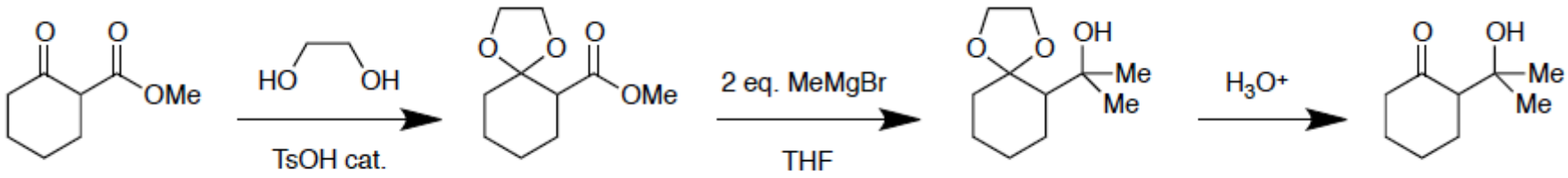
Protecting Groups

The Necessity of Protecting Groups

In order to selectively react only one of multiple similar or identical functional groups of a molecule, the other groups often need to be protected. These groups are therefore temporarily transformed into another functional group by reaction with a protecting reagent. The resulting functionality is termed *protecting group*.

Subsequent to carrying out the desired reaction, the original functional group is reinstalled by removal of the protecting group using a selective reagent.

Example: The ester group of a β-ketoester needs to be reacted with a Grignard reagent. Since the ketone is more electrophilic and would react preferably with an organometallic nucleophile, this functionality is temporarily transformed into an acetal by acid-catalyzed reaction with ethylene glycol. Following the Grignard reaction, the ketone is reestablished by acidic aqueous hydrolysis of the acetal.



A protecting group must fulfill a number of requirements:

1. The protecting group reagent must react *selectively* (kinetic chemoselectivity) *in* good *yield* to give a protected substrate that is stable to the projected reactions.

2. The protecting group must be *selectively* removed in good yield by readily available reagents.

3. The protecting group should not have additional functionality that might provide additional sites of reaction.

Introduction of a protective group adds additional steps to a synthetic scheme.
Hence, one should strive to keep the use of protecting groups to a *minimum* and avoid them if possible.

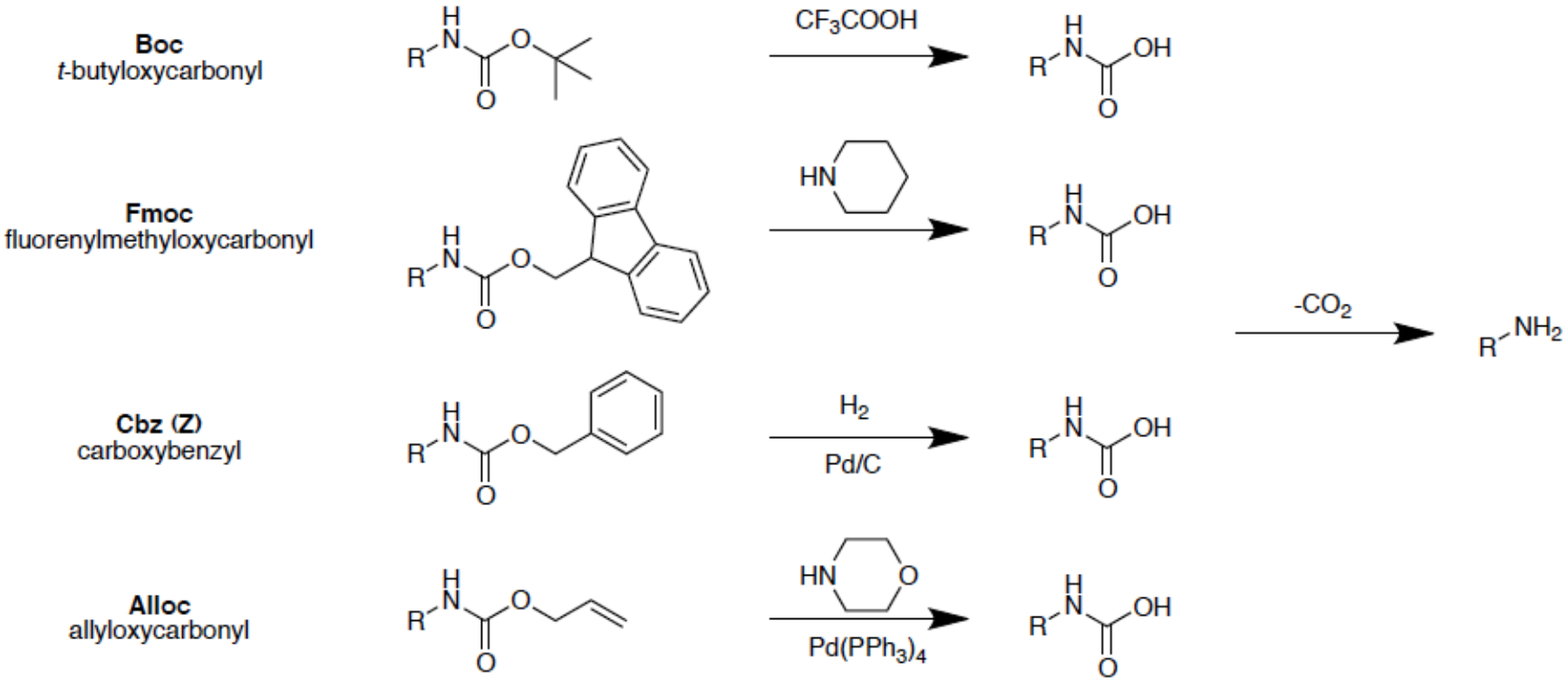
The use of reagents that form strong bonds and thus drive the reactions forward by a favorable change in enthalpy allows quantitative protection and deprotection. Alternatively, liberation of gases can not only provide the required increase in total entropy, but also remove some products from the equilibrium and thus drive the reaction to completion.

Di-*tert*-butyl dicarbonate (Boc_2O) is a popular reagent to protect amines as carbamates, which are much less nucleophilic. The protection reaction is driven by formation of carbon dioxide.

Orthogonality

Synthesis of complex organic molecule might require the use of multiple protecting groups for similar functional groups. When of two protecting groups, the first group can be selectively removed by applying reaction conditions that leave the second group unaffected and vice versa, these two protecting groups are termed *orthogonal* to each other. This concept can be extended to any number of functional groups.

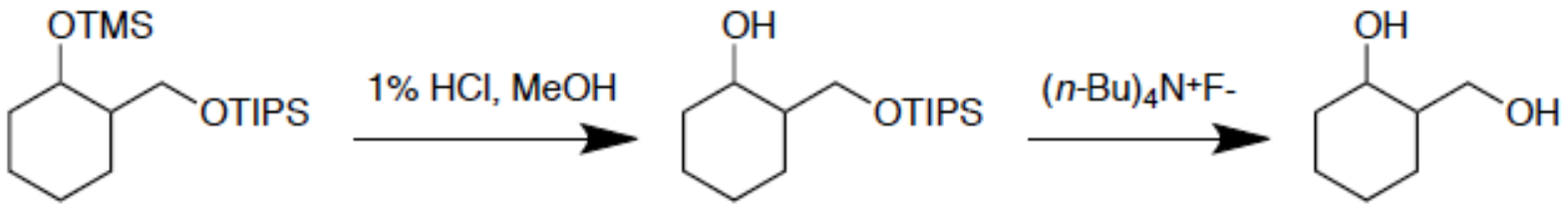
Amines can be protected by the Boc-, Fmoc-, Cbz-, or Alloc protecting group, which are removed by acids, bases, hydrogenolysis, or transition metals respectively, while each group remains intact under the other conditions.



Modulated Lability

Besides orthogonal protection groups, structurally similar protection groups that posses differential 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*Bu)Me_2 (20,000) < -Si(*i*Pr)$_3$ (700,000).

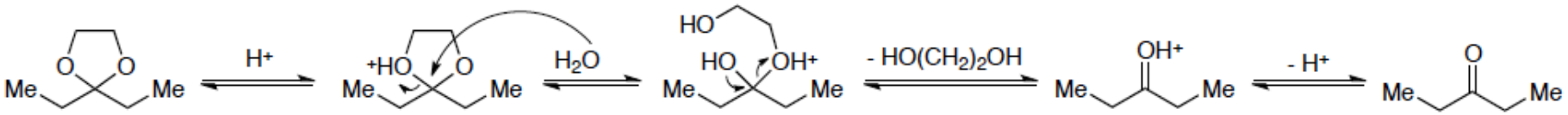
In addition to acidic aqueous conditions, trialkylsilyl ethers can be cleaved by basic aqueous conditions and most rapidly by fluoride ions, commonly provided as tetrabutylammonium fluoride (TBAF). Here, the particularly strong Si-F bond (135 kcal/mol; Si-O is 110 kcal/mol) is the driving force for deprotection.

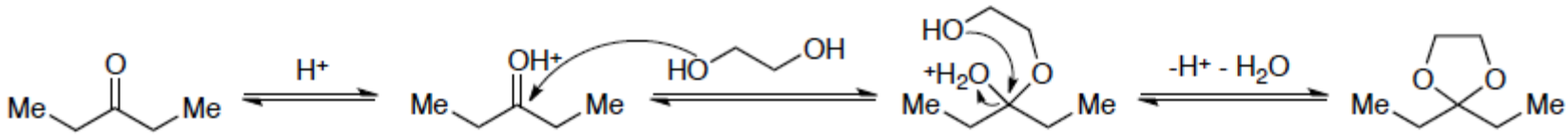


Deprotection Mechanisms

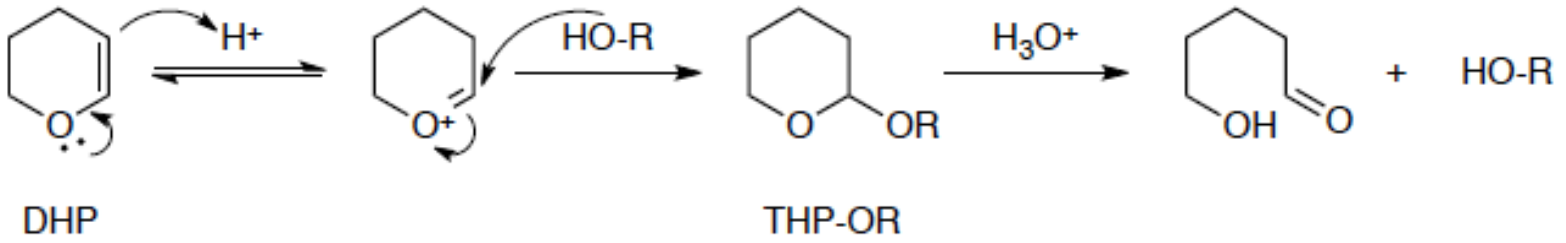
Acidic Deprotection

Acidic conditions foster hydrolysis of many protecting groups and in the case of acetals likewise catalyze their installation.

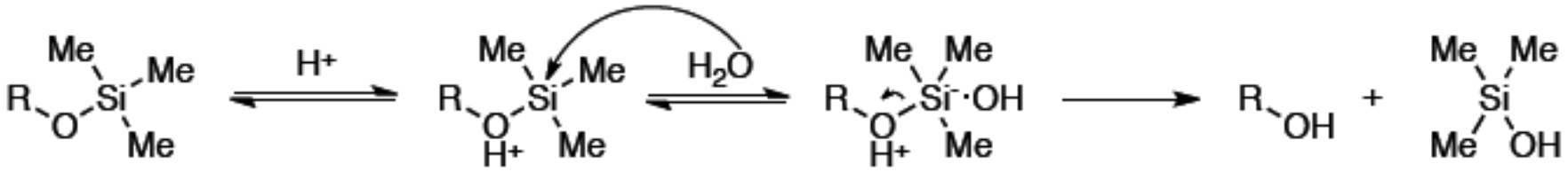




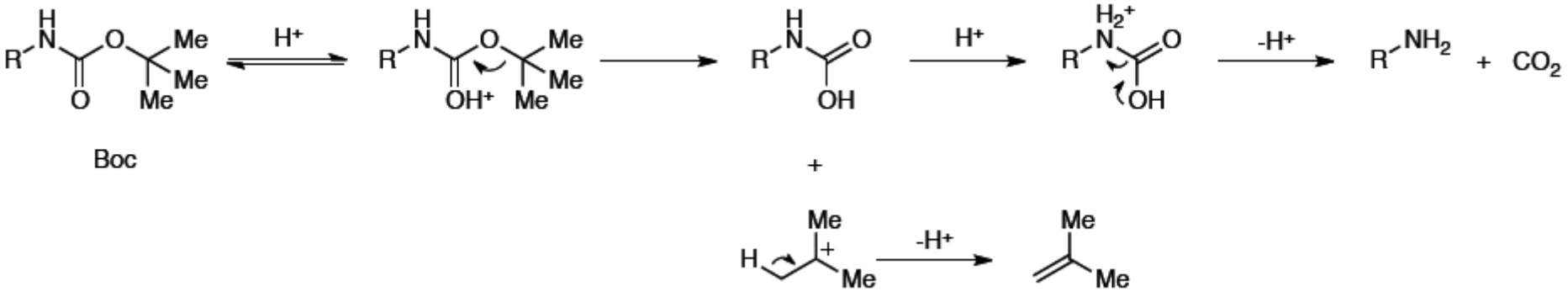
A popular reagent to install acetal protection groups for alcohols is dihydropyran (DHP). The acetal, abbreviated as RO-THP (tetrahydropyranyl) can be installed by acid-catalysis without water as byproduct.



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. The pentavalent intermediate collapses to release the hydroxyl group.

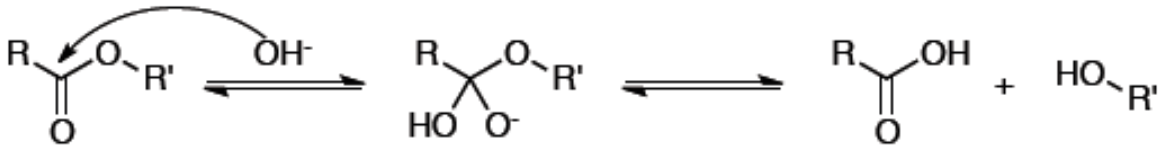


Formation of a stabilized carbocation is often implemented in the design of protecting groups to facilitate cleavage under acidic conditions.

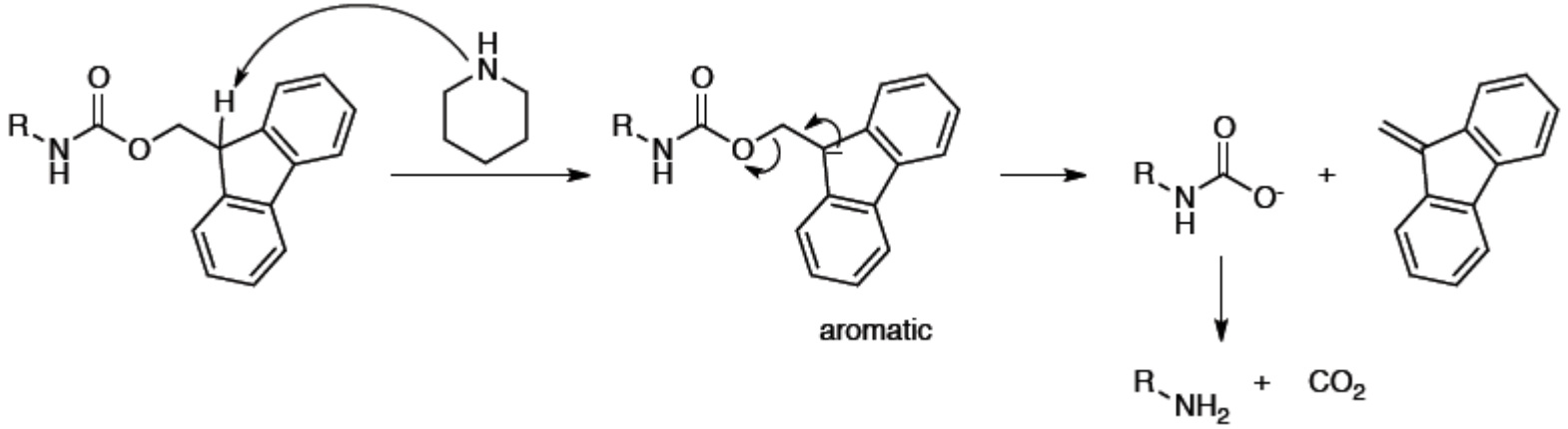


Basic Deprotection

Esters are equally used to protect carboxylic acids and 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 withstands hydrolysis under basic conditions.

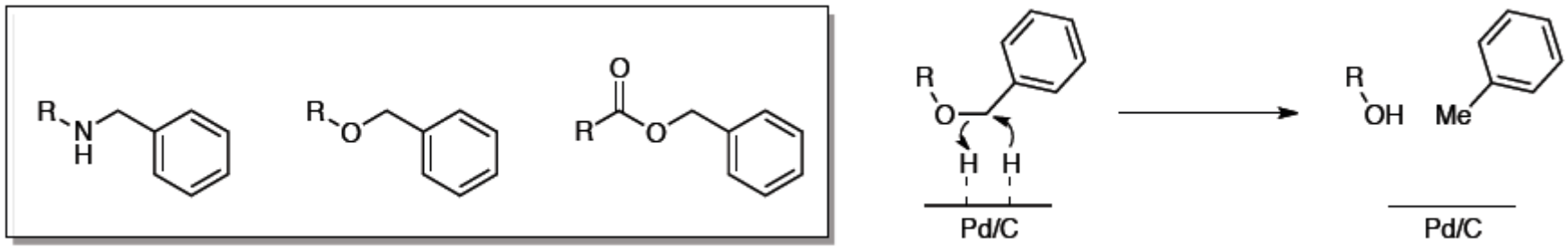


The removal of the amine protecting Fmoc group is initiated by abstraction of a relatively acidic C-H proton, immediately followed by elimination (E1cB mechanism). The resulting carbamic acid decomposes under formation of carbon dioxide and the amine.



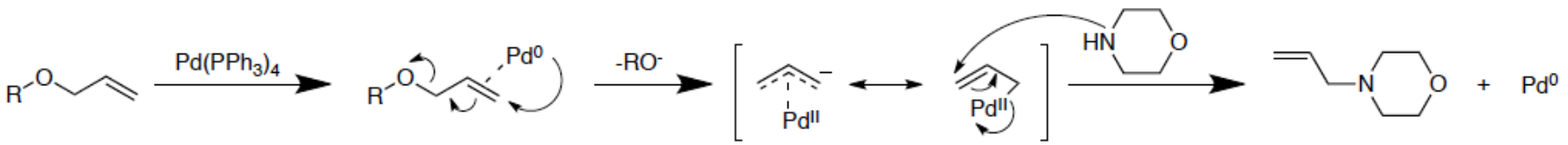
Hydrogenolysis

Benzyl protection groups are employed for various functionalities and can be removed by catalytic hydrogenation

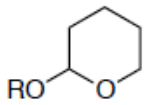
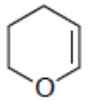
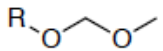
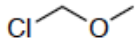
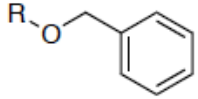
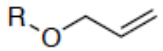
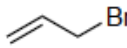
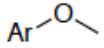
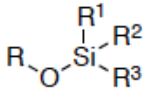
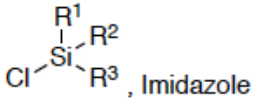
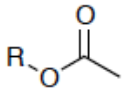
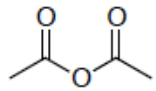
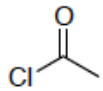


Transition-metal catalyzed group transfer

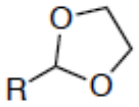
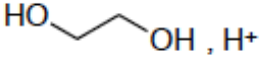
Allylic protection groups can be removed by coordination to a transition metal. In order to employ only catalytic amounts of precious metals, a suitable acceptor (often morpholine) is added to which the allyl group is transferred.



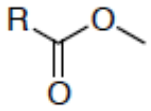
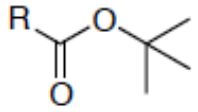
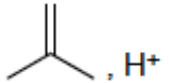
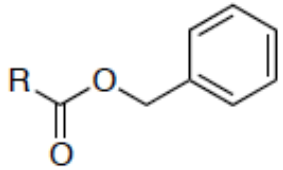
Alcohols

Class	Name	Structure	Protection	Deprotection	Comment
Acetal	tetrahydropyranyl (THP)		 , H+	H_3O^+	
	methoxymethyl (MOM)		 , Base	H_3O^+	
Ether	benzyl ether (Bn)		NaH, BnBr	H_2, Pd/C	NaH to deprotonate alcohol
	alllyl ether		 , NaOH	$Pd(PPh_3)_4$, morpholine	
	methyl ether (Me)		NaH, MeI	BBr_3	only for aromatic alcohols
Silyl ether	trialkylsilyl ether		 , Imidazole	H_3O^+, OH^-, F^- (TBAF)	imidazole acts as nucleophilic catalyst and neutralizes the byproduct HCl
Ester	acetic acid ester		 or  , pyridin	K_2CO_3, $MeOH/H_2O$ or LiOH $MeOH/H_2O$	

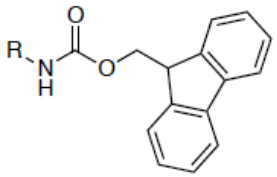
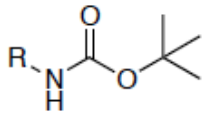
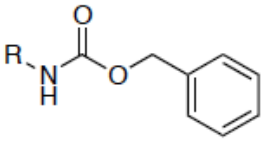
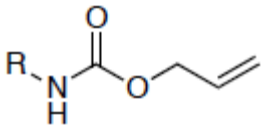
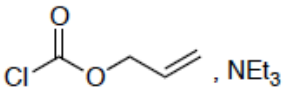
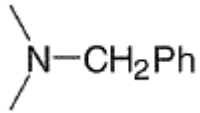
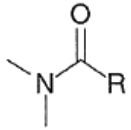
Aldehydes/Ketones

Class	Name	Structure	Protection	Deprotection
Acetal	dioxolane			H_3O^+
Alkenes	Wittig Reaction and Ozonolysis		Ph_3P^+-Me Br^-, KO^tBu	1. O_3, 2. Me_2S

Carboxylic acids

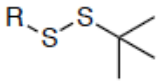
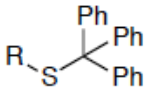
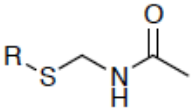
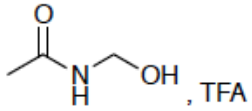
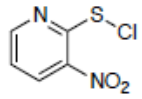
Class	Name	Structure	Protection	Deprotection
Ester	methyl ester		CH_2N_2	LiOH, H_2O
	t-butyl ester		 , H^+	TFA
	benzyl ester		DCC, BnOH or BnOCOCl, Et_3N	H_2, Pd/C

Amines

Class	Name	Structure	Protection	Deprotection
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
Benzylamine	Bn		$PhCH_2Br$, NEt_3	H_2, Pd/C
Amides	Ac		Ac_2O,	H_3O^+

Phthalimide……

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	Triphenyl-methyl (Trityl, Trt)		Ph_3C-Cl	TFA	
Aminothio-acetal	*S*-Acetamido-methyl (Acm)			1.  2. 2-mercaptoethanol or $NaBH_4$	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.