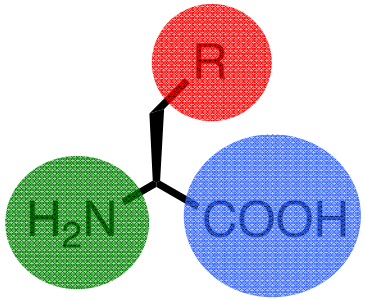
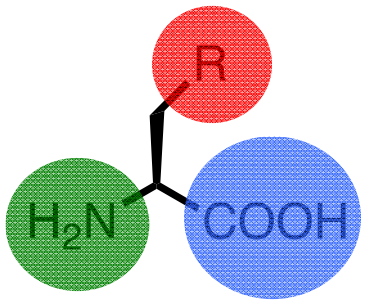
Protecting Groups (PG)



General Considerations

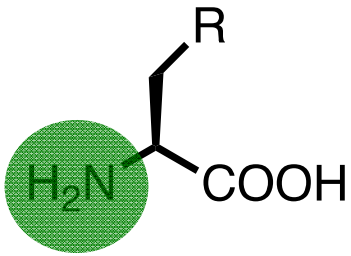
- Avoid undesired side reaction
- PGs have to be
  - Easily introduced and safely removed
  - Stable in reaction conditions
  - Orthogonal
- Which groups need protection?



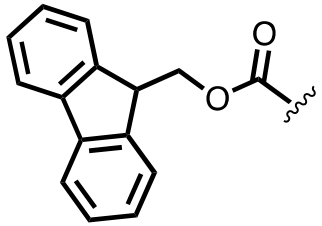
If R contains NH_2, OH, SH, COOH or other reactive functionalities

Review: Albericio et al., *Chem. Rev.*, **2009**, *109*, 2455

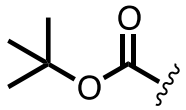
α-Amine PGs



Most common



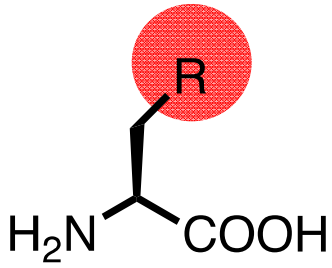
Fmoc
9-Fluorenylmethoxycarbonyl



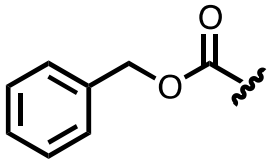
Boc
tert-Butyloxycarbonyl

Introduction	Fmoc-Cl	Boc_2O
Removal	Piperidine	TFA
Stable	Acidic conditions, Hydrogenation	Basic conditions, Hydrogenation
Orthogonal	Boc, Z, Trt, Alloc	Fmoc, Z, Trt, Alloc

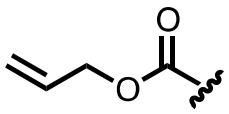
Amine PGs



Amino Acids: Lysine



Cbz, Z
Benzyloxycarbonyl

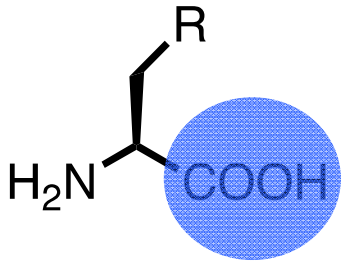


Alloc
Allyloxycarbonyl

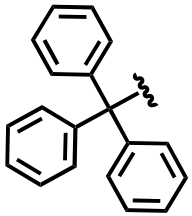
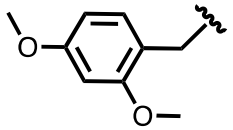
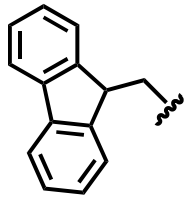
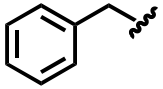
Introduction	Cbz_2O, Cbz-Cl	$Alloc_2O$, Alloc-Cl
Removal	H_2	$Pd(PPh_3)$, $PhSiH_3$
Stable	Basic and Acidic conditions	Basic and Acidic conditions
Orthogonal	Boc, Fmoc, Trt	Boc, Fmoc, Trt

Other protecting group: **Boc**

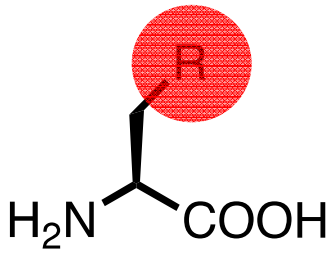
Carboxylic acid PGs



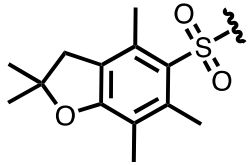
For α-carboxylic acids, Aspartic and Glutamic Acid

	 **^{t}Bu** *tert*-Butyl	 **Trt** Trityl	 **Dmb** 2,4-Dimethoxybenzyl	 **Fm** 9-Fluorenylmethyl	 **Bn** Benzyl
Introduction	Isobutene	Trt-Cl	Dmb-OH, Dmb-Cl	Fm-OH	Bn-Cl, Bn_2O
Removal	90% TFA	1% TFA in CH_2Cl_2	1% TFA in CH_2Cl_2	20% Piperidine	TFMSA, HF, H_2, NaOH
Stable	Basic conditions, Hydrogenation	Basic conditions, Hydrogenation	Basic conditions, Hydrogenation	Acidic Conditions, Hydrogenation	Basic and Acidic Conditions
Orthogonal	Fmoc, Z, Trt, Alloc	Fmoc, Alloc	Fmoc, Alloc	Boc, Trt, Alloc	Boc, Fmoc, Trt, Alloc

Guanidinium PGs



Amino Acids: Arginine



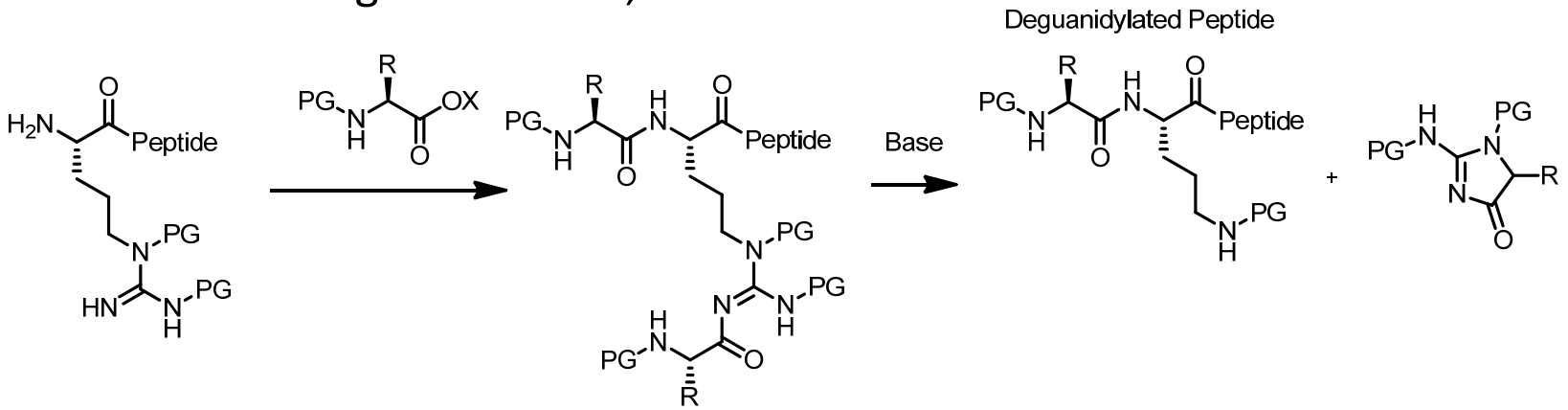
Pbf
2,2,4,6,7-Pentamethyl-
2,3-dihydrobenzofuran-5-sulfonyl

Introduction	Pbf-Cl
Removal	90% TFA
Stable	Basic conditions, Hydrogenation
Orthogonal	Fmoc, Trt, Alloc

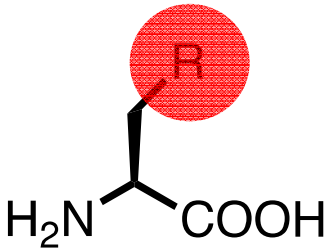
Protect one or two nitrogen atoms

Other protecting group: **Boc**

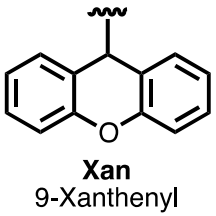
Side reactions: deguanidilation, lactamization



Amide PGs

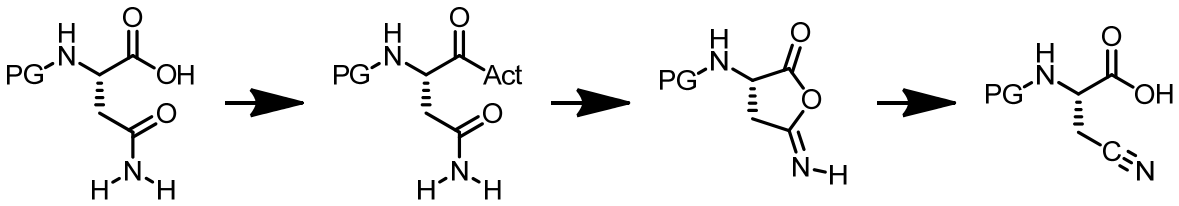


Amino Acids: Asparagine and Glutamine

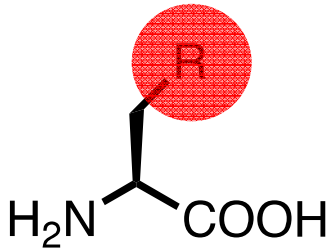


Introduction	Xan-OH
Removal	90% TFA, scavengers
Stable	Basic conditions, Hydrogenation
Orthogonal	Fmoc, Trt, Alloc

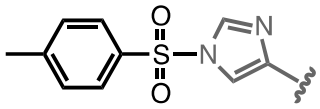
- Other protecting group: **Trt**
- Often used without protection
- Prone to dehydrogenation under basic conditions



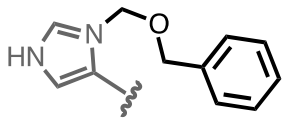
Imidazole PGs



Amino Acids: Histidine

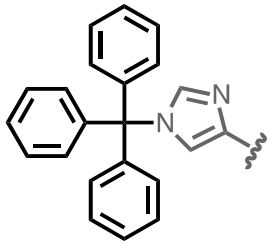


Tos
Tosyl



Bom
Benzyloxymethyl

Introduction	Ts-OH	Bom-Cl
Removal	HF	HF, TFMSA-TFA
Stable	Acidic conditions	Basic conditions
Orthogonal	Boc, Trt	Boc, Fmoc, Trt

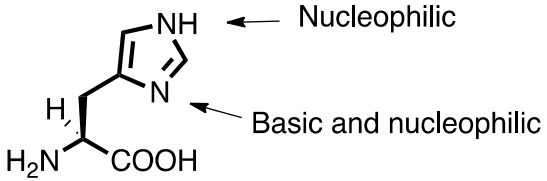


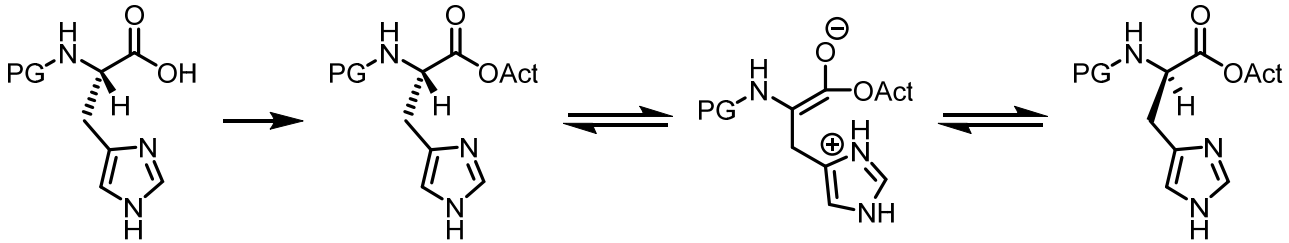
Trt

Other protecting group: **Trt, Boc**

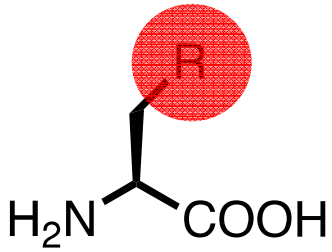
Protection of N^{τ} decreases basicity of N^{π}

Prone to racemization: N^{π} abstracts H^{α}

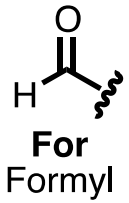




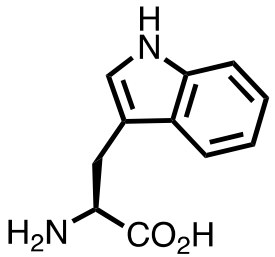
Indole PGs



Amino Acids: Tryptophan

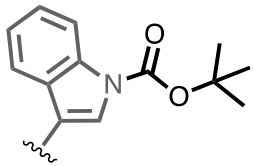


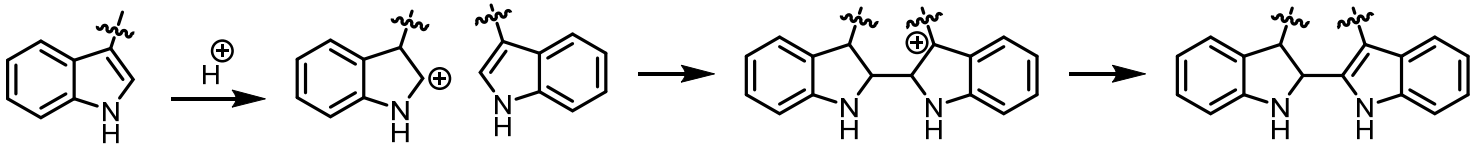
Introduction	Paraformaldehyde
Removal	HF, Piperidine
Stable	Acidic conditions
Orthogonal	Boc



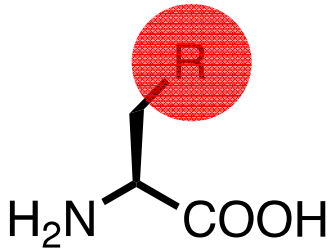
Other protecting group: **Boc**

Side reaction: Dimerization

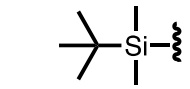




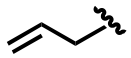
Hydroxyl PGs



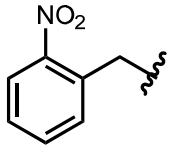
Amino Acids: Serine, Threonine, Hydroxyproline, Tyrosine



TBDMS
tert-Butyldimethylsilyl



Al
Allyl

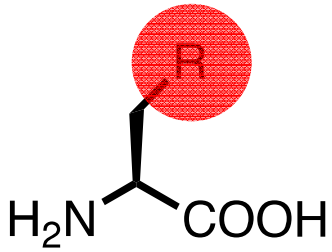


ONB
o-Nitrobenzyl
(also **PNB**)

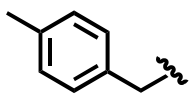
Introduction	TBDMS-Cl	Allyl	ONB-Br
Removal	TBAF, 35% TFA	$Pd(PPh_3)_4$, scavengers	Photolytic cleavage (320 nm)
Stable	Basic conditions	Basic and Acidic Conditions	Acidic and mild basic conditions
Orthogonal	Fmoc	Boc, Fmoc, Z	Fmoc, Boc

Other protecting groups: **Bn** and **^{t}Bu**

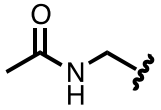
Thiol PGs



Amino Acids: Cysteine



Meb
p-Methylbenzyl



Acm
Acetamidomethyl

Introduction	Meb-Br	Acm-OH
Removal	HF, $MeSiCl_3$	I_2, DTNP, Tl(III), Hg(II),
Stable	Basic conditions	Basic and Acidic conditions
Orthogonal	Boc, Fmoc, Trt, Alloc	Boc, Fmoc, Alloc

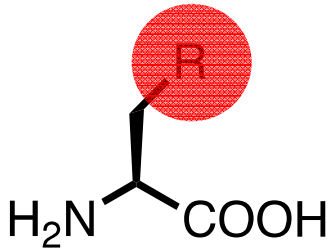
Other protecting group: **Trt**

Protected thiols can still undergo several side reaction

Ex: β-Elimination, reaction with carbocations, ….

Scavengers are necessary during deprotection (TIPS, p-anisole, …)

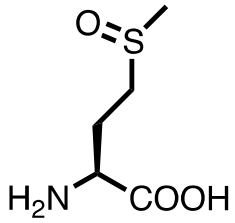
Thioether PG



Amino Acids: Methionine

In Fmoc-strategy SPPS

Used unprotected but thioanisole or ethylmethylsulfide added during cleavage and general deprotection to avoid oxidation

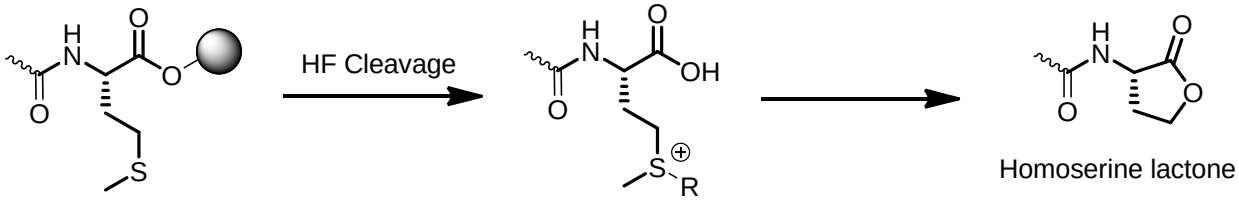


In Boc-strategy SPPS

Met is directly coupled as Met sulfoxide and reduced at the end of the synthesis

Reduction: HF + scavengers, N-Methylmercaptoacetamide

Side reaction: S-alkylation, oxidation, lactonization



Fmoc-Strategy SPPS

Fmoc: αNH

Boc: Lysine, Tryptophan, Histidine

Pbf: Arginine

Trt: Cysteine, Aspartic acid, Glutamic acid

Acm: Cysteine

tBu: Serine, Threonine, Hydroxyproline, Tyrosine, Aspartic acid, Glutamic acid