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: R₂N-CH₂Ph or R₂N-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 H₂ 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.

\[ \text{N-H} \xrightarrow{\text{Ac}_2\text{O} \; \text{or RCOCl}} \text{N} = \text{O} \; \text{Me} \]

\[ \text{NH}_2 \xrightarrow{\text{HNO}_3 \; \text{at any conditions}} \text{Oxidation Products} \]

\[ \text{Me} \xrightarrow{\text{O}_2 \text{C} - \text{O}} \xrightarrow{\text{N-phenylacetamide or acetonilide}} \]

\[ \text{NHCOMe} \xrightarrow{\text{HNO}_3, \text{AcOH} \; \sim 10 ^\circ \text{C}} \text{ortho-isomer as minor product} \]

1. crystallisation from ethanol
2. $\text{H}_2\text{O}^+$, heat

\[ \text{NH}_2 \xrightarrow{\text{1. } \text{H}_3\text{O}^+ \; \text{heat}} \text{4-nitroaniline} \]
The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines:

c) Carbamates: N-COOR:

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.

\[
\text{N-H} \xrightarrow{\text{ClOR}} \xrightarrow{\text{K}_2\text{CO}_3 \text{ or Et}_3\text{N}} \text{N-OOR} \\
(R = \text{Me or Et})
\]

The benzylxycarbonyl 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 benzylxycarbonyl chloride in the presence of a tertiary amine. The protected amine is stable to both aqueous base and aqueous acid.

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

\[
\text{PhOH} + \text{ClO}_2\text{C} \rightarrow \text{ClO}_2\text{CPh}
\]

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.

\[
\text{N-H} \xrightarrow{\text{Et}_3\text{N}} \xrightarrow{\text{Me}} \text{N-OOCMe} + \text{MeOH} + \text{CO}_2
\]

\[
\text{OOCMe} = \text{Boc}
\]
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-fluorenymethyloxycarbonyl (Fmoc). This is put on by treating the amine with the corresponding chloride or azide in presence of pyridine or NaHCO₃.

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.

Thus N-Cbz may be deprotected by hydrogenolysis (Pd-C, H₂), N-Boc is susceptible to acid hydrolysis (TFA in dichloromethane or HCl in MeOH) and 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.*
The Logic of Organic Synthesis: The use of Protecting Groups:

C] Protection of amines::

c) Carbamates: N-COOR:

\[
\text{Ph} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\text{H}_2, \text{Pd} \quad \text{H}_3\text{O}^+ \\
\text{N} \quad \text{O} \quad \text{H} \\
\text{Me} \quad \text{Me} \\
\text{N} \quad \text{O} \quad \text{H} \\
\text{H}_3\text{C} - \text{Ph}
\]

susceptible to H₂, cat.,
resists both acid and base

susceptible to acid,
resists both base and H₂, cat.

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.

\[
R\text{-COOH} + R_1\text{-M} \rightarrow R\text{-COOM} + R_1\text{-H}
\]

\(pK_a\) ca. 3-5 \(\text{M = Li, MgX etc.}\)

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.

\[
\begin{align*}
\text{no deprotonation from heteroatom} \\
\text{unlike as in } X = \text{COOH}
\end{align*}
\]

strong base

\[
X\text{ enolate}
\]

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

a) Alkyl esters: \(\text{RCOOR}^+\):

Protection:

The most popular methods for esterification include the following approach:

\[
R_1\text{-COOH} \rightarrow \text{any one of the six methods} \rightarrow R_1\text{-COOR}
\]

\(i)\) ROH, H\(^+\) (-H\(2\)O, Fischer esterification)
\(ii)\) SOCl\(_2\), then ROH, Et\(_3\)N
\(iii)\) Na\(_\text{H}\) then R-I (for primary R only)
\(iv)\) CH\(_2\)N\(_2\) (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: $\text{RCOOR}'$

Protection:

The most popular methods for esterification include the following approach:

1. $\text{ROH, } \text{H}^+ (- \text{H}_2\text{O}, \text{Fischer esterification})$
2. $\text{SOCl}_2$, then $\text{ROH, Et}_3\text{N}$
3. $\text{NaH}$ then $R$-$i$ (for primary $R$ only)
4. $\text{CH}_2\text{N}_2$ (for $R$ = Me only)
5. $\text{ROH, DCC, DMAP}$ (for all sorts of alcohols)
6. $\text{ROH, PPh}_3, \text{DEAD}$ (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.

- W. Steglich (1933-)
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.

\[
\text{RCOOH} + \text{Me} = \text{Me} \rightarrow \text{RCOOC}_2\text{Me} + \text{H}_2\text{O}
\]

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\text{AL}_2, with Li in polar, aprotic solvents):

\[
\begin{align*}
\text{R} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\text{O}^{-} & \quad \text{Me}^{-}
\end{align*}
\]

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

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

\[
\text{RCOOC}_2\text{Me} + \text{F}_3\text{C-COOH} \rightarrow \text{RCOOH} + \text{MeC} = \text{Me}
\]

This ester hydrolysis proceeds via the A\text{AL}_1 mechanism, as you very well know. Try writing it out.

Benzylic esters are rapidly deprotected by hydrogenolysis:

\[
\text{RCOOC}_2\text{Ph} \rightarrow \text{H}_2, \text{Pd-C} \rightarrow \text{RCOOH} + \text{H}_2\text{C-Ph}
\]

This offers a selective way of cleaving phenyl 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: $\text{RCOOR}^-$:

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:

\[ \text{H}_2\text{NCH}_2\text{CO}_2\text{H} \]

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

\[ \text{H}_2\text{NCH}_2\text{CO}_2\text{H} \quad 1,2\text{-diX} \quad \text{C-N} \quad \text{H}_2 \quad \text{H}_2\text{NCH}_2\text{CO}_2\text{H} \quad \text{FGI} \quad \text{CH}_3\text{CO}_2\text{H} \]

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 $\text{S}_\text{N}2$ 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 LiAlH₄, but not for RLi because the protons at C(α) may be deprotonated.

Deprotection:

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

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 oxanylmethyl ester in a two-step procedure:

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.
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 vigorous, 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:

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