PROTECTING GROUPS (PGs)

Useful synthetic reagents and procedures are often characterized by their ability selectively to transform a substrate. The selectivity may concern stereo- and regiochemistry, but may also be a question of which functional groups in the molecule are transformed preferentially: this is known as chemoselectivity. Sometimes it simply isn't possible to devise a reaction which carries out a desired transformation while leaving other functional groups in the molecule untouched. This is often the case in multi-stage syntheses of complex, polyfunctional molecules. When this happens, it is necessary to mask or protect functional groups temporarily, in order that they are not affected by reactions transforming functions in other parts of the molecule. The functional group used to effect this protection is called a protecting group (PG). A good protecting group meets several criteria:

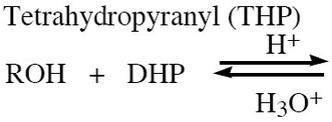
- it is readily introduced into the molecule under mild conditions
- it is stable to the reaction conditions used to effect the desired transformation
- it is readily removed under mild conditions

Synthesis of complex molecules will often require the use of several different PGs. It is then important to be able to selectively remove specific PGs without removing others. In practice, few protecting groups meet all of the above criteria, and so many, many PGs have been developed. We will look at some of the FGs that most commonly need to be protected, and the most common PGs used for doing this.

PROTECTION OF ALCOHOLS — **Stable to**

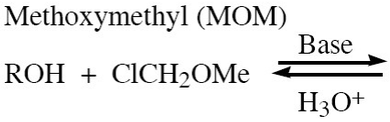
1. Acetals

a) Tetrahydropyranyl (THP)



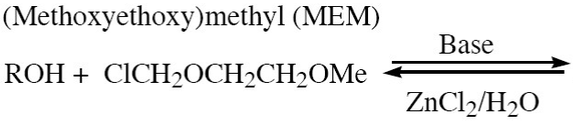
Base, RM, H_2

b) Methoxymethyl (MOM)



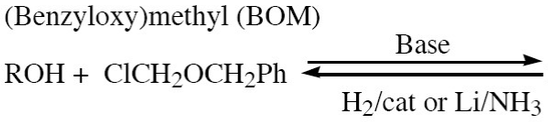
Base, RM, H_2

c) (Methoxyethoxy)methyl (MEM)



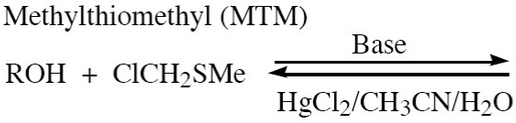
Base, RM, H_2

d) (Benzyloxy)methyl (BOM)



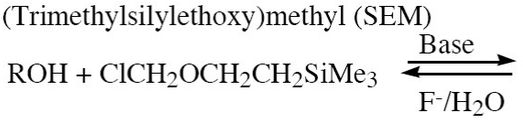
Base, RM,

e) Methylthiomethyl (MTM)



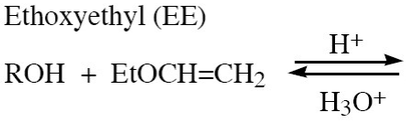
Base, RM,
mild H_3O^+

f) (Trimethylsilylethoxy)methyl (SEM)



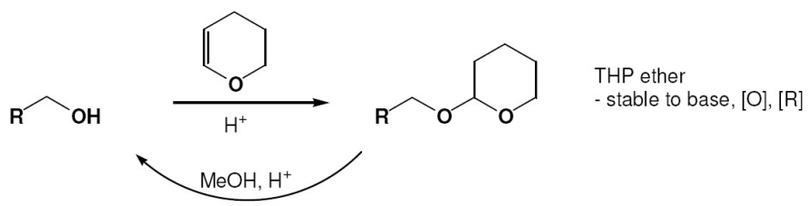
Base, RM, H_2

g) Ethoxyethyl (EE)



Base, RM, H_2

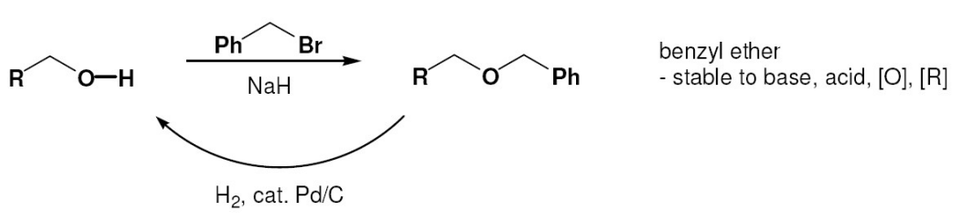
Tetrahydro pyranyl (THP): These are introduced by the reaction of the alcohol with dihydropyran in the presence of a catalytic amount of acid. They are removed by the action of methanol/catalytic acid. They are stable to base, oxidising agents and reducing agents. One problem with them is that a new asymmetric centre is formed when they are introduced – if the starting alcohol already has an asymmetric centre, then this will result in mixtures of diastereomers.



2. Ethers

		Stable to
a) Methyl	ROH $\underset{\text{TMSI or } BBr_3}{\overset{\text{NaH; MeI}}{\rightleftharpoons}}$ ROMe	everything
b) Benzyl (Bn)	ROH $\underset{H_2\text{/cat or Li/}NH_3\text{ or TMSI}}{\overset{\text{NaH; } PhCH_2Cl}{\rightleftharpoons}}$ ROBn	base, RM, Δ, mild H_3O^+
c) Trityl (Tr)	ROH $\underset{H_3O^+\text{ or } H_2\text{/cat or Li/}NH_3}{\overset{Ph_3CCl\text{/pyr}}{\rightleftharpoons}}$ ROTr	base, RM, Δ
d) Dimethoxytrityl	ROH $\underset{Cl_2CHCOOH\text{ or } H_2\text{/cat or Li/}NH_3}{\overset{(p\text{-MeOPh})_2PhCCl\text{ (DMTrCl)/pyr}}{\rightleftharpoons}}$ RODMTr	base, RM, Δ
e) Allyl	ROH $\underset{\text{2) } H_3O^+}{\overset{\text{NaH; allyl-Cl}}{\rightleftharpoons}}$ $ROCH_2CH{=}CH_2$	H_3O^+, base, Δ
f) *t*-Butyl	ROH $\underset{\text{non-aq. } H^+\text{ or TMSI}}{\overset{Me_2C{=}CH_2/H^+}{\rightleftharpoons}}$ RO*t*-Bu	base, H_2, Δ, H_3O^+
g) (*p*-Methoxyphenyl)methyl (MPM) or *p*-Methoxybenzyl (PMB)	ROH $\underset{\text{DDQ or CAN}}{\overset{p\text{-}MeOC_6H_4CH_2Cl\text{/base}}{\rightleftharpoons}}$ $ROCH_2C_6H_4OMe$	base, Δ, very mild H_3O^+
h) (2,4-Dimethoxyphenyl)methyl (DMPM)	ROH $\underset{\text{mild DDQ or CAN}}{\overset{2,4\text{-}(MeO)_2C_6H_3CH_2Cl\text{/base}}{\rightleftharpoons}}$ $ROCH_2C_6H_3(OMe)_2$	base, Δ

Benzyl (Bn) ethers: These are formed by the reaction of the alcohol with benzyl chloride or benzyl bromide in the presence of a base. The attractive feature of these ethers is that they may be removed under *neutral* conditions by catalytic hydrogenation. They can be removed by dissolving metal reduction also: Li + ammonia is standard.



3. Silyl ethers

a) Trimethylsilyl (TMS)

$$ROH + Me_3SiCl \underset{H_2O/MeOH/\text{trace } H^+/OH^-}{\overset{\text{pyridine}}{\rightleftharpoons}} ROSiMe_3 \text{ (ROTMS)} \qquad H_2, \Delta$$

b) Triethylsilyl (TES)

$$ROH + Et_3SiCl \underset{\text{mild } H^+ \text{ or } OH^-}{\overset{\text{pyridine}}{\rightleftharpoons}} ROSiEt_3 \text{ (ROTES)} \qquad H_2, \Delta$$

c) *t*-Butyldimethylsilyl (TBS or TBDMS)

$$ROH + t\text{-}BuMe_2SiCl \underset{F^-/H_2O}{\overset{\text{imidazole}}{\rightleftharpoons}} ROSiMe_2tBu \text{ (ROTBS, ROTBDMS)} \qquad H_2, \text{ mild } H_3O^+, \text{ mild } OH^-, RMgX$$

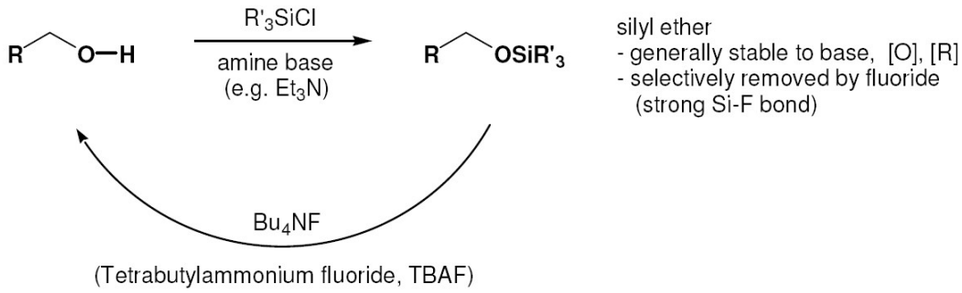
d) Triisopropylsilyl (TIPS)

$$ROH + iPr_3SiOTf \underset{F^-/H_2O}{\overset{\text{Base}}{\rightleftharpoons}} ROSiiPr_3 \text{ (ROTIPS)} \qquad H_2, \text{ mild } H_3O^+, \text{ mild } OH^-, RMgX$$

e) *t*-Butyldiphenylsilyl (TPS)

$$ROH + t\text{-}BuPh_2SiCl \underset{F^-/H_2O}{\overset{\text{Base}}{\rightleftharpoons}} ROSiPh_2tBu \text{ (ROTPS)} \qquad H_2, \text{ mild } H_3O^+, \text{ mild } OH^-, RMgX$$

Silyl ethers: These are introduced by the reaction of the alcohol with the appropriate chlorosilane in the presence of a tertiary amine base. Very usefully, they may be removed selectively by the action of fluoride anion. Trimethylsilyl (TMS) ethers are too acid-sensitive to be good protecting groups in synthesis, but several more stable derivatives have been developed. The most important ones are *t*-butyldimethylsilyl (TBDMS) and t-butyldiphenylsilyl (TBDPS) ethers. The latter are more acid-stable.



4. Esters

a) Acetate (Ac) $\quad ROH + Ac_2O \underset{\text{base}/H_2O \text{ or MeOH}}{\overset{\text{pyr}}{\rightleftharpoons}} ROAc \qquad \text{mild } H_3O^+, H_2, \Delta$

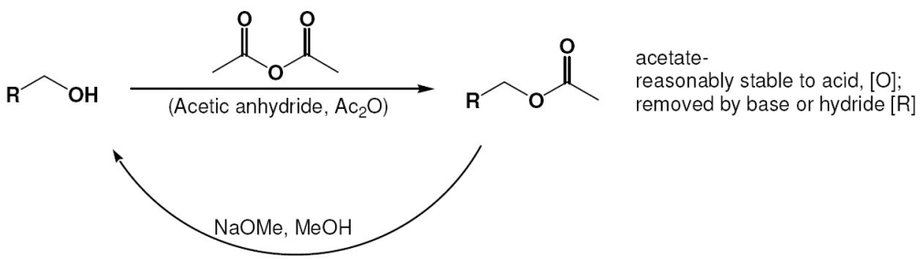
b) Benzoate (Bz) $\quad ROH + BzCl \underset{\text{base}/H_2O \text{ or MeOH}}{\overset{\text{pyr}}{\rightleftharpoons}} ROBz \qquad \text{mild } H_3O^+, H_2, \Delta$

c) Pivaloate (Pv) $\quad ROH + PvCl \underset{\text{strong base or hydride}}{\overset{\text{pyr}}{\rightleftharpoons}} ROPv \qquad \text{mild } H_3O^+, \text{mild } OH^-, H_2, \Delta$

d) Formate $\quad ROH + AcOCHO \underset{\text{mild base}/H_2O \text{ or MeOH}}{\overset{\text{pyr}}{\rightleftharpoons}} ROCHO \qquad \text{mild } H_3O^+, H_2, \Delta$

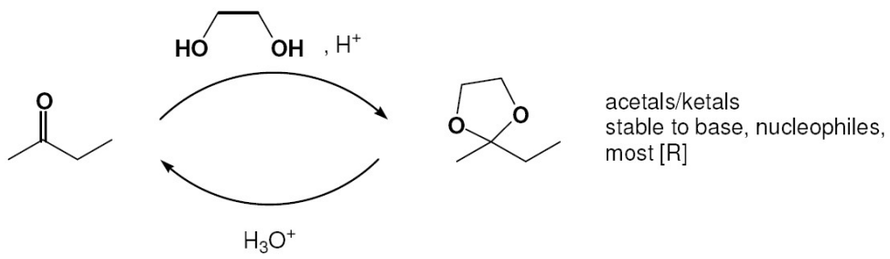
Esters: Formation of an ester will remove the acidic OH proton and reduce the nucleophilicity of the O-lone pair (it is now "tied up" in resonance with the C=O). Many esters are stable to acidic conditions, and they are most commonly used to protect an -OH group from oxidation to the corresponding carbonyl compound. Many different esters are used, but acetates (ethanoates) are

by far the most common. Acetates are usually formed by reaction of the alcohol with acetic anhydride in pyridine. Deprotection is usually effected by treatment of the acetate with sodium methoxide in methanol. Primary alcohols react more quickly than secondary alcohols, enabling selective protection in alcohols containing more than one -OH group.



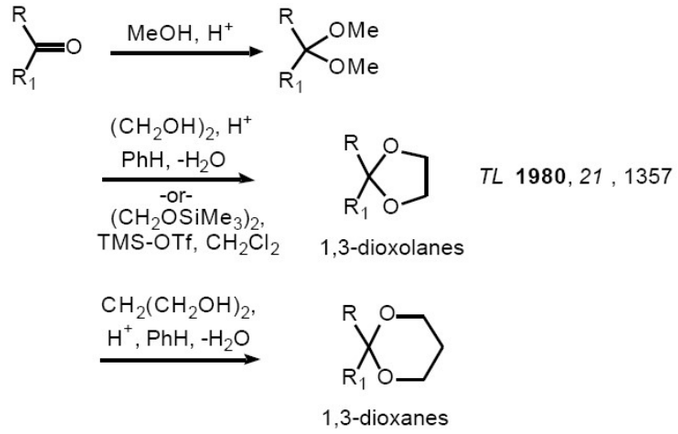
PROTECTION OF CARBONYL GROUPS

We know already that carbonyl groups (aldehydes and ketones) are susceptible to nucleophilic attack (including reduction) and deprotonation, and therefore the main requirement of any carbonyl protecting group is to withstand these processes. Aldehydes and ketones are usually protected as their acetals or ketals, by reaction with diols (1,2- or 1,3-) under acid catalysis. These acetals/ketals are stable to most neutral, basic and reducing conditions: they are removed by dilute aqueous acid.

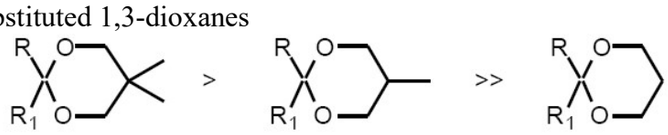


- **cyclic and acyclic ketals and acetals**

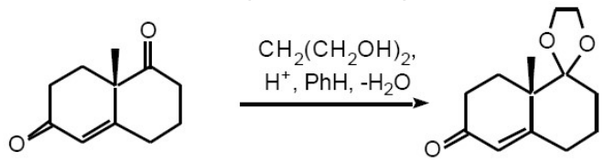
- Stable to base; removed with H3O+



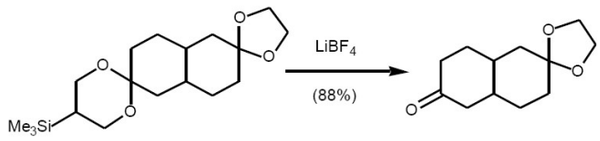
Cleavage rate of substituted 1,3-dioxanes



Ketal formation of α,β-unsaturated carbonyls are usually slower than for the saturated case.

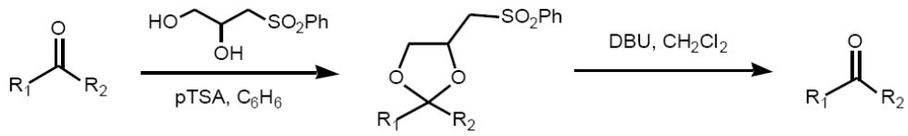


Fluoride cleavable ketal:



TL **1997**, *38*, 1873

Base cleavable ketal:

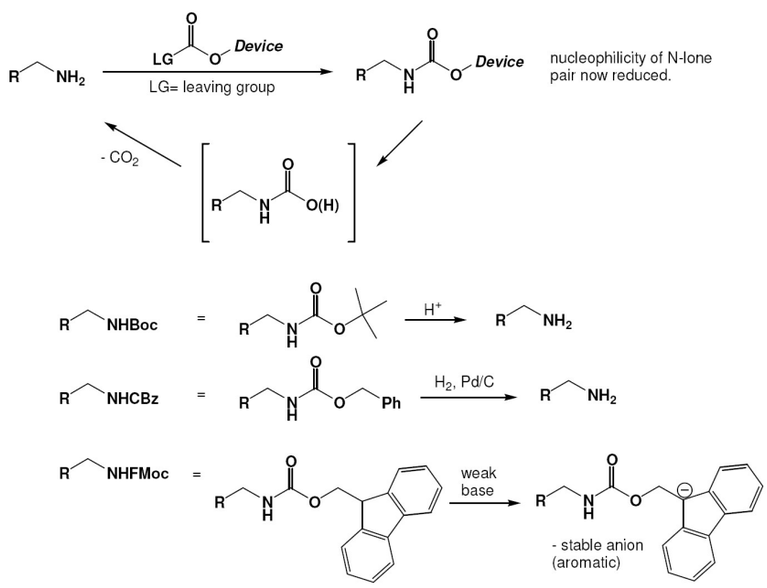


PROTECTION OF AMINES

Amines need to be protected for similar reasons to alcohols (though they are more nucleophilic, and the amine NH proton is much less acidic than the alcohol OH). So several of the above protecting group strategies used for alcohols will also work for amines (*e.g.* formation of benzyl amines; conversion to amides (rather than esters)).

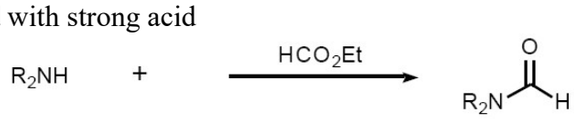
Carbamates

A distinct class of PG commonly used for amines – is the carbamate group. Usefully, there are several different types which may be removed under complementary conditions. They all consist of a group ("Device") which is easily removed to allow loss of CO_2, regenerating the free amine.

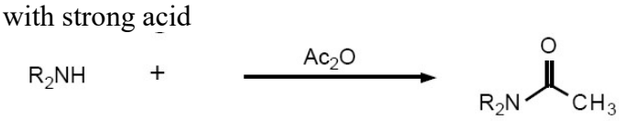


Amides

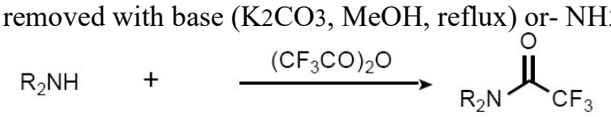
Formamides - removed with strong acid



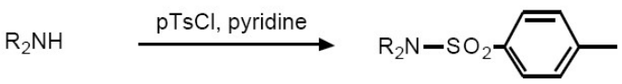
Acetamides- removed with strong acid



Trifluoroacetamides - removed with base (K_2CO_3, MeOH, reflux) or- NH_3, MeOH

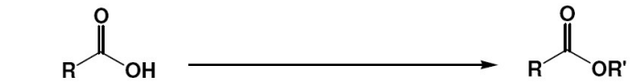


Sulfonamides p-Toluenesulfonyl (Ts) - removed with Strong acid, - sodium Naphthalide, - Na(Hg)

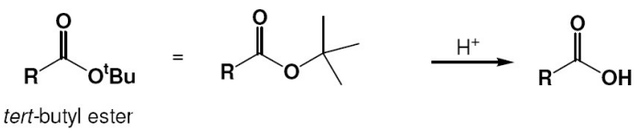


PROTECTION OF CARBOXYLIC ACIDS

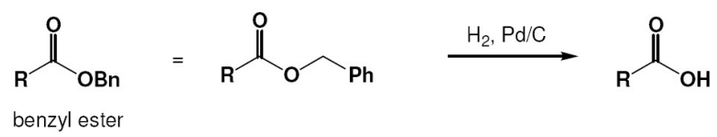
We often need to protect carboxylic acids because their ability to act as a proton source can lead them to react with organometallic reagents (*e.g.* organolithiums, Grignards). Ester formation is one common strategy. Certain esters are especially useful as they can be removed under selective conditions, as was the case for carbamate protection of amines.



e.g.

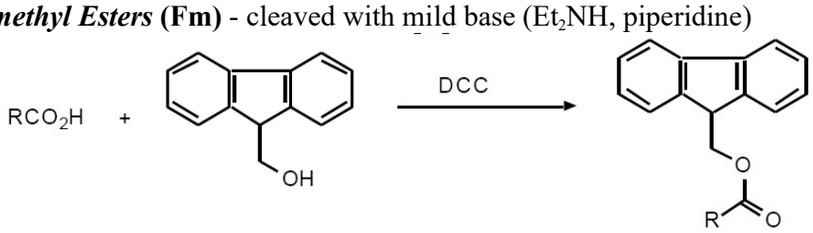


tert-butyl ester

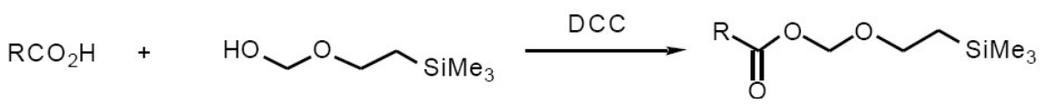


benzyl ester

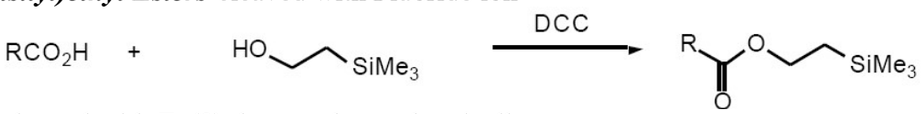
***9-Fluorenylmethyl Esters* (Fm)** - cleaved with mild base (Et_2NH, piperidine)



***2-Trimethylsilyl)ethoxymethyl Ester* (SEM)** - Cleaved with Bu4NF in DMF



2-(Trimethylsilyl)ethyl Esters-cleaved with Fluoride ion



Haloesters- cleaved with Zn(0) dust or electrochemically