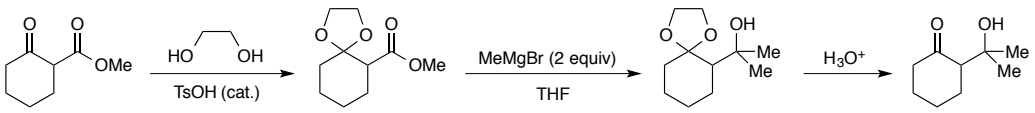
Protecting Groups - Synthesis I (Lecture 8)

1 Introduction

1.1 The Necessity of Protecting Groups

To selectively transform only one of multiple similar or identical functionalities within the same molecule, the other functional groups often need to be protected. This means that they are temporarily transformed into other functional groups, so called 'protecting groups', by reaction with a suitable 'protecting reagent'. Later in the synthesis, the protecting group can be removed by means of selective reagents to restore the original functional group.

Example: The ester group of a β-ketoester is intended to be transformed into a tertiary alcohol upon treatment with a Grignard reagent. However, the ketone of the β-ketoester is more electrophilic compared to the ester functionality and would therefore preferably be attacked by the nucleophilic Grignard reagent. To circumvent this undesired reactivity the ketone is temporarily transformed into an acetal (protecting group for ketones) by acid-catalyzed reaction with ethylene glycol (protecting reagent). Subsequently, the Grignard reaction is performed to convert the ester into a tertiary alcohol. In a final step, the ketone is reestablished by acidic aqueous hydrolysis of the acetal (removal of the protecting group).



1.2 Requirements for Protecting Groups

The use of a protecting group adds two steps to a synthesis: One for protection, the other one for deprotection. Both steps need to be virtually quantitative to not significantly affect the overall yield of the synthesis. Furthermore, they should require cheap reagents and mild reaction conditions, so that other functionalities present in the molecule remain unaffected.

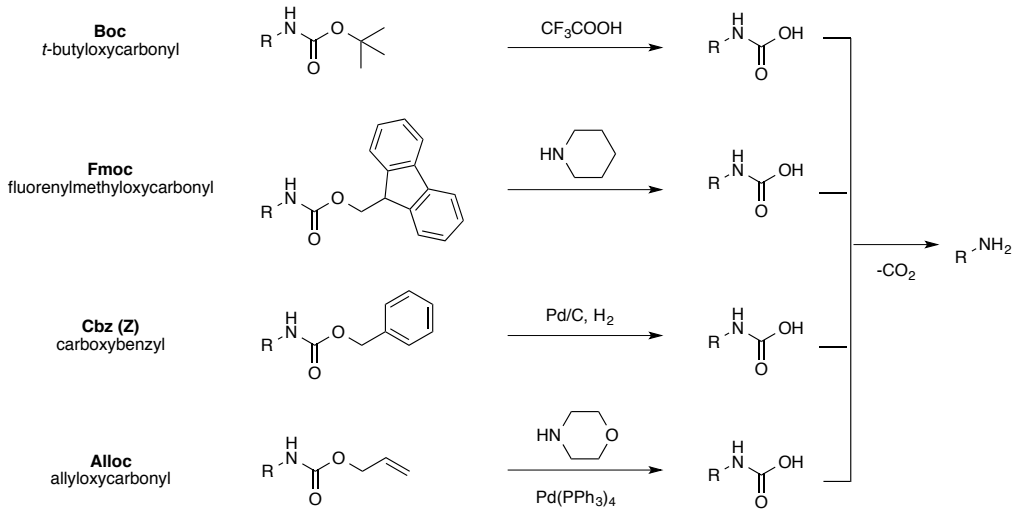
Quantitative protection and deprotection can be achieved using reagents that form strong bonds and thus drive the reactions forward by a favorable change in enthalpy. Alternatively, liberation of gases can provide the required increase in total entropy, and thus drive the reaction to completion.

Example: Di-*tert*-butyl dicarbonate (Boc_2O) is a popular reagent to protect amines as carbamate protecting groups, which are less nucleophilic. The protection reaction is driven to completion by the formation of carbon dioxide.

1.3 Orthogonality

Synthesis of complex organic molecules often requires the use of multiple protecting groups for similar or identical functional groups. When one protecting group can be selectively removed by applying specific reaction conditions that don't affect the other groups and vice versa, these two protecting groups are orthogonal to each other. This concept can be extended to any number of functional groups.

Amines can be protected by Boc-, Fmoc-, Cbz-, or Alloc protecting groups, which are removed by acids, bases, hydrogenolysis, or the use of transition metals respectively. Each group remains intact under the other reaction conditions.



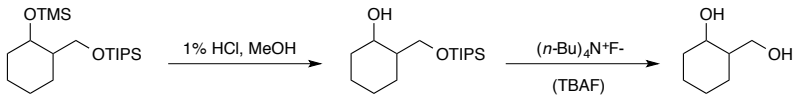
1.4 Modulated Lability

Besides orthogonal protecting groups, structurally similar protecting groups that have different reactivities towards certain cleaving conditions can be employed for selective deprotection. The classical examples are trialkylsilyl ethers. Their relative stability towards acidic hydrolysis (given in parentheses) increases with increasing steric bulk of the alkyl groups bound to the silicon.

$$–SiMe_3\ (1) < –SiEt_3\ (64) < –Si(t\text{Bu})Me_2\ (20{,}000) < –Si(i\text{Pr})_3\ (700{,}000).$$

In addition to acidic aqueous conditions, trialkyl silyl ethers can be cleaved by basic aqueous conditions and most rapidly by fluoride ions, commonly provided by tetrabutylammonium fluoride (TBAF). In the following example, the particularly strong Si–F bond (Si–F: 135 kcal/mol, Si–O: 110 kcal/mol) is the driving force for deprotection.

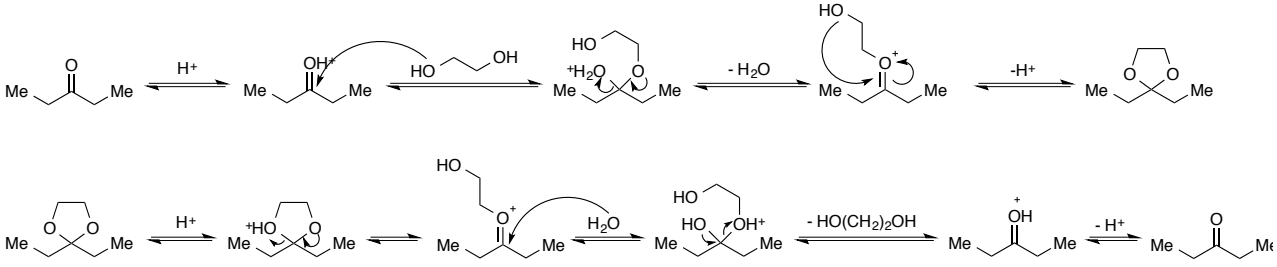
The TIPS (triisopropylsilyl) protecting group remains intact after treatment with dilute acid. TIPS protecting groups and other sterically demanding trialkyl silyl ethers need fluoride ions to be deprotected.



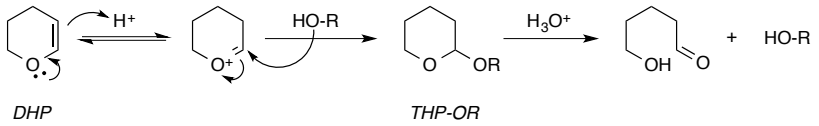
2 Deprotection Mechanisms

2.1 Acidic Deprotection

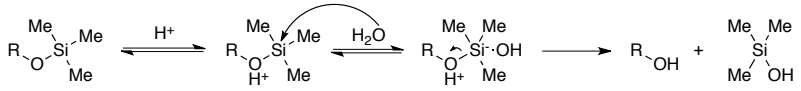
Acidic conditions promote hydrolysis of many protecting groups and in the case of acetals also catalyze their installation (see the example depicted below).



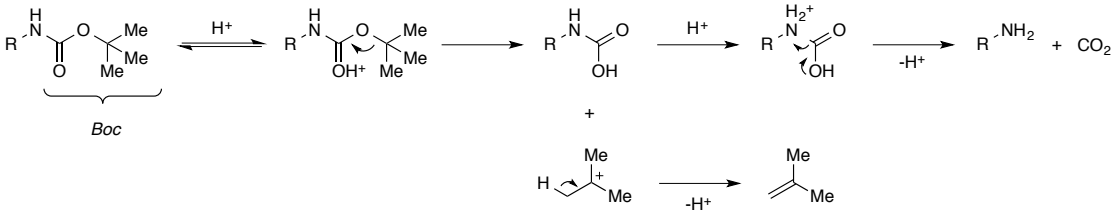
A popular reagent to install acetal protecting groups of alcohols is dihydropyran (DHP). The acetal, abbreviated as RO-THP (tetrahydropyranyl), can be installed by acid-catalysis without formation of water as byproduct.



Acid catalyzed cleavage of trialkylsilyl ethers is initiated by protonation of the ether oxygen followed by nucleophilic attack of a water molecule on the silicon. Subsequently, the pentavalent intermediate collapses to release the hydroxyl group.

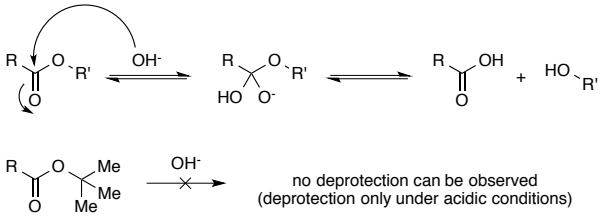


Formation of a stabilized carbocation is often implemented in the design of protecting strategies to facilitate cleavage of the protecting group under acidic conditions.

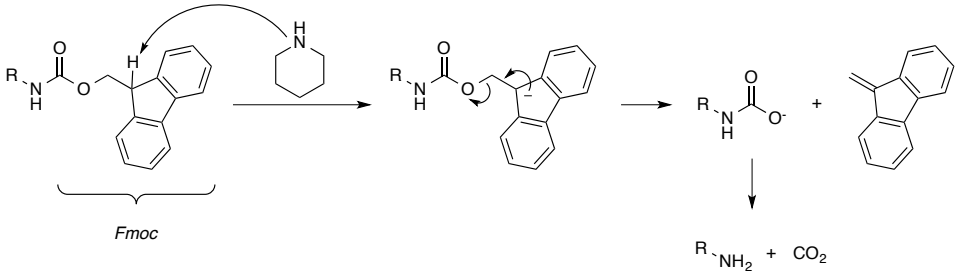


2.2 Basic Deprotection

Esters are used to protect not only carboxylic acids but also alcohols. If the alkyl group is not too sterically demanding, ester hydrolysis can be catalyzed by hydroxide ions. However, in case of the bulky *tert*-butyl group, the ester does not undergo hydrolysis under basic conditions.

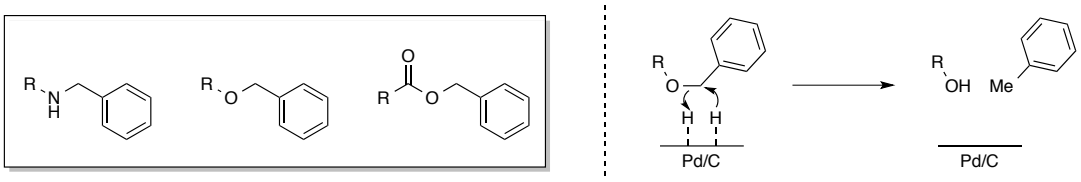


The removal of the amine protecting Fmoc is initiated by abstraction of a relatively acidic C–H proton, immediately followed by elimination (E1cB mechanism). The resulting carbamic acid decomposes under formation of carbon dioxide and the amine.



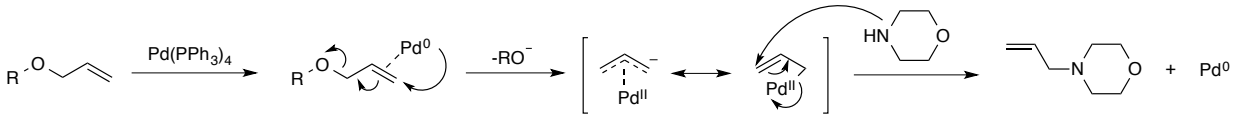
2.3 Hydrogenolysis

Benzyl protection groups are employed for various functionalities and can be removed by catalytic hydrogenation and many other conditions depending on the substrate.



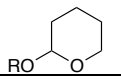
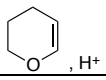
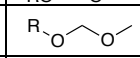
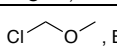
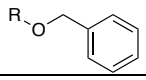
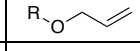
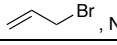
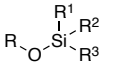
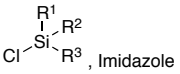
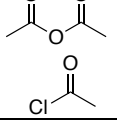
2.4 Transition-Metal Catalyzed Group Transfer

Allylic protection groups can be removed by coordination to a transition metal. To employ only catalytic amounts of the precious metal species, a suitable acceptor (often morpholine) to which the allyl group can be transferred is added

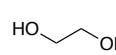


3 Protection Groups sorted by Functionalities

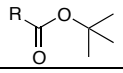
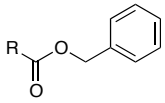
3.1 Alcohols

Class	Name	Structure	Protection	Deprotection	Comment
Acetal	tetrahydropyranyl (THP)			H_3O^+	
	methoxymethyl (MOM)			H_3O^+	
Ether	benzyl ether (OBn)		NaH, BnBr	H_2, Pd/C	
	allyl ether			$Pd(PPh_3)_4$, morpholine	
	methyl ether (OMe)		NaH, MeI	BBr_3	Only for aromatic alcohols!
Silyl ether	trialkyl silyl ether			H_3O^+ or OH^- or F^- (TBAF) for bulky silyl ethers	Imidazole acts as nucleophilic catalyst and neutralizes the byproduct HCl.
Ester	acetate ester			K_2CO_3, $MeOH/H_2O$ or LiOH $MeOH/H_2O$	

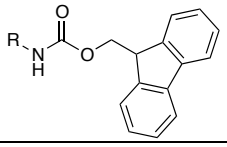
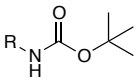
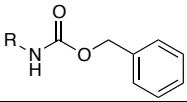
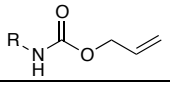
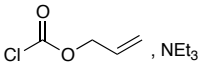
3.2 Aldehydes/Ketones

Class	Name	Structure	Protection	Deprotection	Comment
Acetal	dioxolane			H_3O^+	
Alkenes	-		Ph_3P^+-Me Br^-, KO*t*Bu *(Wittig)*	1. O_3, 2. Me_2S *(Ozonolysis)*	

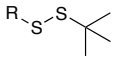
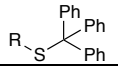
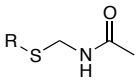
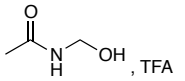
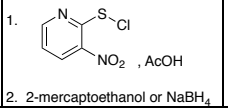
3.3 Carboxylic acids

Class	Name	Structure	Protection	Deprotection	Comment
Ester	methyl ester		CH_2N_2	LiOH, H_2O	
	t-butyl ester			TFA	
	benzyl ester		DCC, BnOH or BnOCOCl, Et_3N	H_2, Pd/C	

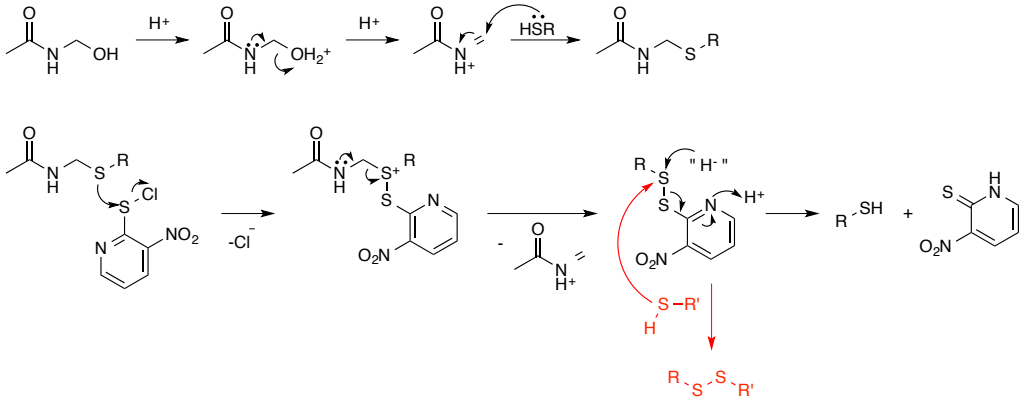
3.4 Amines

Class	Name	Structure	Protection	Deprotection	Comment
Carbamate	Fmoc		Fmoc-Cl, $NaHCO_3$	piperidine	
	Boc		Boc_2O	TFA	
	Cbz (Z)		BnOCOCl, NEt_3	H_2, Pd/C	
	Alloc			$Pd(PPh_3)_4$, morpholine	

3.5 Thiols

Class	Name	Structure	Protection	Deprotection	Comment
Disulfide	*S*-*t*-butyl disulfide		*t*-BuSH, O_2	$NaBH_4$, or 2-mercaptoethanol	R-SS-R homodimers can also be used for protection. Oxidation can be enforced using O_2, H_2O_2 or I_2.
Thioether	Triphenylmethyl (Trityl, Trt)		Ph_3C-Cl	TFA	
Aminothio-acetal	*S*-Acetamidomethyl (Acm)				3-Nitro-2-pyridyl-sulfenylchloride is abbreviated Npys-Cl.*

* The protection of thiols as aminothioacetal is initiated by acid-catalyzed formation of an iminium ion which is subsequently attacked by the free thiol. Usage of Npys-Cl as a cleavage agent removes not only the aminothioacetal but also yields an activated disulfide from which asymmetric disulfide bonds can be formed.



For photocleavable protecting groups see: - *Chem. Rev.* **2013**, *113*, 119–191.

- *Photochem. Photobiol. Sci.*, 2002, **1**, 441–458