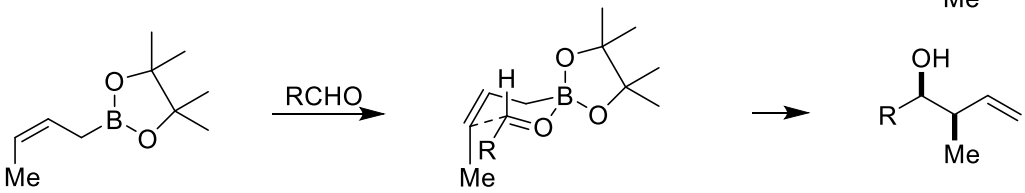
5.3.1 Allylation with allylboranes (A)

Allylation



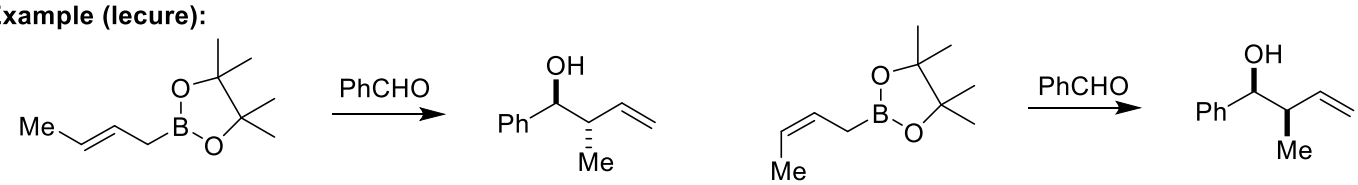
Crotylation



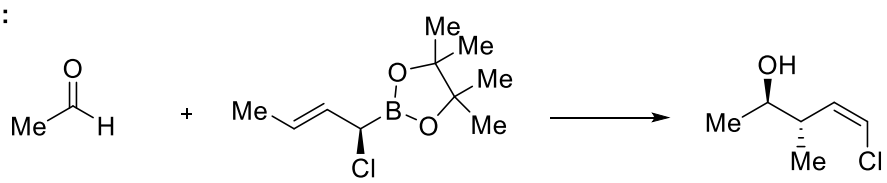


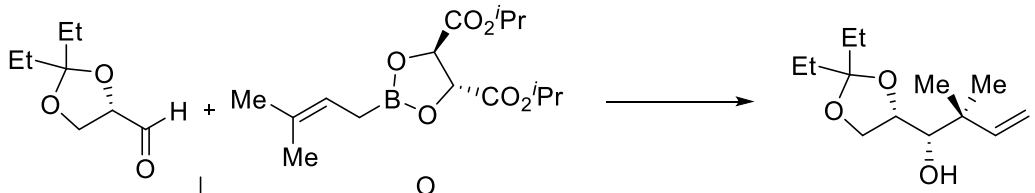
Allylation of aldehydes with allyl boranes follow a chair transition state, with the R substituent in equatorial position. The reaction is stereospecific:The *anti* product is obtained form the *E* olefin, and the *syn* product form the *Z* olefin.

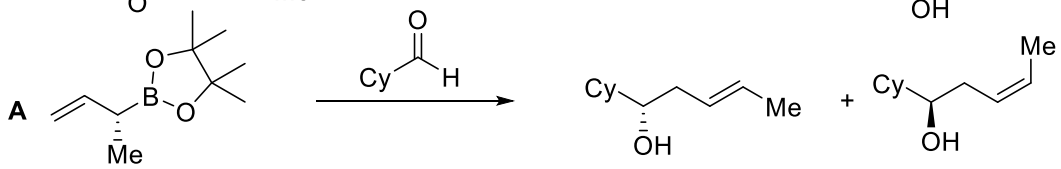
Example (lecure):



Examples (Exercises):







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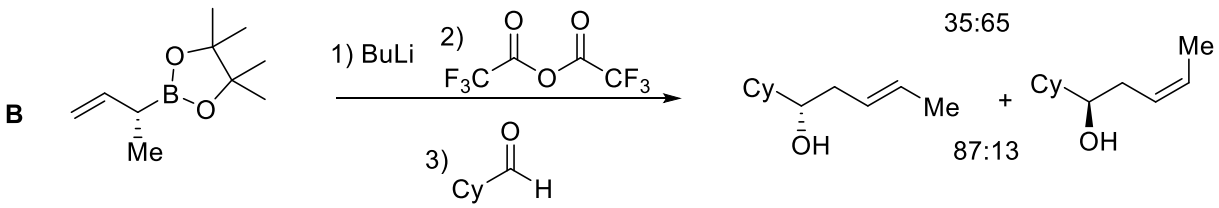

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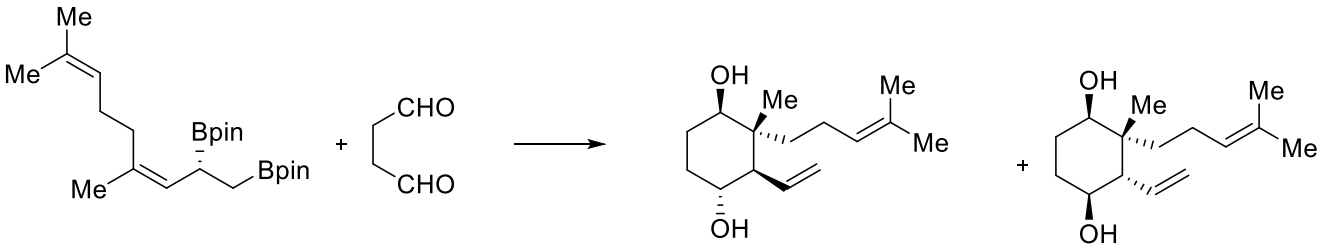

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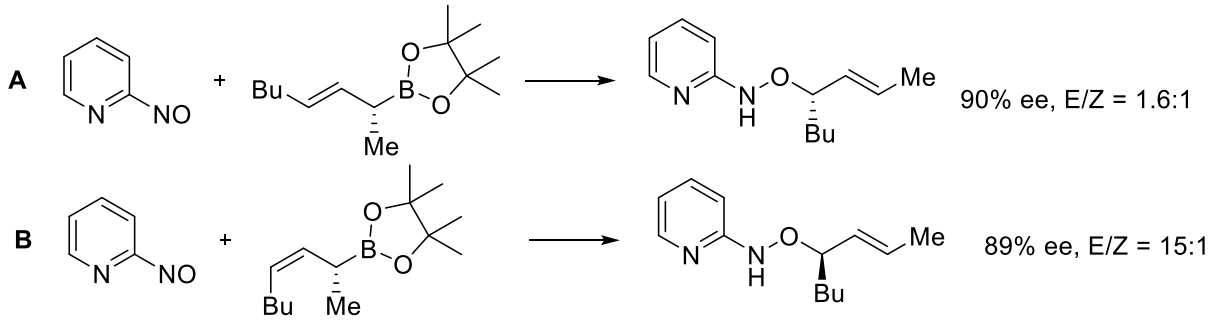
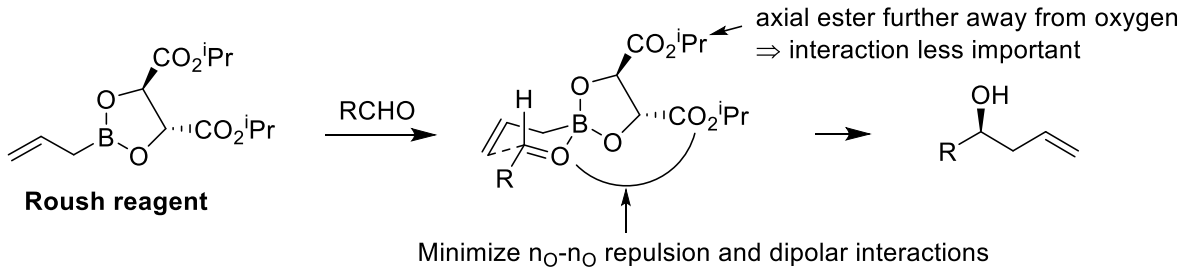
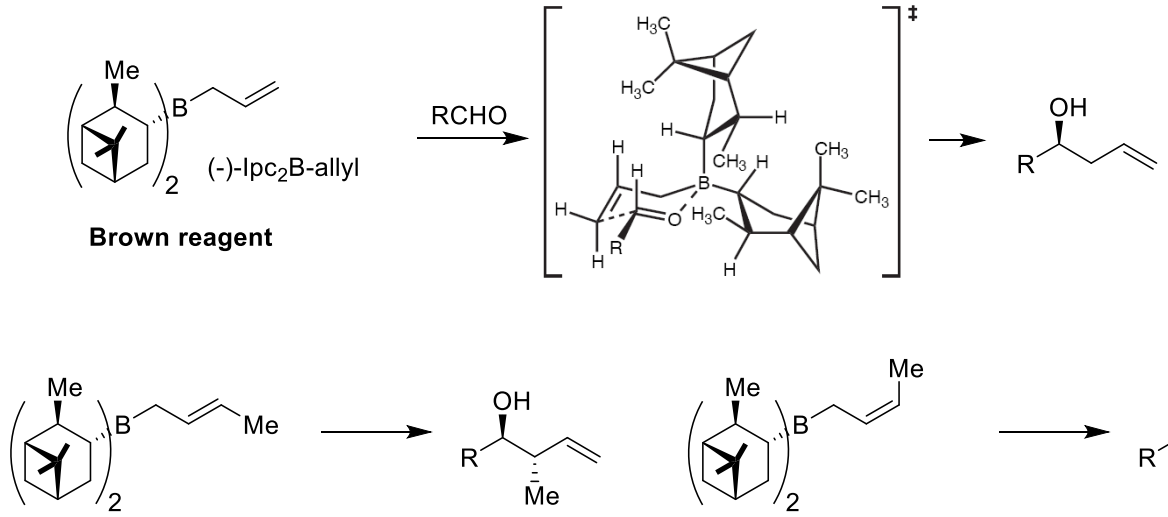


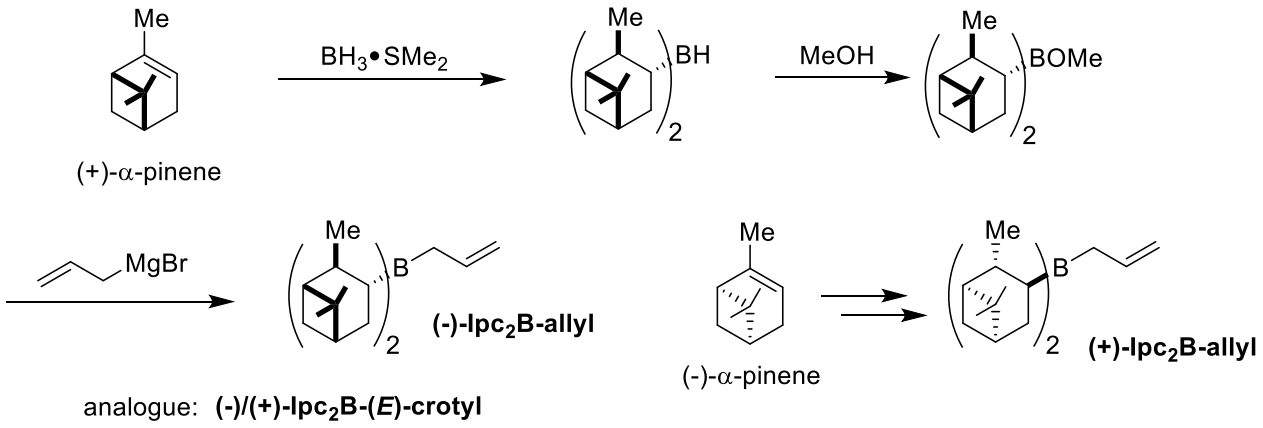
Chiral reagents for carbonyl allylation (A)

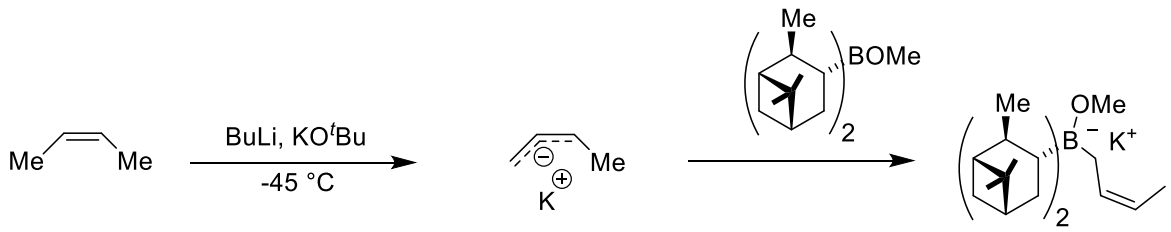




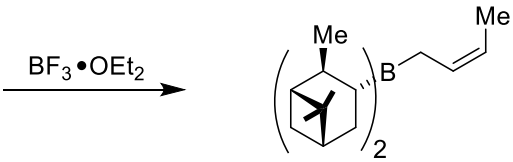
Allylation with chiral boron reagents give usually good enantioselectivity. The Roush reagent is derived from tartaric acid and selectivity can be rationalized by electronic repulsion between oxygen atoms in the chair transition state. The selectivity of the Brown reagent is based on sterics and is often higher.

Synthesis of Brown reagent from α-pinene (B)





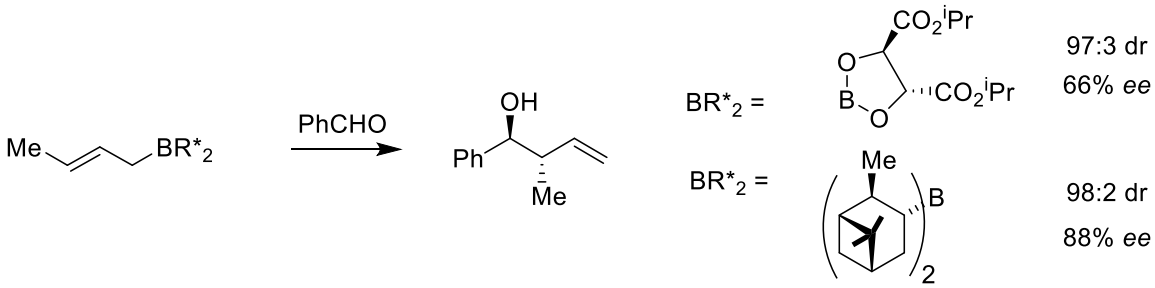
no isomerization cis/trans
at - 45 °C



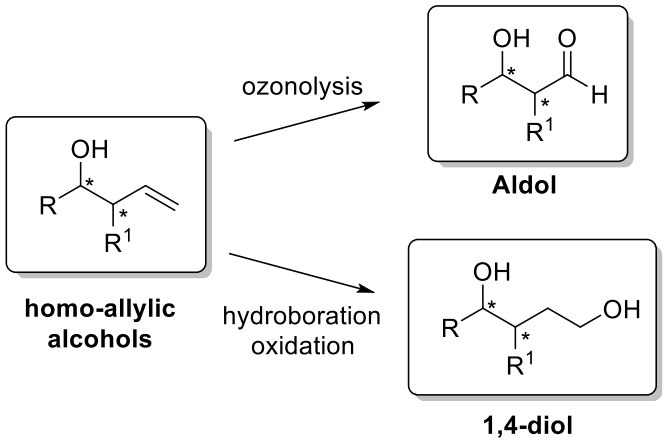
(-)-Ipc$_2$B-(*Z*)-crotyl (similar: **(+)-Ipc$_2$B-(*Z*)-crotyl**)

The synthesis of Brown reagents is possible in a few steps form α-pinene (hydroboration, boronic ester formation, Grignard addition). The synthesis of the (*Z*)-crotyl reagent is more difficult, as the *cis*-Grignard reagent isomerizes to give the *trans*. The best method goes via formation of the allyl potassium at low temperature formed using a very strong base (the mixture BuLi/KO^{t}Bu, known as **Schlosser base**). At this temperature, the isomerization is not taking place. The obtained boronate is then reacted with BF$_3$•OEt$_2$.

Example (lecture)

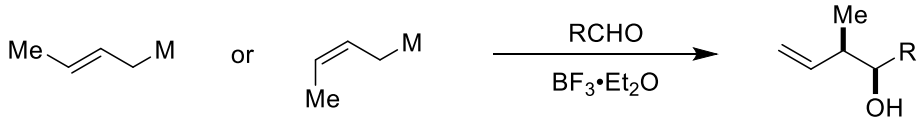


Retrons for allylation with boron reagents (B)



The retron for allylation are homo-allylic alcohols. By using the correct reagents, all stereoisomers can be obtained. Alkenes are useful precursors for other functional groups. For example, ozonolysis gives access to the aldol products and hydroboration followed by oxidation gives 1,4-diols.

5.3.2 Other allylations (C)



M = SnR_3, SiR_3

Other important allylation methods use silanes and stannanes (reactions of Sakurai and Keck). As these metals are coordinatively saturated, non-cyclic transition states are followed and the reations are usually not stereospecific. Felkin-Anh and chelate model can be used in the case of chiral aldehydes. Often, the *syn* product is obtained.

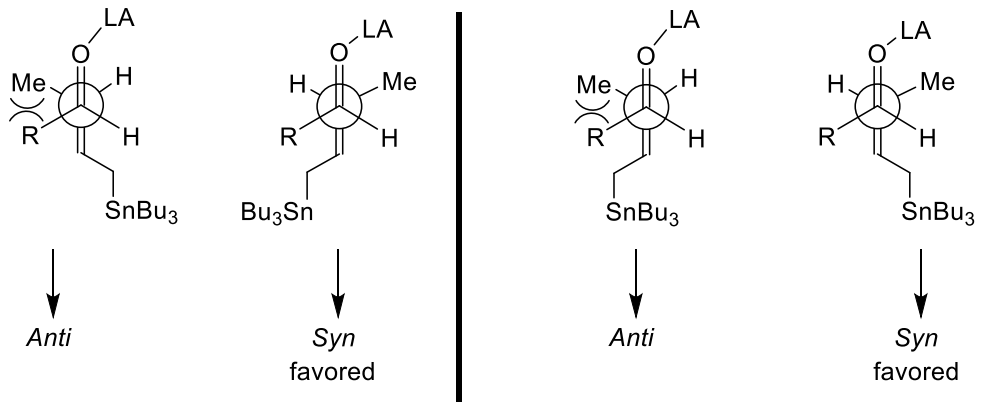
Models for the selectivity with non-cyclic transition states

The *syn* selectivity is observed for (*E*) and (*Z*)-crotyl reagents and has not been yet fully rationalized. Two models have been proposed

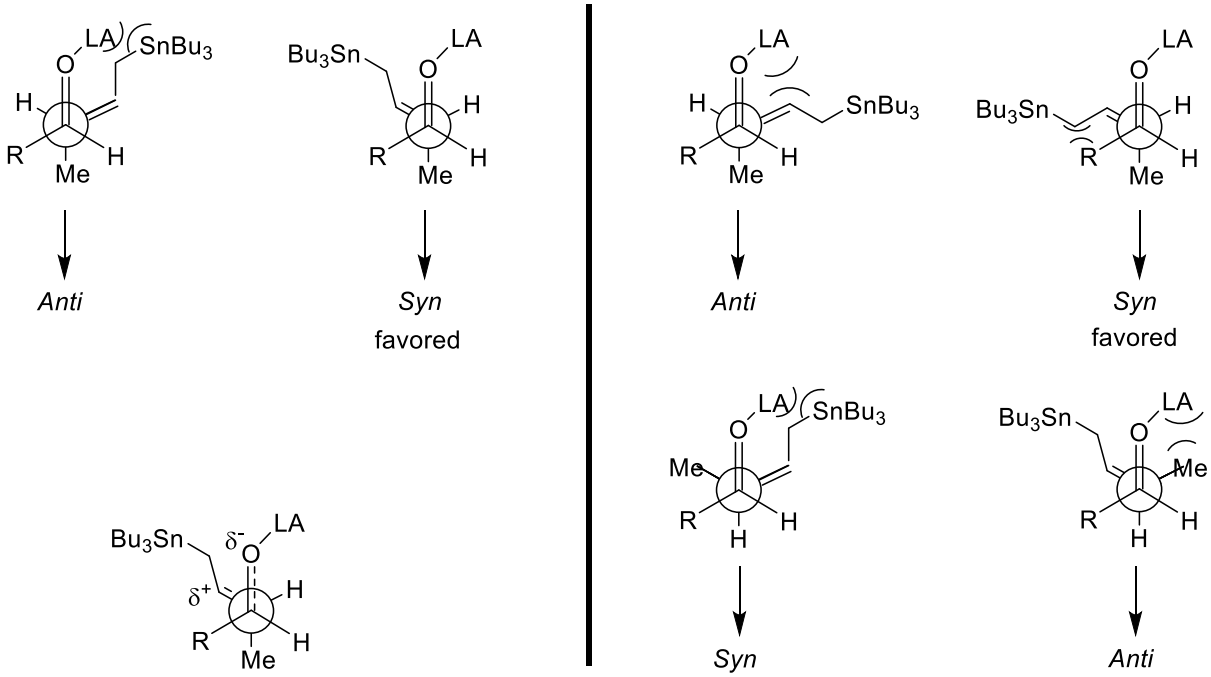
Yamamoto model: The large Sn group is place in antiperiplanar position in the transition state. The interactions Me-R are minimized. It is difficult to rationalize why this interaction should be determining.

Denmark-Keck model: Seebach proposed that synperiplanar transition states are favored, as they lead to a favorable electrostatic interaction in the transition state. The most important interaction is then between substrate and Lewis acid. Only transition states leading to the *syn* product can minimize steric interactions with the Lewis acid.

Yamamoto model *J. Am. Chem. Soc.* **1980**, *102*, 7107.



Denmark-Keck model *Tetrahedron* **1989**, *45*, 1053,



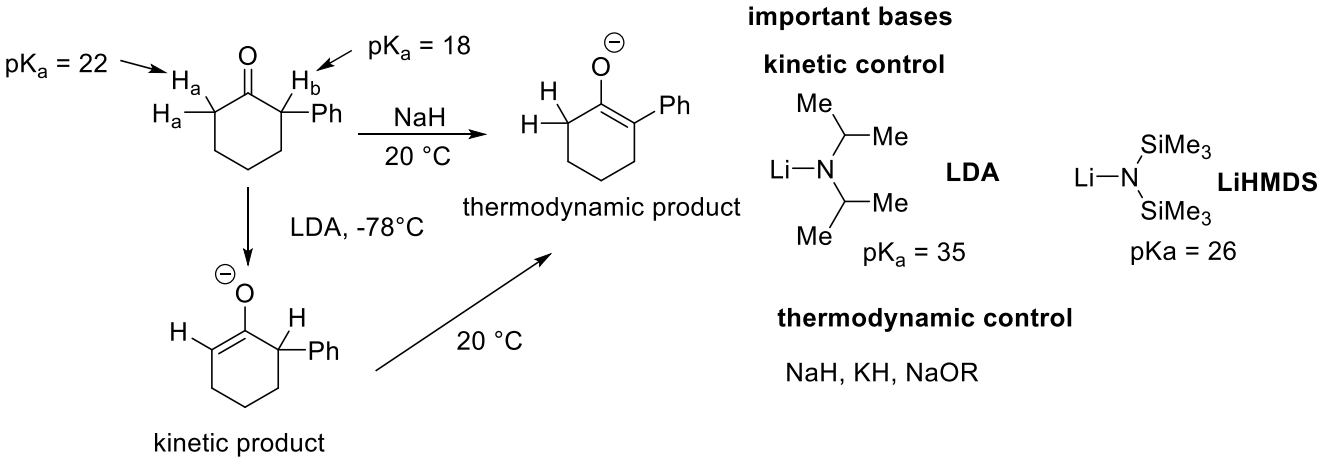
Stabilisation via electrostatic interactions

6. Enolate Generation and reactivity

6.1 Stereoselective generation of enolates (A)

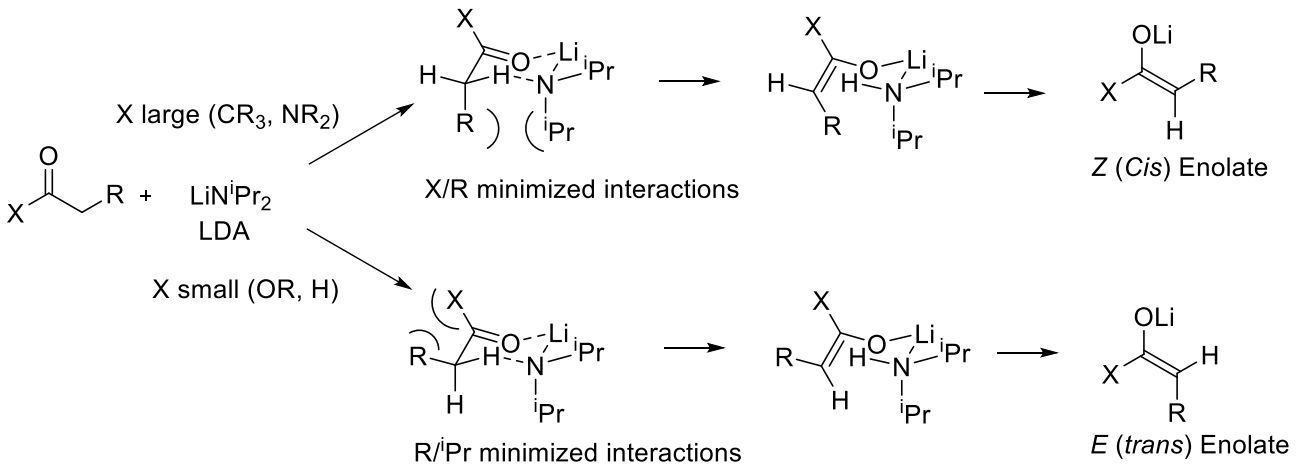
Bibliography: Fonctions et réactions organiques II, Bruckner, Ch. 13.1, p. 519-543. Carey Sundberg B, Ch. 1.1, p.1-21. Evans lecture 22-22a.

Regioselectivity: thermodynamic vs kinetic control

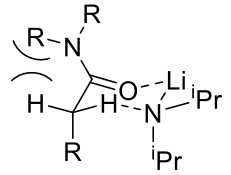


The regioselectivity of enolate formation can be controlled by the reaction conditions. A strong, large base and low temperature favor the kinetic product (less-substituted enolate). It is important to use strong but not nucleophilic bases (LDA and LiHMDS for example, but not BuLi). At higher temperature, the kinetic product isomerizes to form the more substituted enolate, the thermodynamic product.

Stereoselectivity: *Z* (*cis*) vs (*E*)-*trans* selectivity



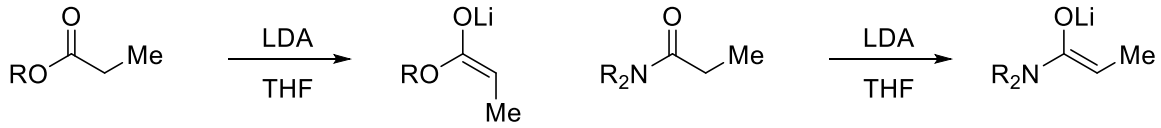
The stereoselectivity for deprotonation with LDA depends on the structure of the carbonyl compounds. The reaction follows a chair transition state. For carbonyls with a small X substituent (esters, aldehydes), the interaction between the R group and the ^{i}Pr group of LDA dominates. Minimization of this interaction leads to the *E* enolate. When the X group is large, interaction between X and R groups dominates, an the *Z* enolate is obtained. In particular, dialkylamides give high *Z* selectivity, due to a strong $A^{1,3}$ strain.



$A^{1,3}$ interaction in dialkylamides

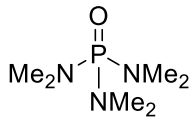
Warning: for facilitating discussion, enolate nomenclature does not follow the CIP rules: the highest priority is always given to OM.

Example (lecture):

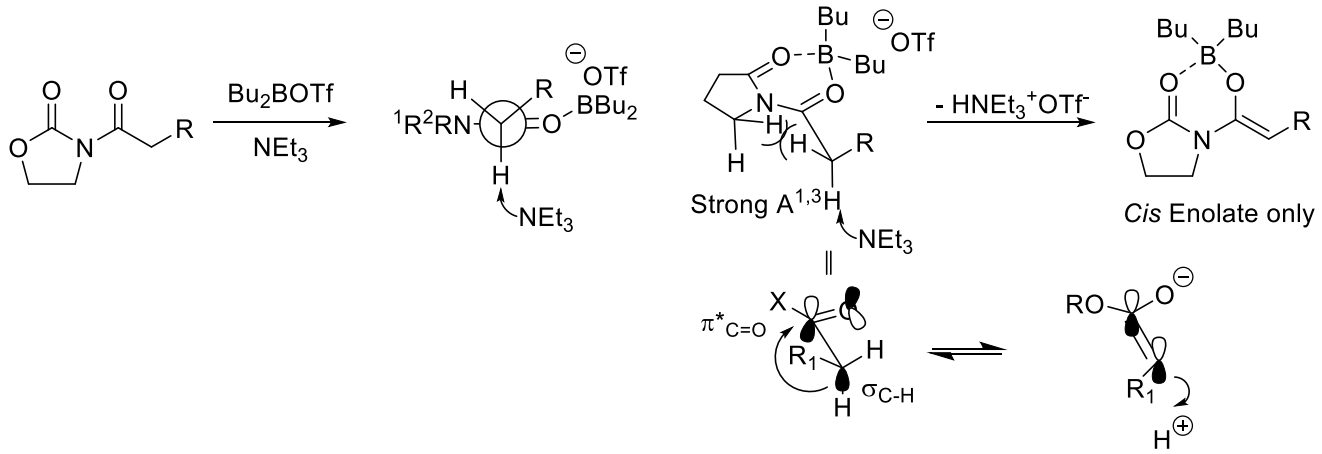


Generation of *Z* enolates with esters

For obtaining *Z* enolates with esters, HMPA (Hexamethylphosphorous triamide) is added as co-solvent. HMPA coordinates to lithium and weakens interactions in the chair transition state, making the interactions X-^{i}Pr less important.

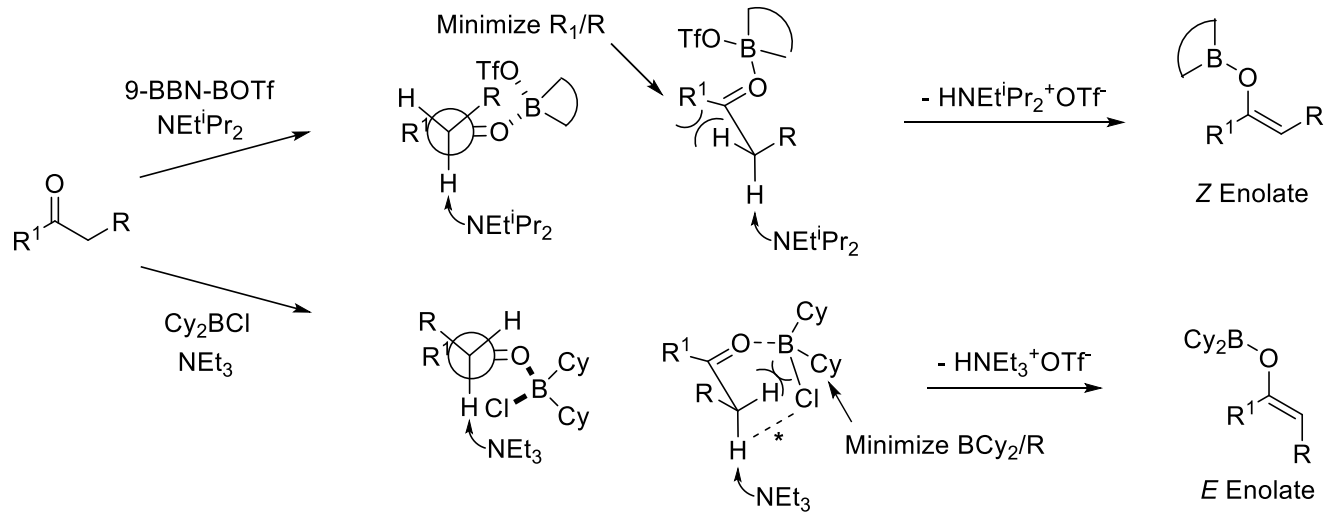


Deprotonation of imides with Bu_2BOTf and NEt_3 (soft enolization)



LDA is a strong base, which cannot be used with sensitive substrates. The soft enolization method is based on the coordination of the carbonyl to a Lewis acid to enhance acidity in α. position. An important example is the formation of boron enolates from imides using Bu_2BOTf and a tertiary amine base. The $A^{1,3}$ strain is minimized in the transtion state, leading to high *Z* selectivity. Based on stereocontrol, the proton perpendicular to C=O is kinetically much more acid (interaction σ_{C-H} with $\pi^*_{C=O}$). **Microreversibility principle**: Protonation of enolates also occurs perpendicular to C=O.

Deprotonation of ketones

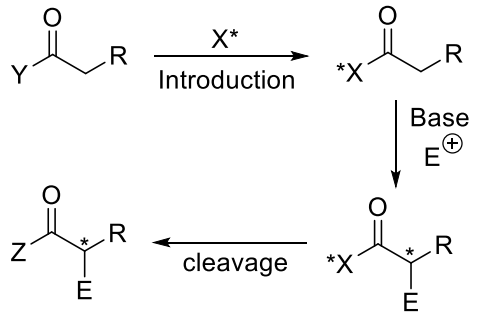


The R^1 group of ketones is of medium size when compared to esters or amides. It is therefore more difficult to control selectivity. The above conditions have been optimized experimentally and rationalization remains difficult. With 9-BBN-OTf, a medium-size Lewis acid with a good leaving group and a large base (NEt^iPr_2, Hünig's base) B coordinates *cis* to the R^1 group, the R/R^1 interaction is minimized. With Cy_2BCl, a large Lewis acid with a less good leaving group, and a smaller base (NEt_3), B coordinates *trans* to the R^1 group and the R/BCy_2 interaction is minimized. An attracting Cl-H interaction has also been proposed in the transition state.

6.2 Chiral auxiliaries and enolate alkylation

Bibliography: Bruckner, Ch. 13.2, p. 543-558. Carey Sundberg B, Ch. 1.2, p. 21-46. Evans lectures 23-23a. Carreira Ch. 3, p. 69-103.

6.2.1 General concept (A)



The chiral auxiliary X* should be:

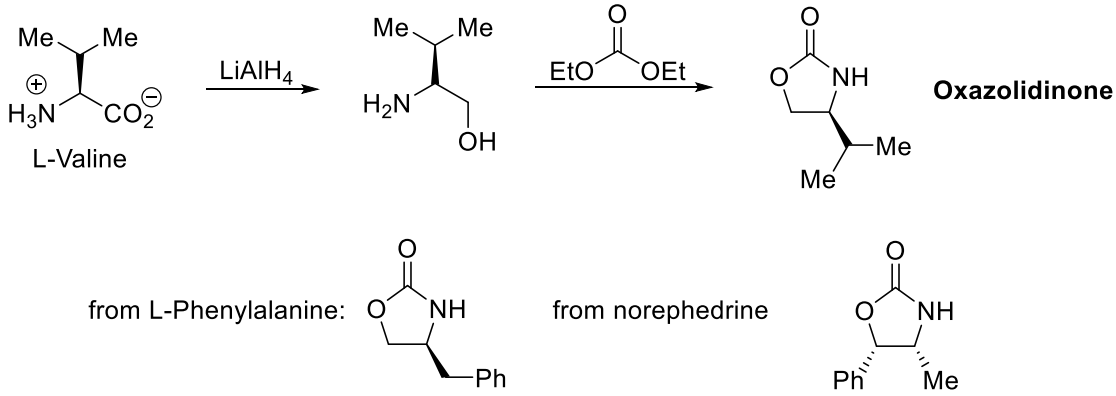
- easy to introduce and to remove
- inducing high selectivity
- cheap and recyclable

Disadvantages: multi-steps, stoichiometric

Advantages: As the auxiliary is covalently bound, good control over selectivity can be achieved and the diastereoisomers can be separated to increase optical purity.

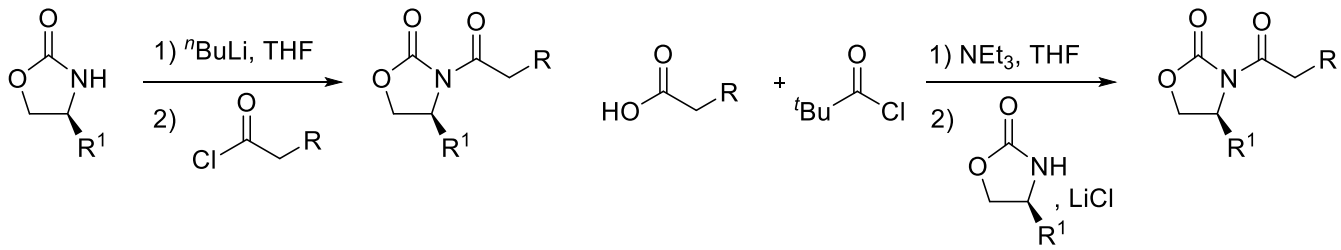
6.2.2 Evans auxiliary

Synthesis



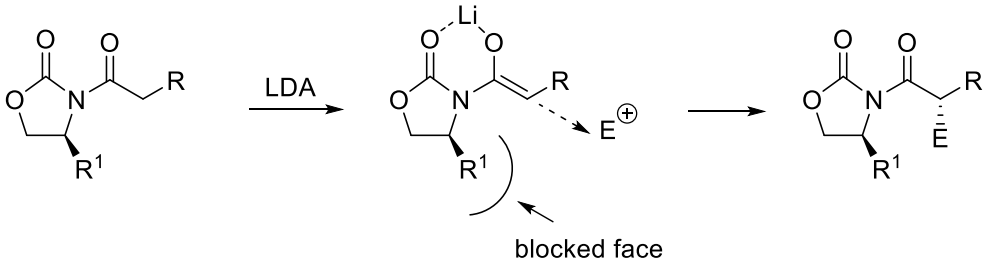
Evans auxiliaries (oxazolidinones) are among the most efficient for enolate alkylation. They are easily obtained from the corresponding amino alcohols by condensation with a carbonate. The most used auxiliaries are derived from the amino acids valine and phenylalanine or from norephedrine (ephedrine lacking the methyl group on nitrogen), which has the reverse absolute configuration. All starting materials are cheap, but ephedrine derivatives are sometimes difficult to obtain due to their use as recreational drugs.

Introduction of the chiral auxiliary



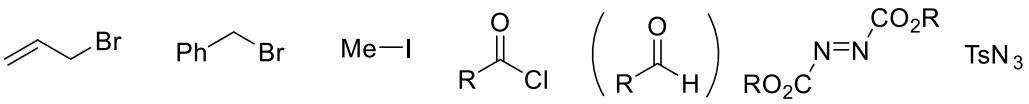
The introduction of the chiral auxiliary is done on an activated carboxylic acid derivative. Two classical methods are the deprotonation of the oxazolidinone with butyl lithium, followed by addition to the acid chloride, and activation as a mixed anhydride with pivaloyl chloride, followed by reaction with the oxazolidinone in presence of triethylamine and LiCl.

Enolate alkylation (A)



***Z* only ($A^{1,3}$strain)**

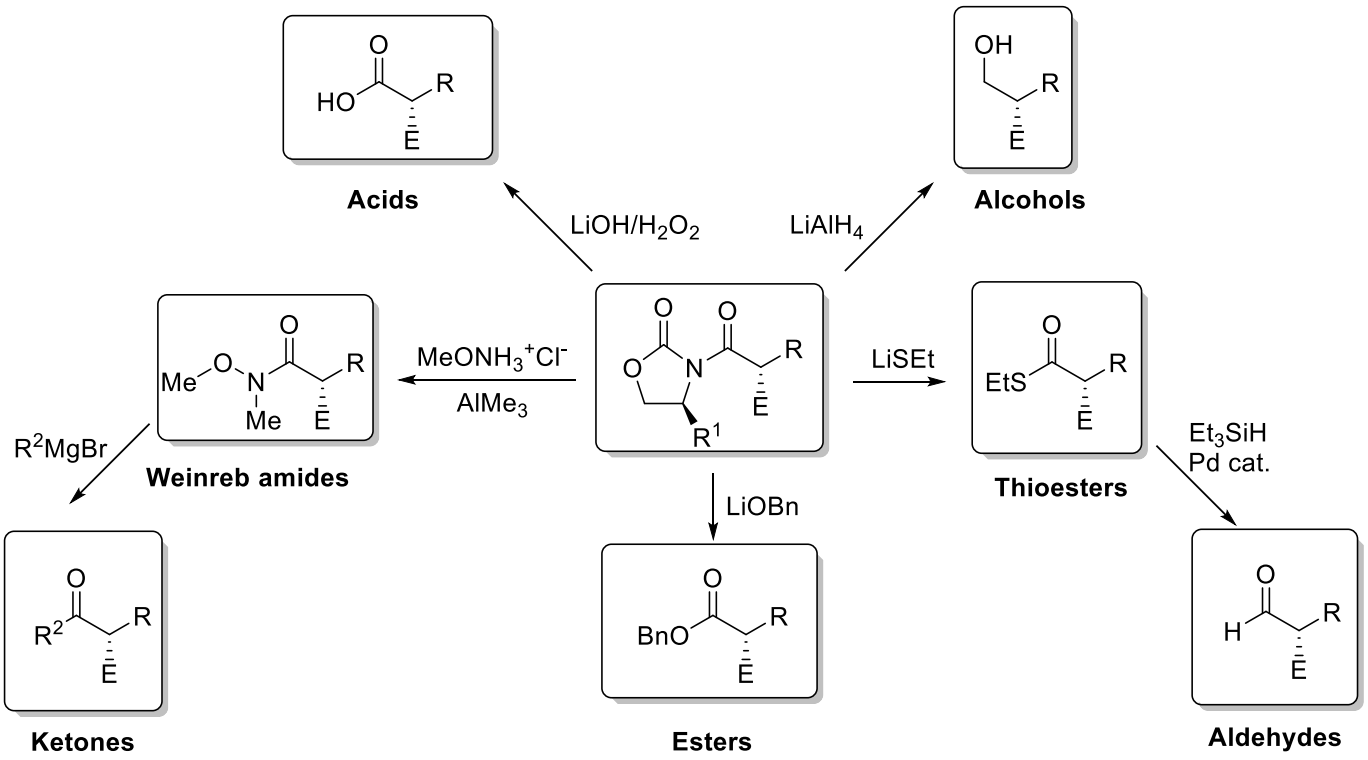
Electrophiles:



The enolate is often generated with LDA, but soft enolization is also possible. A lithium chelate is formed, fixing the conformation. The *cis* enolate is formed to avoid $A^{1,3}$ strain, as described in the previous section. The electrophile comes form the face opposite to the R^1group.

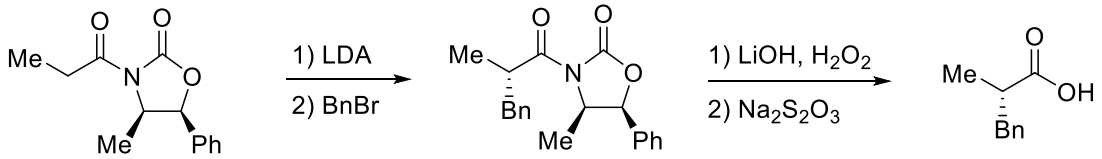
Imides enolates are moderate nucleophiles. Relatively strong electrophiles are therefore required, such as allyl halogenides or aldehydes (warning: the mechanism is different with aldehydes, see chapter 7). Other halogenides only react sluggishly. Better results are obtained with sodium enolates, but the Evans auxiliary is generally not a good choice for weak electrophiles. The method is not limited to the formation of C-C bonds: for example, amination with azodicarboxylates or azides is also possible.

Cleavage of the auxiliary: retrons for the alkylation of enolates (B)

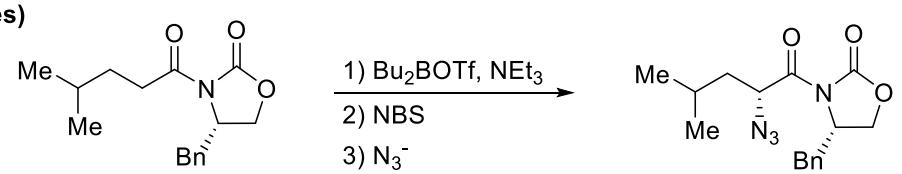


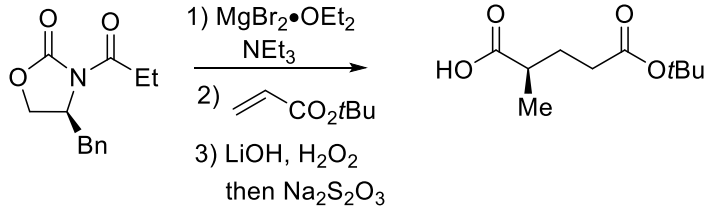
Evans auxiliaries are especially useful, as they can be converted in one step into useful building blocks for organic synthesis, such as esters, carboxylic acids or alcohols. The addition of hydrogen peroxide for the saponification accelerates the reaction and allows the isolation of the untouched auxiliary. Ketones and aldehydes can be obtained via the Weinreb amides and thioesters respectively.

Example (lecture)



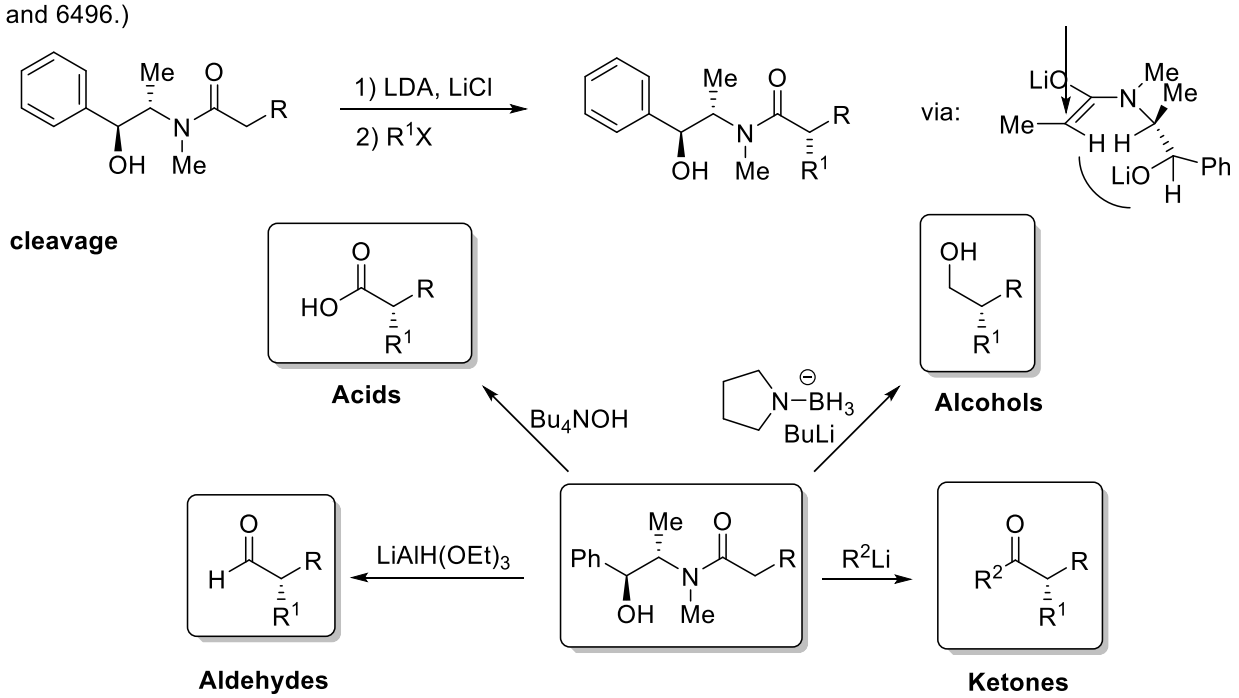
Examples (exercises)





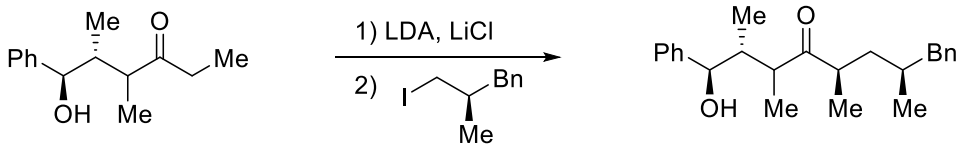
6.2.3 Other chiral auxiliaries (B)

Myers auxiliary (pseudoephedrine derivatives) (*J. Am. Chem. Soc.* **1994**, *116*, 9361; **1995**, *117*, 8488; **1997**, *119*, 656 and 6496.)



The Myers auxiliary is also frequently used in modern organic synthesis. It is obtained from pseudoephedrine.The selectivity is based on the minimization of the $A^{1,3}$ strain in the transiton state, with the attack from the face opposite to the largest group. The main difference with the Evans auxiliary is the formation of an amide enolate instead of an imide enolate. Consequently, the enolate is more nucleophilic and can react with weaker electrophiles, such as non-activated alkyl halogenides or epoxides. Auxiliary cleavage is facilitated by intramolecular attack of the alcohol, making hydrolysis possible under mild conditions. Furthermore, the conversion into aldehydes or ketones is also possible.

Example (lecture)



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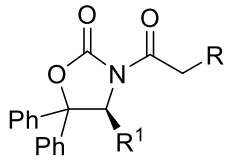
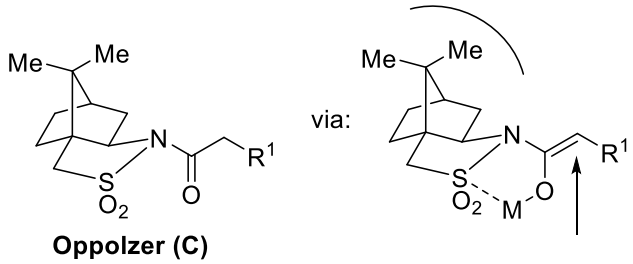
Other auxiliaries



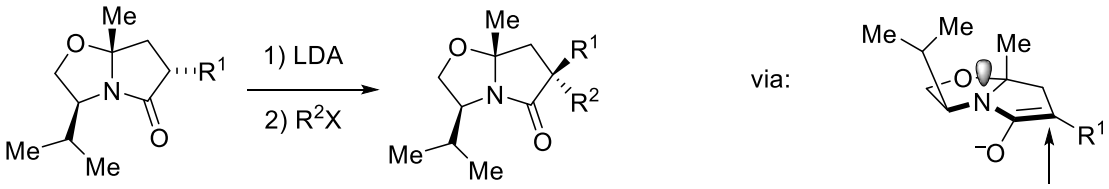
Seebach-Evans (B)

The Seebach-Evans auxiliary works like Evans auxiliary, but gives highly crystalline compounds, which makes purification easier.



Oppolzer (C)

The Oppolzer auxiliary developed in Geneva is derived from camphor. It gives also excellent results in enolate alkylation. The electrophile attacks the face opposite to the largest group on the auxiliary.



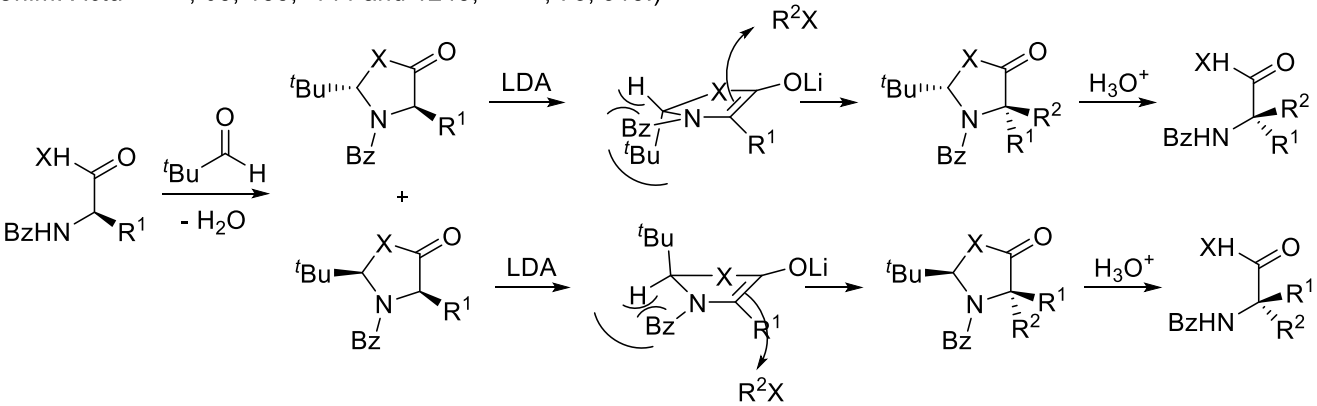
Meyers (**C**) (*J. Am. Chem. Soc.* **1998**, *120*, 7429.)

Meyers auxiliary is synthesized from valinol and is especially useful for the synthesis of quaternary stereocenters. This is possible due to its bicyclic structure, which prevents the formation of enolate isomers. Such quaternary stereocenters cannot be made using Evans auxiliary, due to the strong $A^{1,3}$ strain.

6.2.4 Auxiliaries for amino acid synthesis (A)

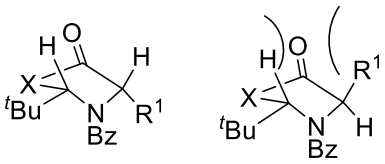
Non-natural amino acids are important building blocks for bioactive compounds.

Seebach method: "self-regeneration" of chirality (A) (*Tetrahedron* **1984**, *40*, 1313*;* **1988**, *44*, 5277. *Helv. Chim. Acta* **1985**, *68*, 135, 144 and 1243; **1992**, *75*, 913.)



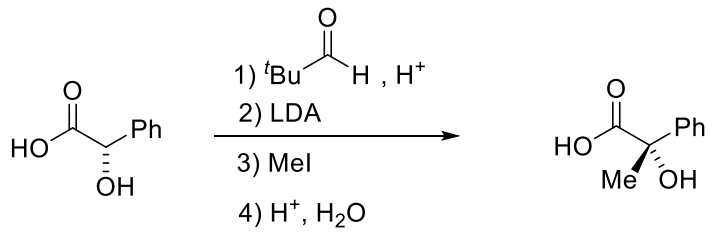
Seebach method utilizes the existing chirality of amino acids to induce the selective formation of a second stereocenter by condensation with pivaldehyde. In this step, the *cis,* the *trans*, or a mixture of both can be obtained, whereas the *cis* is usually favored. After separation, the new stereocenter is conserved during enolate formation and the electrophile attacks the face opposite to the ^{t}Bu group ("regeneration" of the chirality of the amino acid). In case of a benzoyl group (Bz) on nitrogen the selectivity is reinforced by a steric effect which brings the ^{t}Bu group in pseudo axial position. Without this group, lower selectivity is obtained. Finally, pivaldehyde is removed via hydrolysis. The Seebach method gives access to non-natural amino acids containing a quaternary center.

Selectivity for the condensation step

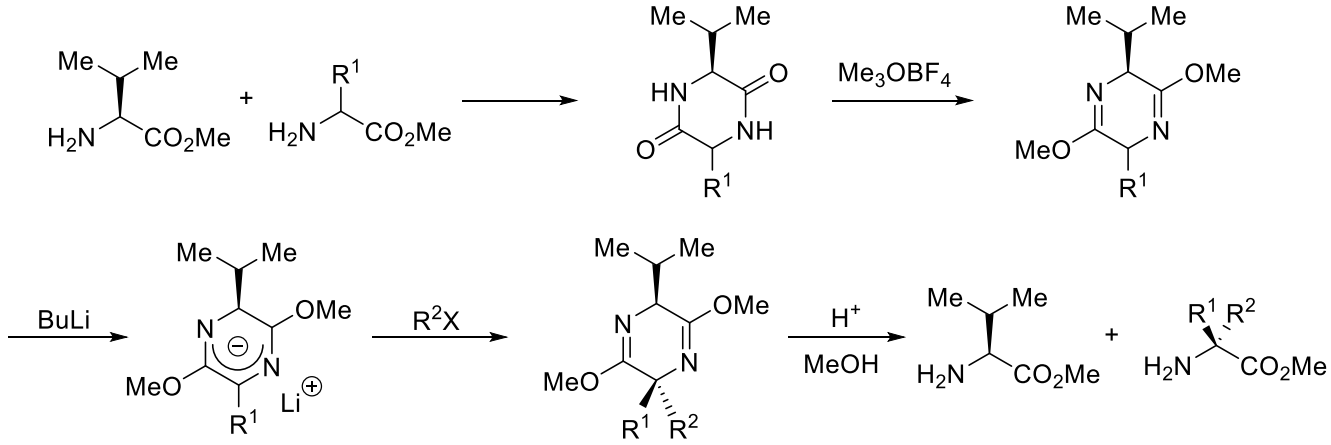


The selectivity during the first step is often moderate (1:1-10:1). The formation of the *cis* product is thermodynamically slightly favored, as the two larger groups can be in position pseudo-equatorial. This product is therefore obtained under conditions favoring thermodynamic control (X = O, high temperature). If X = NMe, it is possible to obtain the *trans* product in acidic media at low temperature (kinetic control) and the *cis* product at high temperature (thermodynamic control).

Example (exercises):

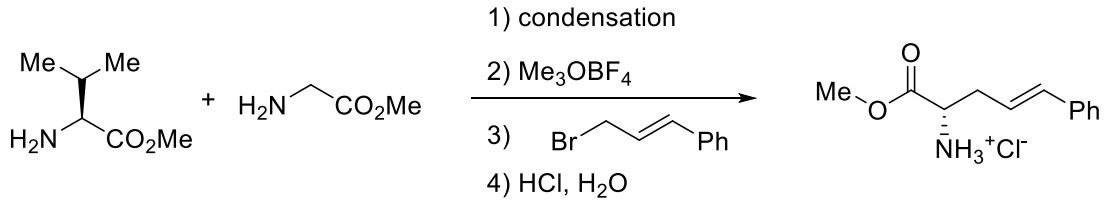


Schöllkopf method (**B**) (*Tetrahedron* **1983**, *39*, 2085.)

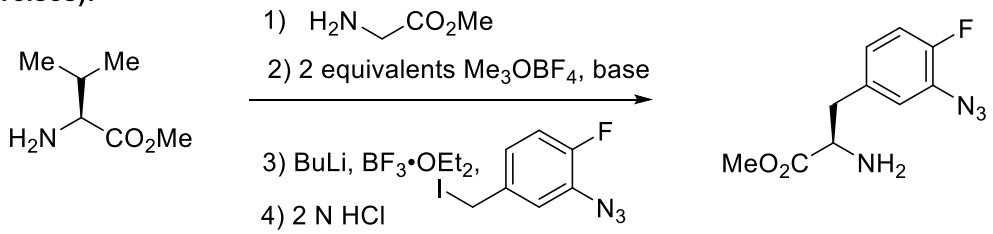


Schöllkopf method is based on the deprotonation of bis-lactime ethers obtained from valine. The electrophile comes from the face opposite to the ^{i}Pr group. This method allows to use racemic amino acids or glycine as starting materials, giving access to a high number of non-natural amino acids.

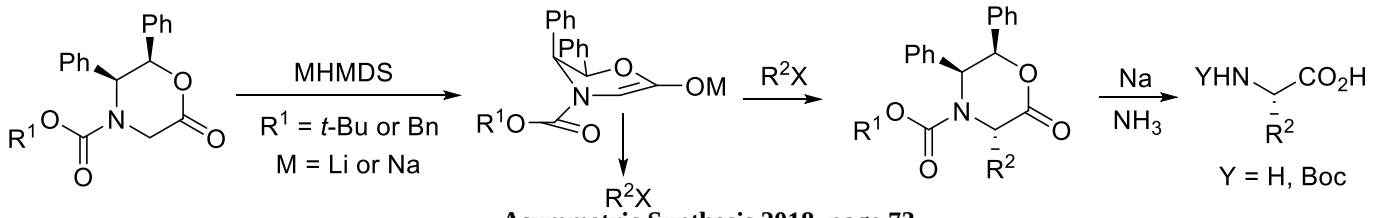
Example (lecture):

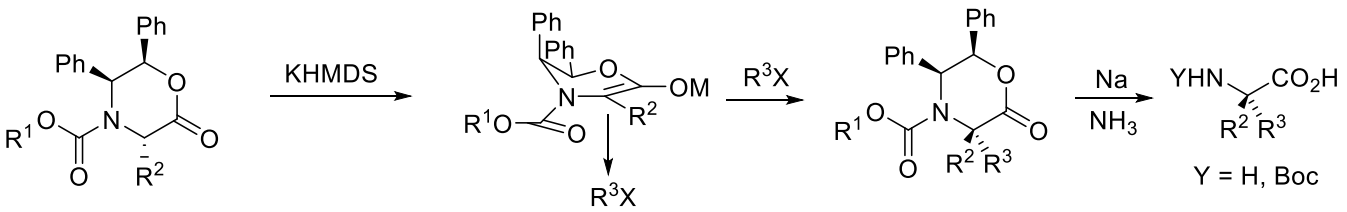


Example (exercises):



Williams Method (C) (*J. Am. Chem. Soc.* **1991**, *113*, 9276.)





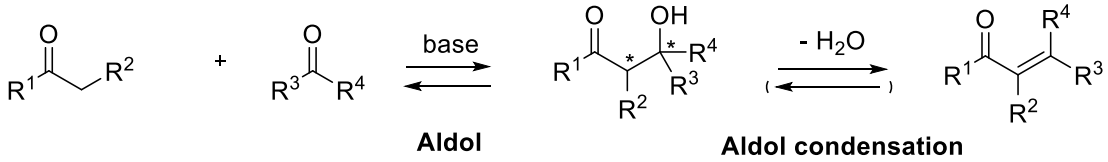
Williams method allows also the synthesis of both tertiary and quaternary amino acids. However, it requires the use of a relatively expensive chiral auxiliary. In the transition state, the phenyl in α position to the nitrogen is in pseudo-axial position, in order to minimize $A^{1,3}$ strain with the protecting group on nitrogen. The phenyl group then blocks one face for the attack of the electrophile.

The three described methods for amino acid synthesis are very robust and still frequently used nowaday. Nevertheless, they require multi-step syntheses with technically difficult processes. Therefore, the synthesis of amino acids via catalytic asymmetric methods is a field of intense current research (see lecture catalytic asymmetric reactions in organic synthesis).

7. Aldol Reaction

Bibliography: Fonctions et réactions organiques II. Carey Sundberg A, Ch. 7.7, p. 682-698; B, Ch. 2.1, 63-139. Evans Lectures 24 and 25. Carreira: Ch. 4, p.103-153. Bruckner, Ch. 13.3, p. 558-565.

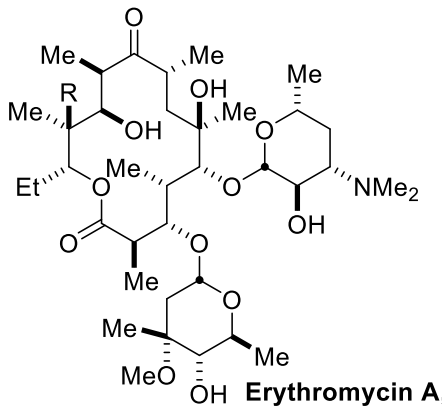
7.1 Importance and biosynthesis of polyketides (A)



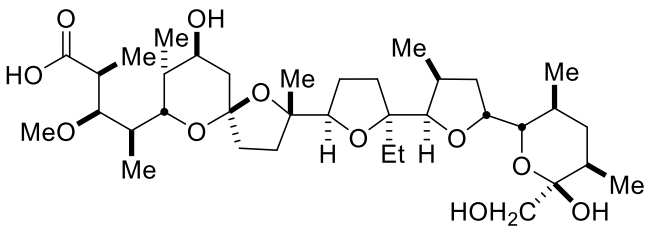
The aldol reaction combines the two fundamental reactivities of carbonyl compounds: the electrophilicity of the carbonyl and the acidity of the proton in α position, allowing access to nucleophilic enolates. Controlling the selectivity of aldol reaction constitutes a formidable challenge, as many factors need to be taken into account: regioselectivity, chimioselectivity and stereoselectivity of the deprotonation, suppression of dimerization and polymerization, suppression of aldol condensation, reversibility of the reaction (in particular for ketones as electrophiles) and control of stereochemistry in potentially two new stereocenters. The reactivity of carbonyl compounds (electrophilicity and acidity) depends on their structure. In decreasing order of reactivity: acid chloride, aldehydes, ketones = thioesters, esters, amides. The nucleophilicity of enolates then follows the reverse order. Classical methods to control the reactivity of aldol reactions have been seen in preceeding lectures: non-enolizable aldehydes (Claisen-Schmidt), double activation (Knoevenagel)),... This course will focus on control over stereochemistry.

Natural polyketides (C)

Antibiotic

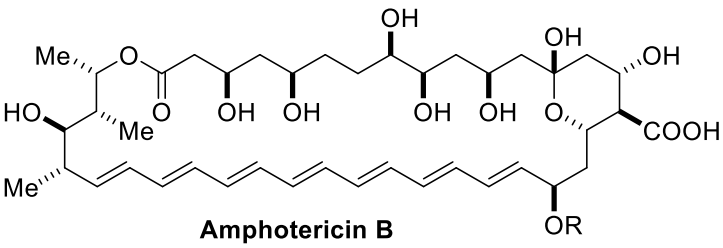


Erythromycin A, R = OH
Erythromycin B, R = H

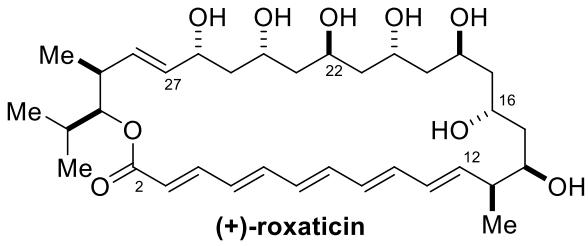


Monensin

Fungicids

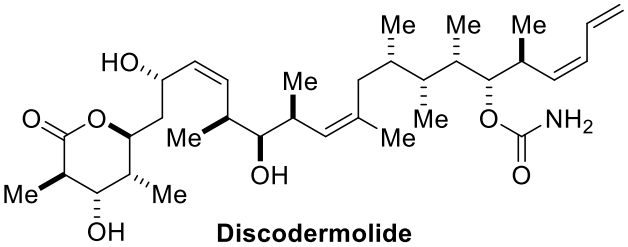


Amphotericin B

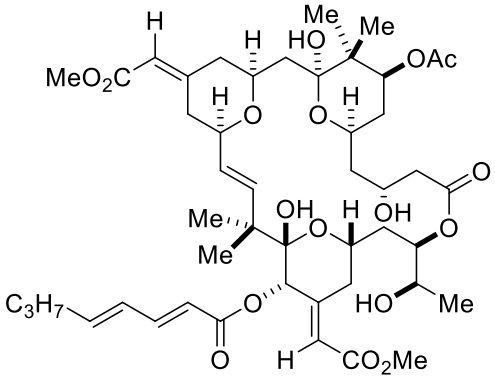


(+)-roxaticin

Anticancers

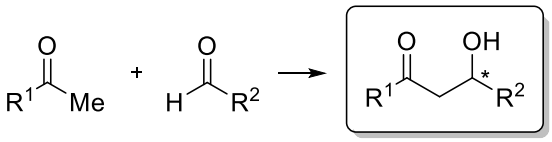


Discodermolide

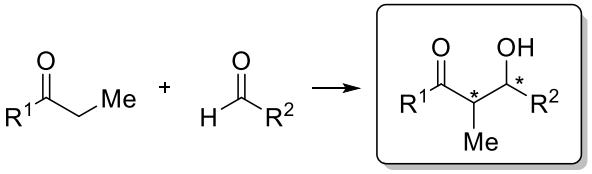


Bryostatin I

The polyketides are one of the most bioactive classes of natural products. They can act as antibiotics, fungicids or anticancers. The aldol reaction (combined with stereoselective reduction methods seen in previous sections) is one of the most efficient method for their synthesis. Natural polyketides are based on two simple modules: "acetate" and "propionate". Consequently, the aldol reactions leading to these building blocks are the most important.



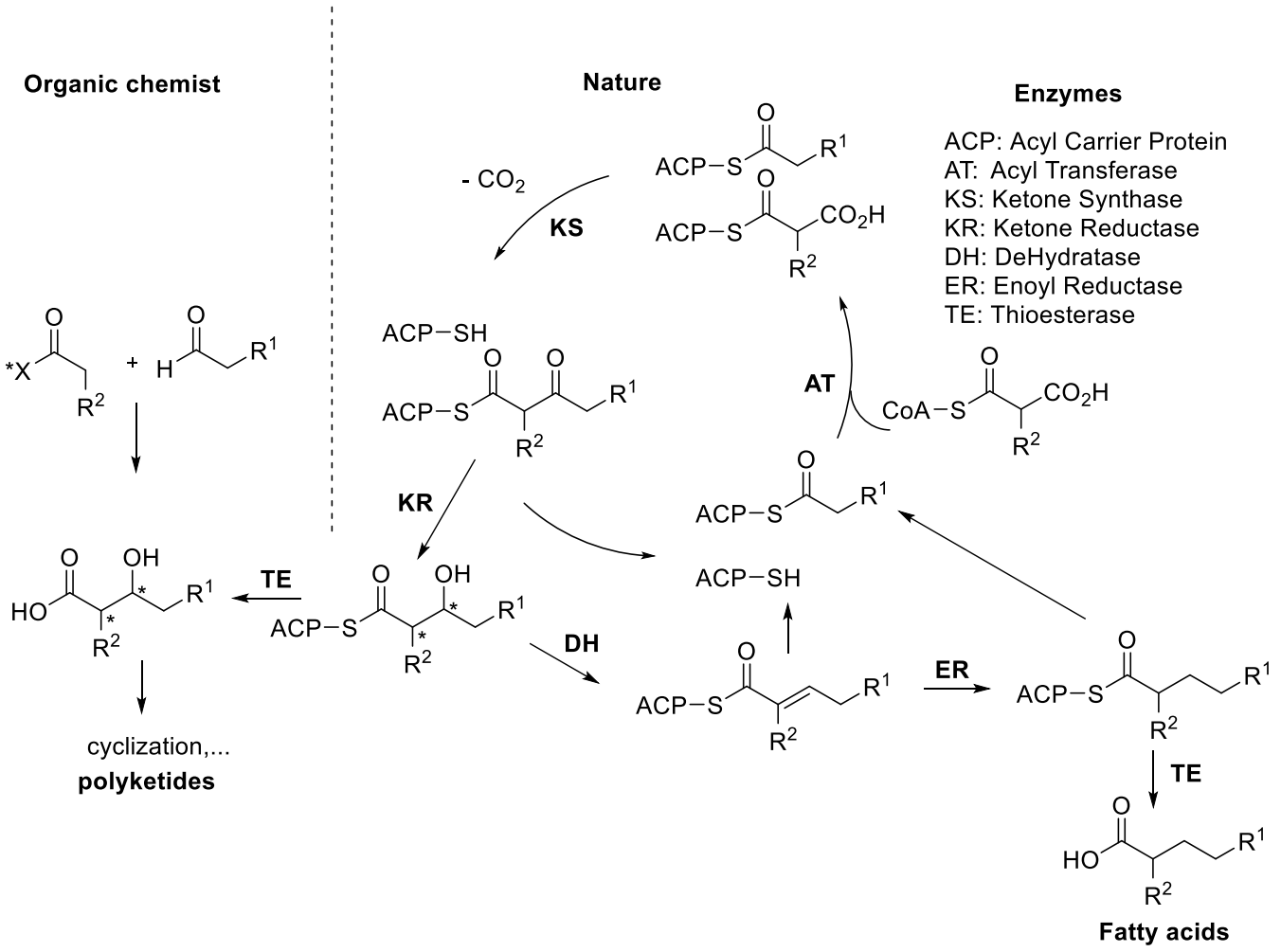
"Acetate Aldol"



"Propionate Aldol"

Biological synthesis of polyketides(C)

Bibliography (Koshla): http://video.google.com/videoplay?docid=8632076149073064786#

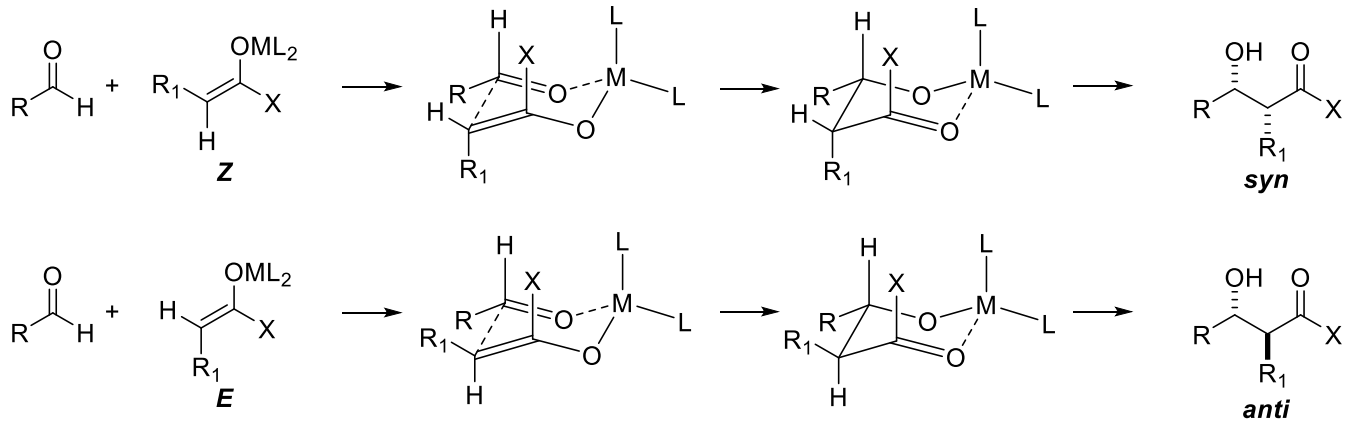


The biological synthesis of polyketides is based on a gene cluster that encodes a complex synthetic module conaining several enzymes. It is based on the reactivity of thioesters, which allows to bind the growing chain to cysteine in enzymes. The new C-C bond is made via a Claisen condensation between two thioesters. To avoid the use of a strong base, nature uses a decarboxylation to generate the enolate. The chain can then grows to form complex molecules. On each added module, several reduction steps are possible to obtain alcohols, olefins or alkanes. The strength of nature is to be able to varry stereochemistry and oxidation state at all the steps of the process. As the end, the chain is liberated and eventually cyclized. The main goal of this metabolism is to synthesize fatty acids, which are highly saturated. Natural products are only secondary metabolites. The details of the biological synthesis with be seen in biochemistry courses.

Although chemists have also developed biomimetic methods for the synthesis of polyketides, the asymmetric aldol reaction constitutes a more efficient alternative. This reaction will now be examined in details. A completely different approach is based on biotechnology: bioengineering of the natural gene clusters gives access to new analogues.

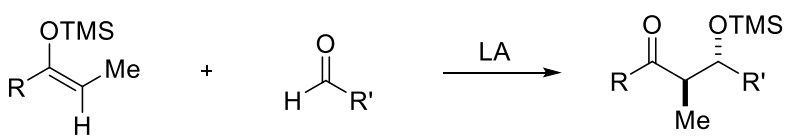
7.2 Zimmermann-Traxler transition state and Mukaiyama aldol (A)

Zimmermann-Traxler transition state (A)

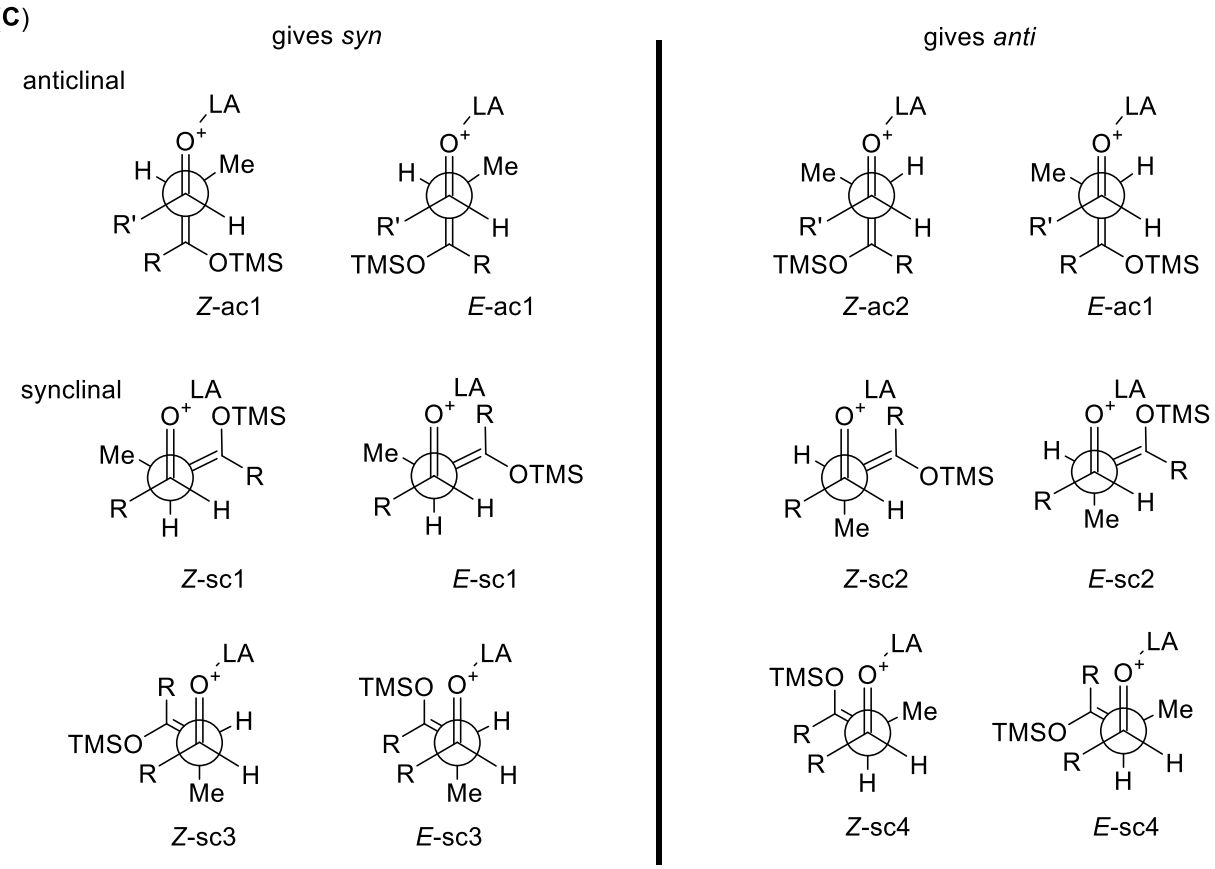


Enolates formed with metals able to coordinate simultaneously the aldehydes, such as Li or B, usually follow a cyclic chair transition state (Zimmermann-Traxler). The aldehyde substituent is in pseudo equatorial position. Consequently, the reaction is stereospecific: *Z* enolates give *syn* products, and *E* enolates give *anti* product. A small and strong Lewis acid like boron favors a tight transition state and lead to a maximal selectivity.

Mukaiyama Aldol (B)

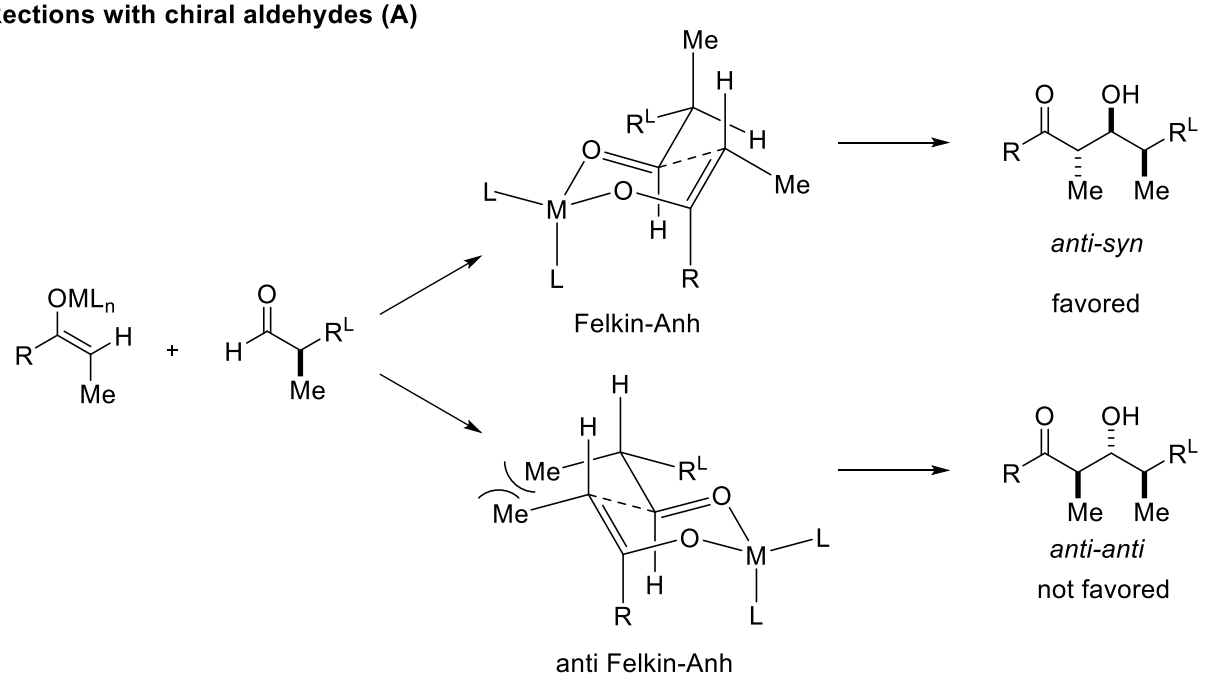


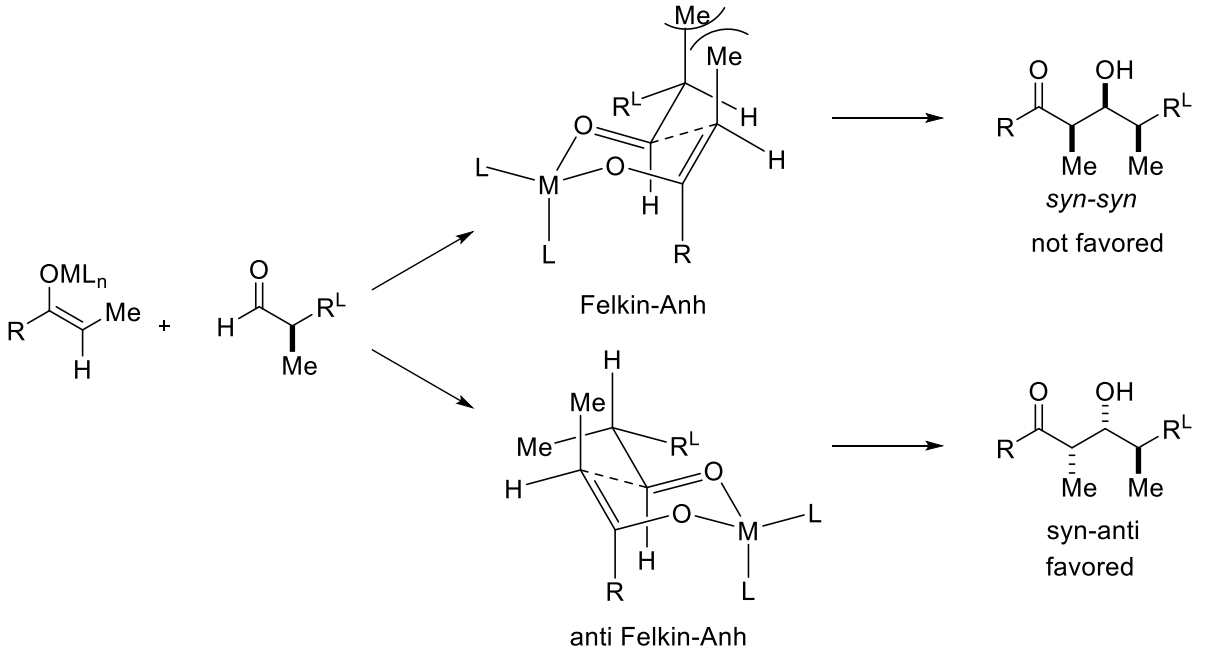
(**C**)



Silyl enolates are saturated and cannot coordinate to the aldehydes. Therefore, a second Lewis acid is needed to promote the reaction, which proceeds via an open transition state. The analysis is more complex, as both synclinal and anticlinal transition states need to be considered. The reaction is not stereospecific and give often (but not always) the *anti* product. The synclinal transition states are slightly favored due to electrostatic interactions. All interactions between R, TMS, Me and LA need to be analyzed to rationalize the selectivity.

Rections with chiral aldehydes (A)

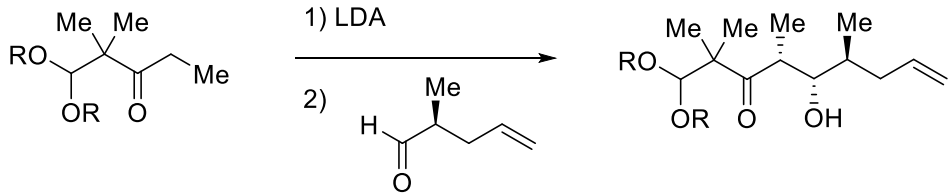




For Mukaiyama aldol reactions, the Felkin-Anh model can usually be used.

For aldol reactions proceeding via the Zimmermann-Traxler transition state, the interactions between the stereocenter on the aldehyde and the substituents on the enolate need to be taken into account. For *trans* enolates, there is no non-favorable interactions for a nucleophilic attack according to Felkin-Anh and the corresponding product is favored. In contrast, for *Z* enolates, an important *syn*-periplanar (double gauche pentane) interaction is present in the transition state corresponding to Felkin-Anh. In this case, the anti-Felkin-Anh product is favored. It is important therefore to always consider the Zimmermann-Traxler transition state.

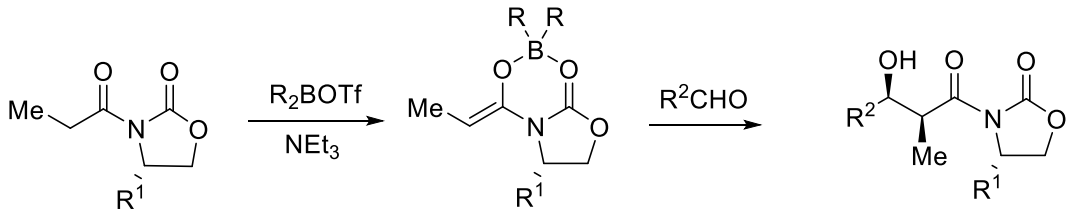
Example (lecture):



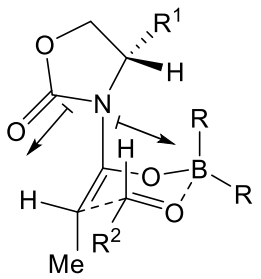
7.3 Aldol reactions with chiral auxiliaries

7.3.1 Reactions with Evans auxiliary (A)

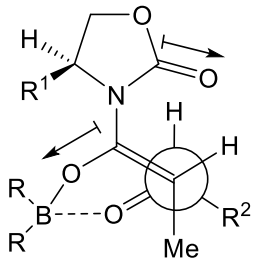
Evans Syn Aldol



Transition state



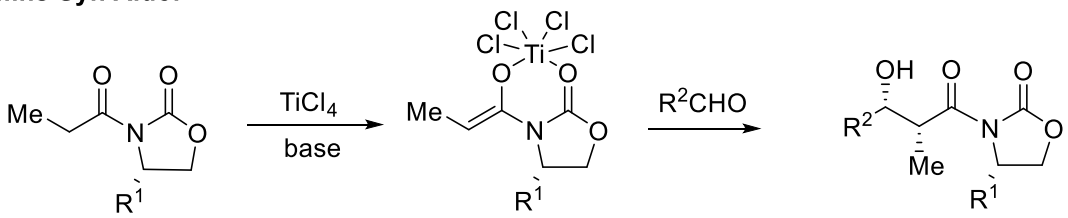
- Chair
- Minimized dipoles
- Aldehyde opposite to R^1

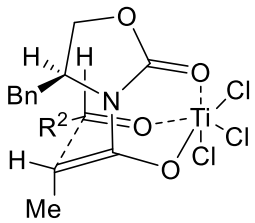


Newman projection from the left

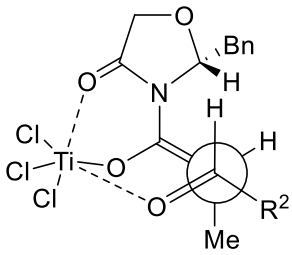
The Evans reaction to give *syn*-aldol propionates is one of the best methods to access these building blocks. A boron enolate is first formed by soft enolization (see previous sections). As the used Lewis acid has only two free coordination sites, it is necessary to release the chiral auxiliary to coordinate the aldehyde and form the Zimmermann-Traxler transition state. At the same time, the carbonyl group of the oxazolidinone turns 180° to minimize dipoles. The aldehyde then comes from the face opposite to the group R^1 of the oxazolidinone. The relative stereochemistry is determined by the enolate geometry and the pseudo-equatorial position of the R^2 group. The absolute stereochemistry is determined by the chiral auxiliary. It is reversed when compared to alkylation reactions.

Crimmins Syn Aldol





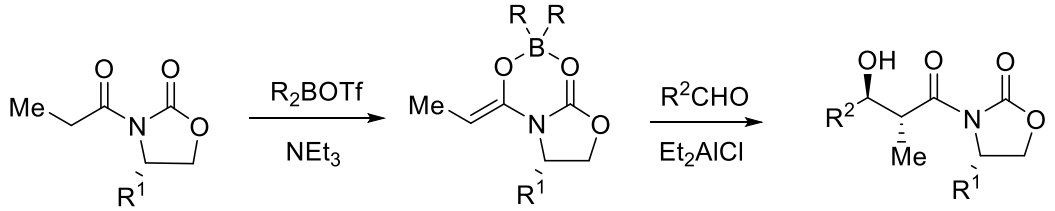
- Chair
- All carbonyls bound to Ti
- Aldehyde opposite to R^1

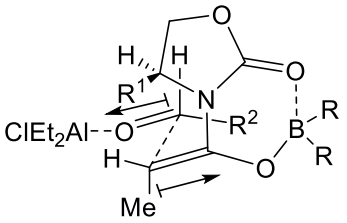


Newman projection from behind

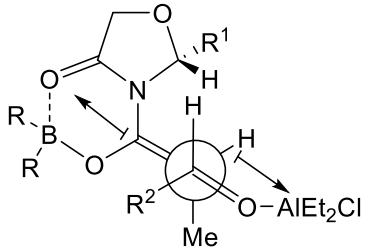
It is in principle possible to invert the absolute stereochemistry by changing the stereochemistry of the chiral auxiliary. Crimmins has shown that it is possible to do it even using the same chiral auxiliary, but with $TiCl_4$ as Lewis acid. As $TiCl_4$ can accept up to 6 ligands, all the carbonyl groups are now bound to titanium and the face of attack of the aldehyde is inverted.

Anti aldol with external Lewis acid





- Non-cyclic transition state
- B bound to the auxiliary
- Minimized dipoles and sterics
- Aldehyde opposite to R^1

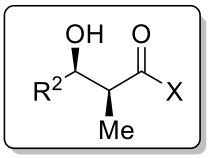


Newman projection from behind

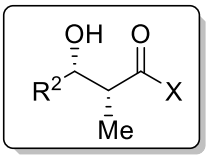
The synthesis of *anti* products is more difficult, as it is not possible to obtain *E* enolates with Evans auxiliary. The cyclic transition state needs therefore to be broken. This is possible by adding a second external Lewis acid, such as $AlEt_2Cl$. In this case, boron stays bound to the auxiliary and the R^1 group blocks one face of the enolate. The dipoles of the aldehyde and the enolate are minimized (antiperiplanar structure). The H group of the aldehyde is placed on the side of the oxazolidinone.

By the choice of reaction conditions and auxiliary, it is therefore possible to synthesize all four stereoisomers!

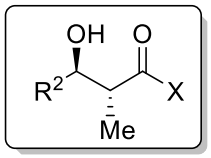
Retrons for Aldol reactions wiht Evans auxiliary (B)



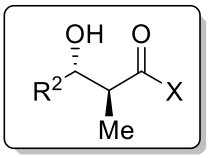
auxiliary derived from:
(*S*)-phenylalanine
(*S*)-valine
and Bu_2BOTf, NEt_3



auxiliary derived from:
(*1S*,*2R*)-norephedrine
and Bu_2BOTf, NEt_3
or
(*S*)-phenylalanine
(*S*)-valine
and $TiCl_4$, NEt_3



auxiliary derived from:
(*S*)-phenylalanine
(*S*)-valine
and Bu_2BOTf, NEt_3
then Et_2AlCl

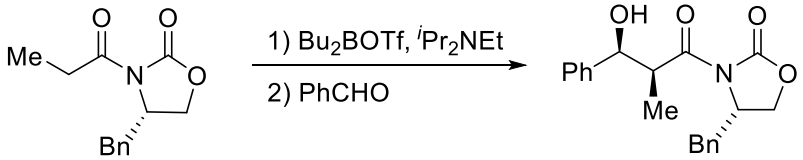


auxiliary derived from:
(*1S*,*2R*)-norephedrine
and Bu_2BOTf, NEt_3
then Et_2AlCl

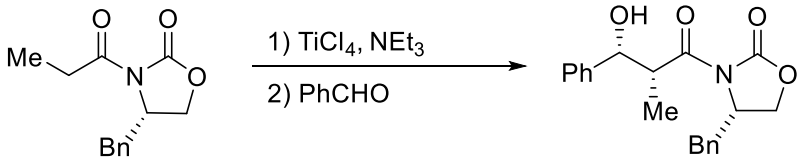
The main strength of the Evans auxiliaries resides in the predictability of the reaction outcome. The exact selectivity of course depends on the specific substituents, but is in general very good for a broad range of R^2 groups. This gives some "security" for synthesis planning and explains the popularity of the method. This is also a strength of organic synthesis when compared wiht biosynthesis. Bioengineering is very efficient to obtain large quantities of a single compound, but the synthesis of analogues is much harder, requiring years of optimization and larger changes remain often not possible.

Examples (lecture):

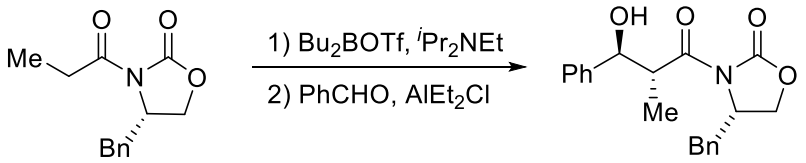
1)



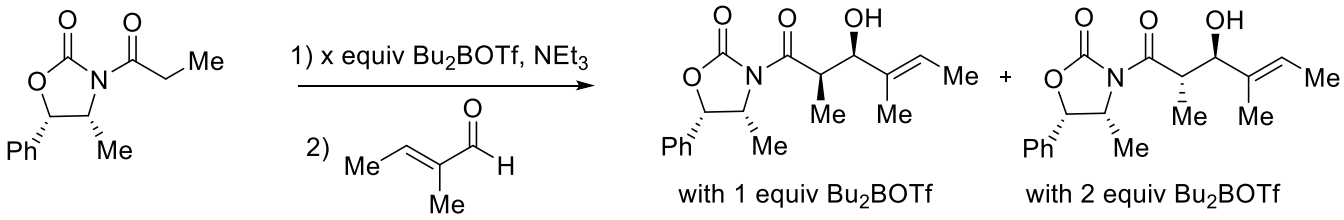
2)

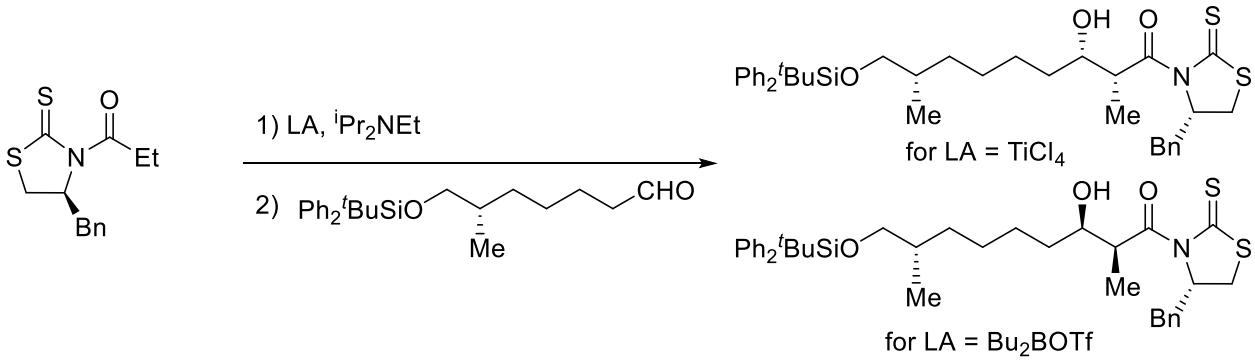


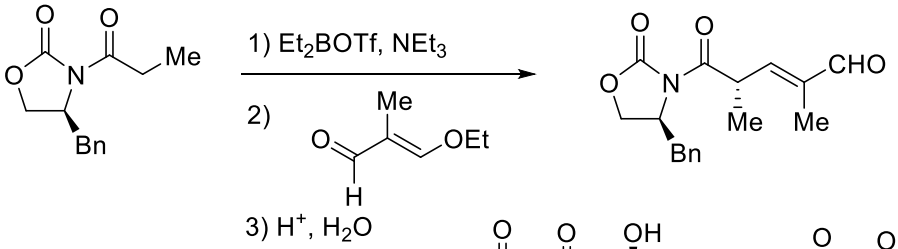
Example lecture):

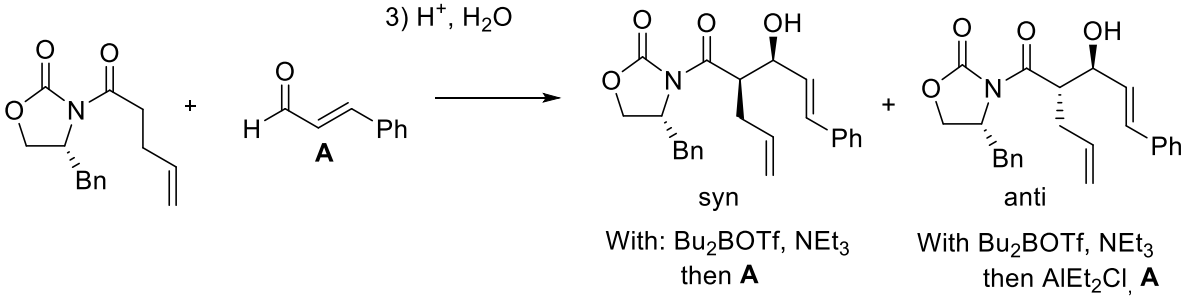


Examples (exercises):

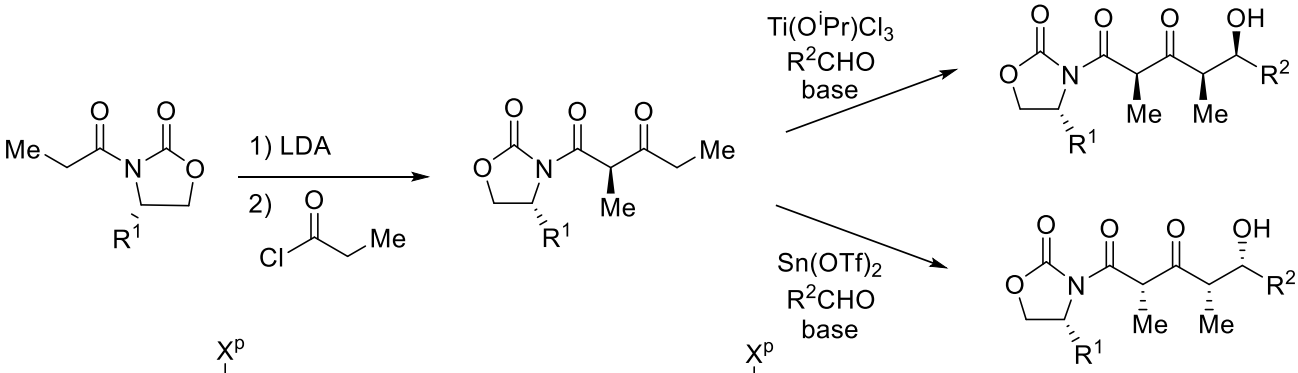


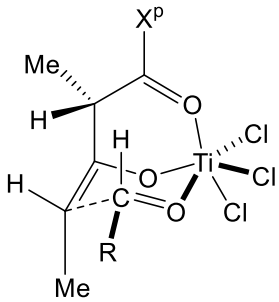


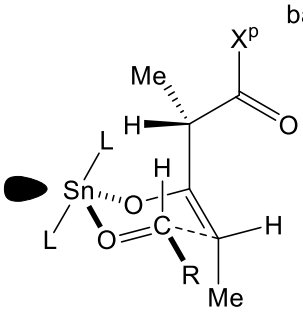


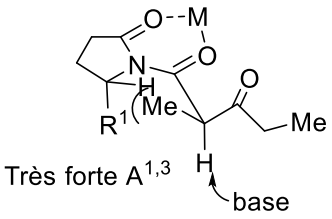


Aldol with dicarbonyls (C) (*J. Am. Chem. Soc.* **1990**, *112*, 866.)





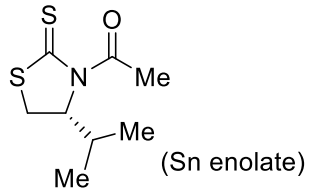




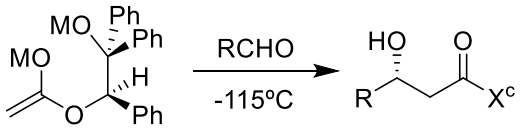
Chiral dicarbonyls can be obtained via the acylation of acide chlorides using Evans auxiliary. As acid chlorides are strong electrophiles, further activation is not required and the transition state described for alkylation can be applied. The fact that the stereocenter between the two carbonyl groups does not epimerize during the reaction is surpising at the first look, but it can be rationalize by the fact that the conformation with the hydrogen perpendicular to C=O is not accessible, due to the $A^{1,3}$ strain. Multi-functionalized products can then be obtained by soft enolization followed by aldol. *syn* products are obtained and the face of attack can be inverted by the choice of Lewis acid. TiO^iPrCl_3 can coordinate the 3 oxygens and the stereocenter between the carbonyls determines the face of attack. $Sn(OTf)_2$ is a weaker Lewis acid, allowing the first carbonyl group to flip and invert the facial selectivity.

7.3.2 Other auxiliaries (C)

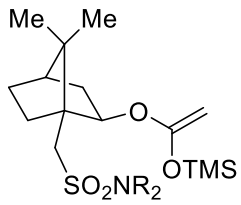
Auxiliaries for "acetate aldol"



Nagao (*J. Org. Chem.* **1986**, *51*, 2391)



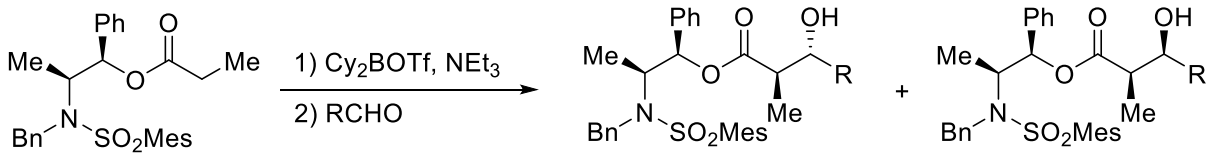
Braun *Tetrahedron Lett.* **1984**, *25*, 5031; **1987**, *28*, 1385.



Oppolzer (*Helv. Chim. Acta* **1986**, *69*, 1699)

Evans auxiliary gives only low selectivity with non-substituted enolates. An alternative is to use the enolate of bromoacetate, and then remove the bromine for example using a radical method. The auxiliaries above are among the best for acetate aldol.

Auxiliaries for *anti* aldol:

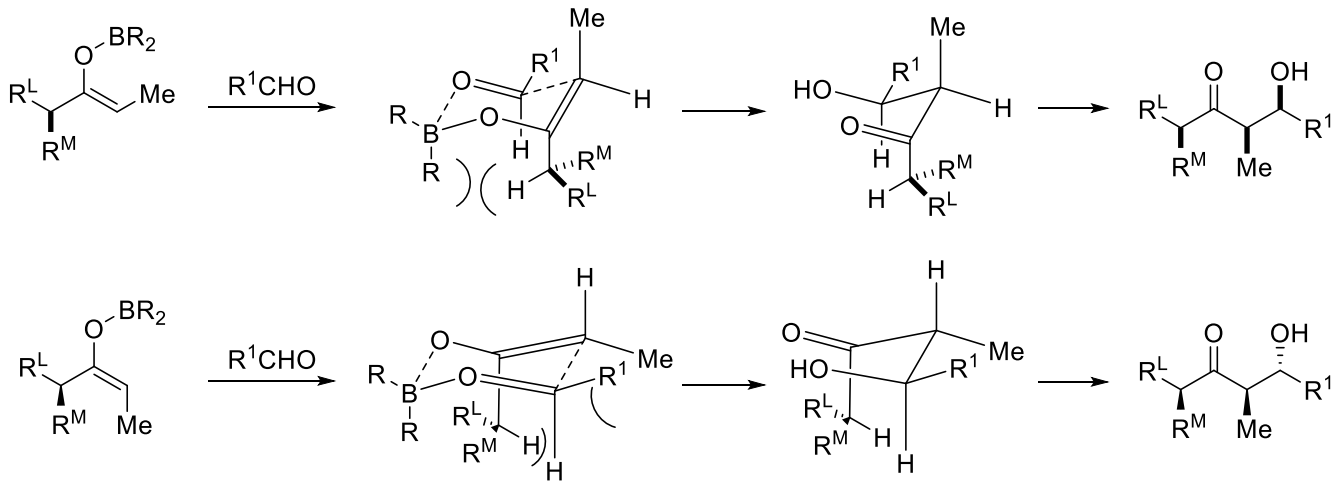


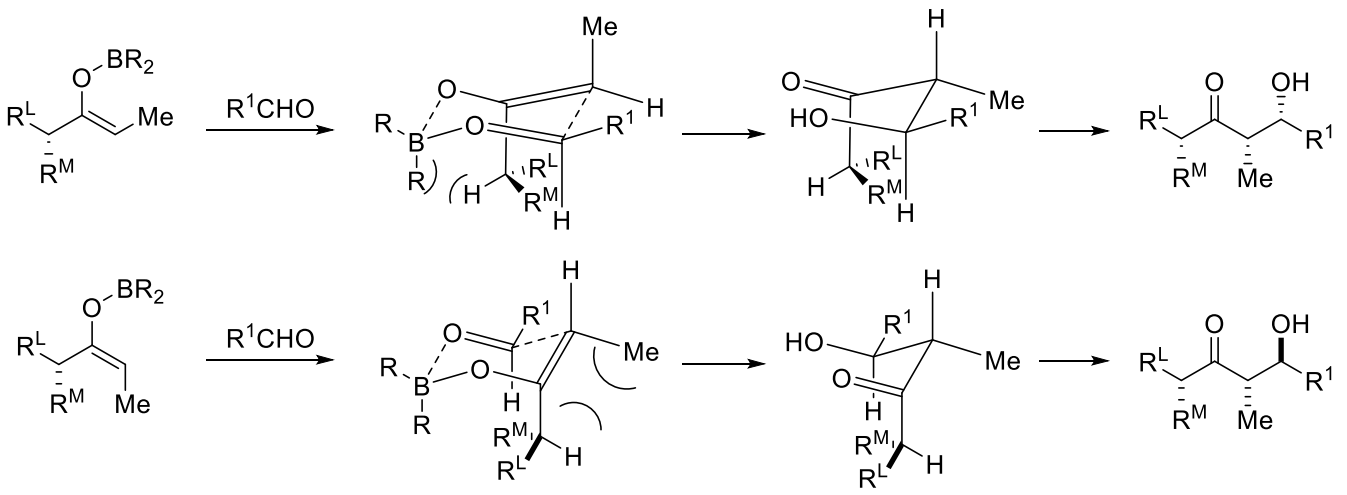
Masamune *J. Am. Chem. Soc.* **1997**, *119*, 2586. maximal diastereoselectivity >99:1

Several auxiliaries have been also developed for *anti* aldols not requiring excess of Lewis acid, such as the one of Masamune.

7.4 Aldol reactions with ketone enolates (Paterson) (A)

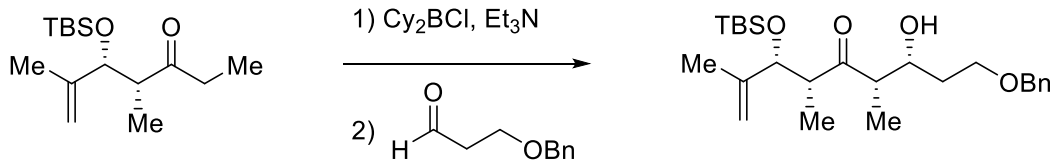
Reactions with chiral ketone enolates:



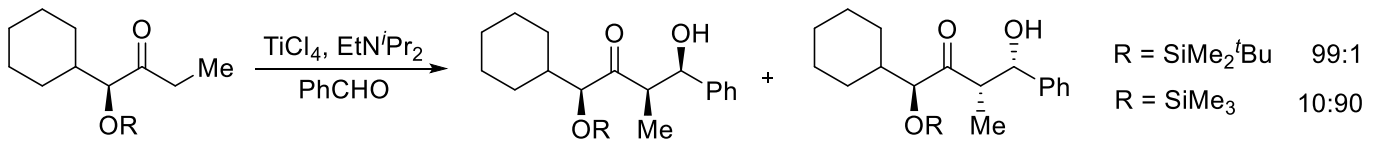


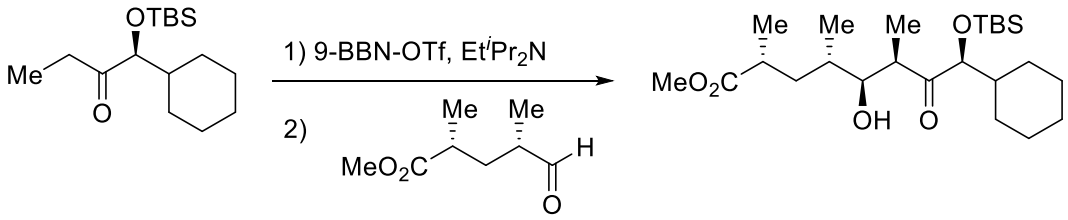
It is more difficult to control selectivity with ketone enolates. Paterson has focused his research on this challenge. Methods were developed to obtain either the *Z* or the *E* enolates (see chapter 6.1). This allowed the formation of *syn* or *anti* products via a Zimmermann-Traxler transition state. The relationship between the R^M group of the enolate and the Me group is generally *syn*. This can be explained by the minimization of steric interactions between the R group on boron and the stereocenter for *Z* enolates (the aldehyde attacks on the side of R^M) or a minimization of the $A^{1,3}$ strain inside the enolate for *E* enolates (the aldehyde attacks on the side of R^M).

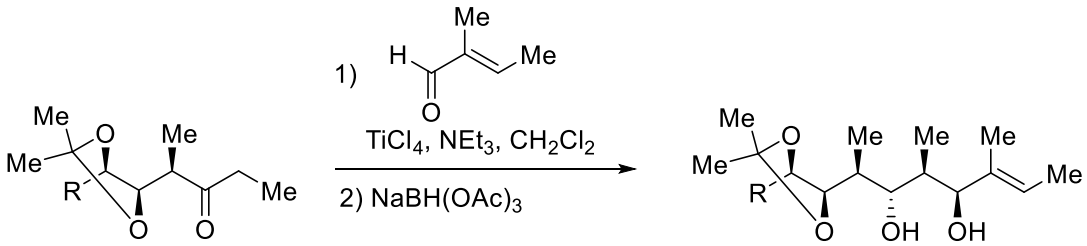
Example (lecture):



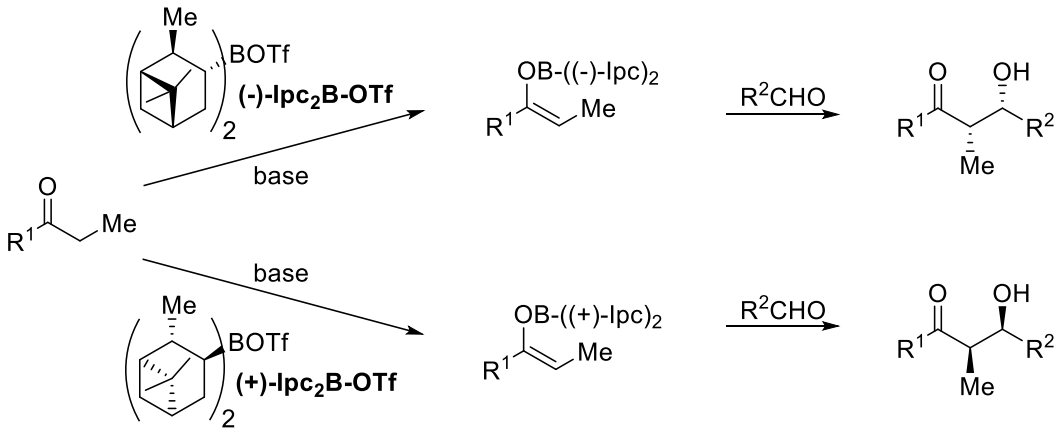
Examples (exercises):





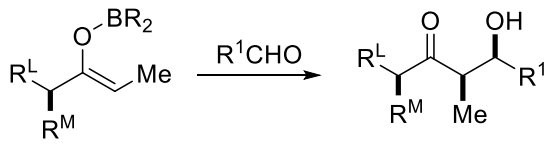


Aldol with chiral boron reagents (C)



Boron derivatives obtained from α-pinene are good reagents for asymmetric aldols with ketone enolates. The reaction goes via the Zimmermann-Traxler transition state, and the absolute stereochemistry is controlled by steric interactions with the Ipc ligand. The analysis is complex.

Double stereocontrol (C)



R = 9-BBN:good selectivity

R = (+)-Ipc: outstanding selectivity (matched)

R = (-)-Ipc: bad selectivity, mixture (mismatched)

When chiral boron reagents are used with chiral enolates and the effects of the boron substituents and the stereocenter on the enolate are in the same direction, a nearly perfect selectivity is observed (**matched case**). In contrast, if both influences go in reverse directions, the selectivity is lower, or even inverted (**mismatched case**). The most interesting reagents are the one able to fully control selectivity (usually rare for the Paterson aldol, more frequent for the Evans aldol). A further degree of complexity is reached if a chiral aldehyde is used.

7.5 Catalytic asymmetric aldol reactions (D)

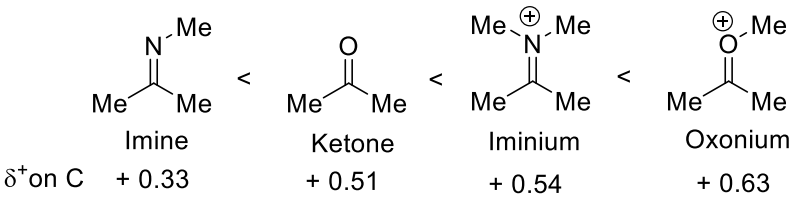
Methods using chiral auxiliaries are robust, but they require multiple steps and stoichiometric quantities of chiral reagents. Current research in the field is therefore focusing on catalytic asymmetric methods. The first successes were based on the use of chiral Lewis acids in the Mukaiyama aldol. More recently, methods combining catalytic generation of enolates and aldol have been developed. It is therefore not needed any more to have a separate step to prepare the enolate, meaning less waste and less basic conditions. These reactions will be seen in a master course (catalytic asymmetric reactions in organic synthesis). We will see a specific example of organocatalysis in chapter 8.

8. Chemistry of imines and enamines

8.1 Chemistry of imines

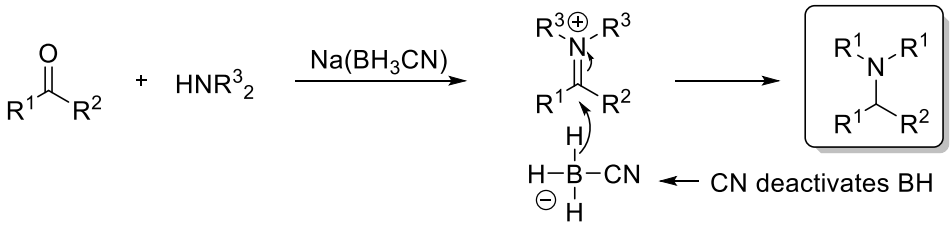
Bibliography: Fonctions et réactions organiques II, Carey Sundberg B, Ch. 2.2, p. 139-148. Carreira Ch. 11, p. 343-389.

Comparison of the reactivity of carbonyl and imine electrophiles (A)



Imines are generally less reactive than carbonyls. However, iminiums are more reactive than carbonyls and the coordination of Lewis or Brønsted acids to imines is stronger, making imines very interesting substrates for catalysis. Furthermore, the extra substituent on the nitrogen allows modulating reactivity, adding a factor of complexity to the chemistry of imines.

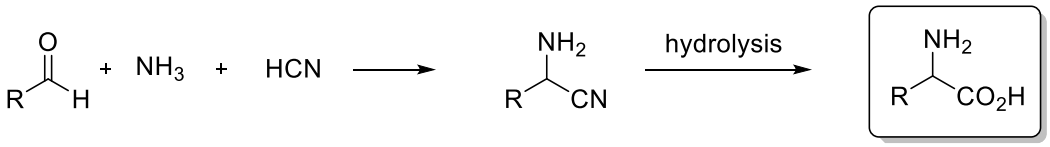
Reductive amination (A)



Reductive amination is a classical example of the reactivity of iminiums. $Na(BH_3CN)$ is less reactive than $NaBH_4$, due to the electron-withdrawing effect of cyanide. Consequently, this reagent reduces aldehydes and ketones only very slowly. Iminiums are more reactive and readily reduced. This reactivity difference allow the direct conversion of aldehydes and ketones to amines via condensation and reduction.

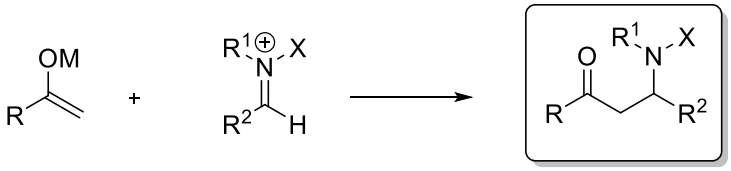
The stereoselectivity of these transformations has been less studied than for carbonyl compounds. In general, the Felkin-Anh and chelate models remain valid.

Strecker amino acid synthesis (B)



The Strecker reaction is one of the oldest (1850) and most important in organic chemistry. It is a very efficient method for amino acid synthesis. The development of asymmetric Strecker methods is an active field of research nowaday.

Mannich reaction (A) = Imine equivalent of aldol reaction



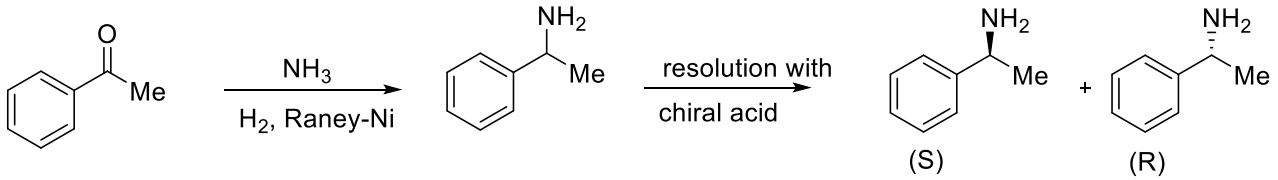
β-amino carbonyls

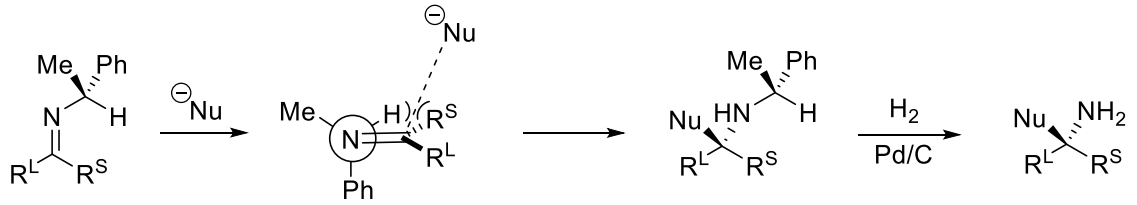
The Mannich reaction is important, as it gives access to β-amino carbonyl compounds, which are building blocks for many bioactive compounds. The development of asymmetric Mannich methods is an active field of research nowaday.

Chiral auxiliaries for imines (A)

A fundamental difference between imines and carbonyls it the possibility to have a chiral auxiliary on the nitrogen.

1-Phenylethylamine (A)



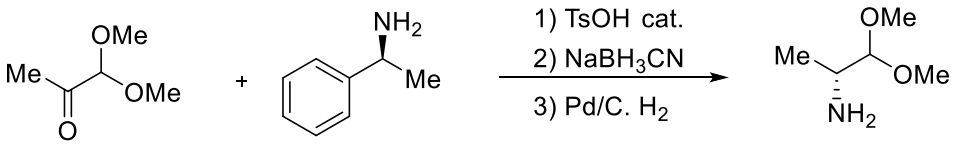


A^{1,3} minimized

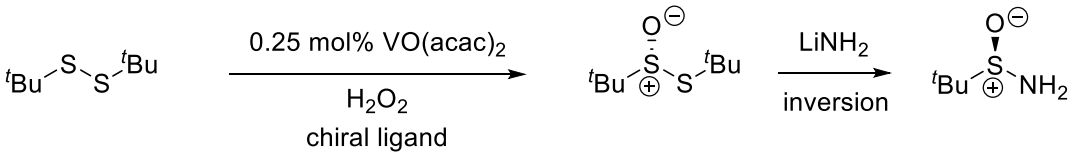
Important Nu: H_2, CN^-

1-Phenethylamine is one of the cheapest chiral amines. Both enantiomers are obtained by resolution of the racemic mixture obtained by reductive amination of acetophenone with chiral acids. In general, the resolution with chiral acids works well with amines, and this method is often preferred to asymmetric synthesis. The *trans* imine is obtained by condensation with ketones to minimize steric interactions with the R^L group. The $A^{1,3}$ strain is then minimized and the nucleophile attacks the face opposite to Ph. This approach is particularly efficient for the hydrogenation of imines (reductive amination) and the Strecker reaction. The chiral auxiliary can be removed via hydrogenation.

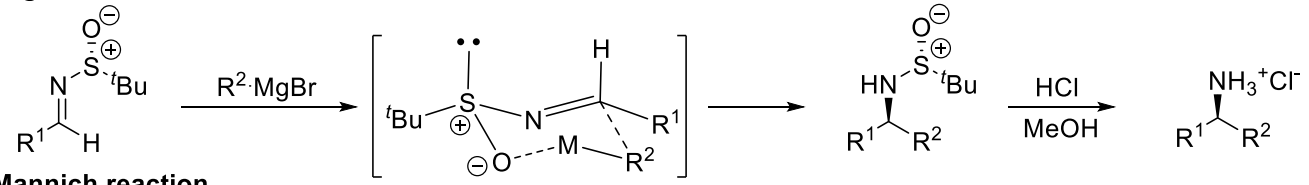
Example (lecture):



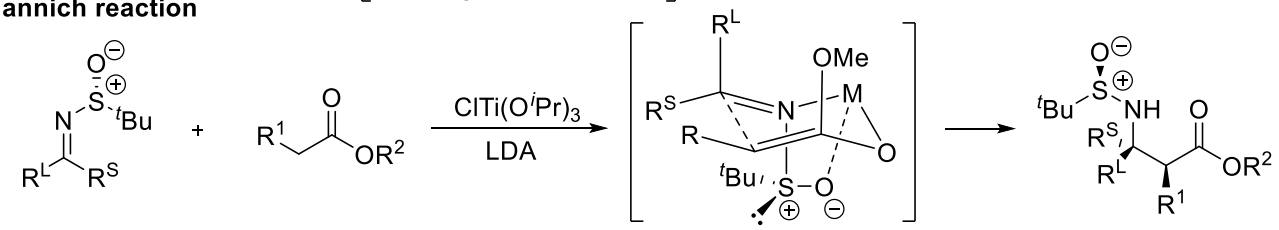
Ellman auxiliary (*Acc. Chem. Res.* **2002**, *35*, 984.) (**A**)



Grignard addition



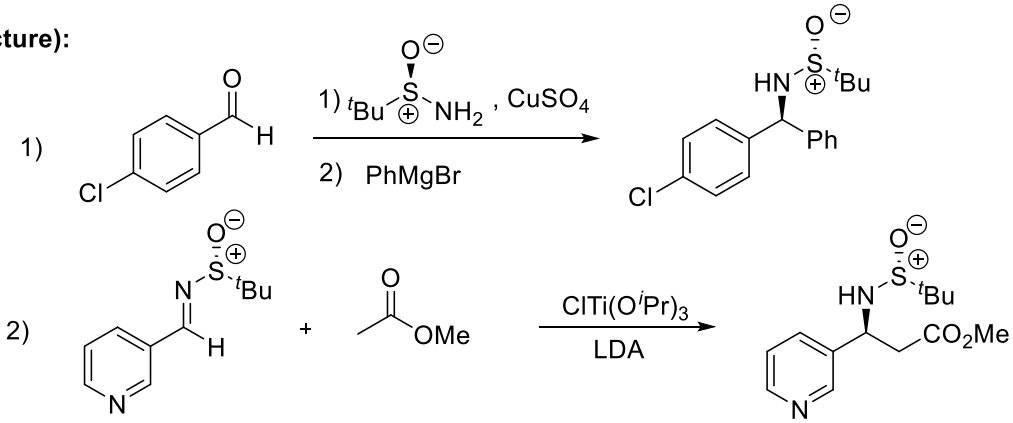
Mannich reaction



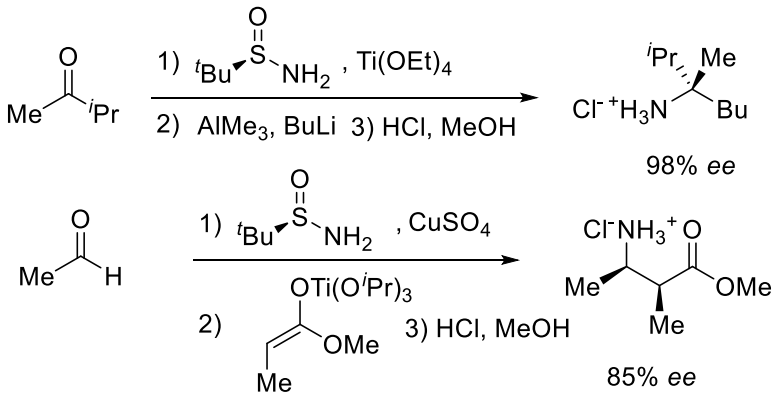
Ellman auxiliary is special, as it is not derived from the natural chiral pool. It is based on configurationally stable sulfoxides. Sulfoxides are an interesting class of chiral auxiliaries, as the presence of the electron pair ensures a maximal size difference between the substituents. The chiral sulfoxide amine is obtained by enantioselective oxidation of a bisulfide, followed by nucleophilic substitution. Condensation with aldehydes or ketones in presence of a Lewis acid then gives exclusively *trans* imines to avoid steric interactions wiht the auxiliary.

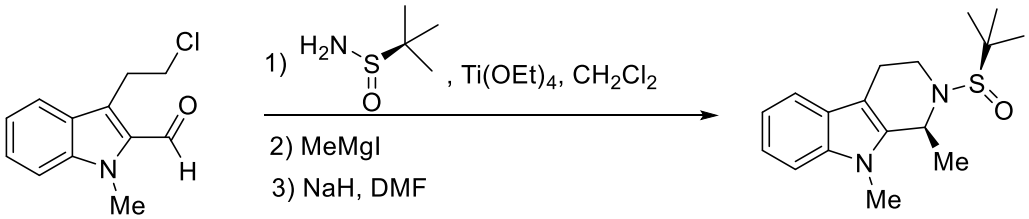
Ellman auxiliary is especially efficient for the addition of hard nucleophiles, such as Grignard reagents or enolates. The reactions occur via 6-atom chair transition states. For Grignard reagents, the ^{t}Bu group is placed in equatorial position. For the Mannich reaction, the nitrogen, the sulfoxide and the enolate are bound to titanium. The *E* enolate is formed selectively and attacks the imine on the side of the electron pair, opposite to the ^{t}Bu group. The auxiliary is easily removed by acid in methanol.

Examples (lecture):



Examples (Exercises):

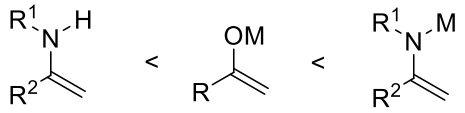




8.2 Chemistry of enamines: Enders auxiliary and organocatalytic aldol

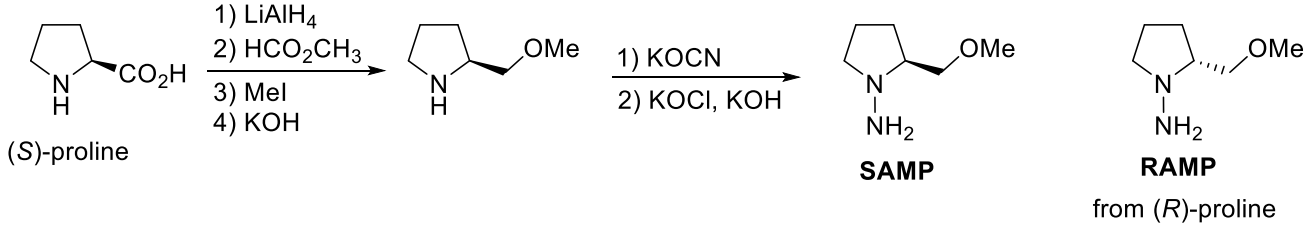
Bibliography: Bruckner, Ch. 12.3, p. 505-512.

Nucleophilicity comparison (A)

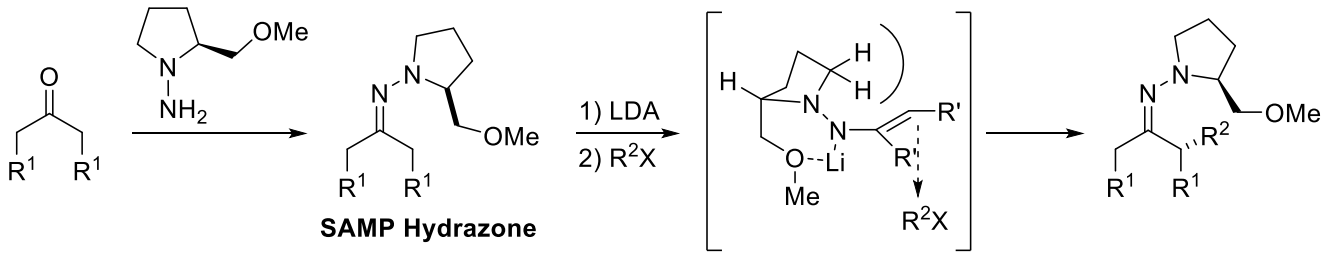


Enamines are easily obtained from iminiums, which are more acidic than carbonyls. They are less nucleophililc than enolates and requires higher temperatures for reactions. Metallo-enamines obtained by deprotonation are in contrast stronger nucleophiles than enolates.

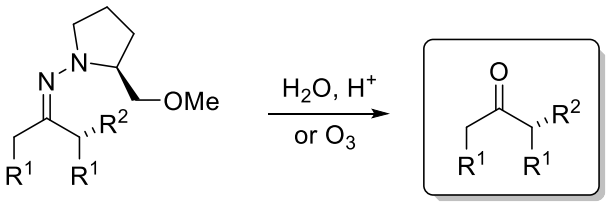
Enders auxiliary for the asymmetric alkylation of ketones (A)



Alkylation of symmetric ketones (A)



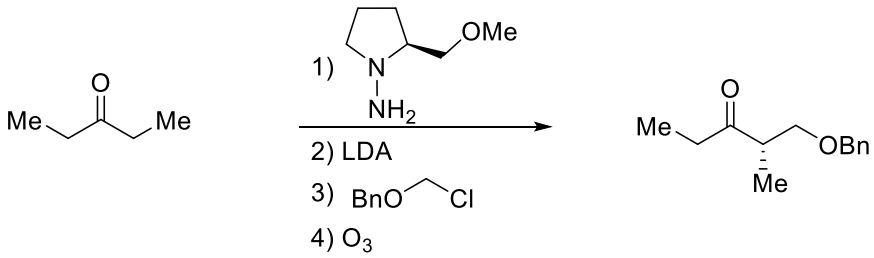
Auxiliary cleavage:



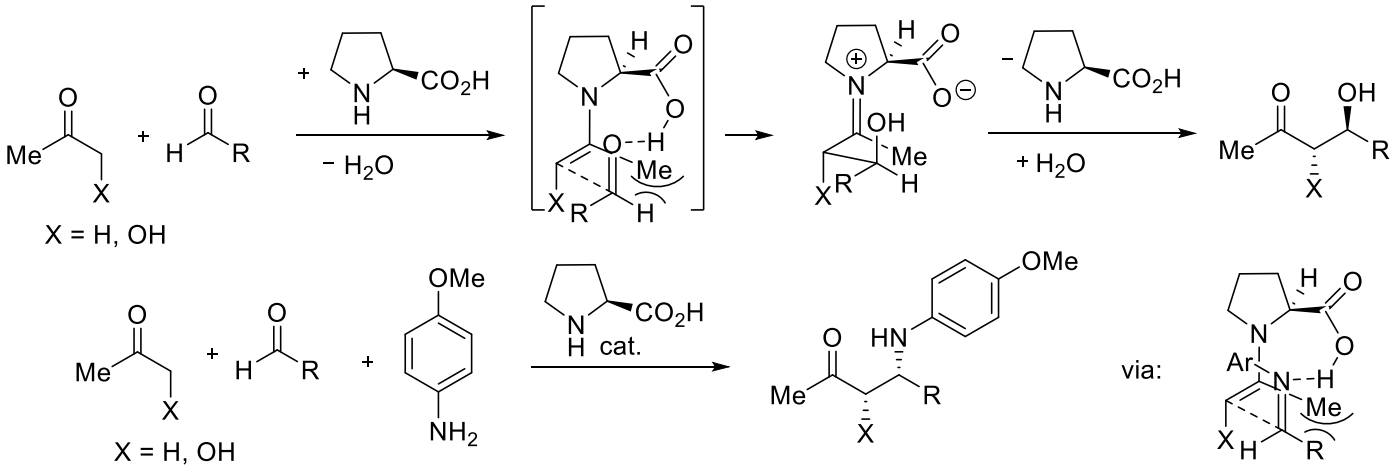
retron

The SAMP and RAMP chiral auxiliaries developed by Enders are obtained in a few steps from (*S*) and (*R*)-proline respectively (reduction, nitrogen protection, methylation, deprotection, amide formation and Hoffmann rearangement). The condensation of hydrazines with ketones is faster and more complete than with amines. The deprotonation of the hydrazones with LDA gives reactive metallo-enamides. Lithium is *trans* to the enamide to minimize sterics and the electrophile attacks the face opposite to the CH_2 group of the pyrrolidine. Enders auxiliaries are among the most efficient for the alkylation of ketones, but the approach works also for aldehydes. The auxiliary can be removed either by hydrolysis or oxidation (ozonolysis).

Example (lecture):

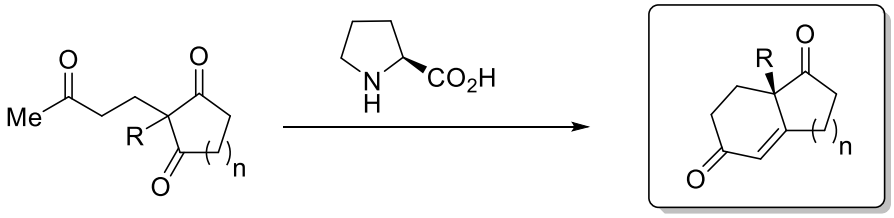


Organocatalytic Aldol and Mannich reactions with proline (A)



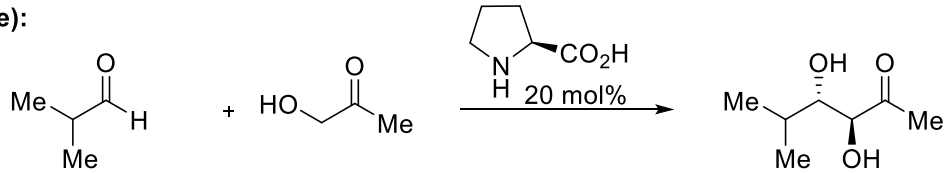
Although the chemistry of enamines in known since a long time, it is only around 2000 that catalytic reactions have been intensively developed. Proline is in particular an excellent catalyst for the direct aldol reaction, and does not require the isolation of the pre-formed enamine. Proline is able of double activation: activation of the ketone as nucleophile via the formation of an enamine and activation of the aldehyde as an electrophile via the proton of the carboxylic acid. A cyclic 9-atom transition state is obtained, with the 6 atoms of the enamine, the aldehyde and the proton forming a pseudo-chair. The *trans* enamine is obtained and the interactions with the Me are minimized to give the *anti* product. In the case of the Mannich reaction, the *trans* enamine and the *trans* imines are obtained *in situ*. As the coordination of the imine by the acid is necessary for activation, the R group is forced on the same side as Me and the *syn* product is obtained. The first reactions using proline were limited to acetone or 2-hydroxy-acetone, but many progress has been obtained since then (see the course catalytic asymmetric reactions in organic synthesis).

Reaction of Hajos-Parrish-Eder-Sauer-Wiechert

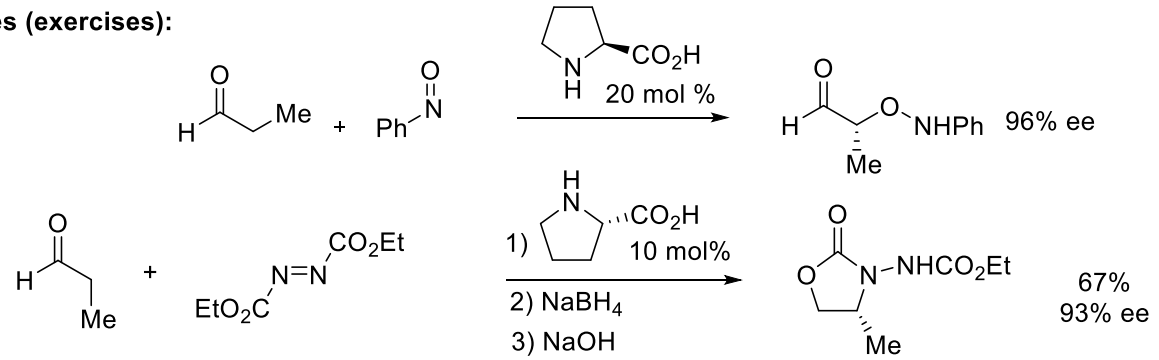


The cyclization reaction developed by Robinson is a cascade reaction: the first step is an intermolecular Michael reaction, the second an intramolecular aldol condensation. This is an important reaction for the synthesis of polycyclic carbocycles, in particular steroids. In the 70's, industrial research groups (Eder-Sauer-Wiechert in Schering and Hajos-Parrish in Roche) discovered that proline is able to catalyse these reactions in an asymmetric way. Perhaps because this research was done only in industry, it took 30 years for academia to realize the potential of proline as catalyst.

Example (lecture):



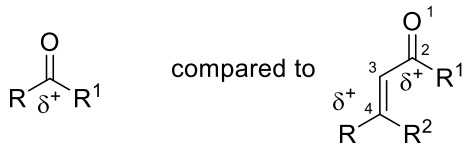
Examples (exercises):



9. Conjugate addition (Michael)

Bibliography: Bruckner, Ch. 10.6, p. 443-457; Ch. 13.6, p. 584-595. Carey-Sundberg B, Ch. 2.6, p. 183-200. Carreira, Ch. 12, p. 389-431.

Vinylogy principle (A)



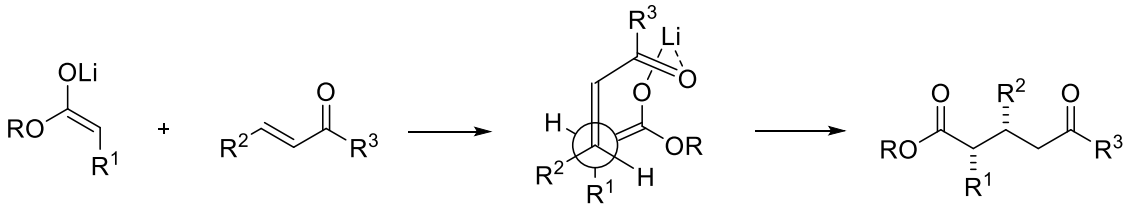
Regioselectivity

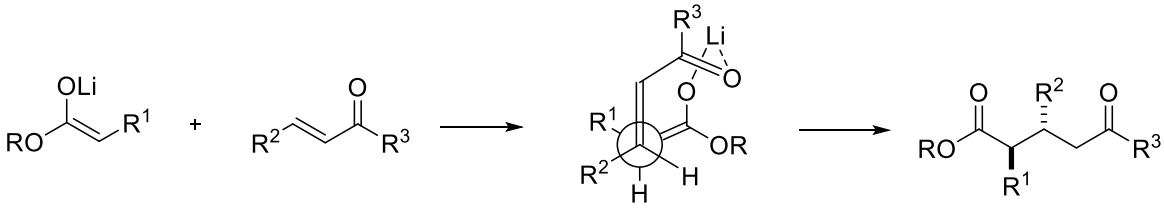
1,2 -Addition favored with hard nucleophiles (Grignards)

1,4 (Michael) Addition favored withi soft nucleophiles (Cuprates)

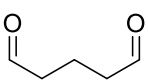
The vinylogy principle tells us that the reactivity in position 4 of conjugated olefins is electrophilic. In fact, the orbital coefficient of the LUMO in conjugated systems are slightly larger in position 4, but the partial charge is higher in position 2. Reactions with hard nucleophiles are controlled by electrostatics and favor attack in position 2. Reactions with soft nucleophiles favor orbital interactions and therefore position 4. A complete analysis of the stereoselectivity of conjugate additions will not be done here, but many principles (and auxiliaries) seen for simple carbonyls remain valid. Catalytic asymmetric conjugate additions are currently an intensive field of research.

Michael reaction (C)





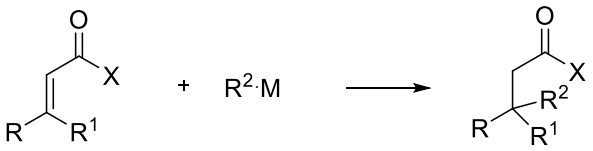
The Michael reaction is the conjugate addition of enolates onto α,β-unsaturated carbonyl compounds. The reaction is stereospecific: *E* and *Z* enolates with *E* olefins give *syn* and *anti* products respectively. The stereospecificity is rationalized by cyclic 8-atom transition states. From the retrosynthetic point of view, the Michael reaction gives access to 1,5-dicarbonyls.



1,5-Dicarbonyl

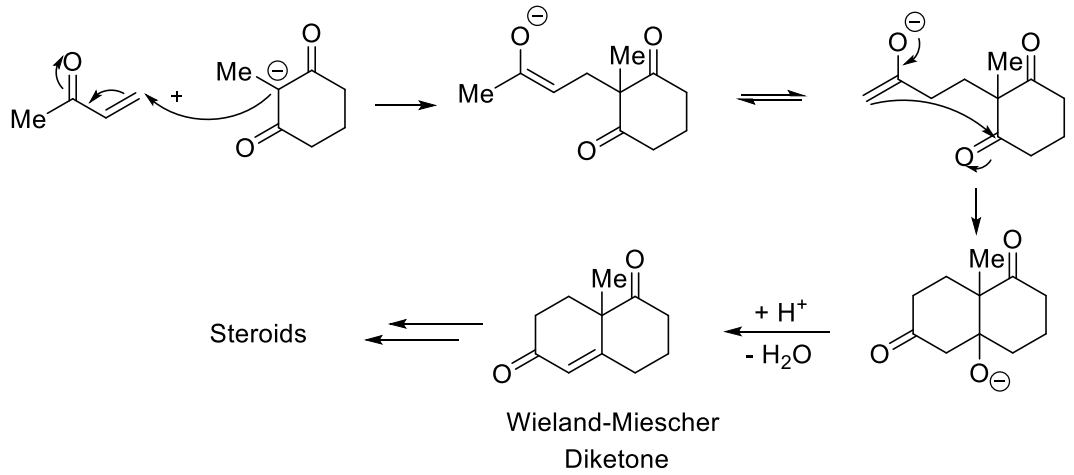
Important applications for conjugate addition (C)

Synthesis of all-carbon quaternary centers



The synthesis of all-carbon quaternary centers is difficult, as they cannot be obtained by addition on carbonyls or hydrogenation. Conjugate additions constitute one of the best way to access these compounds.

Robinson Annulation

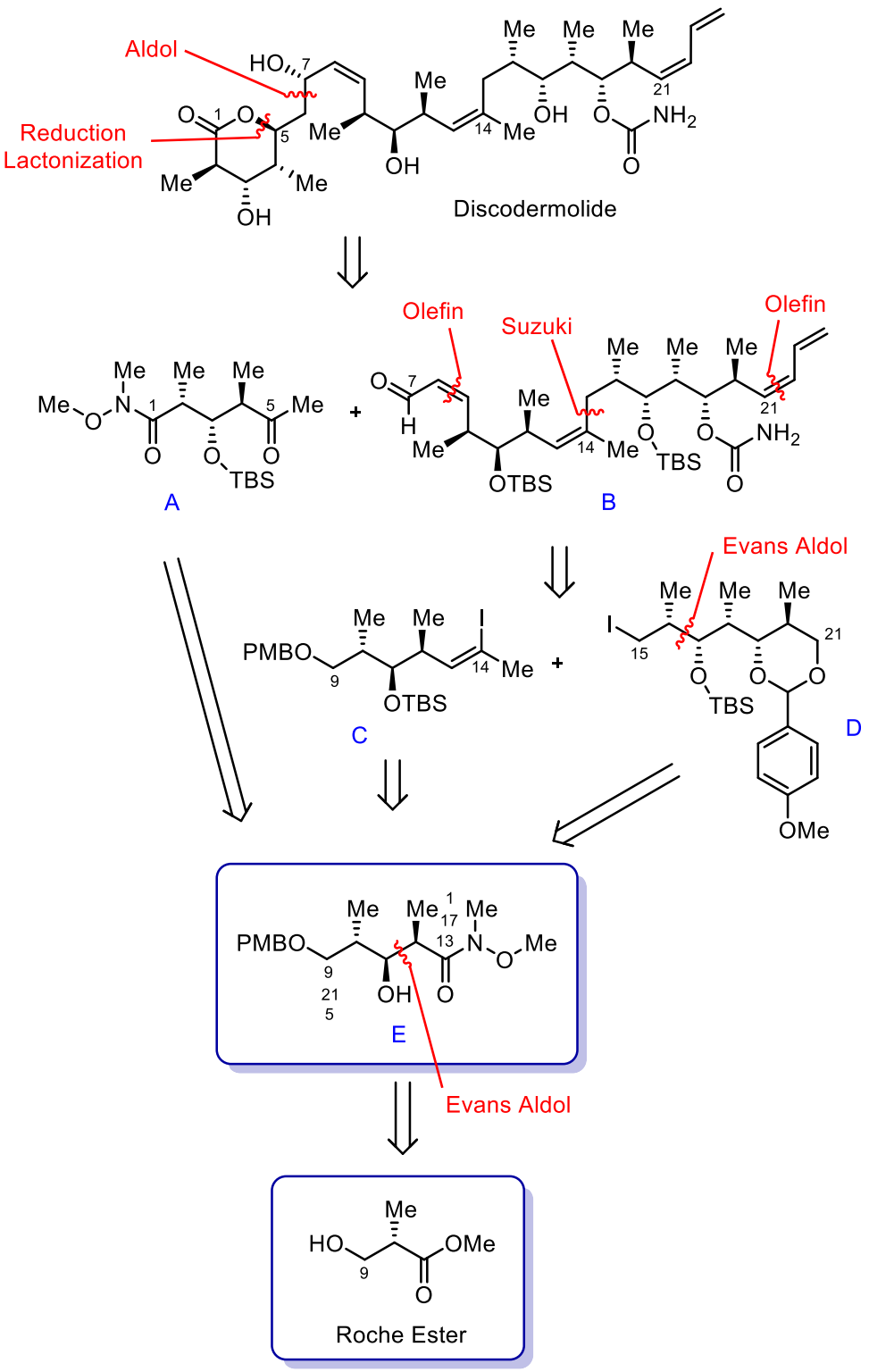


10. Discodermolide Synthesis

Bibliography: Org. Proc. Res. Dev. **2004**, *8*, 92-130.

The total synthesis of Discodermolide of Novartis leading to 60 g of natural product will be described in the lecture.

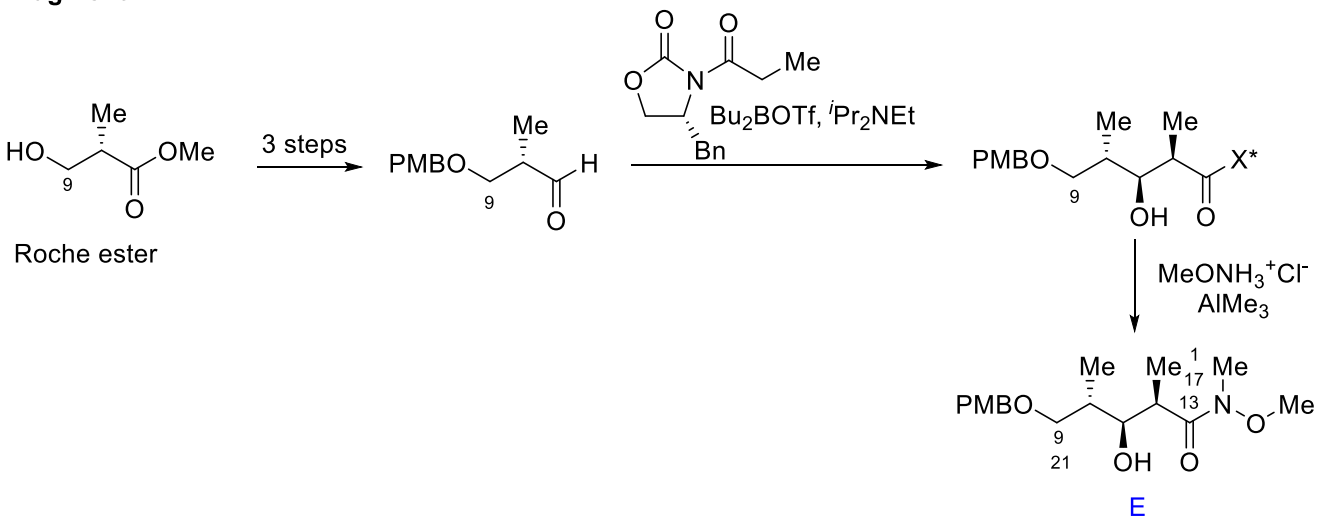
10.1 Retrosynthesis (D)



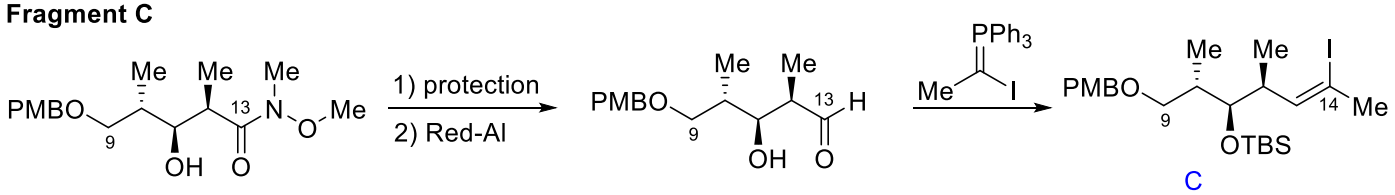
10.2 Synthesis (B)

The key steps are important examples for the previous chapters of the lecture

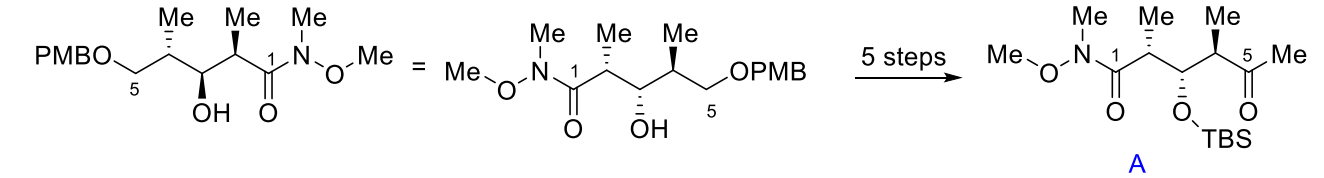
Fragment E



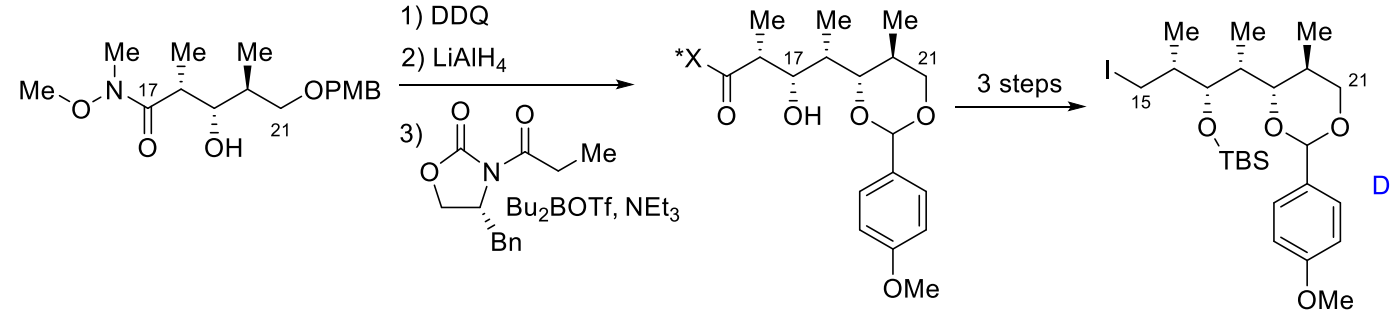
Fragment C



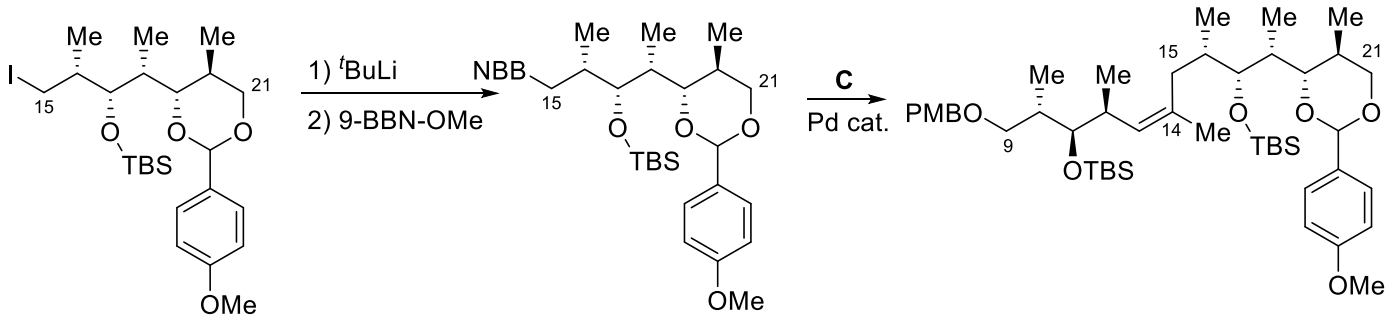
Fragment A

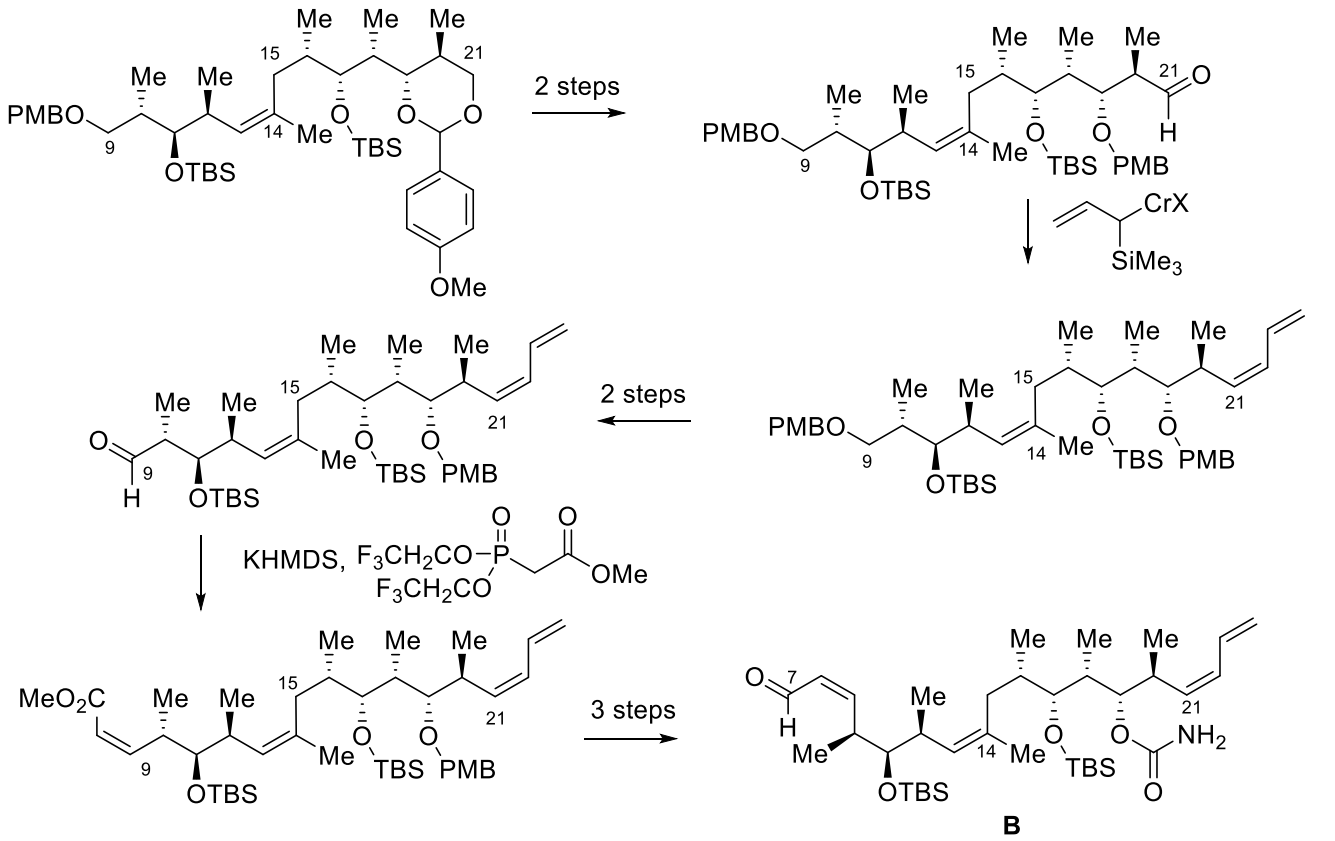


Fragment D

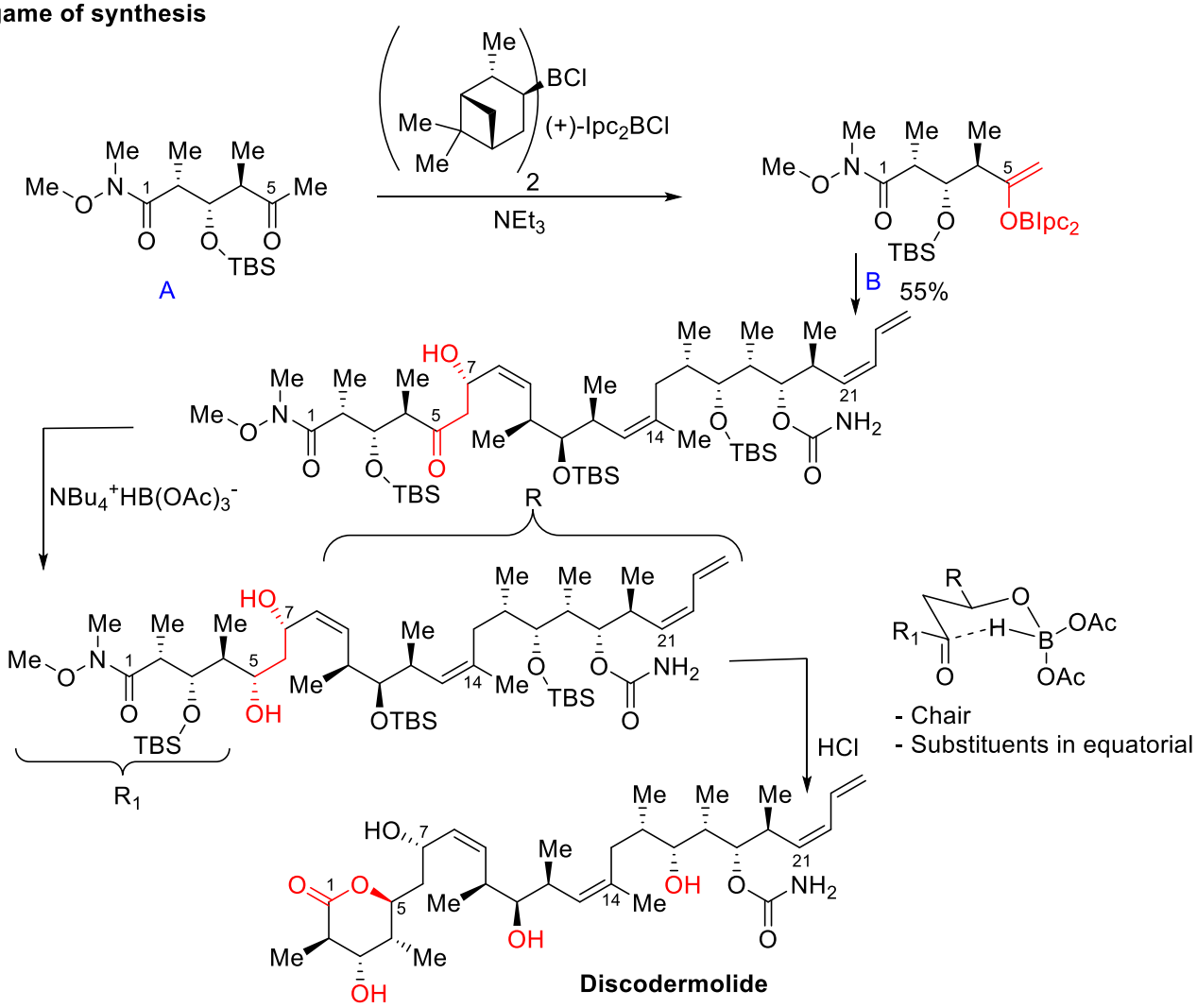


Fragment B





Endgame of synthesis

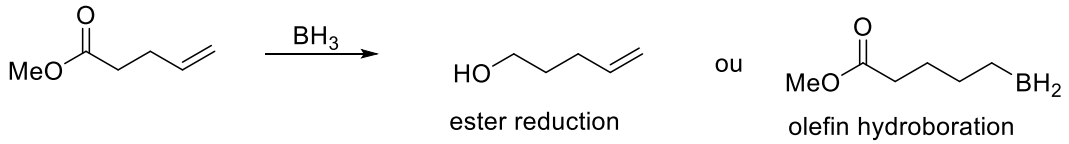


11 FAQ

11.1 What is selectivity in organic chemistry?

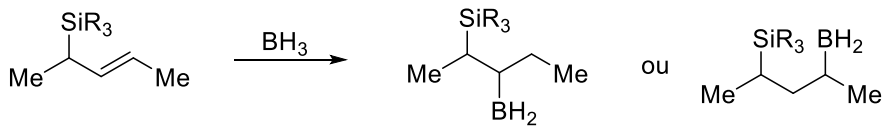
In organic chemistry, we speak of selectivity when several products are possible, but one is formed as the major one. There are several types of selectivity: chimioselectivity, regioselectivity and stereoselectivity (further divided in diastereoselectivity and enantioselectivity)

Chimioselectivity: selectivity between two different functional groups which can react under the reaction conditions.



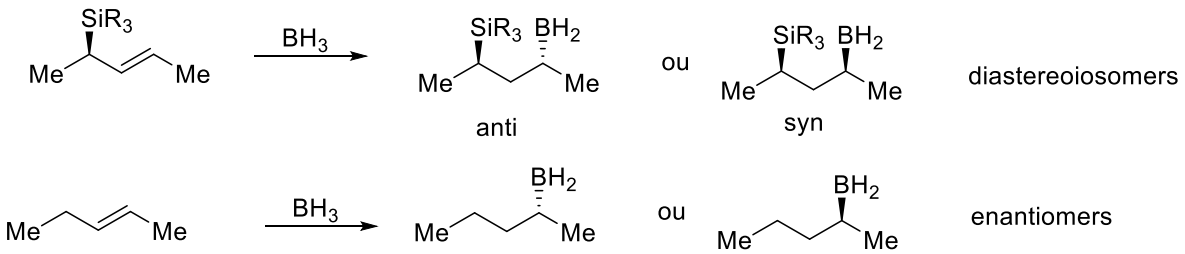
Example related to olefins: When a carbonyl group is present, there is a selectivity issue between carbonyl reduction and hydroboration of the alkene. The hydroboration is usually favored. Chimioselectivity issues are often encountered in complex molecules and require the use of protecting groups.

Regioselectivity: Selectivity between 2 positions in a system with similar reactivity



Example: regioselectivity in the hydroboration of olefins.

Stereoselectivity: Selectivity in the formation of stereoisomers (same connectivity, but different orientation in space (= configuration)). When the starting material contains at least one element of chirality, diastereoisomers can be obtained (diastereoselectivity). When the starting material does not contain chirality elements, enantiomers can be obained (enantioselectivity) .



Example: The hydroboration of chiral olefins led to the formation of diastereoisomers, the one of non-chiral olefins to enantiomers. Enantioselectivity can be obtained only with a chiral reagent or catalyst.

In an exercise/exam or when planning a synthesis, it is essential to consider all types of selectivity!

11.2 What is a detailed mechanism?

A mechanism is sufficiently detailed if it can rationalize the fomation of the observed product(s) satisfyingly. Giving an exact definition is difficult, as it is always possible to go deeper into the reaction mechanism. In this course, this means mostly describing all steps with the Lewis model (arrows for electron movements) and three-dimensional models to rationalize stereoselectivity. In some case, describing molecular orbitals can be also necessary. The best way to get a good impression of adequate mechanism descriptions is to look at the solutions given for the exercises.

11.3 Why is stereochemistry often not drawn in the mechanism?

Of course, stereochemistry is always there! It is often easier to analyze a problem stepwise for better understanding. In a first step, stereochemistry is ignored to focus on reactivity. In a second step, stereoselectivity issues are examined with tridimensional models. A stepwise approach towards scientific questions is an essential step to develop critical thinking.

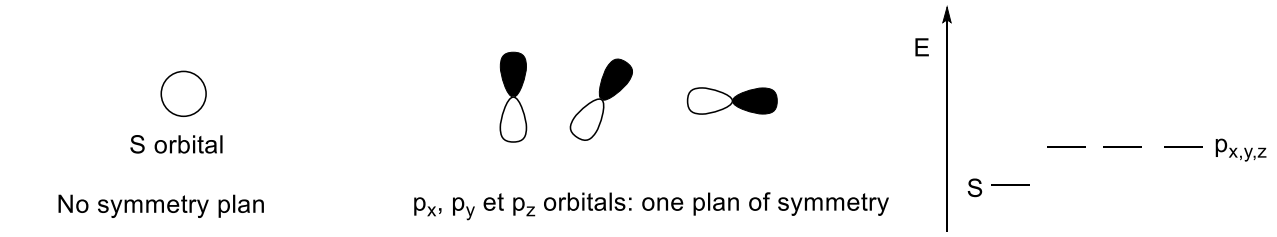
11.4 How to represent orbitals correctly, including their phase?

Litterature: - Ian Fleming, Molecular Orbitals and Organic Chemical Reactions, 2009, Wiley.

In this course on blackboard, the negative and positive phases of orbitals are drawned as empty/filled.

a) atomic orbitals: s, p, d, f

In organic chemistry, is is especially important to know the form, the symmetry and the relative energy of the s and p orbitals. The d and f orbitals are important for inorganic and organometallic chemistry.

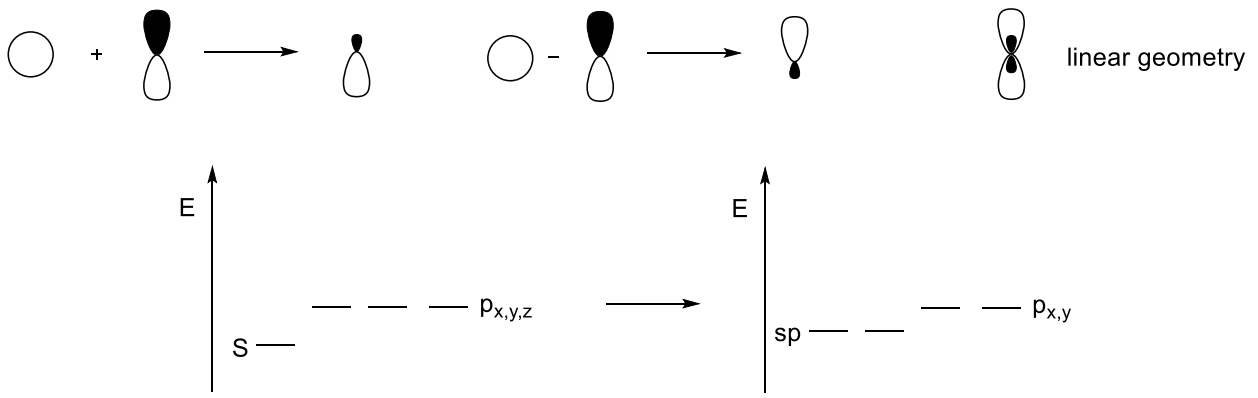


Electrons are more stabilized in s orbitals, as they have higher probability close to the positively charged nucleus. S orbitals are therefore lower in energy.

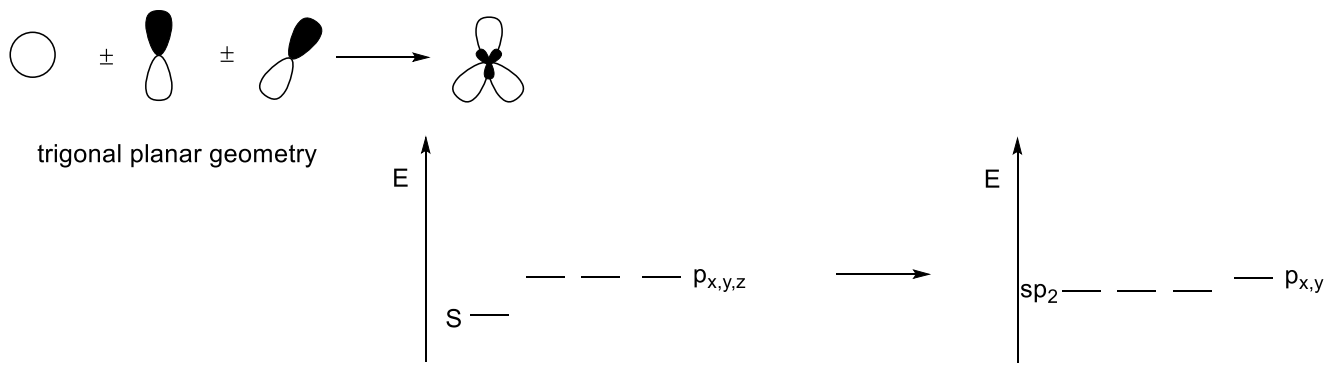
b) Orbital hybridation

The hybridation (= mixing, linear combination) of orbitals is possible especially for second row elements, in particular for carbon. It allows the optimization of orbital interactions in dependence on geometry.

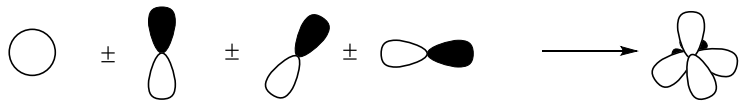
sp orbital: 1 x s ± 1 x p



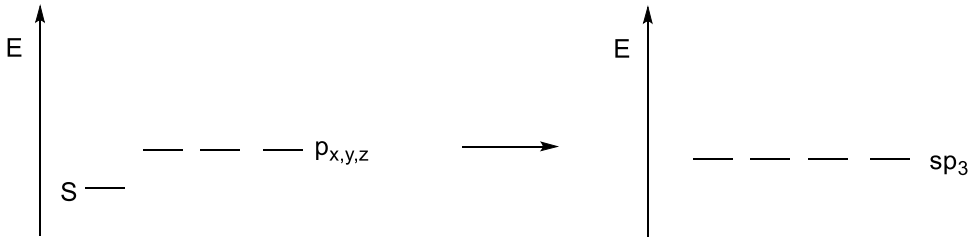
sp_2orbital: 1 x s ± 2 x p



sp_3 orbital: 1 x s ± 3 x p



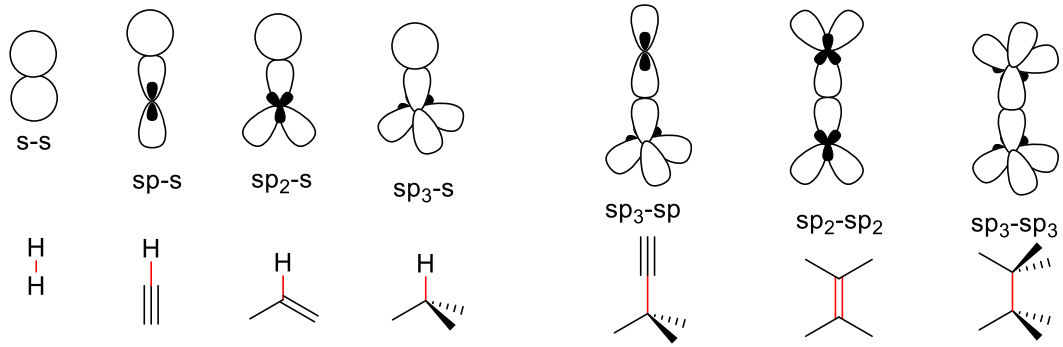
tetrahedral geometry



Interactions between orbitals: pi (π) and sigma (σ) bonds.

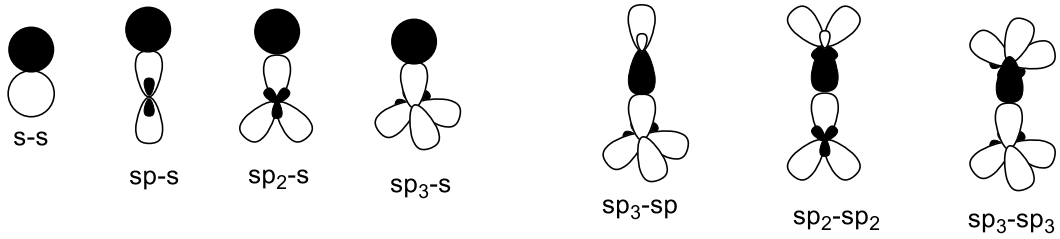
Bonding interaction between orbitals of same phase:

examples



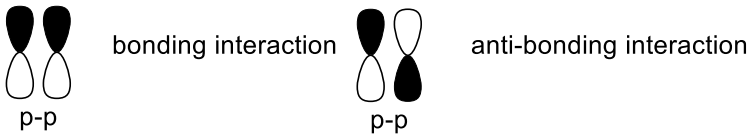
Anti-bonding interactions between orbitals of opposite phase:

examples



For the case sp, sp_2, et sp_3, orbitals not part of the bond are also drawn to show the geometry

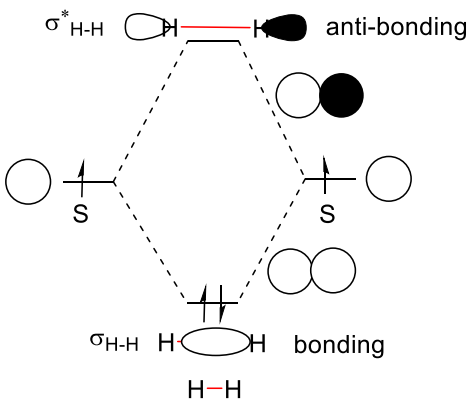
pi bond: phase inversion wiht the symmetry plan along the bond.



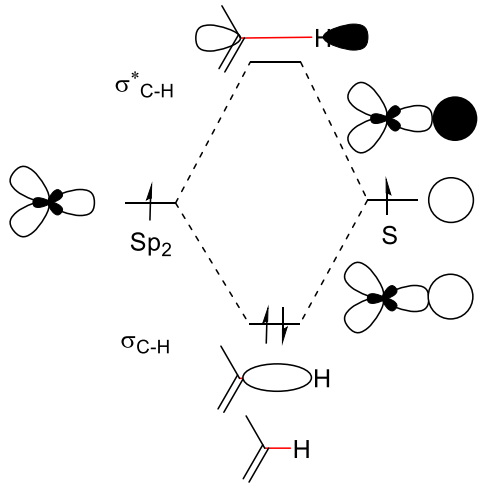
c) Molecular orbitals

Molecular orbitals are obtained by combination of atom orbitals. There are the same number of molecular orbitals as starting atom orbitals, divided in three categories: bonding, non-bonding and anti-bonding. Sigma bonds have no phase inversion along the plan containing the bond. Pi bonds have a phase inversion along the plan containing the bond.

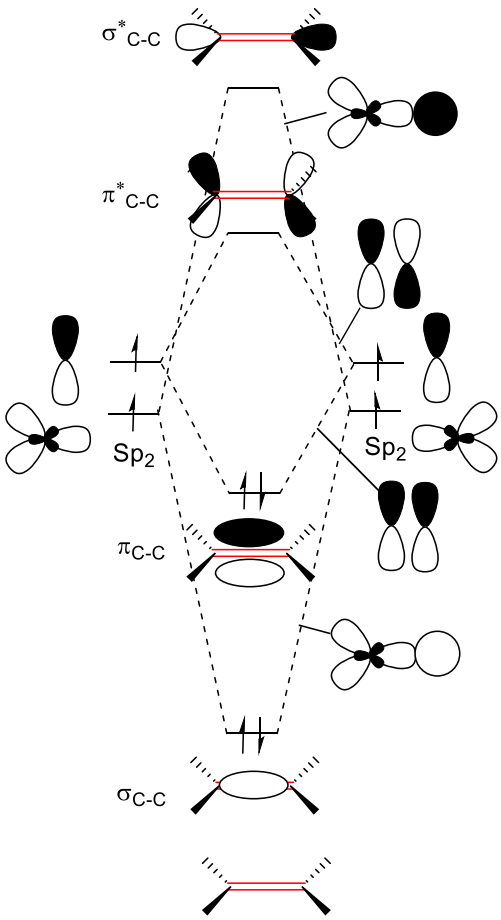
sigma bond H-H



sigma bond Csp_2-H



ethylene: sigma and pi bonds



Atomic orbitals describe the situation before bond formation, molecular orbitals are the final result in the molecule. To have the complete molecular structure, it is necessary to consider all possible combination between atomic orbitals.

Organic chemists often use an approximation: hybridation of the s and p orbitals according to the molecule geometry, then consider sigma bonds along bonds, and pi bonds in conjugated systems. This representation is not always the best, but it is intuitively the easiest to understand, as it is very close to the Lewis model.

Once the molecular orbitals have been formed, secondary interactions between orbitals can be considered (see section 3.4), in particular between the HOMO and the LUMO. These interactions are less strong than in covalent bonds, but they can be highly useful to rationalize the structure and reactivity of the molecules.

Frequent mistakes observed in exercise sessions:

- Mix-up between orbital phases, bonding and anti-bonding orbitals and charges. Take care not to mix these concepts!

- Mix-up between atomic orbitals, interaction between orbitals and molecular orbitals. Often in organic chemistry, only the atomic orbitals are drawn, even in the molecules, which can be confusing. Usually, only interactions between atomic orbitals are shown. This is due to the fact that the final form of molecular orbitals is not easy to predict, except in very simple molecules like ethane or methane.

11.5 Nucleophiles and Electrophiles

Key issue: How to determine the relative nucleophilicity and electrophilicity of functional groups in organic compounds?

This is a fundamental question in organic chemistry, which has unfortunately no simple answer. The reactivity will depend on the structure of the nucleophile aand electrophile, as well as the reaction conditions. Three approaches can be recommended:

1) Use basic concepts of organic chemistry to estimate orbital energy (See Section 3.4). In fact, electrons in the highest energy orbital (HOMO) usually react as nucleophiles. The lowest unoccupied orbital (LUMO) reacts as electrophile. To determine the relative energy of orbitals, it is necessary to know the relative electronegativity of atoms (for example according to Pauling http://fr.wikipedia.org/wiki/%C3%89lectron%C3%A9gativit%C3%A9.) The electrons on the most electronegative atoms will be the lowest in energy, and therefore less nucleophilic (and inversely the empty orbital on more electronegative atoms are more electrophilic). It is important therefore to remember these values. The second essential factor is delocalization. Delocalized electrons are more stable, therefore less nucleophilic. For electrophiles, if it is possible to transfer partially electrons in the empty orbital, the electrophilicity decreases. A few examples can be found in chapter 1.3.1. With only a few concepts memorized, it is possible to analyze many situations in organic chemistry.

2) Use the correlation between basicity and nucleophilicity. This correlation is not perfect, as it describes only the specific nucleophilicity towards protons, which can be different for other electrophiles. The advantage is that many pKa tables are available (See for example the Bordwell scale (http://www.chem.wisc.edu/areas/reich/pkatable/index.htm).

3) Finally, other scales have been established using other electrophiles than proton, for example carbocations. The Mayr group at LMU München has established highly useful scales to compare the reactivity of nucleophiles and electrophiles:

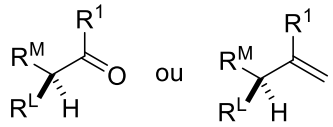
http://www.cup.lmu.de/oc/mayr/CDmayrPoster.html

The last two approaches are more precise, but require access to databases.

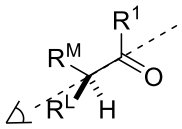
11.6 How to draw in 3D?

It is important to draw cleanly in three dimensions to explain stereoselectivity in organic chemistry. There are no "rules" for drawing: each chemist may have another favorite way to draw the molecule, as long as others can clearly follow his/her reasoning. Herein, a few hints are given to help drawing by proceeding stepwise. Three important systems are described: acyclic pi systems (olefins and carbonyls), cyclohexanes and cyclohexenes.

1) Acyclic Systems

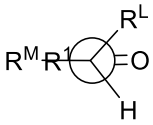


Step 1: Choose the angle of vision



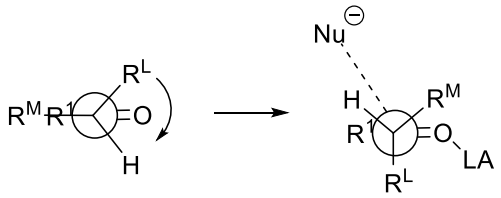
The choice of the point of view is naturally free, but should help the analysis. The stereocenter should be in the axis of vision, allowing to draw more relevant Newman projections.

Step 2: Draw the starting situation in 3D



For acyclic systems, the Newman projection is often one of the best to analyze stereoselectivity issues. The easiest is first to draw the situation given in the question. Often, this is not the most favorable conformation.

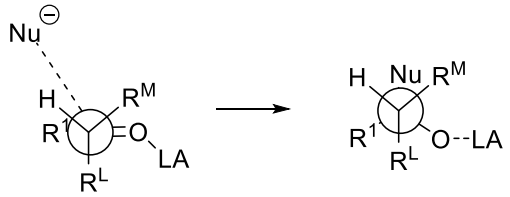
Step 3: Rotate around single bond(s) to analyze conformations



Felkin-Anh

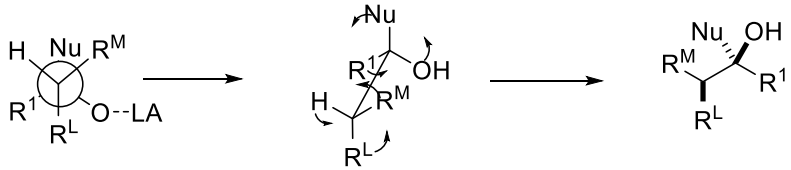
The next step is to rotate single bonds to analyse the possible conformations. In this example, the stereocenter in front has been rotated, but one can also turn around the atom on the back and let the stereocenter fixed. Conformation analysis is then done according to the models seen in the course (eg Felkin Anh) to identify the most favorable transition state for the reaction.

Step 4: Form the bond



Then the bond is formed. In a first step, it is best to keep the same projection to avoid errors

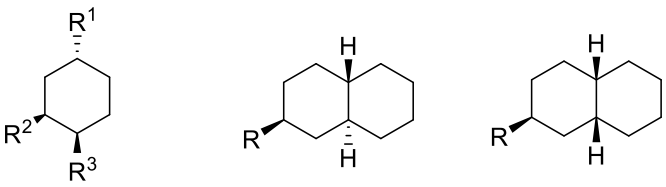
Step 5: Go back form 3D to "2D"



In the last step, it is necessary to go from the Newman projection back to the planar drawing, chosing the drawing style given in the exercise (most often the carbon chain in "zigzag" and the other substituents in the front or back. It is also possible to determine the absolute configuration (R or S) beforehand to avoid errors. As a check, the stereocenters already present in the starting material and which did not react obviously need to stay in the same absolute configuration! In this step, it can be useful to draw a representation in perspective first.

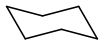
At the beginning, it is good to go slowly and draw each step. With training, it is possible to go faster and do several steps in one.

2) Cyclohexanes



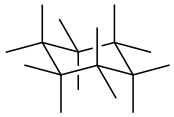
A **B** **C**

Step 1: Draw a chair



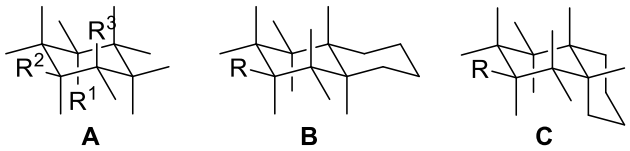
Very often, a chair needs to be drawn for a 6-membered ring. The 6-membered ring can be part of a molecule or represent a transition state. Take care to draw opposite bond in a parallel manner.

Step 2: Draw equatorial and axial substituents



Especially at the beginning, it is important to draw first equatorial and axial substituents in the correct orientation, without including their exact structure. If the orientation is not correct, analysis of stereochemistry will become very difficult.

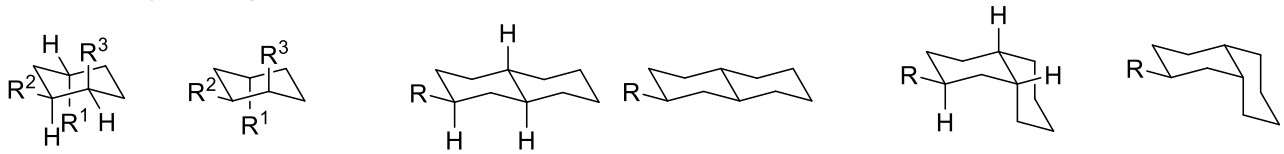
Step 3: Introduce substiuent different from H



A **B** **C**

It is now possible to introduce substituents taking care of having the correct stereochemistry. If there are several rings, it is easier to start with the most substituted one, or the most important one to analyze the selectivity of the reaction.

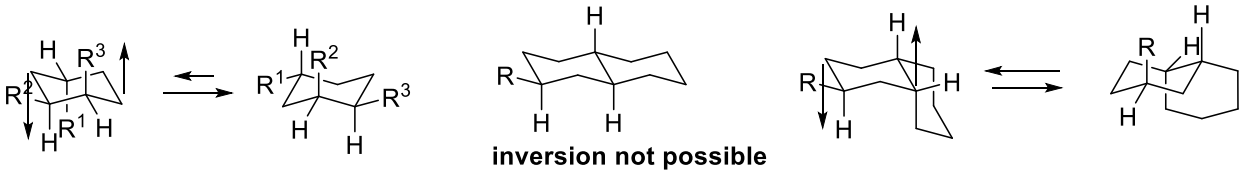
Step 4: Simplify drawing



A **A** **B** **B** **C** **C**

The drawing can be then simplified by drawing protons only on stereocenters, or not at all.

Step 5: Consider chair inversion and analyze

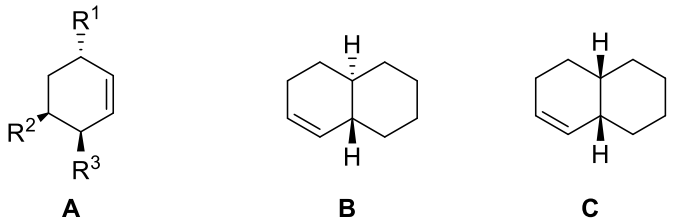


inversion not possible

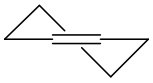
A **A** **B** **C** **C**

A very important step for stereoanalysis with 6-membered ring is the inversion of the equatorial/axial positions. As for acyclic systems, it is very possible that the fist drawn conformation is not the most favored or most reactive one. It is only with all conformations available that the analysis of selectivity can truly begin.

3) Cyclohexenes (also for epoxides and enolates)

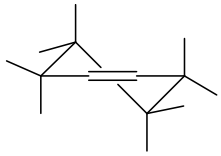


Step 1: draw a half-chair



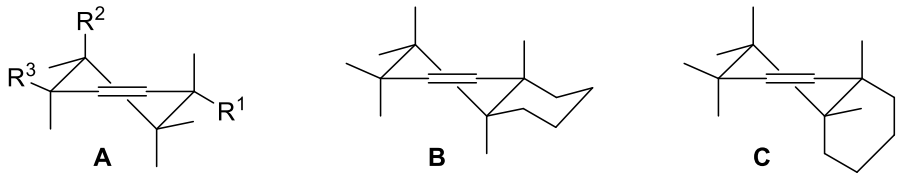
There are several ways to draw a cyclohexene. It is particularly useful to draw a face view in a half-chair conformation.

Step 2: Draw substituents in positions pseudo equatorial/axial



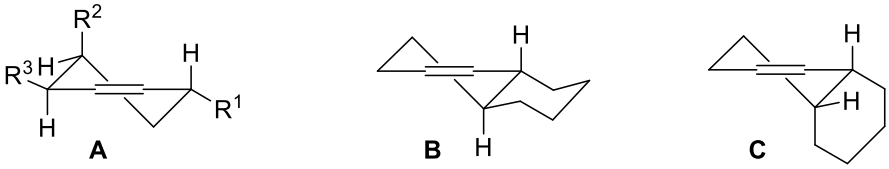
The advantage of the face view is to be able to draw substituents in pseudo equatorial/axial orientations. In this projection, the substituents on the double bond are exactly in the plan of vision, and therefore not drawn.

Step 3: Introduce substituents different from H

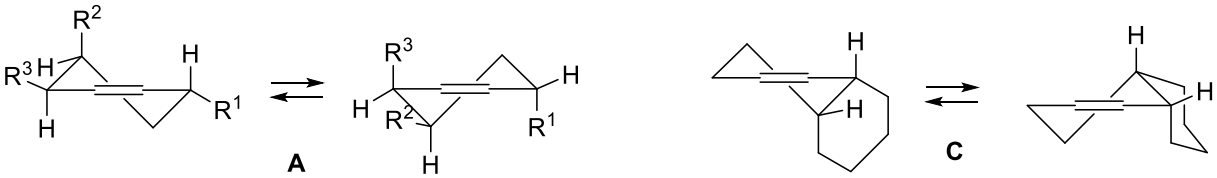


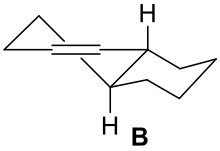
Substituents can now be introduced, taking care of having the correct stereochemistry! If there are several rings, it is often easier to start with the cyclohexene.

Step 4: Simplify the drawing



Step 5: Consider inversion of the half-chair and analyze

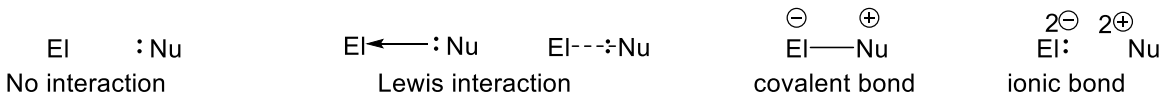




inversion not possible

A very important step for stereoanalysis with 6-membered ring is the inversion of the equatorial/axial positions. As for acyclic systems, it is very possible that the fist drawn conformation is not the most favored or most reactive one. It is only with all conformations available that the analysis of selectivity can truly begin.

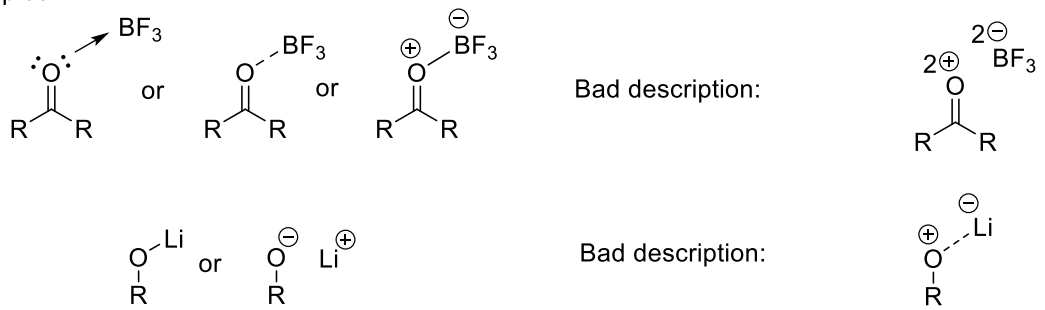
11.7 How to draw polar bonds correctly?



The Lewis way of drawing molecules cannot describe accurately bonding, as there are a broad range of interactions between an electron-rich center (nucleophile, Nu) and an electron-poor center (electrophile, El or E^+). In case of weak Lewis interactions, an arrow or a pointed line is often drawn (dative bond). In this case, the electrons are considered to stay on the nucleophile. When the interaction is stronger, a covalent bond is drawn, with shared electrons on both atoms. At this stage, it is necessary to correct formal charges: negative on electrophile and positive on nucleophile, as one electron has been transferred (assuming neutral nucleophile and electrophile at the start). This is a pure formalism, and give no indication on the real electronic density. The extreme case (rare in organic molecules) is the complete transfer of electrons to give ionic interactions between cation and anion.

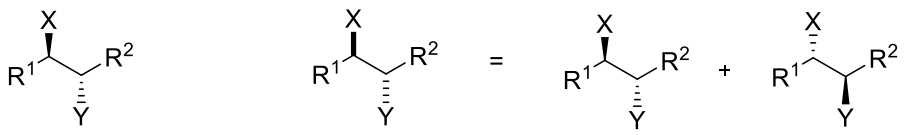
Although certain cases are clear cut, many interactions are in between (strong Lewis acid-base interaction = partial covalent bond, covalent bond with strong ionic character,...). It is important to analyze each situation based on the atom properties (electronegativity, bond strength ...)

examples:



Often not enough care is taken to have correct bonding. For example, a covalent bond is drawn for all types of interactions without care of formal charges. These imprecisions should be avoided.

Stereochemistry



One convention for chiral compound is often used: "triangle bond" = optically pure substance with determined absolute configuration. "rectangle" bond: racemic mixture, only the relative configuration is known.

At the black board, usually only "triangle bonds" are drawn for esthetic reasons, even for racemic mixtures. Please keep in mind that enantiopure compounds can be obtained only if the starting material is enantiopure, or if chiral reagents or catalysts are used.

11.8 In many exercises, a proton is appearing at the end which is not coming from the reaction conditions.

In a broad majority of organic reactions, a work-up with an aqueous solution is done (basic, neutral or acid). Because this is so frequently used, it is not eplicitely drawn below the reaction arrow. A typical example is the reduction of carbonyl compounds, in which a metal-oxygen bond is usually obtained. The latter is then hydrolyzed by water during work-up. In general, you can always assume an aqueous work-up at the end of the reaction, which can explain the origin of "missing protons".

11.9 Is it possible to use other drawing techniques/projections than used in the lecture?

Yes of course, as long as the answer is clear. It is even recommended to everybody to develop his/her own drawing routine, as the self-developed approach is often easier to remember. One should always consider if the chosen projection is well-suited to answer the question. An excessively automatized approach can lead to errors.

11.10 In the lecture notes, there are more information than in class, what is required for the exam?

In fact, due to time limitation all information in the lecture notes cannot be discussed in class. For help, supplementary information has been divised as following:

- Supplementary examples using concepts very close to what has been seen in the class. Thes examples are part of the exam and should be clear with what has been seen in the class.

- General information to be able to make links with other fields (bio-, physical and medicinal chemistry for example). These concepts are not part of the exam, but are important to see connections between courses.

- Supplementary information concerning topics later seen in details at the master level. This is not part of the exam. However, if you join another university for master, these topics may have already been seen at the bachelor level. These important examples are therefore especially important for students intending to leave EPFL for their master.

- Important concepts which could not be seen in course due to time limitations. This will be explicitely explained during the course.

The categories are explicitely shown in the script.

11.11 How to determine stabilization by delocalization? What are substituent effects in conjugated systems?

Before considering substituent effect, it is important to remember which factors make a resonance structure important. The best representation of the molecule is made by the weighted sum of the resonance structures

1) Resonance structures are generated by moving electrons only, without changing connectivity and spacial orientation of atoms.

2) The tridimensional structure of the molecule needs to fit the proposed resonance (for example a double bond requires a planar structure

3) The octet rule needs to be respected for the atoms of the second row (but not for higher rows like P, S, ...)

4) Number of bonds should be maximized

5) Charges should be minimized

6) Negative charges should be on more electronegative atoms and positive charges on more electropositive atoms

7) Cyclic planar arrangements of 4n + 2 electrons are favored (aromaticity)

Rules 1-3 are strict, all resonance structures should follow them.

Rules 4-7 allow to determine the relative importance of the possible resonance structures.

When all factors favor one structure, it is easy to determine the relative importance, but sometimes it is not the case. However, the reactivity can be often better rationalized using a minor resonance structure, in particular charged ones. In conjugated system, donor and acceptor functional groups are able to add or remove electrons from conjugated systems, leading to resonance structures according to rule 6. Typical donors are alcohols, ethers, amines, thiols, halogens. Typical acceptors are esters, ketones, aldehydes, cyanides, nitro groups, .. Of course, the groups can have an effect only if rules 1-3 are respected.

For analyzing a reaction, it can be important to analyze resonance structures on the starting material (influence on the partial charges induced by electronegativity, which can change the strength of nucleophiles and electrophiles), the product and especially reactive intermediates (carbocations, anions, radicals, ...). The Hammond postulate tell us that reactive intermediates are similar to the transition state. Their stabilization is therefore important to lower the transition state and facilitate the reaction.

11.12 How to determine the energy of orbitals

Answer:

1) Estimation of the relative energy of orbitals

The estimation of the relative energy of orbitals in simple organic molecules is based on electronegativity. The electronegativity is defined by the electron affinity of atoms (in general, it increases closer to the full octet and for small atoms).The higher the electronegativity, the more stabilized the electrons, the lower the orbital energy. By extension, if a molecular obital (a bond) contains an electronegative atom, its energy is lower (see the lower relative energy of sigma C-O bonds compared to C-C bonds in the course).

2) Orbital interactions

Three factors are essential for orbital interactions

A) The number of electrons: Ideally, all binding orbitals are full and all anti-bonding orbitals are empty. This can be for example obtained by the interaction of a full orbital (2 electrons) with an empty one.

B) Geometrical overlap: The overlap of orbitals in space is essential for their interaction. The largest the overlapping volume, the highest the stabilization. In this way, electrons are more delocalized, and therefore stabilized.

C) The energy difference of orbitals, estimated according to 1). The interaction of orbitals of the same energy is ideal. The largest the difference in energy, the weakest the interaction. Combining rules A and C tell us that the most important interactions are between the HOMO (Highest Occupied Molecular Orbital) and the LUMO (Lowest Unoccupied Molecular Orbital), or in general between FMOs (Frontiers Molecular Orbitals). The interaction between HOMO and LUMO gives two new HOMO and LUMO orbitals. The new HOMO is more stable and the new LUMO less stable. Overall, it is therefore important to have a fit both in geometrical overlap and energy.

The most important interaction between orbitals in organic chemistry is the covalent bond (80-110 Kcal/mol energy for sigma bonds). The hybridation model (see question 11.4), although not very accurate from the thoeretical point of view, allows to rationalize most effects in organic chemistry. The rules in 2) allows us to classify the reactivity of the different types of bonds: sigma < pi < lone pair. The lower stabilization of pi bond can be explained by the less ideal overlap of orbitals in the pi bonds.

In this course, we usually start directly from the molecular orbitals describing the covalent bonds, and consider then smaller secondary effects between bond orbitals and lone pairs orbitals. These effects are much smaller (for example 1.2 Kcal/mol for the anomeric effect), but essential to understand the structure and reactivity of organic molecules. To understand if an interaction is important or not, it is needed to be able to order them according to the rules above.

The orbital model works very well for covalent bonds, but for more ionic bonds, stablization by Coulomb effects (electrostatic + -) becomes more important.

11.13 What is an axis of chirality?

Answer:

Some molecules have no stereocenters, but have an axis of chirality.

The term of chirality axis is often used in a confusing way. In this course, it has been used for the axis of bond rotation used to give the absolute configuration (R or S). It contains the higher number of bonds and corresponds to the distortion in one dimension which leads to the loss of the tetrahedral symmetry. Two examples are the allenes and the binaphthyls. For allenes, the chirality axis is on the two double bonds. For binaphthyls, it is on the bond linking the two aromatic systems, for which the rotation is hindered.

It is important not to mix up the chirality axis with the C2-axis of symmetry often present in these molecules.