BSc SEMESTER-IV HONS ORGANIC CHEMISTRY; PAPER-CC-10

ADVANCED RETROSYNTHESIS

General overview.

1. **Introduction**: summary on disconnections and normal carbonyl reactivity. Definition of disconnection, FGI (functional group interconversion), synthon and reagent, synthetic strategies and tactics. Examples of *one-group* and *two-group* disconnections. Revision of normal carbonyl reactivity.

2. **2-Group disconnections: unnatural reactivity patterns and other strategies**
   - 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
   - 2.2. **Functional group interconversion: amine synthesis**
   - 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:
       - 2.3.3.1. Enolate + α-functionalised carbonyl compound
       - 2.3.3.2. Enolate + α,β-unsaturated nitrocompound (Michael-type acceptors
       - 2.3.3.3. Epoxide based transformations
     - 2.3.4. Functional group addition (retrosynthetic technique of introducing a required functional group to facilitate a certain chemical transformation)
   - 2.4. **Synthetic approaches to cyclic systems**
     - 2.4.1. Cycloadditions
     - 2.4.2. Conventional methods of acyclic chemistry
     - 2.4.3. Other methods
   - 2.5. **Reconnection strategies**
     - 2.5.1. Ozonolysis of cycloalkenes
     - 2.5.2. Baeyer-Villiger rearrangement
     - 2.5.3. Beckmann and related rearrangements

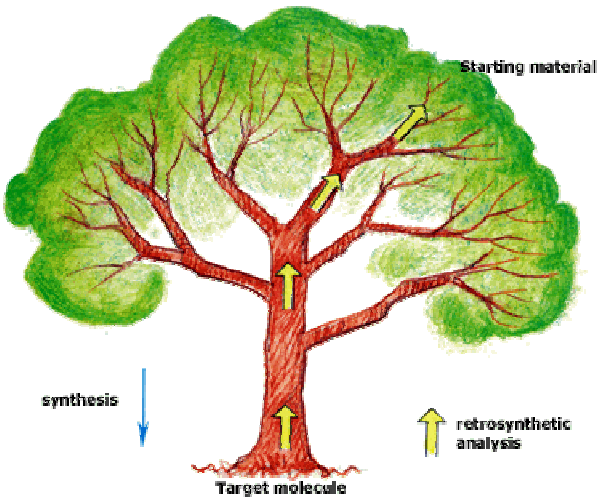
3. **Summary of retrosynthetic strategies; some guidelines for retrosynthetic analysis; useful synthons**.

1. Introduction: summary on disconnections.

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 transformation of a molecule to a synthetic precursor is accomplished by

- ***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.

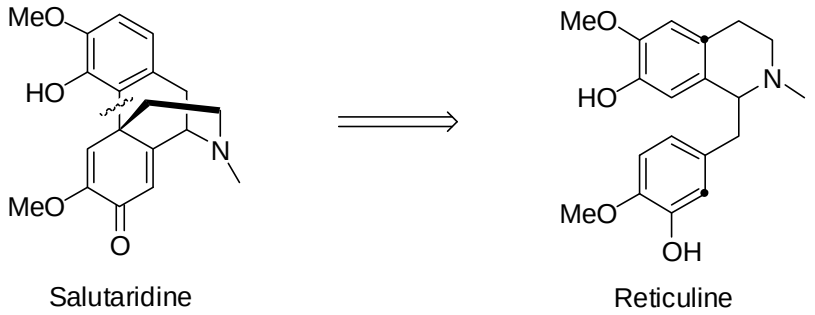


Each structure thus derived from TM then itself becomes a TM for further analysis. Repetition of the process eventually produces a tree of intermediates having chemical structures in the nodes and possible chemical transformations as pathways from bottom to TM. One should avoid excessive branching and proliferation of useless pathways. Strategies for control and guidance are of the utmost importance.

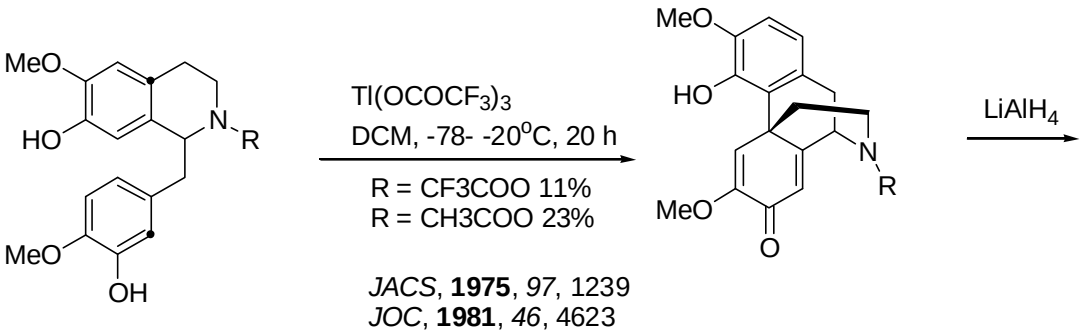
Synthetic Strategies: Choosing the way along the retrosynthetic tree, synthetic planning.
Synthetic Tactics: How a specific bond or set of bonds at a given site can be efficiently created.

Two main Synthetic Strategies:

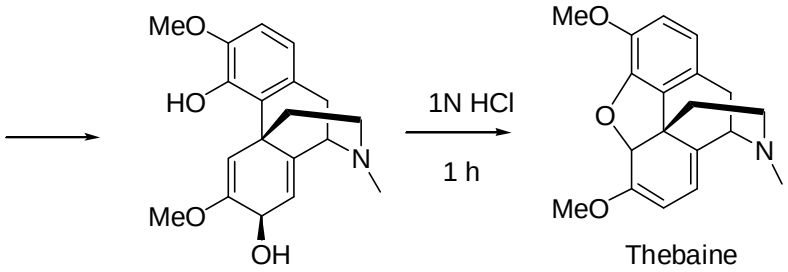
1) Strategic disconnection approach



Salutaridine Reticuline



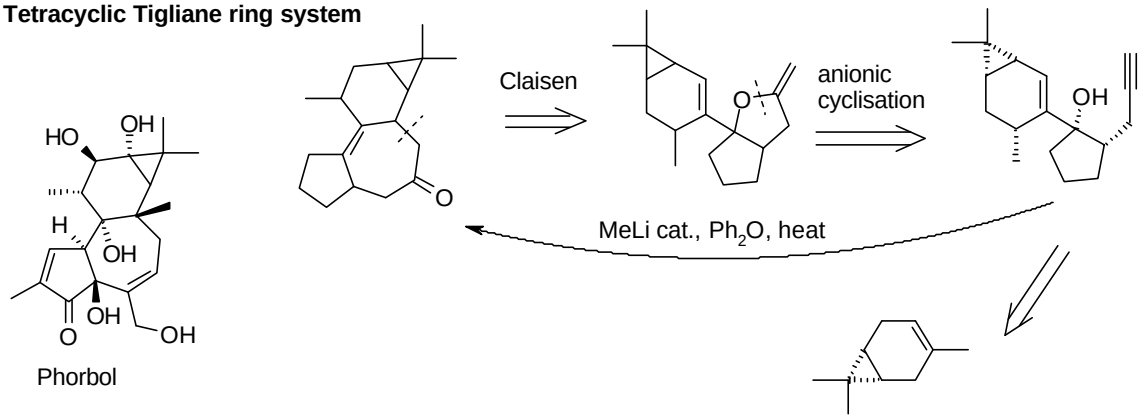
JACS, **1975**, *97*, 1239
JOC, **1981**, *46*, 4623



Thebaine

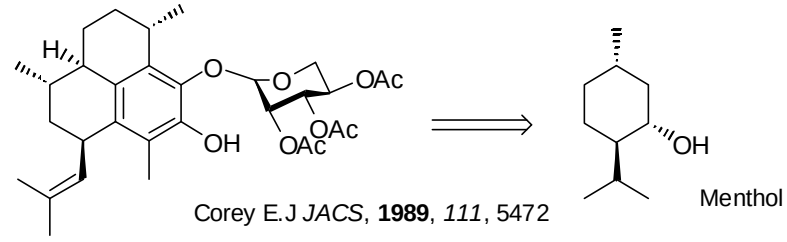
2) Strategic structure approach

Tetracyclic Tigliane ring system

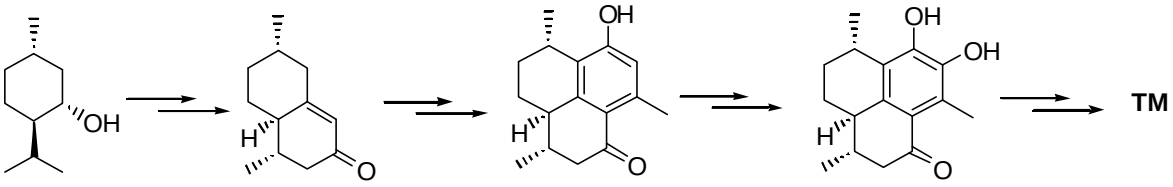


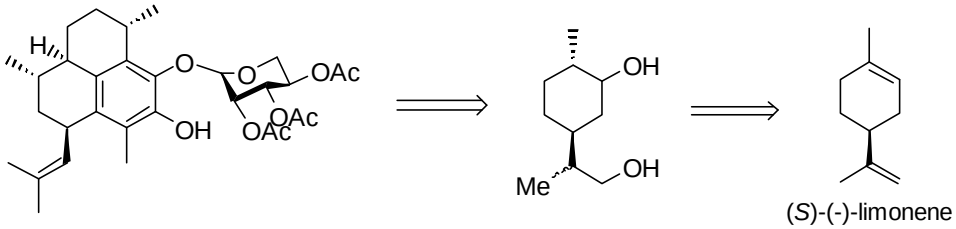
Ovaska TV *et al*, *Org. Lett.* **2001**, *3*, 115

Pseudopterosin A



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



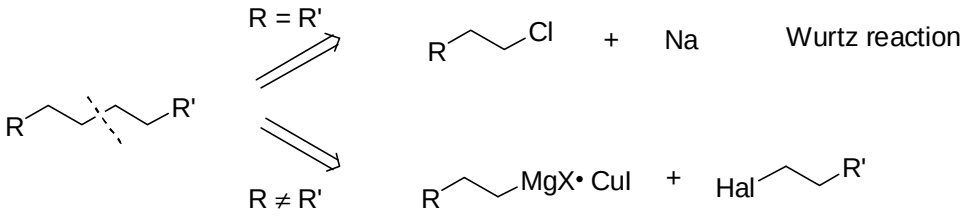


Corey E.J *JACS*, **1998**, *120*, 12777

Synthetic Tactics.

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

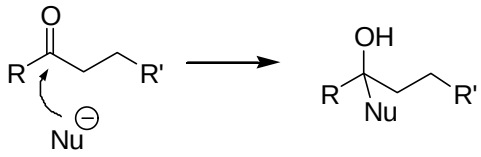
a) *C-C bond with no functional group present*:



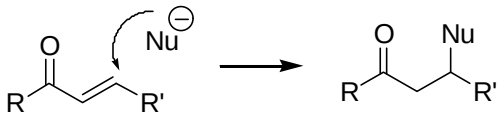
b) *One-group disconnections based on normal carbonyl reactivity*.

Normal carbonyl reactivity:

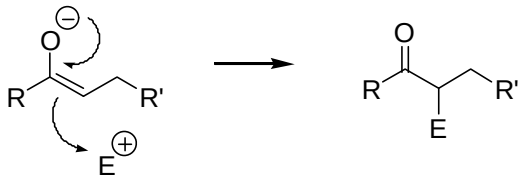
ACCEPT electrons at the C=O carbon



ACCEPT electrons at the β-carbon of the enone



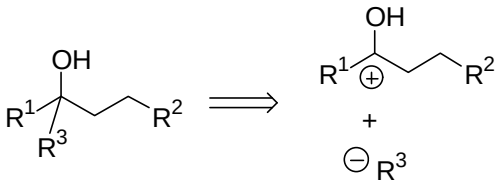
DONATE electrons to the α-carbon *via* the enolate



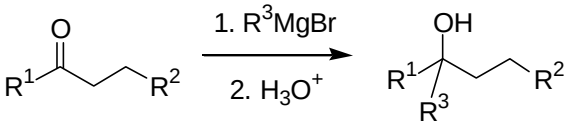
Synthetic planning should show an analysis of the problem followed by synthetic solution.

Alcohols

Analysis

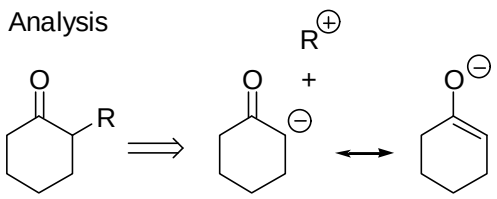


Synthesis



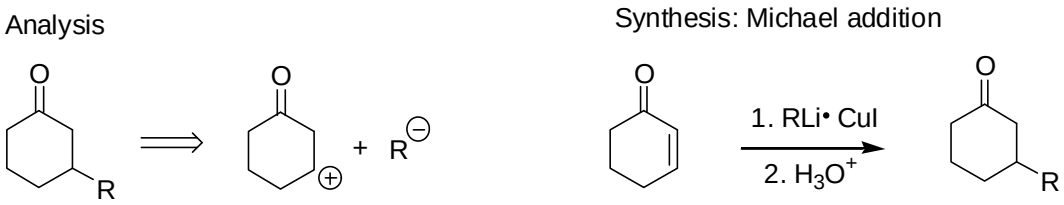
Carbonyl compounds brunched at α-carbon.

Analysis

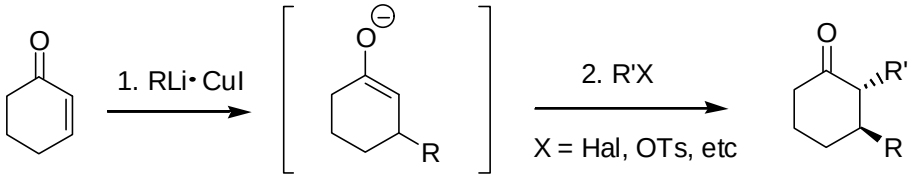


Synthesis

Carbonyl compounds branched at β-carbon.

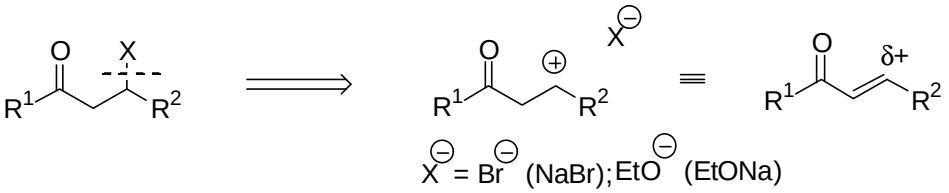


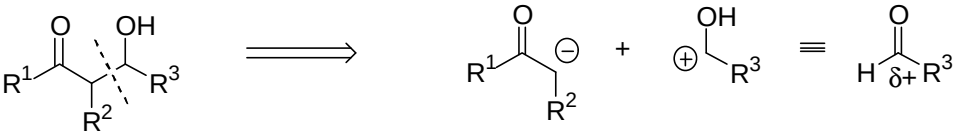
Combination of the last two synthetic approaches allows the introduction of two new groups:

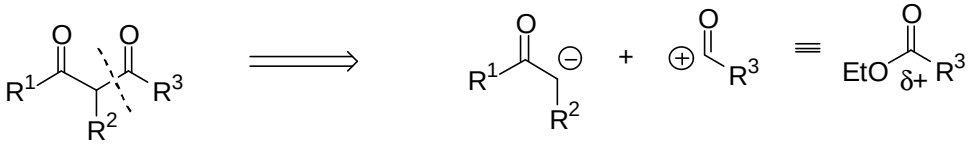


c) *Two-group disconnections based on normal carbonyl reactivity.*

1,3-Difunctionalised compounds

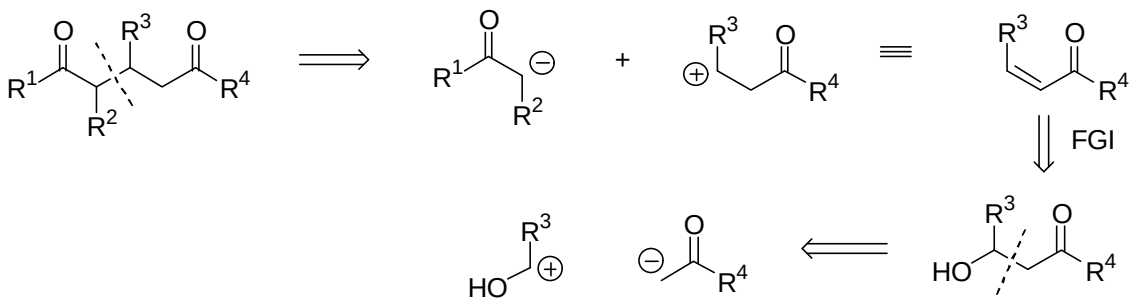


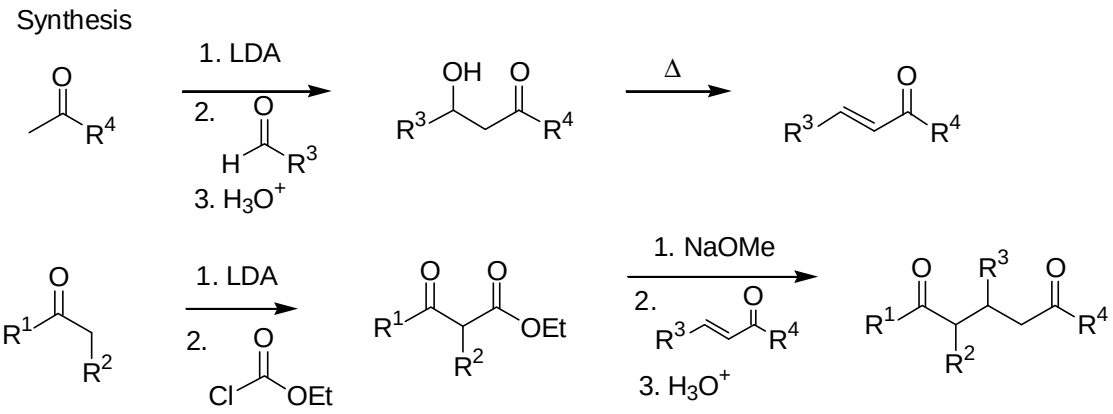




1,5-Difunctionalised compounds

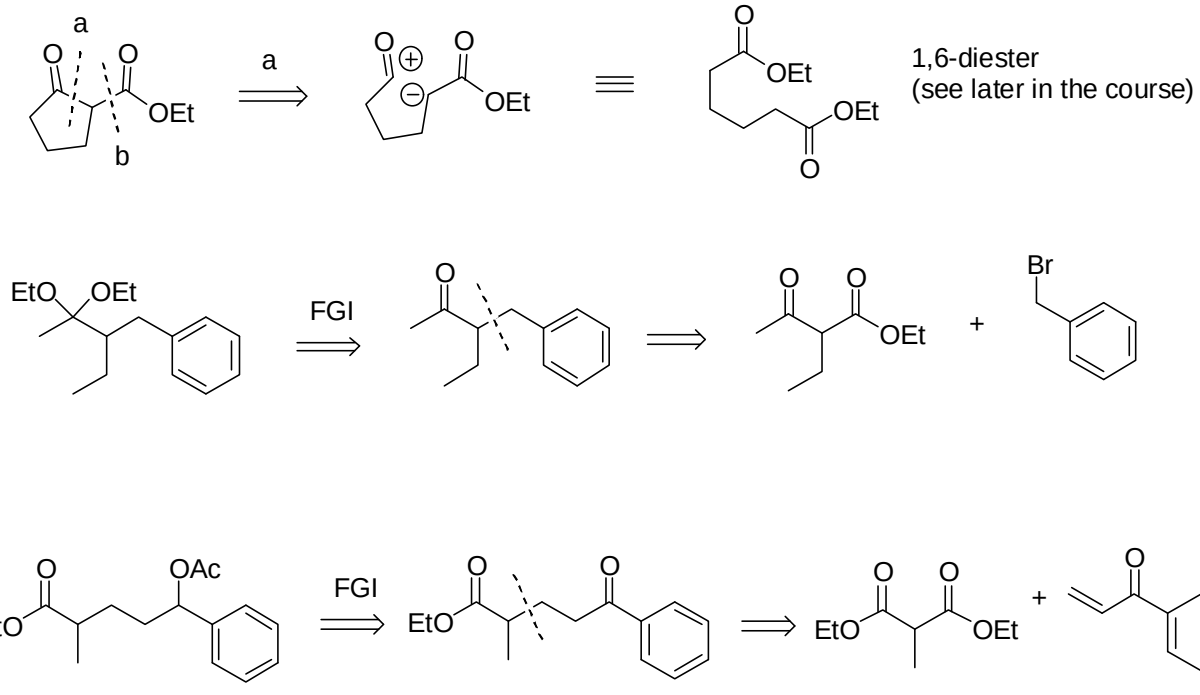
Analysis





Examples of retrosynthetic disconnections.

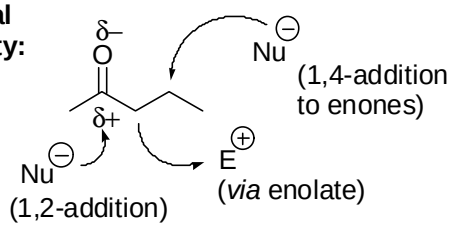
The synthetic planning can be based on a key disconnection, on a key intermediate or, in more complex systems, on the combination of both. Functional group interconversions (FGI) are frequently used to prepare molecule for the intended disconnection step.



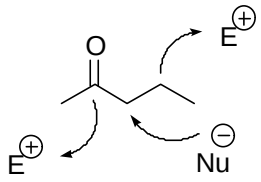
2. 2-Group disconnections: unnatural reactivity patterns and other strategies

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

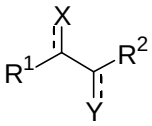
Normal polarity:



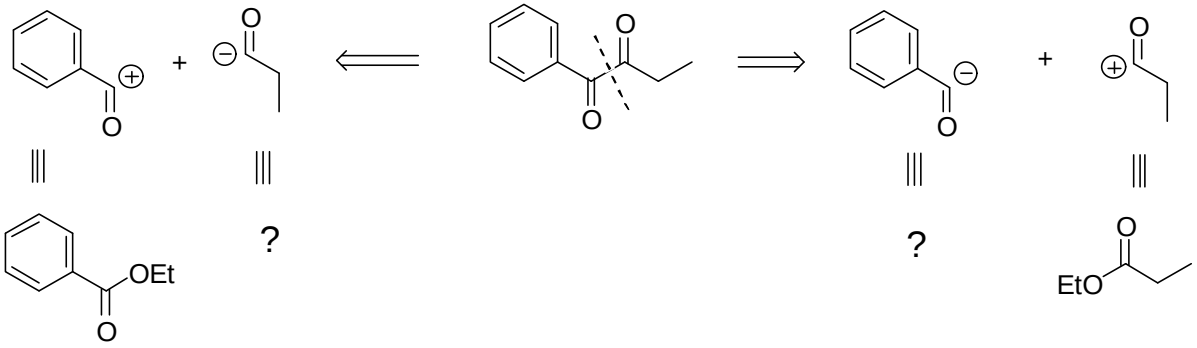
Reversed polarity (*umpolung*):



2.1. Synthetic strategies for 1,2-difunctionalysed compounds.



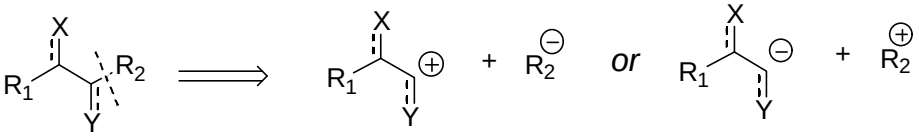
1,2-Difunctionalised compounds *cannot* be prepared by the type of disconnections used for 1,3- and 1,5-difunctionalised compounds.



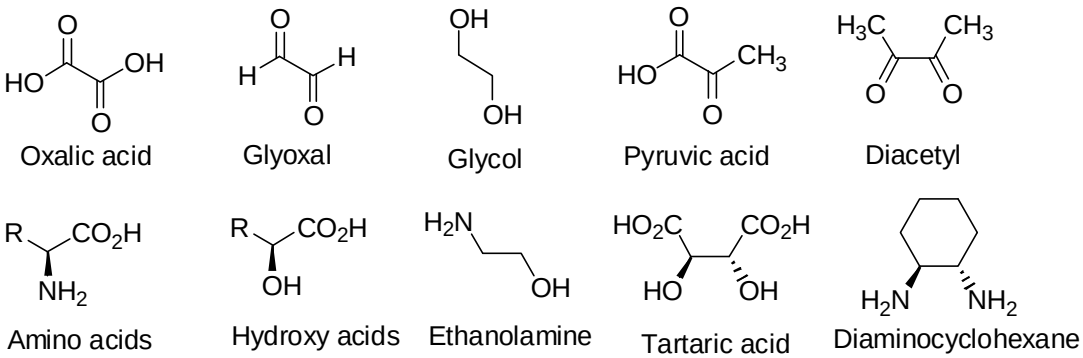
2.1.1. Use of available starting materials

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.

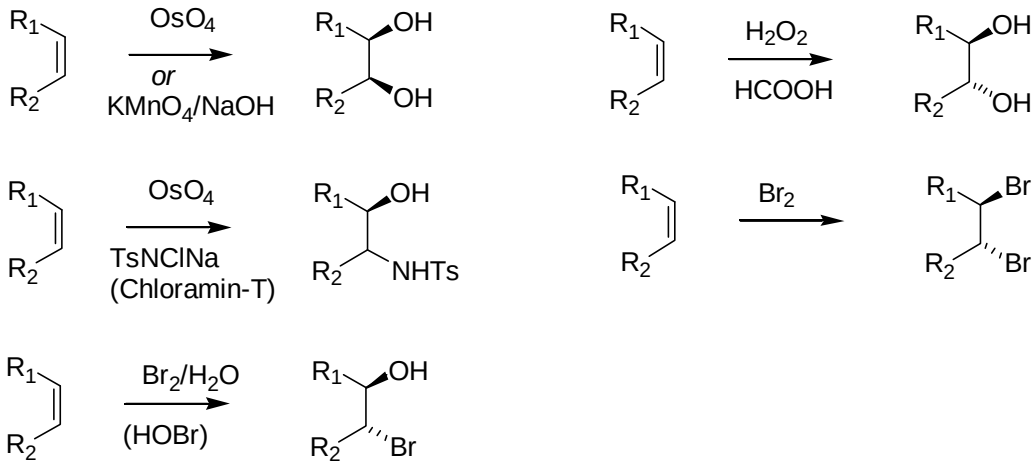


A selection of commercially available 1,2-difunctionalised compounds:

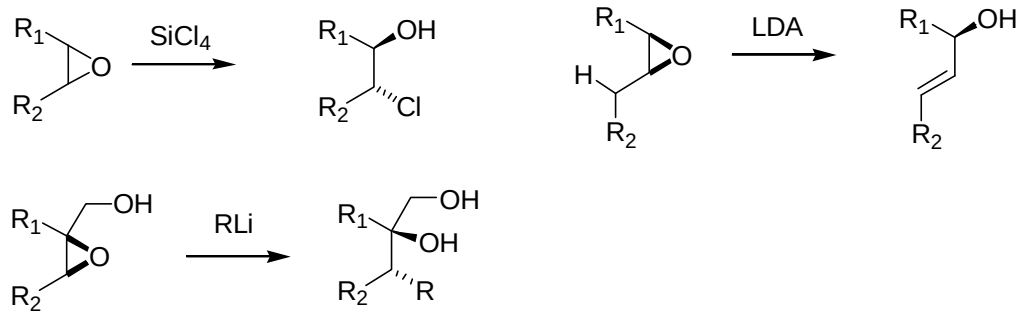


2.1.2. Difuctionalisation of alkenes and opening of epoxides (*revision*)

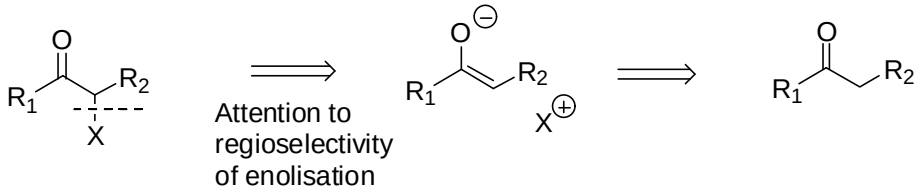
Alkenes:



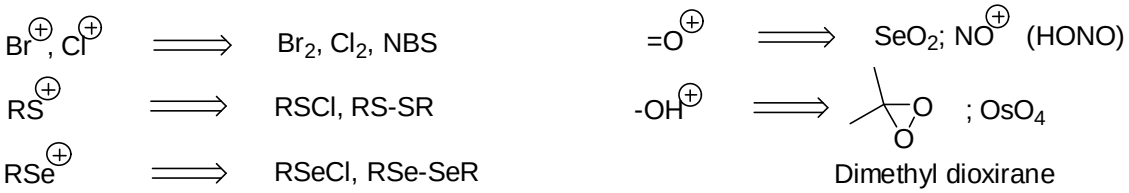
Epoxides:



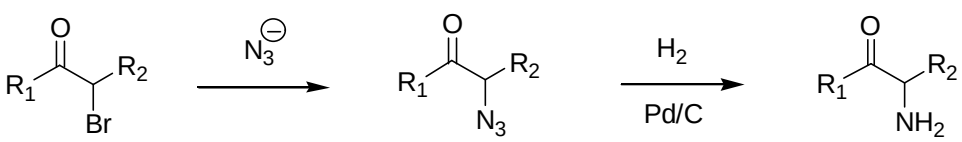
2.1.3. a -Functionalisation of carbonyl compounds



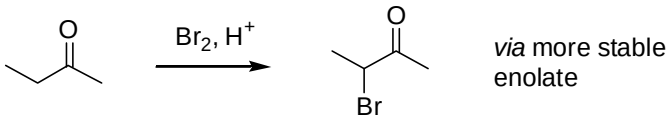
A selection of synthetic equivalents for $X^{\oplus}$:



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

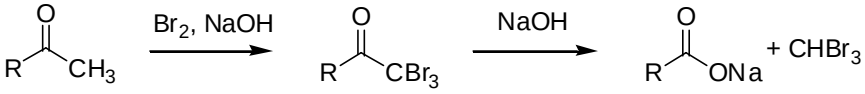


Examples:

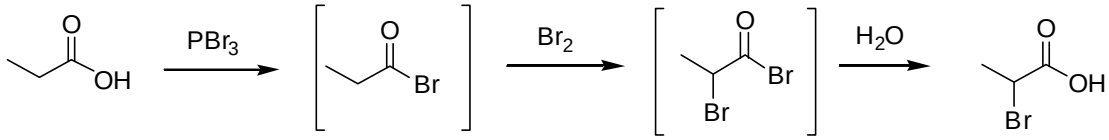


via more stable enolate

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

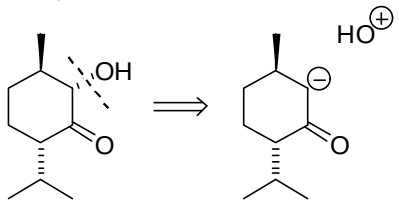


Carboxylic acids are readily halogenated in the presence of PBr_3:

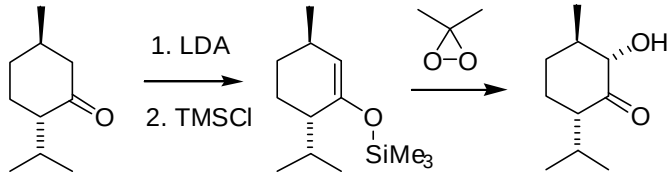


Application in synthesis:

Analysis

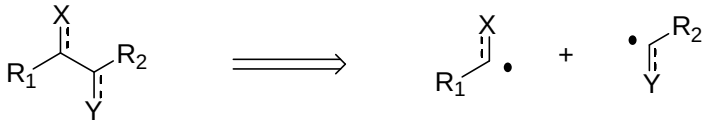


Synthesis



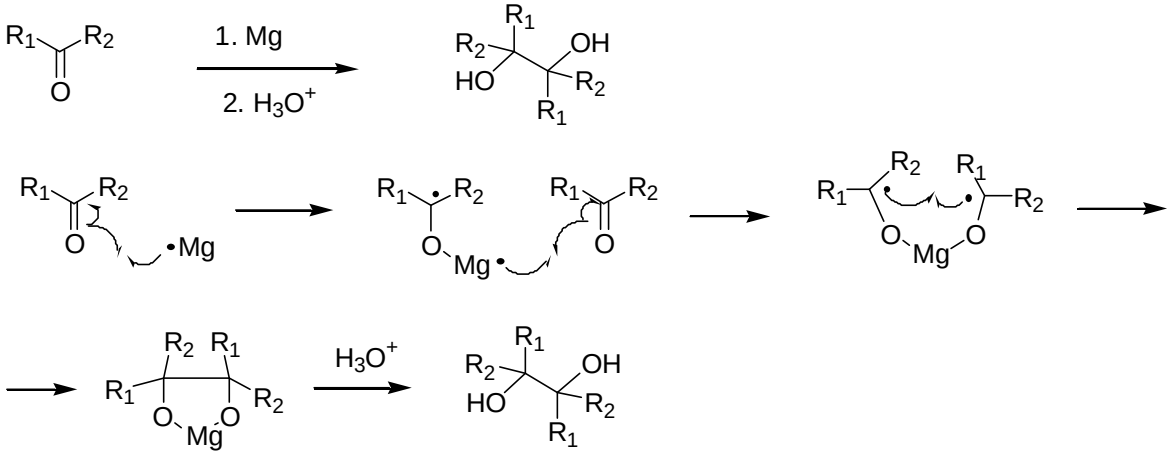
Strategies 2.1.4 and 2.1.5 are based on disconnection between the two FGs.

2.1.4. Radical coupling

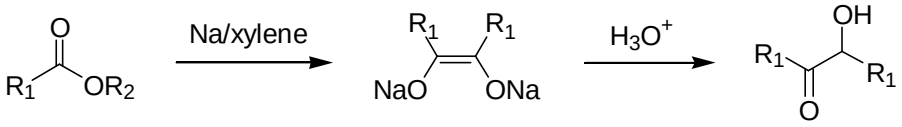


Radical coupling is only good when two identical molecules are being coupled ($R_1 = R_2$, X = Y) or when the reaction proceeds intramolecularly.

Pinacol reaction:

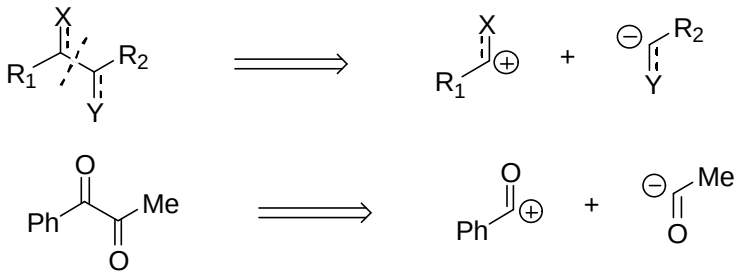


Acyloin condensation:



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

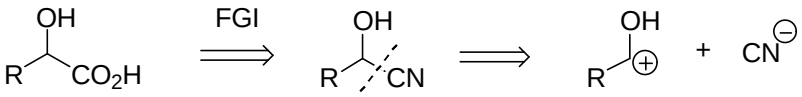
2.1.5. Umpolung strategies



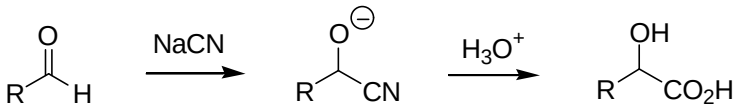
The type of disconnection shown here requires acyl-anion Me-C=O which does not exist, and moreover, cannot be made by deprotonation of the corresponding aldehyde MeCHO. The **reversal of normal carbonyl reactivity (umpolung)** is required here. A number of synthetic equivalents of acyl-anion have been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

2.1.5.1. Cyanide anion + electrophilic carbonyl

Analysis

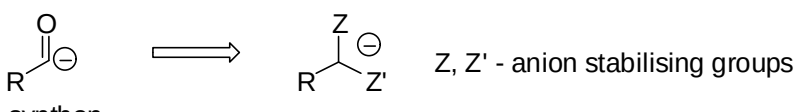


Synthesis

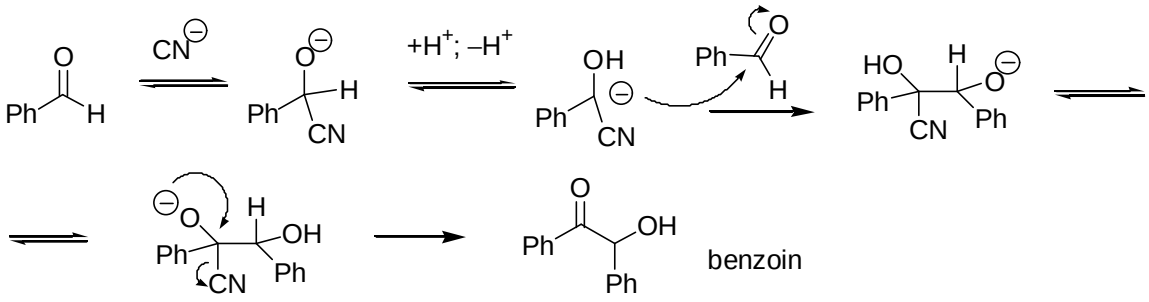


Note: CN^- is an ambident nucleophile.

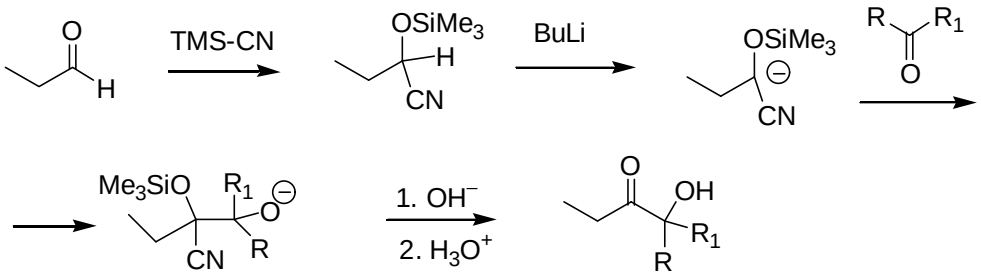
Strategies 3.1.5.2 and 3.1.5.3 are based on replacing the carbonyl oxygen with an anion-stabilising groups:



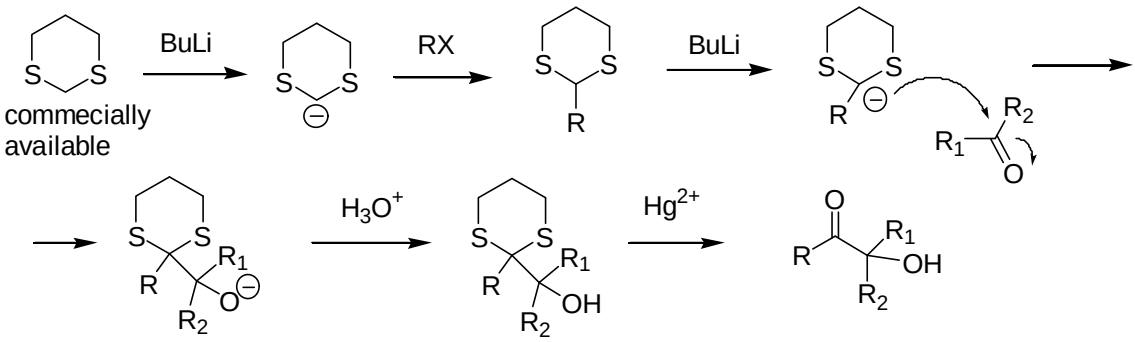
2.1.5.2. *Cyanohydrins, benzoin condensation*



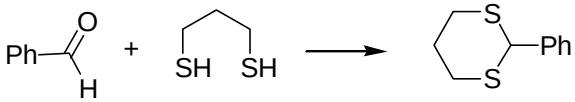
The reaction works well only on aromatic aldehydes, however, cyanohydrins of aliphatic aldehydes can be protected as silyl ethers and after deprotonation reacted in a similar way with different carbonyl compounds.



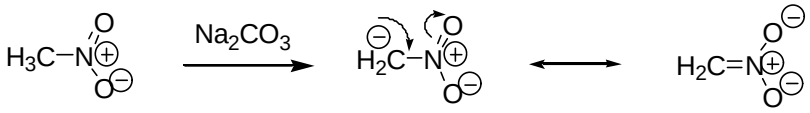
2.1.5.3. *Dithians (thioacetal) nucleophile + electrophilic carbonyl*



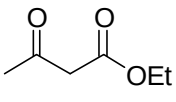
Note: RX ≠ PhX, instead



2.1.5.4. *Nitroalkane nucleophile + electrophilic carbonyl*

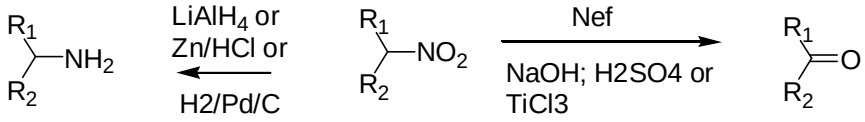


pK_a ~ 10, compare with

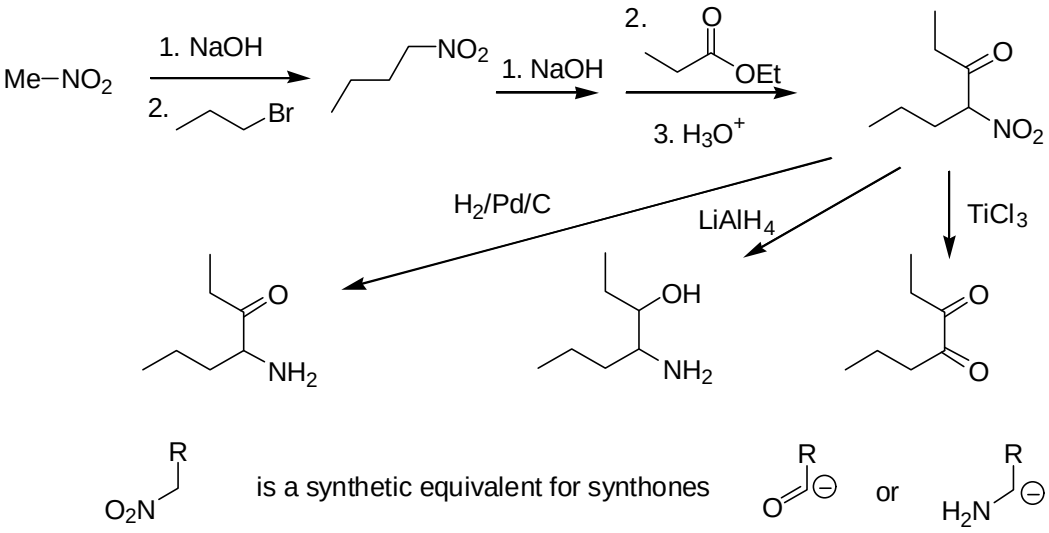


pK_a = 11

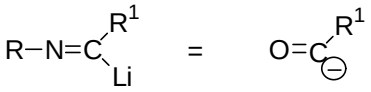
Nitro groups are rarely desirable themselves, however they can undergo useful FGIs:



Synthetic application:

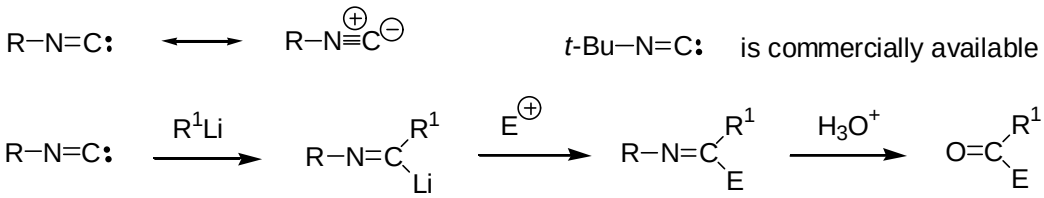


2.1.5.5. Imidoyl nucleophile + electrophilic carbonyl

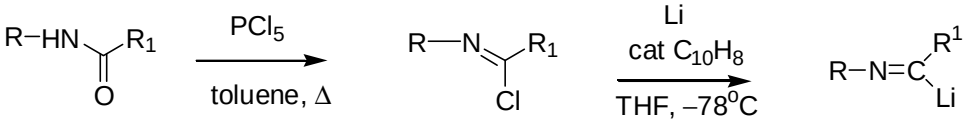


Preparation:

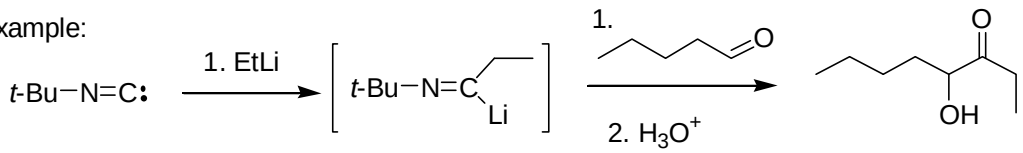
a) From isonitriles



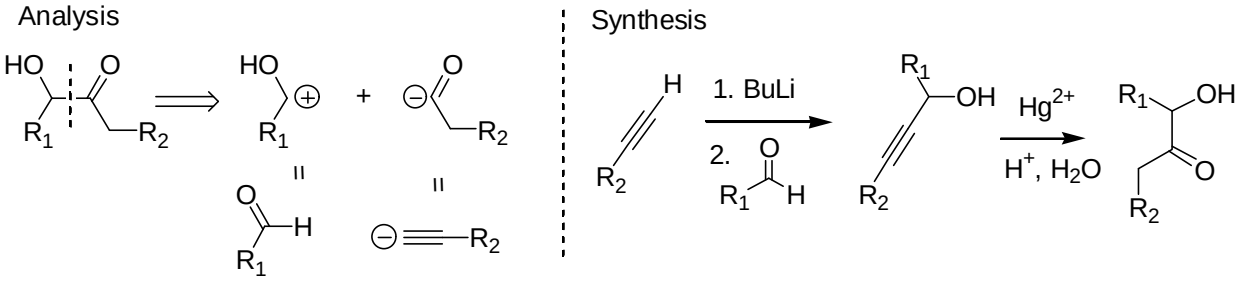
b) From amides via chloroimines



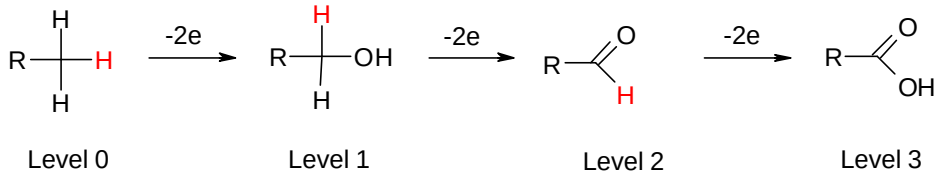
Example:



2.1.5.6. Alkyne nucleophile + electrophilic carbonyl



2.2 Functional group interconversion, amine synthesis



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.

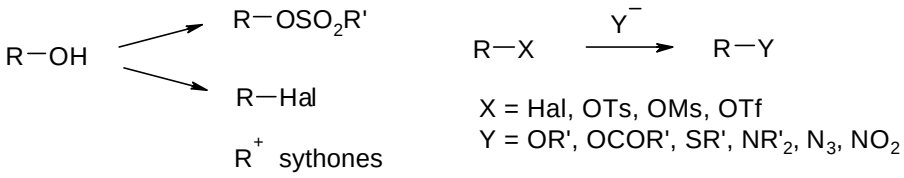
Oxidation level 3 (alkane – 6e):
COOH, COX (X = OR, Hal, OCOR, NR_2); C≡N, C=C-C=O, C=C-C≡C

Based on the oxidation level of carbon, the two main types of FGIs can be identified:

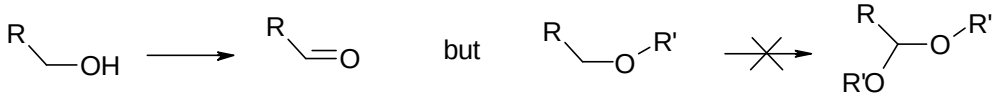
Type 1. Isohypsic transformations with no change to the oxidation level of carbon

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

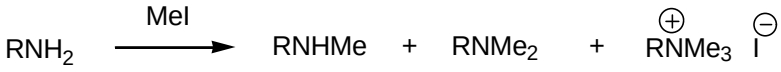
In general, on the same oxidation level any functional group interconversion can be performed in more or less easy way:



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



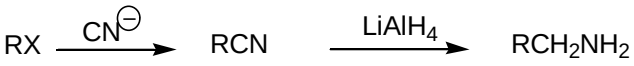
Other important kind of transformations – interconversion of nitrogen containing functions. With amines, alkylation usually produce mixtures:



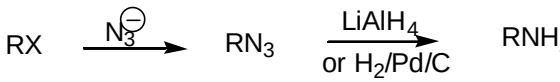
Alternative strategies are based on reduction of other nitrogen-containing FGs:

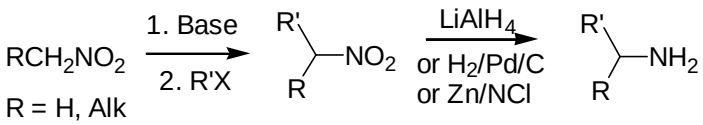
Primary amines:

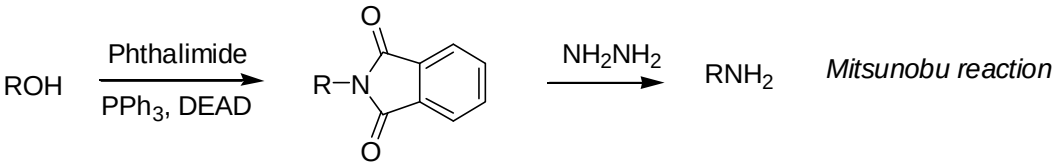
Primary amines at primary carbon



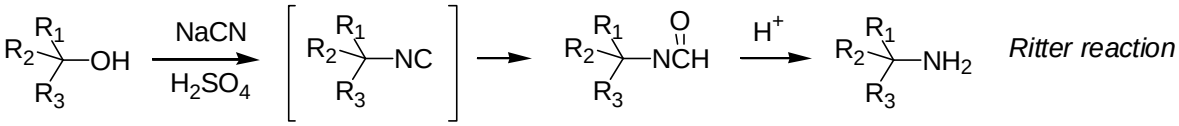
Primary amines at primary or secondary carbon







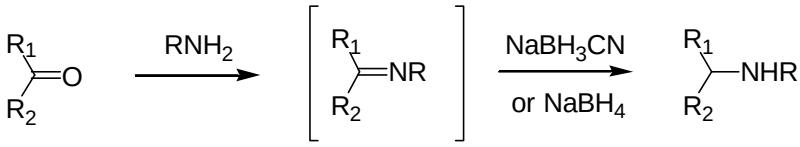
Primary amines at secondary or tertiary carbon



The Ritter reaction with alkylnitriles produces secondary amines

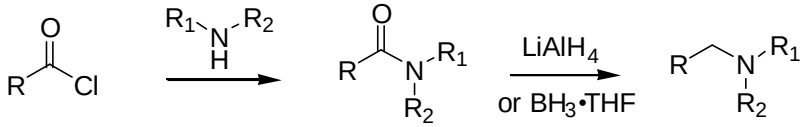
Secondary amines:

Reductive amination



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

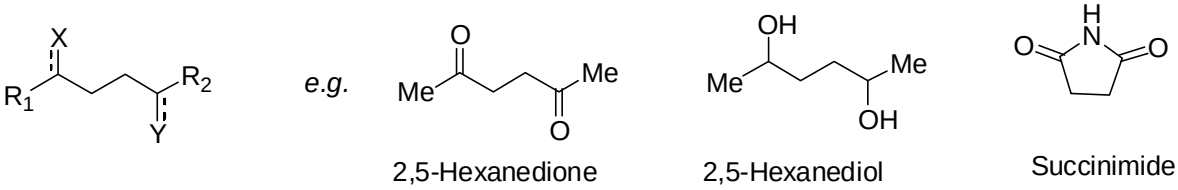
Secondary and tertiary amines:



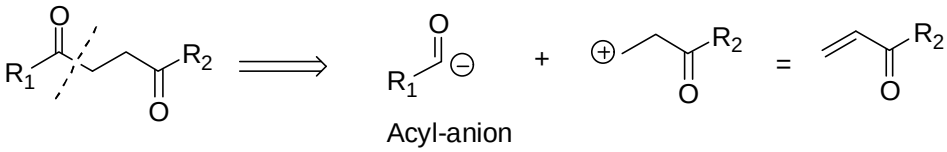
The method is also suitable for the preparation of primary amines ($R_1 = R_2 = H$).

2.3. Synthetic strategies for 1,4-difunctionalised compounds

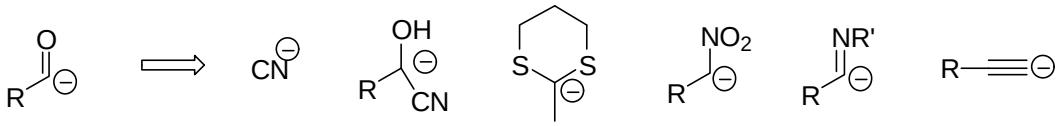
Approaches the synthesis of 1,4-difunctionalised compounds share a lot of common features with methods of preparation of 1,2-analogues discussed in the part 2.1. Again, there are a few commercially available derivatives but in this case the strategies are mainly based on disconnection between the FGs.



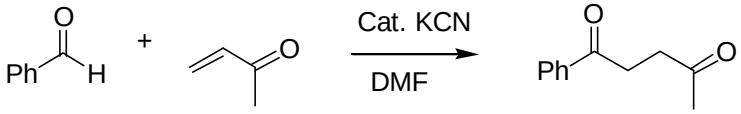
2.3.1. Acyl equivalent + Michael acceptor



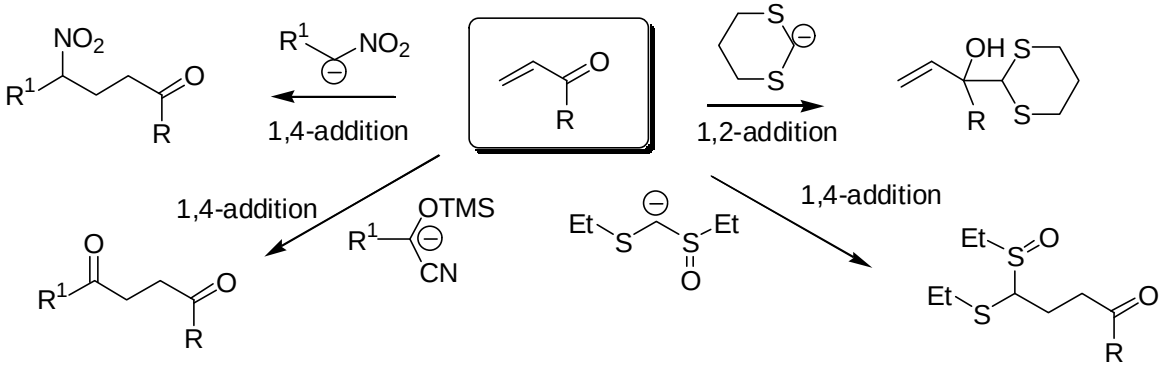
This approach is closely related to the synthesis of 1,5-dicarbonyl derivatives via addition of enolates to α,β-unsaturated carbonyl compounds. However this time, acyl-anion synthons are employed as nucleophiles. A selection of such reagents has been discussed in the section **2.1.5. Umpolung Strategies**.



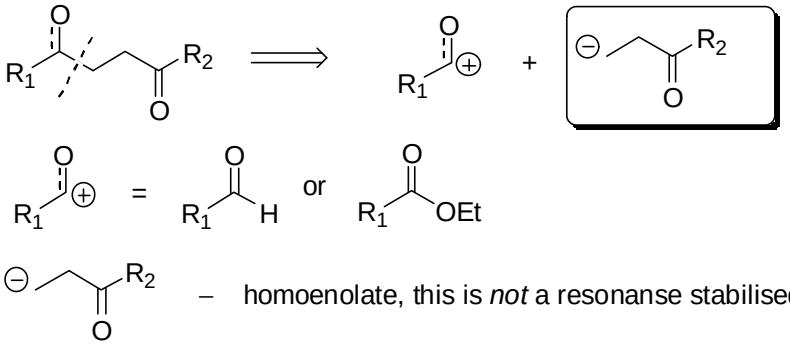
Examples:



Regioselectivity issues:

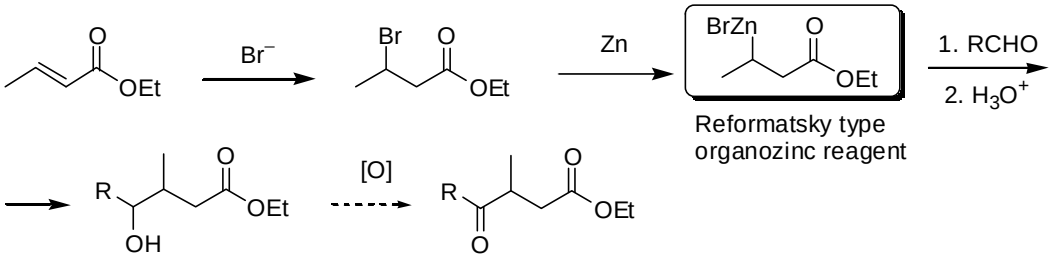


2.3.2. Homoenolate + electrophilic carbonyl



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

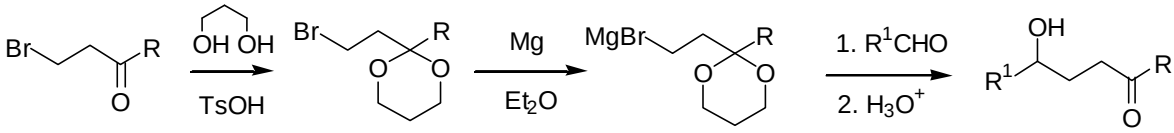
Ester homoenolates (Zn and Ti):



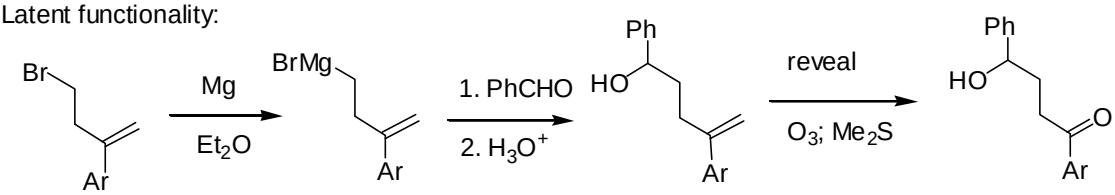
Ketone or aldehyde homoenolates:

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.

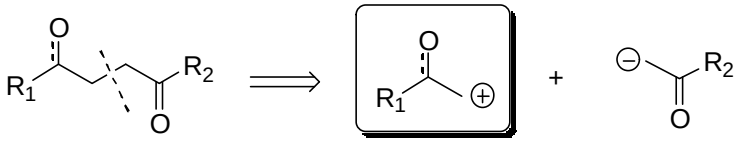
Protection:

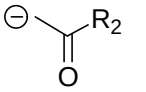


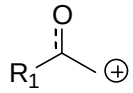
Latent functionality:



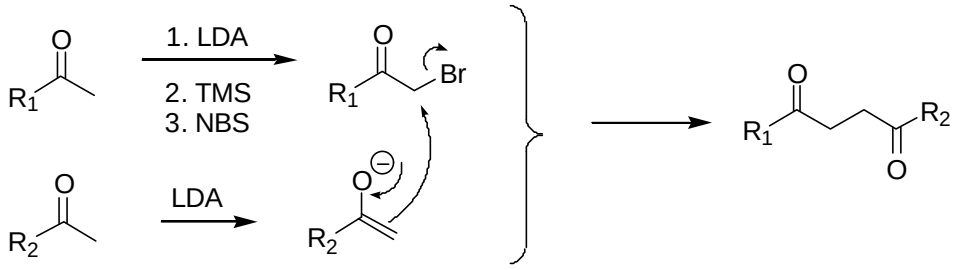
2.3.3. Additional umpolung strategies:



 – standard enolate

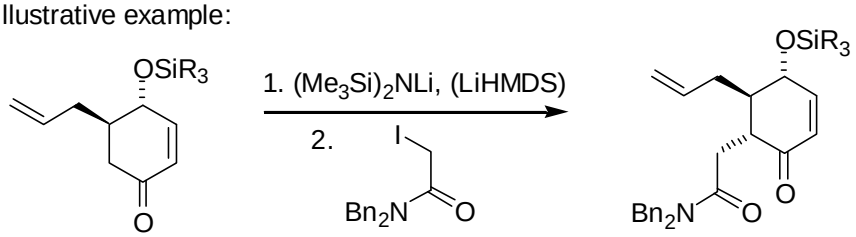
 – electrophilic centre in α-position to carbonyl group

2.3.3.1. Enolate + α-functionalised carbonyl compound

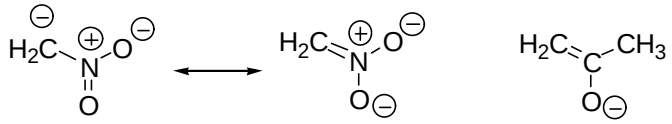


Note: α-bromoketone can be protected as ketal first to prevent enolisation during the reaction

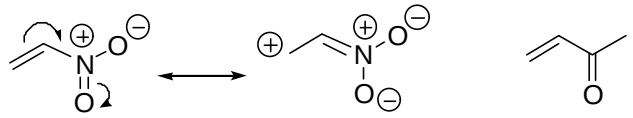
Illustrative example:



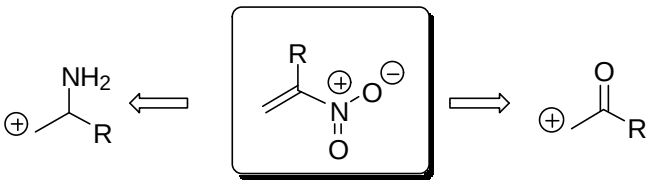
2.3.3.2. Enolate + α,β-unsaturated nitrocompound (Michael-type acceptors)



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

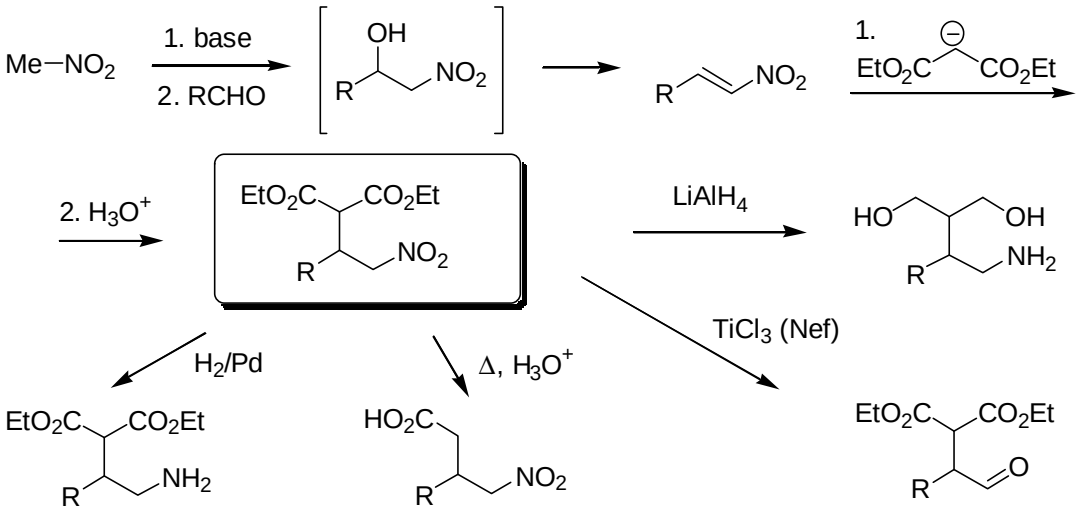


Nitroalkenes resemble α,β-unsaturated carbonyl compounds (Michael acceptors) but have one carbon atom less.

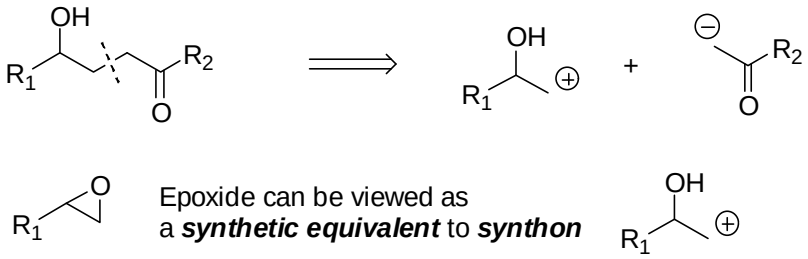


Nitroalkenes can be viewed as reagents for carbonyl and nitrogen based functionalities

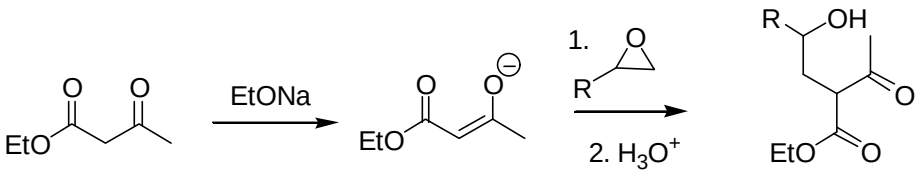
Examples:



2.3.3.3. Epoxide based transformations

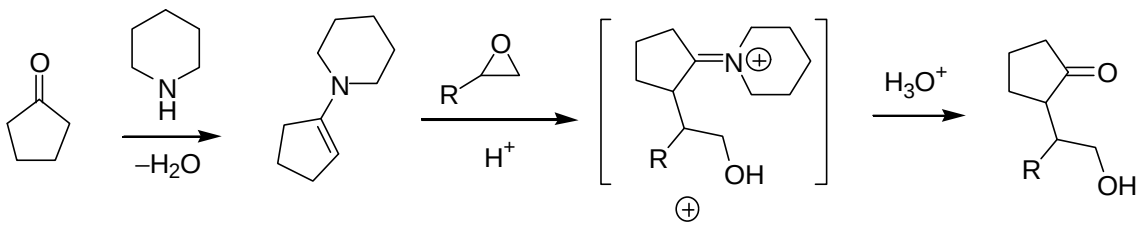


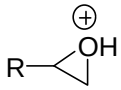
a) Opening of epoxides with enolates of β-dicarbonyl compounds:



In general, epoxides are opened by nucleophiles at the ***less hindered side (S_N2 type)***

b) Opening of epoxides with enamines catalysed by acids:

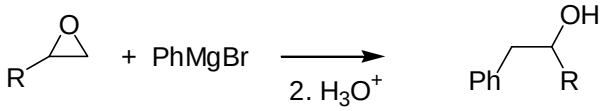


In acid, the reaction proceed *via* intermediate 

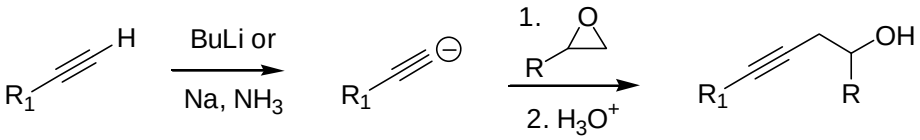
The opening occures at the side with ***more stable cation (S_N1 type)***

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

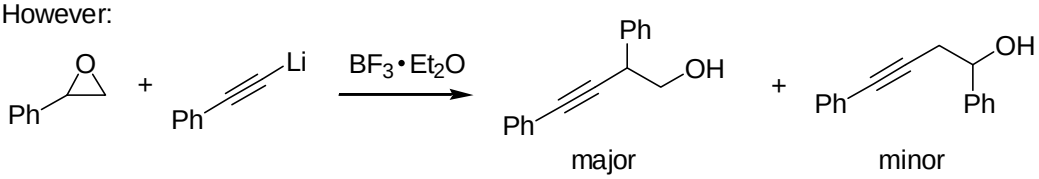
Nucleophiles include CN^-, dithiane anions, Grignar reagents, *e.g.*:



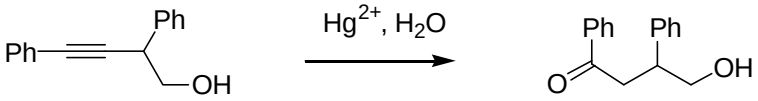
Use of alkynyl anions:



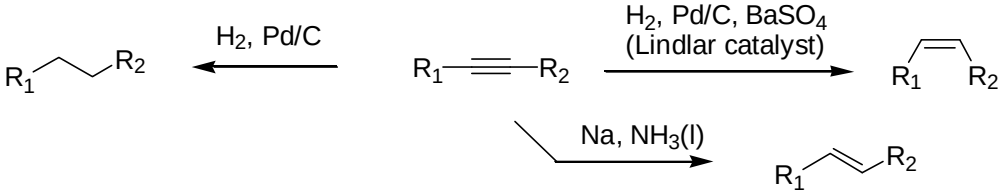
However:



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

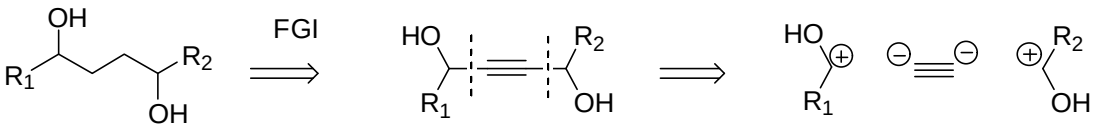


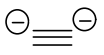
Note: other usefull transformations of alkynes include chemo- and stereoselective reduction:



2.3.4. Functional group addition (retrosynthetic technique of introducing a required functional group to facilitate a certain chemical transformation)

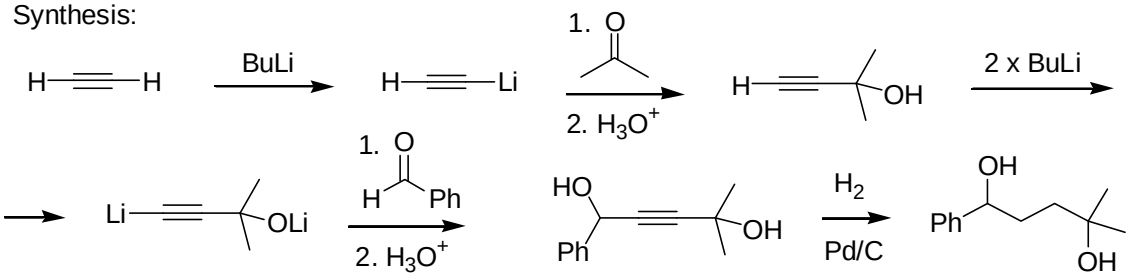
Alkynyl-anions have already proved to be useful reagents for acyl-anion synthons, In addition, synthetic versatility of alkyne functionality can be further exploited in organic synthesis.





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

Synthesis:



Unfunctionalised alkanes as target structures:

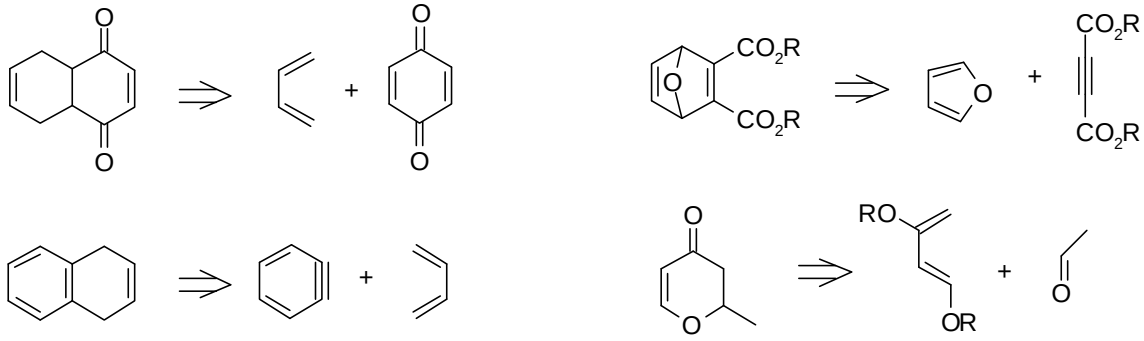
Functional Group Addition (**FGA**) strategy employed in the example above to facilitate the construction of the required structural arrangement can be further extended to retrosynthetic analysis of target molecules with few or no functional groups. **FGA** is a **retrosynthetic technique**, the corresponding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

FG	Conditions for FG removal
C≡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

2.4. Synthetic approaches to cyclic systems.

2.4.1. Cycloadditions

Some types of Diels-Alder disconnections:

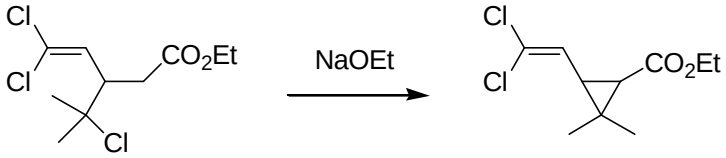


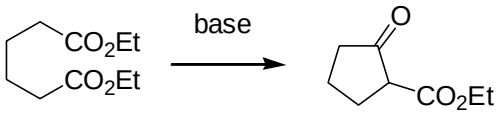
2.4.2. Conventional methods of acyclic chemistry

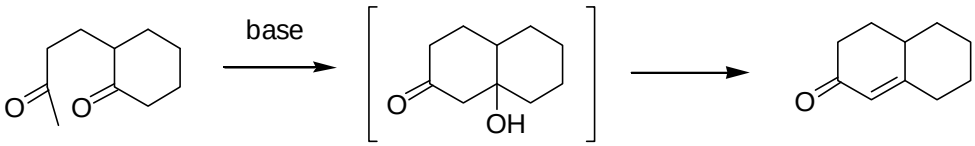
For the construction of ring systems a set of conventional disconnections can be considered, including intramolecular S_N2, Robinson annulation, aldol, Dieckmann, etc.

Intramolecular reactions are usually favoured kinetically over intermolecular rections. 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.

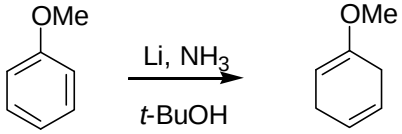
Some examples of cyclisation reactions:



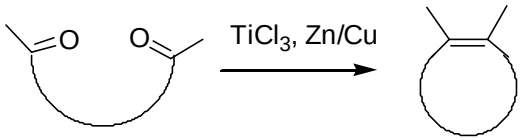




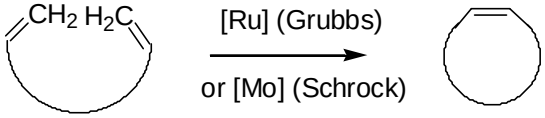
2.4.3. Other methods



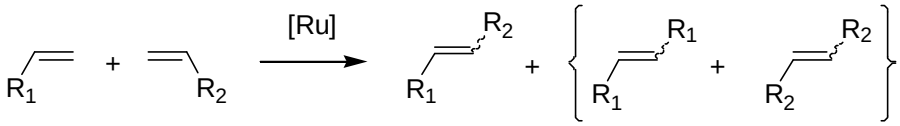
Birch reduction



McMurry coupling



Ring Closing Alkene Metathesis



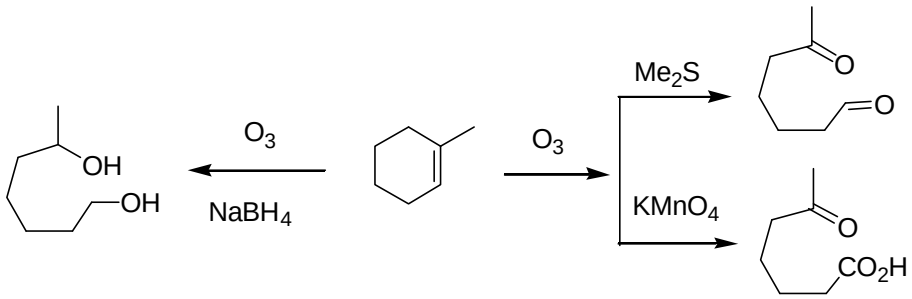
Cross Metathesis

2.5. **Reconnection strategies**

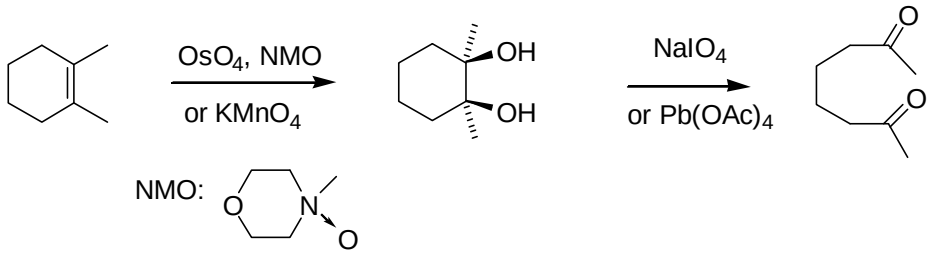
In retrosynthetic analysis, open chain 1,6-difunctionalised compounds can be linked to appropriate cyclic precursors. In this case, the term “disconnection” is applied to ***reconnection*** strategies, which can also be used to make compounds with two functional groups related to each other as 1,5-,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

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.

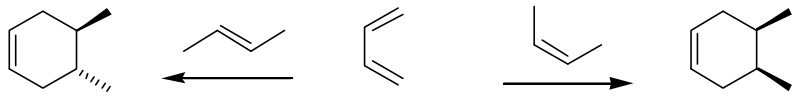


Similar transformation can be also achieved in an indirect way:



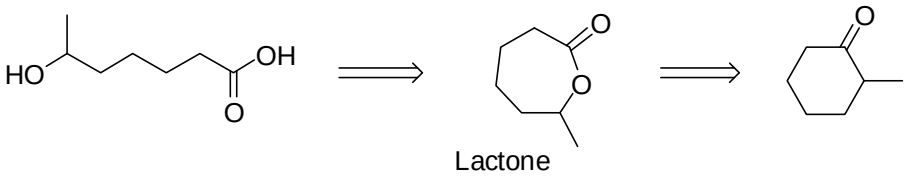
This strategy requires synthetic access to 6-membered unsaturated rings. The best way to make such precursors is Diels-Alder cycloaddition reaction (see above in the course):

The reaction is stereospecific



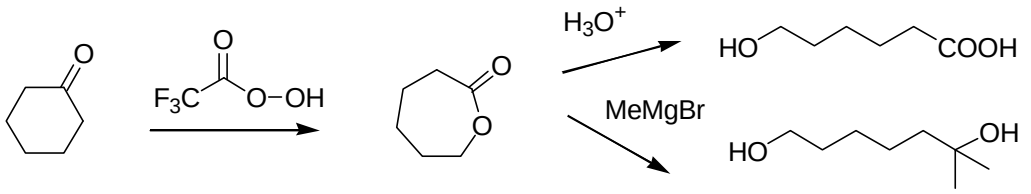
2.5.2. Baeyer-Villiger rearrangement

Another type of reconnection strategies is hydrolysis of lactones:

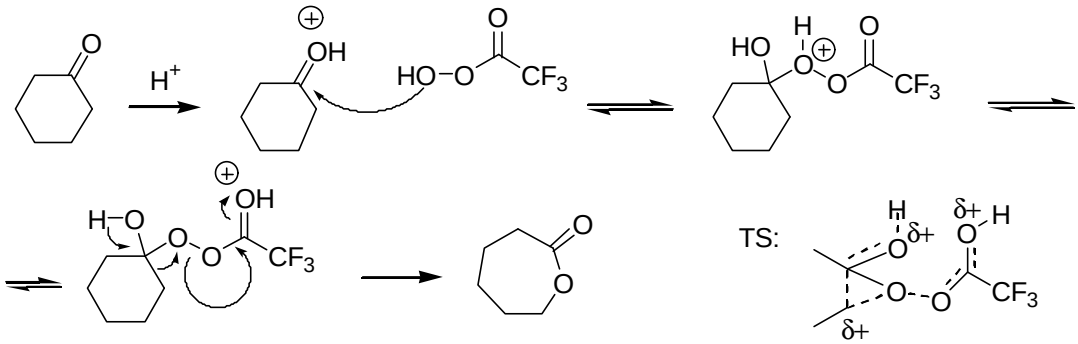


Lactone

The required lactones can be prepared from cyclic ketones by a ring expansion reaction, the **Baeyer-Villiger rearrangement**:



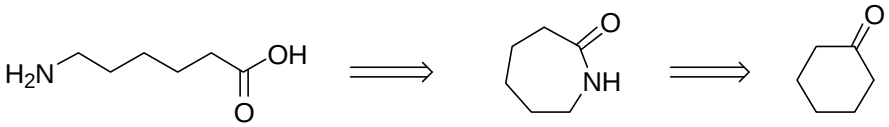
Mechanism:



The reaction is regioselective. Migration order: $3^o > 2^o \sim Ar > 1^o$. The group better capable to stabilise carbocation in the transition state migrates preferentially.

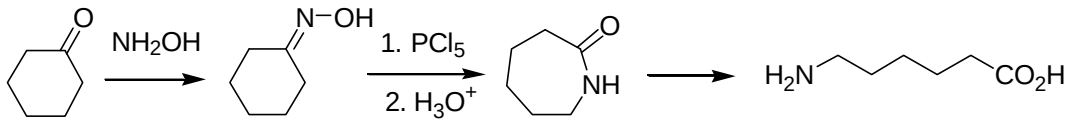
2.5.3. Beckmann and related rearrangements

Analogously, a reconnection strategy for 6-amino acids is hydrolysis of lactams:

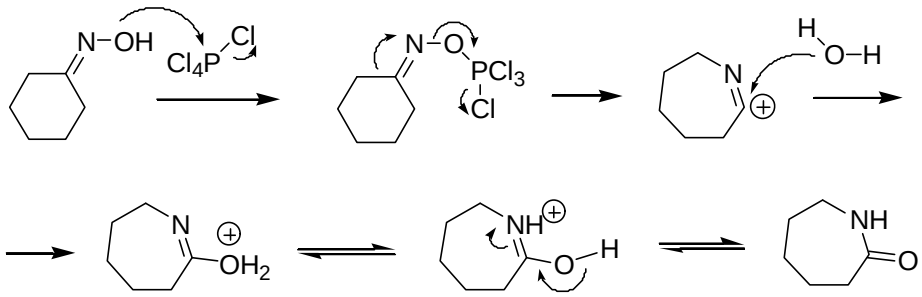


Lactam

Lactams can be prepared from cyclic ketones by the **Beckmann rearrangement**:

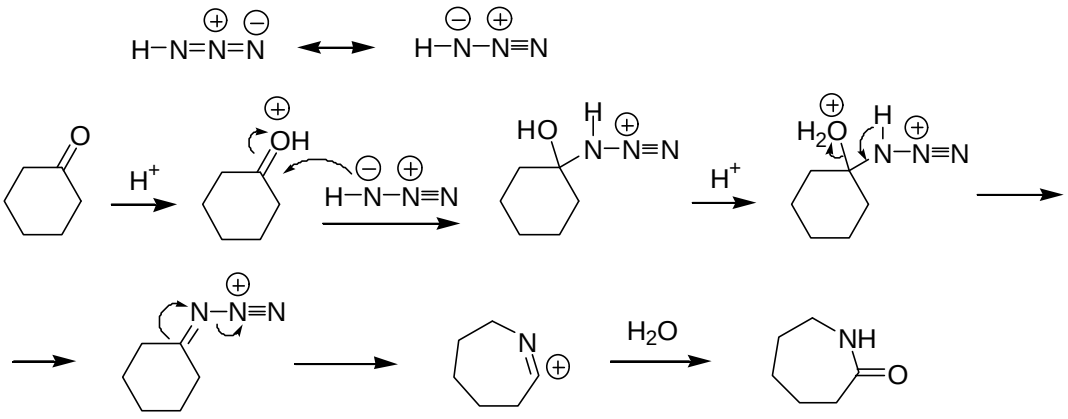


Reaction mechanism:

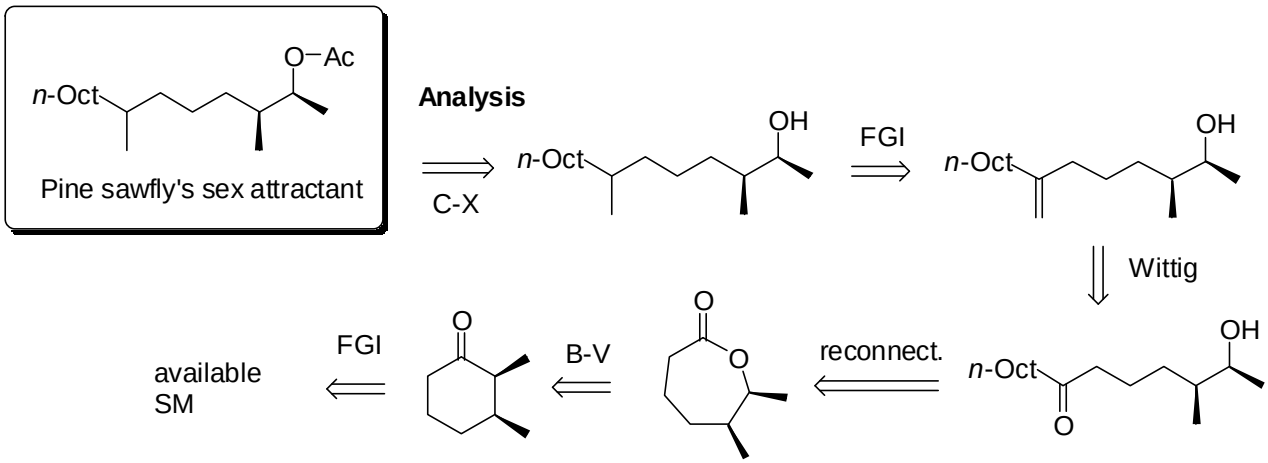


Usually, the group positioned *anti* to oxime is migrating.

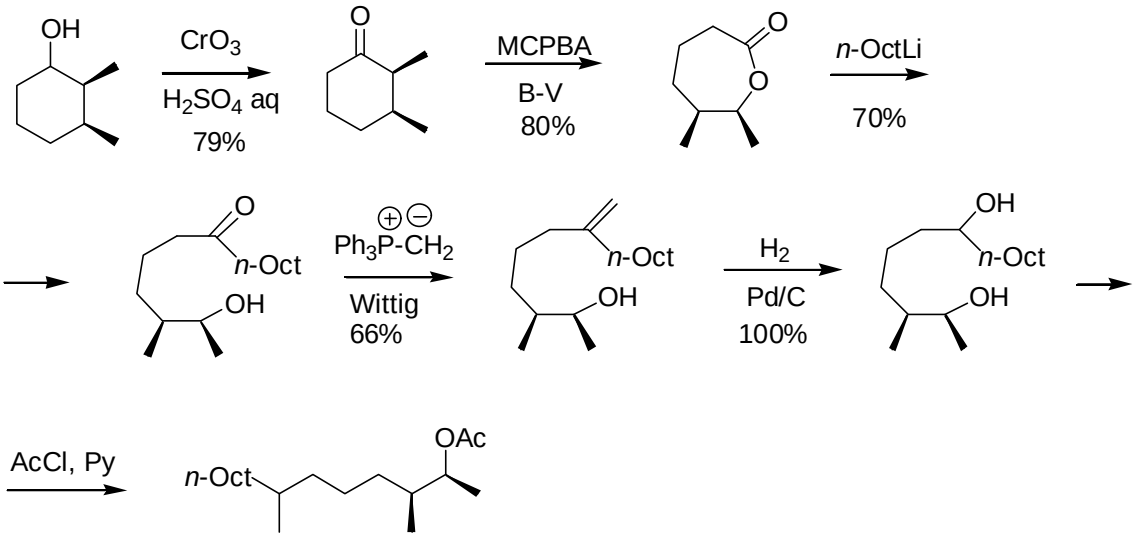
A related process which involves addition of hydrazoic acid to carbonyl compounds catalysed by sulphuric acid is called **Schmidt reaction**:



Synthetic application:

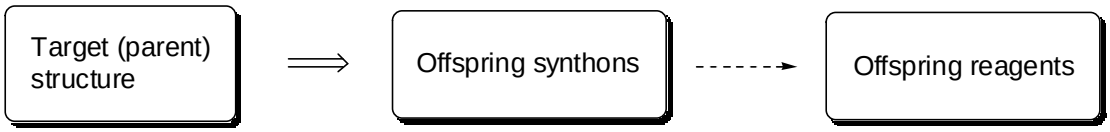


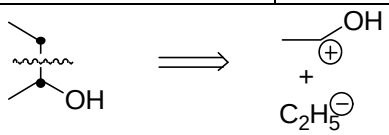
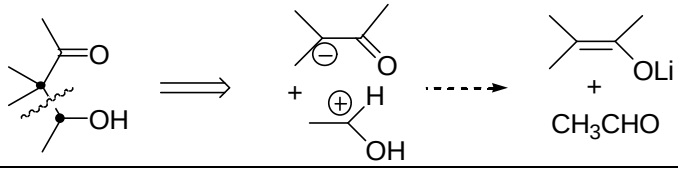
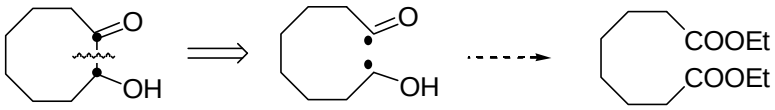
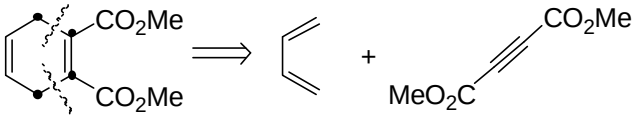
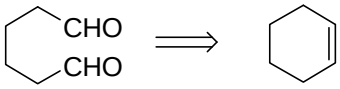
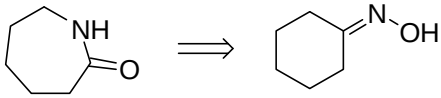
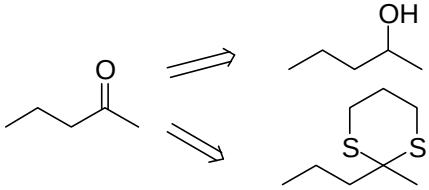
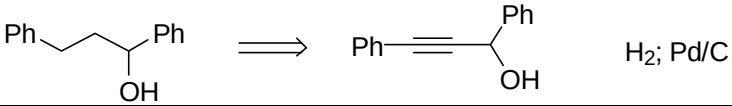
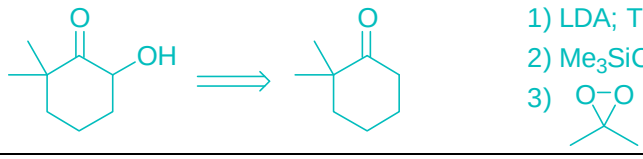
Synthesis



3. Summary of retrosynthetic strategies; some guidelines for retrosynthetic analysis; useful synthons.

3.1. Elementary retrosynthetic analysis



Transformation type	Target molecule	Synthons	Reagents and reaction conditions
One-group disconnection			1) 0°C (THF) 2) NH_4Cl/H_2O
Two-group disconnection (heterolytic)			1) –78°C → rt (THF) 2) NH_4Cl/H_2O
Two-group disconnection (homolytic)			1) Na/Me_3SiCl toluene, Δ 2) H_2O
Electrocyclic disconnection			synthones ≡ reagents (benzene, Δ)
Reconnection			O_3/Me_2S CH_2Cl_2; –78°C
Rearrangement			H_2SO_4; Δ
Functional group interconversion (FGI)			CrO_3/H_2SO_4; acetone $HgCl_2$; acetonitrile
Functional group addition (FGA)			H_2; Pd/C
Special case of FGI - Functional group removal (FGR)			1) LDA; THF; -78°C 2) Me_3SiCl 3)

3.2. 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,
    - disconnect rings from chains,
    - use symmetry,
    - disconnect at a branch point,
    - separate into equal sized pieces,
    - 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.

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.

3.3. Summary of synthons and synthetic equivalents used in the course.

Table 1. Some "natural" synthons

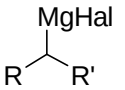
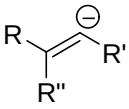
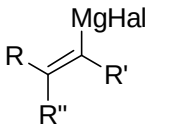
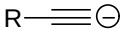
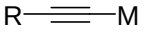
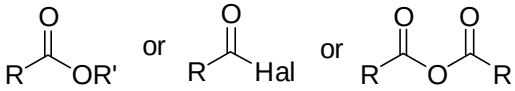
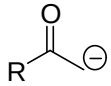
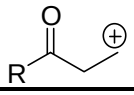
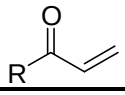
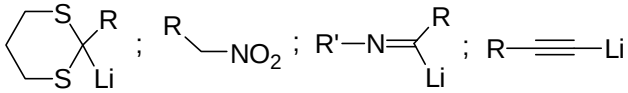
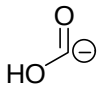
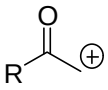
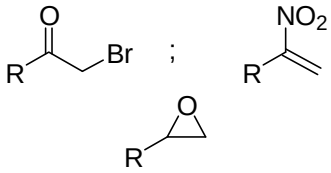
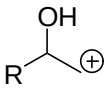
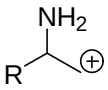
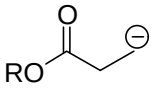
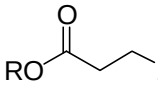
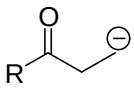
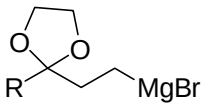
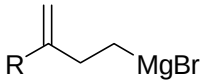
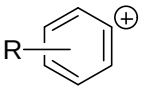
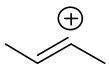
Synthon	Synthetic equivalent
Br^-	NaBr
N_3^-	NaN_3
RO^-	RONa made from ROH
RS^-	RSNa made from RSH
 alkyl, allylic or benzylic	alkyl, allylic or benzylic  Hal = Br, I
 alkyl, allylic or benzylic	alkyl, allylic or benzylic  or cuprate for Michael addition
 vinyl or aryl	vinyl or aryl  or cuprate for Michael addition
	 M = Li, MgHal
	
	
	Methyl acetoacetate or dimethyl malonate are often used as starting materials
	

Table 2. Some "unnatural" synthons

Synthon	Synthetic equivalent
Br^+	Br_2
O^{2+} or HO^+	SeO_2 or dimethyl dioxirane
RS^+	RSCl or RSSR
 acyl anion	
	CN^- (KCN)
	
	
	 after reduction ($LiAlH_4$ or H_2/Pd-C)
 homoenolate	
 homoenolate	 or 
 and 	Avoid this type of disconnection as the corresponding reactions require transition metal catalysis.

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