University of Zagreb
Faculty of Chemical Engineering and Technology
Study programme Chemical and Environmental Technology

FORMATION OF NEW C-C BOND

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METHODS FOR CREATING A NEW C-C BOND

1. *ortho-STRATEGY FOR AROMATIC COMPOUNDS*
2. *σ-METAL COMPLEXES*
3. *CONTROLLED MICHAEL REACTIONS*
4. *SPECIFIC ENOLE EQUIVALENTS*
5. *EXTENDED ENOLATS*
6. *ALLYL ANIONS*
7. *HOMOENOLATES*
8. *ACYL-ANION EQUIVALENTS*

1. *ortho*-STRATEGY FOR AROMATIC COMPOUNDS

1.1. Traditional Methods

1.1.1. Friedel-Crafts reactions and Fries rearrangement

1.1.2. Claissen partitions

1.2. Use of lithium

1.2.1. *ortho*-lithiation

1.2.2. Lithiation - more guiding groups

1.2.3. Multiple lithiation

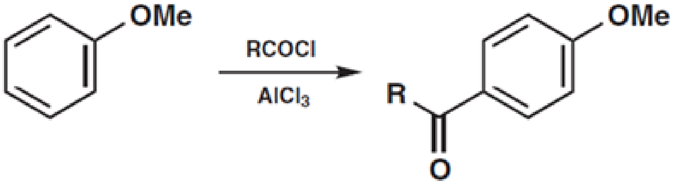
1.2.4. Halides

1.2.5. α-lithiation

1. *ortho*-STRATEGY FOR AROMATIC COMPOUNDS

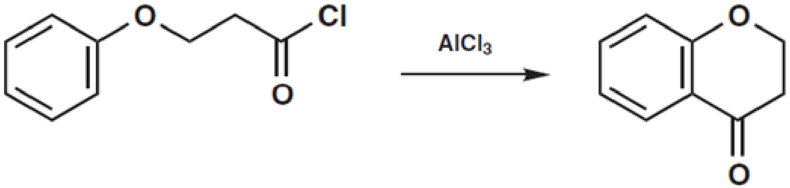
- electrophilic aromatic substitution - *o*, *m* and *p* positions
- mostly a mixture of products
- modern organic chemistry requires the formation of a single isomer in high yield
- large substituents typically direct the electrophilic substitution to the *p*-position

Friedel-Crafts alkylation and acylation

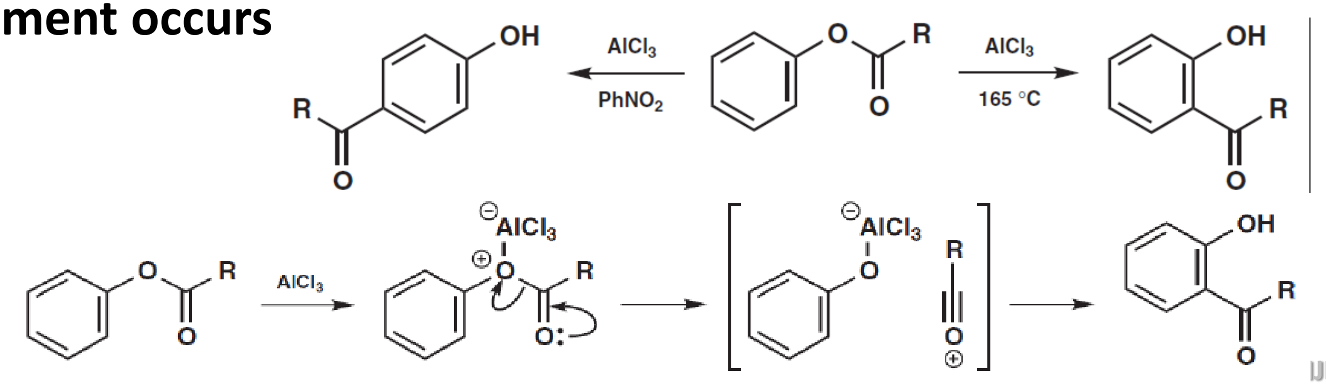


1.1.1. Friedel-Crafts reactions and Fries rearrangement

- if the acyl chloride is attached to the O atom via a short chain of C atoms intramolecular cyclization occurs



- if the acid group is attached directly to the O atom as an ester Fries rearrangement occurs

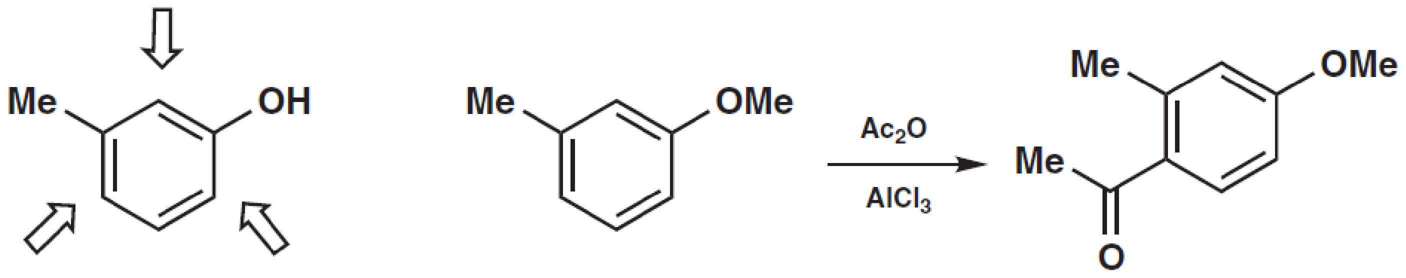


1. *ortho*-STRATEGY FOR AROMATIC COMPOUNDS

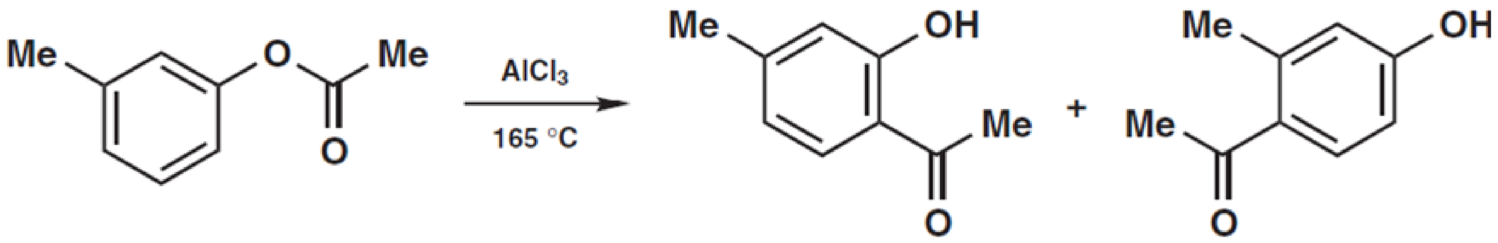
1.1.1. Friedel-Crafts reactions and Fries rearrangement

Examples:

Friedel-Crafts acylation:



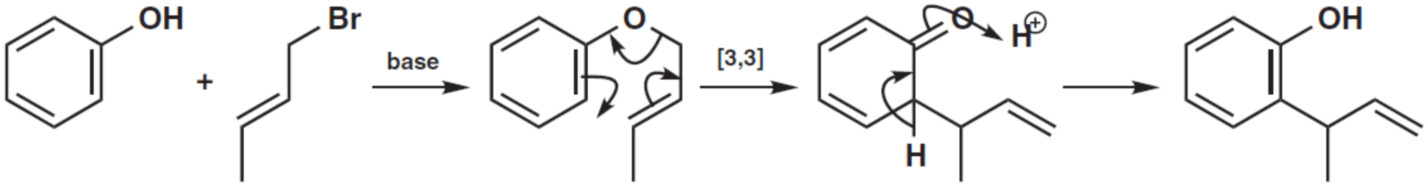
Fries rearrangement:



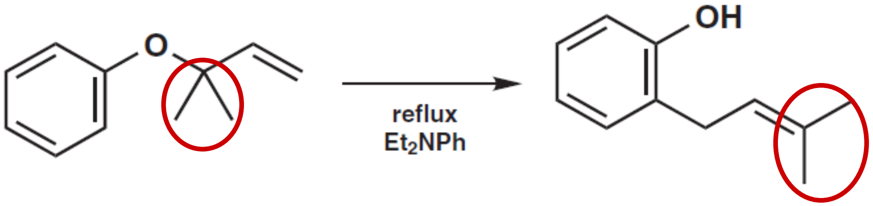
1. *ortho*-STRATEGY FOR AROMATIC COMPOUNDS

1.1.2. Claissen partitions

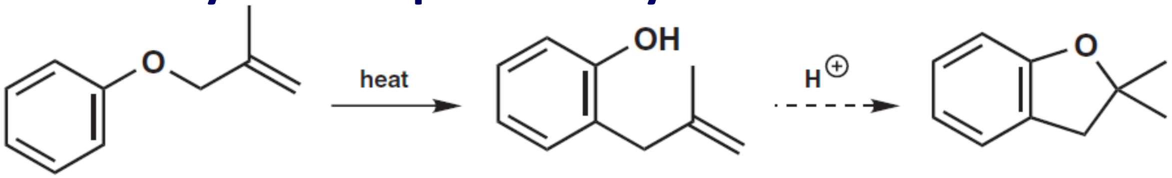
- allyl ether undergoes [3,3] sigmatropic rearrangement to give phenol with allyl substituent in *o*-position



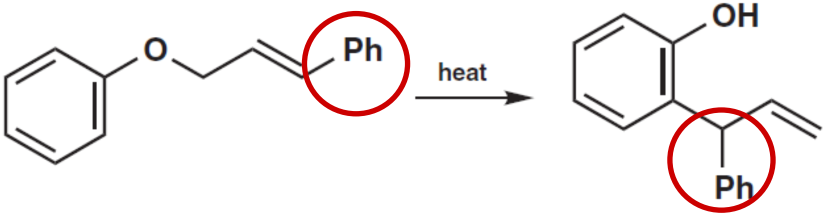
- substituents adjacent to the O atom terminate at the end of the double bond



- substituents that are in the middle of the allylic system do not create a problem of regioselectivity but the products cyclize into esters

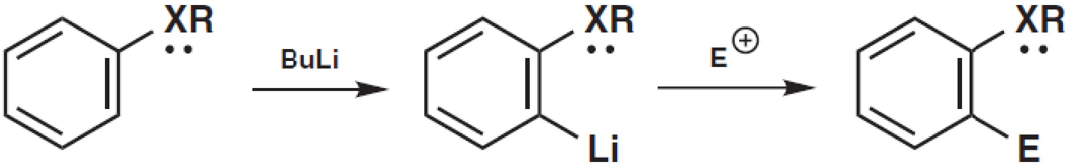


- substituents that are at the end of the double bond end up in a position next to the aromatic ring



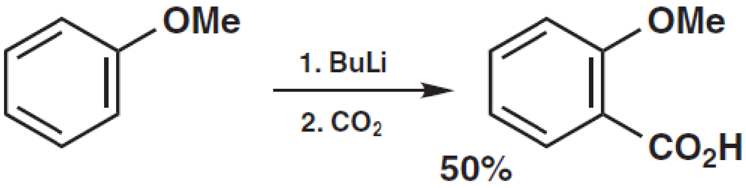
1.2. THE USE OF LITHIUM

- **lithium is introduced into the *ortho* position of an already substituted aromatic ring - *ortho* or direct lithiation - proton and lithium atom exchange reaction**



1.2.1. ortho LITHIATION

- **OMe is an *o*-directing group**
- **The O atom is coordinated with the organolithium reagent**

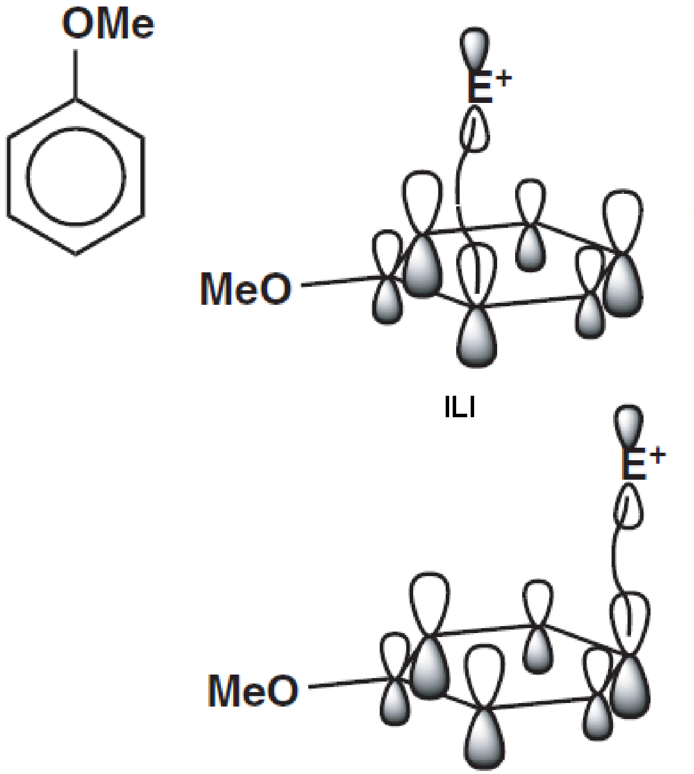


1.2. THE USE OF LITHIUM

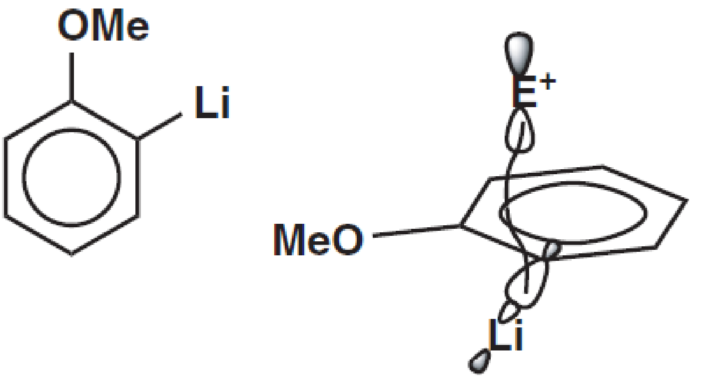
Regioselectivity - *ortho* vs *para*:

- ❖ lithium significantly increases the reactivity of the benzene ring
- ❖ the reaction of the lithiated aromatic ring with the electrophile is regiospecific

✓ anisole reacts in the *o*- and *p*-position with π-electrons



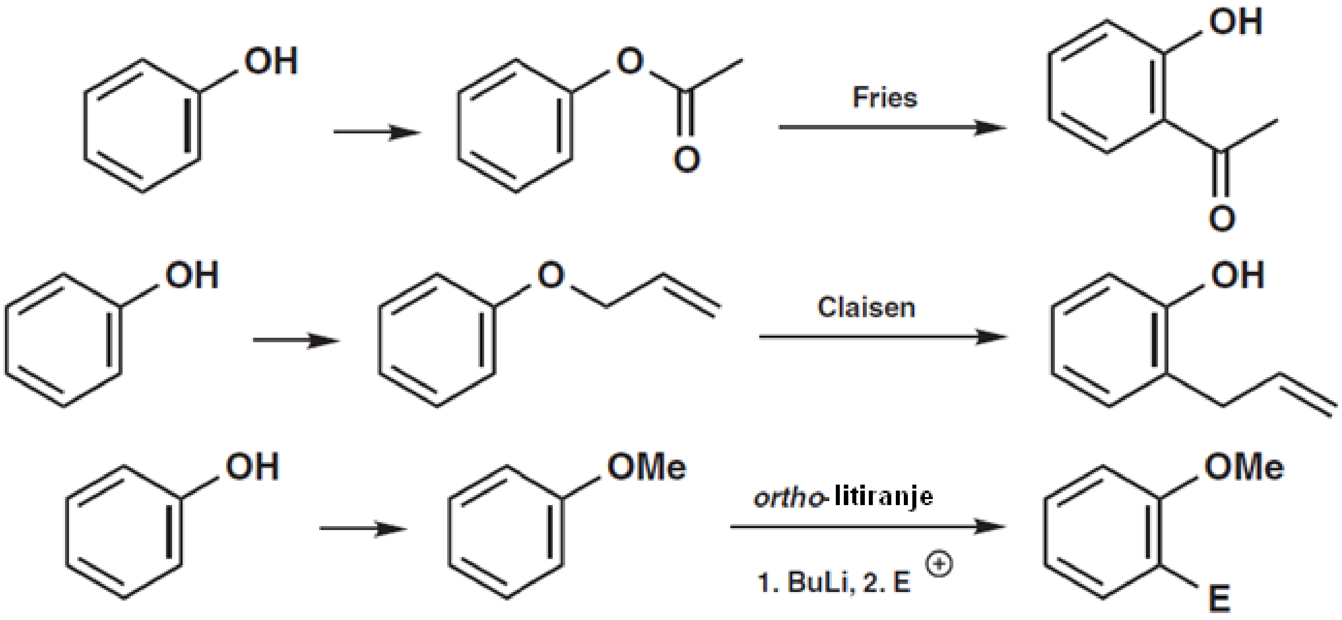
❖ lithium anisole reacts in the *o*-position with σ-electrons



1.2. THE USE OF LITHIUM

Directing groups:

- Fries and Claissen partitions require the existence of an O atome in an adjacent position
- *ortho*-lithiation strategy - O otom or any other guiding group helps lithiation



There are two aspects to the function of steering groups:

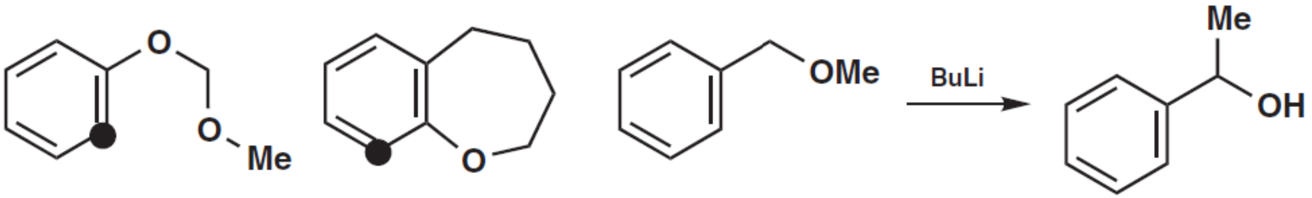
1) can coordinate with the organometallic reagent
2) increase the acidity of neighbouring hydrogen

1.2. THE USE OF LITHIUM

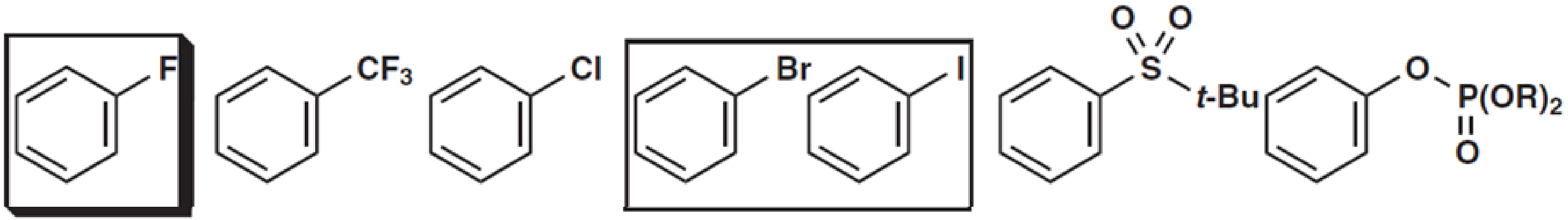
Oxygen-containing directing groups

❖aromatic compounds with an O atom in adjacent positions are easily lithified

❖if the O atom is away from the aromatic ring, it directs *ortho*-lithiation very poorly

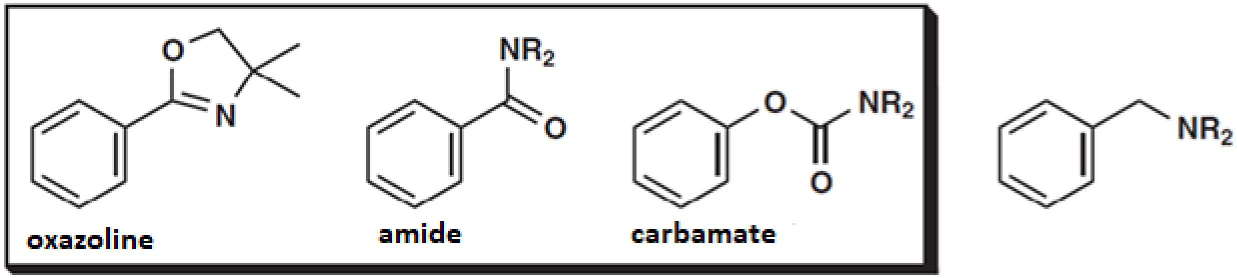


Halogens, sulfonates and phosphates



Directing groups containing nitrogen atom

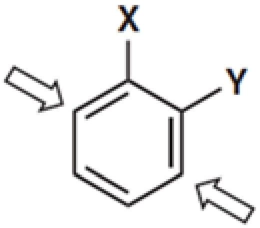
❖ oxazolines, amides and carbamates are most commonly used as *ortho*-targeting groups - very easily introduced



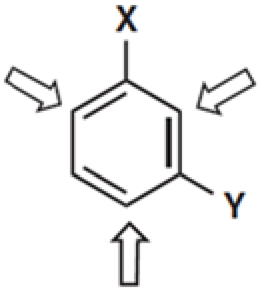
1.2. THE USE OF LITHIUM

Regioselectivity – *ortho* vs *ortho*:

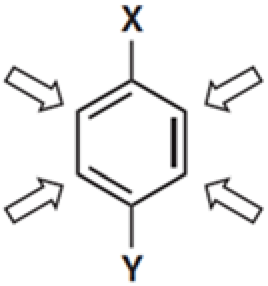
- two directing groups in the aromatic ring



X i Y ortho



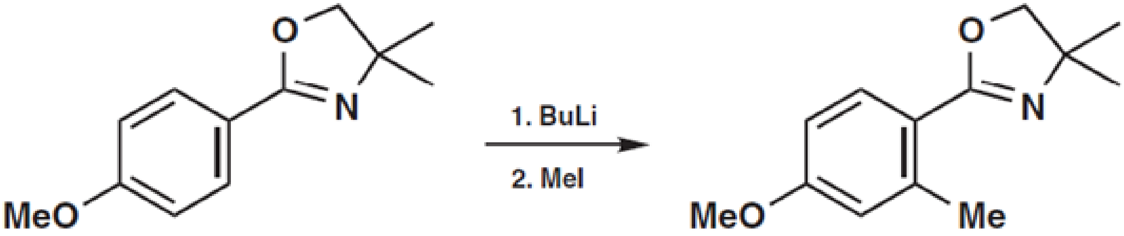
X i Y meta

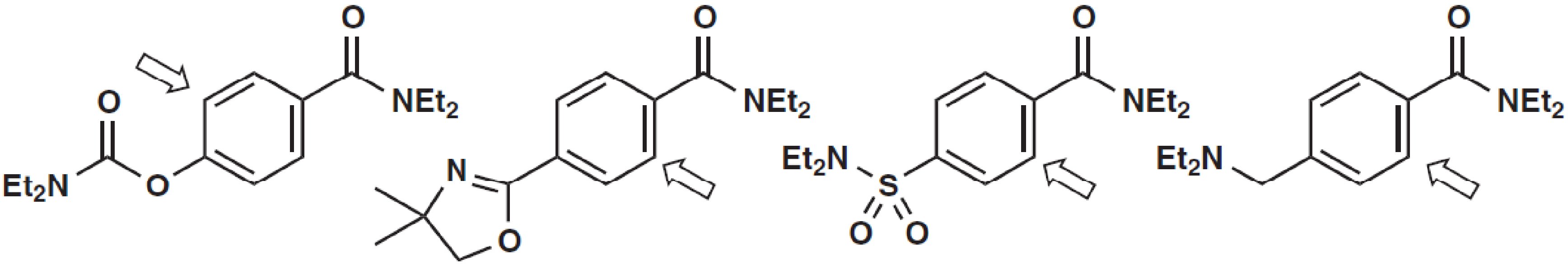


X i Y para

X i Y : ortho-

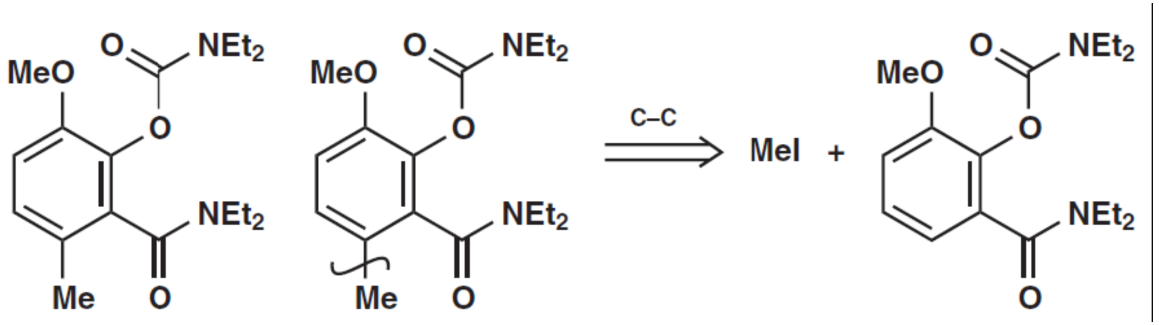
Example: *ortho*-lithiation goes to an adjacent position of a group that is more strongly directing



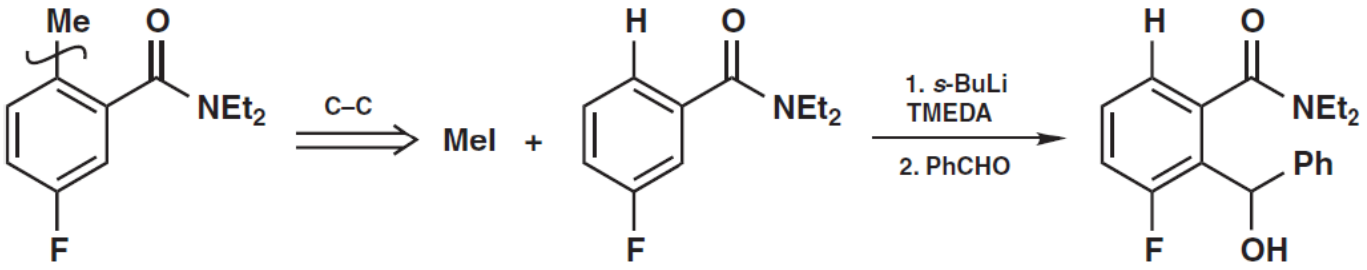


1.2. THE USE OF LITHIUM

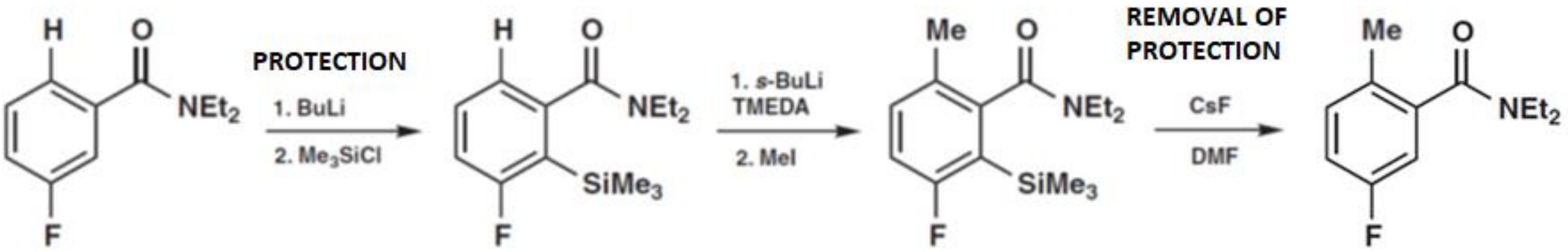
- three directing groups in the aromatic ring
- the amide group is more strongly ortho-directing than methoxy



- two directing groups in the meta position



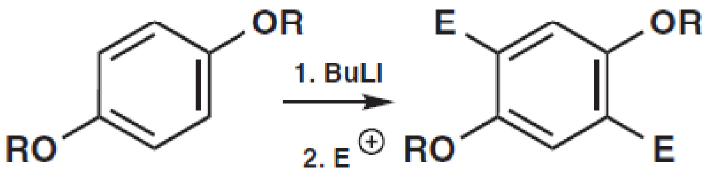
- the use of a protective group to block the position between the two directing groups



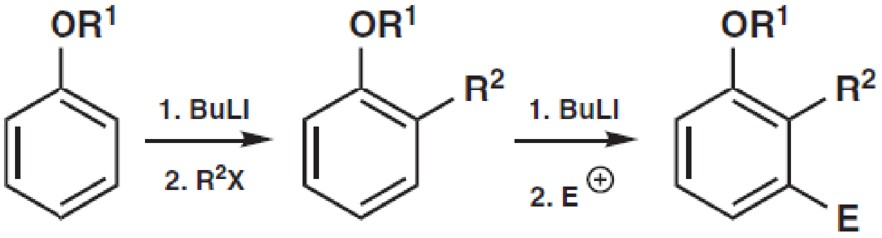
1.2. THE USE OF LITHIUM

The possibility of multiple lithiation of the aromatic ring:

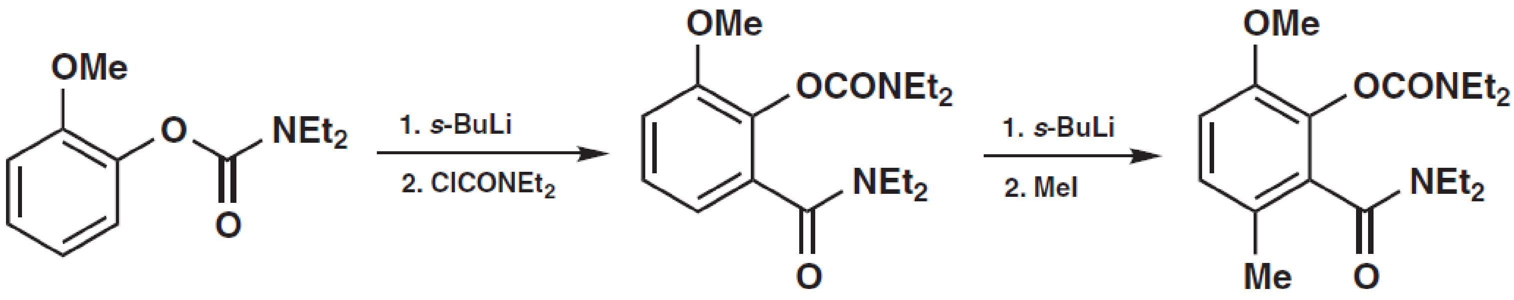
R is a directing group



R_1 and R_2 are directing groups



✓ **the group which is introduced can direct the lithium**

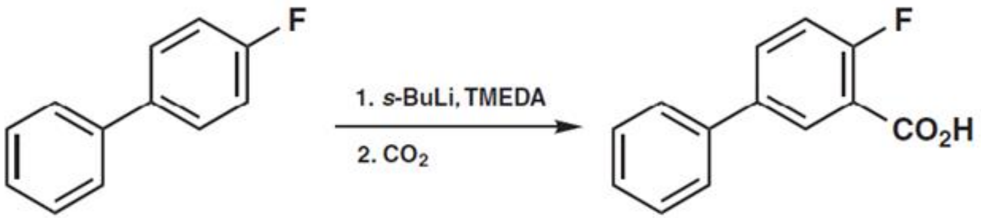


1.2. THE USE OF LITHIUM

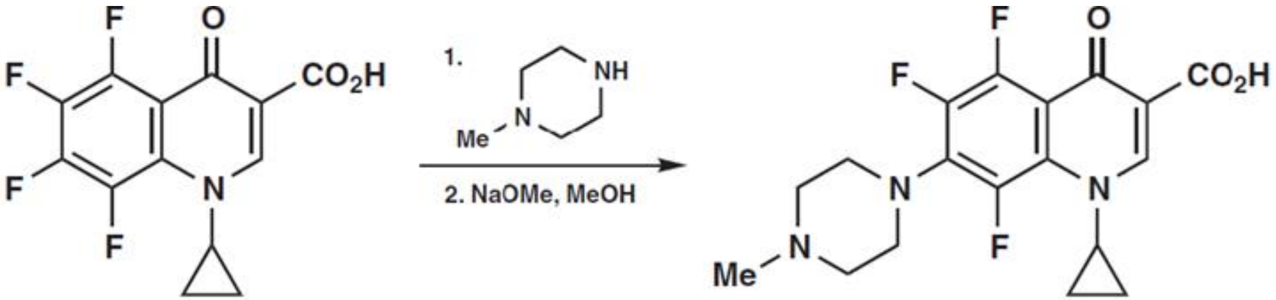
1.2.4. HALOGENIDES

✓ FLUORINE

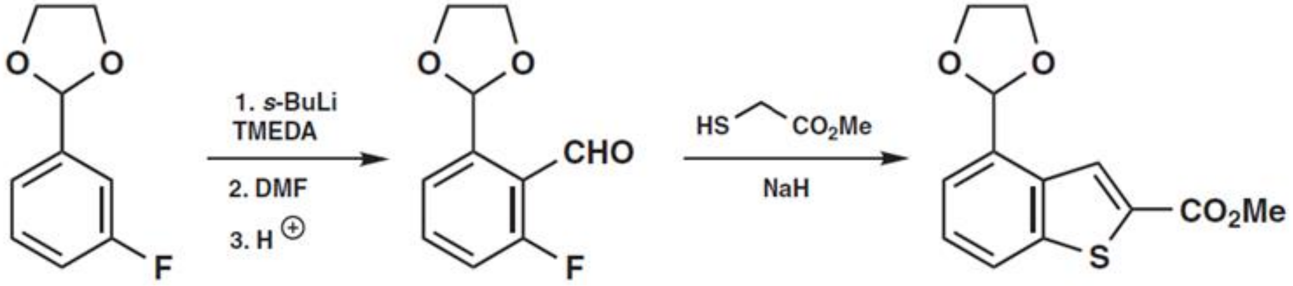
- *ortho*-directing group:



- leaving group:



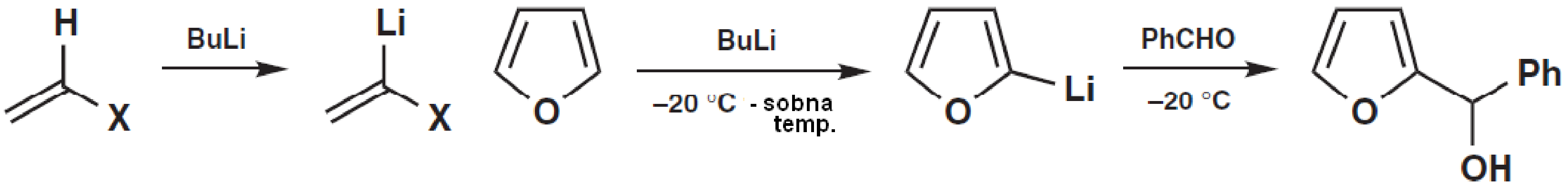
- *ortho*-directing group and leaving group:

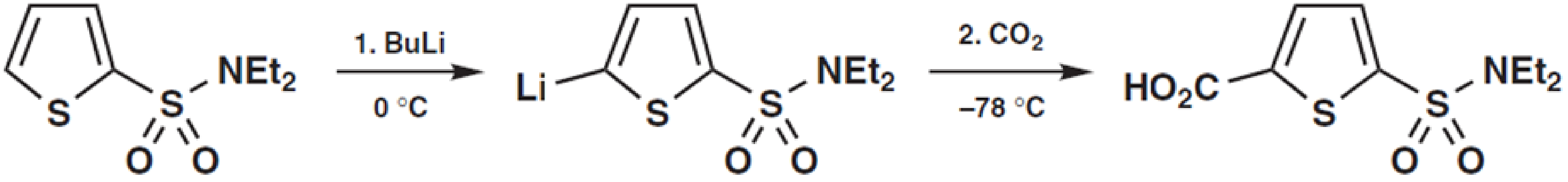


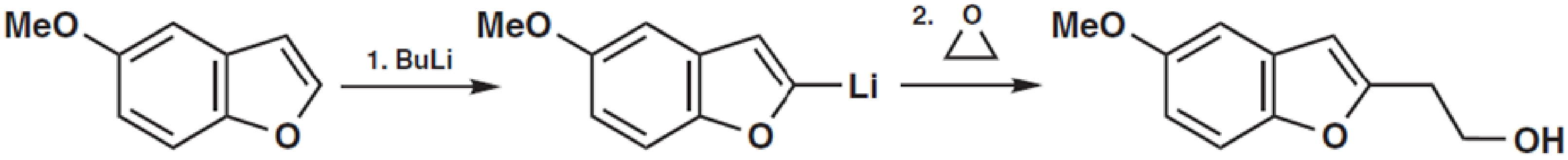
1.2. THE USE OF LITHIUM

1.2.4. α-LITHIATION

- characteristic of the sp^2 C atom and the α-position relative to the heteroatom



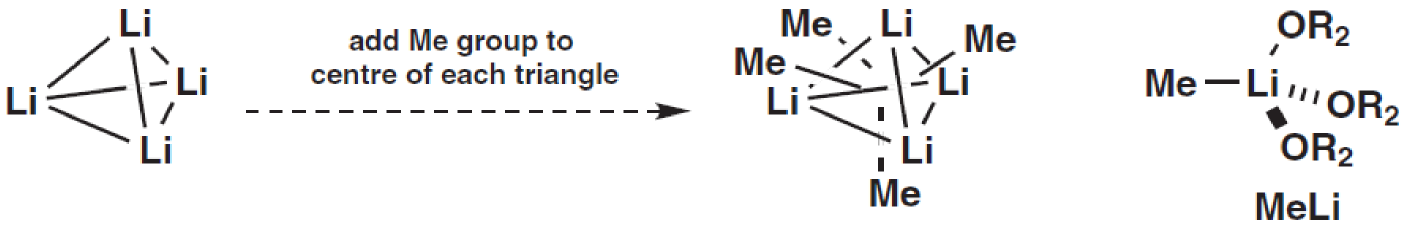




2. σ-METAL COMPLEXES

Structure of organolithium compounds

- σ-complexes have a direct metal-carbon bond



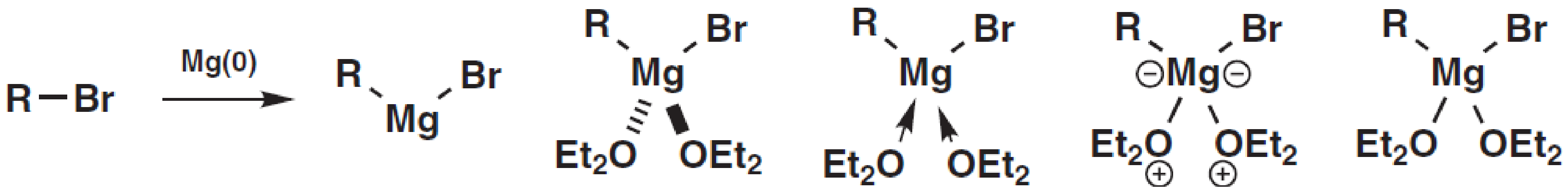
Li atoms in MeLi

MeLi

MeLi
in solution

Formation of organometallic σ-complexes by oxidative insertion

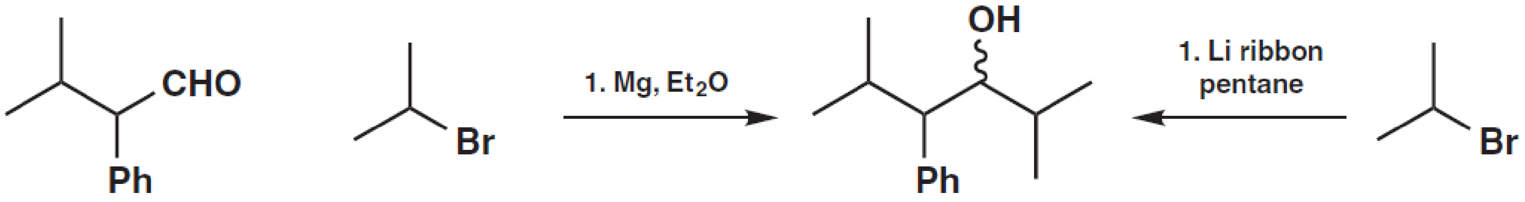
- formation of Grignard reagent by oxidative insertion
- insertion of a metal atom between carbon and halogen where it is simultaneously subject to oxidation from Mg (0) to Mg (II)



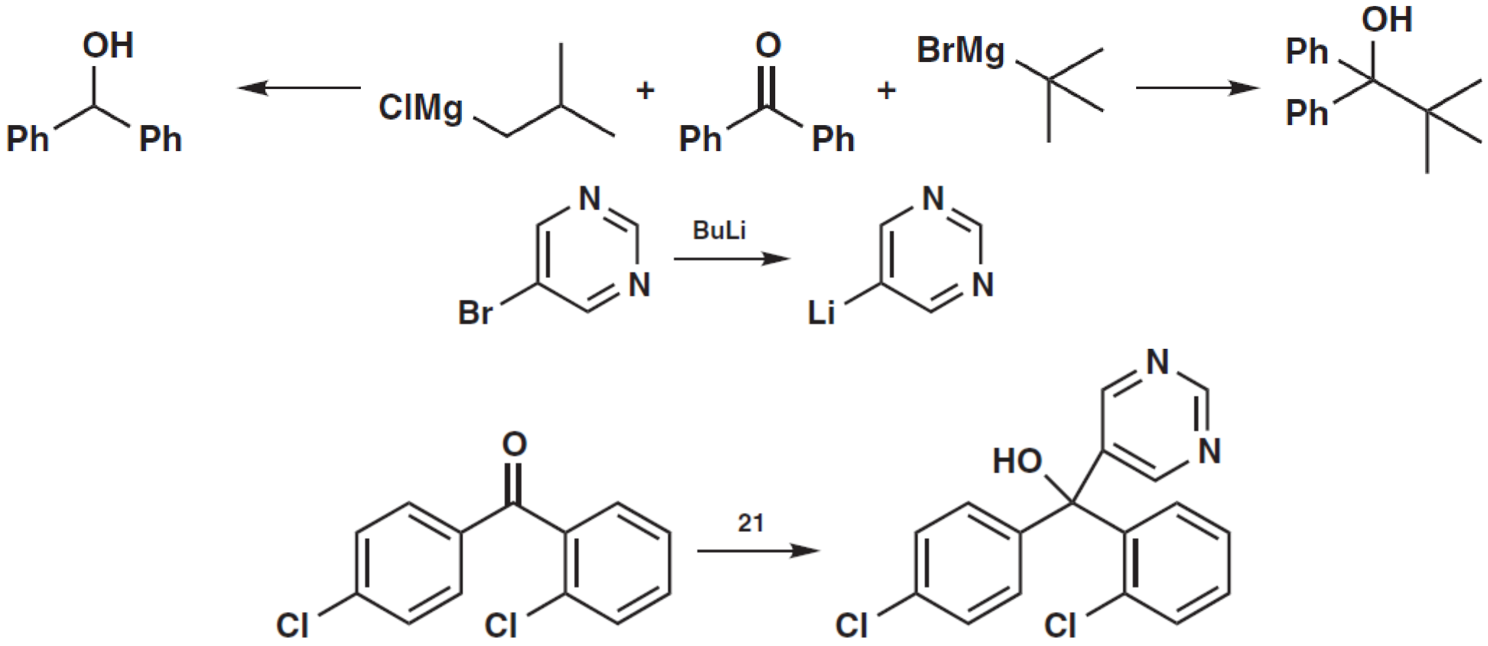
2. σ-METAL COMPLEXES

Reactions of organolithium and organometallic reagents

- **problems that may occur are related to enolization with RLi and reduction with RMgX**



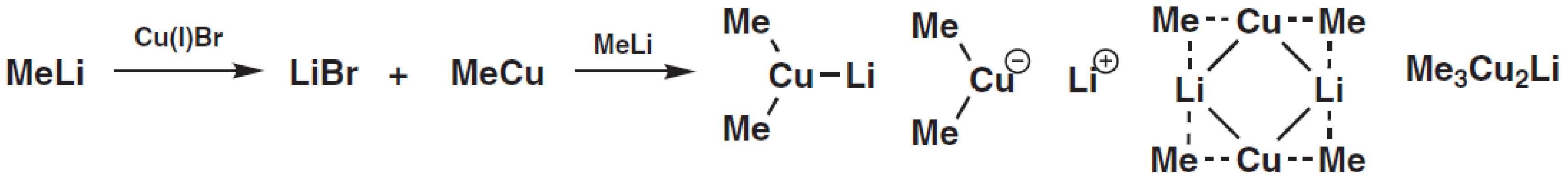
- **addition with *t*-BuMgBr and reduction with *i*-butyl MgCl Grignard**



Transition metal complexes

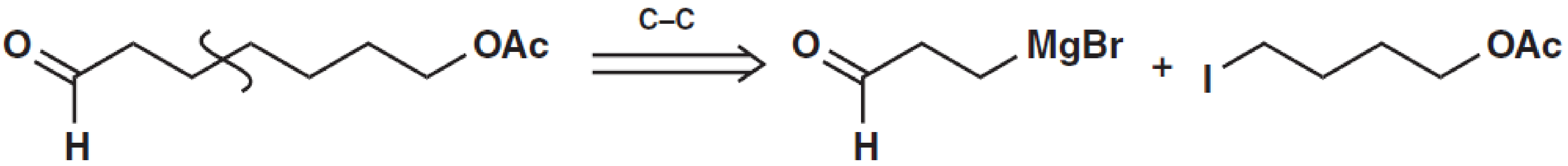
Acylation with acyl chlorides

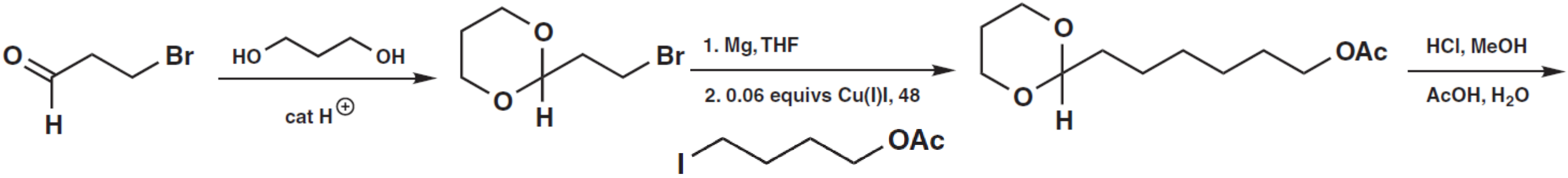
- σ-complexes of metals other than Mg and Li are prepared from organolithium or Grignard reagents
- nucleophilic substitution without changing the oxidation state of the metal



Examples:

$$\mathrm{BuLi} \xrightarrow[\mathrm{THF}]{\mathrm{Cu(I)I}} \mathrm{Bu_2CuLi} \xrightarrow{n\text{-}C_7H_{15}\text{-}I} n\text{-}C_{11}H_{24} = n\text{-undecane}$$

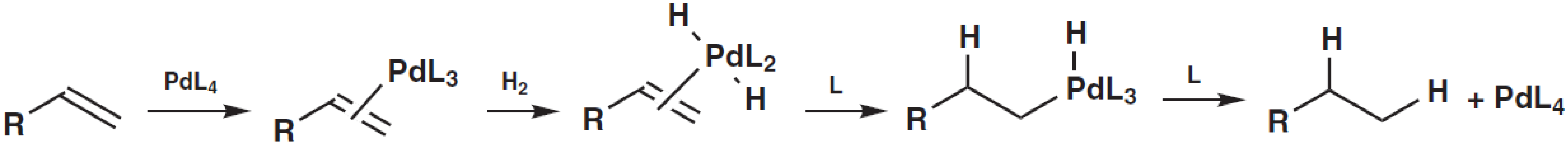




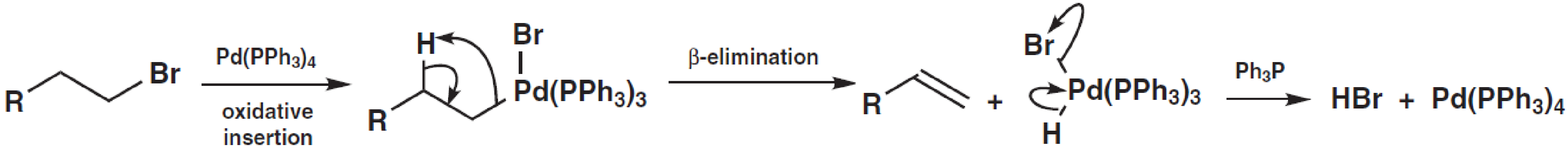
Transition metal complexes

Paladium σ-complexes

- soluble reagents such as Pd(PPh_3)$_4$, $PdCl_2$ or Pd(OAc)$_2$ are often used in the reactions
- catalytic reactions, carbonyl group introduction reactions
- reactions hydrogenation in solution - Pd forms stable π-complexes with alkenes - by inserting hydrogen atoms σ-complexes are formed

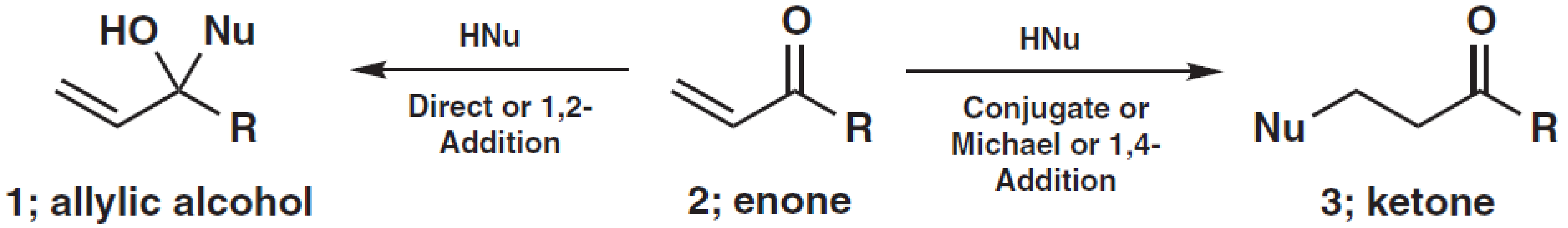


- Pd σ-complexes are not stable
- Pd is subjected to oxidative insertion into the alkyl halide molecule to give an σ-complex that immediately loses a proton



3. CONTROLLED MICHAEL REACTIONS

- **Michael addition** (conjugated or 1,4-addition) - addition of nucleophiles to electrophilic alkene, most often to unsaturated carbonyl compound - mostly 1,4-addition to double bond



1; allylic alcohol

2; enone

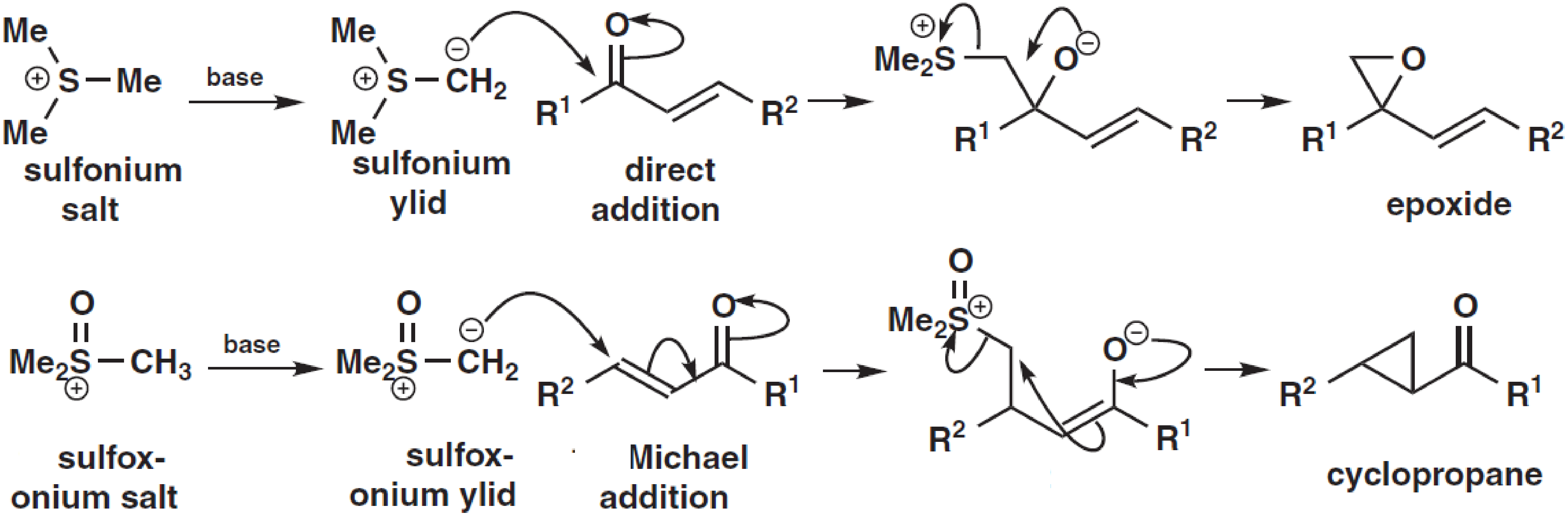
3; ketone

Basic rules of Michael's addition:

- direct or 1,2-addition - allyl alcohol is a kinetic product
- conjugated or 1,4-addition - a saturated carbonyl compound is a thermodynamic product
- the most reactive Michael acceptors have a tendency to 1,2-add (CHO> AlkCO> ArCO> CO2R> CN) and the less reactive have a tendency to 1,4-add
- the most reactive, basic nucleophiles tend to have 1,2-additions, the less reactive and the weakly basic 1,4-additions
- large substituents next to the C = O group, due to steric interference, may direct the addition to the other side

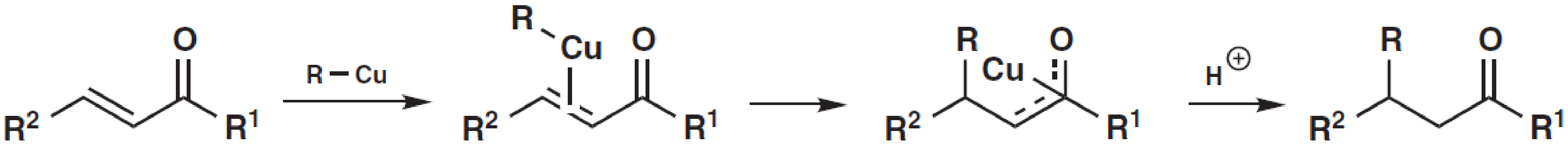
3. CONTROLLED MICHAEL REACTIONS

- **sulfur ylides react with aldehydes or ketones to give epoxides**
- **direct or 1,2-addition of sulfur ylides to unsaturated aldehydes or ketones produces epoxides and conjugated or 1,4-addition produces cyclopropanes**



The use of copper in Michael's additions

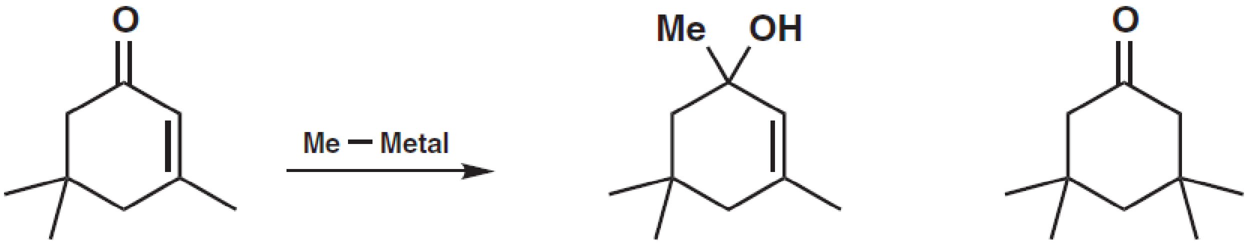
- **organo-copper σ-complexes for 1,4-Michael addition**



η^2 alkene complex

η^3 enolate complex

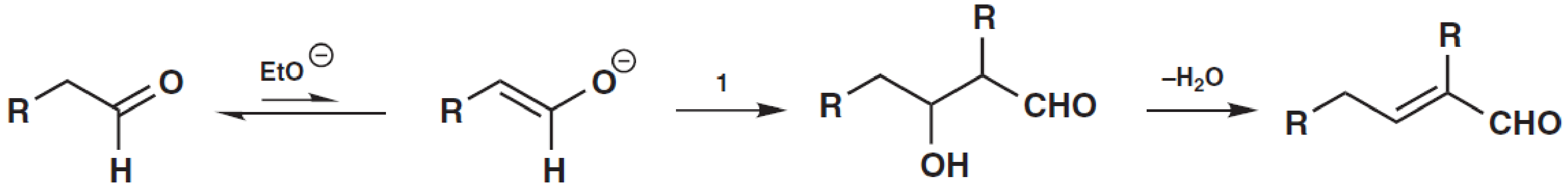
- **catalytic amounts of Cu_2Cl_2 affect the regioselectivity of the reaction and the majority product is the one obtained by 1,4-addition**



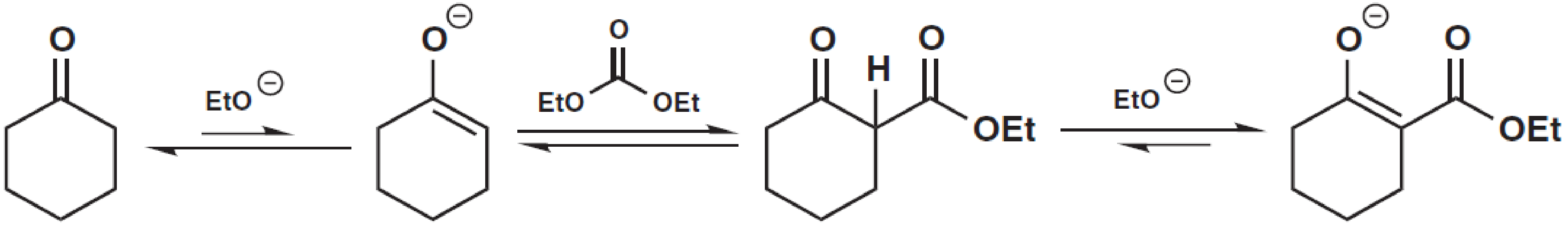
	allylic alcohol	saturated ketone
Me – Metal = MeMgBr	98.5:	:1.5
Me – Metal = MeMgBr + cat. Cu_2Cl_2	17.5:	:82.5

4. SPECIFIC ENOLE EQUIVALENTS

- the chemistry of enolate is very important in organic synthesis
- enolates are synthetic equivalents for d synthons
- are formed from carbonyl compounds with weak bases
- aldehydes react with themselves to give aldols



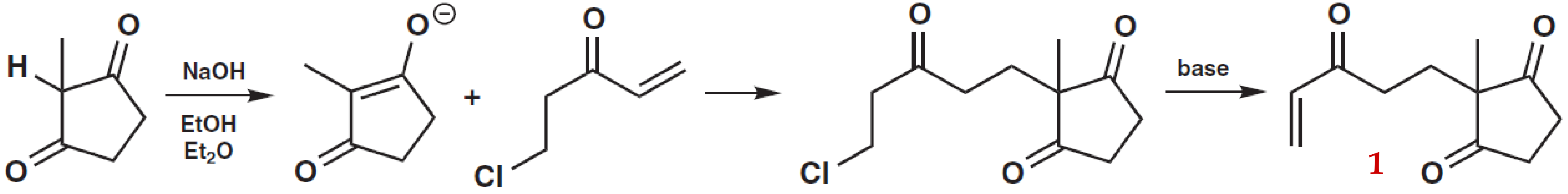
- less reactive ketones react with other carbonyl compounds



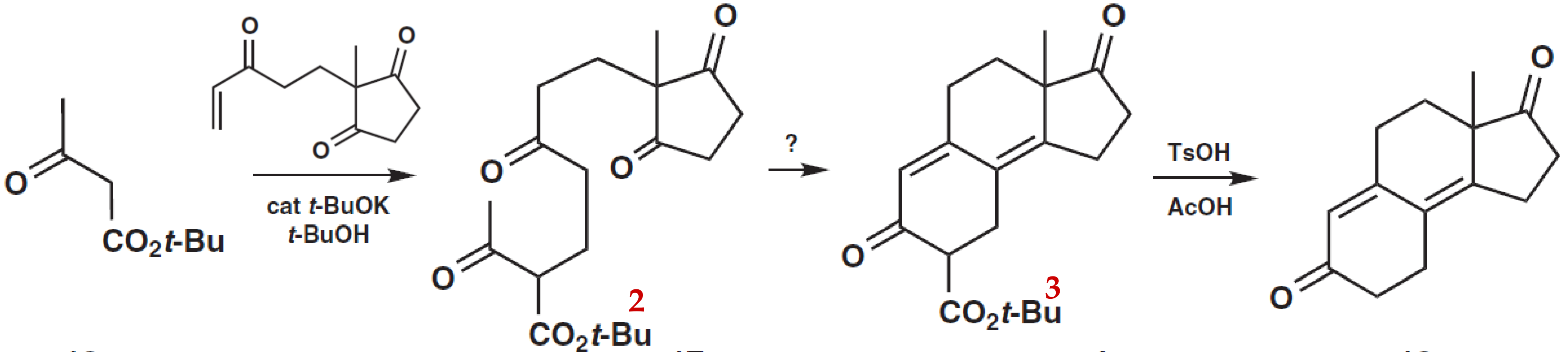
specific enolate.

4.1. Enolates from 1,3-dicarbonyl compounds

- **condensation of the stable enolate with enone gives Michael 's adduct which by elimination gives enone 1**

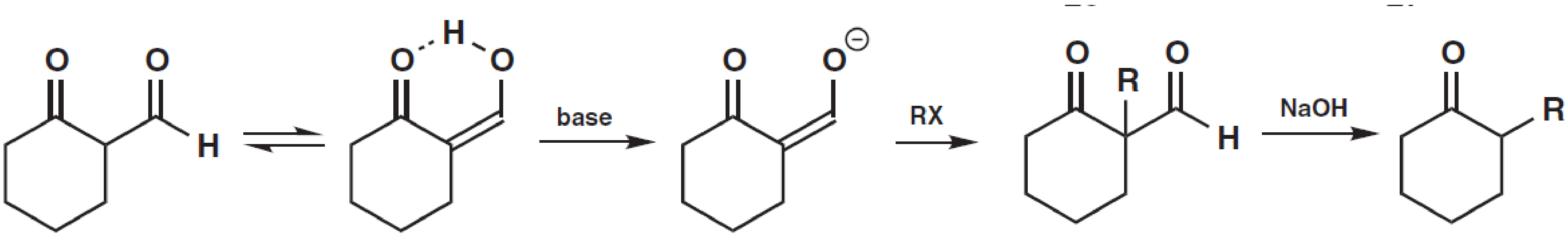


- **enon 1 gives in the next Michael addition with β-ketoester intermediates 2 and / or 3**

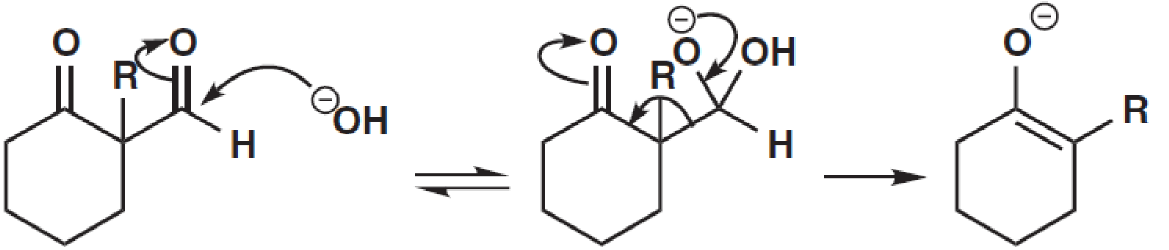


4.1. Enolates from 1,3-dicarbonyl compounds

- are not suitable for aldehyde reactions
- the aldehyde group usually has another function, e.g., alkylation of the ketone

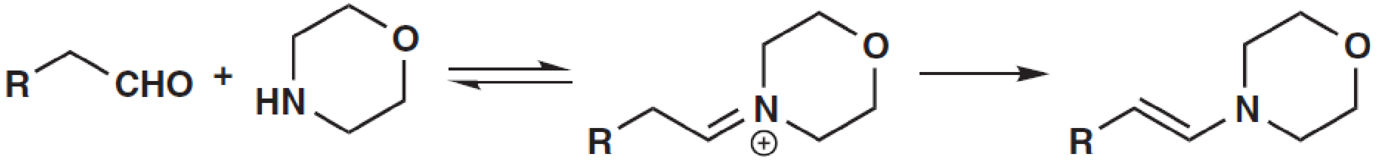


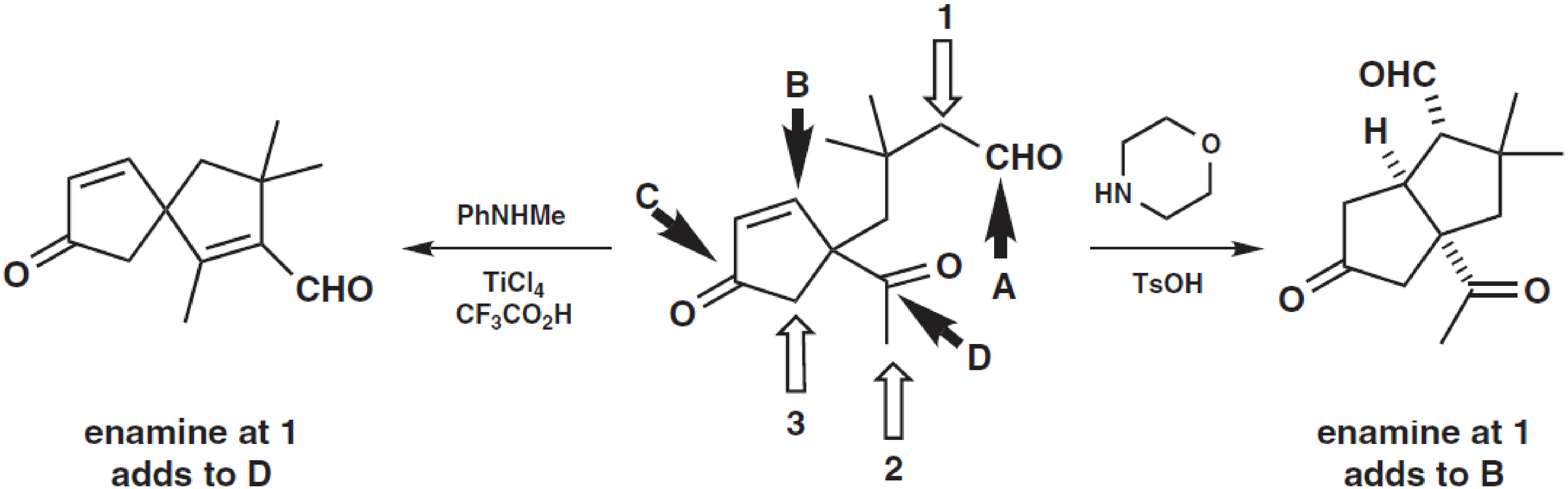
- when the position between the two carbonyl groups is blocked, nucleophile attack occurs on the more electrophilic C atom



4.2. Enamines and aza-enolates

- enamines are specific enolates that react well with aldehydes, secondary amines react best
- they are highly reactive in reactions with alkyl halides and in Michael additions



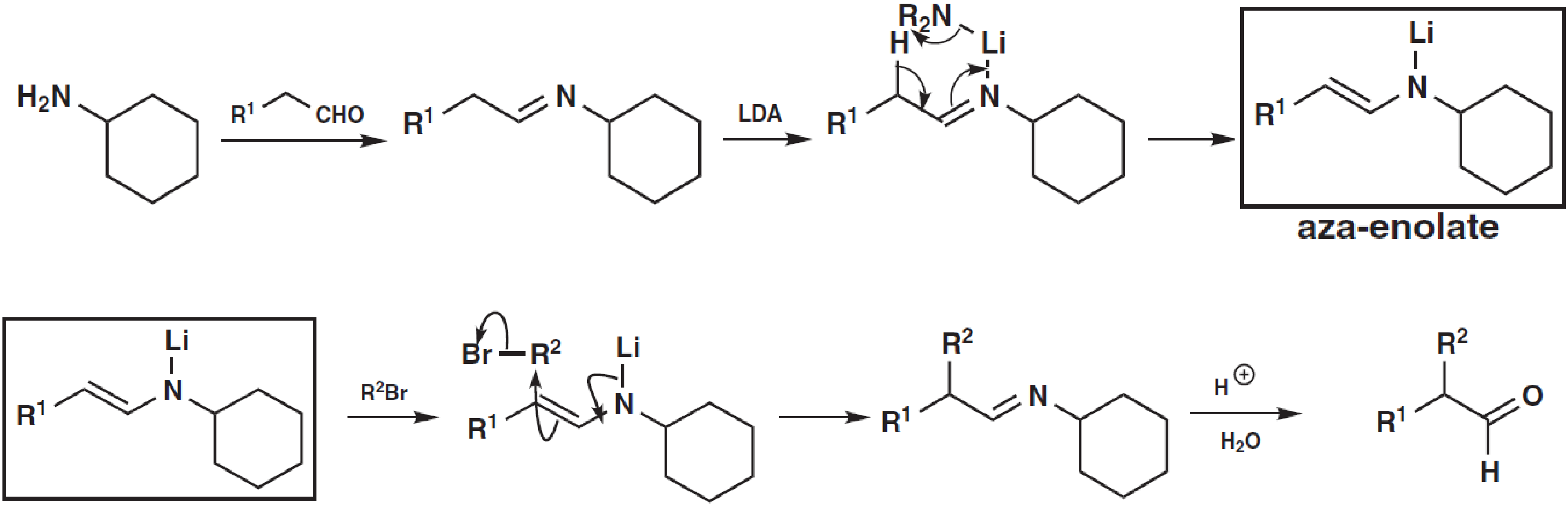


enamine at 1
adds to D
aldol conensation

enamine at 1
adds to B
Michael adition

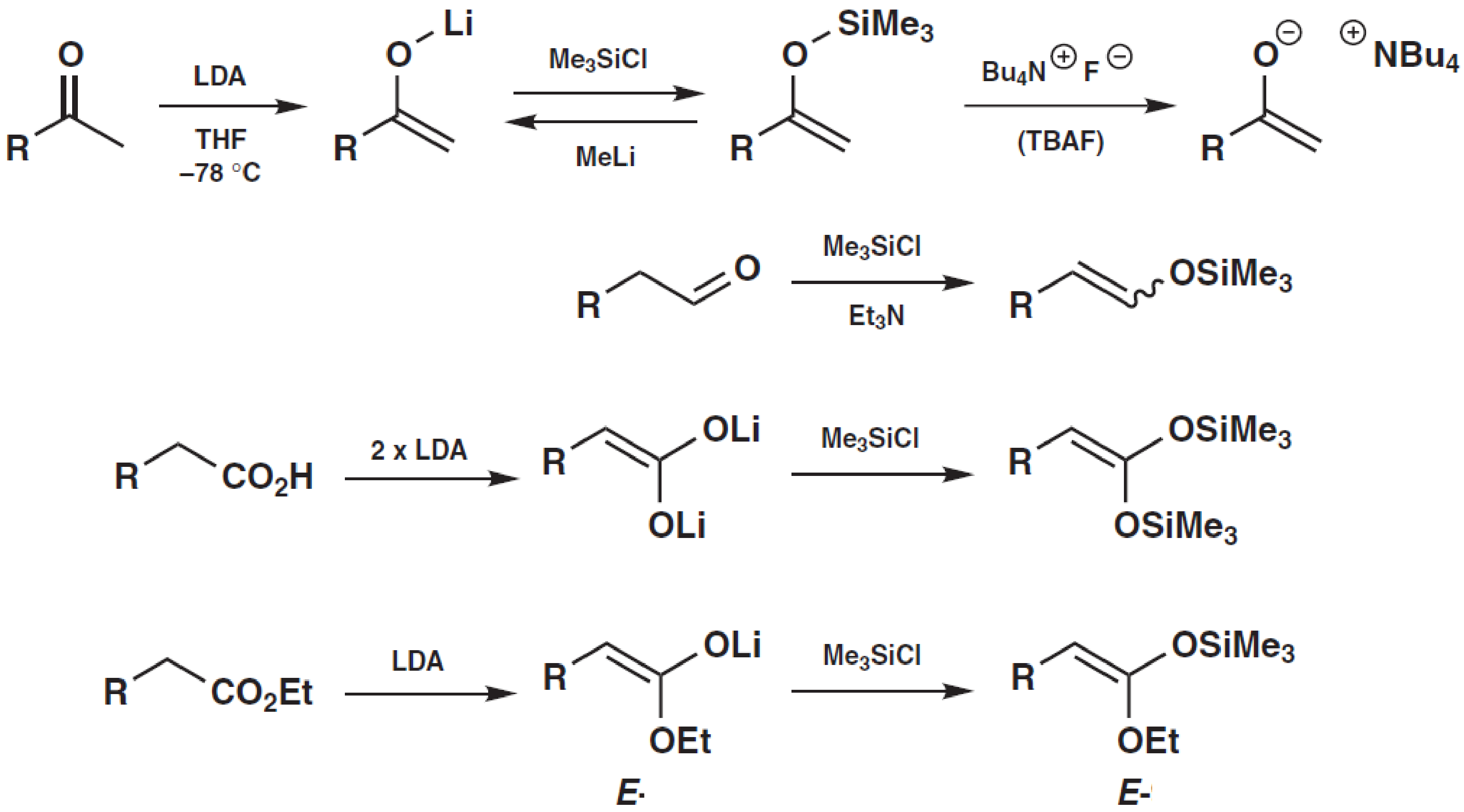
4.2. Enamines and aza-enolates

- alkylation with simple alkyl halides goes very badly with enamines because alkylation at the N atom occurs most often
- treatment of imines with LDA produces aza-enolates which are easily alkylated on the C atom, most often with primary but also secondary alkyl halides



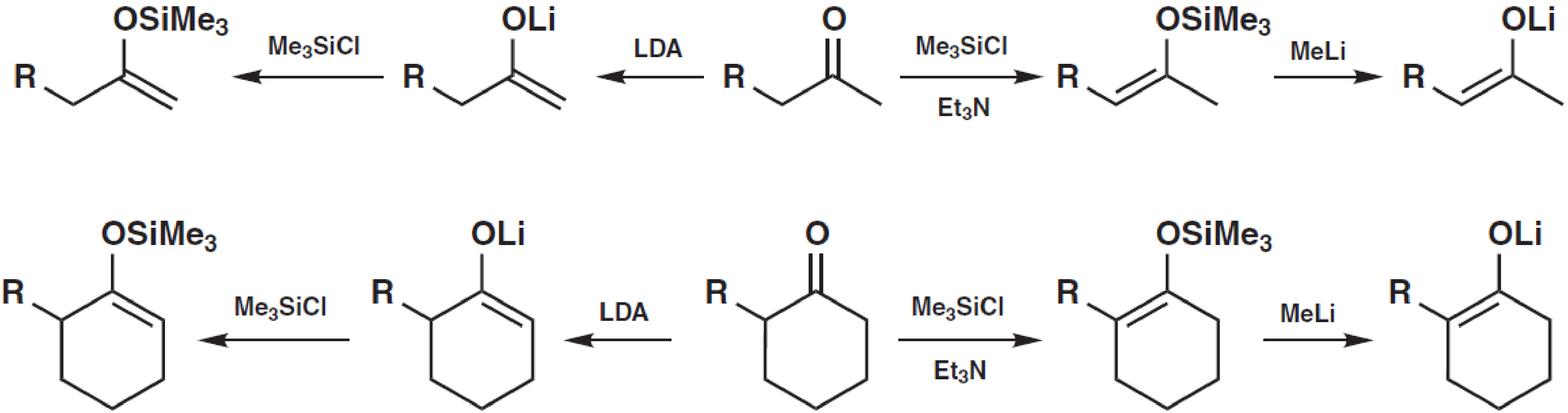
4.3. Lithium enolates and silyl-enol ethers

- the widest application in modern organic synthetic chemistry



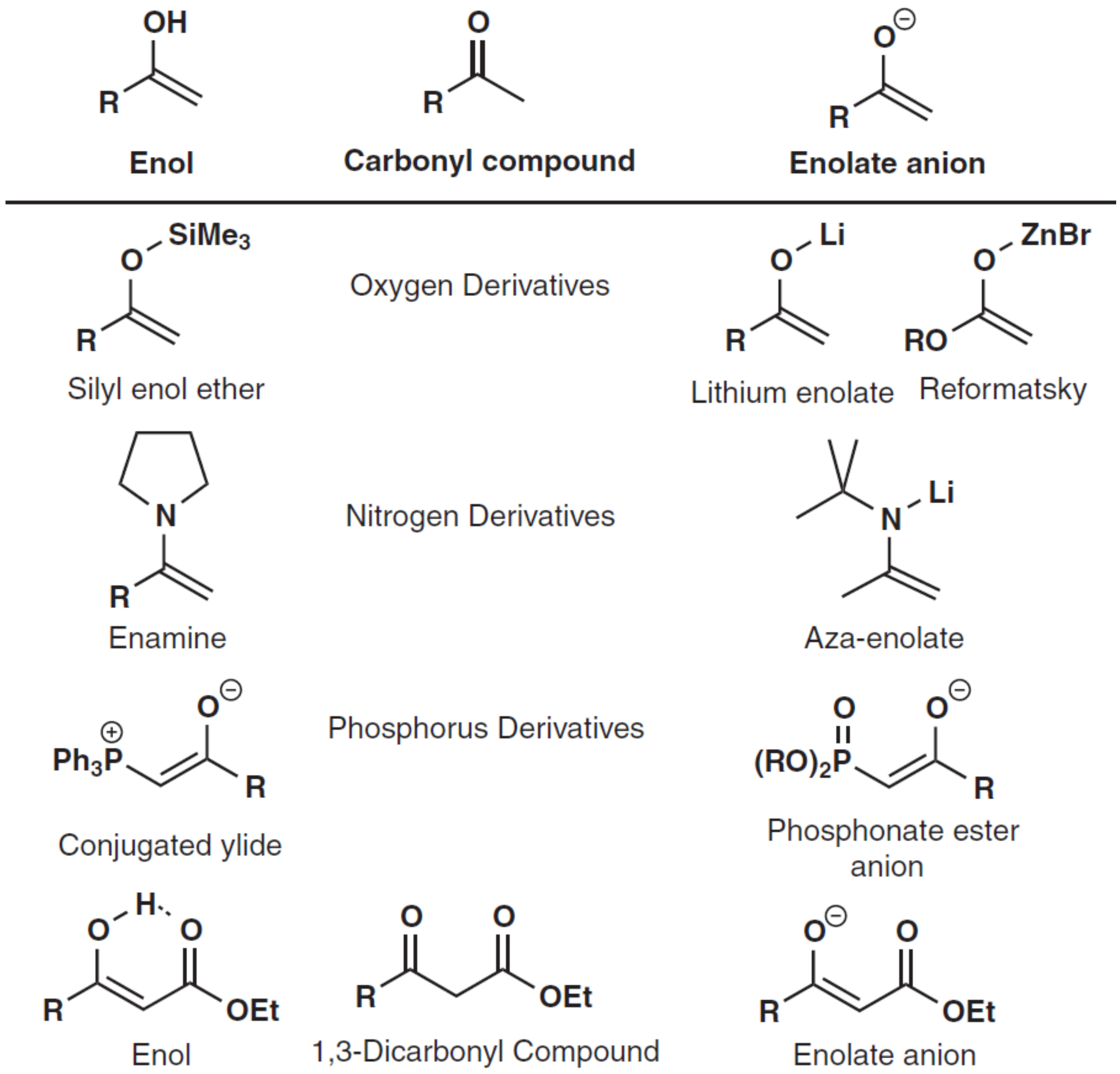
4.3. Lithium enolates and silyl-enol ethers

- **the widest application in modern organic synthetic chemistry**



- **ketones with one primary or secondary alkyl group give less substituted Li-enolates and more substituted Si-enol ethers**

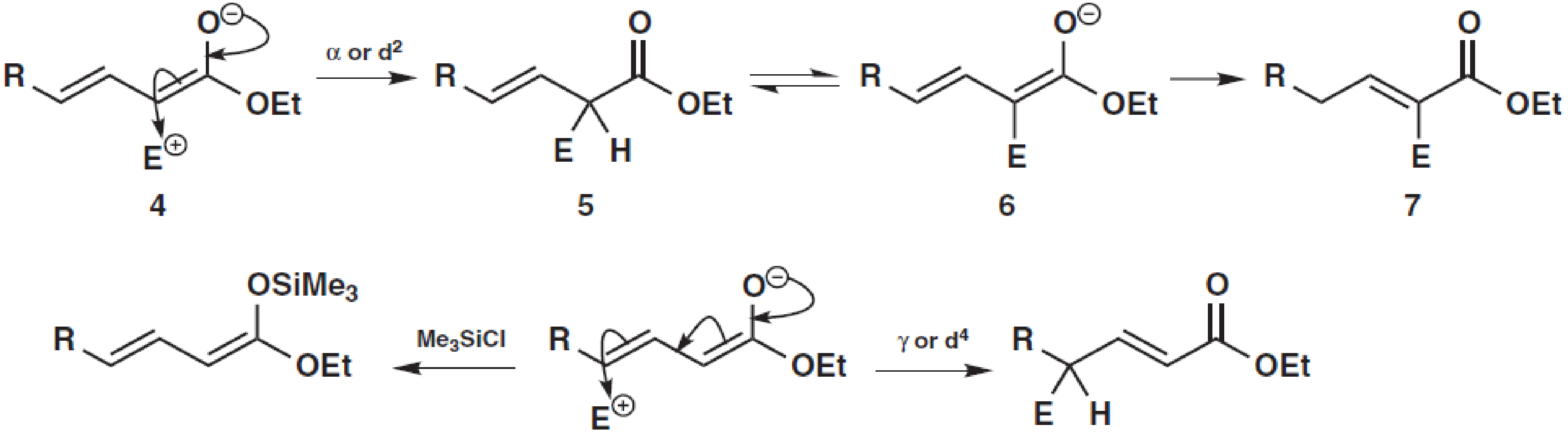
4.3. Lithium enolates and silyl-enol ethers



5. EXTENDED ENOLATS

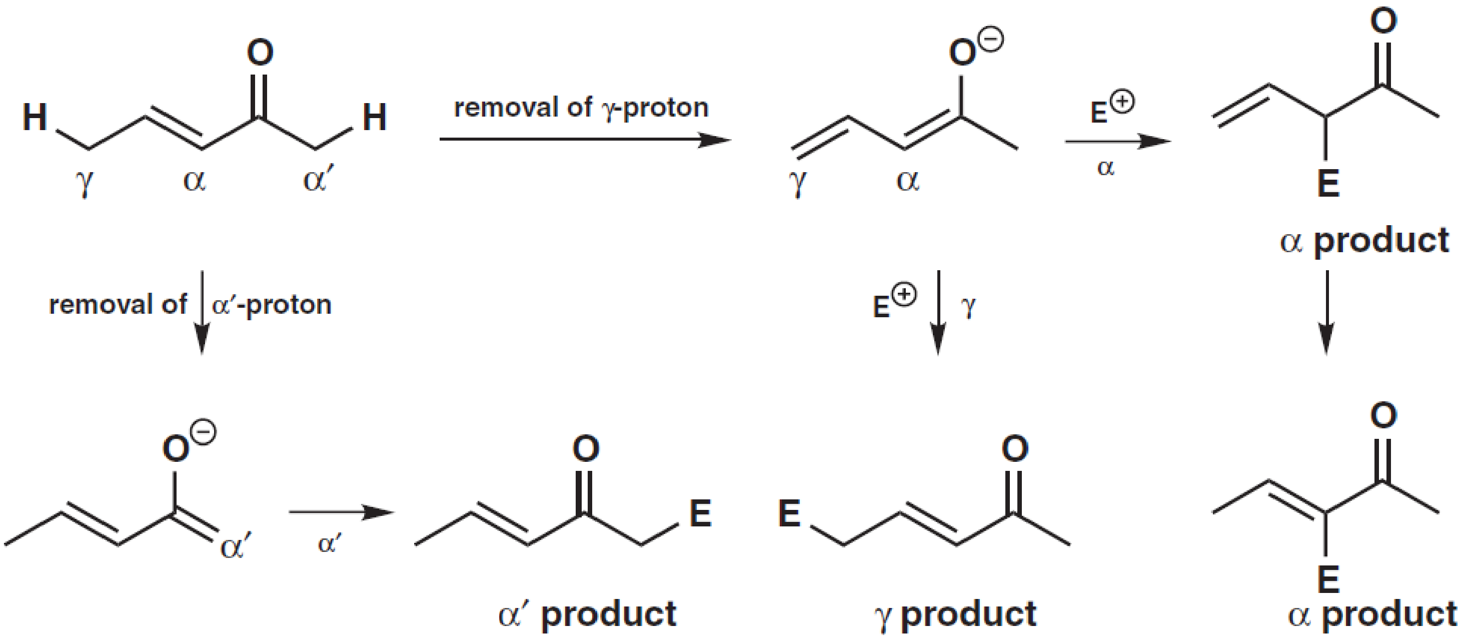
- **prolonged conjugation into a double bond**

- **the reaction at the α-position produces an unconjugated ester which becomes conjugated by proton transfer over the extended enolate while the reaction at the γ-position directly produces a conjugated ester**

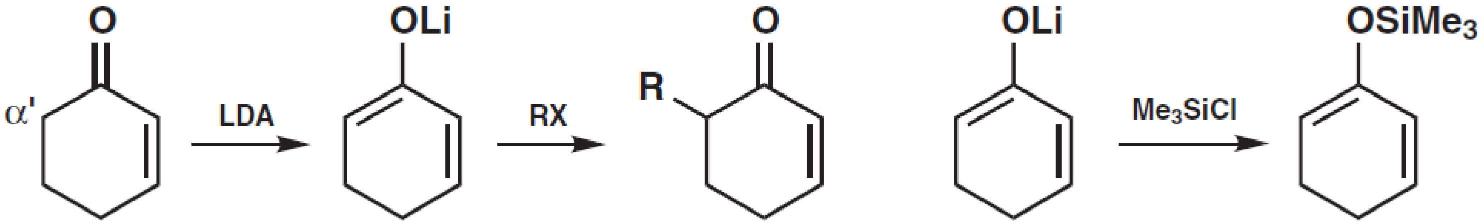


Prolonged enolates from unsaturated ketones

- ketones enolyze at the α'-position - 4 possible products



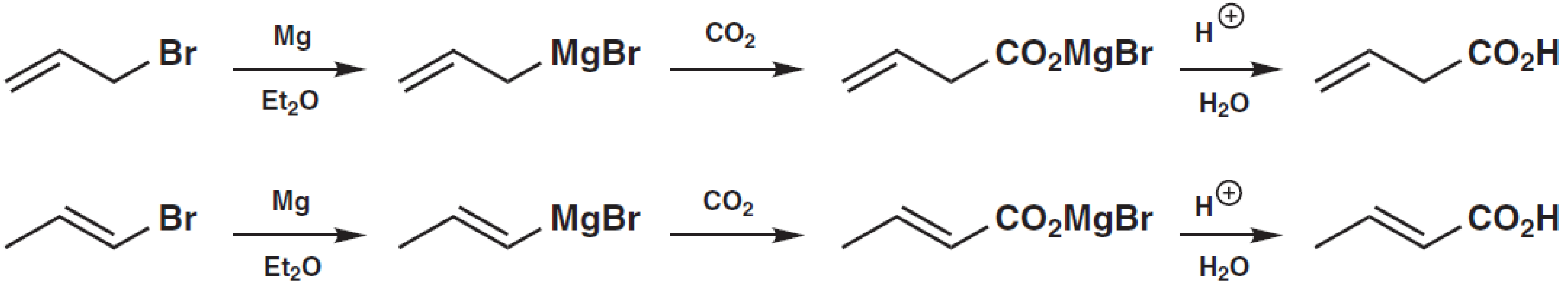
- alkylation of lithium enolates takes place at the α′-position and silylation at the O atom



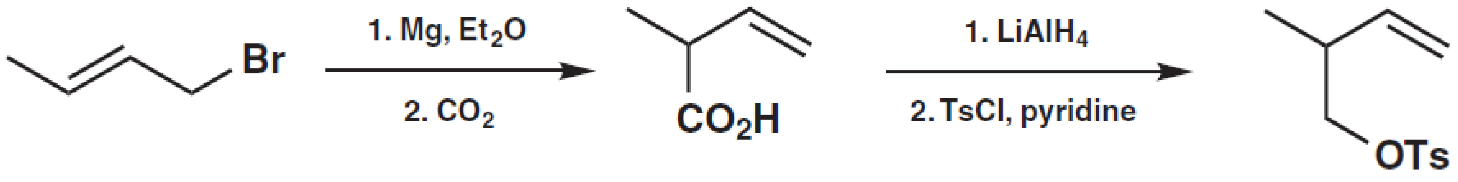
6. ALLYL ANIONS

Allyl Grignard reagents

- when halogen is attached to a C atom that is up to a double bond we have a highly reactive allyl bromide and a weakly reactive Grignard reagent
- when halogen is directly attached to the double bond we have non-reactive vinyl bromide and highly reactive Grignard reagent

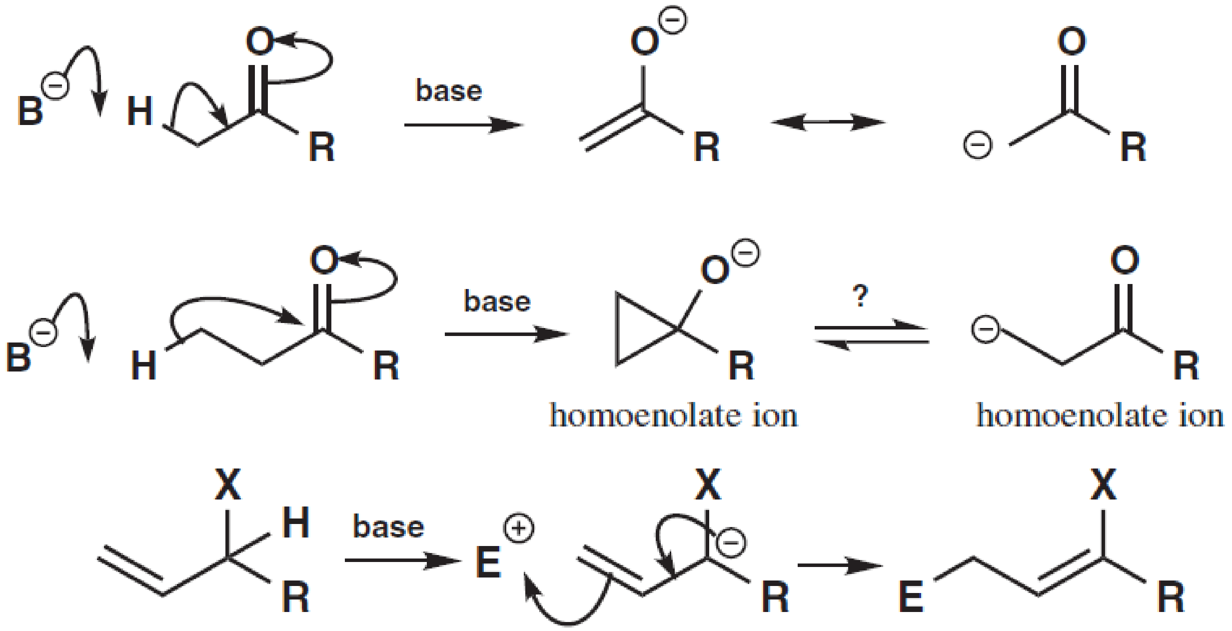


- stable allyl radicals - polymerization or reaction occurs on the wrong side of the allyl system



7. HOMOENOLATES

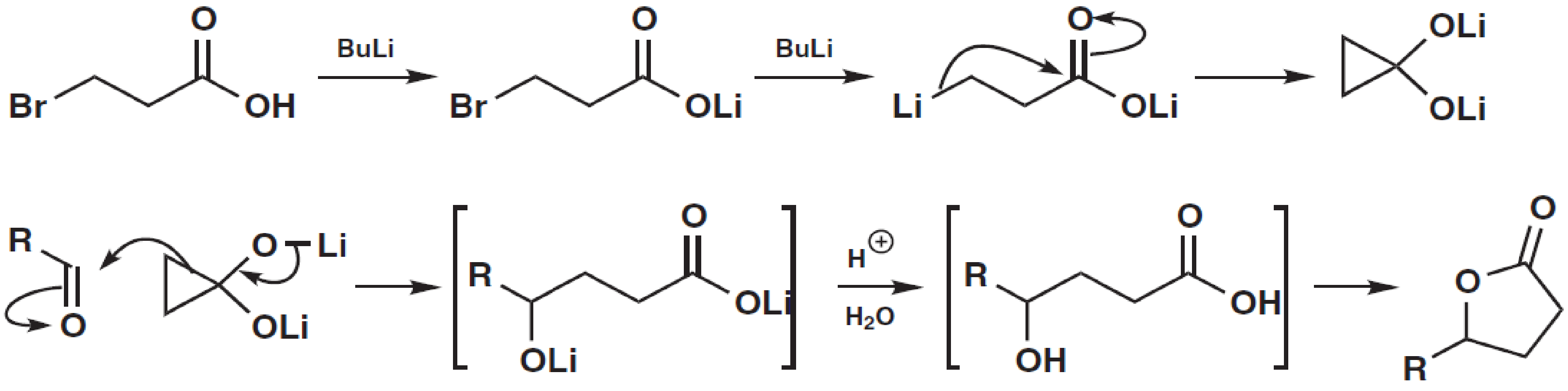
- homoenolization is the removal of a β-proton to form a homoenolate ion



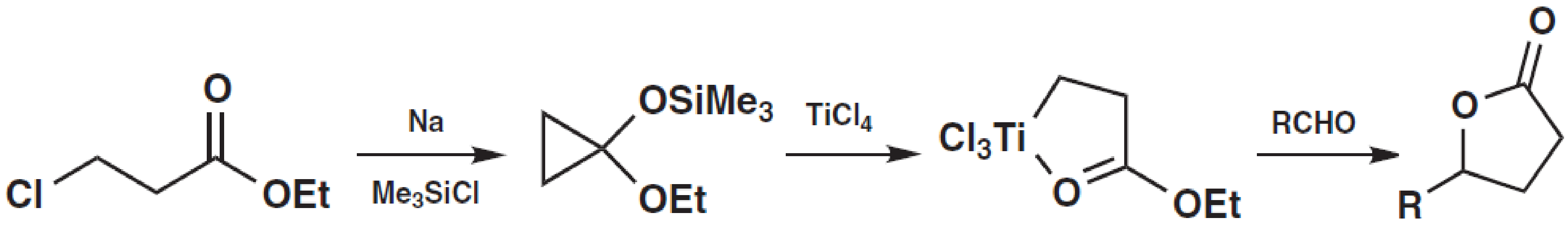
offensive strategy

7.1. "Direct" strategy for the preparation of homoenolate equivalents

- **the true homoenolates used in the synthesis are obtained by metallization of 3-halocarboxylic acids**



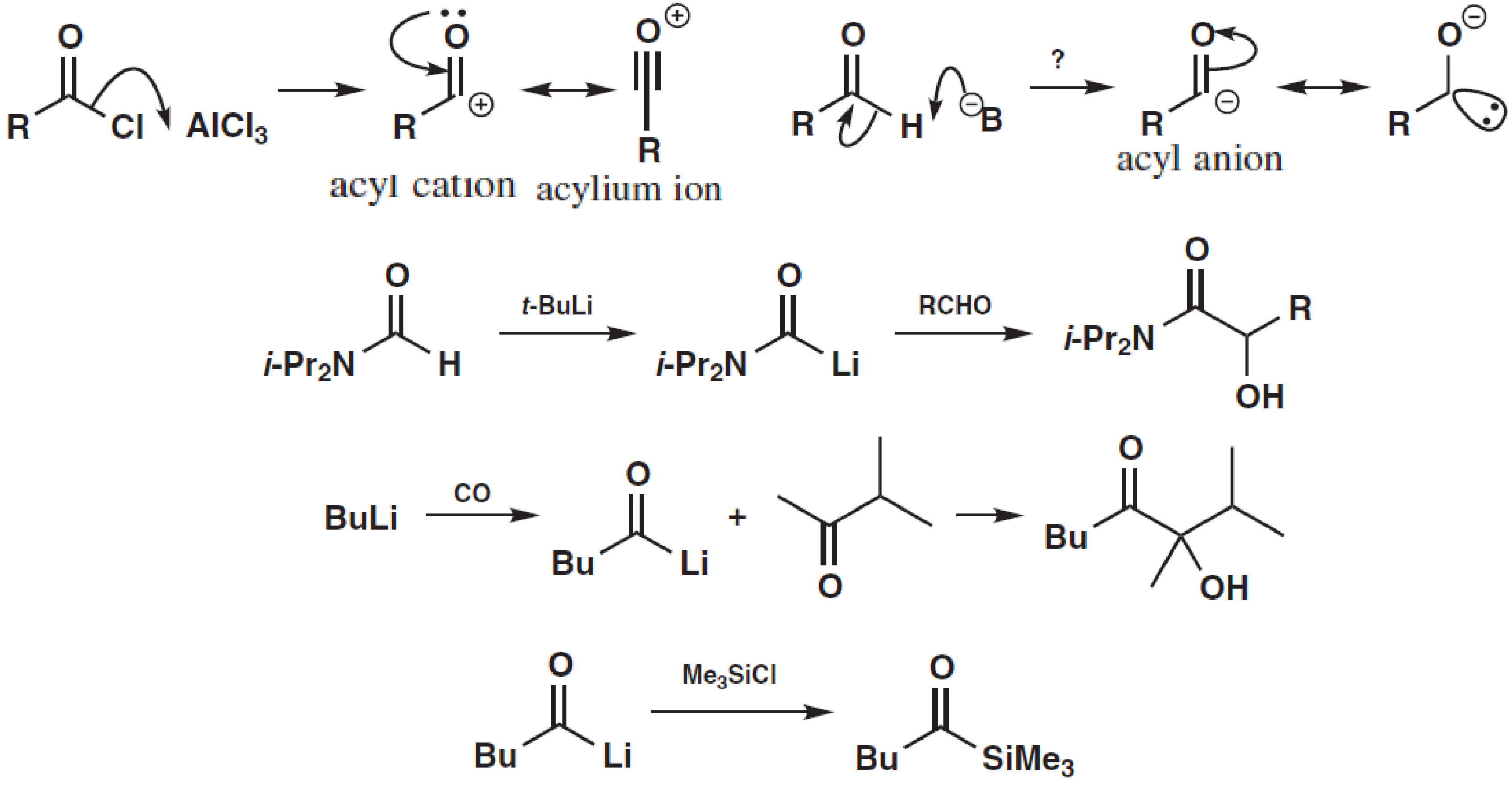
- **ester homoenolates**



γ-laktones

8. ACYL ANION EQUIVALENTS

- **acyl cation or acilium ion** is easily prepared from acyl halide and Lewis acid and acyl anion can be prepared from aldehyde and base



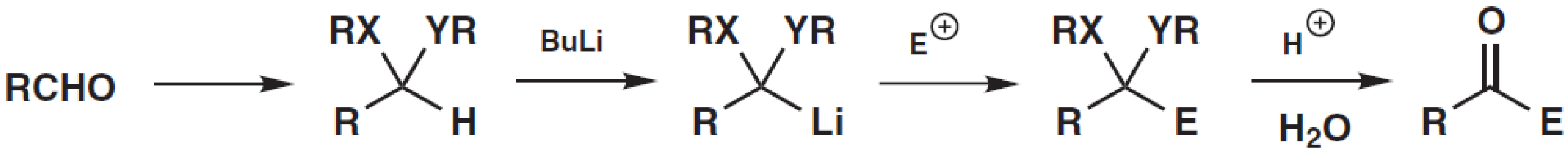
8. ACYL ANION EQUIVALENTS

Three main types of acyl anionic equivalents:

1. reagents that can be considered as modified acetals (protection for aldehydes)
2. masked carbonyl compounds (nitroalkanes)
3. substituted vinyl-lithium compounds

Modified acetals as acyl anionic equivalents

- each acetal of an aldehyde can be used as an acyl anion and the X and Y atoms stabilize the anion
- usually one substituent stabilizes the anion (CN, S) while the other helps in the hydrolysis reaction (O, N)



Learning outcomes of the teaching unit

✓ know the most important methods for creating a C-C bond

✓ understand the most important ortho strategies for obtaining aromatic compounds

✓ understand the importance of lithium use in organometallic chemistry and organic synthesis planning

✓ be able to predict the position of the lithium with respect to the type of substituents on the aromatic ring

✓ understand s-complexes of metals and their application in synthesis

✓ understand the importance of controlled Michael additions

✓ be able to use the chemistry of specific enol equivalents and extended enolates in retrosynthesis and planning the synthesis of the target molecule

✓ understand the importance of allyl anions, homoenolates and acyl anionic equivalents