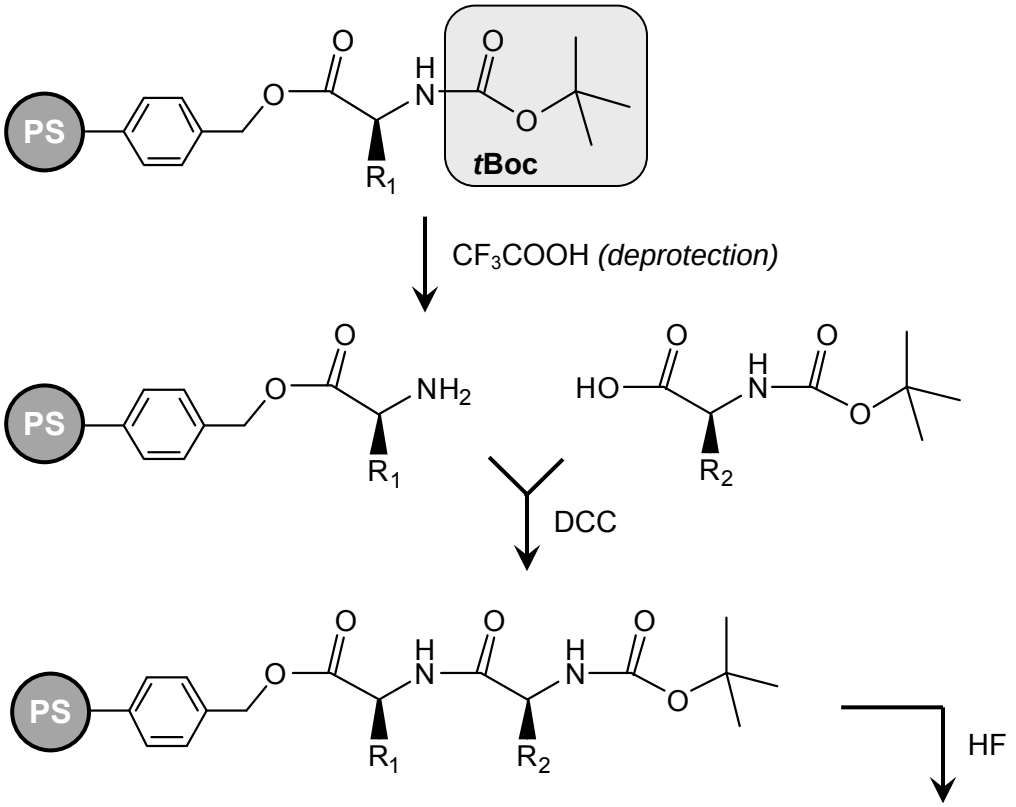
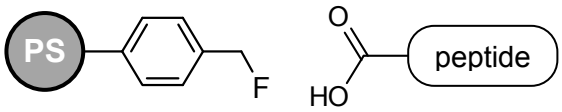
Chemistry 2302

Workshop 24
Fmoc Chemistry in Peptide Synthesis

In class, we discussed how *tert*-butoxycarbonyl (*t*Boc) protected amino acids can be used in the synthesis of peptides on polystyrene supports. Once a *t*Boc-protected amino acid has been coupled to a support-bound amine, removal of the *t*Boc protecting group allows subsequent coupling reactions to occur.

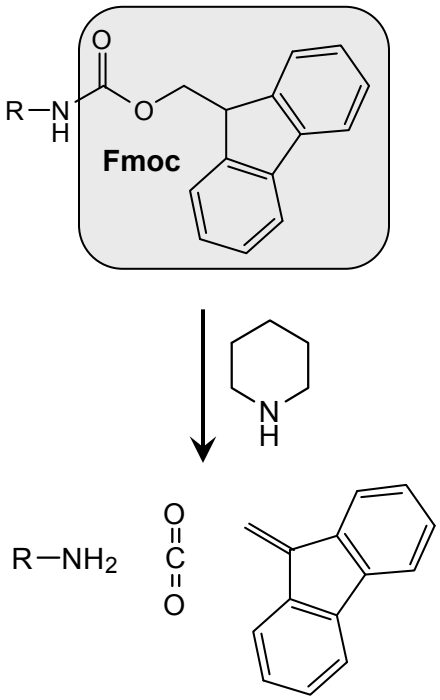


This overall scheme works because the benzyl ether that connects the peptide to the solid support is stable in CF_3COOH, but can be cleaved with an even stronger acid than CF_3COOH—such as hydrofluoric acid (HF).

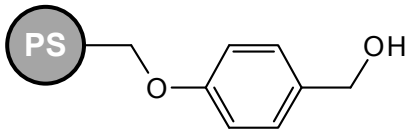


1. Draw a mechanism for the last step above—cleavage of the benzyl ether linker in HF. Keep in mind that HF is a very strong acid, but F^- is a terrible nucleophile, so S_N2 will not occur here.

HF is extremely toxic, and as a result peptide synthesis laboratories don't frequently use the tBoc protecting group. Instead, many current syntheses use the fluorenylmethoxycarbonyl (Fmoc) protecting group, which can be deprotected in a mild base like piperidine. As a result, these labs can use a solid-phase linker that is cleaved more easily by a milder acid.



2. Design a solid-phase synthesis of the tripeptide Gly-Ala-Leu, using Fmoc-protected amino acids and Wang resin (a polystyrene support with a linker that is cleaved in CF_3COOH).



Wang resin