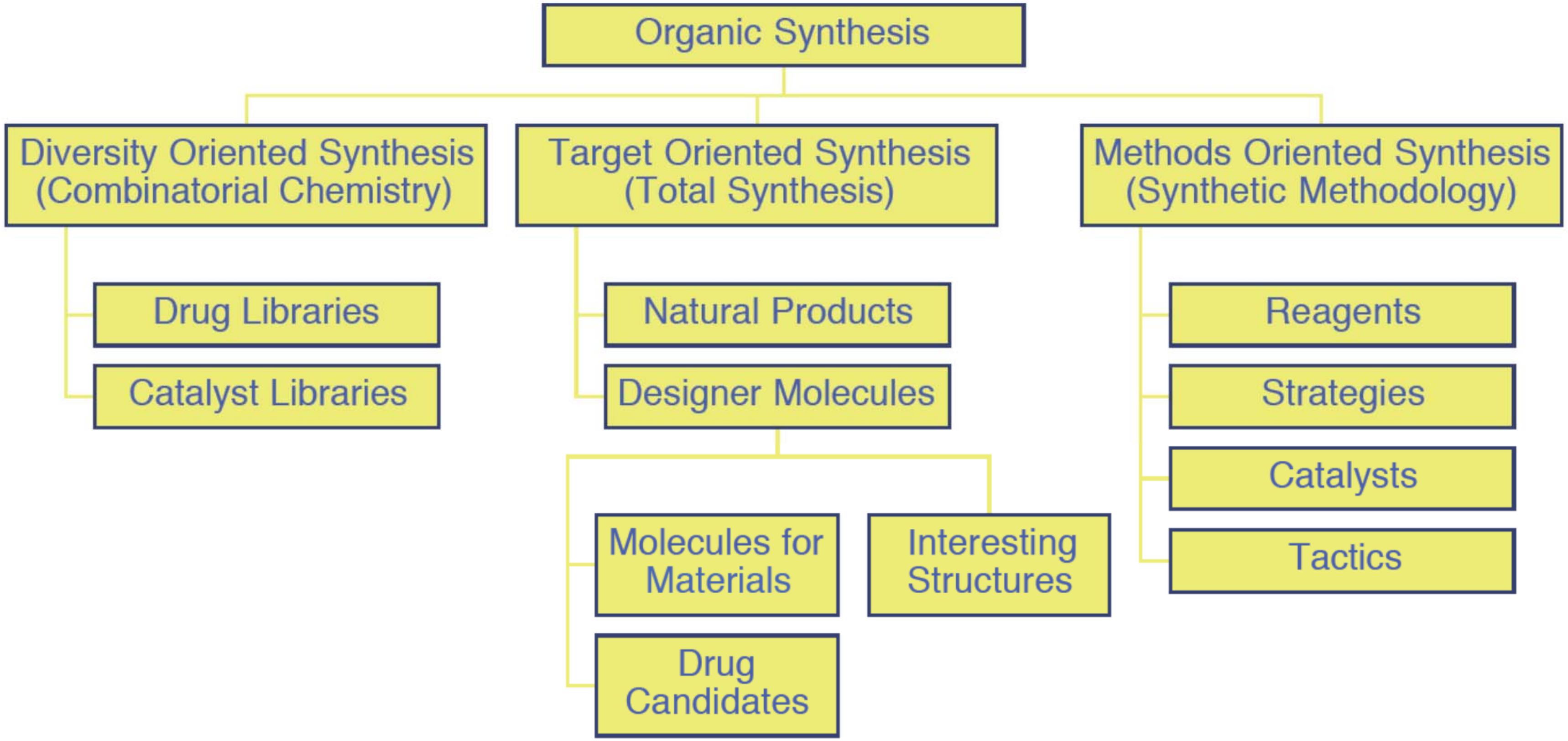
What is Organic Synthesis?

- Sir John W. Cornforth defines ***chemical synthesis*** as:

  "the intentional construction of molecules by means of chemical reactions"
- "Intentional" stress the key planning aspects of every synthesis exercise
- Chemical synthesis is divided into two branches
  - Inorganic Synthesis
  - Organic Synthesis
- Organic Synthesis typically embraces
  - Small organic molecules
  - Large biomolecules

- Sir John W. Cornforth
  - born in Australia in 1917
  - became deaf as a child
  - Univ. of Sussix, GB
- 1975 Nobel Prize in Chemistry
  - for stereochemistry of enzyme reactions
  - shared with V. Prelog

Organic Synthesis Classifications

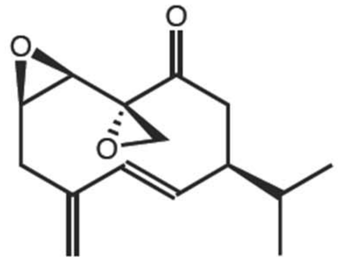


Organic Synthesis

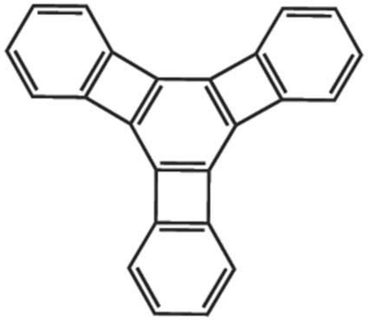
- Diversity Oriented Synthesis (Combinatorial Chemistry)
  - Drug Libraries
  - Catalyst Libraries
- Target Oriented Synthesis (Total Synthesis)
  - Natural Products
  - Designer Molecules
    - Molecules for Materials
    - Drug Candidates
    - Interesting Structures
- Methods Oriented Synthesis (Synthetic Methodology)
  - Reagents
  - Strategies
  - Catalysts
  - Tactics

Why Synthesize Organic Molecules?

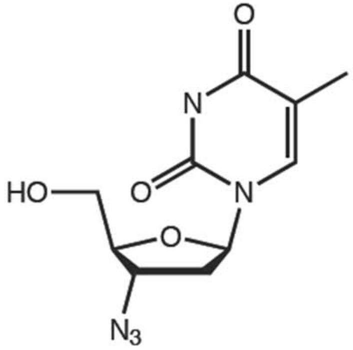
- To prove their structure
  - periplanone B was proved by synthesis



- To understand their structure/function
  - Discover new drugs
  - Interesting molecules



- To produce them for sale
  - AZT (Retrovir®) and other anti-HIV drugs are made by synthesis



- To discover new reactions, strategies
- Because they are there
  - The challenge!

Facets of Organic Synthesis

- Rigor
    - Both intellectual and physical
- Coupling with other areas of chemistry
    - Structure
    - Mechanism
    - Spectroscopy
    - Separation Science
- The chance to directly impact human health and well being
- Coupling with other disciplines
- The ability to create
    - Most other areas of science study nature, they do not create new entities
- Geometric, artistic, esthetic perception
    - The beauty of molecules
    - The beauty of a great synthesis
- Unlimited complexity
- Endless variety
- Challenge up to the impossible
- Sheer excitement
    - When that key reaction works!
    - When you finish a synthesis!

A Good Synthesis Should:

- Start from readily available materials
- Be brief
- Use efficient and selective reactions
- Avoid extreme or unsafe reagents or reactions
- Be flexible
  - Have a Plan B if Plan A does not work
- Be adaptable
  - Very important for chemical discovery
- Be “green” and cost effective
  - Very important for chemical production
- Be innovative, elegant, even artistic

To Plan a Good Synthesis, You Need to

- Know Reactions
- Know Reactions
- Know Reactions
  - March, Advanced Organic Chemistry; a reaction bible
  - LaRock, Comprehensive Organic Transformations; how to get from A to B
  - Fieser & Fieser and the Encyclopedia of Reagents for Organic Synthesis (EROS); what is the right reagent for the job? How should you use it?

Name Reaction !!!!

- Understand
  - Chemical reactivity
  - Functional group interactions
- Be comfortable with organic reaction mechanisms and arrow pushing
- Understand and be able to extend principles of
  - Conformation
  - Stereochemistry

Selectivity: The Key to Synthetic Efficiency

- Chemoselectivity
  - The reaction of one functional group in preference to others
- Regioselectivity
  - The formation of one regioisomer in preference to others
- Diastereoselectivity and Enantioselectivity
  - The formation of one stereoisomer in preference to others
- Atom economy

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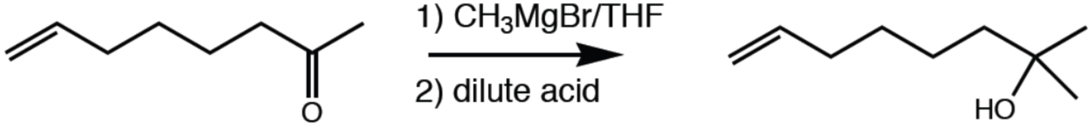
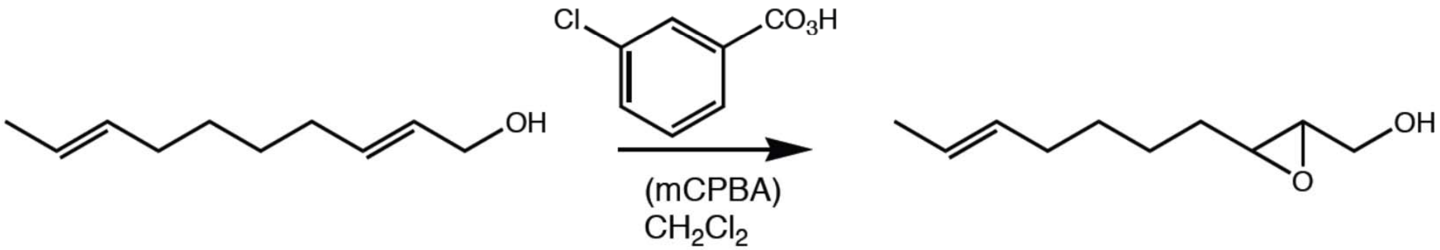
Chemoselective Reactions

- An easy chemoselective reaction



  - The nucleophile adds to the polarized C=O, not C=C

- A more difficult chemoselective reaction

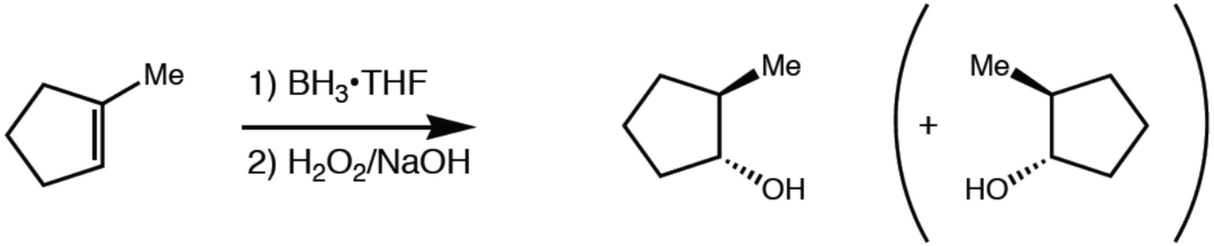


  - The allylic alcohol directs the epoxidation to the nearby C=C
  - The reaction is diastereoselective (trans only), not enantioselective

- Chemoselectivity
  - The reaction of one functional group in preference to others
- Regioselectivity
  - The formation of one regioisomer in preference to others
- Diastereoselectivity and Enantioselectivity
  - The formation of one stereoisomer in preference to others

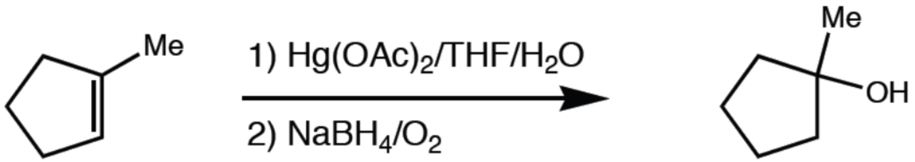
Regioselective Reactions

- This reaction is regioselective and diastereoselective, but not enantioselective



by implication

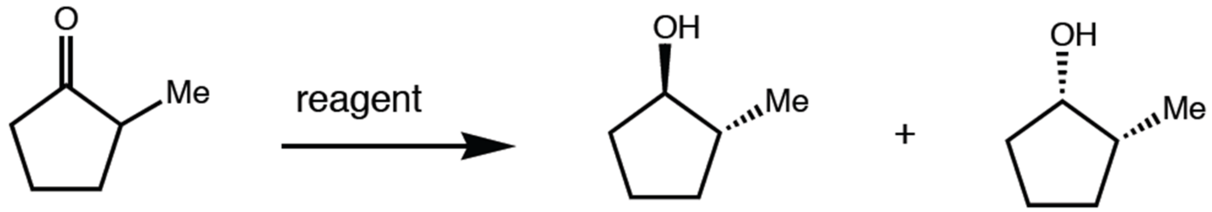
- This reaction gives the other regioisomer. There is no issue of stereoselectivity



- Chemoselectivity
  - The reaction of one functional group in preference to others
- Regioselectivity
  - The formation of one regioisomer in preference t others
- Diastereoselectivity and Enantioselectivity
  - The formation of one stereoisomer in preference to others

Stereoselective Reactions

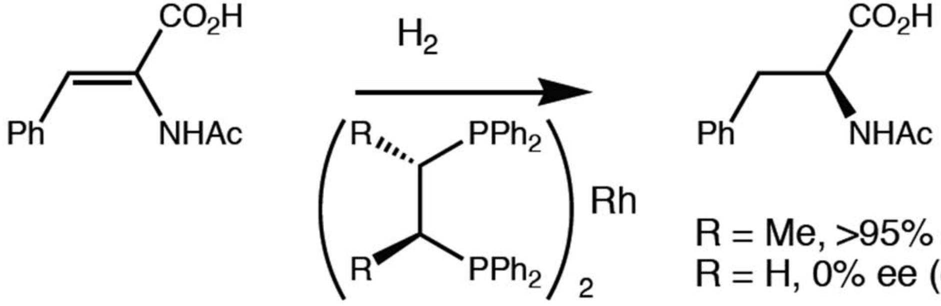
- These reactions are diastereoselective, but the starting ketone is racemic



LiEt$_3$BH is called L-Selectride

reagent	*trans/cis*
NaBH$_4$	74/26
LiEt$_3$BH	2/98

- This reaction is enantioselective



R = Me, >95% ee (chiraphos)
R = H, 0% ee (dppe)

Chemoselectivity :

functional groups of the same type

Regioselectivity :

position in a molecule

Stereoselectivity :

stereoisomers – cis/trans, exo/endo, etc

Enantioselectivity :

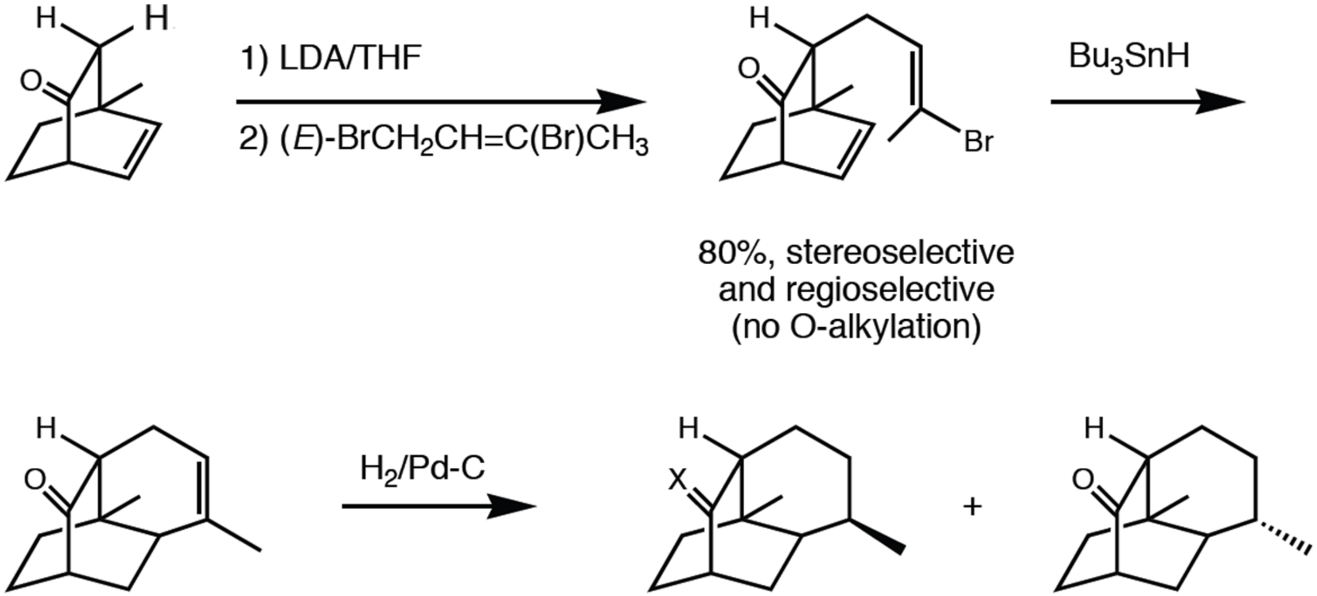
stereoisomers – absolute configuration

Specificity :

complete selectivity - chemo-, regio-, stereo-

- Chemoselectivity
  - The reaction of one functional group in preference to others
- Regioselectivity
  - The formation of one regioisomer in preference to others
- Diastereoselectivity and Enantioselectivity
  - The formation of one stereoisomer in preference to others

Selectivity in Action: Seychellene



80%, stereoselective
and regioselective
(no O-alkylation)

70%, regioselective
and chemoselective
(no addition to C=O)

85/15

X = O, nor-seychellone
X = CH_2, seychellene

Scope and Atom Economy

- The Wittig reaction has a broad scope and is often stereoselective, but it ranks low in atom economy

$$R^1{-}CHO + Ph_3P{=}CHR^2 \xrightarrow{\hspace{2em}} R^1CH{=}CHR^2 + Ph_3P{=}O$$

1 equiv of base is needed to generate the ylide

MW = 278

- The alkene metathesis reaction has a narrow scope and gives isomeric mixtures, but ranks high in atom economy

$$R^1CH{=}CH_2 + R^2CH{=}CH_2 \xrightarrow{\text{catalyst}} R^1CH{=}CHR^2 + CH_2{=}CH_2$$

MW = 28

Classifications of Synthesis -01

Linear synthesis :

- The target compound is made through a series of linear transformation

A → B → C → D

Suppose the yield is 50% for each reaction,
the overall yield of D is only 12.5% from A.

Convergent synthesis :

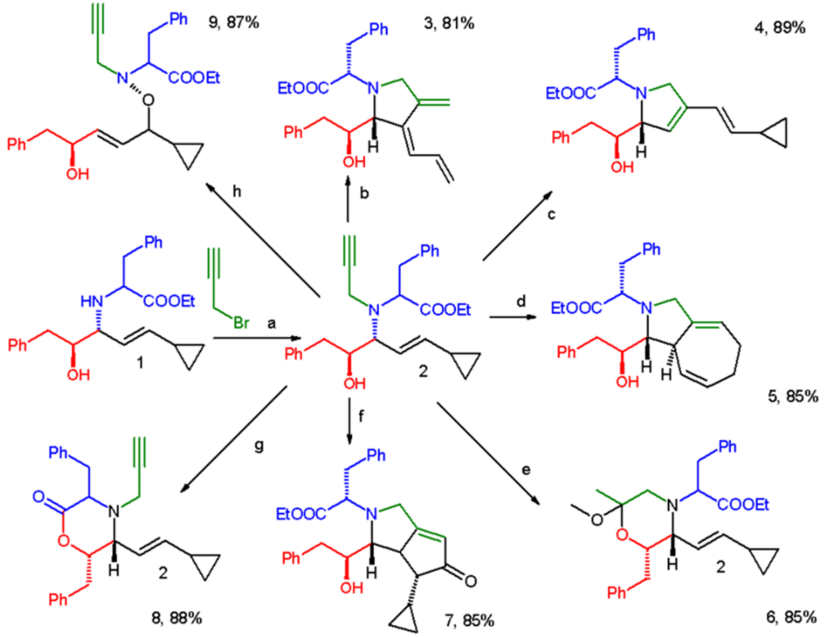
- Individually made compounds are convergently brought together to make the target compound
- Convergent synthesis is applied in the synthesis of complex molecules and involve **fragment coupling** and **independent synthesis**

A → B (50%)
C → D (50%)
B + D → E (25%)
Suppose the yield is 50% for each reaction,
the overall yield of E (25%) looks much better.

Classifications of Synthesis -02

Divergent synthesis :

- A **divergent synthesis** is a strategy with the aim to improve the efficiency of chemical synthesis.
- It is often an alternative to convergent synthesis or linear synthesis.
- In one strategy divergent synthesis aims to generate a library of chemical compounds by first reacting a molecule with a set of reactants.
- This methodology quickly diverges to large numbers of new compounds



Classifications of Synthesis -03

Combinatorial synthesis :

- The characteristic of combinatorial synthesis is that different compounds are *generated simultaneously under identical reaction conditions in a systematic manner,* so that ideally the products of all possible combinations of a given set of starting materials (termed building blocks) will be obtained at once.

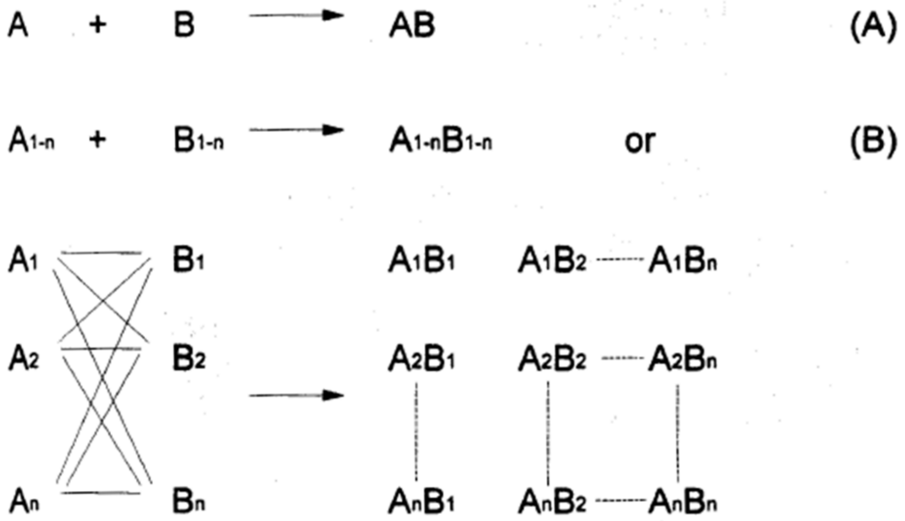
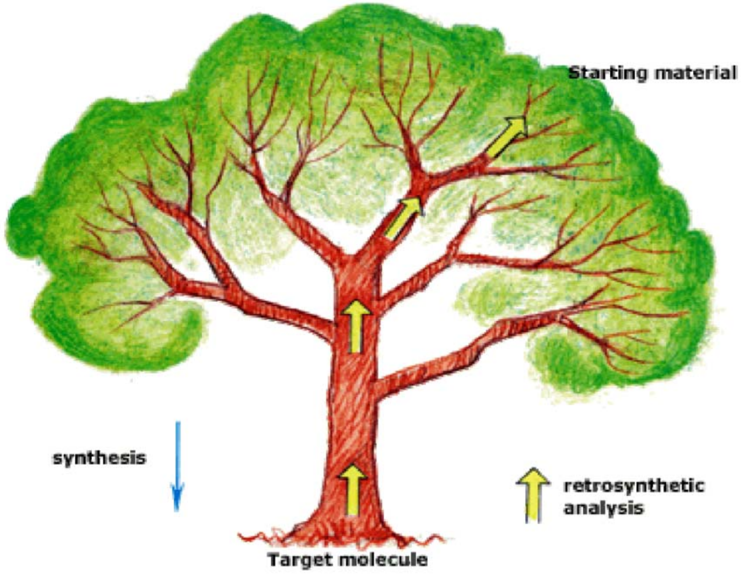


Figure 1.2. (A) In general, in a conventional synthesis one starting material A reacts with one reagent B resulting in one product AB. (B) In a combinatorial synthesis different building blocks of type A (A1–An) are treated simultaneously with different building blocks of type B (B1–Bn) according to combinatorial principles, i.e. each starting material A reacts separately with all reagents B resulting in a combinatorial library A1–nB1–n.

Retrosynthesis

Retrosynthesis analysis is a problem solving technique for transforming the structure of ***synthetic target molecule*** (***TM***) to a sequence of progressively simpler structures along the pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. (E. J Corey)

The primary goal of retrosynthetic analysis is the reduction of structural complexity.



Molecular complexity

(1) Molecular size
(2) Cyclic connectivity or topology
(3) Element or functional group content
(4) *Stereocenter* content/density
(5) Centers of high chemical reactivity
(6) Kinetic (thermal) instability.

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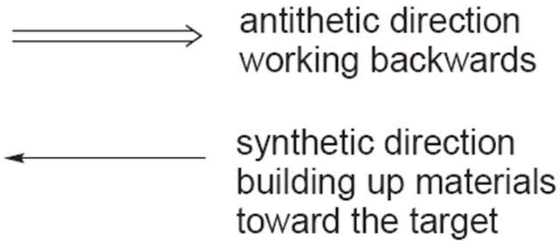
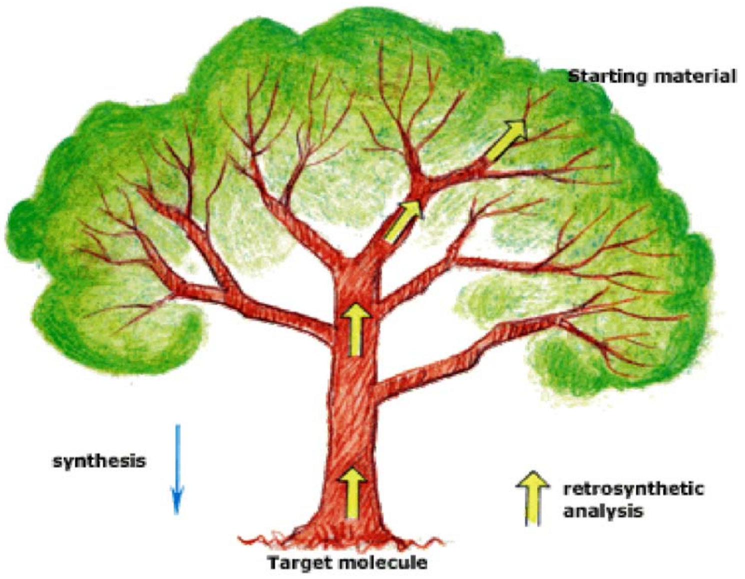


antithetic direction
working backwards

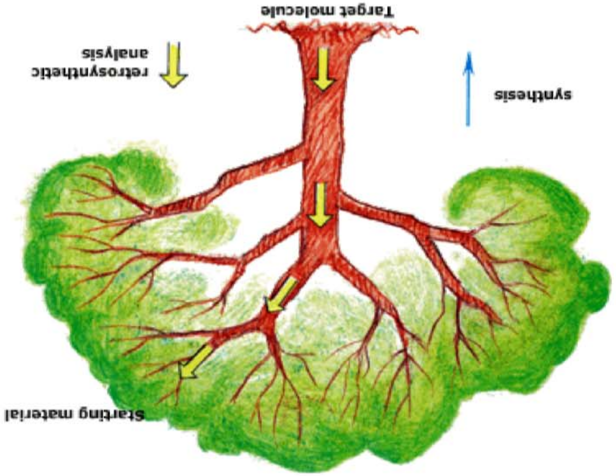
synthetic direction
building up materials
toward the target



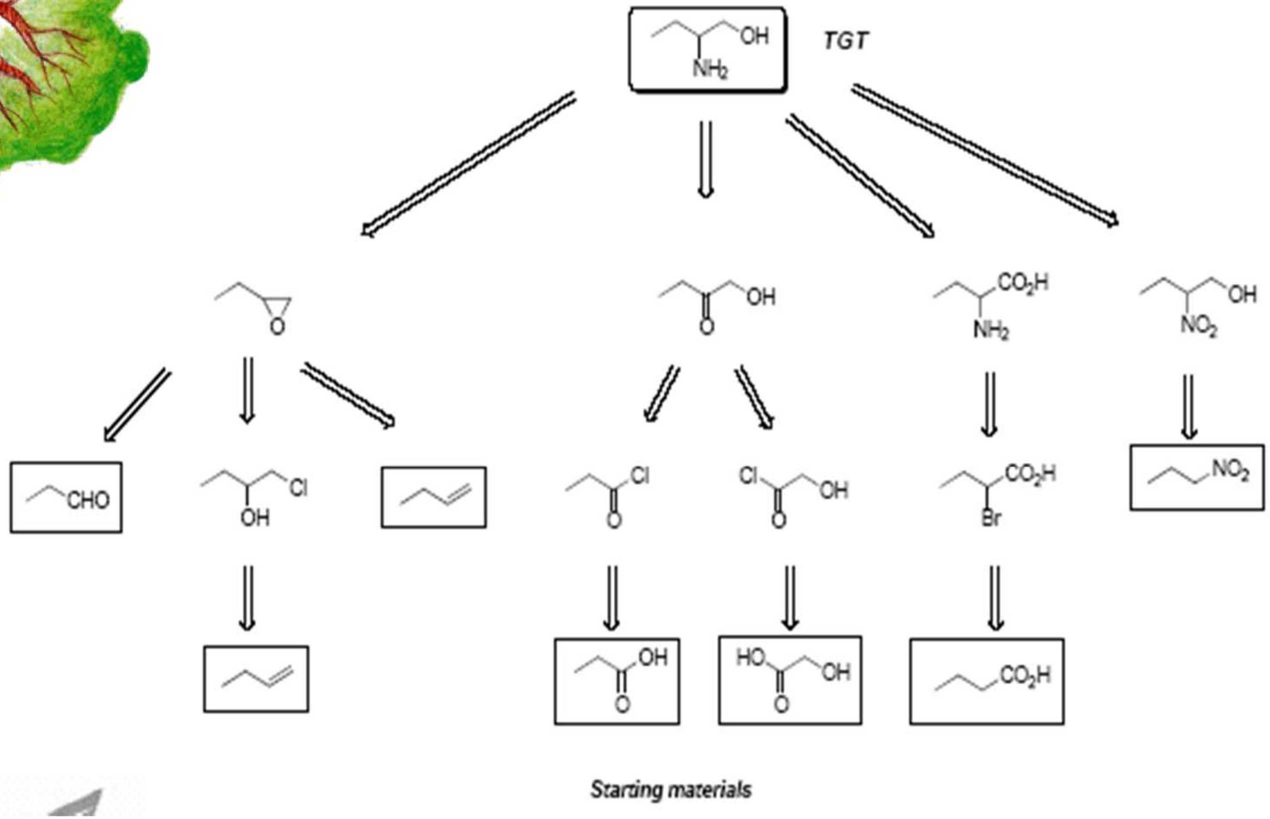
- ***Synthetic Strategies***: Choosing the way along the retrosynthetic tree, synthetic planning.

- ***Synthetic Tactics***: How a specific bond or set of bonds at a given site can be efficiently created.

Retrosynthesis



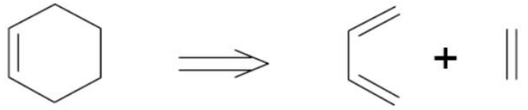
Synthesis Tree - Example



Vocabulary of Retrosynthesis

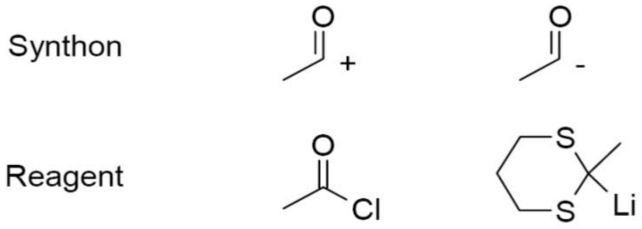
- ***Disconnection***: the reverse operation to a synthetic reaction, the imagined cleavage of a bond
- ***Functional Group Interconversion (FGI)***: the process of converting one functional group into another by substitution, addition, elimination, reduction, or oxidation.

Retron – The minimal substructural element in a target structure which keys the direct application of a disconnection to generate a synthetic precursor. For instance, in Diels-Alder reaction the ***retron***, a minimal keying element, is 6-membered ring with a π-bond:



Reagent – compound used in practice for a synthon.

Synthon – An idealised fragment, usually cation or anion, resulting from a disconnection. May or may not be an intermediate in the corresponding reaction.



Synthetic Strategies

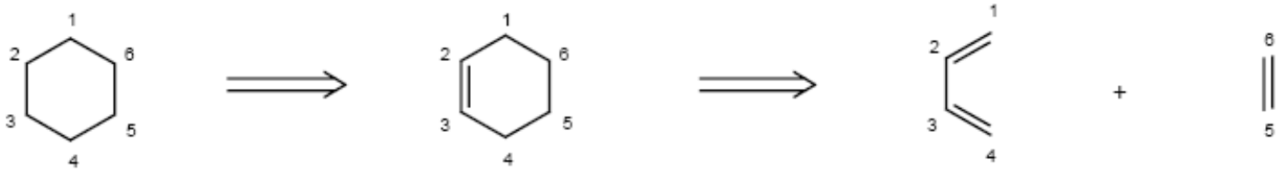
Categorized by Corey

1. Transform-based strategies:
2. Structure-goal strategies:
3. Topological strategies:
4. Stereochemical strategies:
5. Functional group-based strategies:

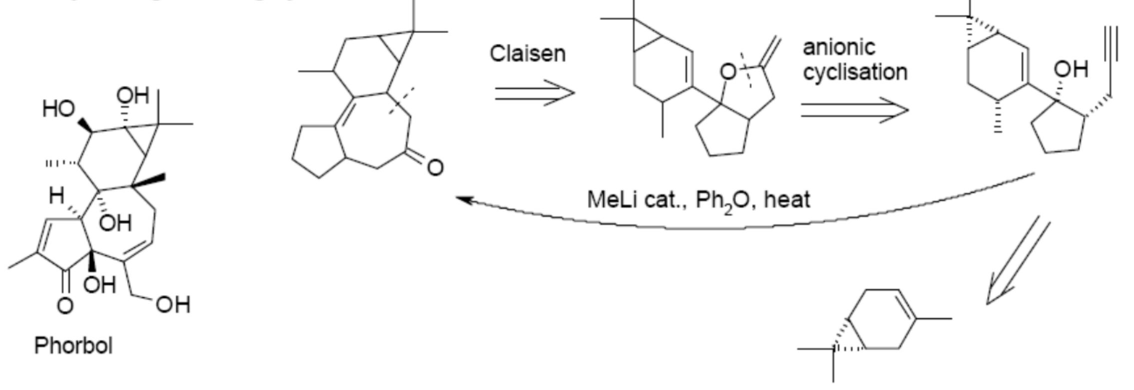
- the *concurrent use of as many of these independent strategies as possible*.
- Such parallel application of several strategies not only speeds and simplifies the analysis of a problem, but provide superior solutions.

Two main Synthetic Strategies -01

1. Transform-based strategies:
    - long range search or look-ahead to apply a powerfully simplifying transform (or a tactical combination of simplifying transforms to a TGT) with certain appropriate keying features.
    - The retron required for application of a powerful transform may not be present in a complex TGT and a number of antithetic steps (subgoals) may be needed to establish it.



Tetracyclic Tigliane ring system



Phorbol

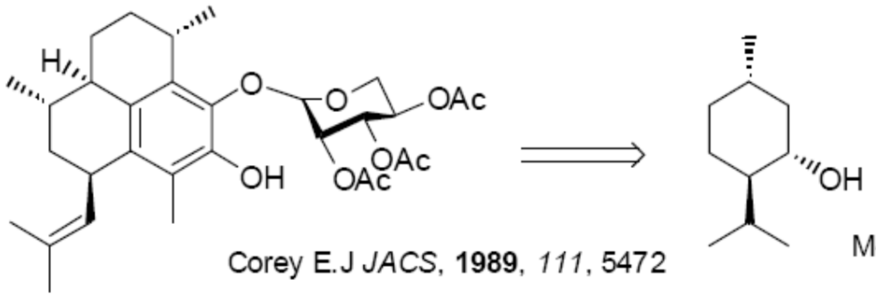
3-Carene

Ovaska TV *et al*, *Org. Lett.* **2001**, *3*, 115

Two main Synthetic Strategies -02

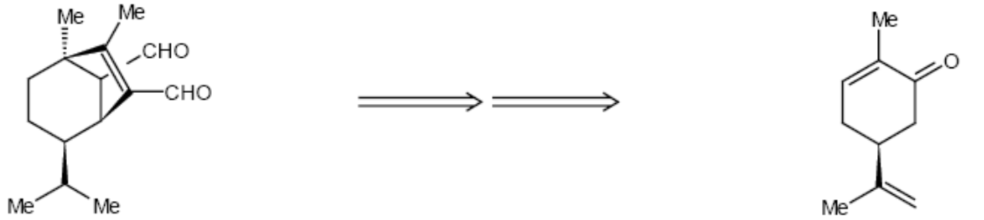
2. Structure-goal strategies:
   - directed at the structure of a potential intermediate or potential starting material.
   - Such a goal greatly narrows a retrosynthetic search and allows the application of bidirectional search techniques.

Pseudopterosin A



Corey E.J *JACS*, **1989**, *111*, 5472

Menthol



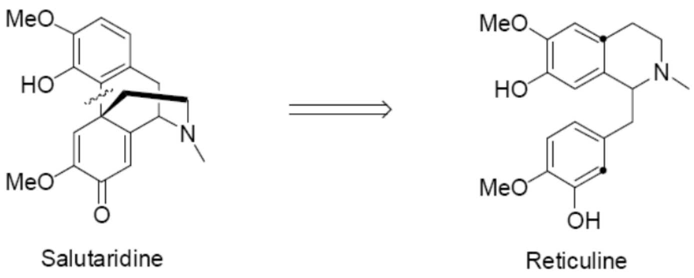
Helminthosporal (105)

(+)-Carvone (106)

Synthetic Strategies -other

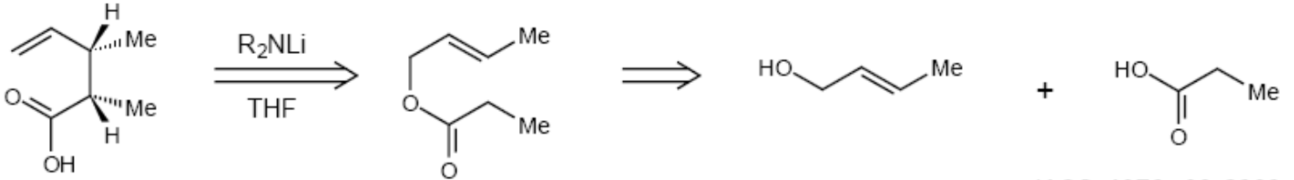
3. Topological strategies:

Recognize strategic bonds and remove them in retrosynthetic direction

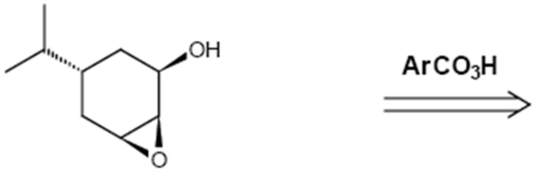


4. Stereochemical strategies:

Strategies which remove the stereocenters



JACS, **1976**, *98*, 2868.

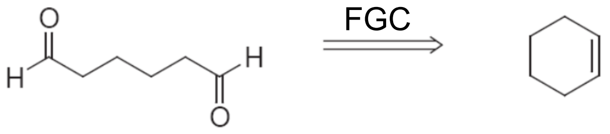


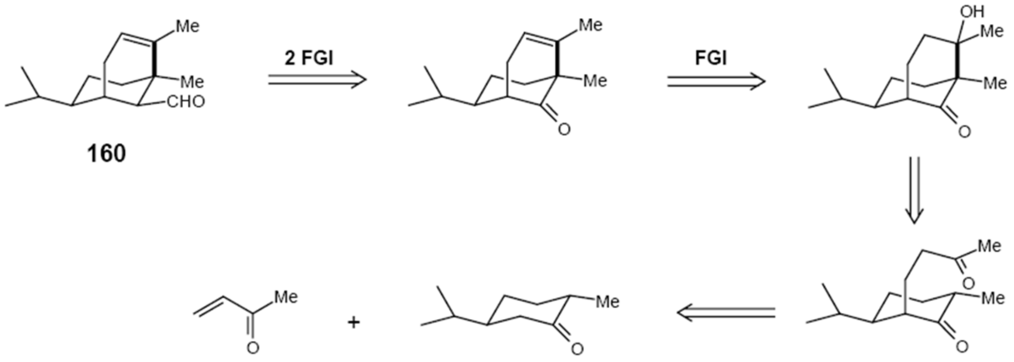
Synthetic Strategies -other

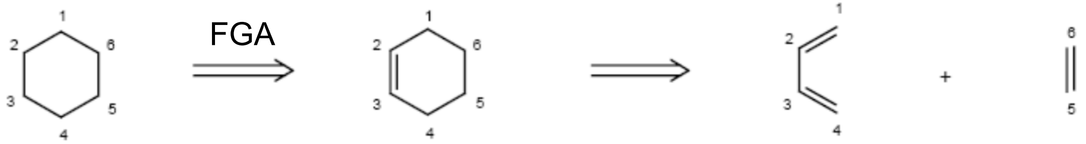
5. Functional group-based strategies:

· ***Functional Group Interconversion (FGI)***: the process of converting one functional group into another by substitution, addition, elimination, reduction, or oxidation.

- •Functional group interconversion (FGI)
- •Functional group combination (FGC)
- •Functional group addition (FGA)







Design and Execution of a Synthesis

Steps in Design and Execution of a Synthesis

1. Selection of a problem
2. Selection of goals to be achieved through synthesis
3. Simplification
4. Generation of synthetic pathways
5. Evaluation of synthetic pathways → assignment of merit
6. Selection of specific reactions and reagents for each step
7. Selection of specific reaction conditions and design of experiments
8. Execution and analysis of results

Retrosynthesis

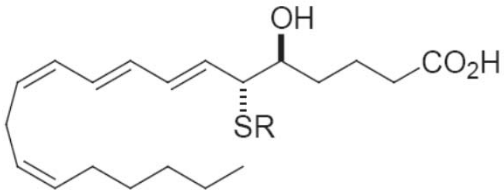
Design and Execution of a Synthesis

1. Selection of a problem

- One of the most important considerations.
- Should be the first consideration, independent of all others. This assures that it is a problem that you want to address.
- Recognize the time and effort involved in the actual conduct of the synthesis.
- This will depend on the setting, circumstances and interests of the individual.

Design and Execution of a Synthesis

2. Selection of goals

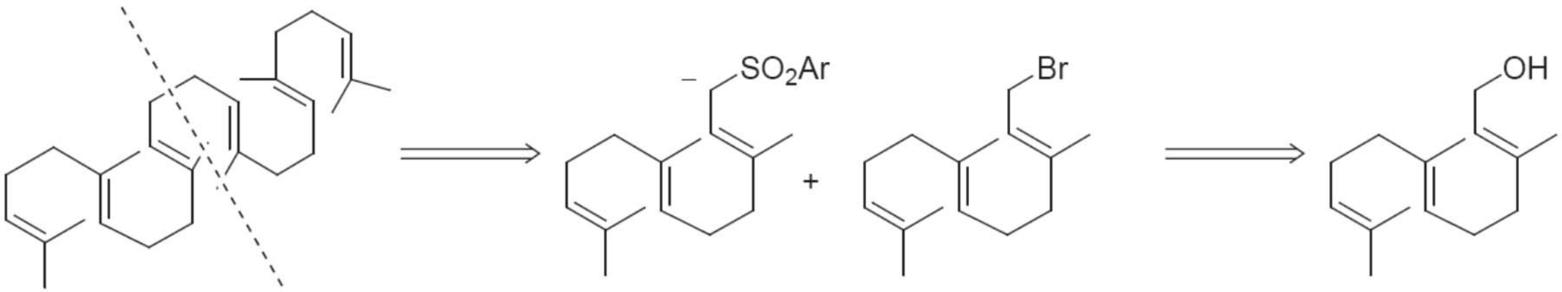


a. Structure determination of SRS-A: the initial intent. The R group on the thiol was not known, so the first synthesis was designed to facilitate the introduction of different R groups permitting a comparison with the endogenous product to confirm the structure.
b. Once the structure was determined, objectives included providing sufficient material for biological testing.
c. Determination of absolute configuration - the chiral centers were unambiguously established through synthesis.
d. Development of a route amenable to analogue preparation: want to inhibit the action of SRS-A (an antagonist development).
e. Biomimetic synthesis (follows the biosynthetic generation of materials) - might constitute a simplification.
f. Development of commercially viable processes.
g. Demonstration of improvements in current methodology.
h. Novel, interesting structures.
i. Common intermediate for a class of structures (divergent synthesis).
j. Mechanism of action of a class of compounds - devise partial structures of the parent compound to define the mechanism of action.
k. Chemistry of a class of compounds.
l. Properties of a class of compounds.

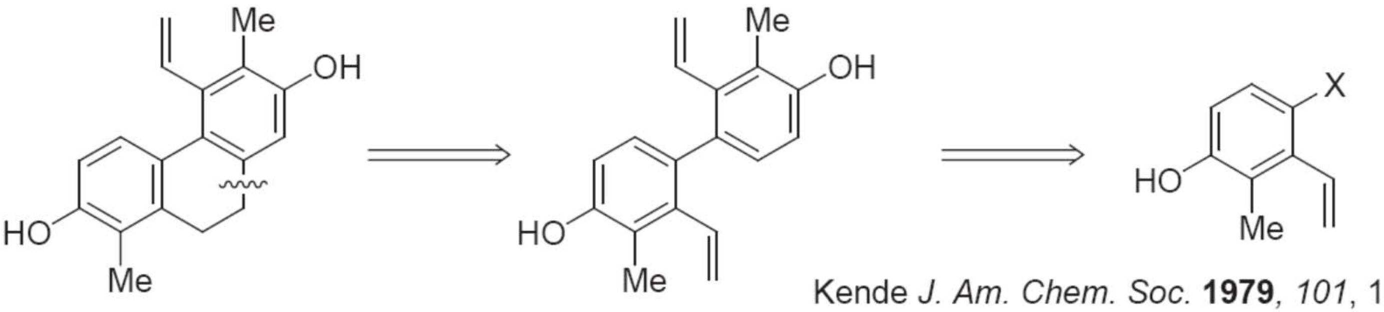
Design and Execution of a Synthesis

3. Simplification and Background Chemistry

a. Recognition of symmetry elements present in a structure.



- combines two halves prepared from a common intermediate at the end of the synthesis.
- Grieco *J. Org. Chem.* **1974**, *39*, 2135.



Kende *J. Am. Chem. Soc.* **1979**, *101*, 1857.

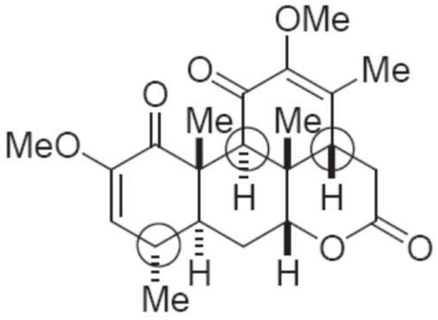
Design and Execution of a Synthesis

3. Simplification and Background Chemistry

b. Background Chemistry

Information available in the literature will provide very important insights required to effectively design a synthesis.

e.g., Quassin



Grieco *J. Am. Chem. Soc.* **1980**, *102*, 7586.

- 7 stereocenters but 3 are epimerizable centers and the natural product possesses the most stable configuration, so a synthesis without stereocontrol of these 3 centers can be used (epimerize later). Need only worry about control of 4 of the 7 stereocenters.

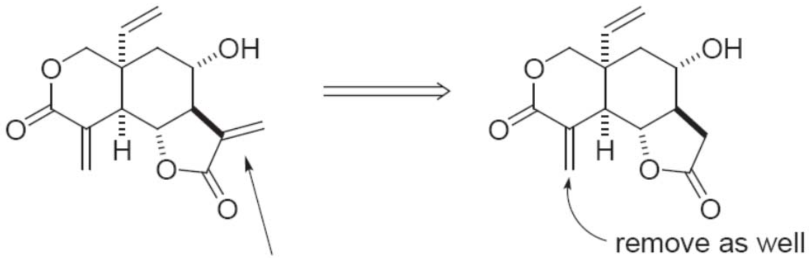
Design and Execution of a Synthesis

3. Simplification and Background Chemistry

c. Recognize and Remove Reactive Functionality

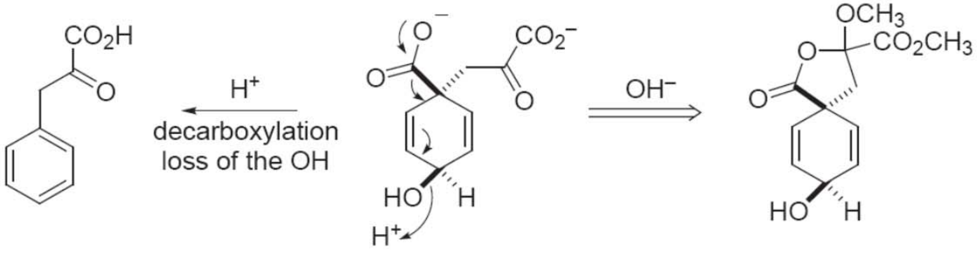
Another key to simplification derived from background chemistry

e.g., Vernolepin



remove as well

- α-Methylene lactone in a *trans* fused 5-membered ring
  This is extraordinarily reactive to nucleophiles (Michael).
  It will not stand up to many synthetic steps/reagents.
- the final step should be introduction of the reactive group.

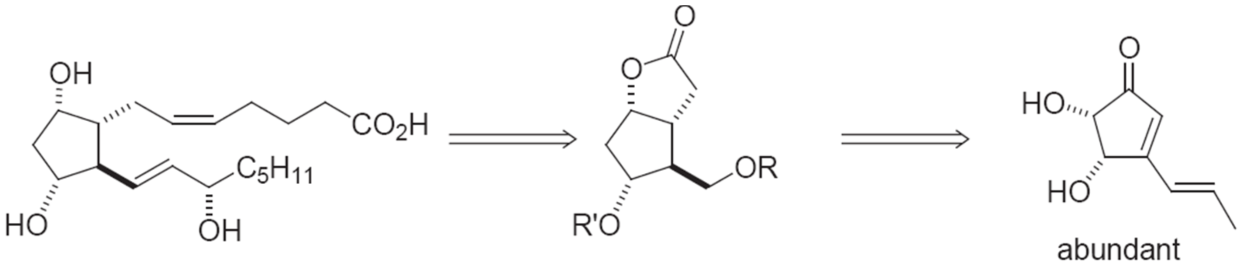


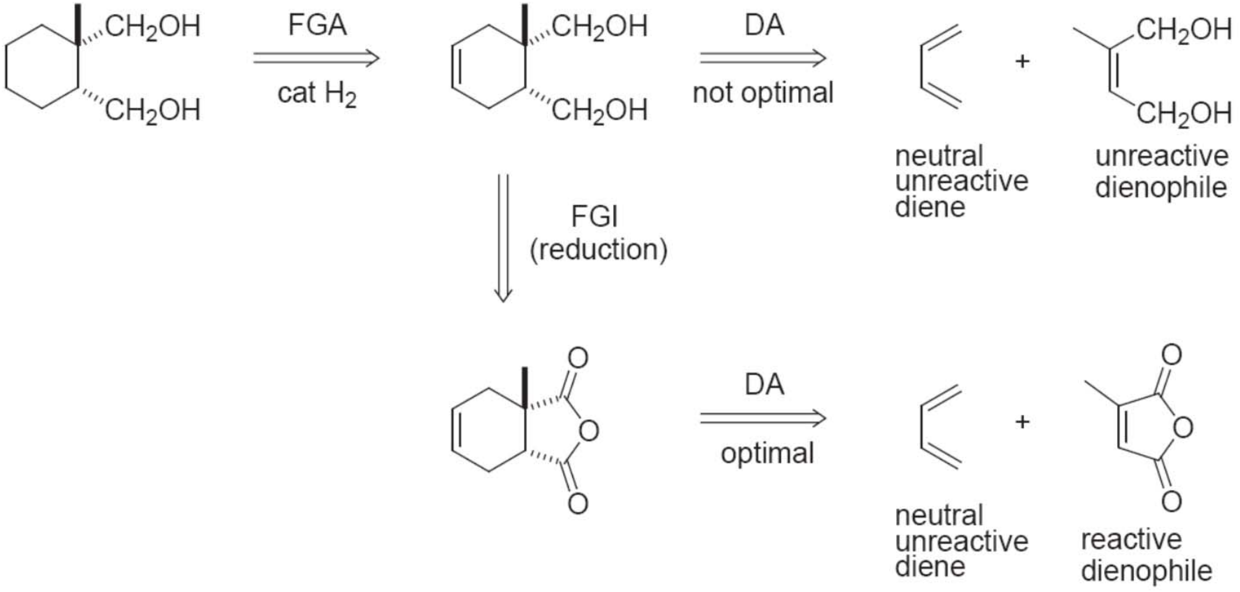
- acid sensitive (derived from background chemistry).
- a successful approach must involve generation
  under basic conditions.

Danishefsky *J. Am. Chem. Soc.* **1977**, *99*, 7740.

Design and Execution of a Synthesis

3. Generation of Synthetic Pathways





Design and Execution of a Synthesis

5. Evaluation of Pathways and Assignment of Merit

a. excellent knowledge of organic chemistry
b. suspect reactions must be recognized - one poor step can ruin the synthesis
c. control of stereochemistry is clear
d. want opportunity for alternatives - reactions that look good on paper aren't always successful in lab

6. Selection of Specific Reactions and Reagents

a. this also requires an excellent knowledge of organic chemistry
b. check the literature for alternative reagents - it is wiser to change reagents than to change the entire synthesis if problems arise
c. many reference texts are available

Design and Execution of a Synthesis

7. Selection of Reaction Conditions

a. reaction temperature
b. solvent
c. knowledge of reaction mechanism
d. consult current and background literature

8. Execution of the synthesis - most difficult and time consuming element of work

a. easy: setting up and conducting the reaction
b. difficult: interpreting the results from the reaction

Guidelines for synthetic planning

Retrosynthetic analysis:

1. Use disconnections corresponding to known ***reliable reactions*** with the highest yields.
2. Disconnect C-C bond according to the FGs present in the molecule, take into account and exploit the ***relationship*** between the FGs. Correlate ***synthons*** with appropriate ***synthetic equivalents***.
3. Employ Functional Group Interconversions (**FGI**), including Functional Group Removal (FGR), as necessary to get useful FGs, use Functional Group Addition (**FGA**) to install a required FG.
4. Aim for ***simplification***:
    - disconnect C-X bonds,
    - use symmetry,
    - separate into equal sized pieces,
    - disconnect rings from chains,
    - disconnect at a branch point,
    - use rearrangements.
5. Try to find a ***key disconnection*** that would bring a considerable simplification to the structure or reveal simple starting materials.
6. Whenever possible, plan a ***convergent*** synthesis.

Guidelines for synthetic planning

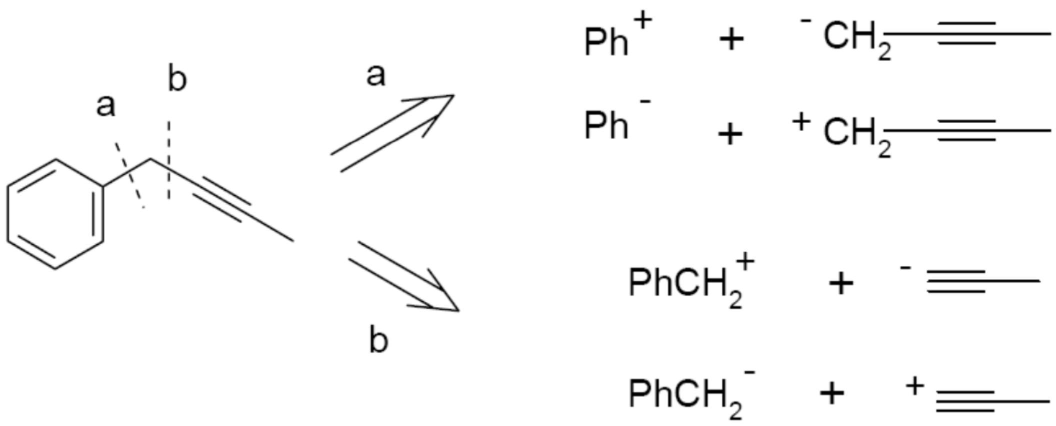
Synthesis:

1. Write the ***synthetic sequence***, including reagents.
2. Check for mutually ***incompatible*** FGs.
3. Check ***compatibility*** between ***FGs*** and ***reagents***.
4. Take into account problems of ***regioselectivity*** and ***chemoselectivity***.
5. Use ***protecting groups*** to resolve these problems.
6. Make sure you make the right **TM**: check for length of carbon chain, size of rings, position of substituents, nature and position of FGs, removal of protecting groups.

General note: retrosynthetic analysis is a problem solving technique that require a broad knowledge of various synthetic methodologies, so integrate all the material acquired from different courses.

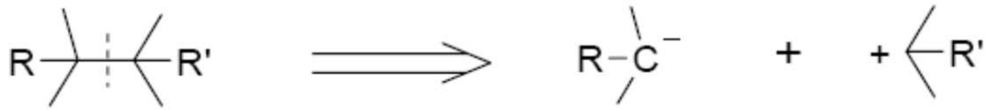
Disconnections

1. Use disconnections corresponding to known reliable reactions, choose disconnection corresponding to the highest yielding reaction.

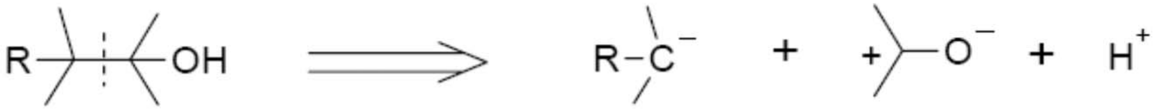


2. Disconnect C-C bond according to the present FGs in the molecule, few examples:

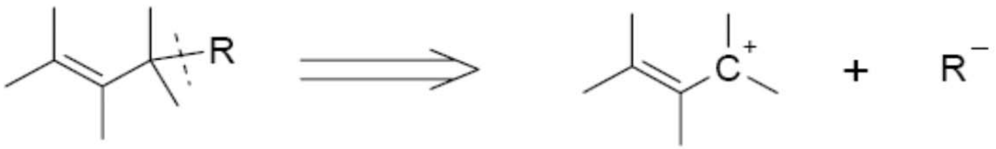
a. C-C bond with no neighbouring functional groups



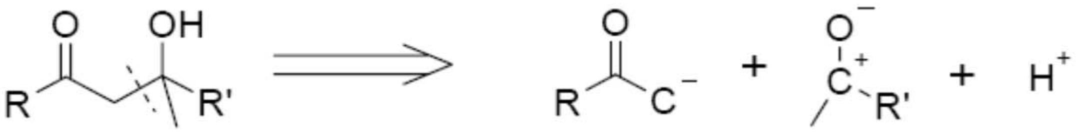
b. C-C bond with one oxygen substituent



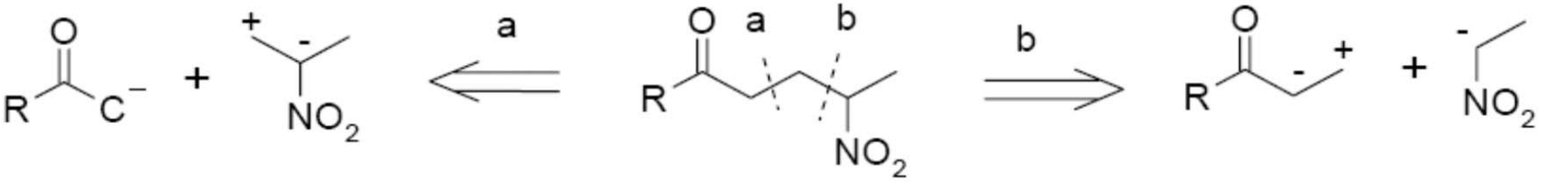
c. Allylic C-C bond



d. C-C bond with two oxygen substituents in positions 1,3

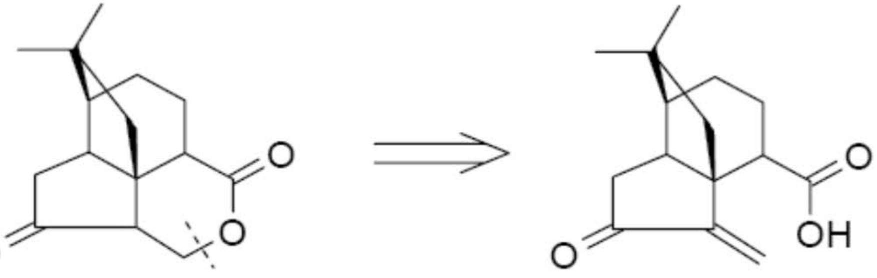


e. C-C bond with two heteroatom substituents in positions 1,2 or 1,4. Umpolung methods.

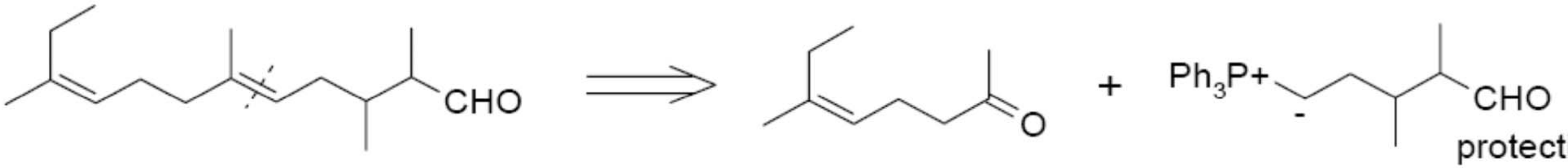


3. Aim for simplification:

a) Disconnect C-X bond (RCO-X)


Quadrone

b) disconnect in the middle of the molecule

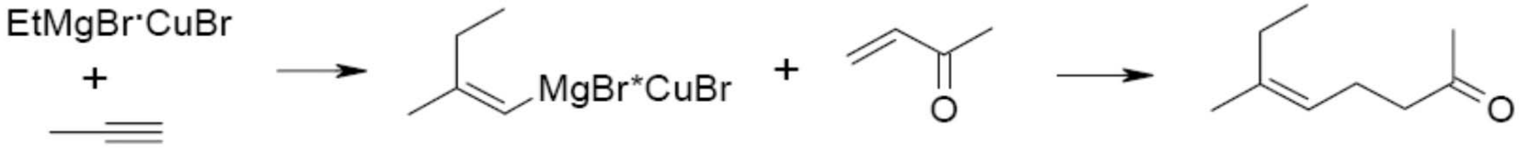

Faranal, Pharaoh's ant trail pheromone

C_9

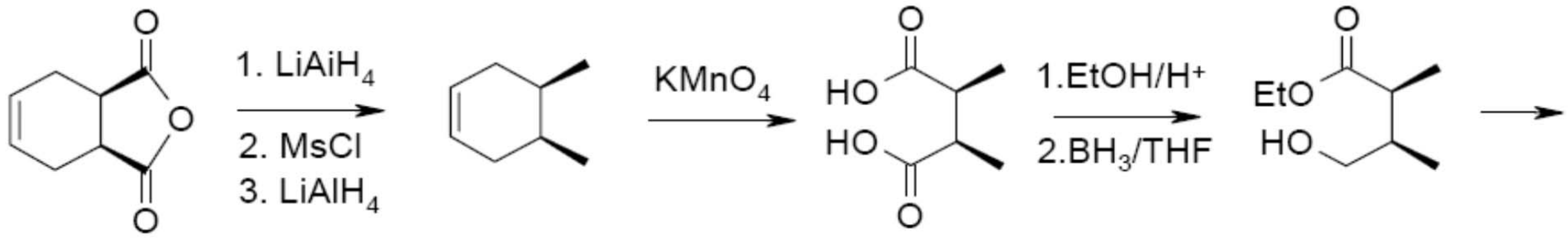
C_7

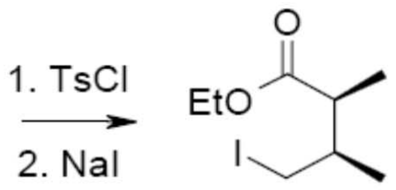
protection needed

C_9:



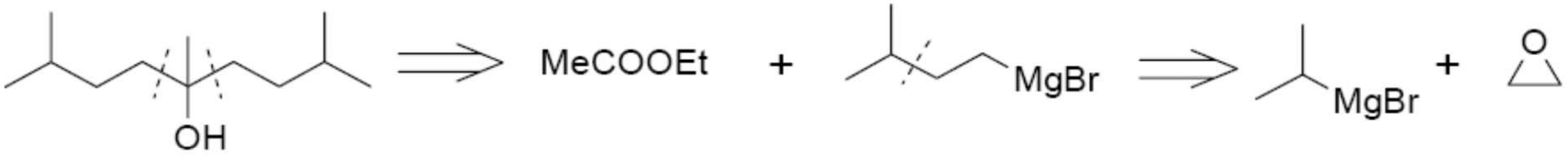
C_7:





Tetrahedron Lett. **1981**, *22*, 5001

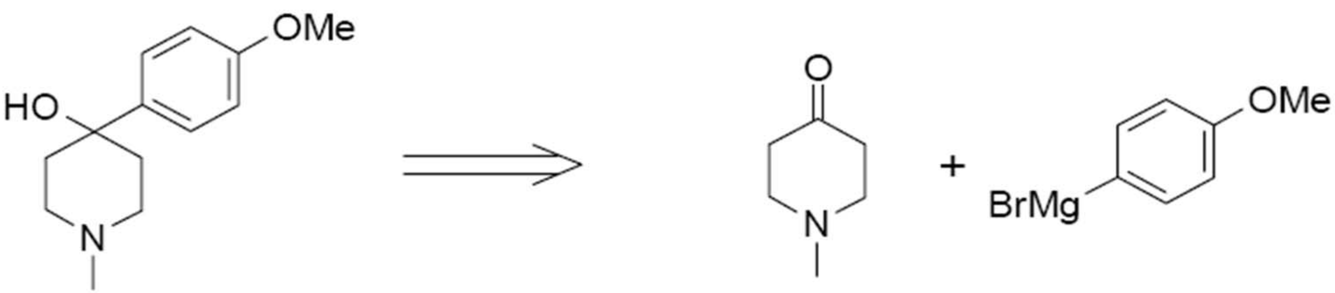
c) disconnect at a branch point
d) use symmetry



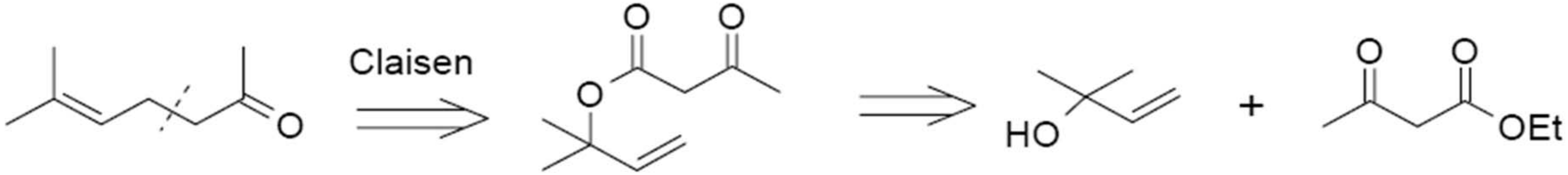
(±)-Hybocarpone

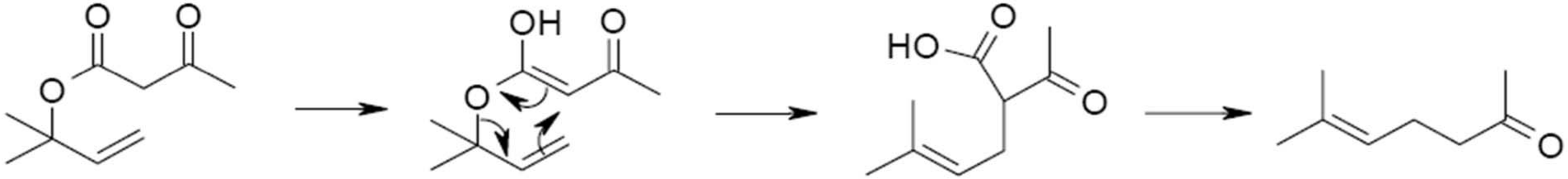
K.C.Nicolaou
Angew. Chem. Int. Ed. **2001**, *40*, 761

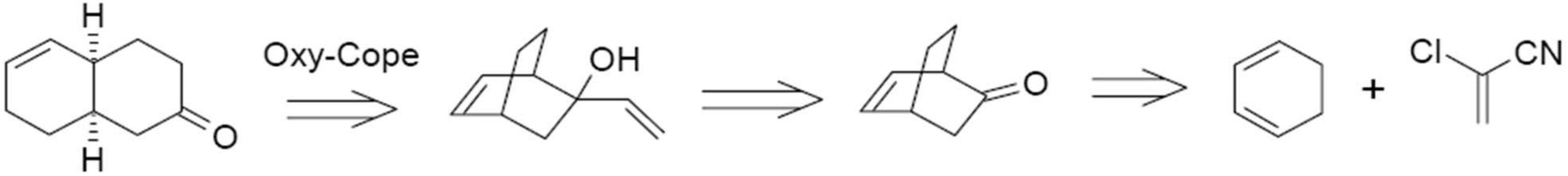
e) disconnect rings from chain



f) use rearrangements



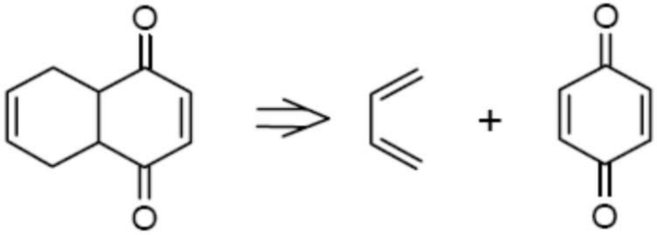


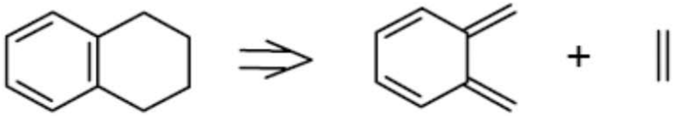


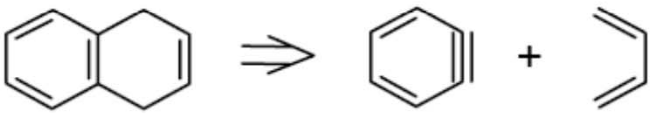
4. Carbocyclic Rings:

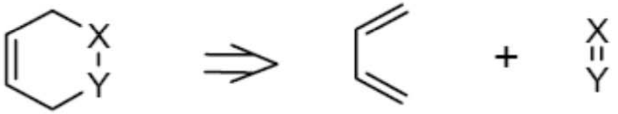
If one or more *6-membered carbocyclic* unit present in the molecule consider a set of disconnection available for construction of 6-membered rings: Diels-Alder, Robinson annulation, aldol, Dieckmann, internal S_N2, Birch reduction, etc.

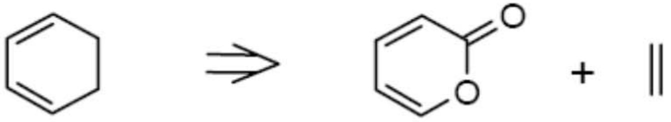
Some types of Diels-Alder disconnections:

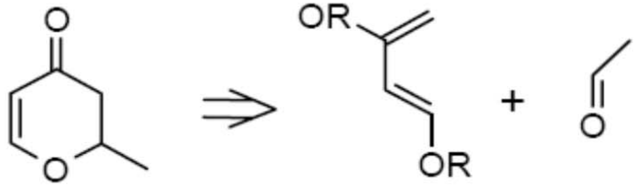




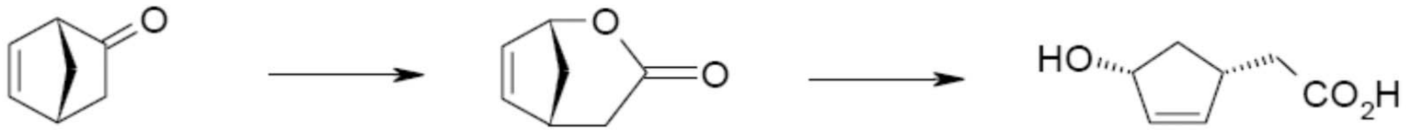


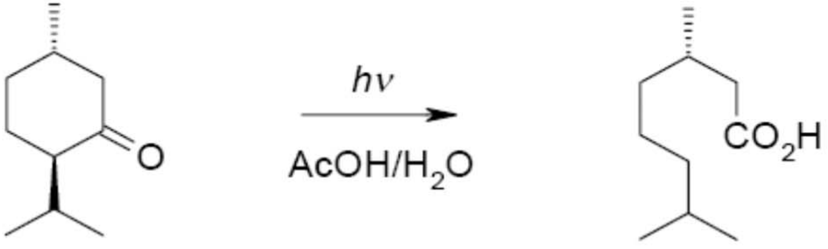


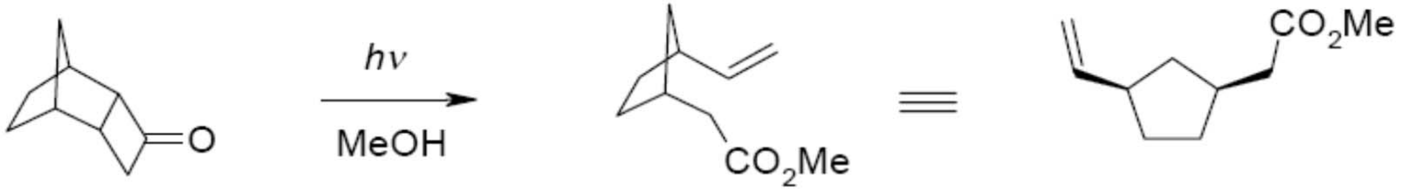


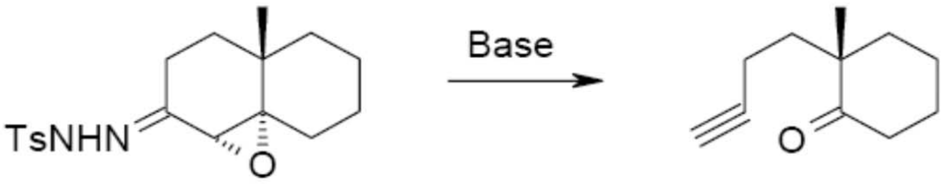


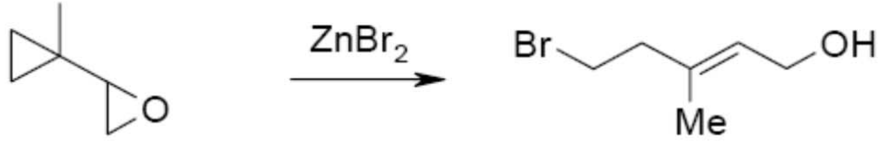
5. Examples of cleavage of C-C bond as a retrosynthetic ***reconnection***





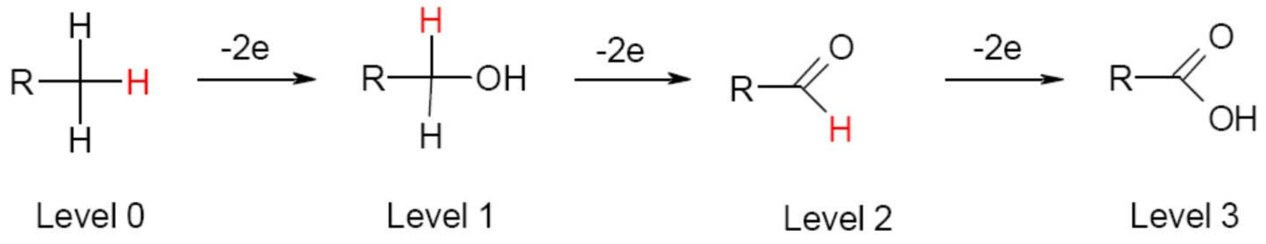






Functional Group Interconversion (FGI)

Classification of functional groups by oxidation state of carbon atoms:



Oxidation level 1 (alkane – 2e):

C-X (X = Hal, OH, OR, OAc, OTs, NR_2, NO_2, SR, *etc*);
C=C

Oxidation level 2 (alkane – 4e):

C=X (X = O, NR); CXY (X, Y = Hal, OR, SR); C=C-X (X = Hal, OR, $OSiR_3$); C≡C; X-C-C-Y; epoxides.

Oxidation level 3 (alkane – 6e):
COOH, COX (X = OR, Hal, OCOR, NR_2); C≡N, C=C-C=O, C=C-C≡C

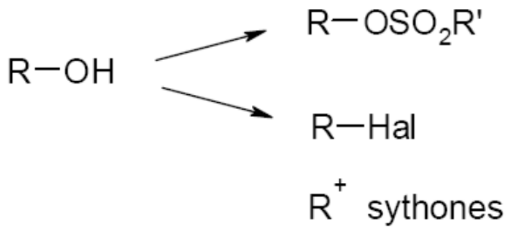
Functional Group Interconversion (FGI)

Based on this classification FGI can be divided into two groups:

Type 1. Isohypsic transformations with no change to the oxidation level of carbon

Type 2. Non-isohypsic transformations, where carbon atom is either reduced or oxidised.

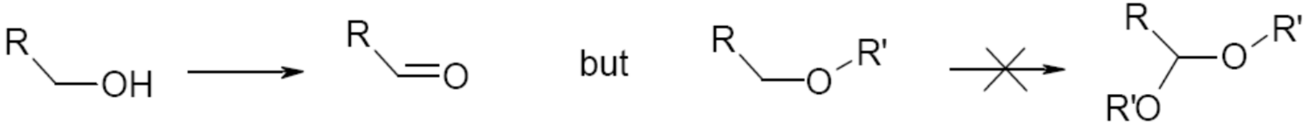
In general, on the same oxidation level any functional group interconversion can be performed in more or less easy way:



$$\text{R—X} \xrightarrow{Y^-} \text{R—Y}$$

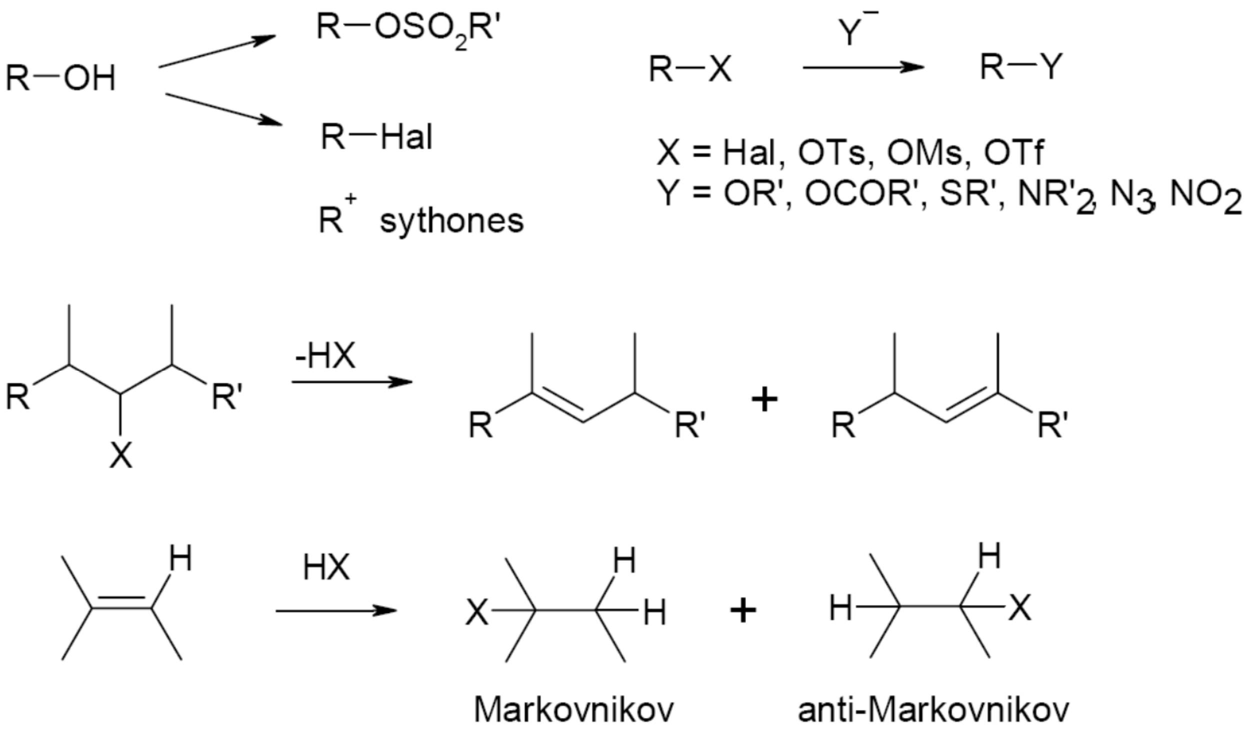
X = Hal, OTs, OMs, OTf
Y = OR', OCOR', SR', NR'$_2$, N$_3$, NO$_2$

However, transformations between levels can be achieved only on certain derivatives:



Functional Group Interconversion (FGI)

Type 1 (no change in oxidation state), Level 1. The most common functions resulting from C-C bond construction are alcohol (Grignard addition to carbonyl compounds, aldol reaction, etc) and olefin (Wittig and related processes, croton condensation, olefin methathesis, etc). In addition, FGI of type 2 often lead to alcohols and olefines (reduction of carbonyl compounds, partial hydrogention)



$R{-}OH \rightarrow R{-}OSO_2R'$

$R{-}OH \rightarrow R{-}Hal$

R^+ sythones

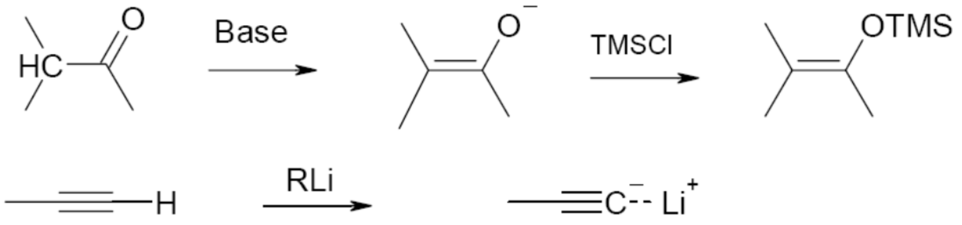
$R{-}X \xrightarrow{Y^-} R{-}Y$

X = Hal, OTs, OMs, OTf

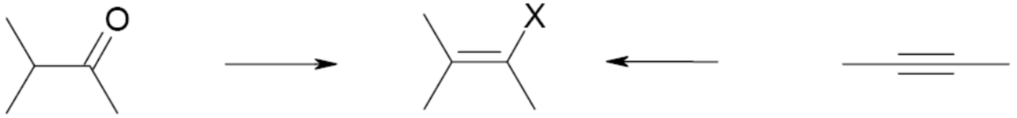
Y = OR', OCOR', SR', NR'_2, N_3, NO_2

Functional Group Interconversion (FGI)

Type 1 (no change in oxidation state), Level 2. The main functional groups are carbonyl compounds (aldehydes and ketones) and alkynes.
Formation of synthetic equivalents of carbanions:



Formation of vinyl derivatives.

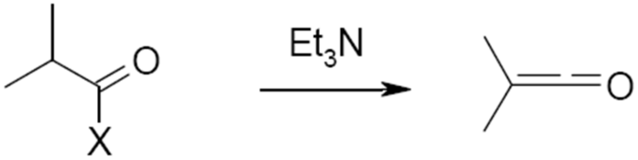


X = Hal, OR, OCOR

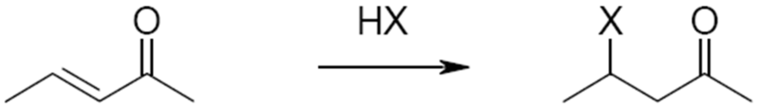
In organic synthesis *vinyl halides* can play a dual role: as *electrophiles* in reaction with organocuprates and as *nucleophiles* when transformed themselves into organometallic derivatives.

Functional Group Interconversion (FGI)

Type 1 (no change in oxidation state), Level 3. The main functional group that allows formation of any other derivative on the same level is acid halide. This is a typical electrophile used to make derivatives of carboxylic acids and in Friedel-Crafts C-C bond forming reactions.



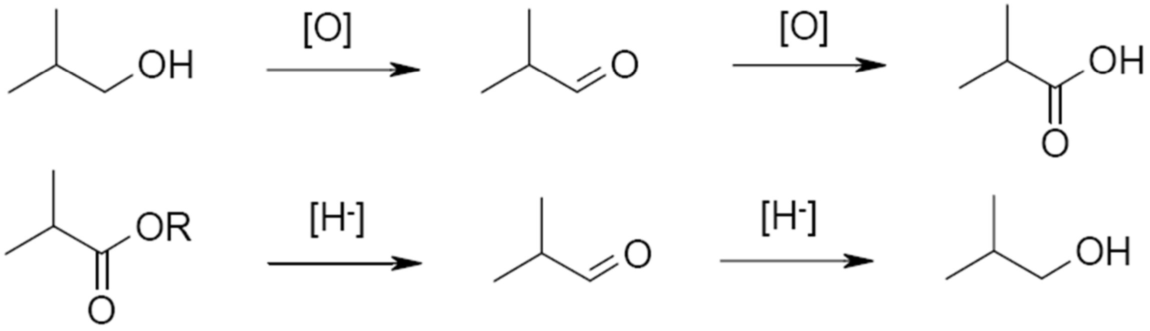
Polyfunctional compounds of level 3 are α,β-unsaturated aldehydes and ketones – good Michael acceptors:



X = OH, Hal, SR. NR_2, etc

Functional Group Interconversion (FGI)

Type 2 transformations. Availability of methods to go from alcohol to carboxylic acid derivatives and back makes alkohol, carbonyl and carboxyl functions synthetically equivalent.



Functional Group Interconversion (FGI)

1. Many functional groups, especially on the same level of oxidation, can be considered as synthetically equivalent so their retrosynthetic interconversions can be planned.

2. As any functional group can be removed, retrosynthetically we can put a functional group in any position of alkane or cycloalkane chain and that would allow assembly of a given C-C fragment. Unfortunately, reverse is not achievable as yet.

Disconnections according to FGs

Disconnection of molecules according to the present FGs in the molecule:

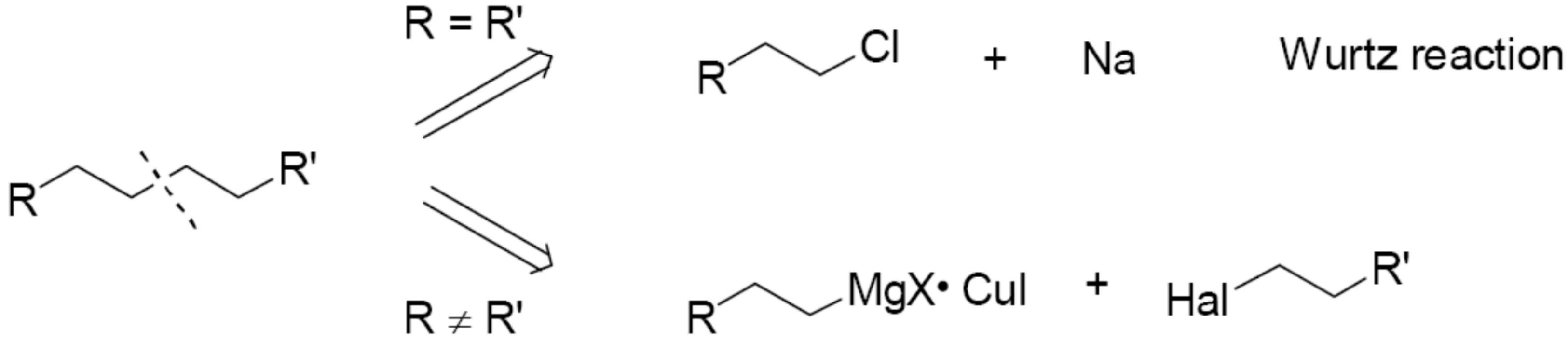
- 1.1. C-C bond with no functional group present:
- 1.2. One-group disconnections based on normal carbonyl reactivity.
- 1.3. Two-group disconnections based on normal carbonyl reactivity.

2-Group disconnections:
unnatural reactivity patterns and other strategies

- 2.1. Synthetic strategies for 1,2-difunctionalysed compounds
- 2.2. Functional group interconversion: amine synthesis
- 2.3. Synthetic strategies for 1,4-difunctionalised compounds
- 2.4. Synthetic approaches to cyclic systems
- 2.5. Reconnection strategies

Disconnection of molecules according to the present FGs in the molecule:

1.1. C-C bond with no functional group present:



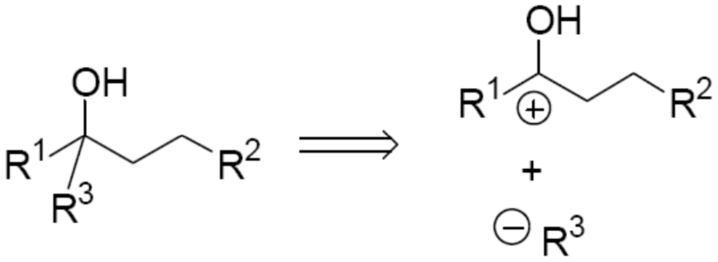
Wurtz reaction

Disconnection of molecules according to the present FGs in the molecule:

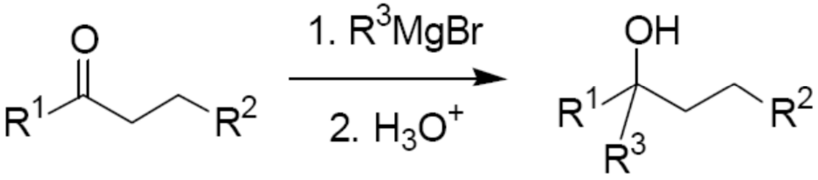
1.2. One-group disconnections based on normal carbonyl reactivity.

Alcohols

Analysis

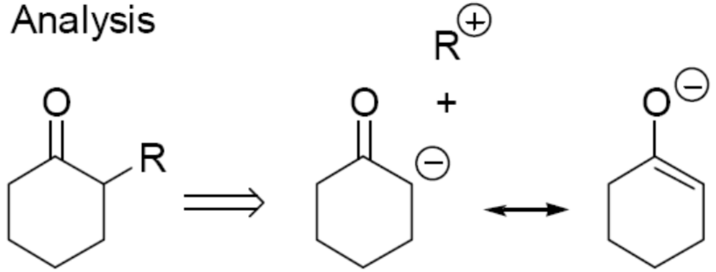


Synthesis



Carbonyl compounds brunched at α-carbon.

Analysis



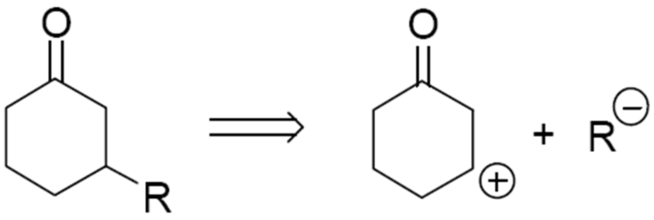
Synthesis

Synthetic planning should show an analysis of the problem followed by synthetic solution.

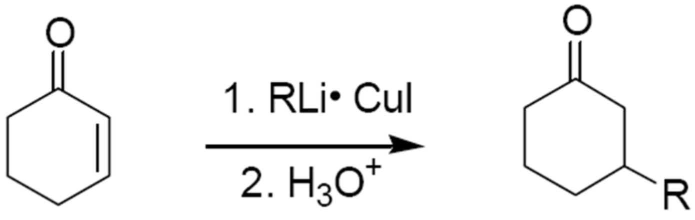
Disconnection of molecules according to the present FGs in the molecule:

1.2. One-group disconnections based on normal carbonyl reactivity.

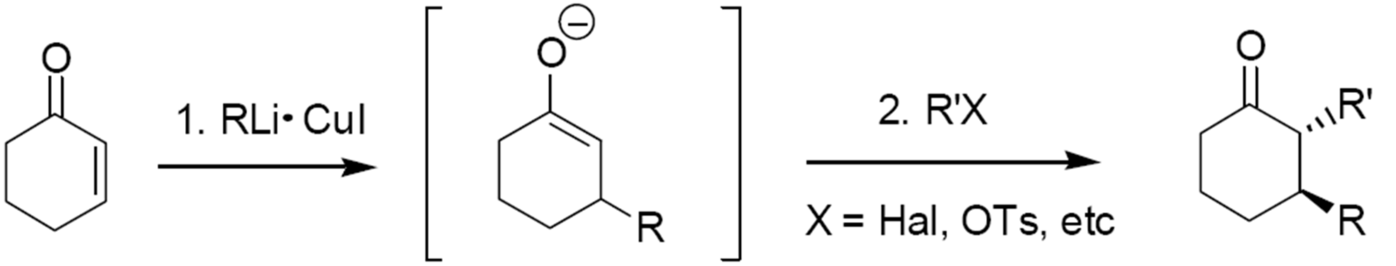
Analysis



Synthesis: Michael addition

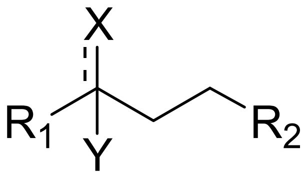


Combination of the last two synthetic approaches allows the introduction of two new groups:

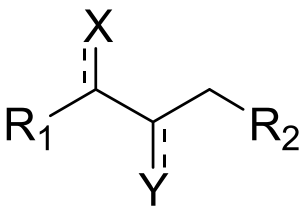


Disconnection of molecules according to the present FGs in the molecule:

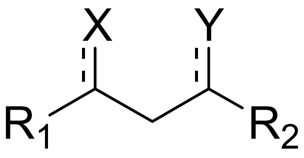
1,x-difunctionalysed compounds



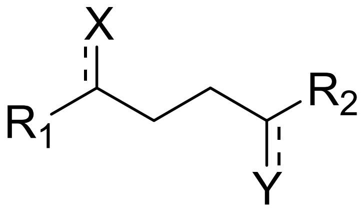
1,1



1,2



1,3

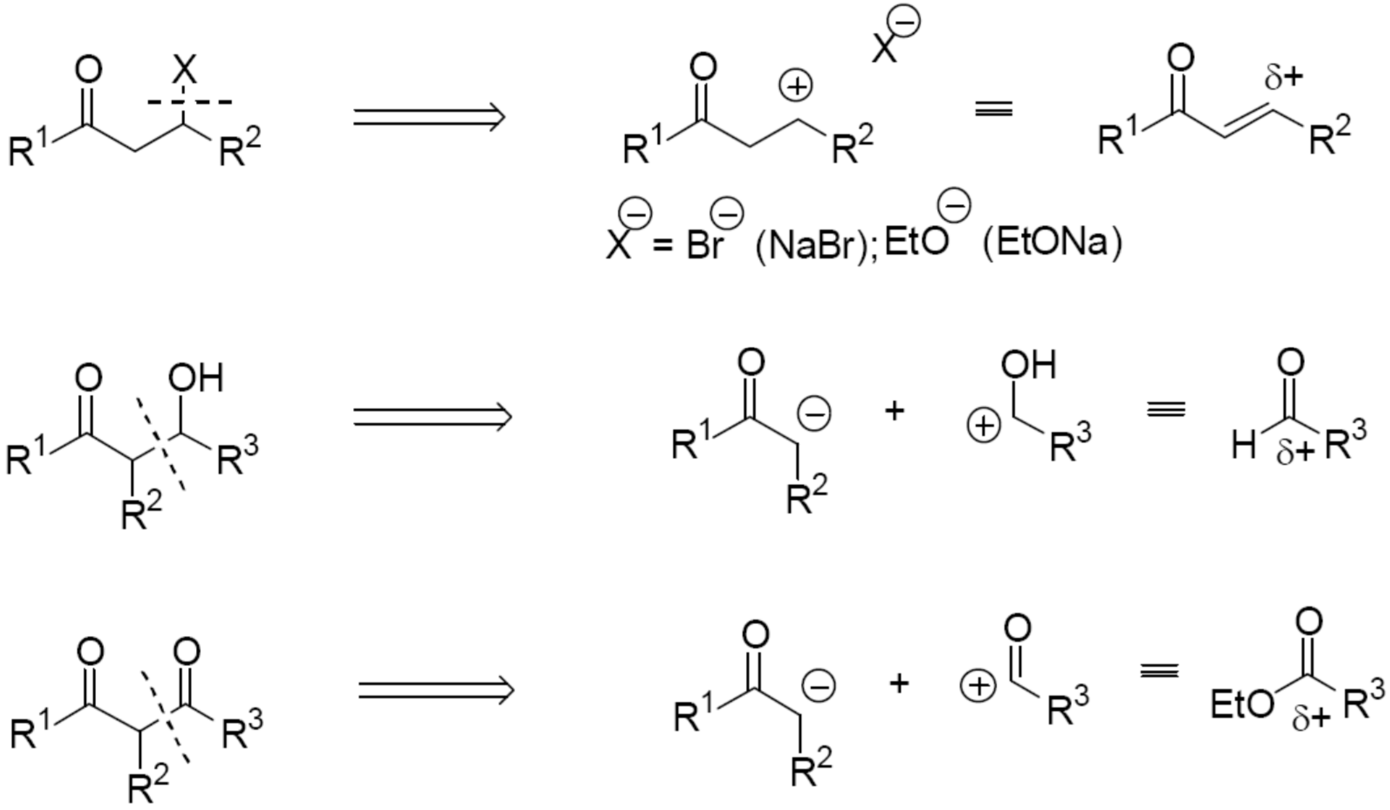


1,4

Disconnection of molecules according to the present FGs in the molecule:

1.3. Two-group disconnections based on normal carbonyl reactivity.

1,3-Difunctionalised compounds

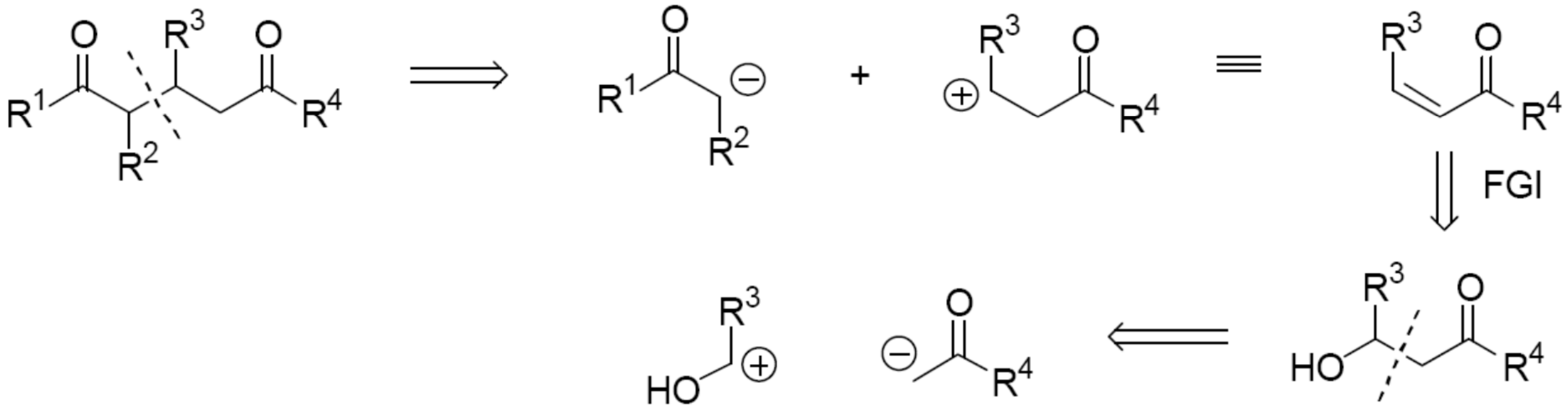


Disconnection of molecules according to the present FGs in the molecule:

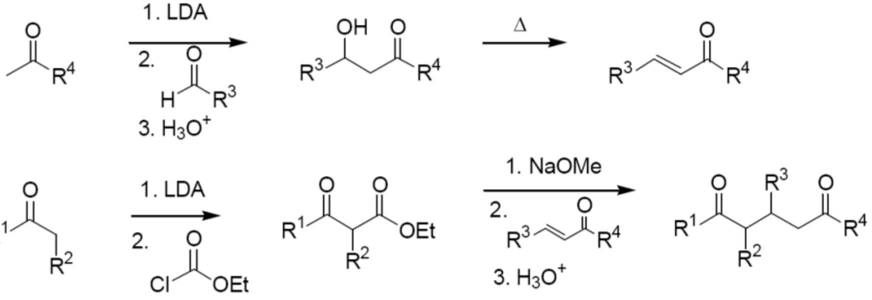
1.3. Two-group disconnections based on normal carbonyl reactivity.

1,5-Difunctionalised compounds

Analysis



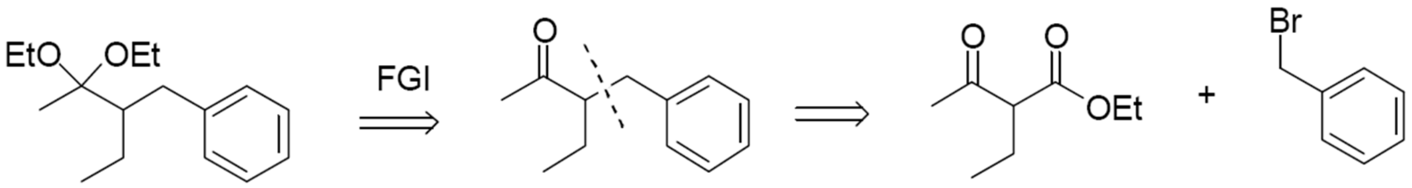
Synthesis

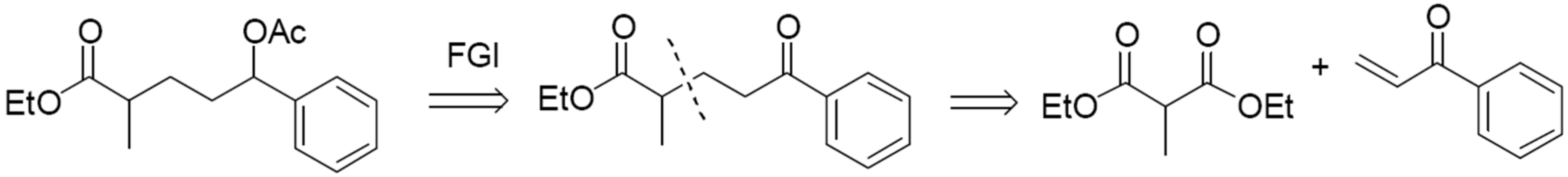


Disconnection of molecules according to the present FGs in the molecule:

1.3. Two-group disconnections based on normal carbonyl reactivity.

Examples of retrosynthetic disconnections.

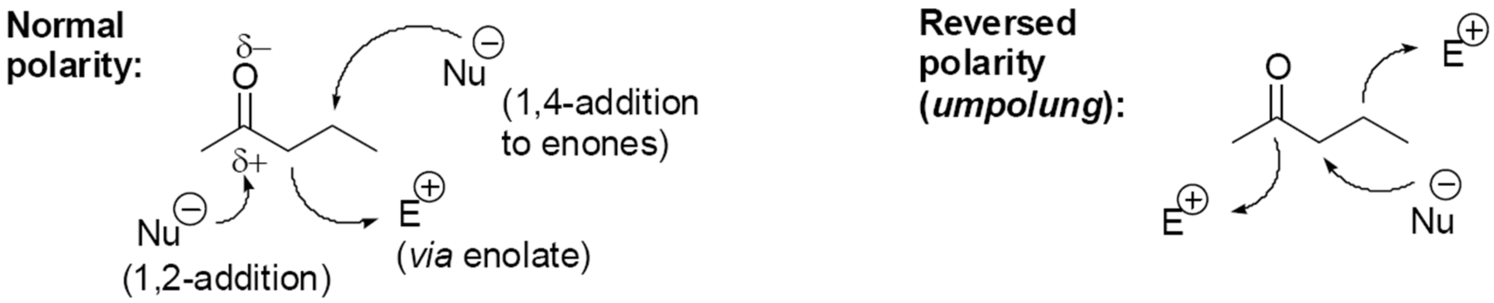




Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

Unnatural or reversed polarity carbonyl reactivity reverses the normal patterns attributable to carbonyl compounds.



2.1. Synthetic strategies for 1,2-difunctionalysed compounds

2.2. Functional group interconversion: amine synthesis

2.3. Synthetic strategies for 1,4-difunctionalised compounds

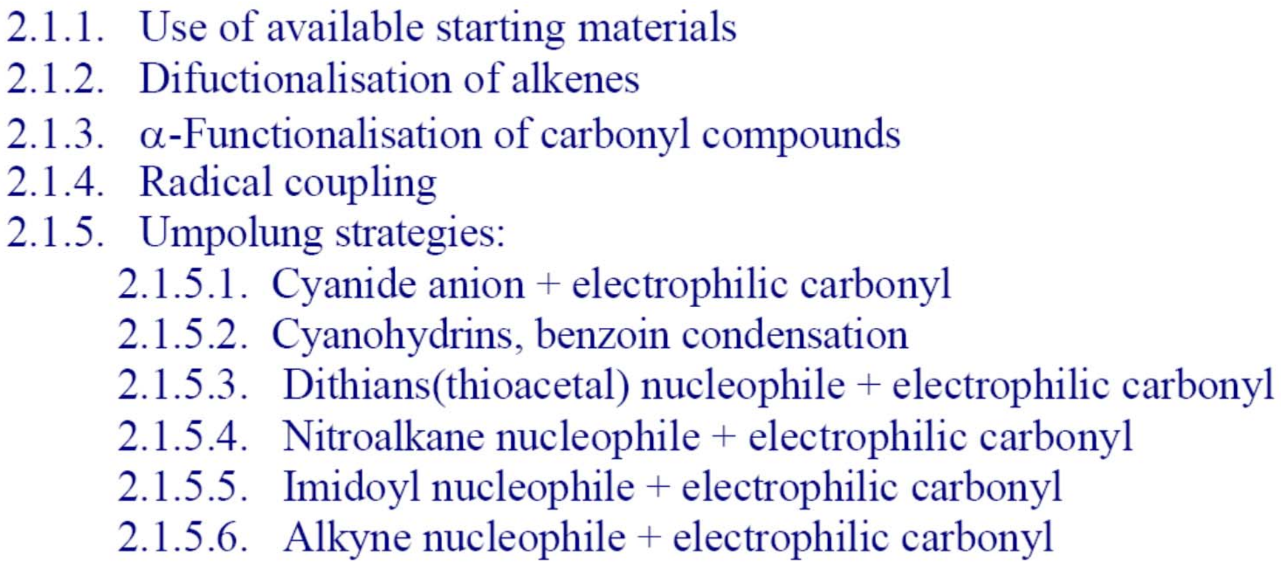
2.4. Synthetic approaches to cyclic systems

2.5. Reconnection strategies

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.1. Synthetic strategies for 1,2-difunctionalysed compounds

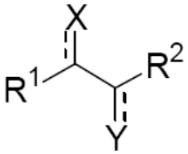


2.1.1. Use of available starting materials
2.1.2. Difuctionalisation of alkenes
2.1.3. α-Functionalisation of carbonyl compounds
2.1.4. Radical coupling
2.1.5. Umpolung strategies:
    2.1.5.1. Cyanide anion + electrophilic carbonyl
    2.1.5.2. Cyanohydrins, benzoin condensation
    2.1.5.3. Dithians(thioacetal) nucleophile + electrophilic carbonyl
    2.1.5.4. Nitroalkane nucleophile + electrophilic carbonyl
    2.1.5.5. Imidoyl nucleophile + electrophilic carbonyl
    2.1.5.6. Alkyne nucleophile + electrophilic carbonyl

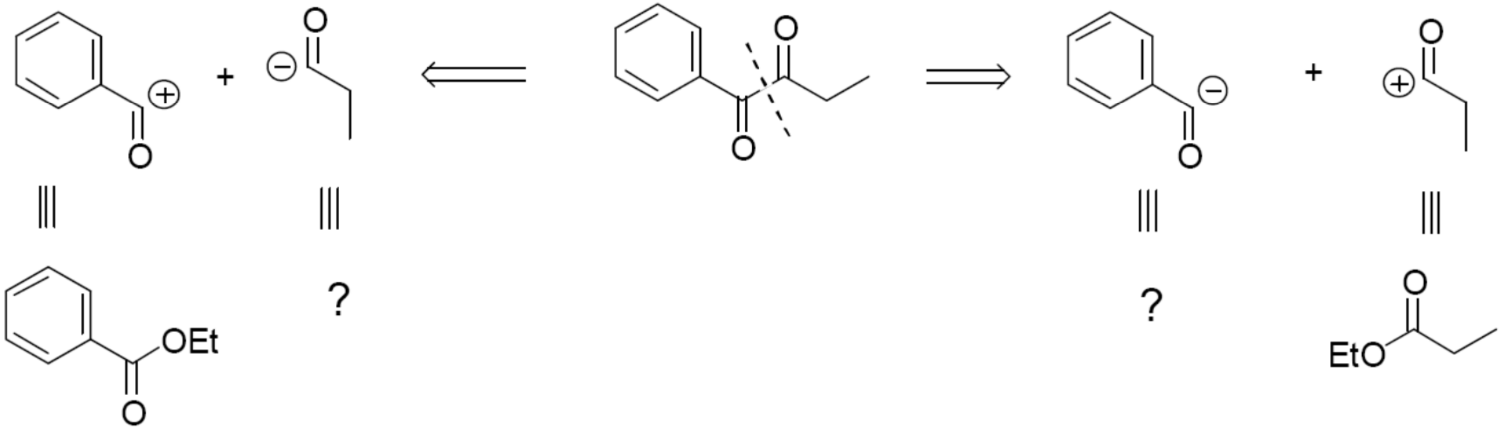
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.1. Synthetic strategies for 1,2-difunctionalysed compounds



1,2-Difunctionalised compounds *cannot* be prepared by the type of disconnections used for 1,3- and 1,5-difunctionalised compounds.



Disconnection of molecules according to the present FGs in the molecule:

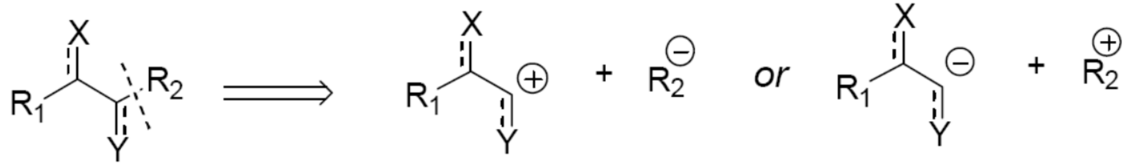
2-Group disconnections: unnatural reactivity patterns

2.1. Synthetic strategies for 1,2-difunctionalysed compounds

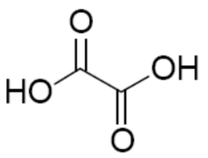
2.1.1. Use of available starting materials

In view of the fact that construction of 1,2-difunctional skeletons is not always a straightforward process, sometimes it is more convenient to disconnect to precursors with 1,2-functionalisation already present in the molecule rather than cut 1,2-relationship.

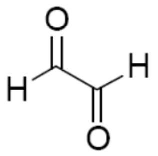
e.g.



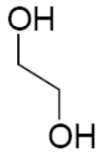
A selection of commercially available 1,2-difunctionalised compounds:



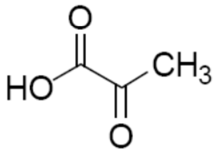
Oxalic acid



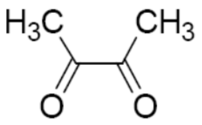
Glyoxal



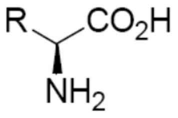
Glycol



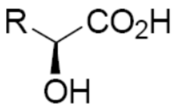
Pyruvic acid



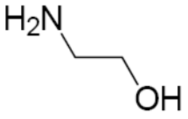
Diacetyl



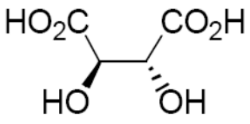
Amino acids



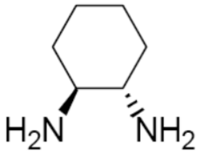
Hydroxy acids



Ethanolamine



Tartaric acid



Diaminocyclohexane

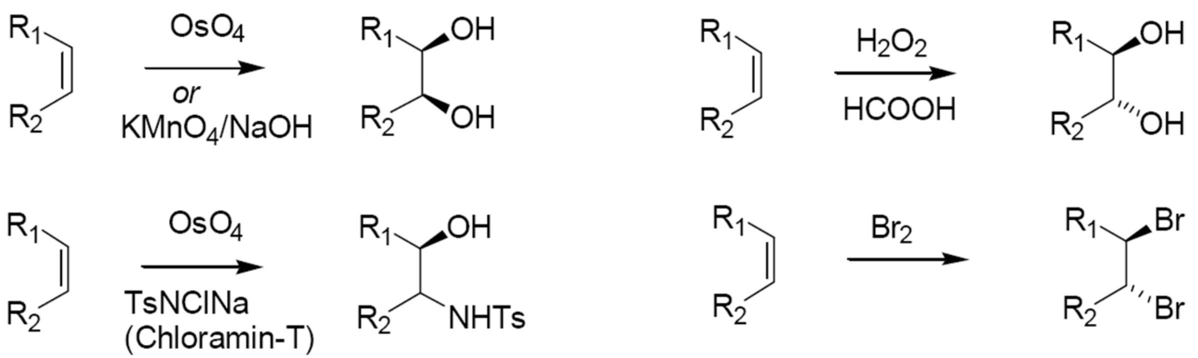
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

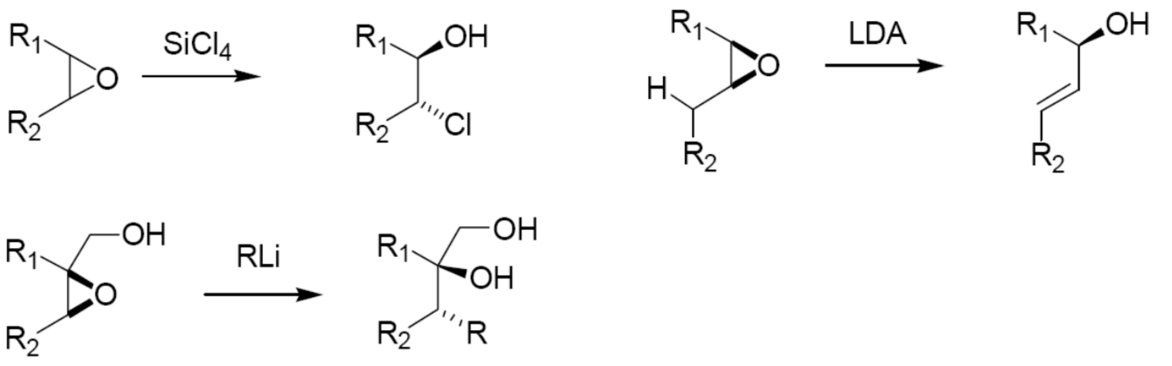
2.1. Synthetic strategies for 1,2-difunctionalysed compounds

2.1.2. Difuctionalisation of alkenes and opening of epoxides

Alkenes:



Epoxides:

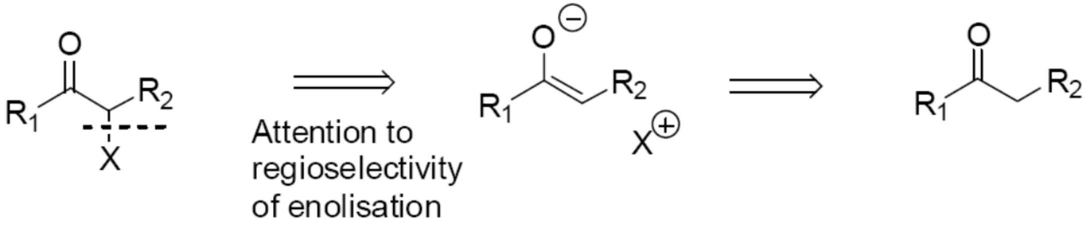


Disconnection of molecules
according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

2.1. Synthetic strategies for 1,2-difunctionalysed compounds

2.1.3. α-Functionalisation of carbonyl compounds



A selection of synthetic equivalents for $X^{\oplus}$:

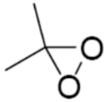
$Br^{\oplus}$, $Cl^{\oplus}$ ⟹ Br_2, Cl_2, NBS

$RS^{\oplus}$ ⟹ RSCl, RS-SR

$RSe^{\oplus}$ ⟹ RSeCl, RSe-SeR

$=O^{\oplus}$ ⟹ SeO_2; $NO^{\oplus}$ (HONO)

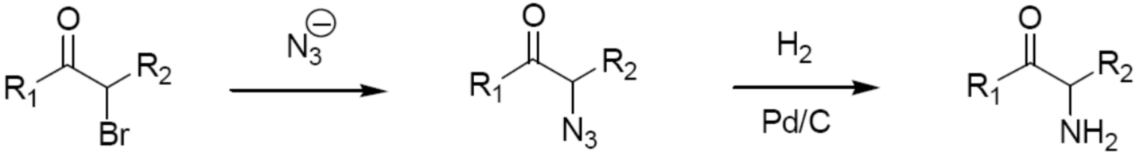
$-OH^{\oplus}$ ⟹



; OsO_4

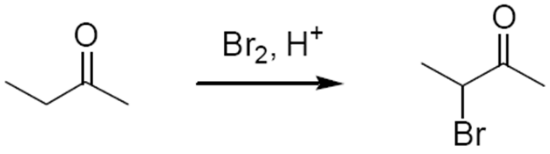
Dimethyl dioxirane

Amines can be introduced by FGI, *e.g.* from α–halocarbonyl compounds *via* azides followed by reduction:



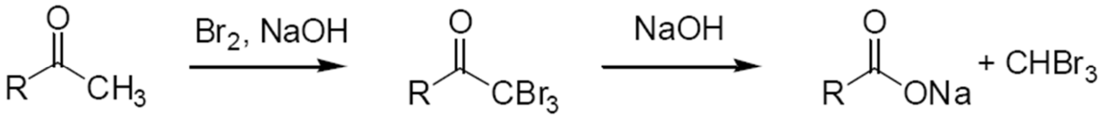
2.1.3. α-Functionalisation of carbonyl compounds

Examples:

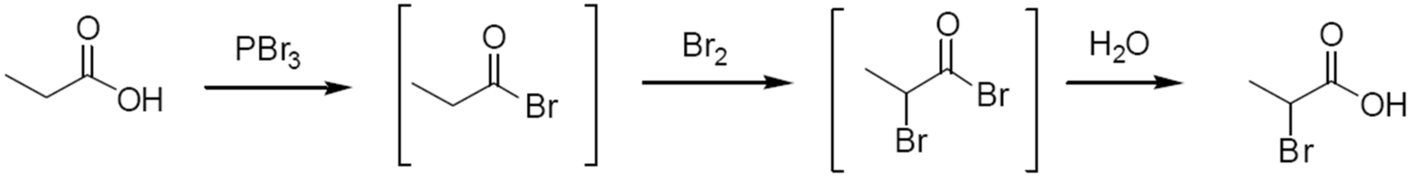


via more stable enolate

However, in basic conditions an excess of reagent can lead to haloform reaction:

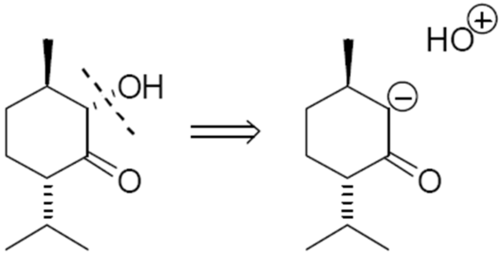


Carboxylic acids are readily halogenated in the presence of PBr_3:

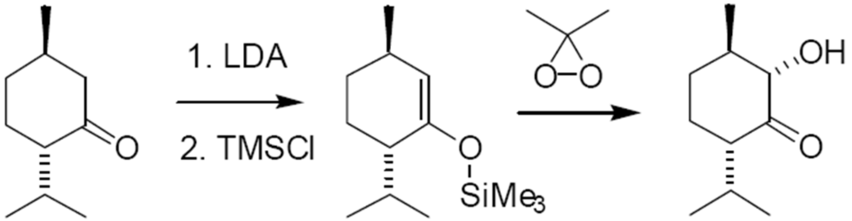


Application in synthesis:

Analysis



Synthesis

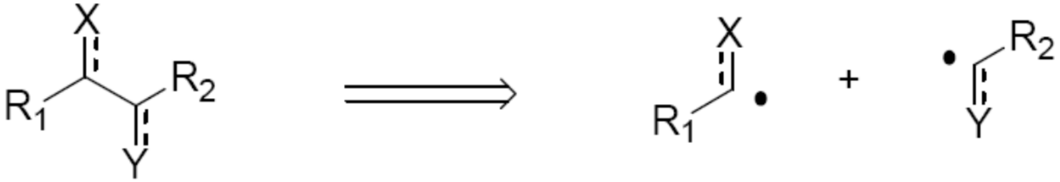


Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.1. Synthetic strategies for 1,2-difunctionalysed compounds

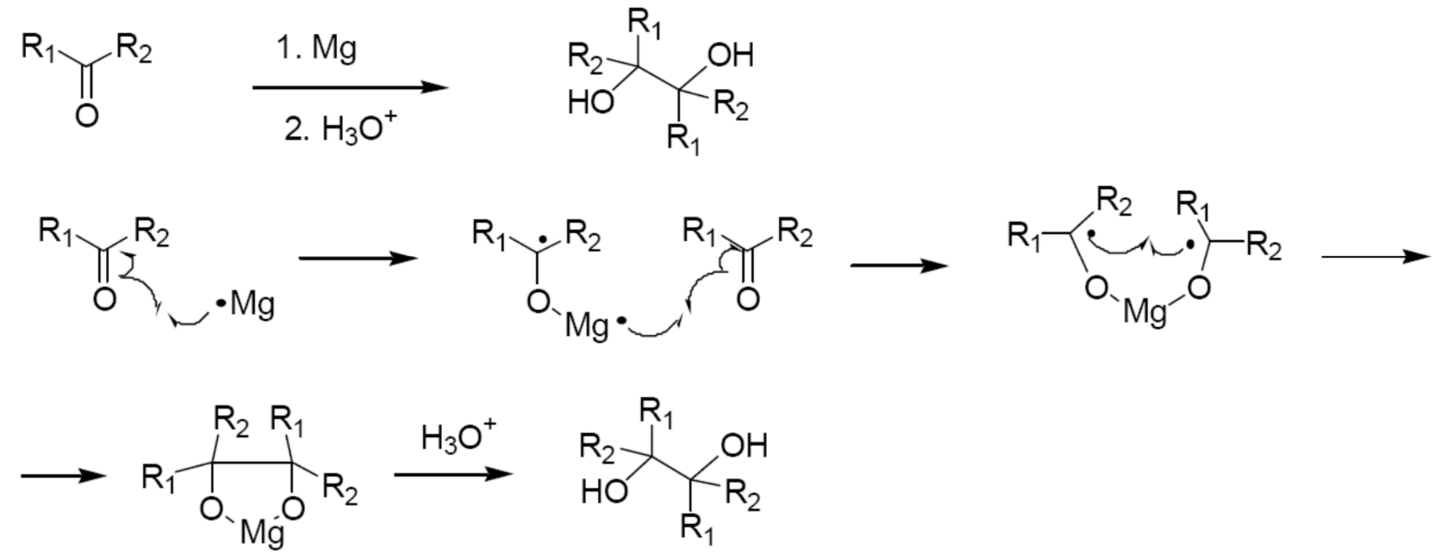
2.1.4. Radical coupling



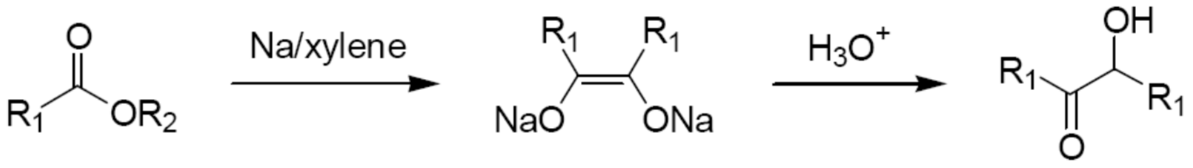
Radical coupling is only good when two identical molecules are being coupled ($R_1 = R_2$, X = Y) or when the reaction proceeds intramolecularly.

2.1.4. Radical coupling

Pinacol reaction:



Acyloin condensation:



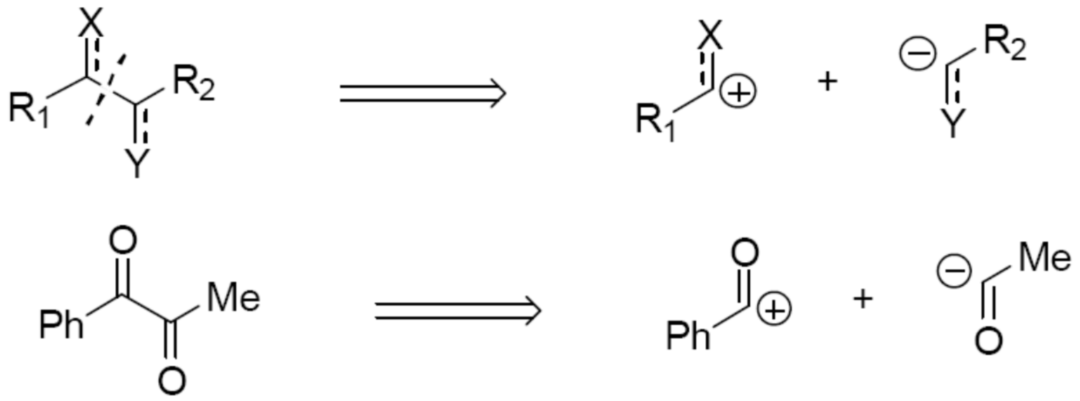
The reaction is used to make cyclic acyloins.
Yields for 6,7 membered rings - 50-60%,
for 10-20 membered rings - 60-95%

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

2.1. Synthetic strategies for 1,2-difunctionalysed compounds

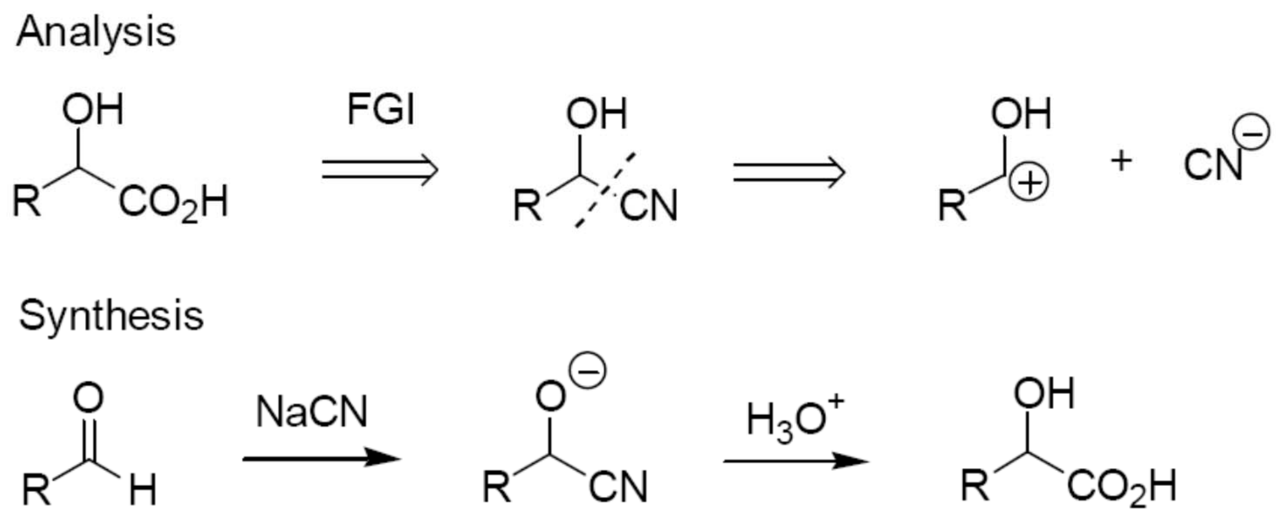
2.1.5. Umpolung strategies



The type of disconnection shown here requires acyl-anion $\mathrm{Me{-}C{=}O}$ which does not exist, and moreover, cannot be made by deprotonation of the corresponding aldehyde MeCHO. The **reversal of normal carbonyl reactivity (umpolung)** is required here. A number of synthetic equivalents of acyl-anion have been developed to carry out this reaction scheme.

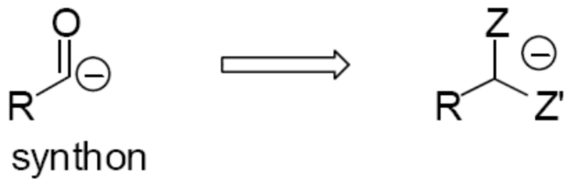
2.1.5. Umpolung strategies

2.1.5.1. *Cyanide anion + electrophilic carbonyl*



Note: CN^- is an ambident nucleophile.

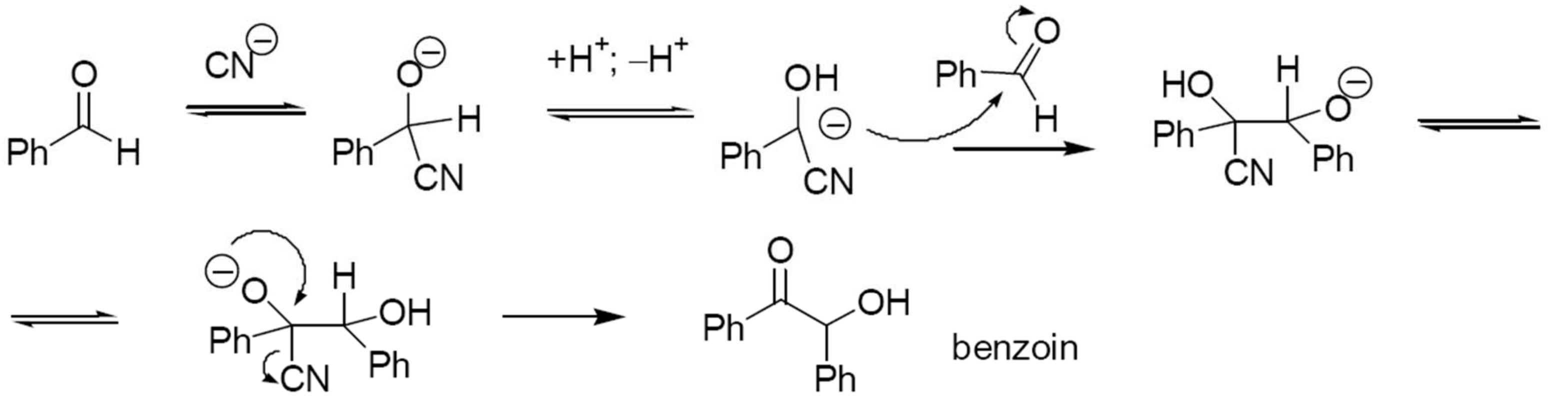
Strategies 3.1.5.2 and 3.1.5.3 are based on replacing the carbonyl oxygen with an anion stabilising groups:



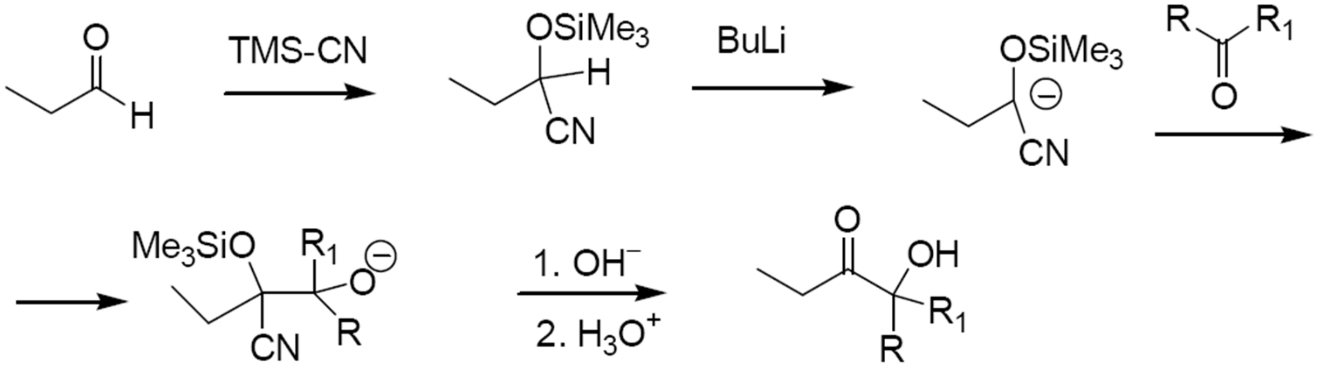
Z, Z' - anion stabilising groups

2.1.5. Umpolung strategies

2.1.5.2. Cyanohydrins, benzoin condensation

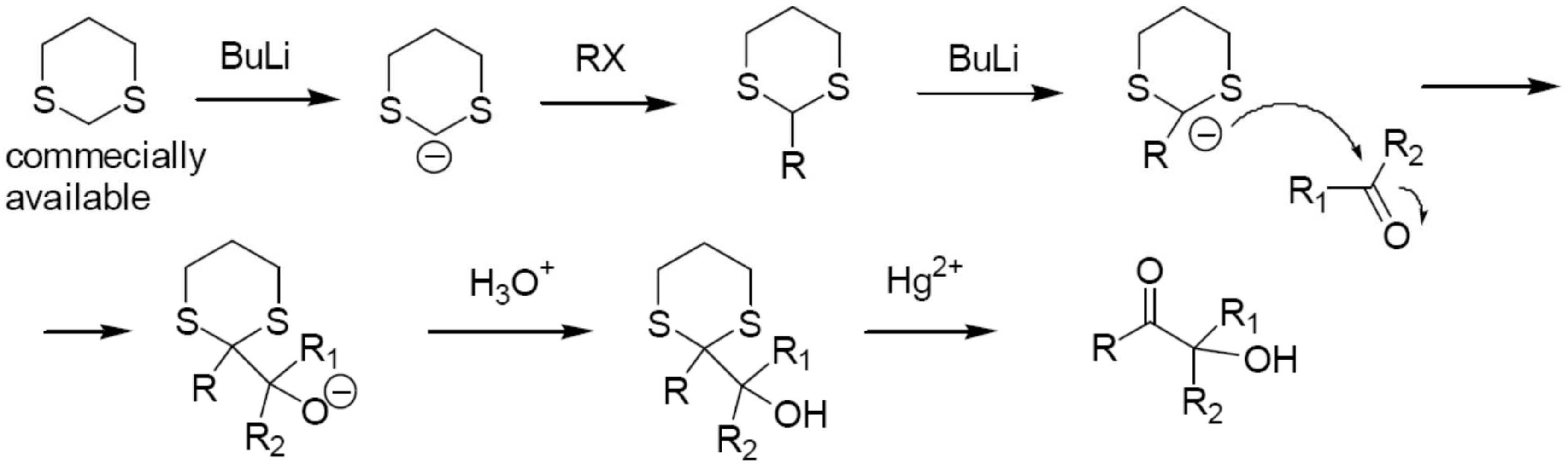


The reaction works well only on aromatic aldehydes, however, cyanohydrins of aliphatic aldehydes can be protected as silyl ethers and after deprotonation reacted in a similar way with different carbonyl compounds.

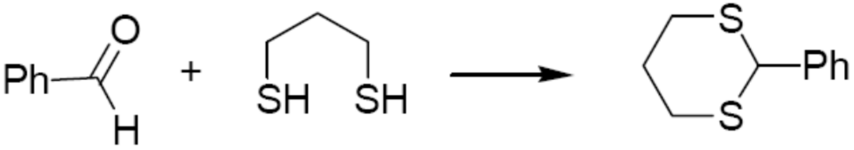


2.1.5. Umpolung strategies

2.1.5.3. *Dithians (thioacetal) nucleophile + electrophilic carbonyl*

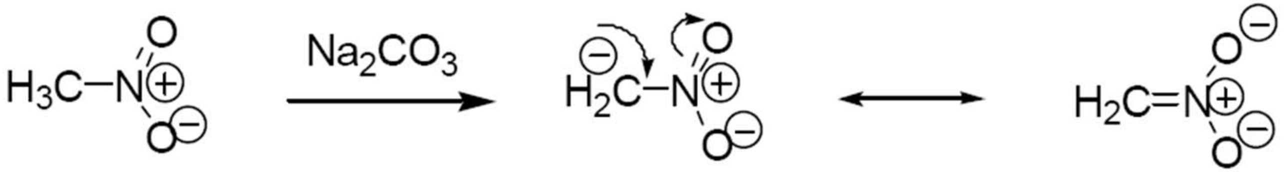


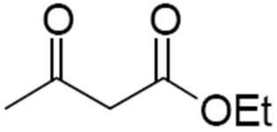
Note: RX ≠ PhX, instead



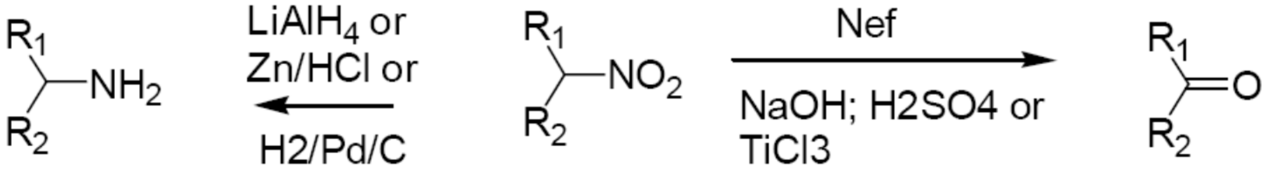
2.1.5. Umpolung strategies

2.1.5.4. *Nitroalkane nucleophile + electrophilic carbonyl*



pK_a ~ 10, compare with  pK_a = 11

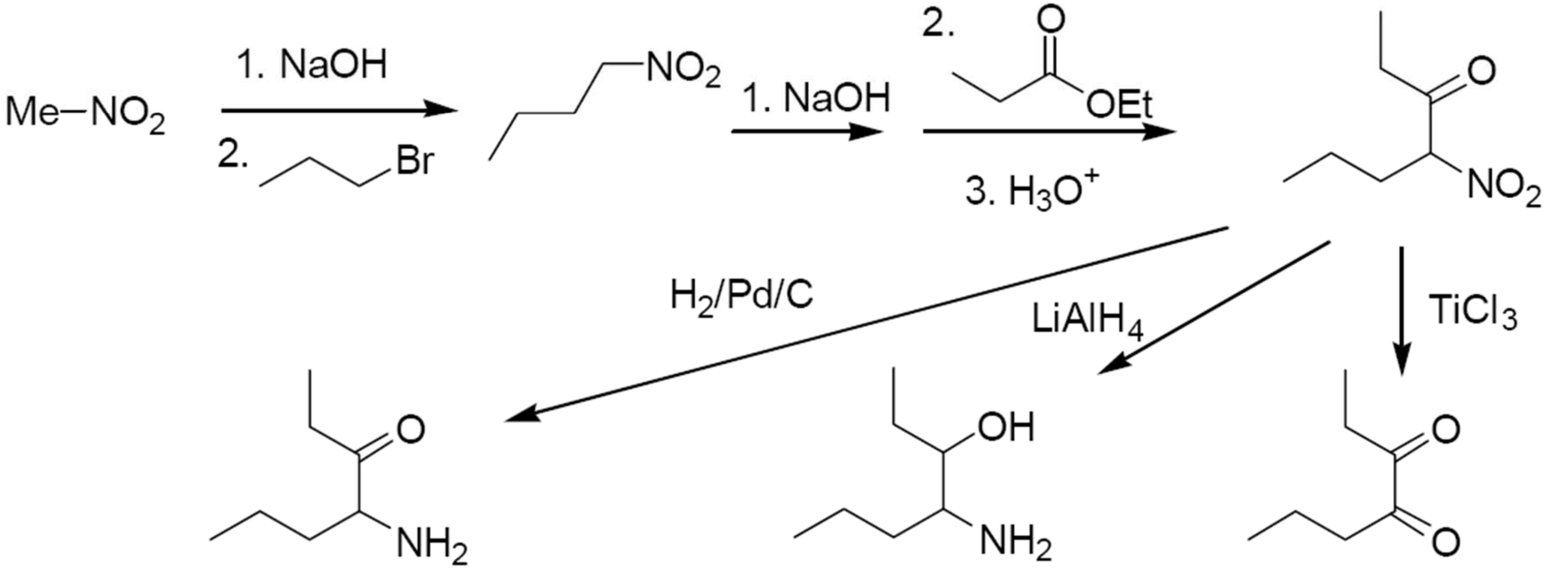
Nitro groups are rarely desirable themselves, however they can undergo useful FGIs:

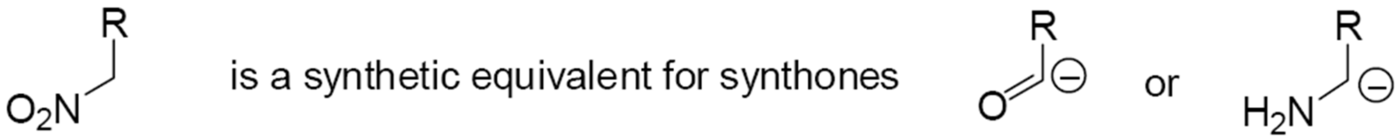


2.1.5. Umpolung strategies

2.1.5.4. *Nitroalkane nucleophile + electrophilic carbonyl*

Synthetic application:

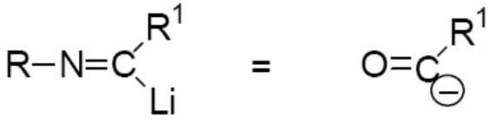




is a synthetic equivalent for synthones

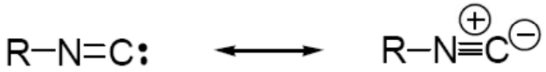
2.1.5. Umpolung strategies

2.1.5.5. Imidoyl nucleophile + electrophilic carbonyl

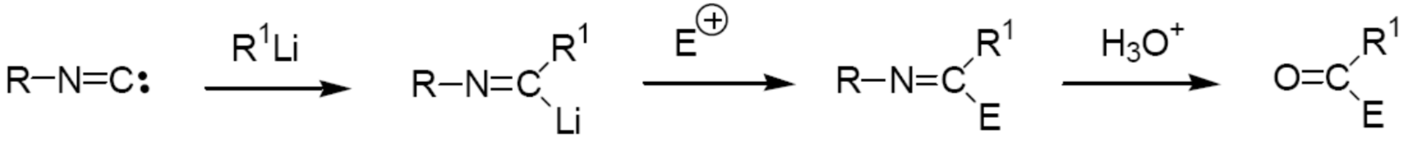


Preparation:

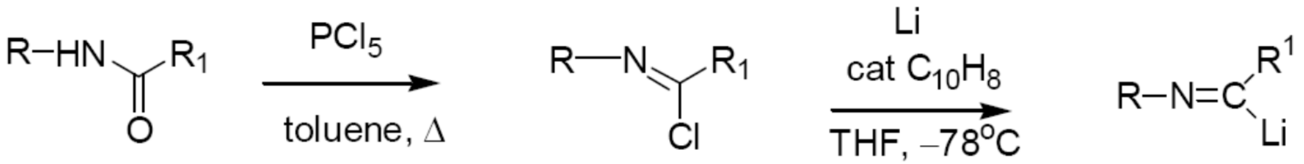
a) From isonitriles



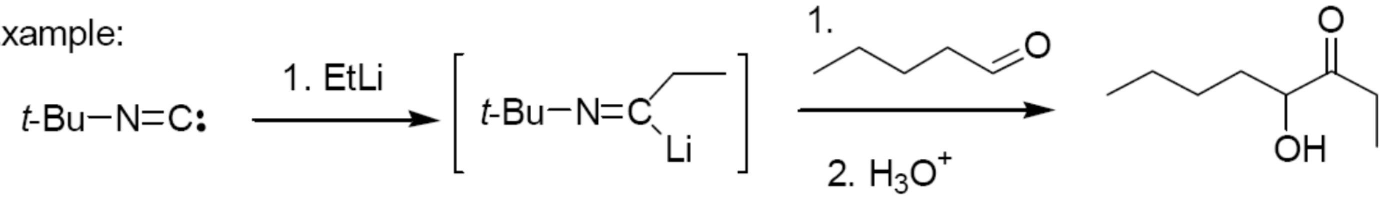
t-Bu−N=C: is commercially available



b) From amides via chloroimines

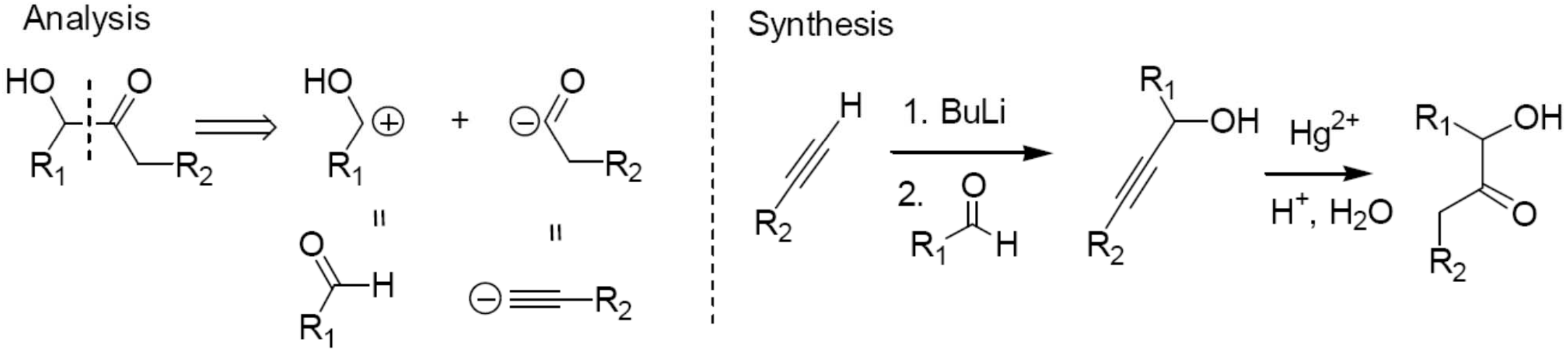


Example:



2.1.5. Umpolung strategies

2.1.5.6. *Alkyne nucleophile + electrophilic carbonyl*

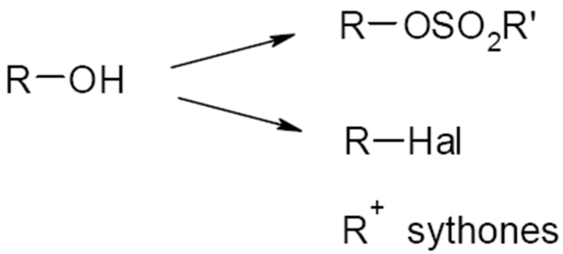


Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

2.2. Functional group interconversion: amine synthesis

In general, on the same oxidation level any functional group interconversion can be performed in more or less easy way:



$R{-}OH \rightarrow R{-}OSO_2R'$

$R{-}OH \rightarrow R{-}Hal$

R^+ sythones

$$R{-}X \xrightarrow{Y^-} R{-}Y$$

X = Hal, OTs, OMs, OTf

Y = OR', OCOR', SR', NR'_2, N_3, NO_2

With amines, alkylation usually produce mixtures:

$$RNH_2 \xrightarrow{MeI} RNHMe + RNMe_2 + R\overset{\oplus}{N}Me_3\ \overset{\ominus}{I}$$

2.2. Functional group interconversion: amine synthesis

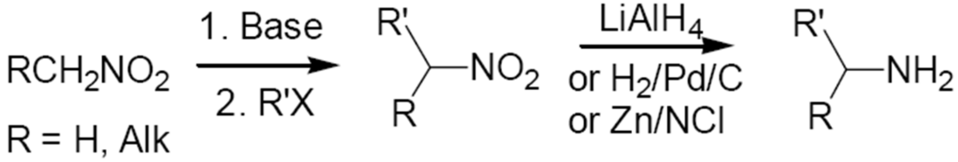
Primary amines:

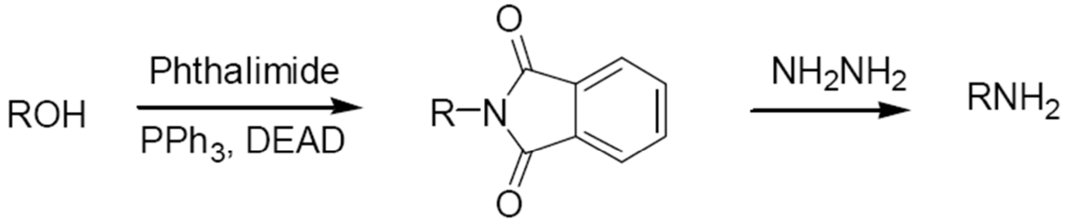
Primary amines at primary carbon

$$RX \xrightarrow{CN^{\ominus}} RCN \xrightarrow{LiAlH_4} RCH_2NH_2$$

Primary amines at primary or secondary carbon

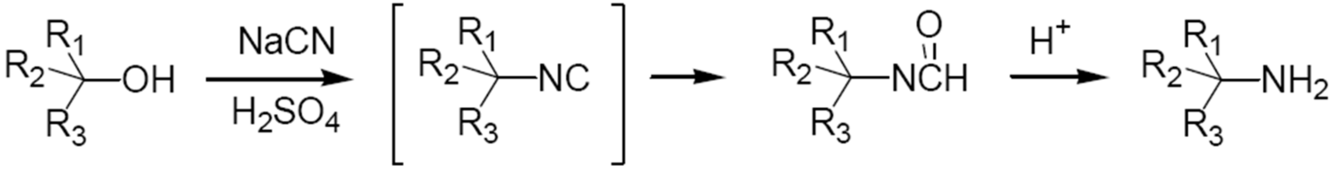
$$RX \xrightarrow{N_3^{\ominus}} RN_3 \xrightarrow[\text{or } H_2/Pd/C]{LiAlH_4} RNH_2$$





Mitsunobu reaction

Primary amines at secondary or tertiary carbon



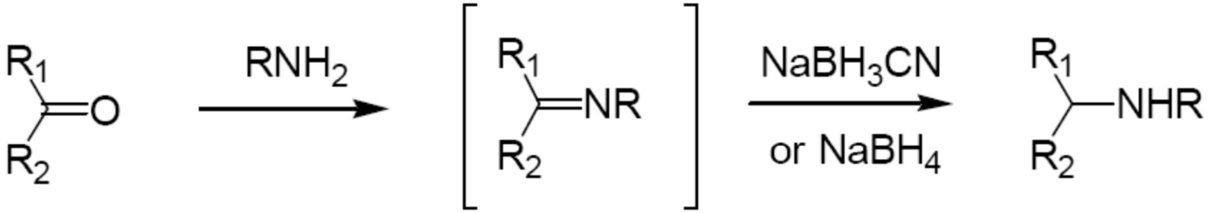
Ritter reaction

The Ritter reaction with alkylnitriles produces secondary amines

2.2. Functional group interconversion: amine synthesis

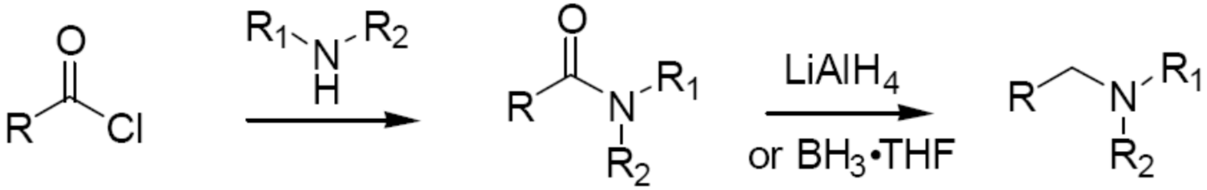
Secondary amines:

Reductive amination



If hydroxylamine (NH_2OH) is used in the place of RNH_2, reduction of the corresponding oxime gives primary amine.

Secondary and tertiary amines:



The method is also suitable for the preparation of primary amines ($R_1 = R_2 = H$).

Disconnection of molecules
according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.3. Synthetic strategies for 1,4-difunctionalised compounds

2.3.1. Acyl equivalent + Michael acceptor

2.3.2. Homoenolate + electrophilic carbonyl

2.3.3. Additional umpolung strategies

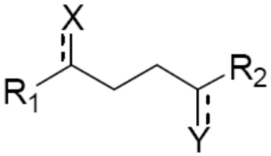
2.3.4. Functional group addition

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

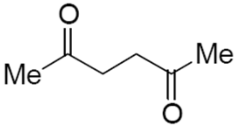
2.3. Synthetic strategies for 1,4-difunctionalised compounds

Approaches the synthesis of 1,4-difunctionalised compounds share a lot of common features with methods of preparation of 1,2-analogues discussed in the part 2.1.

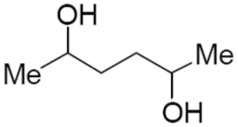


- There are a few commercially available derivatives
- In this case the strategies are mainly based on disconnection between the FGs.

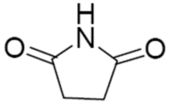
e.g.



2,5-Hexanedione



2,5-Hexanediol



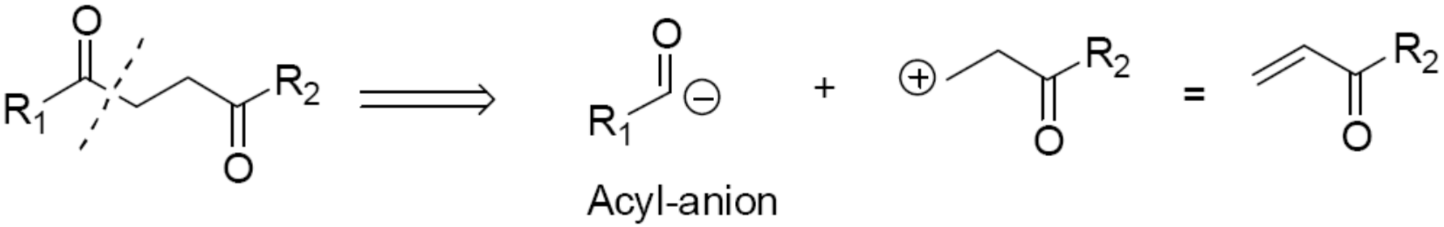
Succinimide

Disconnection of molecules according to the present FGs in the molecule:

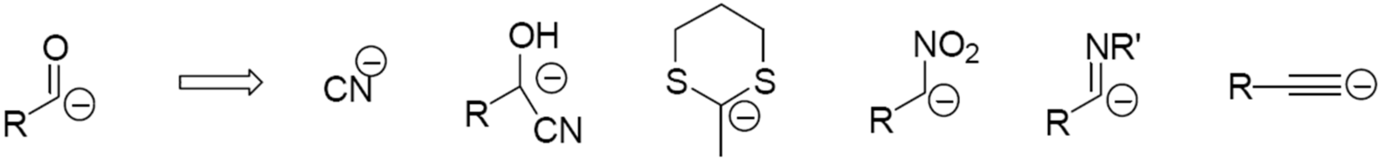
2-Group disconnections: unnatural reactivity patterns

2.3. Synthetic strategies for 1,4-difunctionalised compounds

2.3.1. Acyl equivalent + Michael acceptor

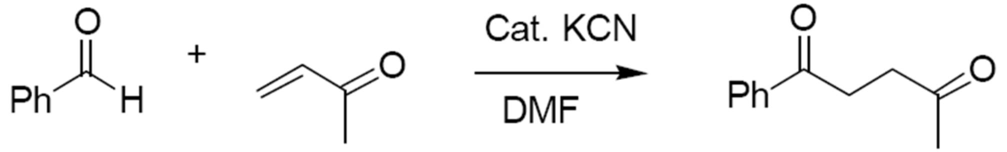


1. This approach is closely related to the synthesis of 1,5-dicarbonyl derivatives via addition of enolates to α,β-unsaturated carbonyl compounds.
2. However this time, acyl-anion synthons are employed as nucleophiles.
3. A selection of such reagents has been discussed in the section **2.1.5. Umpolung Strategies**.

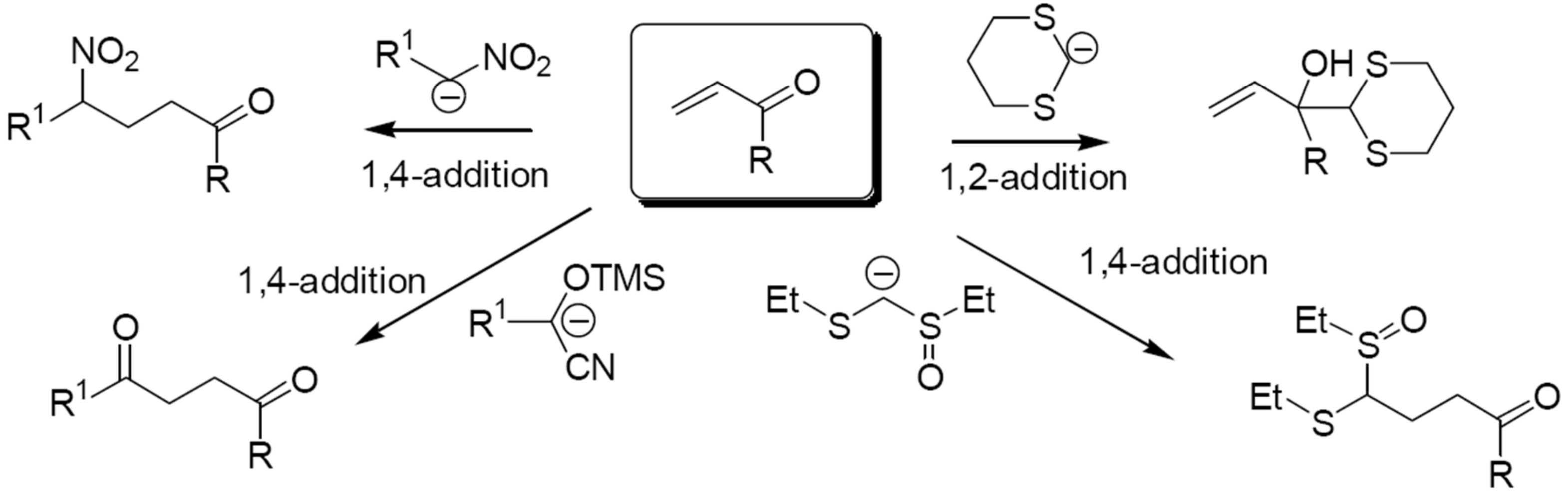


2.3.1. Acyl equivalent + Michael acceptor

Examples:



Regioselectivity issues:

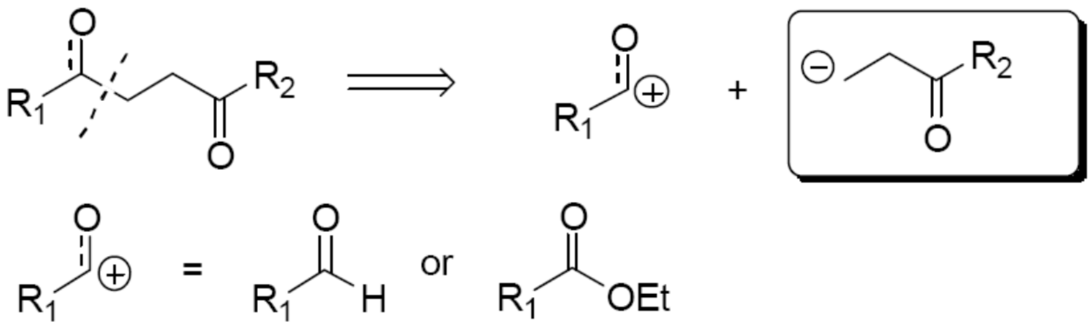


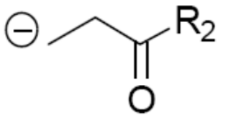
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

2.3. Synthetic strategies for 1,4-difunctionalised compounds

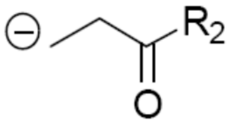
2.3.2. Homoenolate + electrophilic carbonyl





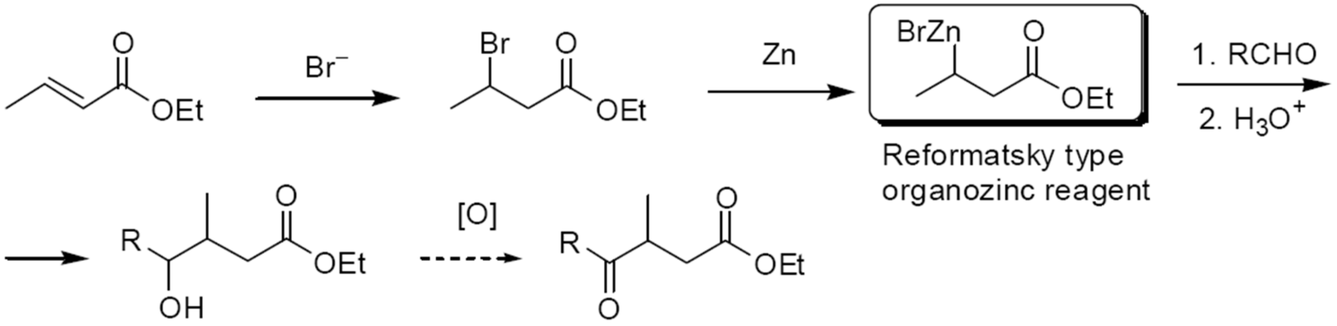
– homoenolate, this is *not* a resonanse stabilised enolate

2.3.2. Homoenolate + electrophilic carbonyl



– homoenolate,

Ester homoenolates (Zn and Ti):

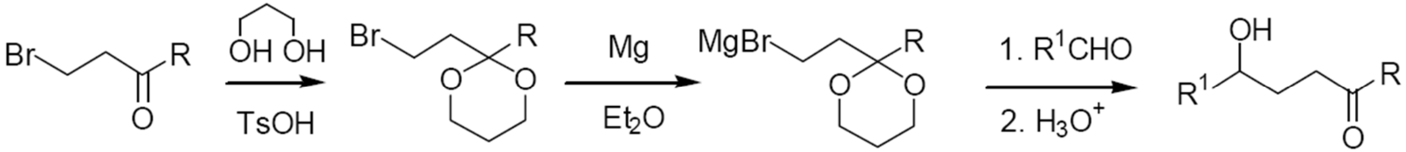


Reformatsky type organozinc reagent

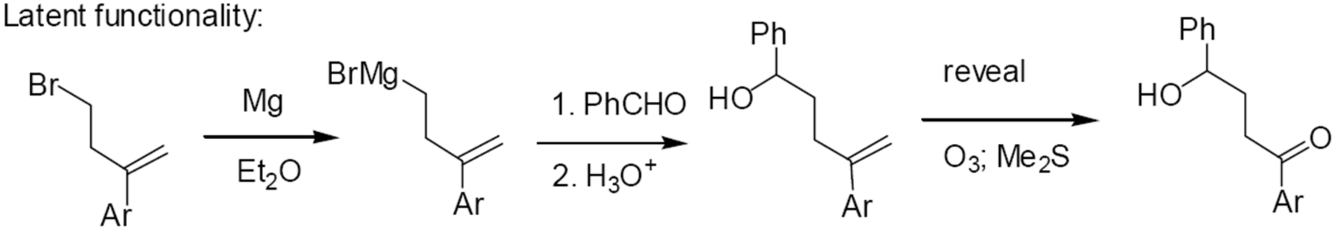
Ketone or aldehyde homoenolates:

Preparation of ketone or aldehyde homoenolates requires a different approach as the carbonyl group must be either protected or masked (latent) in the anionic reagent.

Protection:



Latent functionality:

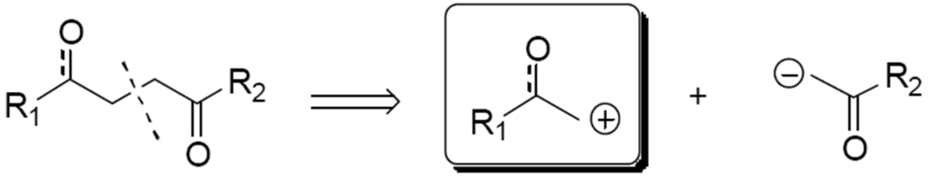


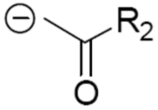
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

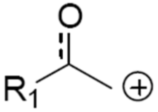
2.3. Synthetic strategies for 1,4-difunctionalised compounds

2.3.3. Additional umpolung strategies





– standard enolate



– electrophilic centre in α-position to carbonyl group

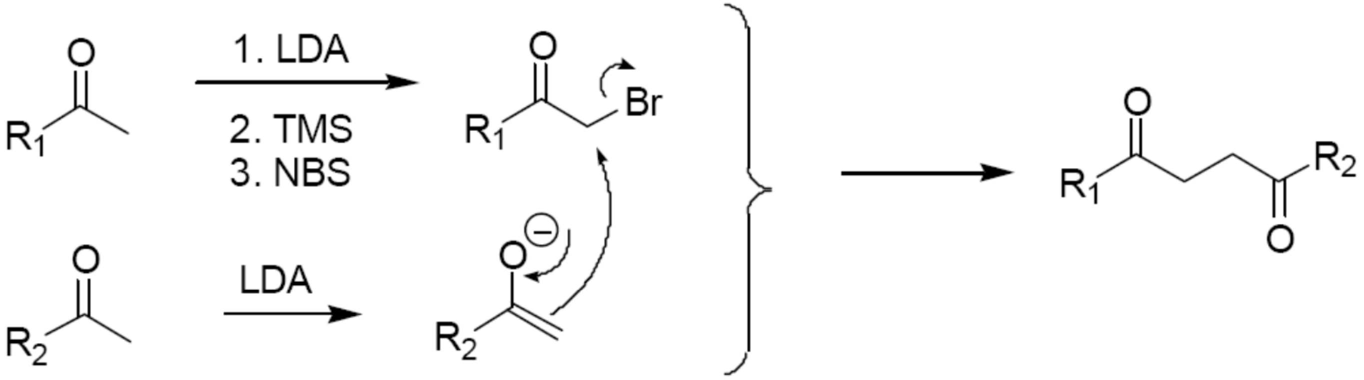
2.3.3.1. Enolate + α-functionalised carbonyl compound

2.3.3.2. Enolate + α,β-unsaturated nitrocompound (Michael-type acceptors)

2.3.3.3. Epoxide based transformations

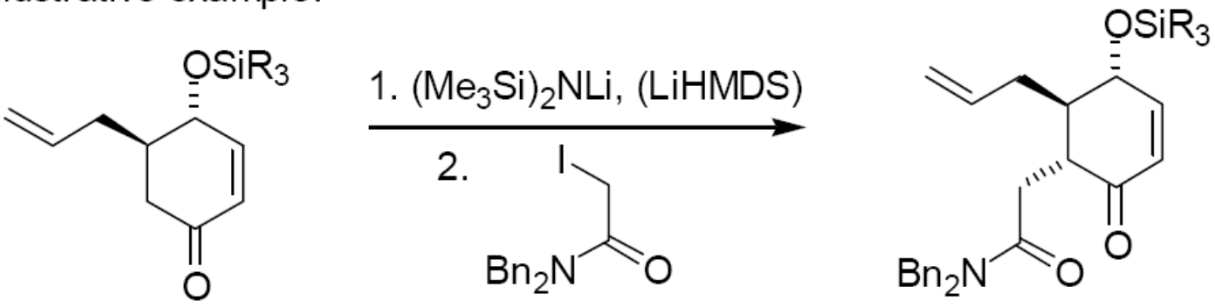
2.3.3. Additional umpolung strategies

2.3.3.1. Enolate + α-functionalised carbonyl compound



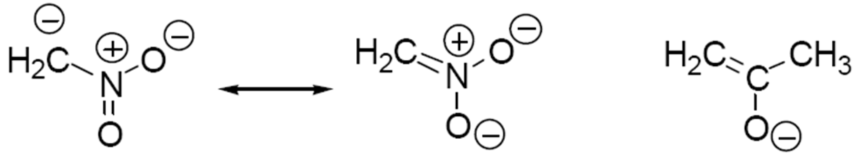
Note: α-bromoketone can be protected as ketal first to prevent enolisation during the reaction

Illustrative example:

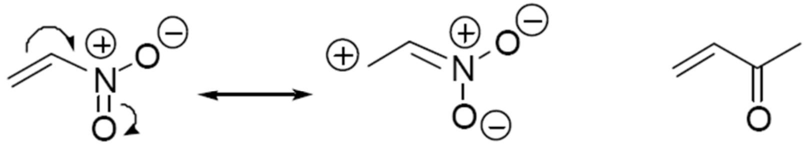


2.3.3. Additional umpolung strategies

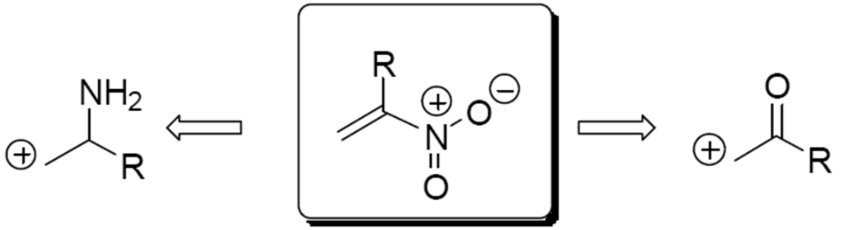
2.3.3.2. Enolate + α,β-unsaturated nitrocompound (Michael-type acceptors)



Nitroalkanes are acyl-anion equivalents, they resemble enolates but have one carbon atom less



Nitroalkenes resemble α,β-unsaturated carbonyl compounds (Michael acceptors) but have one carbon atom less.

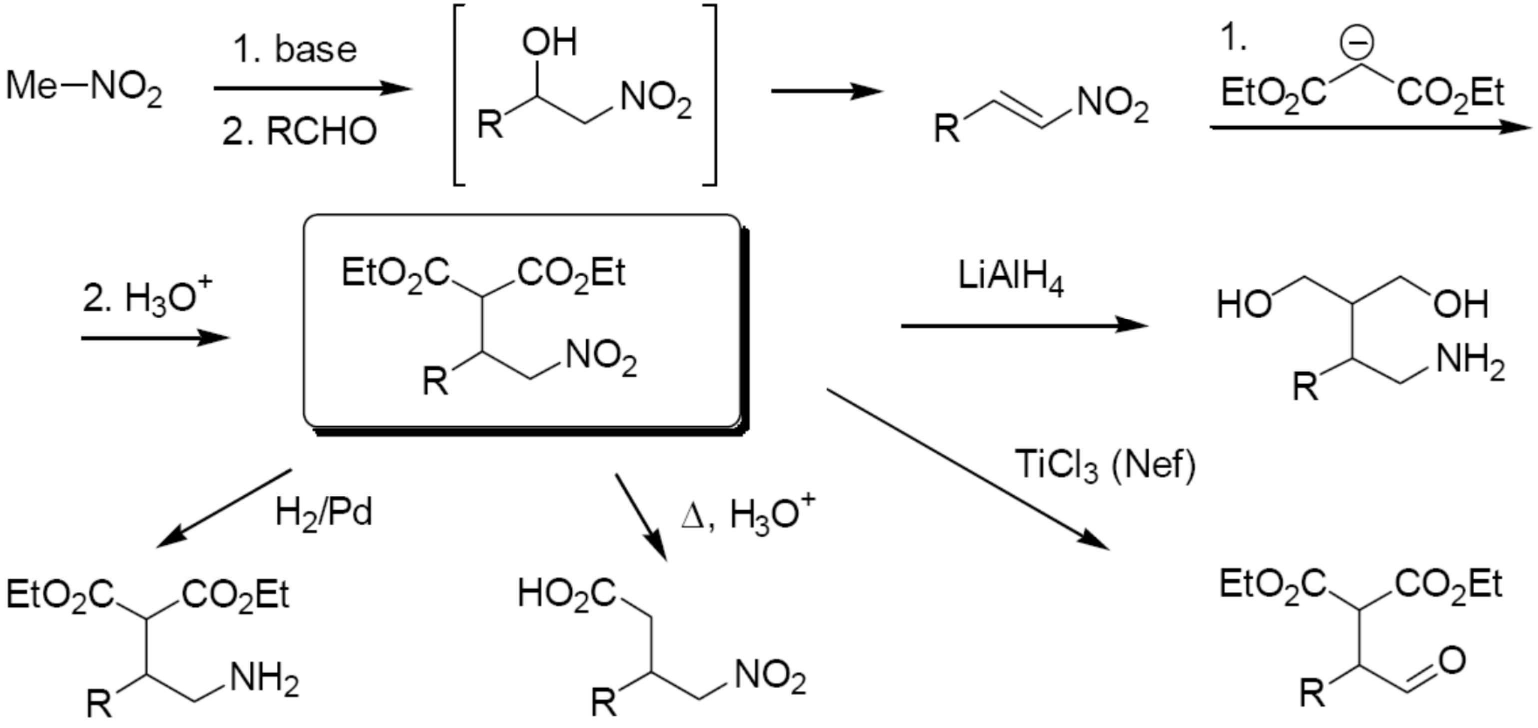


Nitroalkenes can be viewed as reagents for carbonyl and nitrogen based functionalities

2.3.3. Additional umpolung strategies

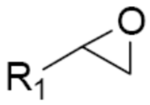
2.3.3.2. Enolate + α,β-unsaturated nitrocompound (Michael-type acceptors)

Examples:

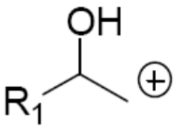


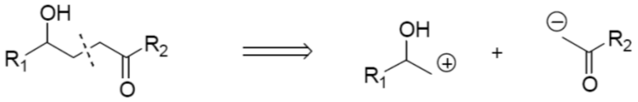
2.3.3. Additional umpolung strategies

2.3.3.2. Epoxide based transformations

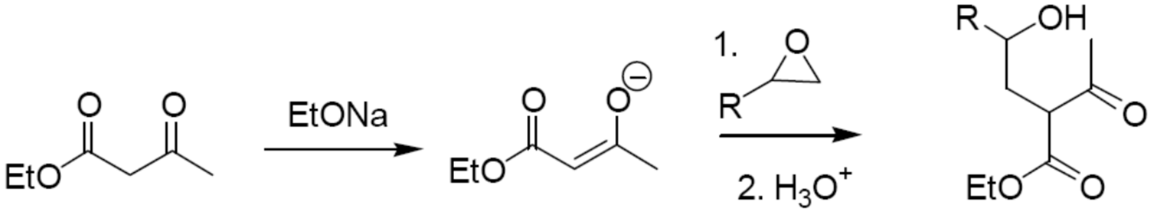


Epoxide can be viewed as
a ***synthetic equivalent*** to ***synthon***



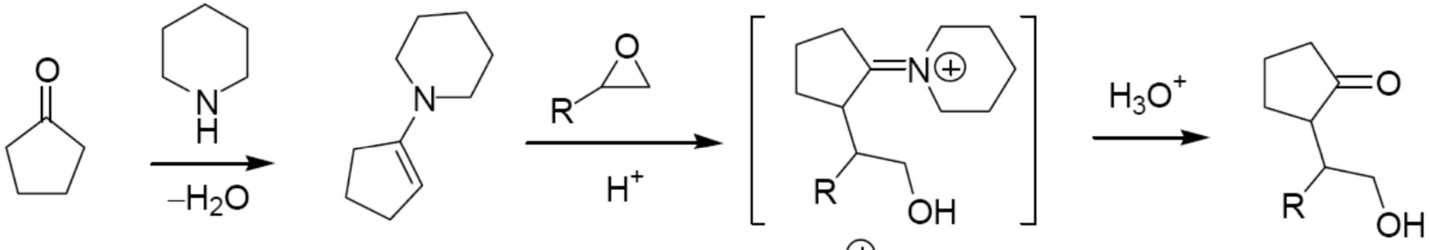


a) Opening of epoxides with enolates of β-dicarbonyl compounds:

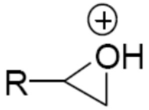


In general, epoxides are opened by nucleophiles at the ***less hindered side (S$_N$2 type)***

b) Opening of epoxides with enamines catalysed by acids:



In acid, the reaction proceed *via* intermediate



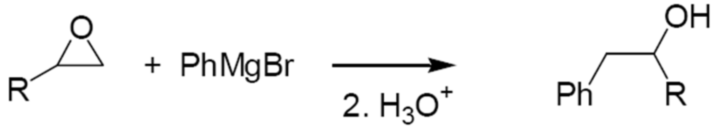
The opening occures at the side with ***more stable cation (S$_N$1 type)***

2.3.3. Additional umpolung strategies

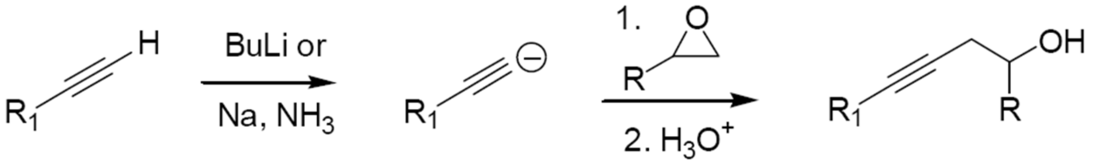
2.3.3.2. Epoxide based transformations

c) Epoxides can be opened with a variety of nucleophiles and are often used for the synthesis of a wide range of alcohols:

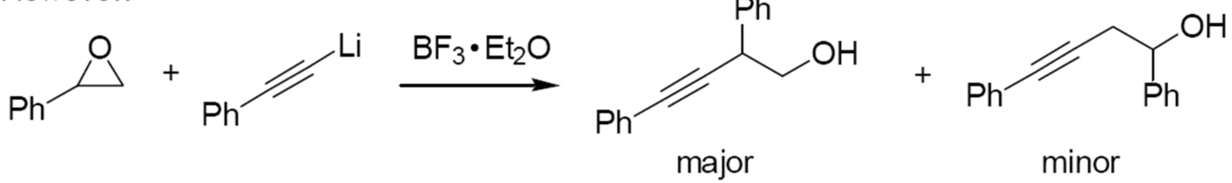
Nucleophiles include CN^-, dithiane anions, Grignar reagents, *e.g.*:



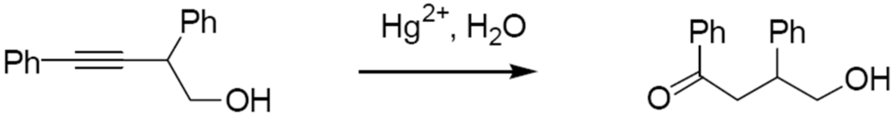
Use of alkynyl anions:



However:



The product can be further converted into 1,4-difunctionalised compound



Disconnection of molecules according to the present FGs in the molecule:

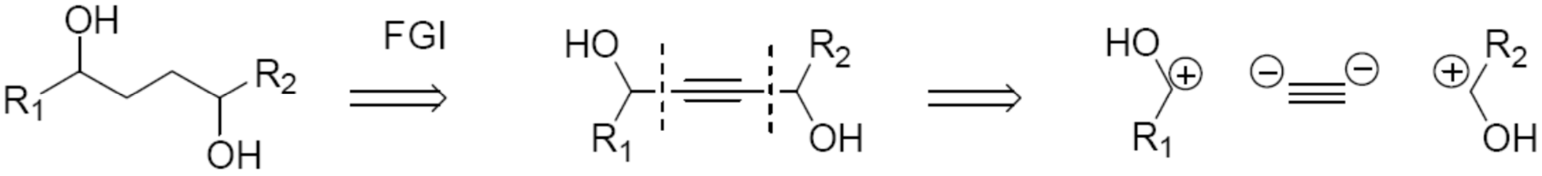
2-Group disconnections: unnatural reactivity patterns

2.3. Synthetic strategies for 1,4-difunctionalised compounds

2.3.4. Functional group addition

Retrosynthetic technique of introducing a required functional group to facilitate a certain chemical transformation

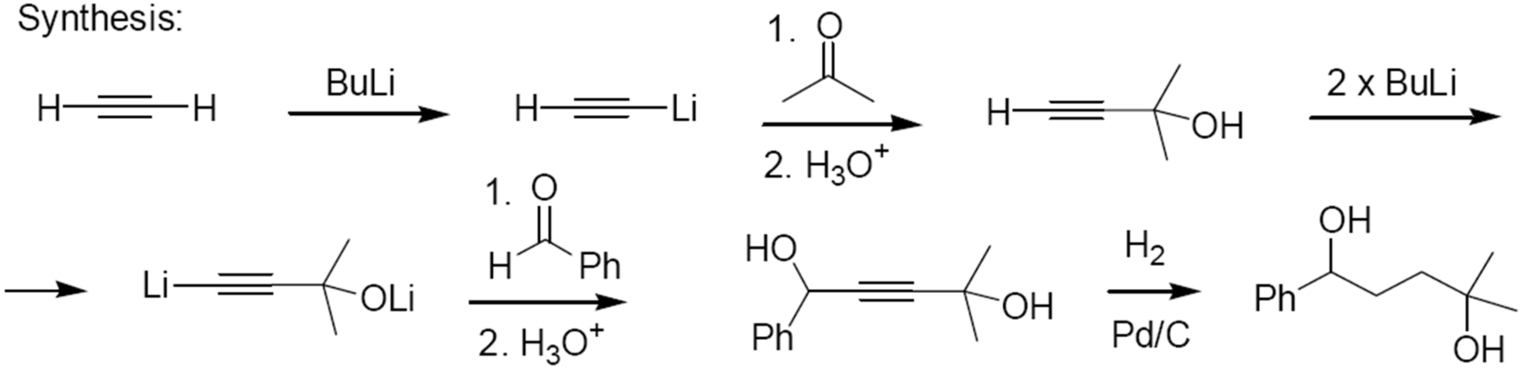
Alkynyl-anions have already proved to be useful reagents for acyl-anion synthons, In addition, synthetic versatility of alkyne functionality can be further exploited in organic synthesis.



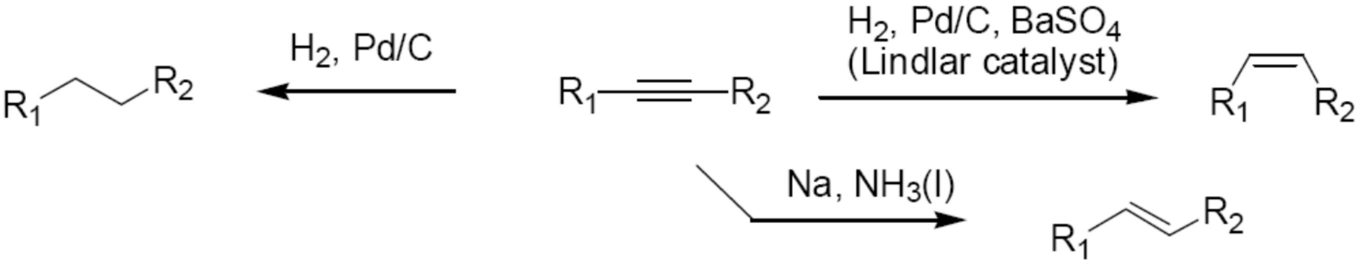
There is no reagent corresponding to this synthon, therefore the synthesis has to proceed stepwise

2.3.4. Functional group addition

Synthesis:

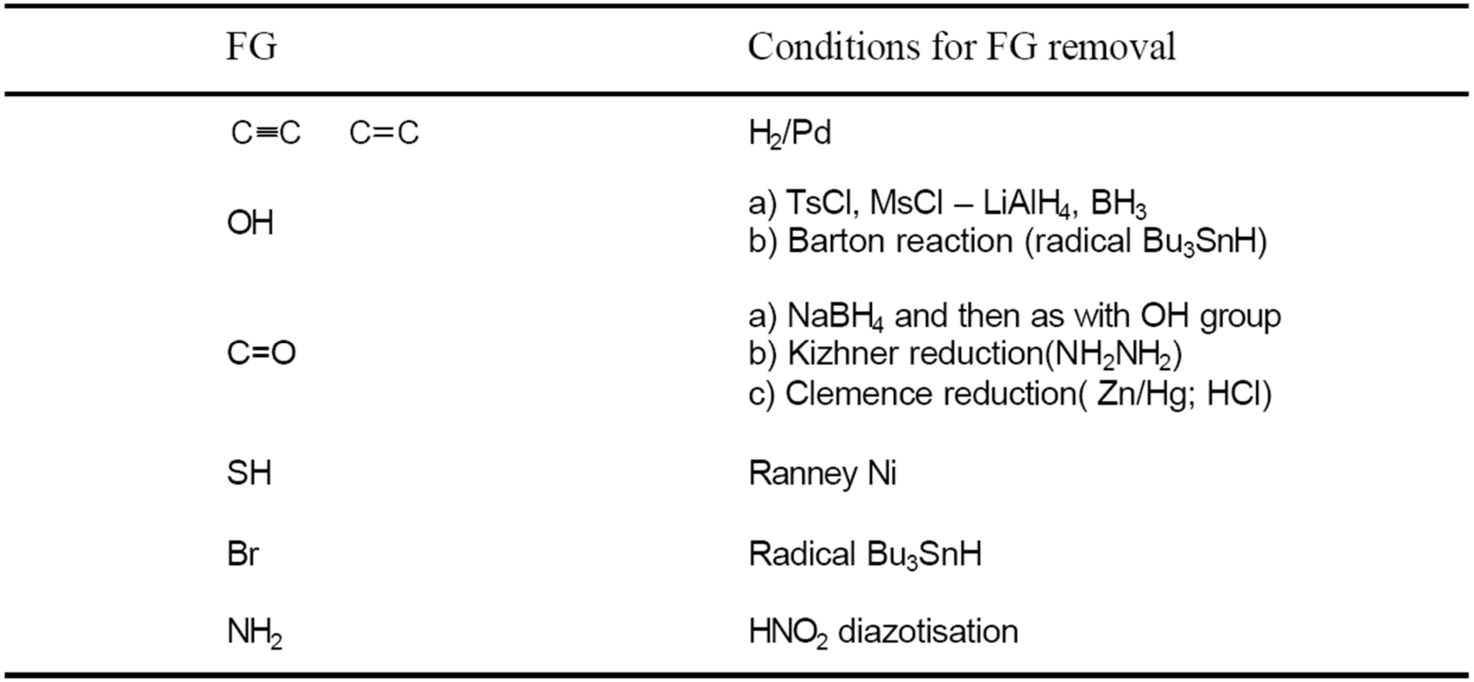


Note: other usefull transformations of alkynes include chemo- and stereoselective reduction:



2.3.4. Functional group addition

Functional Group Addition (**FGA**) strategy employed in the example above to facilitate the construction of the required structural arrangement can be further extended to retrosynthetic analysis of target molecules with few or no functional groups. **FGA** is a **retrosynthetic technique**, the corresponding **synthetic** procedure is functional group **removal**.



FG	Conditions for FG removal
$C\equiv C$ $C=C$	H_2/Pd
OH	a) TsCl, MsCl – $LiAlH_4$, BH_3 b) Barton reaction (radical Bu_3SnH)
$C=O$	a) $NaBH_4$ and then as with OH group b) Kizhner reduction(NH_2NH_2) c) Clemence reduction(Zn/Hg; HCl)
SH	Ranney Ni
Br	Radical Bu_3SnH
NH_2	HNO_2 diazotisation

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.4. Synthetic approaches to cyclic systems

2.4.1. Cycloaddition

2.4.2. Conventional methods of acyclic chemistry

2.4.3. Other methods

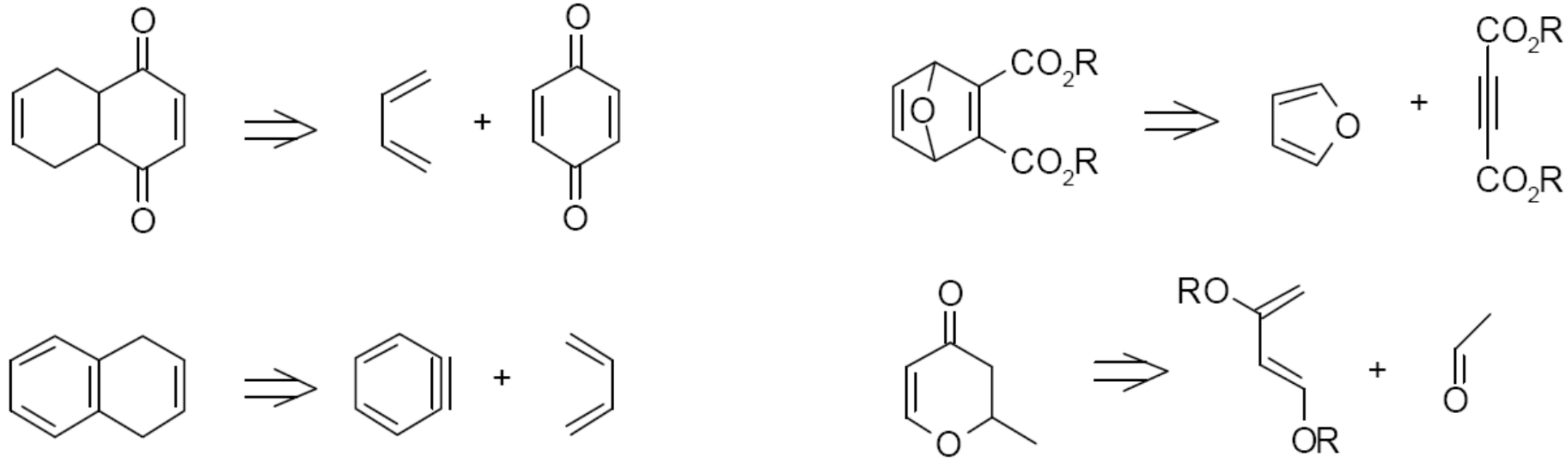
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.4. Synthetic approaches to cyclic systems

2.4.1. Cycloaddition

Some types of Diels-Alder disconnections:



Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.4. Synthetic approaches to cyclic systems

2.4.2. Conventional methods of acyclic chemistry

For the construction of ring systems a set of conventional disconnections can be considered, including intramolecular SN2, Robinson annulation, aldol, Dieckmann, etc.

Intramolecular reactions are usually favoured kinetically over intermolecular reactions.

- This factor is greatest for 3- and 5-membered ring formation, and to lesser extent for 6- and 7- membered cycles.
- On the other hand, thermodinamic factors strongly favour formation of 6-membered rings.
- Taking both kinetic and thermodinamic factors into account, 5-,6- and 7- membered rings are easy to make, 3-membered rings are also easy to make but often break down under the conditions of their formation, while 4-membered rings are very difficult to make and require different synthetic approaches.

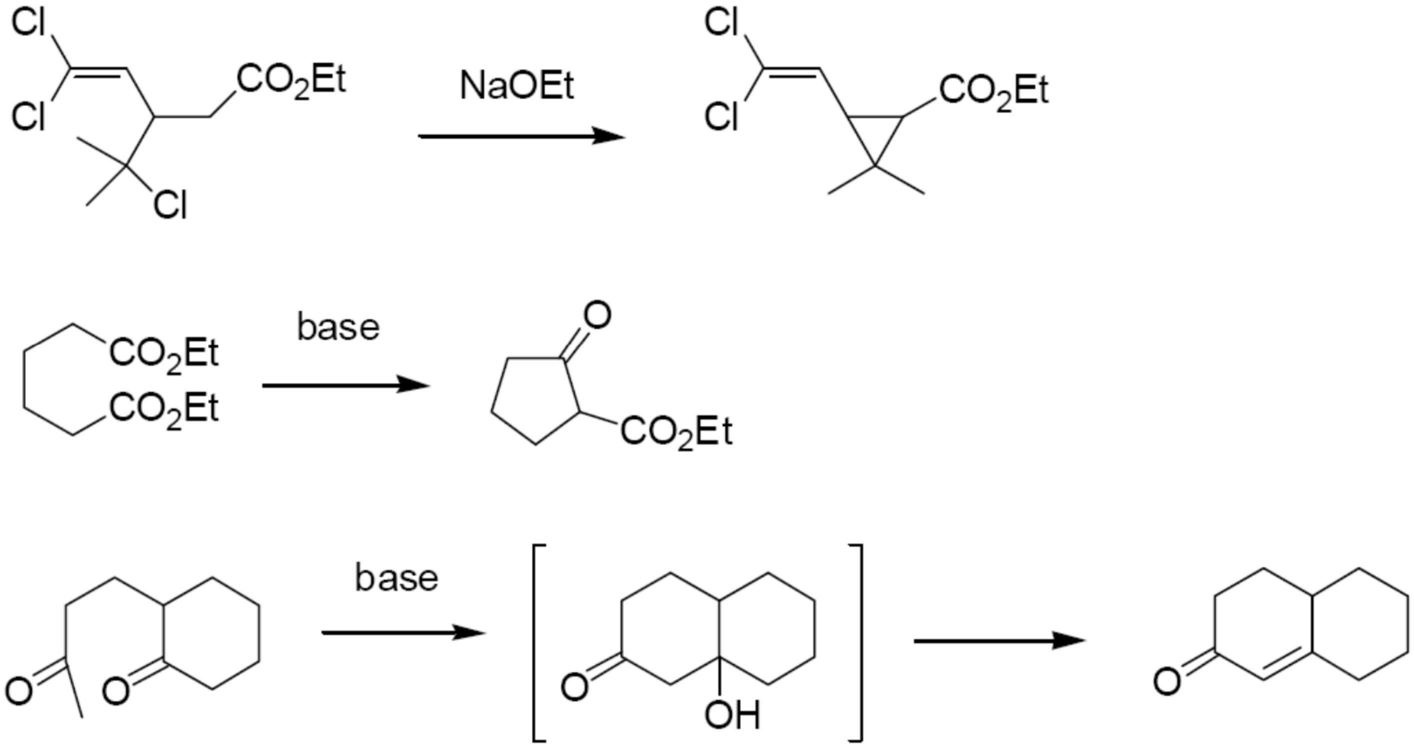
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.4. Synthetic approaches to cyclic systems

2.4.2. Conventional methods of acyclic chemistry

Some examples of cyclisation reactions:

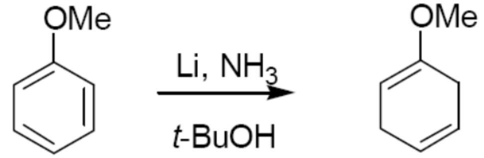


Disconnection of molecules according to the present FGs in the molecule:

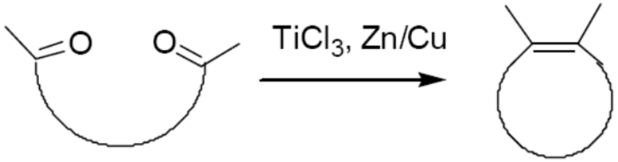
2-Group disconnections: unnatural reactivity patterns

2.4. Synthetic approaches to cyclic systems

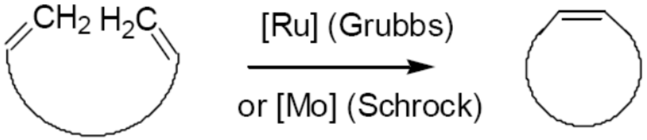
2.4.3. Other methods



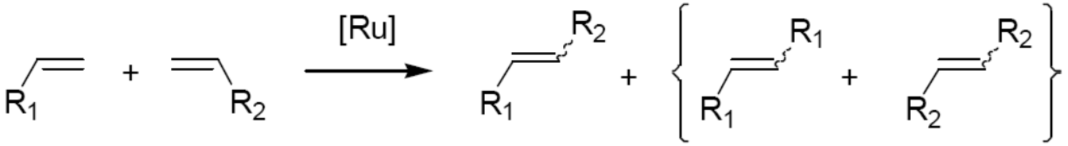
Birch reduction



McMurry coupling



Ring Closing Alkene Metathesis



Cross Metathesis

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: <u>unnatural reactivity patterns</u>

2.5. Reconnection strategies

2.5.1. Ozonolysis of cycloalkenes

2.5.2. Baeyer-Villiger rearrangement

2.5.3. Beckmann and related rearrangements

In retrosynthetic analysis, open chain 1,6-difunctionalised compounds can be linked to appropriate cyclic precursors.
In this case, the term “disconnection” is applied to ***reconnection*** strategies, which can also be used to make compounds with two functional groups related to each other as 1,5-, 1,7- and others.

Disconnection of molecules according to the present FGs in the molecule:

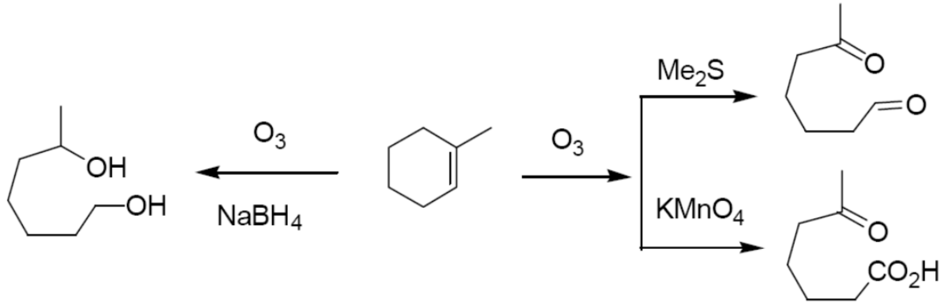
2-Group disconnections: unnatural reactivity patterns

2.5. Reconnection strategies

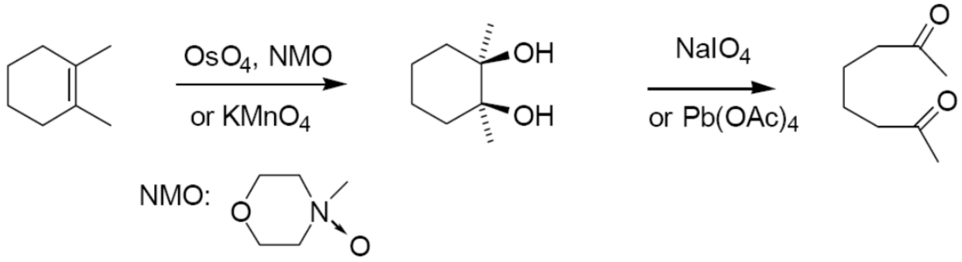
2.5.1. Ozonolysis of cycloalkenes

Functional groups with 1,6-relationship are too far apart for any conventional disconnection strategies.

However, it is known that ozonolysis of cyclohexene creates two functional groups which are exactly 1,6-related.



Similar transformation can be also achieved in an indirect way:

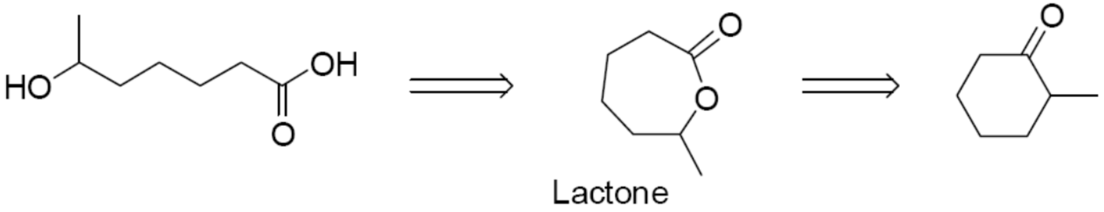


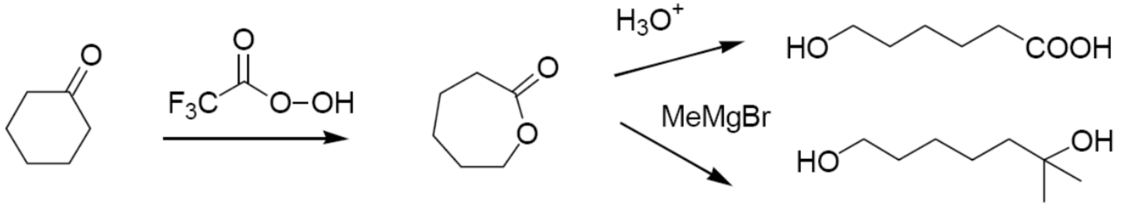
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

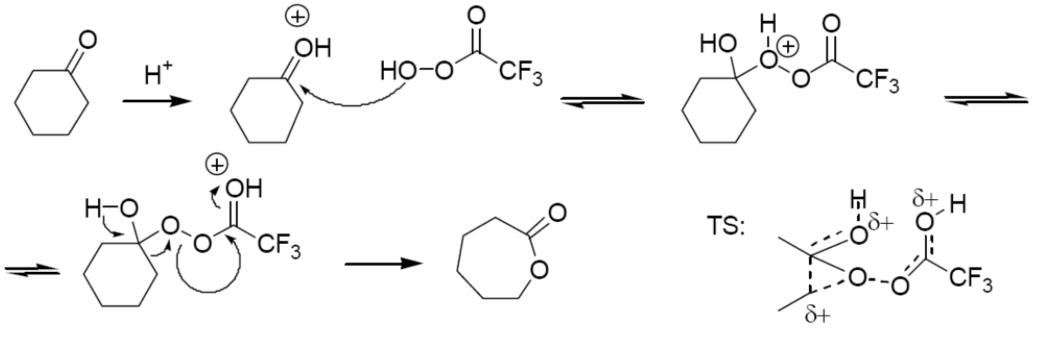
2.5. Reconnection strategies

2.5.2. Baeyer-Villiger rearrangement





Mechanism:



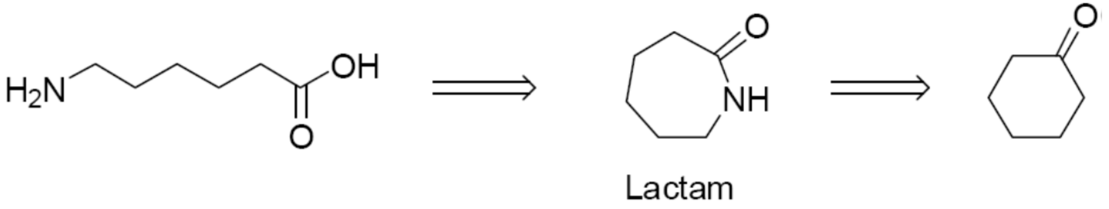
The reaction is regioselective.
Migration order: 3 > 2 ~ Ar >1.

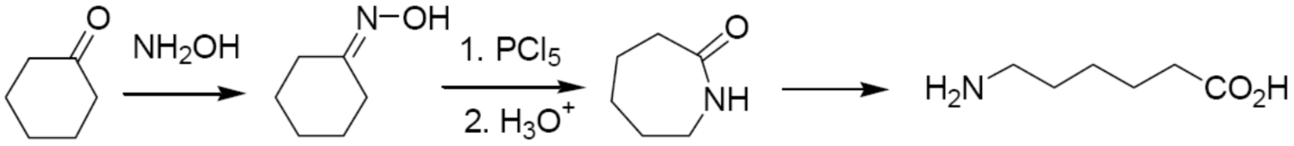
Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

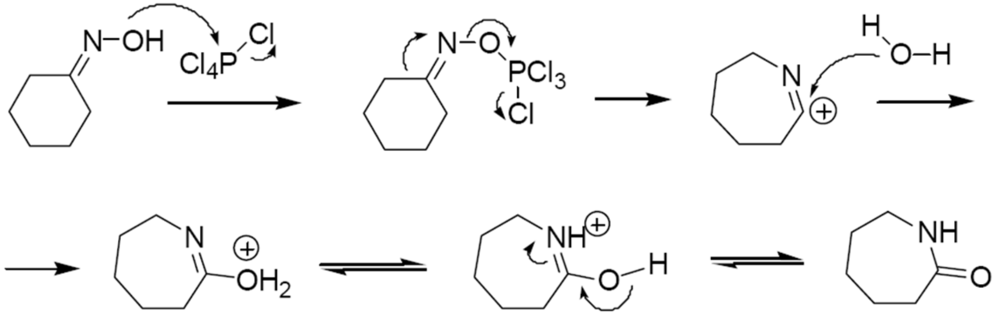
2.5. Reconnection strategies

2.5.3. Beckmann and related rearrangements





mechanism:

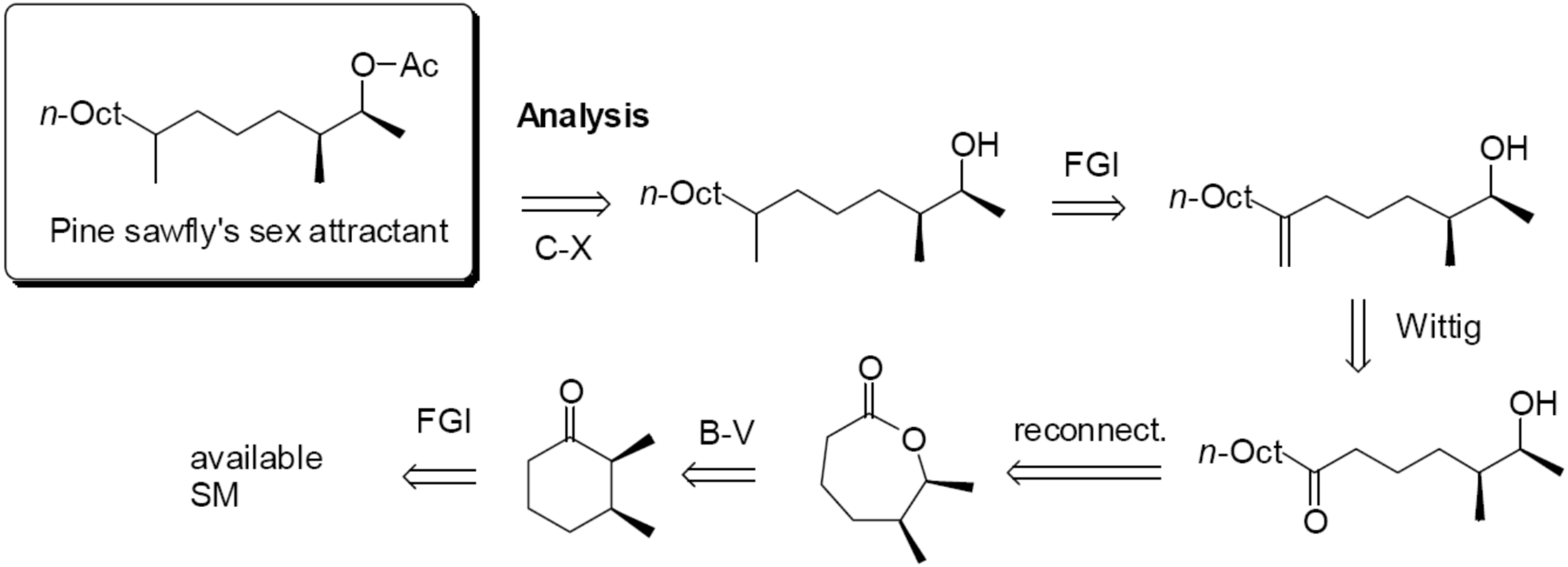


the group positioned *anti* to oxime is migrating.

Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.5. Reconnection strategies



Disconnection of molecules according to the present FGs in the molecule:

2-Group disconnections: unnatural reactivity patterns

2.5. Reconnection strategies