Organic Chemistry-4

Semester-4, CBCS

Course: CEMA CC-4-8-TH

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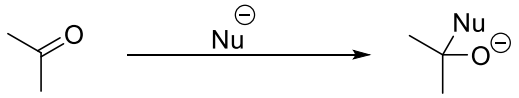
Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

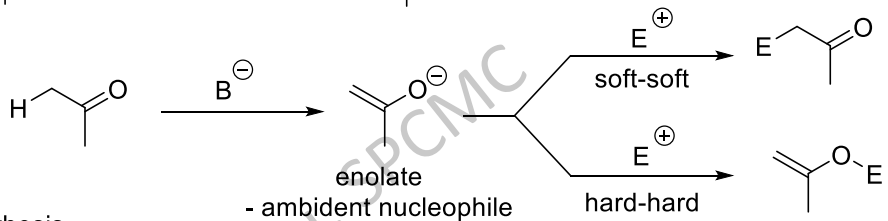
The Logic of Organic Synthesis: The use of Protecting Groups:

B] Protection of carbonyl groups in aldehydes and ketones:

The carbonyl group is electrophilic and prone to nucleophilic attack.:



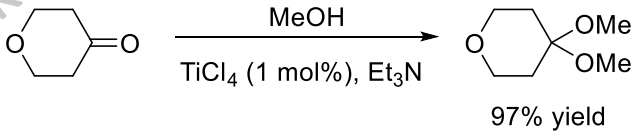
In addition, its presence renders the α-hydrogen acidic that can quench highly basic species present in the medium and resulting in the formation of nucleophilic enolate ion that can participate in competing side reactions such as aldol addition.



Carbonyl protection is thus a central requirement for a successful organic synthesis.

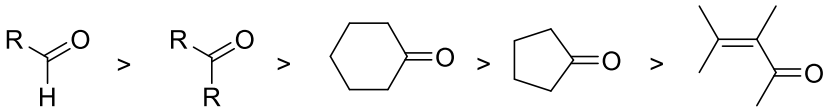
a) *O*,*O*-acetals:

Protection: Acyclic and cyclic acetals are the most important carbonyl protecting groups of aldehydes and ketones. The acetal protective group is introduced by treating the carbonyl compound with an alcohol, an orthoester, or a diol in the presence of a Lewis acid catalyst. Water, if formed, is removed efficiently by azeotropic distillation. In recent years, several transition metal catalysts such as $TiCl_4$ have been shown to offer major advantage over general Brønsted acid catalysts.

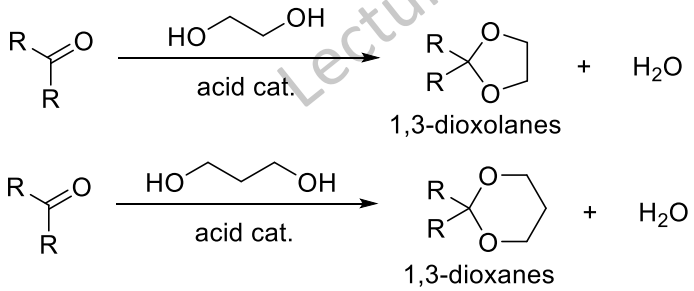


Notable features of carbonyl acetalisation are:

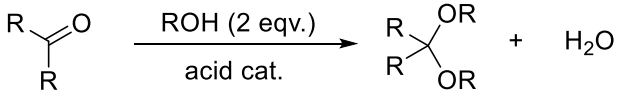
i) The general order of reactivity of various carbonyl groups (steric effects may cause a reversal of the reactivity order) is as follows:



ii) 1,3-Dioxanes (six-membered cyclic acetals) derived from ketones hydrolyze faster than the corresponding 1,3-dioxolanes (five-membered cyclic acetals). These acetals are derived from heating the carbonyl compound with the corresponding diol and an acid catalyst (PPTS, $BF_3.OEt_2$ or TsOH) with provisions of azeotropic removal of water. The formation of acetals with diols provides an entropic advantage over the use of two equivalents of an alcohol.



is entropically more advantageous to



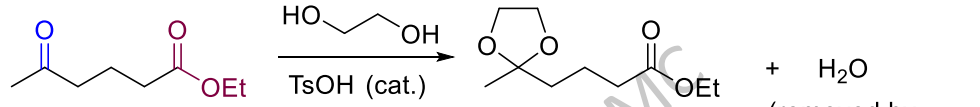
The Logic of Organic Synthesis: The use of Protecting Groups:

B] Protection of carbonyl groups in aldehydes and ketones:

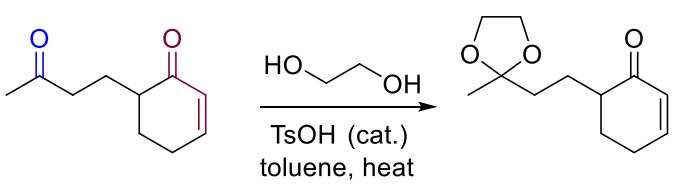
a) *O*,*O*-acetals:

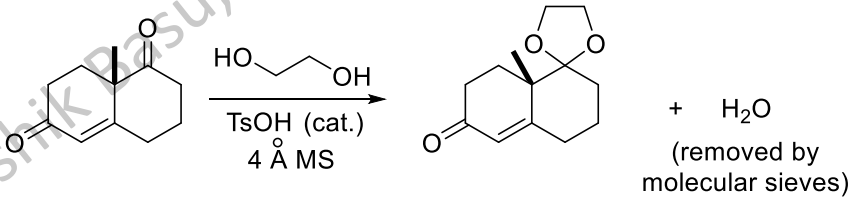
Notable features of carbonyl acetalisation are (contd.):

iii) The selective protection of a reactive carbonyl group in the presence of a less reactive one is possible:



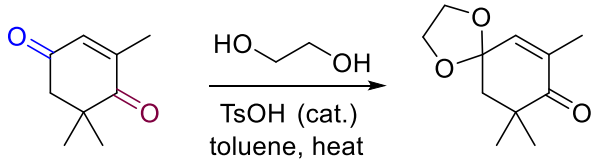
ketone is more electrophilic than ester

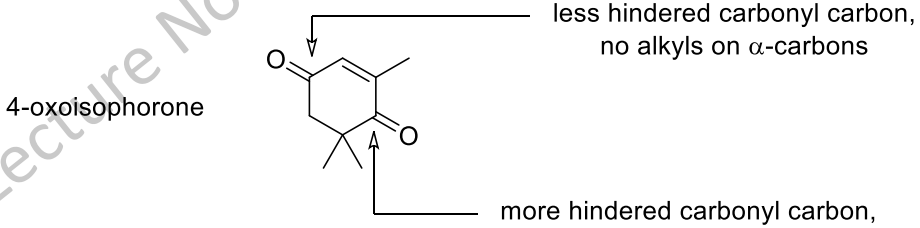




unconjugated ketone is more electrophilic than the conjugated one

iv) Acetalisation changes a trigonal planar carbonyl carbon into a tetrahedral centre with increased proximity of the ligands attached to that centre, there is an increase in the steric bulk associated with the formation of acetal. It is therefore possible to acetalise a less hindered carbonyl of the two carbonyls present in the same molecule. A case in point is reaction of 4-oxoisophorone with ethylene glycol:





v) Acetals are stable to - a) strong aqueous bases, b) nucleophilic reducing agents, c) organometallic reagents (RLi, RMgX, etc.), d) oxidations under nonacidic conditions, e) Na or Li/NH_3 reductions.

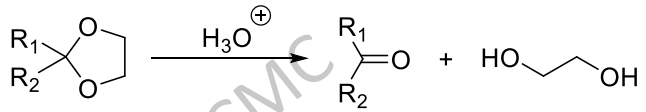
The Logic of Organic Synthesis: The use of Protecting Groups:

B] Protection of carbonyl groups in aldehydes and ketones:

a) *O*,*O*-acetals:

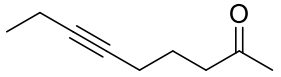
Deprotection:

The most common method of deprotecting an acetal is to use hydrolysis by dilute acid.

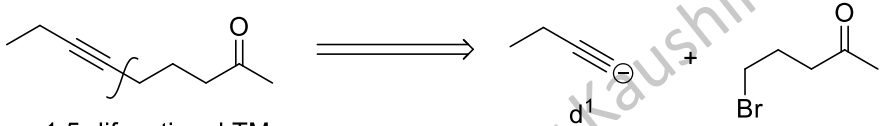


Let us consider an example where the protection strategy for a carbonyl uses acetal:

Target: To synthesise:



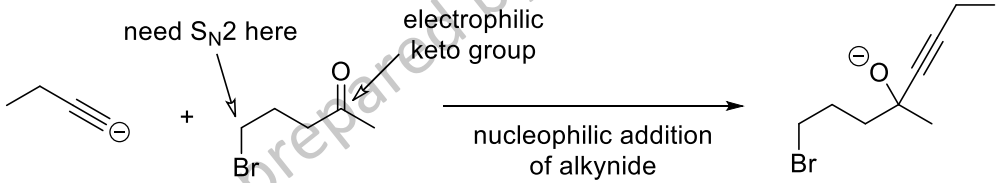
Retrosynthetic analysis:



1,5-difunctional TM

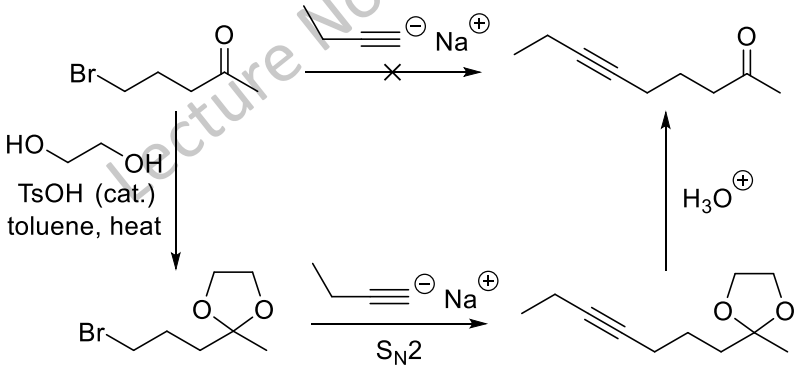
γ-bromoketone - represents an a^4 synthon (retrosynthetic analysis done before)

Problem with the strategy:



direct reaction not possible as carbanion would attack the electrophilic keto group

Solution: Protect keto as acetal



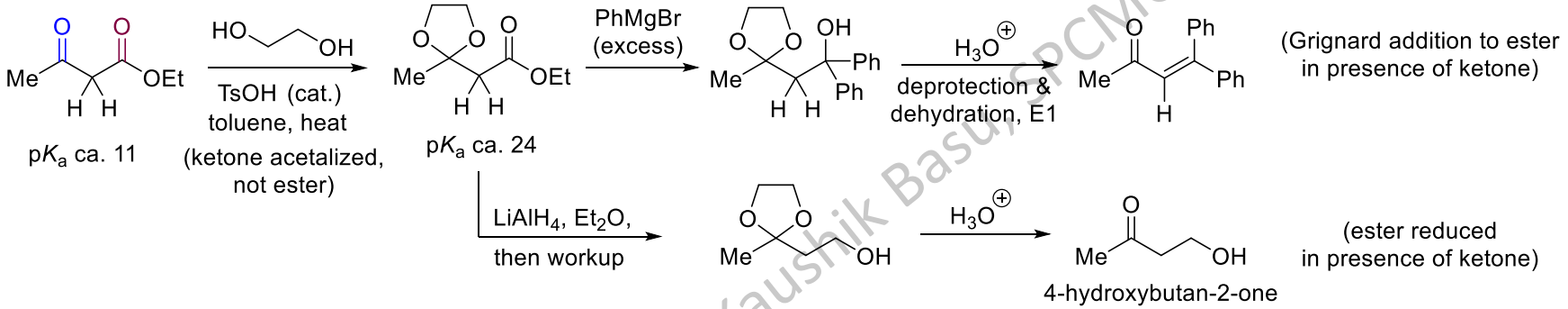
Cyclic acetals are thus ideal for preventing undesired nucleophilic addition to the carbonyl group.

The Logic of Organic Synthesis: The use of Protecting Groups:

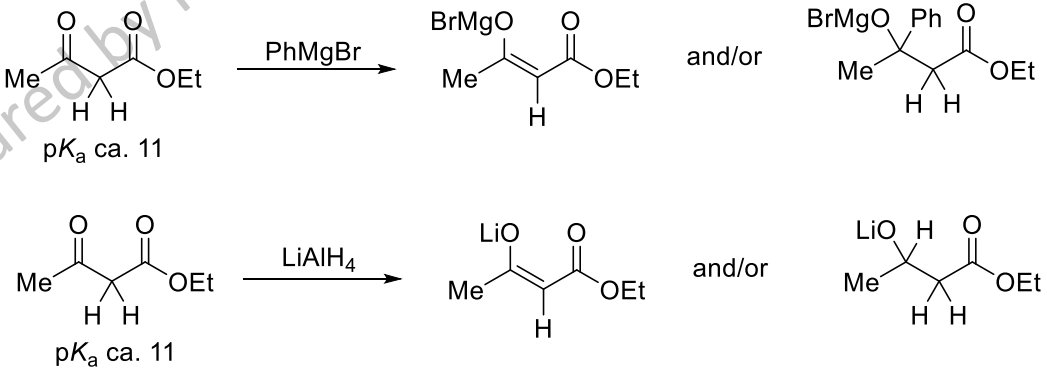
B] Protection of carbonyl groups in aldehydes and ketones:

a) *O*,*O*-acetals:

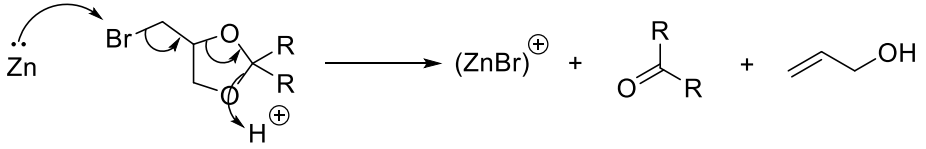
Cyclic acetals are also ideal for avoiding potentially problematic deprotonation of acidic α-protons; here is another example where the second problem is rampant without protection strategy:



Any direct reaction of ethyl acetoacetate with either LAH or phenylmagnesium bromide is bound to give a predominant neucleophilic attack at the more electrophilic keto group and/or deprotonation of the doubly activated methylene proton.



If the carbonyl group must be regenerated under non-hydrolytic conditions, α-halo alcohols such as 3-bromopropane-1,2-diol or 2,2,2-trichloroethanol can be used for acetal formation. These groups can be removed by reduction with zinc, which induces β-elimination, e.g.



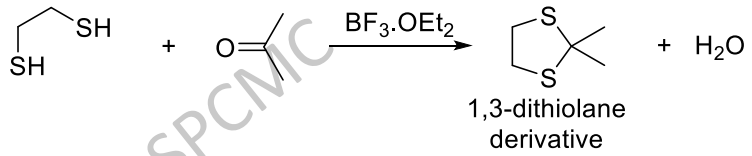
The Logic of Organic Synthesis: The use of Protecting Groups:

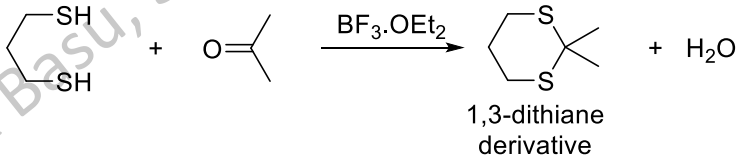
B] Protection of carbonyl groups in aldehydes and ketones:

b) *S*,*S*-acetals:

Protection:

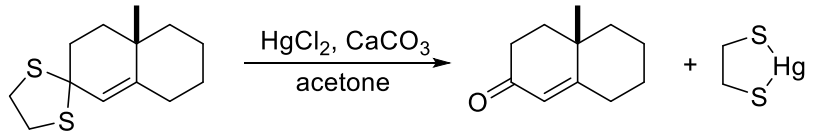
The preparation of thioacetals involves treatment of the carbonyl substrate with a dithiol in the presence of an acid catalyst, usually TsOH or $BF_3.OEt_2$. Since thioacetals are quite stable toward hydrolysis, there is no special need to remove the H_2O formed during the reaction.



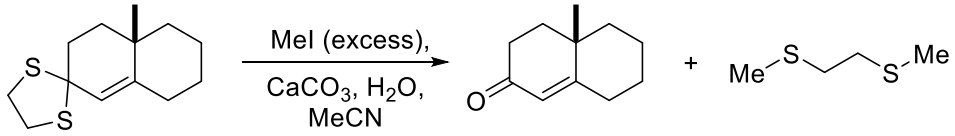


Deprotection:

S,*S*-acetals' deprotection takes advantage of the high affinity of sulfur for heavy metal ions, such as Hg(II). Neutralization of the acid generated during hydrolysis with HgO or $CaCO_3$ allows for the presence of a wide variety of functional groups.

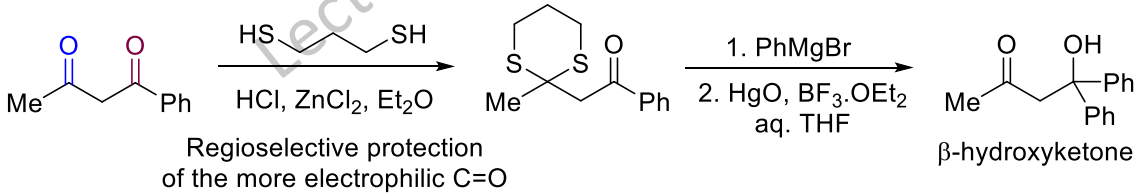


The alkylation of sulfur with reactive alkylating agents, such as MeI results in thioacetal deprotection without using the toxic Hg(II) ions:



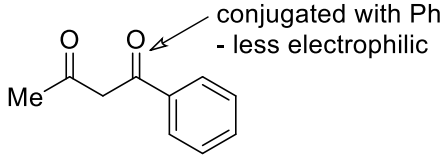
Try these deprotection reactions' mechanism and see if you can get to the end.

Here is one example of the dithiane PG in action where a selective protection of the more reactive ketone of the two is achieved:



Regioselective protection of the more electrophilic C=O

β-hydroxyketone

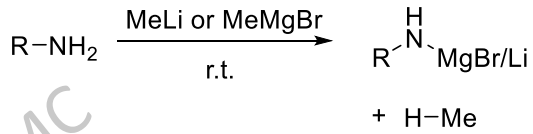


Direct reaction with PhMgBr would have resulted is nucleophilic addition to the ketomethyl, not on benzoyl.

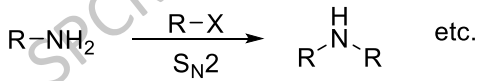
The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

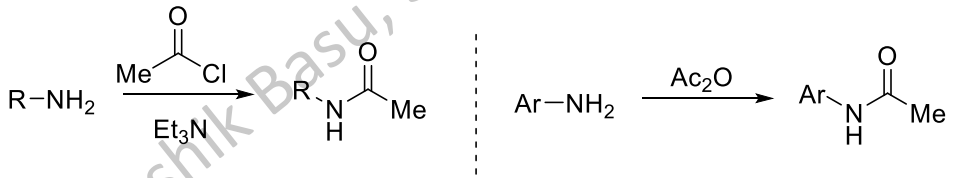
Primary and secondary amines are prone to oxidation, and although proton removal by basic reagents is not as great a problem as it is with alcohols because of the nitrogen's lower electronegativity, N-H bonds do undergo full metallation on exposure to strong bases such as organolithiums and Grignard reagents.



Moreover, the amino group possesses a lone electron pair, which can be protonated or reacted with electrophiles (R-X).



To render the lone pair less reactive, the amine can be converted into an amide via acylation (recall the ester PG for alcohols in this regard which follow the same principle).

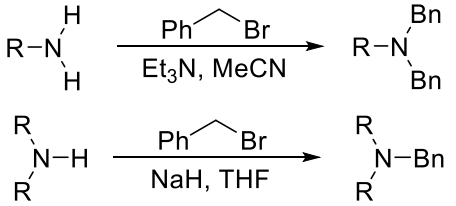


Because amines compete for electrophiles so effectively it can be very difficult to handle molecules that bear free amines - both from the point of view of reactivity and ease of purification - therefore a good plan is to keep the amine in its protected form for as long as possible, only deprotecting it at the very end of the sequence.

a) *N*-benzylamines: $R_2N\text{-}CH_2Ph$ or $R_2N\text{-}Bn$:

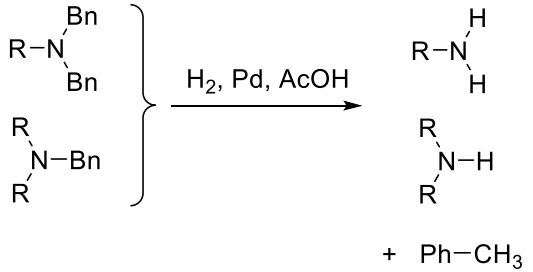
Protection:

N-Benzyl groups (*N*-Bn) are especially useful for replacing the N-H protons in primary and secondary amines when exposed to organometallic reagents or metal hydrides. Depending on the reaction conditions, primary amines can form mono and/or dibenzylated products. These are nucleophilic substitution reactions at the benzylic position.



Deprotection:

Hydrogenolysis of benzylamines with Pd catalysts and H_2 in the presence of an acid regenerates the amine. Generally, benzylamines are not cleaved by Lewis acids.



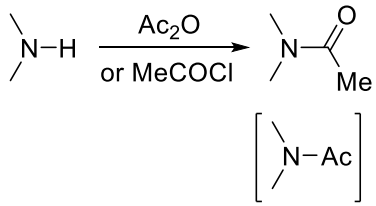
The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

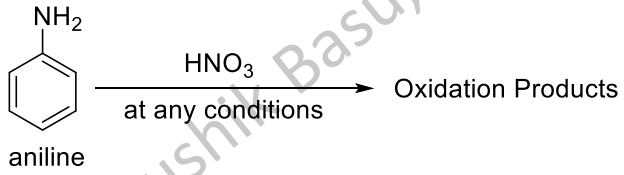
b) Amides: N-COR:

Protection:

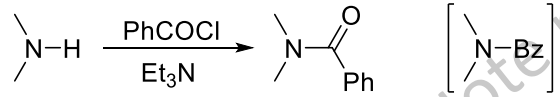
Acylation of primary and secondary amines with acetic anhydride or acid chlorides furnishes the corresponding amides in which the basicity of the nitrogen is reduced (how?), making them less susceptible to attack by electrophilic reagents.

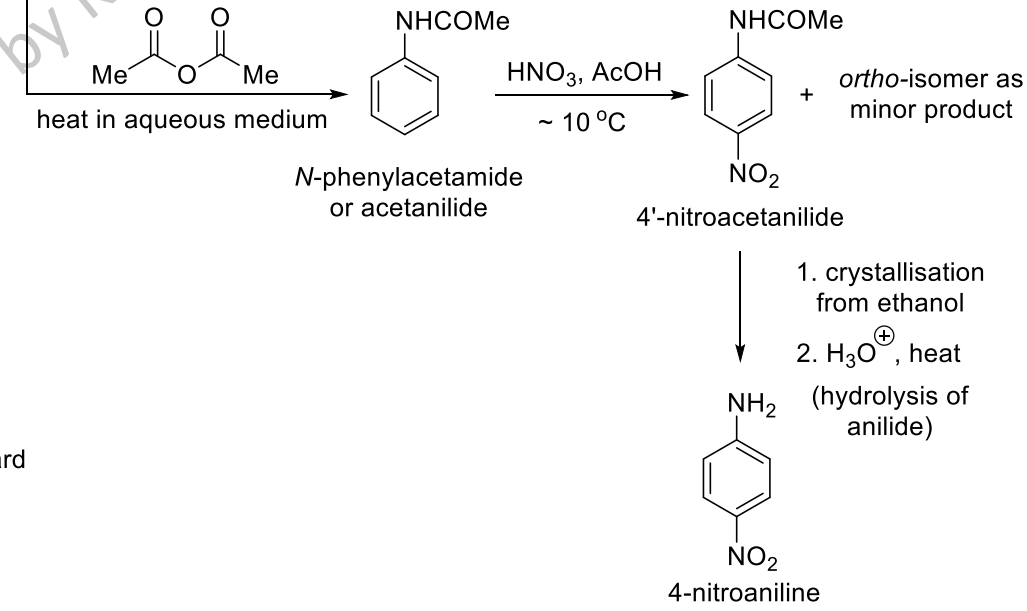


Recall in this regard that the nitration of aniline to 4-nitroaniline requires protection of the amino group first by acetylation so that oxidation of the ring and protonation of the amine N is avoided.



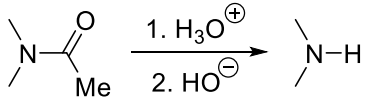
Benzamides (*N*-Bz or *N*-COPh) are formed by the reaction of amines with benzoyl chloride in pyridine or trimethylamine. The group is stable to pH 1-14, nucleophiles, organometallics (except organolithium reagents), catalytic hydrogenation, and oxidation.





Deprotection:

Acidic hydrolysis and subsequent workup in alkaline medium is the standard deprotection method. Benzamides are hydrolysed in 6N hydrochloric acid.

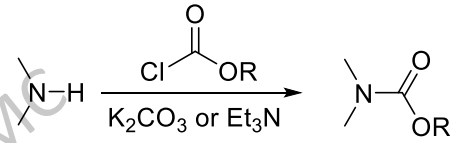


The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

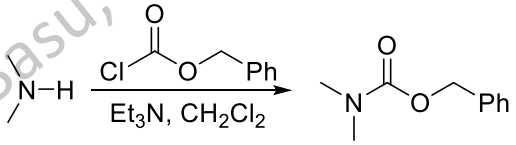
c) Carbamates: N-COOR (esters of carbamic acid):

Treatment of primary and secondary amines with methyl or ethyl chloroformate in the presence of a tertiary amine (that acts as a base) furnishes the corresponding methyl and ethyl carbamates, respectively. The protected amines behave like amides; hence, they no longer act as nucleophiles. They are stable to oxidizing agents and aqueous bases but may react with reducing agents.

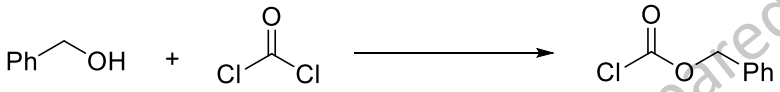


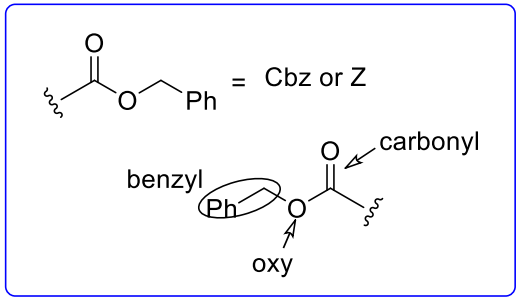
(R = Me or Et)
ester of carbamic acid dev.

The benzyloxycarbonyl group (abbreviated as Cbz or Z) is one of the most important nitrogen-protecting groups in organic synthesis, especially in peptide synthesis. It is introduced by reacting the amine with benzyloxycarbonyl chloride in the presence of a tertiary amine. The protected amine is stable to both aqueous base and aqueous acid.

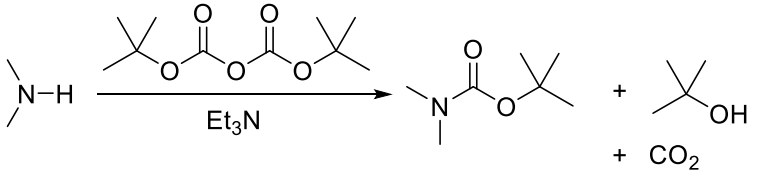


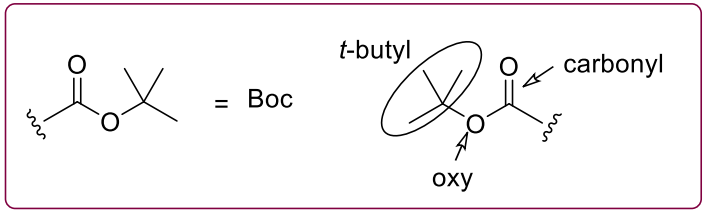
The bezyloxycarbonyl chloride reagent is prepared by reacting benzyl alcohol with phosgene in toluene solution or neat.





The *t*-butoxycarbonyl group (Boc) is another widely used protecting group for primary and secondary amines. It is inert to hydrogenolysis and resistant to bases and nucleophilic reagents but is more prone to cleavage by acids than the Cbz group. The Boc group is installed by reacting the amine with di *t*-butyl dicarbonate (or Boc anhydride, Boc_2O) in aqueous or organic solvent in presence of a base, with the concomitant formation of innocuous by-products *t*-butanol and carbon dioxide.



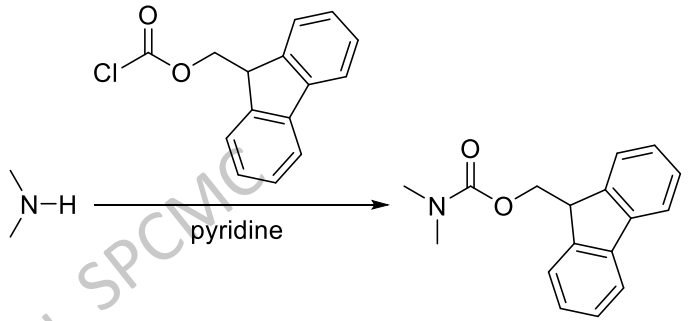


The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

c) Carbamates: N-COOR:

The other important carbamate-based PG for an amine is the 9-fluorenylmethyloxycarbonyl (Fmoc). This is put on by treating the amine with the corresponding chloride or azide in presence of pyridine or $NaHCO_3$.



Deprotection:

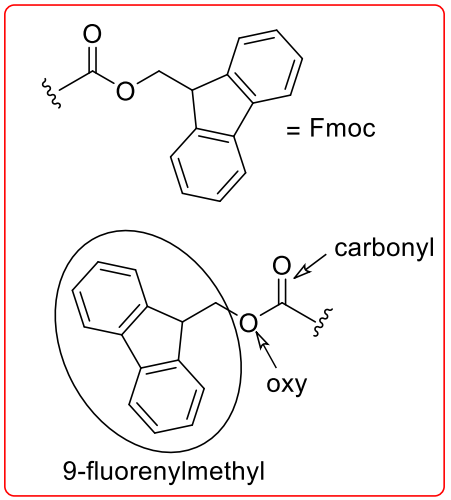
The popularity of carbamates as PGs for amine group stems from the fact that the deprotection conditions of the *N*-OCOR moiety can be varied widely depending on the choice of the R component. In general, the PG is removed to reveral the carbamic acid which decarboxylates and affords the amine.

Thus.

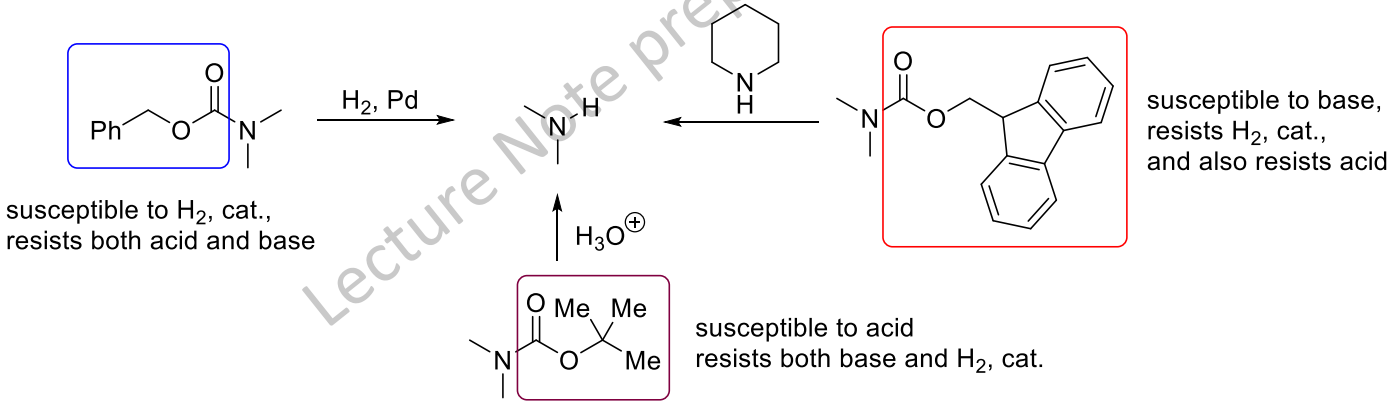
i) *N*-Cbz may be deprotected by hydrogenolysis (Pd-C, H_2),

ii) *N*-Boc is susceptible to acid hydrolysis (TFA in dichloromethane or HCl in MeOH) and

iii) *N*-Fmoc is usually cleaved under basic condition with an amine (piperidine or morpholine in DMF).



N-Boc is stable towards hydrogenolysis and basic medium, *N*-Fmoc group withstands the acid condition quite well and it is also resistant to hydrogenolysis, while *N*-Cbz is stable in both base and acid.

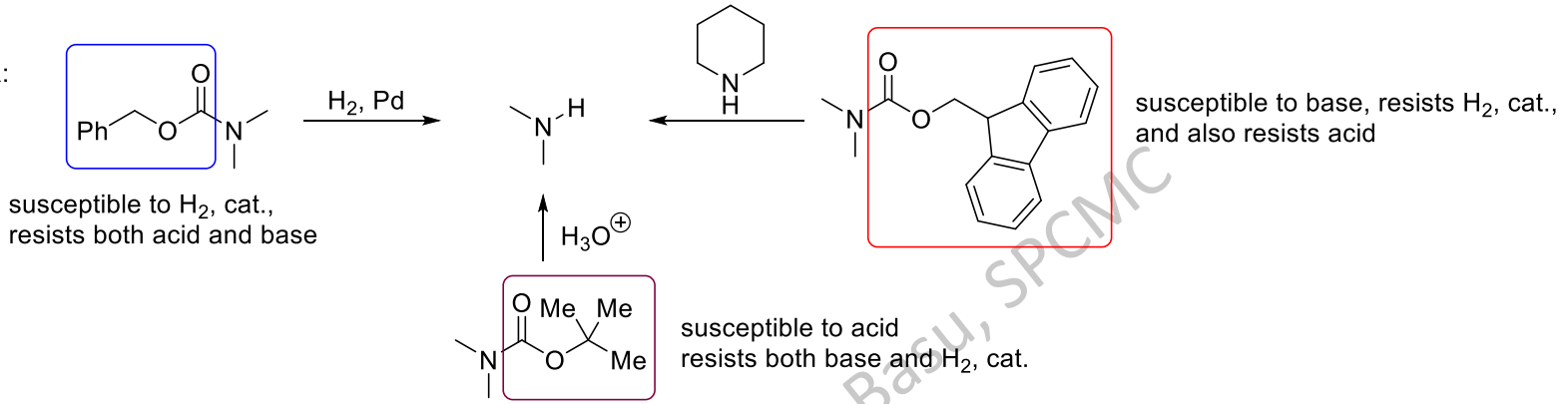


These three PGs therefore constitute a complementary set where the deprotection condition for one does not affect the other two and *vice versa*. These are called *orthogonal* PGs.

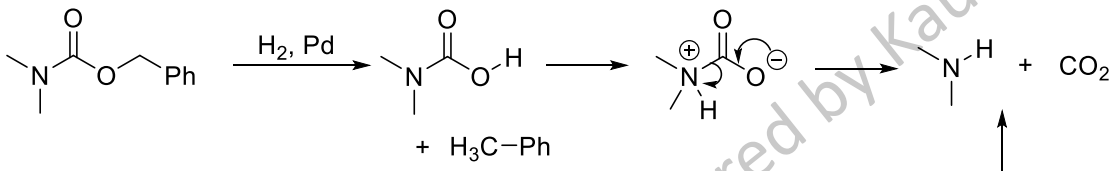
The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

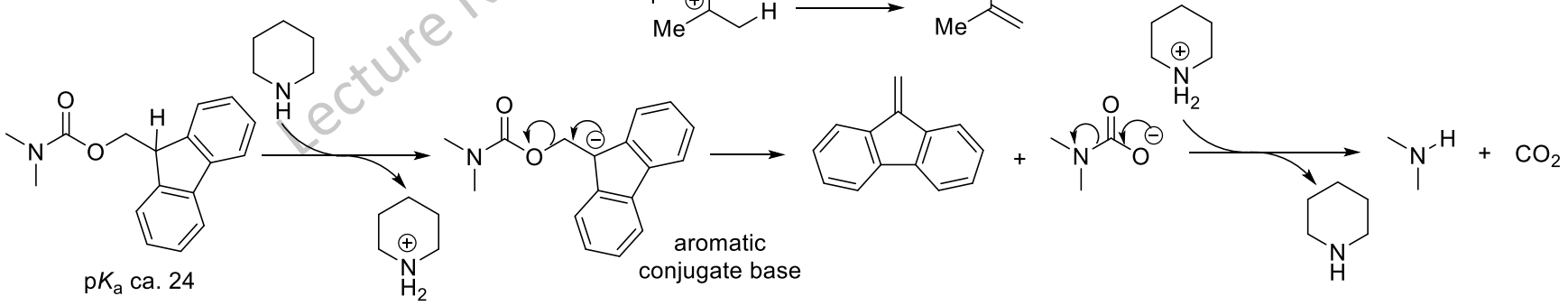
c) Carbamates: N-COOR:



The deprotection mechanisms for each of these involve liberation of the carbamic acid derivative (N-COOH) one way or the other, which decarboxylates and releases the amine.



The deprotection mechanism of the *N*-Boc and *N*-Fmoc groups are elimination reactions, can you name the types?



The Logic of Organic Synthesis: The use of Protecting Groups:

D] Protection of carboxylic acids:

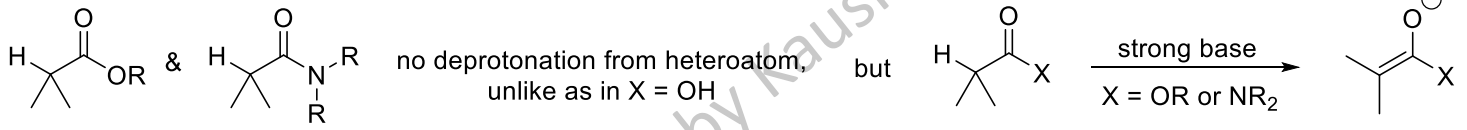
Proton removal from carboxylic acids presents a threat to potentially valuable organometallic reagents, resulting in an alkane and a metal carboxylate.

pK_a ca. 3-5 M = Li, MgX etc.

If this carboxylate does not lead to serious side reactions and if the organometallic reagent is readily available, then use of an excess of the reagent can bypass this problem.

Usually, neither of these requirements are fulfilled and carboxylic acid PGs are needed.

Furthermore, protection against enolisation or attack of nucleophiles may become necessary; few PGs meet all of these demands.
Esters and amides remove the problem of carboxyl proton and the latter provides good protection against many nucleophiles but neither prevent enolisation by strong bases.

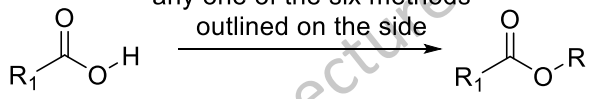


However, orthoesters provide a complete protection for the carboxylic acid group. Let us discuss these one by one.

a) Alkyl esters: RCOOR':

Protection:

The most popular methods for esterficiation include the following approach:



i) ROH, $H^{\oplus}$ (- H_2O, Fischer esterification)
ii) $SOCl_2$, then ROH, Et_3N
iii) NaH then R-I (for primary R only)
iv) CH_2N_2 (for R = Me only)
v) ROH, DCC, DMAP (for all sorts of alcohols)
vi) ROH, PPh_3, DEAD (Mitsunobu reaction)

You should be already familiar with the first four techniques (make sure you are!).

We will provide only examples of the last two but their mechanistic details are reserved for the future.

The Logic of Organic Synthesis: The use of Protecting Groups:

D] Protection of carboxylic acids:

a) Alkyl esters: RCOOR':

Protection:

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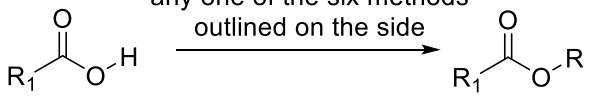

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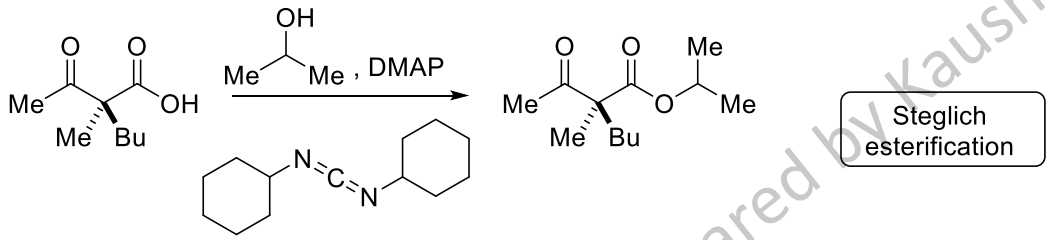
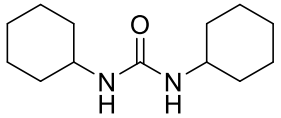


Dicyclohexylcarbodiimide (DCC)

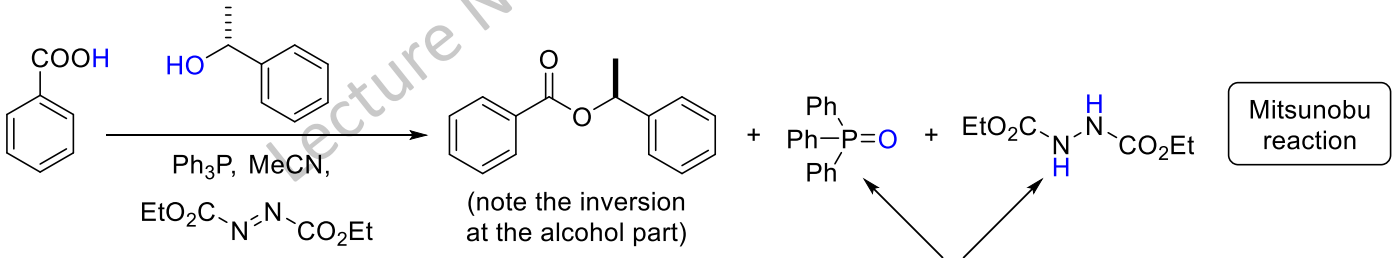
captures the water released



Dicyclohexylurea (DCU)

W. Steglich
(1933-)

O. Mitsunobu
(1934-2003)



Diethylazodicarboxylate (DEAD)

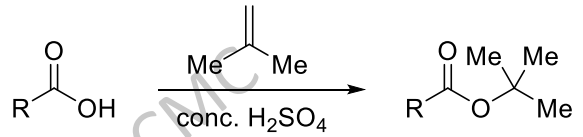
the elements of water are captured here

The Logic of Organic Synthesis: The use of Protecting Groups:

D] Protection of carboxylic acids:

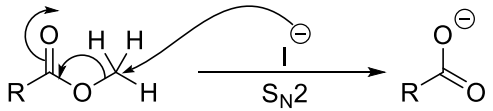
a) Alkyl esters: RCOOR':

Tert-butyl esters are easily made from electrophilic addition to isobutene, or via the reaction of acid chloride with *t*-butanol. This is a particularly useful PG because the *t*-BuO group provides steric shielding of the carbonyl carbon, thereby lowering its susceptibility to attack by nucleophilic reagents. In addition, it is removed easily with acid hydrolytic conditions.



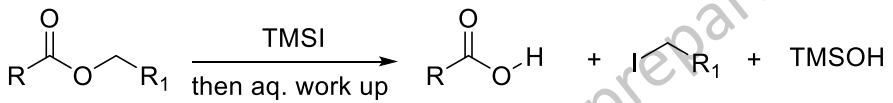
Deprotection:

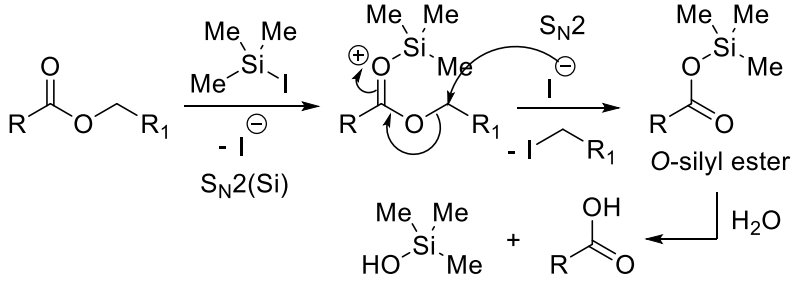
As a corollary of offering a fairly low level of protection, the lower alkyl esters - particularly methyl esters - are removed under relatively mild conditions, e.g. alkali metal hydroxides or carbonates in aqueous or alcoholic solution. These unhindered esters may also be cleaved with nucleophilic substitution ($B_{AL}2$, with LiI in polar, aprotic solvents):



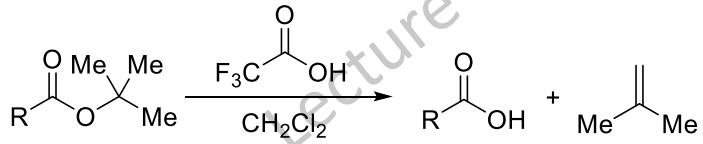
This offers a selective way of cleaving methyl esters in presence of other ester groups such as ethyl or phenyl esters.

Trimethylsilyl iodide (TMSI) offers an opportunity of dealkylating alkyl esters under mild, neutral condition:



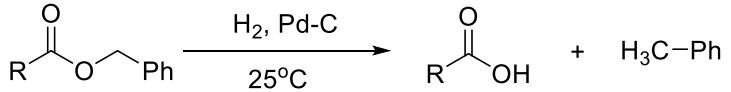


Tert-butyl esters are easily removed with TFA or TsOH or HCl or HBr:



This ester hydrolysis proceeds via the $A_{AL}1$ mechanism, as you very well know. Try writing it out.

Benzylic esters are rapidly deprotected by hydrogenolysis:



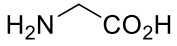
This offers a selective way of cleaving benzyl esters in presence of other ester groups such as methyl or ethyl esters.

The Logic of Organic Synthesis: The use of Protecting Groups:

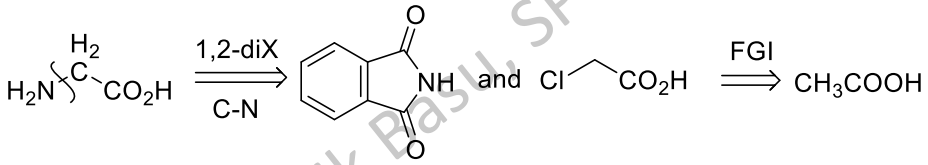
D] Protection of carboxylic acids:

a) Alkyl esters: RCOOR':

Let us consider one example where an ethyl ester PG is used to mask a carboxylic acid group.

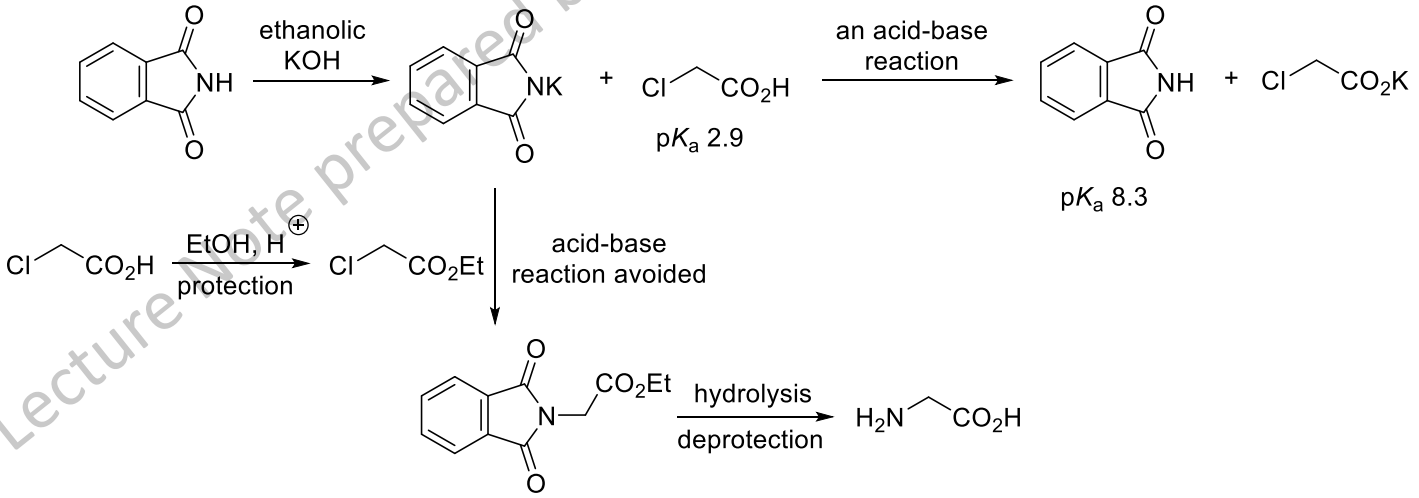
Consider the synthesis of the amino acid glycine: 

To synthesise glycine, we may consider the following retrosynthetic analysis:



So, it is a Gabriel phthalimide synthesis. But we cannot use the chloroacid as then an acid-base reaction would take over.

So, we use the ethyl ester instead and once the S_N2 reaction with potassio phthalimide is over, we can deprotect the ethyl ester by hydrolysis.



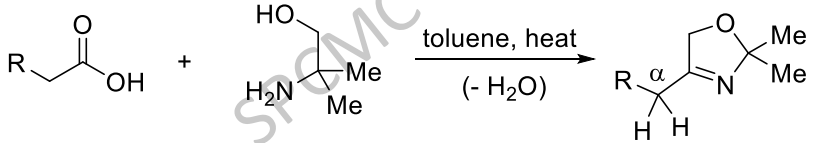
The Logic of Organic Synthesis: The use of Protecting Groups:

D] Protection of carboxylic acids:

b) Oxazolines:

Protection:

1,3-Oxazolines protect both the carbonyl and hydroxyl groups of a carboxyl group. The starting material, 2-amino-2-methylpropanol, is readily available. The oxazoline moiety serves as a PG toward RMgX and $LiAlH_4$, but not for RLi because the protons at C(α) may be deprotonated.

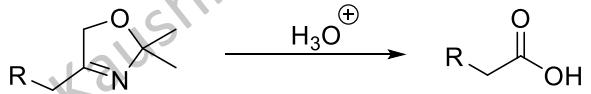


1,3-oxazoline

Note the *gem*-dimethyl group's contribution in facilitating the cyclisation (Thorpe-Ingold effect).

Deprotection:

Acidic hydrolysis of 1,3-oxazoline releases the carboxylic acid.

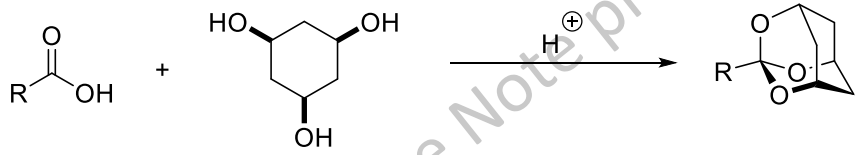


1,3-oxazoline

c) Orthoesters:

Protection:

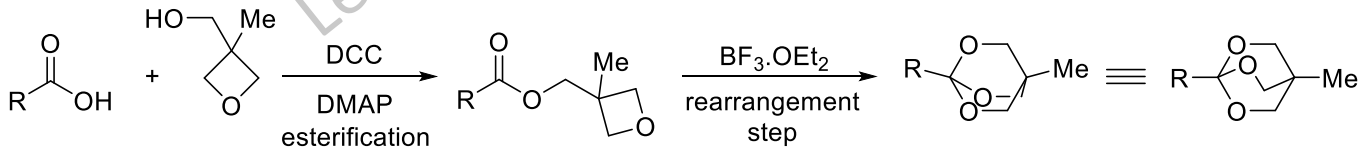
These are essentially acetal derivatives of ester. They offer a complete protection to carboxylic acids from bases and nucleophiles. These are prepared either directly from the acid or via an oxytanylmethyl ester in a two-step procedure:



cis,cis-1,3,5-trihydroxycylohexane (phloroglucitol)

a trioxaadamantyl (TOA) derivative - a tricylic orthoester

The mechanism of formation of these orthoesters is decidedly complicated, so we leave it at that. It may seem surprising to you that these groups successfully resist any overtures from Grignard reagents, particularly considering the fact that you have learned to fromylate Grignard reagents using $HC(OR)_3$ where you have found the orthoester to freely react with the organometallic compound. These cyclic orthoesters are, however, more robust and are entirely compatible with RMgX.



oxytanylmethyl ester

trioxabicylco[2.2.2]octane (OBO) derivative

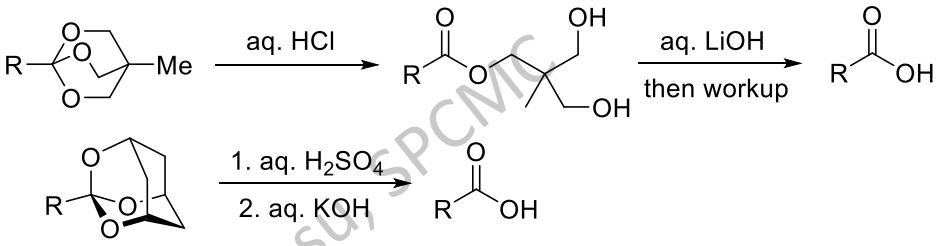
The Logic of Organic Synthesis: The use of Protecting Groups:

D] Protection of carboxylic acids:

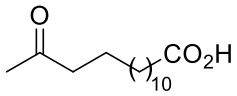
c) Orthoesters:

Deprotection:

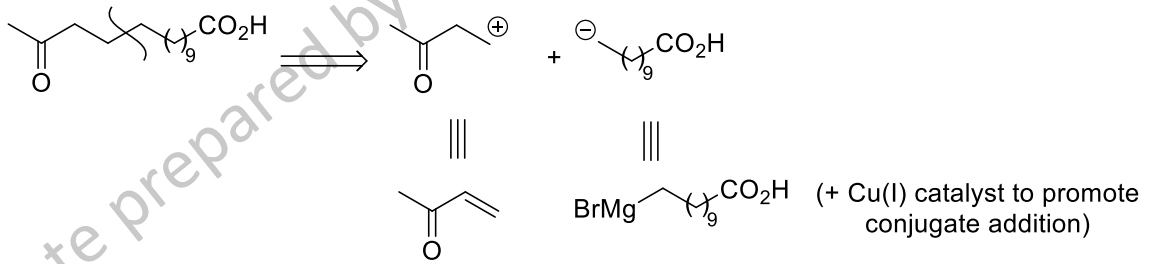
These orthoesters' deprotection protocol is a two-steps sequence. First is an acid hydrolysis (for the TOA group, the condition is more vigourous, for reasons that we will not discuss here) that generates an ester which is then hydrolysed in base ($B_{Ac}2$):



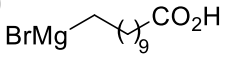
Let us conclude by demonstrating the potency of these cyclic orthoesters as PGs for carboxylic acid groups. Suppose you are to synthesise the following target molecule:



For which, you have come up with the following retrosynthetic plan:



Clearly, the success of your plan depends upon finding a protected version of



Which in itself cannot exist as the Grignard regent would be destroyed by self-protonation.
So we need to protect the -COOH group. How?
Esters won't do, because they are prone to nucleophilic attack by Grignard reagents. Then? The answer is cyclic orthoesters. Here is how it is done: