Iris Biotech

PROTECTING GROUPS

Version: IB13_1

Empowering Peptide Innovation

With this guiding theme in mind, Iris Biotech's mission is to support researchers by supplying

- innovative technologies,
- rare compounds,
- as well as a broad portfolio on standard consumables,

available in flexible quantities from small scale to bulk quantities. To fulfill our dedication "Empowering Peptide Innovation", we are attending various conferences, symposia, and exhibitions each year. This allows us to remain in direct contact with scientists all over the world, both from academia and industry, to exchange knowledge, and to gather new ideas to tackle your current challenges.

Guided by our dedication to provide

- competent service,
- as well as novel substances and
- latest technologies,

Iris Biotech is your trusted partner for the world of peptides, while having strong expertise in associated disciplines. Thus, our portfolio comprises reagents and tools for the synthesis and modification of peptides, e.g., amino acids, resins and solvents but also for related technologies such as drug delivery, linkerology® and life sciences.

Owed to the growing demand for tailor-made compounds, our portfolio is fine-tuned by our custom synthesis service at Iris Biotech Laboratories. Our skilled scientists offer profound expertise in

- *de novo* route development,
- upscaling towards larger scale production,
- as well as synthesis optimization for increased efficiency.

Examples are the synthesis of rare chiral building blocks, unnatural amino acid derivatives, sophisticated orthogonal protecting groups, heterocycles, building blocks for nucleotides, PEGs and PEG-analogs as well as specific linkers for controlled drug delivery and release.

Amino Acids ***Building Blocks*** ***Life Sciences*** ***Drug Delivery*** ***Reagents*** ***Resins*** ***Linkerology®*** ***Click Chemistry***

Portfolio Overview

Peptide Synthesis and Modification

(Protected) Amino Acids

Standards such as Fmoc-D/L-AAA and Boc-D/L-AAA, Smoc amino acids for peptide synthesis in water, variety of protecting groups (e.g., Pbf, Trt, ^{t}Bu, Bzl, Acm, Mob, SIT, Phacm, Allocam, Mmt), unusual amino acids, fluorinated derivatives, substituted prolines, arginine analogs

Building Blocks

Amino alcohols, amino aldehydes, diamines and hydrazines, (pseudoproline) dipeptides, polyamines and spermines, fatty acid derivatives, peptide nucleic acids (PNAs)

Reagents

Coupling reagents, solvents and scavengers, protecting groups

Resins

Preloaded resins (e.g., based on Trityl, TCP, TentaGel, Methoxybenzhydryl, Merrifield, PAM, Rink, Wang), scavenger resins, hydrazone resins, poly(acrylamide) resins, Cyclover

Linkerology® and Drug Delivery

Linkers for Solid Phase Peptide Synthesis

Cleavable Linkers

Val-Ala-based, Val-Cit-based, disulfide-based, Dde-helping hands, pH-sensitive linkers

Photo-Activatable Linkers

Functionalized Linkers

Clickable linkers, trifunctional linkers, linkers with maleimide function, cross-linkers, selective N-term acylation and biotinylation, 5HP2O

PROTACs

Ligands, linkers & modules

Fullerenes, Poly(2-oxazolines), Dextrans & Plant-Derived Cholesterol

Superparamagnetic Iron Oxide Nanoparticles

Poly-Amino Acids

Poly-Arg, Poly-Glu, Poly-Lys, Poly-Orn, Poly-Sar

PEGylation

Branched PEGylating reagents, (amino-)PEG-acids, PEG-amines & hydrazides & guanidines, reagents for Click-conjugation, Biotin-PEG-reagents, PEG-thiols, PEG-maleimides, other PEGylating reagents

Life Sciences

Biotinylation Reagents

Carbohydrates

Galactose, Glucose, Mannose, Xylose and others

Drug Metabolites

Peptides

Substrates & Inhibitors

E.g., protein kinase inhibitors, substrates for fusion (Halo/Snap/Clip)-tagged proteins

Natural Products

Dyes and Fluorescent Labels

E.g., ICG, AMC, DAPI

Maillard & Amadori Reaction Products

Large portfolio of derivatives useful as standards for food, pharma and cosmetics industry

Vitamins

Custom Synthesis

Your project requires a compound not listed in our portfolio?
Get in contact and inquire about our custom synthesis capabilities.

Our experienced scientists are excited to accept your synthetic challenge!
In such cases, your request undergoes the following stages:

Step-by-Step Analysis

- Customer's demands

Process Evaluation

- Detailed literature review
- Synthetic possibilities

Strategy Development

- Protocol development
- Method development and validation
- Customized synthesis

Quality Consistency

- Identity confirmation
- Purity verification

Our Service Promise

All our services are based on high standards, transparency & documentation, trust, honesty & confidentiality, as well as the required know-how.

High Standards

- Values: sustainability & responsibility
- State-of-the-art equipment & latest technologies
- High quality standards
- Qualified suppliers & regular audits

Transparency & Documentation

- Talk to our specialists – customer care
- Certificates of analysis & origin
- Impurity profiling
- Safety data sheets
- Analytical and process reports

Trust, Honesty & Confidentiality

- Intergenerational business valuing partnerships
- Meeting the customer's expectations
- Integrity towards our customers

Our Know-How

- One-step reactions & complex multi-step synthesis
- Scalability from mg to kg quantities
- Route scouting

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1. Introduction

Peptide synthesis and the design of sophisticated modifications often require the protection of specific functional groups to facilitate selective reactions. As the complexity of synthetic targets has increased, so has the demand for effective protecting groups. These protecting groups act as temporary shields of functional groups that might otherwise be incompatible with certain reaction conditions, thus allowing for selective transformations without unwanted side reactions or degradation.

Protecting groups can generally be classified into several categories: temporary protecting groups are removed after each synthetic step, while permanent protecting groups remain stable throughout all synthetic operations and are typically deprotected at the end of synthesis, often alongside the peptide´s release from the resin. Semi-permanent protecting groups stay intact during peptide assembly, but can be removed in the presence of the permanent protecting group. Safety-catch protecting groups are stable under certain conditions until a chemical or photochemical trigger converts them into a labile form. They are especially useful when functional groups need to be deprotected in a precise order, e.g., to create defined disulfide bonds.

Selecting an appropriate protecting group requires a comprehensive evaluation of reactants, reaction conditions, and functional groups involved in the synthetic sequence. The steric and electronic properties of the functional group being protected are particularly important. For example, a bulky protecting group may obstruct the access of reagents, while its electronic characteristics can either stabilize or destabilize the group depending on the specific reaction environment. It is essential to identify which functional groups are susceptible to which reaction conditions in order to ensure that they will not interfere with the desired transformation.

In multi-step syntheses, the use of orthogonal protecting groups is crucial for maintaining control over the process. The concept of “orthogonality” was first introduced by Barany and Merrifield in 1977. They describe that orthogonal protecting groups can selectively be removed under distinct conditions, enabling the (chemo- and/or regio-)selective deprotection of one group without affecting others. This is especially important when multiple protecting groups are employed simultaneously, as it allows for the independent manipulation of each functional group (see *Fig. 1*).

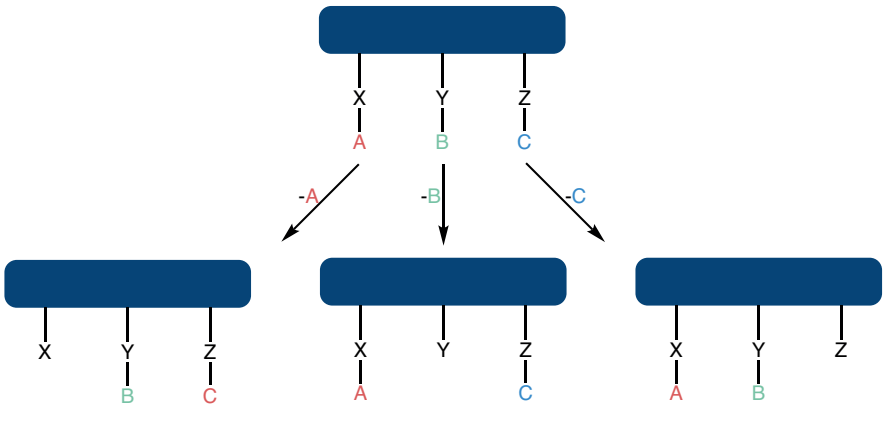


Fig. 1: Concept of orthogonal protecting groups according to Schelhaas et al.

2. Amine (Dab, Dap, Lys, Orn) Protecting Groups

Aliphatic amines can be found in diaminobutyric acid (Dab), diaminopropionic acid (Dap), lysine (Lys), and ornithine (Orn). It is important to protect the side-chain amine functionality to avoid unwanted acylation, which can lead to the formation of undesired branched peptides. Due to the higher pK_a value (see *Fig. 2*) of the ω-amino group in the side-chains of these molecules compared to the α-amino group, the ω-amino group exhibits greater nucleophilicity. Consequently, more electron-rich protecting groups are necessary to effectively shield the ω-amino functionality.

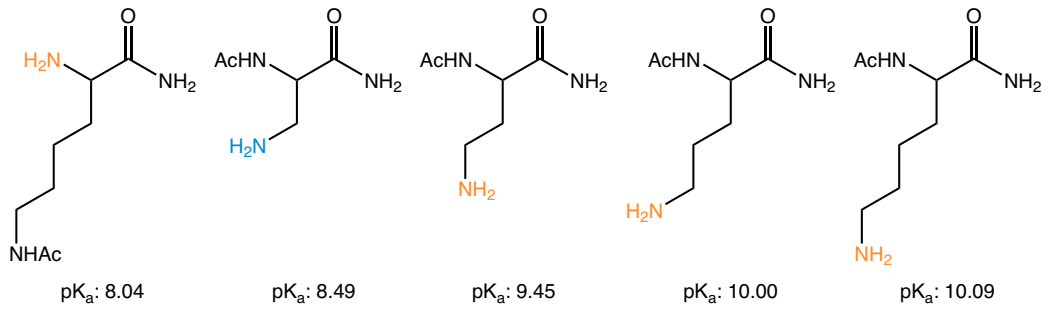
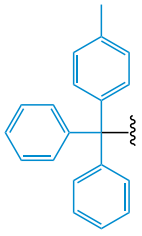
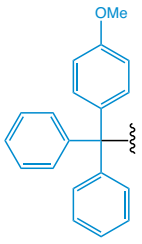


Fig. 2: Comparison of pK_a values of the α-amino group and the ω-amino groups of Dab, Dap, Orn, and Lys.

However, the ω-amino groups offer a wide range of possibilities for modifying peptides, such as labeling and attaching drugs, carbohydrates or fatty acids. They also allow for the construction of various peptide forms, including cyclizations and peptide dendrimers. Therefore, orthogonal protecting groups are particularly suitable for these applications.

Tab. 1: Protecting groups for side-chain amino functionalities and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	4-Methyltrityl (Mtt)	1% TFA in DCM TFA/MeOH/DCM (1:2:98) TFA/TIS/DCM (1:2:97) AcOH/TFE/DCM (1:2:97) DCM/HFIP/TFE/TES (6.5:2:1:2:0.5)	• Side-chain modifications prior to full cleavage • Selective removal with mild acidic conditions	
2	4-Methoxytrityl (Mmt)	2% TFA in DCM AcOH/TFE/DCM (1:2:7)	• Side-chain modifications prior to full cleavage • Selective removal with mild acidic conditions • Improved deprotection in comparison to Mtt	

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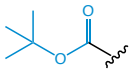
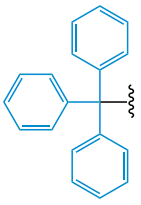
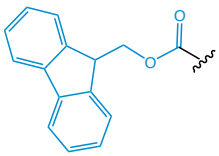
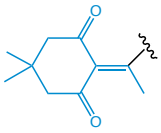
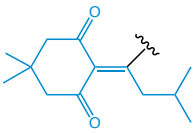
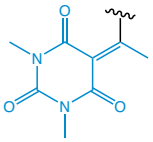
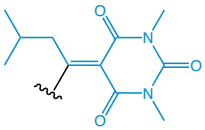
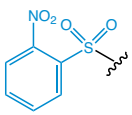
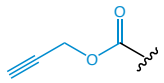
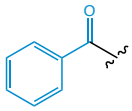
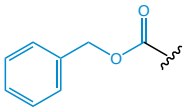
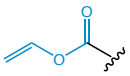
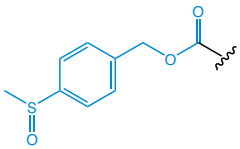
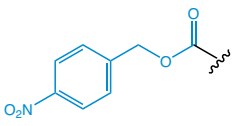
Protecting Groups

Entry	Protecting group	Removal conditions	Remarks	Structure
3	*tert*-Butoxycarbonyl (Boc)	3 M HCl, EtOAc 4 M HCl, dioxane 20-25% TFA in DCM	• Standard-protecting group in Fmoc strategy	
4	Trityl (Trt)	Ag(I) Hg(II) HBr/AcOH TFA/TIS (9:1) HBF_4/scavengers I_2	• Used in side-specific derivatization • Orthogonal to Fmoc strategy	
5	9-Fluorenylmethyl-oxycarbonyl (Fmoc)	5% piperidine 20% piperidine 50% morpholine	• Used in the synthesis of cyclic or branched peptides in the Boc strategy	
6	4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (Dde)	2-5% hydrazine in DMF	• Side-chain modifications prior to full cleavage by TFA • Note: hydrazine treatment is not compatible with Fmoc protecting group • Dde might migrate to free amino groups (scrambling)	
7	1-(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl (ivDde)	2-5% hydrazine in DMF	• Side-chain modifications prior to full cleavage by TFA • Note: hydrazine treatment is not compatible with Fmoc protecting group • More robust than Dde	
8	1-(1,3-Dimethyl-2,4,6-trioxo-1,3-diazinan-5-ylidene) ethyl (MeDmb)	2% hydrazine in DMF 2% hydroxylamine in DMF	• Side-chain modifications prior to full cleavage by TFA • Reduced scrambling in comparison to Dde	
9	1-(1,3-Dimethyl-2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)-3-methylbutyl (ivDmb)	2-5% hydrazine in DMF	• Side-chain modifications prior to full cleavage by TFA • Most promising scrambling suppression	
10	Nitrobenzenesulfonyl (Ns, *o*-NBS)	2-mercaptoethanol, DBU in DMF 0.5 M thiophenol, K_2CO_3 in DMF	• Applied in alkylation reactions of ε-amino group	

Entry	Protecting group	Removal conditions	Remarks	Structure
11	2-(Trimethylsilyl) ethoxycarbonyl (Teoc)	TBAF in ACN	· Can be used for side-specific derivatization · Orthogonal to Fmoc and Cbz chemistry · Not stable in Boc strategy conditions	
12	Prop-2-ynyloxy carbonyl (Pryoc/ Poc)	$Co_2(CO)_8$ + 5-7% TFA in DCM $allyl_2Pd_2Cl_2$ $[(PhCH_2NEt_3)MoSO_4]$ in ACN (ultrasonic irradiation)	· Click conjugation · Deprotection by using Pd in living cells possible	
13	Benzyl (Bn, Bzl)	H_2,Pd/C Nb_2O_5/C		
14	Benzyloxycarbonyl (Cbz, Z)	H_2,Pd/C HBr in AcOH TFA-thionanisol HF BBr_3	· TFA stable	
15	Formyl	HF, scavengers (EDT) piperidine 1 M NH_2OH		
16	Allyloxycarbonyl (Alloc)	$Pd(PPh_3)$ cat., scavengers: $H_3N{\cdot}BH_3$, $Me_2NH{\cdot}BH_3$ or $PhSiH_3$	· Scavengers are mandatory to prevent allylation of amine group	
17	Trifluoroacetyl (TFA)	K_2CO_3 Na_2CO_3 2 M aq. piperidine at rt (6-12 h)	· Orthogonal to Fmoc/*t*Bu strategy	
18	Acetyl (Ac)	1.2 N HCl, reflux 85% hydrazine 70 °C Hog kidney acylase	· Acetylated lysine can be used to study protein structure, interactions, and activity	
19	Azido (N_3)	PMe3 in toluene, water or dioxane	· Click conjugation	
20	4-Methylsulfinyl-benzyloxycarbonyl (Msz)	$SiCl_4$/TFA/anisole Me3SiCl/Ph3P in THF, followed by acidification with TFA NH_4I/Me2S/TFA	· Orthogonal safety-catch protecting group	
21	*p*-Nitrobenzyloxy-carbonyl (pNZ)	$SnCl_2$, HCl(dioxane) in DMF H_2 cat.	· Limits undesired removal of α-Fmoc group of Lys or Orn after side-chain deprotection	

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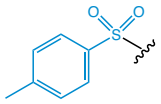
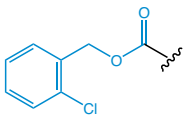
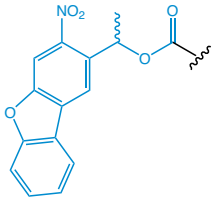
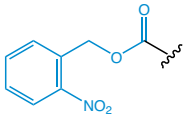
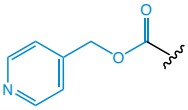
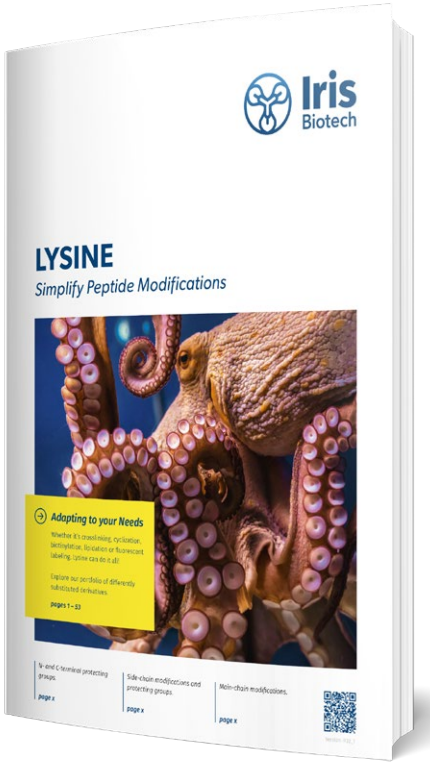
Protecting Groups

Entry	Protecting group	Removal conditions	Remarks	Structure
22	Tosyl (Tos)	Sodium naphthalenide in DME Sodium anthracenide Bu_3SnH, AIBN, toluene		
23	2-chlorobenzyloxy-carbonyl (2Cl-Z)	transfer hydrogenolysis ammonium formate/ Pd/C HF, scavengers TFMSA-TFA H_2 cat.	· Standard protecting group in Boc strategy	
24	1-(3-Nitro-dibenzo-furan-2-yl)-ethoxy-carbonyl (NDBFOC)	UV-light (365 nm)	· selective deprotection by photolysis · one- & two-photon sensitive protecting group · application in living cells possible	
25	2-Nitrobenzyl (oNB)	UV-light (365 nm)	· selective deprotection by photolysis	
26	Isonicotinyloxycar-bonyl (iNoc)	Zn dust in 50% AcOH, Pd/C(10%)/H2, SmI_2 in aq. DMF	· Hydrophilic protecting group · Stable to TFA, HF	

Check out our new flyer about Lysine derivatives!



3. Indole (Trp) Protecting Groups

The indole moiety of tryptophane (Trp) is prone to alkylation and oxidation.

- **Alkylation:** The alkylation of the indole ring in Trp residues is a significant concern, particularly in acidic conditions. This risk arises primarily from carbocations generated during the cleavage of protecting groups or resin linkers such as Wang linkers. Additionally, **Trp dimerization** can occur under acidic conditions (see *Fig. 3*).

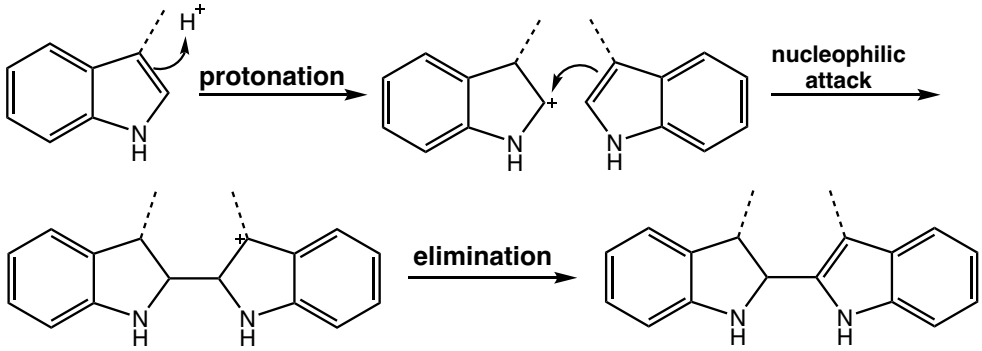


Fig. 3: Dimerization of Trp.

In the Fmoc/*t*Bu solid-phase peptide synthesis strategy, careful selection and use of scavengers during TFA cleavage from the resin are essential to mitigate these issues. Studies have documented the potential alkylation of Trp by cations derived from thioanisole, while triethylsilane (TES) may reduce the indole ring. Although the Boc protecting group is commonly employed for Trp, its incomplete removal can sometimes occur, leading to side reactions (see *Fig. 4*). To ensure complete removal of residual protecting groups it is recommended to subject the peptides to an extended treatment in a mild acidic environment after cleavage .

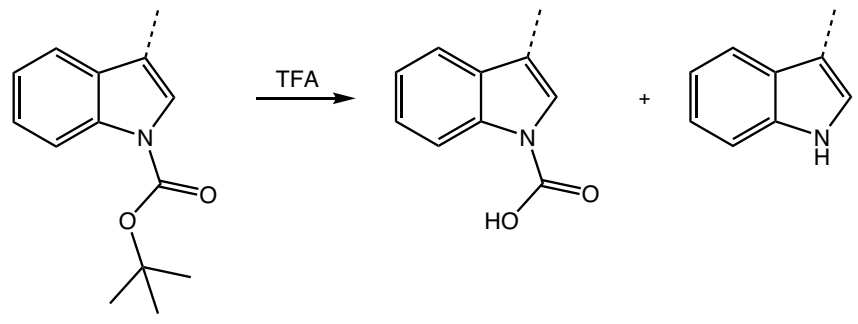


Fig. 4: Insufficient removal of the Boc-protecting group of Trp.

Introduction
Amine (Dab, Dap, Lys, Orn) Protecting Groups
Indole (Trp) Protecting Groups
Imidazole (His) Protecting Groups
Guanidino (Arg) Protecting Groups
Hydroxyl (Alcohol) (Hyp, Ser, Thr) Protecting Groups
Phenol (Tyr) Protecting Groups
Carboxylic Acid (Asp and Glu) Protecting Groups
Amide (Asn and Gln) Protecting Groups
Thiol (Cys) Protecting Groups
Selenol (Sec) Protecting Groups
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- **Oxidation:** The indole ring of Trp can undergo oxidation, leading to the formation of various products, such as oxindole derivatives. Oxidation can occur under physiological conditions and both acidic as well as basic conditions, especially in the presence of oxidizing agents such as H_2O_2,O_2, or DMSO/HCl. This process is rather complex and can result in different oxidized species (see *Fig. 5*).

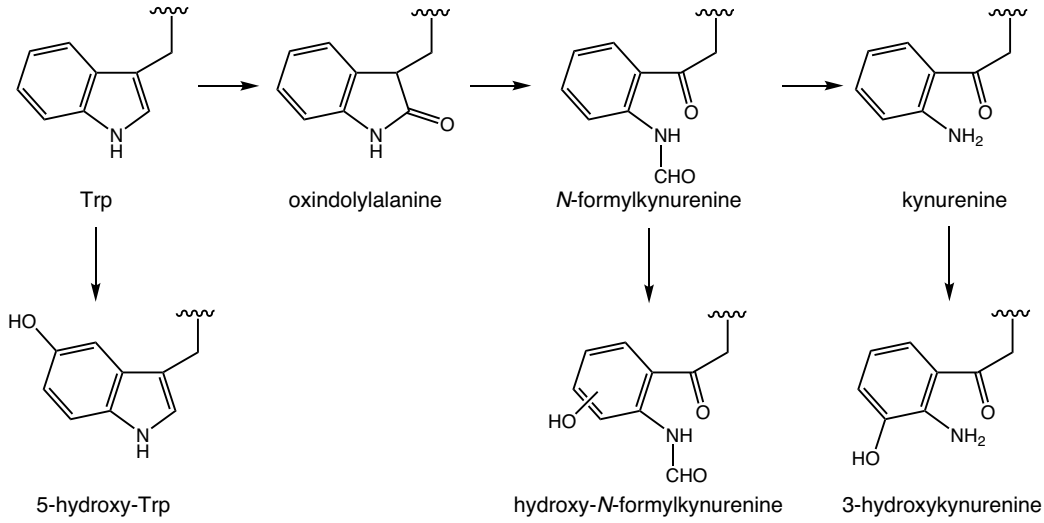
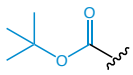
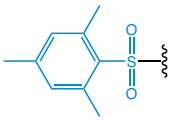


Fig. 5: Example of oxidized species of the Trp indol.

Tab. 2: Protecting groups for the indol moiety of Trp and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	*tert*-Butoxycarbonyl (Boc)	3 M HCl, EtOAc 25°C 4 M HCl, dioxane 95% TFA in DCM	· Standard protecting group in Fmoc strategy	
2	Mesitylsulfonyl (Mts)	1 M TFMSA/TFA or MsOH	· Alternative protecting group in Boc strategy, avoids HF	
3	Formyl	HF, scavengers (EDT), piperidine, 1 M NH_2OH	· Standard protecting group in Boc strategy	

4. Imidazole (His) Protecting Groups

The imidazole ring of histidine (His) contains two nucleophilic nitrogen atoms (N^{π} and N^{τ}). Since the N^{τ} position is sterically more accessible, it is usually the site for introducing a protecting group. However, N^{π} is not entirely unreactive; it can abstract the α-hydrogen intramolecularly, initiating an autocatalytic process, as depicted in *Fig. 6*. The protonated intermediate can either tautomerize into the corresponding enolate species or undergo re-protonation that may lead to racemization. This process is accelerated at elevated temperatures such as during microwave irradiation. To mitigate racemization, it is advisable to introduce a protecting group at the N^{τ} position that has a strong electron-withdrawing character or provides greater steric shielding, rendering N^{π} less reactive and reducing the likelihood of racemization.

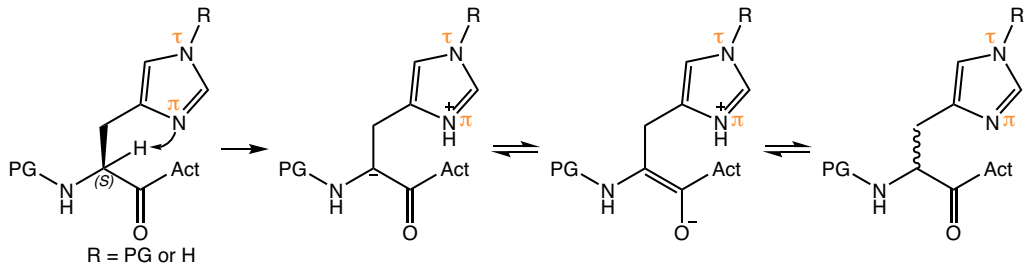
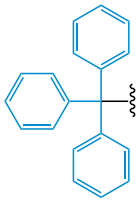
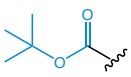
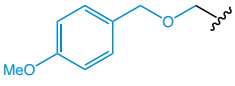
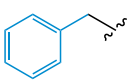


Fig. 6: Proposed racemization process of His.

Tab. 3: Protecting groups for the imidazole group of His and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	Trityl (Trt)	95% TFA	· Standard protecting group in Fmoc strategy · Epimerization might occur despite the bulkiness of the Trt group · Cannot selectively be removed by mild acidic treatment	
2	*tert*-Butoxycarbonyl (Boc)	3 M HCl, EtOAc 25°C 4 M HCl, dioxane TFA in DCM	· Reduces epimerization through electron-withdrawing character of the Boc group · Reported instability by prolonged exposure to piperidine	
3	4-Methoxybenzyloxymethyl (Mbom)	95% TFA	· Best suppression of epimerization	
4	Benzyl (Bzl)	cyclohexadiene, Pd-black		

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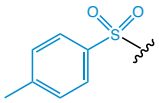
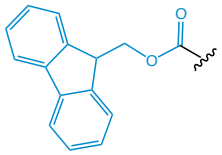
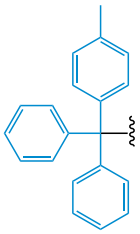
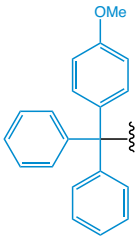
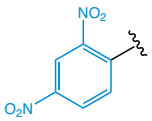
Protecting Groups

Entry	Protecting group	Removal conditions	Remarks	Structure
5	Tosyl (Tos)	HF, scavengers	• Standard protecting group in Boc strategy • Not stable in presence of N_α groups and HOBt	
6	9-Fluorenyl-methyl-oxycarbonyl (Fmoc)	5% piperidine 20% piperidine 50% morpholine 50% dicyclohexylamine 50% diisopropylethylamine	• Reported application in peptide-oligonucleotide conjugates	
7	4-Methyltrityl (Mtt)	15% TFA in DCM	• More acid labile than Trt	
8	4-Methoxytrityl (Mmt)	5% TFA in DCM	• More acid labile than Trt • Selective removal by mild acidic conditions	
9	Dinitrophenol (Dnp)	thiophenol, DBU in DMF	• Commonly used in Boc strategy • Incomplete removal possible • Susceptible to nucleophiles • Incompatible with Fmoc strategy as Dnp might attack free amino function • Must be removed before last α-Boc group	

5. Guanidino (Arg) Protecting Groups

Due to its high basicity (pK_a = 12.5), the guanidino group of arginine (Arg) predominantly exists in its protonated form during solid-phase synthesis. Deprotonation can occur through washing steps between Fmoc removal and coupling with 0.25 M HOBt. This increases the risk of deguanidination which occurs after acylation of the neutral guanidino group and leading to the conversion of arginine into ornithine (see *Fig. 7*).

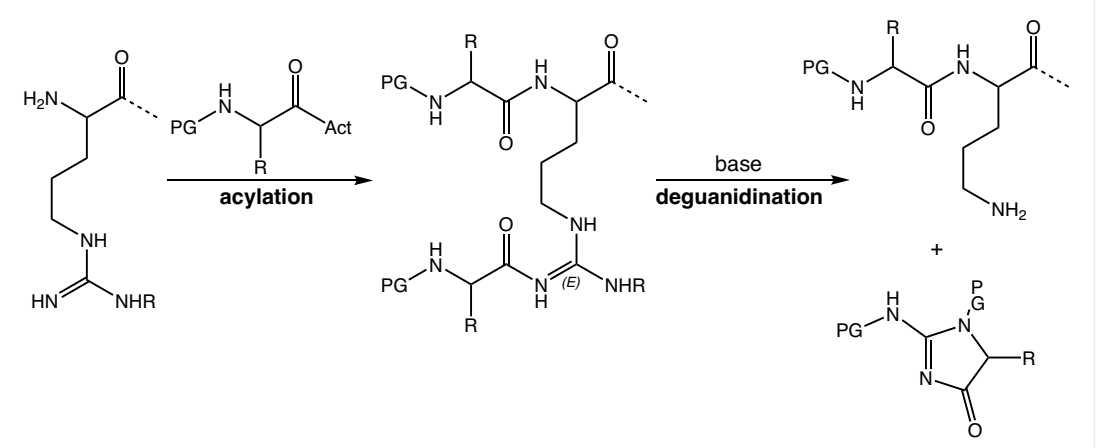


Fig. 7: Mechanism of base-catalyzed deguanidination of Arg.

Additionally, the guanidino group of arginine, like other functional groups in amino acids, is prone to intramolecular cyclization, resulting in the formation of a δ-lactam (see *Fig. 8*).

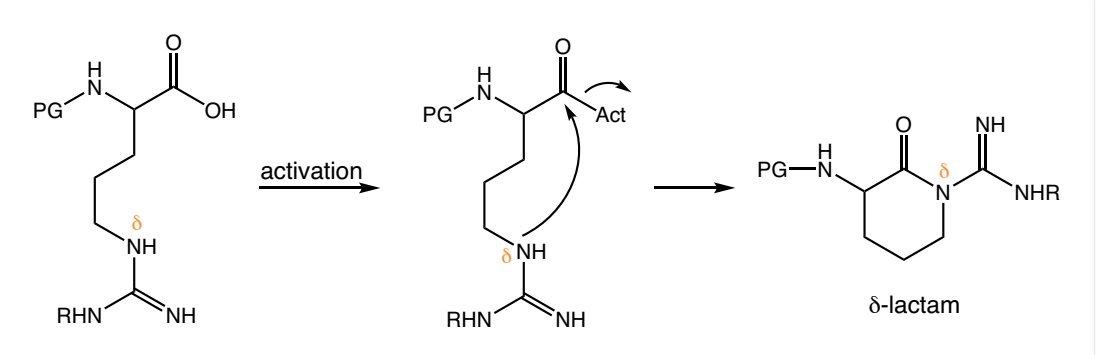


Fig. 8: δ-Lactam formation of Arg (R = H or PG).

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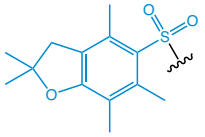
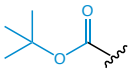
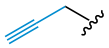
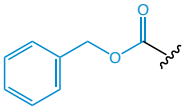
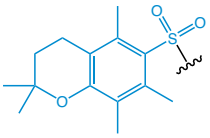
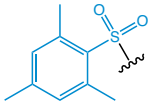
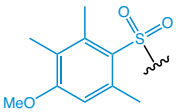
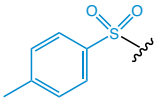
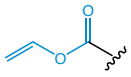
Tab. 4: Protecting groups of Arg´s guanidino residue and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	2,2,4,6,7-Pentamethyl-dihydrobenzfuran-5-sulfonyl group (Pbf)	90% TFA + scavangers (H_2O + TIS)	· Standard protecting group in Fmoc strategy · More acid labile than Pmc group	
2	*tert*-Butoxycarbonyl (Boc)	90-95% TFA in DCM	· Prevents deguanidation, but does not suppress δ-lactam formation · Low coupling rates	
3	Propargyl	$[(PhCH_2NEt_3)_2MoS_4]$	· Click conjugation	
4	Benzyloxycarbonyl (Cbz, Z)	H_2/Pd	· Applied in both Boc and Fmoc strategy · Removal requires prolonged reaction times	
5	2,2,5,7,8-Pentamethyl-chromanyl-6-sulfonyl (Pmc)	90% TFA scavengers (H_2O + TIS)	· Used in Fmoc strategy · Alkylation of Trp possible during TFA cleavage	
6	Mesitylsulfonyl (Mts)	TFMSA-TFA-thioanisol	· Used in Boc strategy · Is more acid-labile than the Tos group	
7	4-methoxy-2,3,6-trimethylphenyl-sulfonyl (Mtr)	95% TFA-thioanisol	· Applied in Fmoc strategy · Replaced by Pbf or Pmc group · In sequences containing several Arg residues Mtr removal might be incomplete	
8	Tosyl (Tos)	HF TFMSA-TFA-anisole Na/NH_3	· Standard protecting group in Boc strategy	
9	Allyloxycarbonyl (Alloc)	$Pd(PPh_3)_4$, barbituric acid	· Compatible with Boc strategy	
10	Nitro (NO_2)	H_2 cat. (Pd black, $SnCl_2$, or $TiCl_3$) HF	· Prevents δ-lactam formation · Multiple Arg(NO_2) residues might lead to difficulties as longer hydrogenation treatment may lead to side reactions of other amino acids	

6. Hydroxyl (Alcohol) (Hyp, Ser, Thr) Protecting Groups

The primary side reactions associated with unprotected hydroxyl functionalities in hydroxyproline (Hyp), serine (Ser), and threonine (Thr) include dehydration *via* β-elimination and *O*-acylation, followed by *O*-to-*N* acyl migration after removal of the amino protecting group (see *Fig. 9*). Notably, the primary hydroxyl group of serine is more prone to these side reactions compared to the secondary hydroxyl groups of hydroxyproline and threonine which exhibit greater stability.

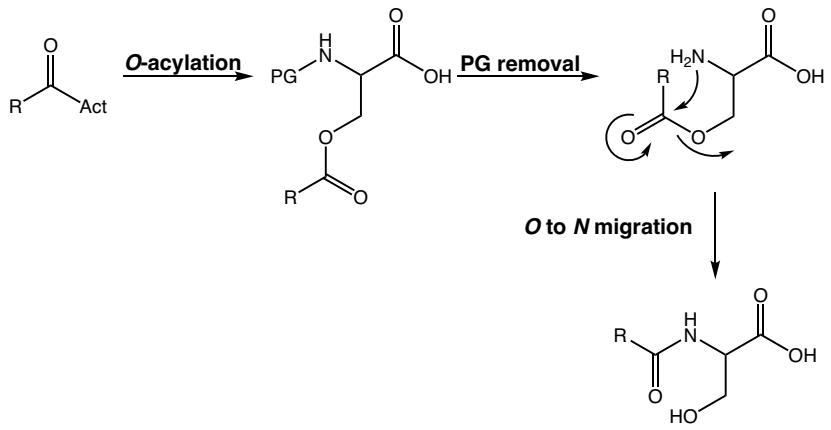
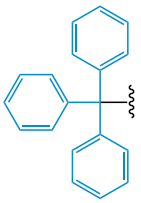
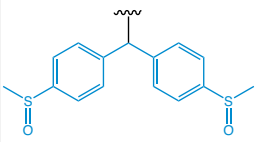


Fig. 9: Mechanism of O-acylation followed by O-to-N acyl migration after PG removal of amino function.

Tab. 5: Protecting groups for the hydroxyl group of Hyp, Ser, and Thr including their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	*tert*-Butyl (*t*Bu)	90% TFA	• Standard protecting group in Fmoc strategy	
2	Trityl (Trt)	1% TFA	• Provides better purity than *t*Bu-protected derivatives	
3	4,4-Bis(dimethyl-sulfinyl)benzhydryl (Msbh)	NH_4I-Me2S $SiCl_4$ SmI_2 Me_3SiCl/Ph_3P	• Removal by reduction of the sulfoxides, followed by acidolysis with TFA. • Orthogonal safety-catch protecting group	

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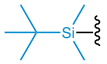
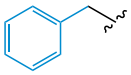
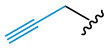
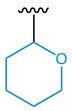
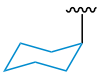
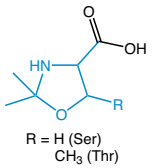
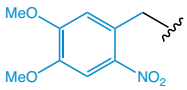
Protecting Groups

Entry	Protecting group	Removal conditions	Remarks	Structure
4	*tert*-Butyldimethyl-silyl (TBDMS)	1 M TBAF 2 M NaOH	• Orthogonal protecting group	
5	Benzyl (Bn, Bzl)	HF, scavengers TFMSA-TFA	• Standard protecting group in Boc strategy	
6	Propargyl	$[(PhCH_2NEt_3)_2MoS_4]$	• Click conjugation	
7	Tetrahedropyranyl (THP)	5% TFA	• Selective removal in mild acidic conditions • Better atom economy that Trt	
8	Cyclohexyl	TFMSA-TFA	• Used in Boc strategy	
9	Pseudoprolines (oxazolidines)	95% TFA and scavengers	• Incorporation of a kink into the peptide backbone • Reduces aggregation during peptide assembly • In combination with Asp: limits aspartimide formation	
10	4,5-Dimethoxy-2-nitrobenzyl (*o*Nv or DMNB)	UV-light (> 350 nm)	• Stable to Fmoc SPPS conditions	

7. Phenol (Tyr) Protecting Groups

Like the hydroxyl groups in hydroxyproline, serine, and threonine, the phenol group of tyrosine (Tyr) is highly susceptible to acylation due to its elevated nucleophilicity. Notably, the increased acidity of the phenol group makes alkyl-type protecting groups less stable when compared to those used for hydroxyproline, serine, and threonine. Additionally, the electron-rich phenolic ring of tyrosine can undergo alkylation at the *ortho*-position. Moreover, the phenolic side-chain is vulnerable to various oxidants and can be oxidized to form modified tyrosine derivatives through both radical and non-radical mechanisms (see *Fig. 10*).

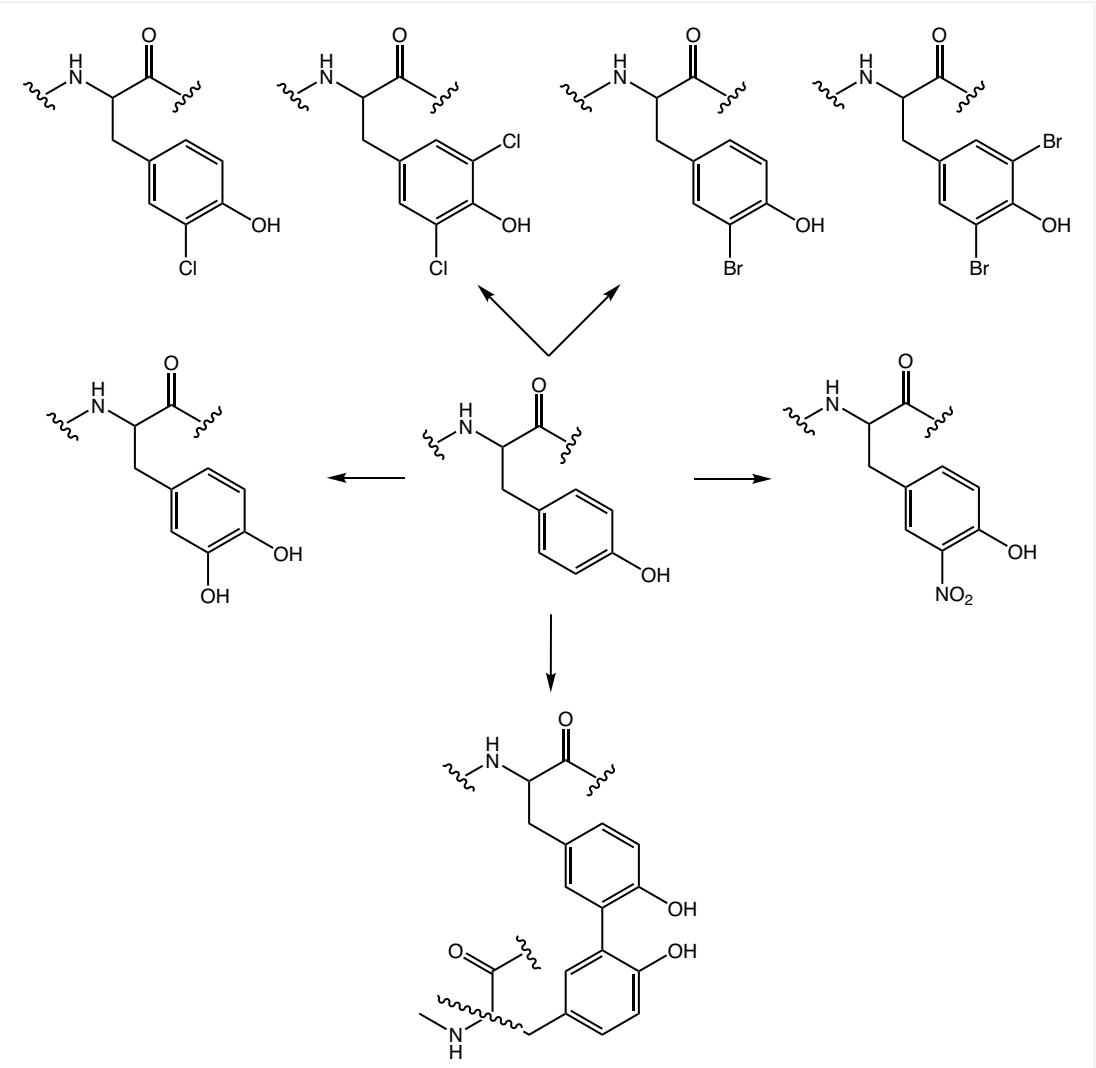


Fig. 10: Examples of oxidized Tyr derivatives.

Introduction
Amine (Dab, Dap, Lys, Orn) Protecting Groups
Indole (Trp) Protecting Groups
Imidazole (His) Protecting Groups
Guanidino (Arg) Protecting Groups
Hydroxyl (Alcohol) (Hyp, Ser, Thr) Protecting Groups
Phenol (Tyr) Protecting Groups
Carboxylic Acid (Asp and Glu) Protecting Groups
Amide (Asn and Gln) Protecting Groups
Thiol (Cys) Protecting Groups
Selenol (Sec) Protecting Groups
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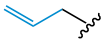
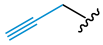
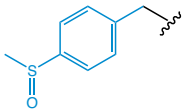
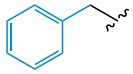
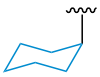
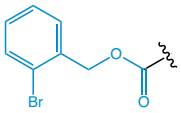
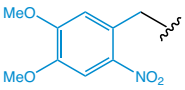
Tab. 6: Protecting groups of Tyr´s phenol functionality and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	*tert*-Butyl (*t*Bu)	35% TFA in DCM	· Standard protecting group in Fmoc strategy	
2	Allyl	$Pd(PPh_3)_4$, scavengers	· Orthogonal to Fmoc and Boc strategy	
3	Propargyl	$[(PhCH_2NEt_3)_2MoS_4]$ in ACN	· Click conjugation	
4	4-(Methylsulfinyl) benzyl (Msib)	M_e3SiCl/Ph_3P	· Orthogonal safety-catch protecting group	
5	Benzyl (Bn, Bzl)	HF, scavengers H_2 cat.	· Removal by HF might lead to benzylation of the aromatic ring	
6	Cyclohexyl	HF TFMSA	· Applied in Boc strategy · Stable towards TFA/DCM (1:1) for 24 h · Used in Fmoc strategy as peptide mimetic at Tyr position.	
7	2-Br-Z		· Standard protecting group in Boc strategy	
8	4,5-Dimethoxy-2-nitrobenzyl (*o*Nv or DMNB)	UV-light (> 350 nm)	· Stable to Fmoc SPPS conditions	

8. Carboxylic Acid (Asp and Glu) Protecting Groups

The carboxylic functions of aspartic acid (Asp) and glutamic acid (Glu) must be equipped with protecting groups as they might be activated during the coupling steps in peptide synthesis, leading to undesirable branched peptides. The choice of a protecting group significantly influences the possible formation of an intramolecular cyclic by-product known as *aspartimide* which can occur during Fmoc deprotection (see *Fig. 11*). This side reaction not only leads to the formation of unwanted mixtures of α- and β-peptides but also induces racemization. It is important to note that glutamic acid (Glu) can also undergo cyclization; however, the formation of a six-membered ring in glutamic acid is kinetically less favored compared to the five-membered ring in aspartic acid.

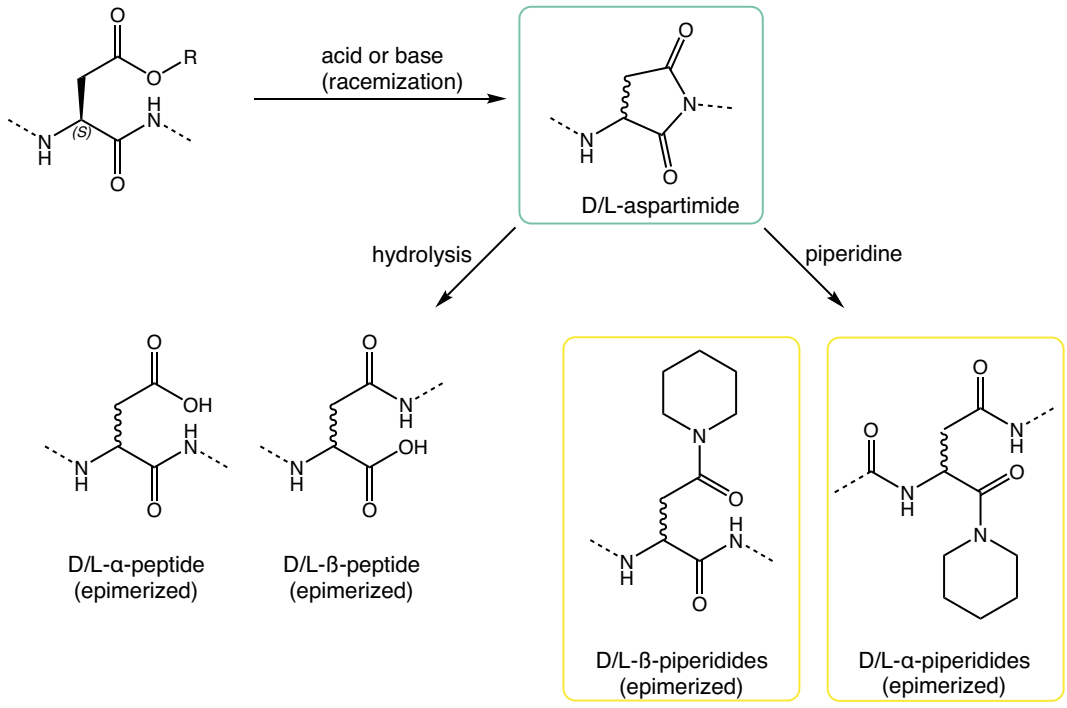


Fig. 11: Aspartimide formation.

For detailed strategies to mitigate aspartimide formation, check out our flyer about aspartimide formation or watch the recording of our online workshop.

Introduction
Amine (Dab, Dap, Lys, Orn) Protecting Groups
Indole (Trp) Protecting Groups
Imidazole (His) Protecting Groups
Guanidino (Arg) Protecting Groups
Hydroxyl (Alcohol) (Hyp, Ser, Thr) Protecting Groups
Phenol (Tyr) Protecting Groups
Carboxylic Acid (Asp and Glu) Protecting Groups
Amide (Asn and Gln) Protecting Groups
Thiol (Cys) Protecting Groups
Selenol (Sec) Protecting Groups
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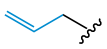
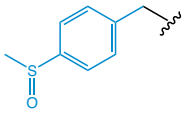
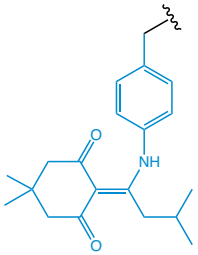
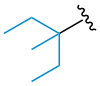
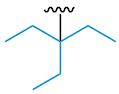
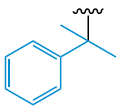
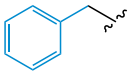
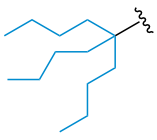
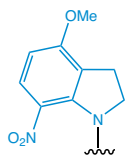
Tab. 7: Protecting groups of the carboxyl group of Asp and Glu and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	*tert*-Butyl ester (O*t*Bu)	90% TFA 4 M HCl	• Standard protecting group in Fmoc strategy • Does not suppress aspartimide formation effectively	
2	Allyl ester (OAll)	$Pd(PPh_3)_4$ + $PhSiH_3$ in DCM	• Limited aspartimide suppression	
3	4-(Methylsulfinyl) benzyl (Msib)	Me_3SiCl/Ph_3P	• Orthogonal safety-catch protecting group • Removal by reduction of the sulfoxide, followed by treatment with TFA	
4	4-[N-{1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl} amino] benzyl ester (ODmab)	2% hydrazine in aq. DMF	• Stable to 20% piperidine	
5	Methylpentyl ester (OMpe)	95% TFA	• Reduction aspartimide formation	
6	Ethylpentyl ester (OEpe)	95% TFA	• Reduction aspartimide formation	
7	2-Phenylisopropyl ester (OPP)	1-2% TFA in DCM	• Selective removal in the presence of *t*Bu-type protecting groups • Applied in the synthesis of cyclic peptides	
8	Benzyl ester (OBn)	TFMSA, HF, H_2 cat., NaOH	• Standard protecting group in Boc strategy • Limited aspartimide suppression	
9	5-n-Butyl-5-nonyl (OBno)	95% TFA	• Reduction aspartimide formation	
10	4-Methoxy-7-nitroindolin-1-yl (MNI)	UV-light (365 nm)	• Reduction of aspartimide formation and pyroglutamate formation	

9. Amide (Asn and Gln) Protecting Groups

Unprotected derivatives of asparagine (Asn) and glutamine (Gln) have been reported to show a poor solubility and therefore slow coupling rates. Apart from that, there are several side reactions which might occur if the side-chain is left unprotected:

- **Deamidation:** Deamidation of asparagine and glutamine occurs under alkaline or high-temperature conditions. This process converts the amide group into a carboxylic acid, producing aspartic acid (from asparagine) or glutamic acid (from glutamine).

- **Hydrolysis:** Under harsh acidic or basic conditions, the amide group of asparagine and glutamine can be hydrolyzed, also converting the amide into a carboxyl group.

- **Cyclization:** The amide side-chain of asparagine is susceptible to intramolecular cyclization, forming a succinimide intermediate that can subsequently undergo hydrolysis to yield either aspartic acid or isoaspartic acid (see *Fig. 12*). This cyclization phenomenon is prevalent under both acidic and basic conditions and can result in racemization or structural rearrangement.

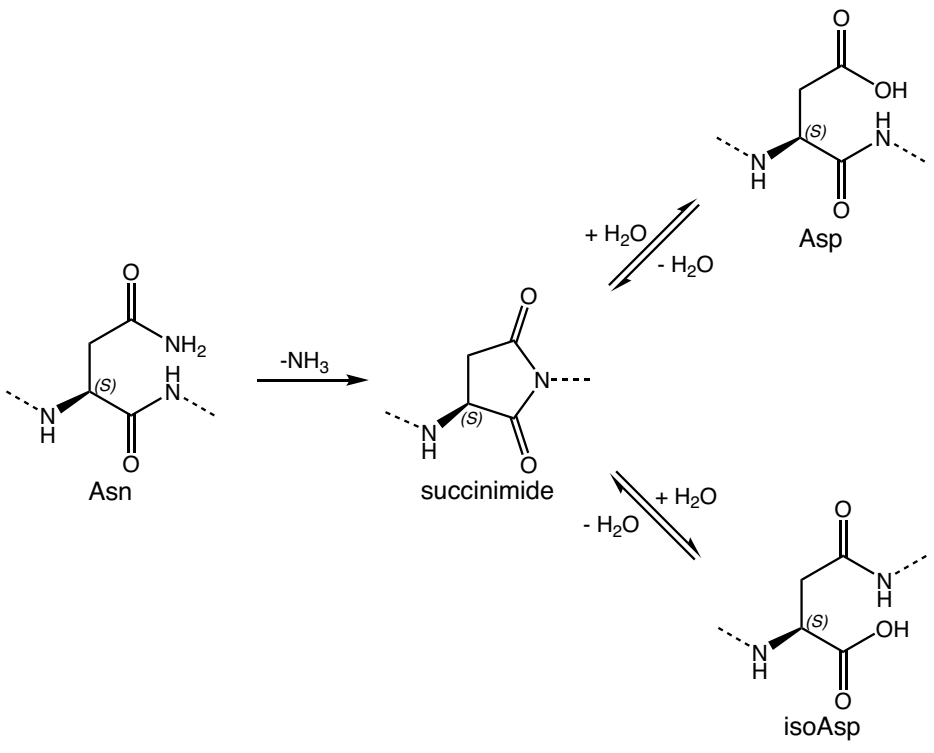


Fig. 12: Succinimide formation.

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The formation of an N-terminal pyroglutamate is a side reaction catalyzed by weak acids and results in truncated peptides (see *Fig. 13*).

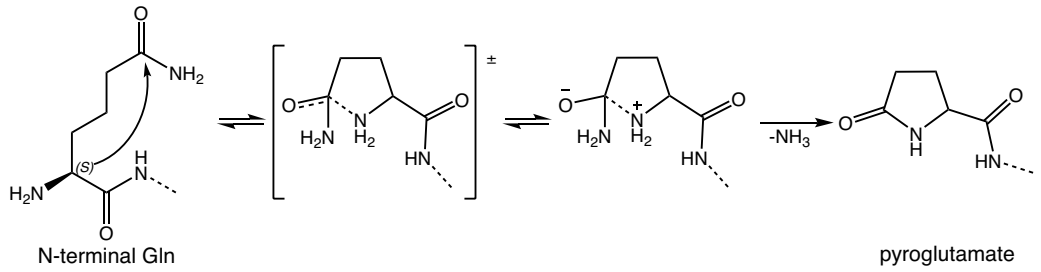


Fig. 13: Pyroglutamate formation.

Coupling protocols involving a base during the activation might lead to a dehydration of asparagine and glutamine (see *Fig. 14*).

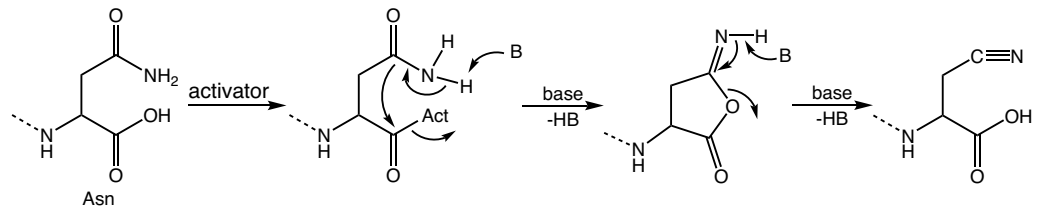
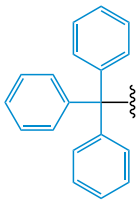
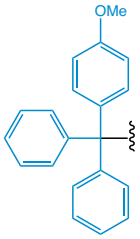
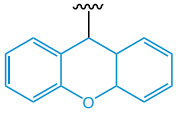


Fig. 14: Dehydration of Asn.

Tab. 8: Protecting groups for amides present in Asn and Gln and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	Trityl (Trt)	95% TFA, H_2O 50% TFA in DCM	· Used in both Boc and Fmoc strategy · Scavengers must be used to avoid Trp alkylation · Prolonged reaction times if the α-NH_2 group is free	
2	4-Methoxytrityl (Mmt)	5% TFA	· More acid-labile alternative to Trt · Recommended for Asn residues with free α-NH_2 group	
3	9H-Xanthen-9-yl (Xan)	90% TFA	· Standard protecting group in Boc strategy but can also be used in Fmoc strategy · Does not require extended reaction times if the α-NH_2 group is free (in contrast to the Trt protecting group)	

10. Thiol (Cys) Protecting Groups

The thiol side-chain of cysteine (Cys) is highly reactive, making it prone to various side reactions such as acylation or alkylation during peptide synthesis. As a result, protection of the thiol group is essential. However, even with the use of protecting groups, the thiol can still undergo certain side reactions, including:

- **Oxidation to disulfides:** The thiol group of cysteine can be oxidized to form disulfide bonds (Cys–S–S–Cys) with another cysteine residue, resulting in cross-linking between peptides or within the same peptide. While disulfide bonds are important for protein folding, uncontrolled oxidation during synthesis may lead to unwanted dimerization or aggregation. Moreover, cysteine thiols can undergo disulfide exchange reactions with existing disulfide bonds, leading to reshuffling of disulfide linkages. This can result in incorrect peptide folding or undesired cross-linking between peptides.

- **Formation of sulfenic, sulfinic, or sulfonic acids:** Under oxidizing conditions, the thiol group can be oxidized to sulfenic acid, sulfinic acid, or sulfonic acid (see *Fig. 15*). These oxidation states progressively modify the cysteine residue and can significantly affect peptide function or structure.

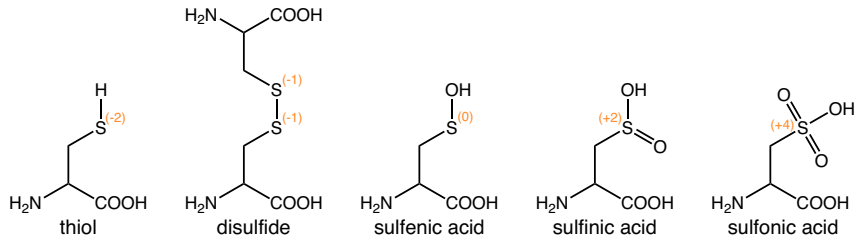


Fig. 15: Oxidation products of Cys.

Check out our brochure about cyclic peptides for different applications of Cys derivatives.

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- **β-elimination:** During Fmoc deprotection, the α-hydrogen of the cysteine side-chain is particularly susceptible to base-induced abstraction (see *Fig. 16*). This deprotonation can lead to the formation of a dehydroalanine intermediate. This side reaction is especially critical in peptides with C-terminal cysteine residues, as nucleophilic attack by piperidine can result in the formation of a piperidinyl-alanine adduct.

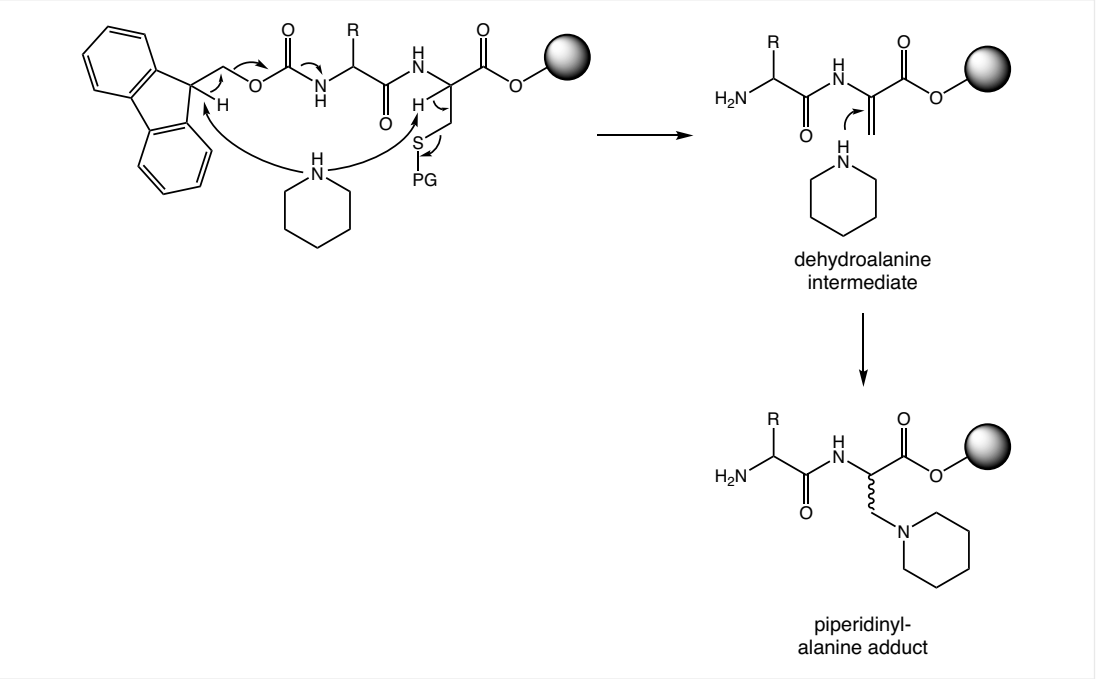


Fig. 16: β-Elimation of a C-terminal Cys followed by nucleophilic attack of piperidine.

- **Racemization:** The cysteine side-chain is highly prone to racemization, irrespective of the specific protecting group used, due to the high acidity of the α-hydrogen. The degree of racemization is influenced by the nature of the thiol protecting group, with susceptibility following the trend: S*t*Bu > Trt > Acm > MeBn > *t*Bu.

- **Thiazolidine formation:** When protective groups on histidine, such as Bom (benzyloxymethyl) or Bum (*tert*-butoxymethyl), are used and release formaldehyde during cleavage, there is a risk of thiazolidine formation with N-terminal cysteine residues (see *Fig. 17*).

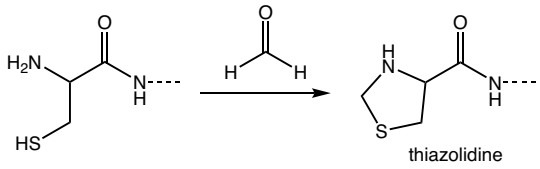
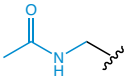
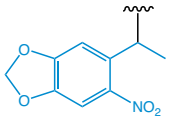
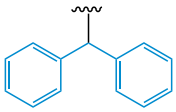
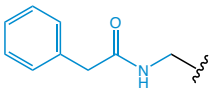
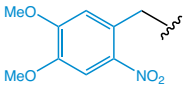
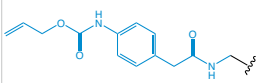
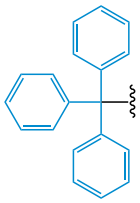
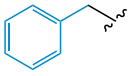


Fig. 17: Thiazolidine formation of N-terminal Cys in the presence of formaldehyde.

- **Reattachment to the resin:** During the removal of the peptide by acidic cleavage carbocations produced from the resin can react with both protected and unprotected cysteine residues, leading to a potential reattachment of the peptide to the resin.

Tab. 9: Protecting groups for the thiol group of Cys and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	Acetamidomethyl (Acm)	I_2 DTNP (2,2'-dithio-bis(5-nitropyridine) Tl(III) Hg(II)	• Stable to standard peptide synthesis conditions • Removed under mild conditions with low impact on racemization • Orthogonal to Trt, *t*Bu, Mbzl, Msbh, and Mmt • Caution must be taken when I_2 is applied for the deprotection as iodination of Trp and Tyr might occur	
2	Methyl-*o*-nitropiperonyl (MDNPE)	UV-Light (< 365 nm)	• Site-specific covalent protein modification possible	
3	Diphenylmethyl (Dpm)	60% TFA	• Used in Fmoc and Boc strategy • Dpm is orthogonal to Trt and Mmt • Applied as Bzl replacement	
4	Phenyl-acetamidomethyl (Phacm)	I_2/AcOH	• Environmentally-friendly alternative to Acm • Similar stability and lability to Acm • Deprotection by *E. coli* penicillin G acylase possible • Orthogonal to Fm, Dnpe, Mbzl • Partially orthogonal to Acm	
5	4,5-Dimethoxy-2-nitrobenzyl (oNv or DMNB)	UV-light (> 350 nm)	• Stable to Fmoc SPPS conditions • Racemization below 0.5%	
6	4-(Allyloxycarbonylamino)phenylacetylaminomethyl (Aapam)	Pd/Bu_3SnH/AcOH	• Used for side-chain modification by solubilizing tags	
7	Trityl (Trt)	25% TFA I_2	• Standard protecting group in Fmoc strategy	
8	Benzyl (Bn, Bzl)	Na/NH_3 HF TMSBr/TFA/ thioanisol	• Requires harsh deprotection conditions	

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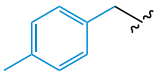
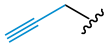
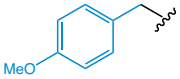
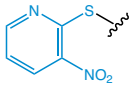
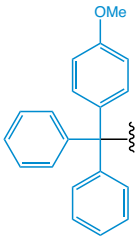
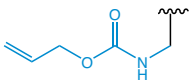
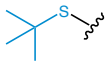
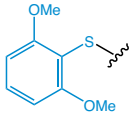
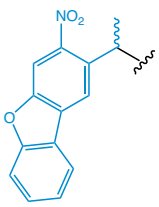
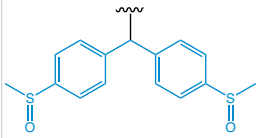
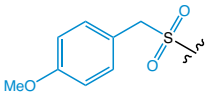
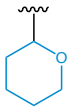
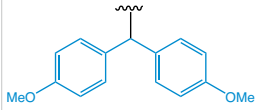
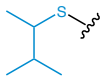
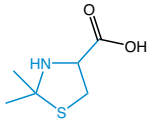
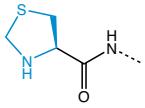
Entry	Protecting group	Removal conditions	Remarks	Structure
9	4-Methylbenzyl (Mbzl)	HF, $MeSiCl_3$ HF/*p*-cresol DMSO/TFA (45 min)	• Similar to Mob but less susceptible to TFA • Is orthogonal to Trt, Acm, *t*Bu, and S*t*Bu	
10	Propargyl	$[(PhCH_2NEt_3)_2MoS_4]$	• Click conjugation	
11	4-Methoxybenzyl (Mob)	TFA/TIS Hg(II) Tl(III)	• Standard protecting group in Boc strategy • Full removal requires very harsh conditions • Also compatible with Fmoc strategy • Cys(Mob) might undergo oxidation	
12	3-Nitro-2-pyridine-sulfenyl (Npys)	aliphatic thiols (MAA or BME) tertiary phosphines in water	• Not compatible with Fmoc SPPS but Boc strategy • Not stable towards TBAF • Applied in solid phase disulfide ligation	
13	4-Methoxytrityl (Mmt)	2% TFA	• Orthogonal to *t*Bu, Dpm, *o*Nv, S*t*Bu, and Acm	
14	Allyloxy-carbonyla-minomethyl (Allocam)	Pd(0)/Bu_3SnH/AcOH	• Replacement of Alloc protecting group for Cys • Good stability againt piperidine • Slightly removed by Boc removal conditions • On resin disulfide formation possible	
15	*tert*-Butylthio (S-*t*Bu)	thiols, phosphines	• Compatible with Boc and Fmoc SPPS • Orthogonal to Trt, Acm, Mbzl, Mob, and *t*Bu	
16	Dimethoxyphenylthio (S-DMP)	20% BME in DMF 5% DTT in DMF DABDT,DIPEA/H_2O/ACN (3:3:94)	• More labile alternative for S*t*Bu • Compatible with Fmoc SPPS • Use more TFA-labile resin if selective removal is desired	
17	Nitrodibenzofuran (NDBF)	UV-light (> 365 nm)	• Two-photon deprotection is also possible at 800 nm • Compatible with Fmoc strategy • Application in living cells possible	

Entry	Protecting group	Removal conditions	Remarks	Structure
18	4,4-Bis(dimethyl-sulfinyl)benzhydryl (Msbh)	NH_4I/DMS/TFA Me_3SiCl/Ph_3P	· Safety-catch protecting group · Stable to Boc and Fmoc strategy	
19	3-(4-Methoxybenzyl) sulfonyl (SO_2Mob)	TFMSA/TFA/H_2O (50:45:5)	· Used to provide cysteine sulfonic acid	
20	Tetrahedropyranyl (THP)	2.5% TFA/TIS/DCM $AgNO_3$	· Selective removal in mild acidic conditions · Better atom economy that Trt · Decreased racemization in comparison with Trt, Dpm or S*t*Bu	
21	*tert*-Butyl (*t*Bu)	TFMSA, Hg(II)	· Regioselective deprotection in presence of Trt, Acm and Mmt · Not removed by [Pd(allyl)Cl]$_2$ therefore in might be used as a orthogonal group to Thz and Acm	
22	4,4'-dimethoxy-benzhydryl (Ddm)	TFA/DCM/TIS/H_2O (10:85:2.5:2.5)	· Provides lowest suppression rates of racemization in Fmoc SPPS	
23	Sec-isoamyl mercaptan 3-methyl-2-butanethiol (SIT)	BME in DMF (1:4), 0.1 M DIPEA 20 eq. DTT, ACN/DIPEA/H_2O (95: 5:5)	· Stable to Fmoc SPPS conditions	
24	Pseudoproline (thiazolidine)	95% TFA and scavengers	· Incorporation of a kink into the peptide backbone · Reduces aggregation during peptide assembly · In combination with Asp: limits aspartimide formation	
25	Thiazolidine (Thz)	H_2O_2, I_2 Pd(II) and MPAA/TCEP or GSH/6 M Gdn · HCl (pH 6.5, 37 °C, 45 min)	· Combined protection of thiol and amino group · Widely used in ligation strategies, but not stable towards NaNO2 treatment in hydrazide ligation · Pd-mediated deprotection was reported *in vivo* to provide an α-oxo aldehyde moiety which can be used for bioconjugation	

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11. Selenol (Sec) Protecting Groups

In general, selenocysteine (Sec) is susceptible to similar side reactions as described for cysteine. However, due to the higher nucleophilicity of the selenol group, these reactions occur with significantly increased reactivity.

- **Oxidation:** The selenol group is easily oxidized to selenenic acid, seleninic acids, or selenonic acid (see *Fig. 18*).

- **Diselenide bond formation:** Selenocysteine can form diselenide bonds (Se–Se) with another Sec residue, similar to disulfide bonds in cysteine, leading to cross-linking or altered peptide structure.

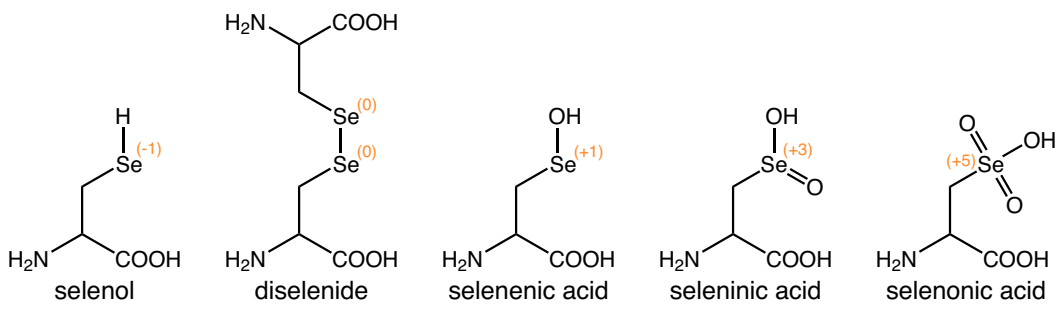
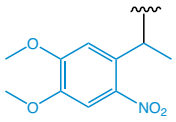
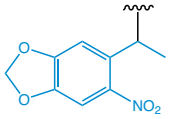
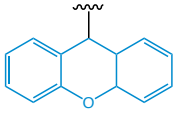
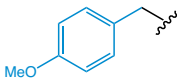
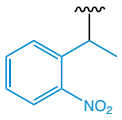
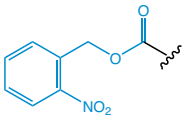


Fig. 18: Oxidation products of Sec.

Tab. 10: Protecting groups for the selenol group of Sec and their typical removal conditions.

Entry	Protecting group	Removal conditions	Remarks	Structure
1	4,5-Dimethoxy-2-nitrobenzyl (DMNB)	UV-light (> 350 nm)	• Stable to Fmoc SPPS conditions	
2	(Methyl-*o*-nitropiperonyl) (MDNPE)	UV-Light (> 365 nm)	• Site-specific covalent protein modification, even in the presence of native cysteine • Incorporated as an unnatural amino acid in response to an amber stop codon	
3	9H-Xanthen-9-yl (Xan)	0.1-0.2% TFA (+ silane or thiol scavengers) 10% TFA + BME	• Compatible with Fmoc SPPS, not with Boc strategy	

Entry	Protecting group	Removal conditions	Remarks	Structure
4	4-Methoxybenzyl (Mob)	95% TFA in H_2O + 0.4 M DTNP 60°C	• Building block for Fmoc SPPS	
5	1-(2-nitrophenyl)ethy (NPE)	UV-light (> 365 nm)	• Incorporated into proteins for site-specific protein modifications	
6	2-Nitrobenzyl (oNB)	UV-light (> 350 nm)	• High one-proton efficiency • Stable to Boc and Fmoc SPPS conditions • Can be cleaved under aqueous conditions	

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In 2001 Iris Biotech GmbH was founded just at the beginning of the Biotech movement and the first remarkable breakthrough of biotech pharma products. Although the biotech field is rather young compared to other industries we believe on long-term business, a good partnership between our business partners and Iris Biotech GmbH and a good reputation. It is our duty as well as our responsibility to maintain and to extend this over the next generations – based on the principles of an honourable and prudent tradesman which based upon the concept of honourable entrepreneurship.

This Code of Conduct has been developed following the "Voluntary Guidelines for Manufacturers of Fine Chemical Intermediates and Active Ingredients" issued by AIME (Agrochemical & Intermediates Manufacturers in Europe) and the requirements of some of our business associates.

Iris Biotech GmbH commits to hold this Code of Conduct and to include and apply its principles in the management system and the company policies.

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Iris Biotech GmbH undertakes business in an ethical manner and acts with integrity. All corruption, extortion and embezzlement are prohibited. We do not pay or accept bribes or participate in other illegal inducements in business or government relationships. We conduct our business in compliance with all applicable anti-trust laws. Employees are encouraged to report concerns or illegal activities in the workplace, without threat of reprisal, intimidation or harassment.

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Iris Biotech GmbH provides a safe and healthy working environment to the employees and protects them from overexposure to chemical and physical hazards. Products are produced, stored and shipped under the guidelines of the relevant chemical and safety legislation. Risks and emergency scenarios are identified and evaluated, and their possible impact is minimized by implementing emergency plans and written procedures. Safety information regarding hazardous materials is available to educate, train and protect workers from hazards. Preventive equipment and facilities maintenance is performed at suitable periods to reduce potential hazards. Employees are regularly trained in health and safety matters and are informed about product properties and risk classification when it is required.

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Iris Biotech GmbH operates in an environmentally responsible and efficient manner, minimizing adverse impacts on the environment. Waste streams are managed to ensure a safe handling, movement, storage, recycling and reuse, before and after being generated. Systems to prevent and mitigate accidental spills and releases to the environment are in place. All required environmental permits and licenses are obtained and their operational and reporting requirements are complied with.

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A quality management system following the Good Distribution Practices (GDP rules) of Active Pharmaceutical Ingredients is established covering all the aspects of the worldwide distribution of products. Regular audits are performed to evaluate the efficiency and fulfilling of the quality system. Process controls to provide reproducible product quality are established. There are preventive maintenance procedures to ensure plant reliability and the lowest risk of failure. Staff is trained periodically about GMP and GDP rules. Procedures are established and installations are designed to avoid cross contamination. Batch and analytical records are kept for inspection and audit purposes for suitable periods according guidelines.

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Research and development staff education is appropriate to their functional activity and they are trained to develop, optimize and scale-up the processes. Intellectual property is respected and know-how protected. Development of manufacturing processes reflects the principles of the Green Chemistry according to the American Chemical Society Green Chemistry Institute. Animal testing is not used unless alternatives are not scientifically valid or accepted by regulators. If animal testing is carried out, animals are treated so that pain and stress are minimized.

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There is no minimum order value. At the time of acceptance of an order Iris Biotech GmbH will either arrange prompt despatch from stock or the manufacture/acquisition of material to satisfy the order. In the event of the latter Iris Biotech GmbH will indicate an estimated delivery date. In addition to all its other rights Iris Biotech GmbH reserves the right to refuse the subsequent cancellation of the order if Iris Biotech GmbH expects to deliver theproduct on or prior to the estimated delivery date. Time shall not be of the essence in respect of delivery of the products. If Iris Biotech GmbH is unable to deliver any products by reason of any circumstances beyond its reasonable control („Force Majeure“) then the period for delivery shall be extended by the time lost due to such Force Majeure. Details of Force Majeure will be forwarded by Iris Biotech GmbH to the buyer as soon as reasonably practicable.

Prices, Quotations and Payments

Prices are subject to change. For the avoidance of doubt, the price advised by Iris Biotech GmbH at the time of the buyer placing the order shall supersede any previous price indications. The buyer must contact the local office of Iris Biotech GmbH before ordering if further information is required. Unless otherwise agreed by the buyer and Iris Biotech GmbH, the price shall be for delivery ex-works. In the event that the buyer requires delivery of the products otherwise than ex-works the buyer should contact the local office of Iris Biotech GmbH in order to detail its requirements. Iris Biotech GmbH shall, at its discretion, arrange the buyer‘s delivery requirements including, without limitation, transit insurance, the mode of transit (Iris Biotech GmbH reserves the right to vary the mode of transit if any regulations or other relevant considerations so require) and any special packaging requirements (including cylinders). For the avoidance of doubt all costs of delivery and packaging in accordance with the buyer‘s requests over and above that of delivery in standard packaging ex-works shall be for the buyer‘s account unless otherwise agreed by both parties. Incoterms 2020 shall apply. Any tax, duty or charge imposed by governmental authority or otherwise and any other applicable taxes, duties or charges shall be for the buyer‘s account. Iris Biotech GmbH may, on request and where possible, provide quotations for multiple packs or bulk quantities, and non-listed items. Irrespective of the type of request or means of response all quotations must be accepted by the buyer without condition and in writing before an order will be accepted by Iris Biotech GmbH. Unless agreed in writing on different terms, quotations are valid for 30 days from the date thereof. Payment terms are net 30 days from invoice date unless otherwise agreed in writing. Iris Biotech GmbH reserves the right to request advance payment at its discretion. For overseas transactions the buyer shall pay all the banking charges of Iris Biotech GmbH. The buyer shall not

be entitled to withhold or set-off payment for the products for any reason whatsoever. Government/ Corporate Visa and MasterCard (and other such credit cards) may be accepted on approved accounts for payment of the products. Personal credit cards are not acceptable. Failure to comply with the terms of payment of Iris Biotech GmbH shall constitute default without reminder. In these circumstances Iris Biotech GmbH may (without prejudice to any other of its rights under these terms) charge interest to accrue on a daily basis at the rate of 2% per month from the date upon which payment falls due to the actual date of payment (such interest shall be paid monthly). If the buyer shall fail to fulfil the payment terms in respect of any invoice of Iris Biotech GmbH Iris Biotech GmbH may demand payment of all outstanding balances from the buyer whether due or not and/or cancel all outstanding orders and/or decline to make further deliveries or provision of services except upon receipt of cash or satisfactory securities. Until payment by the buyer in full of the price and any other monies due to Iris Biotech GmbH in respect of all other products or services supplied or agreed to be supplied by Iris Biotech GmbH to the buyer (including but without limitation any costs of delivery) the property in the products shall remain vested in Iris Biotech GmbH.

Shipping, Packaging and Returns

The buyer shall inspect goods immediately on receipt and inform Iris Biotech GmbH of any shortage or damage within five days. Quality problems must be notified within ten days of receipt. Goods must not be returned without prior written authorisation of Iris Biotech GmbH. Iris Biotech GmbH shall at its sole discretion replace the defective products (or parts thereof) free of charge or refund the price (or proportionate price) to buyer. Opened or damaged containers cannot be returned by the buyer without the written prior agreement of Iris Biotech GmbH. In the case of agreed damaged containers which cannot be so returned, the buyer assumes responsibility for the safe disposal of such containers in accordance with all applicable laws.

Product Quality, Specifications and Technical Information

Products are analysed in the Quality Control laboratories of Iris Biotech GmbH's production partners by methods and procedures which Iris Biotech GmbH considers appropriate. In the event of any dispute concerning reported discrepancies arising from the buyer's analytical results, determined by the buyer's own analytical procedures, Iris Biotech GmbH reserves the right to rely on the results of own analytical methods of Iris Biotech GmbH. Certificates of Analysis or Certificates of Conformity are available at the discretion of Iris Biotech GmbH for bulk orders but not normally for prepack orders. Iris Biotech GmbH reserves the right to make a charge for such certification. Specifications may change and reasonable variation from any value listed should not form the basis of a dispute. Any supply by Iris Biotech GmbH of bespoke or custom product for a buyer shall be to a specification agreed by both parties in writing. Technical information, provided orally, in writing, or by electronic means by or on behalf of Iris Biotech GmbH, including any descriptions, references, illustrations or diagrams in any catalogue or brochure, is provided for guidance purposes only and is subject to change.

Safety

All chemicals should be handled only by competent, suitably trained persons, familiar with laboratory procedures and potential chemical hazards. The burden of safe use of the products of Iris Biotech GmbH vests in the buyer. The buyer assumes all responsibility for warning his employees, and any persons who might reasonably be expected to come into contact with the products, of all risks to person and property in any way connected with the products and for instructing them in their safe handling and use. The buyer also assumes the responsibility for the safe disposal of all products in accordance with all applicable laws.

Uses, Warranties and Liabilities

All products of Iris Biotech GmbH are intended for laboratory research purposes and unless otherwise stated on product labels, in the catalogue and product information sheet of Iris Biotech GmbH or in other literature furnished to the buyer, are not to be used for any other purposes, including but not limited to use as or as components in drugs for human or animal use, medical devices, cosmetics, food additives, household chemicals, agricultural or horticultural products or pesticides. Iris Biotech GmbH offers no warranty regarding the fitness of any product for a particular purpose and shall not be responsible for any loss or damage whatsoever arising there from. No warranty or representation is given by Iris Biotech GmbH that the products do not infringe any letters patent, trademarks, registered designs or other industrial rights. The buyer further warrants to Iris Biotech GmbH that any use of the products in the United States of America shall not result in the products becoming adulterated or misbranded within the meaning of the Federal Food, Drug and Cosmetic Act (or such equivalent legislation in force in the buyer's jurisdiction) and shall not be materials which may not, under sections 404, 505 or 512 of the Act, be introduced into interstate commerce. The buyer acknowledges that, since the products of Iris Biotech GmbH are intended for research purposes, they may not be on the Toxic Substances Control Act 1976 („TSCA") inventory. The buyer warrants that it shall ensure that the products are approved for use under the TSCA (or such other equivalent legislation in force in the buyer's jurisdiction), if applicable. The buyer shall be responsible for complying with any legislation or regulations governing the use of the products and their importation into the country of destination (for the avoidance of doubt to include, without limitation, the TSCA and all its amendments, all EINECS, ELINCS and NONS regulations). If any licence or consent of any government or other authority shall be required for the acquisition, carriage or use of the products by the buyer the buyer shall obtain the same at its own expense and if necessary produce evidence of the same to Iris Biotech GmbH on demand. Failure to do so shall not entitle the buyer to withhold or delay payment. Any additional expenses or charges incurred by Iris Biotech GmbH resulting from such failure shall be for the buyer's account. Save for death or personal injury caused by negligence of Iris Biotech GmbH, sole obligation of Iris Biotech GmbH and buyer's exclusive remedy with respect to the products proved to the satisfaction of Iris Biotech GmbH to be defective or products incorrectly supplied shall be to accept the return of said products to Iris Biotech GmbH for refund of the actual purchase price paid by the buyer (or proportionate part thereof), or replacement of the defective product (or part thereof) with alternative product. Iris Biotech GmbH shall have no liability to the buyer under or arising directly or indirectly out of or otherwise in connection with the supply of products by Iris Biotech GmbH to the buyer and/or their re-sale or use by the buyer or for any product, process or services of the buyer which in any way comprises the product in contract tort (including negligence or breach of statutory duty) or otherwise for pure economic loss, loss of profit, business, reputation, depletion of brand, contracts, revenues or anticipated savings or for any special indirect or consequential damage or loss of any nature except as may otherwise be expressly provided for in these terms. All implied warranties, terms and representations in respect of the products (whether implied by statute or otherwise) are excluded to the fullest extent permitted by law. The buyer shall indemnify Iris Biotech GmbH for and against any and all losses, damages and expenses, including legal fees and other costs of defending any action, that Iris Biotech GmbH may sustain or incur as a result of any act or omission by the buyer, its officers, agents or employees, its successors or assignees, its customers or all other third parties, whether direct or indirect, in connection with the use of any product. For the avoidance of doubt and in the event that Iris Biotech GmbH supplies bespoke or custom product to the buyer's design or specification, this indemnity shall extend to include any claim by a third party that the manufacture of the product for the buyer or the use of the product by the buyer infringes the intellectual property rights of any third party.

General

Iris Biotech GmbH shall be entitled to assign or sub-contract all or any of its rights and obligations hereunder. The buyer shall not be entitled to assign, transfer, sub-contract or otherwise delegate any of its rights or obligations hereunder. Any delay or forbearance by Iris Biotech GmbH in exercising any right or remedy under these terms shall not constitute a waiver of such right or remedy. If any provision of these terms is held by any competent authority to be invalid or unenforceable in whole or in part the validity of the other provisions of these terms and the remainder of the provision in question shall not be affected. These terms shall be governed by German Law and the German Courts shall have exclusive jurisdiction for the hearing of any dispute between the parties save in relation to enforcement where the jurisdiction of the German Courts shall be non-exclusive.

Get in Contact

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Distribution Partners

The list contains the current distributors of Iris Biotech in different regions of the world. The latest list of distribution partners and contact details is available at: *www.iris-biotech.de/distribution-partner*

China:

Chengdu Yoo Technology Co., Ltd.

Japan:

BizCom Japan, Inc.

Shigematsu & Co., Ltd

Cosmo Bio Co., Ltd.

USA & Canada:

Peptide Solutions LLC

India, Bangladesh, Oman, Sri Lanka, United Arab Emirates:

Sumit Biosciences Pvt Ltd.

Empowering Peptide Innovation