ORTHOGONALITY OF PROTECTING GROUPS

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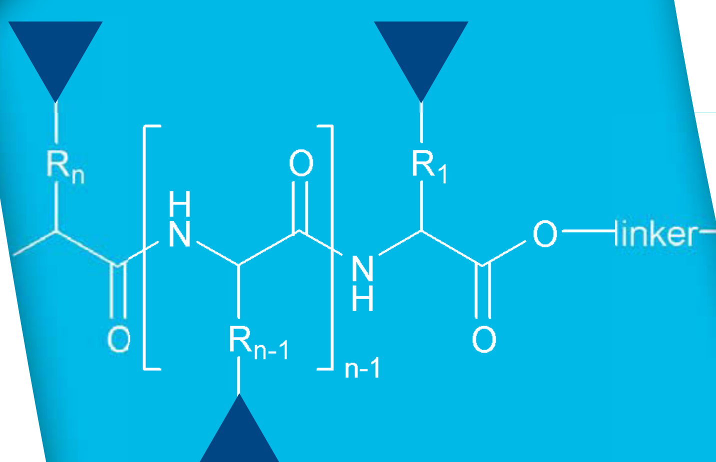
PIONEERING PARTNER FOR PEPTIDES



ORTHOGONALITY OF PROTECTING GROUPS

The term "orthogonal" was coined by Barany and Merrifield in 1977 to designate "classes of protecting groups which are removed by differing chemical mechanisms. Therefore they can be removed in any order and in the presence of the other classes. Orthogonal protection schemes allow milder overall reaction conditions as well as the synthesis of partially protected peptides" (G. Barany and R.B. Merrifield). The combination Fmoc/tBu is truly orthogonal whereas, under the conditions of Boc-SPPS, Boc/Bzl is not, as both protecting groups are cleaved by acids. As Boc can be selectively removed in the presence of Z/Bzl, the combination has been termed "quasi-orthogonal".

Orthogonal Protection

Fmoc/tBu probably is the most popular "orthogonal" combination of protecting groups. According to the definition of this term by Barany and Merrifield [1], this combination is truly orthogonal, Fmoc can be removed selectively in the presence of tBu and the latter is split off under conditions leaving the amino-protecting group intact. On the other hand, the pairs Boc/OPp or Fmoc/ivDde are merely quasi-orthogonal because both groups are acid-labile or cleaved by bases, respectively. OPp can be removed selectively in the presence of Boc/tBu by "weak acid", and Fmoc by piperidine/DMF with preservation of ivDde protection, whereas the order of deprotection cannot be reverted.

Modified peptides may be sensitive towards both bases and acids, so it should be kept in mind that Aloc/OAll and Z/Bzl may be removed under neutral conditions.

Thus, when conceiving the synthesis of more complex or modified peptides (e.g. side-chain cyclized peptides), the tactics of synthesis, i.e. the choice of side-chain

UNUSUAL AMINO ACIDS

In addition to our comprehensive choice of derivatives of all stereoisomers of the 20 canonical amino acids we offer an extensive range of unusual amino acids, which can serve as building blocks for the synthesis of peptide analogs and for use in structure-activity relationship (SAR) studies. Furthermore, these compounds are valuable chiral educts for organic synthesis.

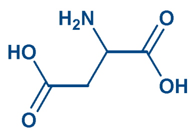
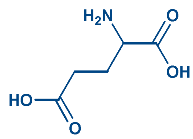
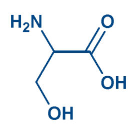
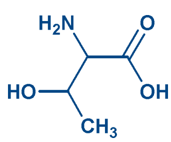
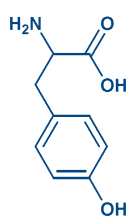
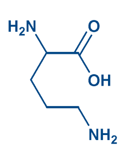
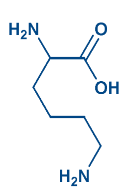
protecting groups and type of resin, has to be considered thoroughly.
For on-resin modification Aloc/OAll, Dde and ivDde/Dmab, Mtt and Mmt/OPp may be selectively cleaved from peptides bound to Wang resin. Aloc can be removed on-resin in the presence of Mmt and vice versa during Fmoc-SPPS. The combination of orthogonal protecting groups allows the synthesis of very complex peptides, impressive examples have been published e.g. by Hirschmann et al. [2] or Royo et al. [3].
Orthogonal protection schemes can also be devised for Boc-SPPS, e.g. Boc/Fm, Boc/allyl. An additional "dimension" of orthogonality, the hydrogenolysis of benzyl-derived protecting groups, is available in solution-phase peptide synthesis. This deblocking method is only rarely used in SPPS. Enzymatically cleavable protecting groups as phenylacetyl have also been employed for peptide modifications, mostly in aqueous solution.
The risk of aspartimide formation has to be kept in mind when considering a postsynthetic modification of the β-carboxy moiety of Asp. This notorious side reaction is facilitated by unhindered β-carboxy protecting groups such as OBzl, OAll or ODmab. The selectively cleavable OPp is nearly as effective as OtBu in suppressing base-catalyzed aspartimide formation [4].
The sterically demanding OMpe group has been developed as an even more efficient tool for preventing this side reaction, but it can't be removed selectively under the conditions of standard Fmoc-SPPS [5].
Even though Glu tends far less than Asp to base-catalyzed cyclization, unhindered γ-carboxyl protective groups as allyl promote the side reaction.
Cysteine requires special consideration when conceiving a synthetic strategy based on multidimensional orthogonal protection, please see our brochure "Cysteine Derivatives" for more details.

References

[1] G.Barany and R.B.Merrifield
J. Am. Chem. Soc. 99, 7363 (1977)
[2] R. Hirschmann et al.
Tetrahedron 54, 7179 (1998).
[3] M.Royo et al.
Tetrahedron Lett. 43, 2029 (2002)
[4] J.L. Lauer et al.
Lett. Peptide Sci. 1, 197 (1994)
M. Mergler et al.
J. Pept. Sci. 9, 36, (2003)
M. Mergler et al.
J. Pept. Sci. 9, 518 (2003).
[5] A. Karlström and A.Undén,
Tetrahedron Lett. 37, 4243 (1996)

Orthogonality "Dimension"	Examples for feasible combinations of protecting groups
2nd	Fmoc/tBu
3rd	Fmoc/tBu/allyl
3rd	Fmoc/tBu/Mmt[1]
3rd	Fmoc/tBu/Dde[1]
4th	Fmoc/tBu/Mmt/allyl
4th	Fmoc/tBu/allyl/Dde
5th	Fmoc/tBu/allyl/Dde/Mmt
5th	Fmoc/tBu/allyl/Dde/Bzl[1,2]
5th	Fmoc/tBu/Mmt/allyl/Dde
6th	Fmoc/tBu/Mmt/allyl/Dde/Bzl

[1] partly quasi-orthogonal
[2] Bzl: hydrogenolytic cleavage

	Protection Type	tBu and Others		Different	
Functionality	Typical Cleavage Conditions	95% aq TFA/ Scavengers		1% TFA/DCM	
COOH		Fmoc-Asp(OtBu)-OH[†,‡,*,x] Fmoc-Asp(OMpe)-OH[*] Fmoc-Asp(OtBu)-OPfp[*] Fmoc-Asp(OtBu)-OSu Fmoc-Asp-OtBu[*] Fmoc-N-Me-Asp(OtBu)-OH	B-1065 B-3560 B-1110 B-1075 B-1735 B-2195	Fmoc-Asp(2-phenylisopropyl ester)-OH[*] Fmoc-Asp-ODmb[*]	B-2475 B-2175
COOH		Fmoc-Glu(OtBu)-OH · H_2O[†,‡,*,x] Fmoc-Glu(OtBu)-OPfp[*] Fmoc-Glu(OtBu)-OSu Fmoc-Glu(OSu)-OtBu Fmoc-N-Me-Glu(OtBu)-OH	B-1315 B-1130 B-1325 B-2310 B-2395	Fmoc-Glu(2-phenylisopropyl ester)-OH	B-2500
OH		Fmoc-Ser(tBu)-OH[†,‡,*,x] Fmoc-Ser(tBu)-OPfp Fmoc-Ser(tBu)-ODhbt Fmoc-N-Me-Ser(tBu)-OH Fmoc-Ser(BSi)-OH[*] Fmoc-Ser(PO(OBzl)OH)-OH[*]	B-1235 B-1180 B-1640 B-3400 B-1225 B-3455	Fmoc-Ser(Trt)-OH	B-2550
OH		Fmoc-Thr(tBu)-OH[†,‡,*,x] Fmoc-Thr(tBu)-OPfp Fmoc-Thr(tBu)-ODhbt Fmoc-allo-Thr(tBu)-OH[*] Fmoc-N-Me-Thr(tBu)-OH Fmoc-Thr(PO(OBzl)OH)-OH[*]	B-1245 B-1185 B-1635 B-1815 B-3420 B-3460	Fmoc-Thr(Trt)-OH	B-2545
OH		Fmoc-Tyr(tBu)-OH[†,‡,*,x] Fmoc-Tyr(tBu)-OPfp Fmoc-Tyr(PO_3(MDPSE)$_2$)-OH Fmoc-Tyr(PO_3Me_2)-OH Fmoc-Tyr(PO(OBzl)OH)-OH[*] Fmoc-Tyr(malonyl-di-OtBu)-OH Fmoc-Tyr(SO_3)-OH sodium salt Fmoc-Tyr(SO_2(ONeopentyl))-OH	B-1255 B-1195 B-2910 B-1990 B-3565 B-2825 B-2765 B-4230		
NH_2		Fmoc-Orn(Boc)-OH[‡,*] Fmoc-Orn(Boc)-OPfp Boc-Orn(Fmoc)-OH[*]	B-1090 B-2155 A-3325		
NH_2		Fmoc-Lys(Boc)-OH[†,‡,*,x] Fmoc-Lys(Boc)-OPfp Boc-Lys(Fmoc)-OH[*] Fmoc-Lys(Boc)(Me)-OH Fmoc-Lys(Boc)(isopropyl)-OH Fmoc-Lys(retro-Abz-Boc)-OH Fmoc-Lys(N-Me-Abz-Boc)-OH Fmoc-N-Me-Lys(Boc)-OH	B-1080 B-1155 A-1610 B-3575 B-2455 B-3180 B-2515 B-3685	Fmoc-Lys(Adpoc)-OH Fmoc-Lys(Mtt)-OH[†,‡,*,x] Fmoc-Lys(4-methoxytrityl)-OH Fmoc-Lys(4-methoxytrityl)-OPfp	B-2520 B-2535 B-3215 B-4470

[†] also available linked to SASRIN resin [‡] also available linked to Wang resin [x] H-derivative linked to 2-Chlorotrityl-resin also available
[*] D-enantiomer also available

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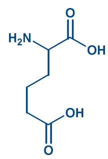
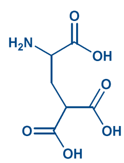
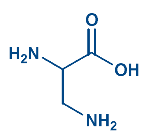
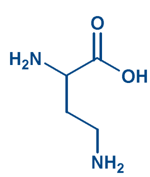
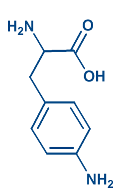
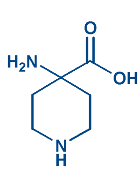
Allyl		Dde and Analogs		Bzl, Analogs and Others	
$Pd(PPh_3)_4/PhSiH_3$		2% $N_2H_4 \cdot H_2O$/DMF[§]		Catalytic Hydrogenation[§§]	
Fmoc-Asp(OAll)-OH	B-2325	Fmoc-Asp(ODmab)-OH	B-3240	Fmoc-Asp(OBzl)-OH*	B-1060
Fmoc-Asp-OAll	B-2715			Fmoc-Asp(OBzl)-OPfp	B-1760
				Fmoc-Asp-OBzl	B-2780
Fmoc-Glu(OAll)-OH*	B-3255	Fmoc-Glu(ODmab)-OH	B-3010	Fmoc-Glu(OBzl)-OH*	B-1310
Fmoc-Glu-OAll	B-2720	Fmoc-Glu-ODmab	B-3005		
				Fmoc-Ser(Bzl)-OH*	B-1200
				Fmoc-Thr(Bzl)-OH*	B-1210
				Fmoc-Tyr(Bzl)-OH†	B-1215
				Fmoc-Tyr(2-bromo-Z)-OH	B-2795
				Fmoc-Tyr(2,6-dichloro-Bzl)-OH	B-1280
Fmoc-Orn(Aloc)-OH*	B-2890	Fmoc-Orn(Dde)-OH	B-3185	Z-Orn(Fmoc)-OH*	C-3325
		Fmoc-Orn(ivDde)-OH	B-4470		
Fmoc-Lys(Aloc)-OH*	B-2240	Fmoc-Lys(Dde)-OH	B-3015	Fmoc-Lys(Z)-OH*	B-1270
		Fmoc-Lys(ivDde)-OH	B-3515	Fmoc-Lys(2-chloro-Z)-OH	B-2790
		Fmoc-Lys(Nde)-OH	B-3380	Z-Lys(Fmoc)-OH*	C-4125
		Dde-Lys(Fmoc)-OH	E-3385		

§ Fmoc is not stable under these cleavage conditions. Dde and analogs may be cleaved selectively in the presence of the other protecting groups listed here §§ Fmoc may not be fully stable in some cases towards hydrogenation

Additional Orthogonally Protected Fmoc Amino Acid Derivatives offered by Bachem				
Aad		α-Aminoadipic Acid	Fmoc-Aad(OtBu)-OH	B-2440
Gla		γ-Carboxy-glutamic Acid	Fmoc-γ-carboxy-Glu(OtBu)$_2$-OH*	B-1265
Dap		α,β-Diaminopropionic Acid	Fmoc-Dap(Adpoc)-OH Fmoc-Dap(Aloc)-OH Fmoc-Dap(Boc)-OH* Fmoc-Dap(ivDde)-OH Boc-Dap(Fmoc)-OH* Z-Dap(Fmoc)-OH*	B-2865 B-2845 B-2380 B-3885 A-3580 C-4200
Dab		α,γ-Diaminobutyric Acid	Fmoc-Dab(Adpoc)-OH Fmoc-Dab(Aloc)-OH Fmoc-Dab(Boc)-OH* Fmoc-Dab(ivDde)-OH Fmoc-Dab(Z)-OH Boc-Dab(Fmoc)-OH	B-2860 B-2850 B-1800 B-4065 B-3250 A-3520
Aph		4-Aminophenylalanine	Fmoc-p-amino-Phe(Boc)-OH* Boc-p-amino-Phe(Fmoc)-OH*	B-1995 A-3975
4-Pip		4-Aminopiperidine-4-carboxylic acid	1-Boc-4-(Fmoc-amino)-piperidine-4-carboxylic acid	B-3115
Various		p-Carboxyphenylalanine 4-Thiahomolysine N-2-Aminoethylglycine β-Piperazinylalanine	Fmoc-p-carboxy-Phe(OtBu)-OH Fmoc-Cys(3-(Boc-amino)-propyl)-OH Fmoc-(N-β-Boc-aminoethyl)-Gly-OH Fmoc-β-(1-piperazinyl)-Ala(Boc)-OH	B-3070 B-3120 B-3285 B-3725

* D-enantiomer also available

Abbreviations

Abz	2-Aminobenzoyl (Anthraniloyl)
Adpoc	1-(1'-Adamantyl)-1-methyl-ethoxycarbonyl
Aloc	Allyloxycarbonyl
Boc	t-Butyloxycarbonyl
Bsi	(or TBDMS) t-Butyldimethylsilyl
Bzl	Benzyl
Dde	1-(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl
Fm	9-Fluorenylmethyl
Fmoc	9-Fluorenylmethyloxycarbonyl
ivDde	1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl
MDPSE	2-(Methyl-diphenyl-silyl)ethyl
Me	Methyl
Mmt	4-Methoxytrityl
Mtt	4-Methyltrityl
Nde	1-(4-Nitro-1,3-dioxoindan-2-ylidene)ethyl
OAll	Allyl ester
OBzl	Benzyl ester
ODhbt	3,4-Dihydro-4-oxo-1,2,3-benzotriazine-3yl ester
ODmab	4-(N-[1(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3-methyl-butyl]amino)benzyl ester
ODmb	2,4-Dimethoxybenzyl ester
OMpe	3-Methyl-pent-3-yl ester
OPfp	Pentafluorophenyl ester
OPp	2-Phenylisopropyl ester
OSu	N-Hydroxysuccinimide ester
OtBu	t-Butyl ester
Ph	Phenyl
tBu	t-Butyl
Trt	Trityl
Z	Benzyloxycarbonyl

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