Peptide Syntheses

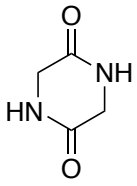
from chapter(s) _____ in the recommended text

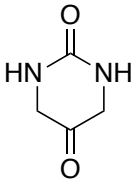
A. Introduction

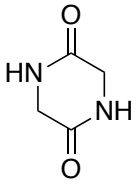
do not
acid

H-Met-Phe-OH H-Met-Met-OH H-Phe-Phe-OH H-Phe-Met-OH

dipeptide *dipeptide* *dipeptide* *dipeptide*







diketopiperazine *symmetrical diketopiperazine* *unsymmetrical diketopiperazine*

would also
impractical synthesis
N- protect one of the fragments and *C-* protect the other.

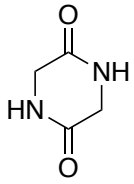
Reactions Of Unprotected Amino Acids

Carboxylic acids *do not* combine with amines
carboxylic acids to *acid* chlorides,

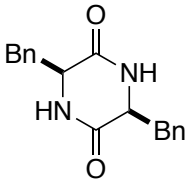
H-Met-Phe-OH H-Met-Met-OH H-Phe-Phe-OH H-Phe-Met-OH

dipeptide *dipeptide* *dipeptide* *dipeptide*

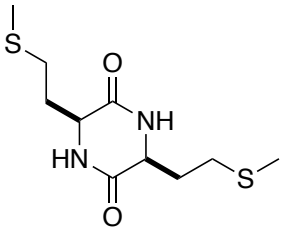
There are also three possible cyclic by-products, *diketopiperazines*, in the reaction above; show these:



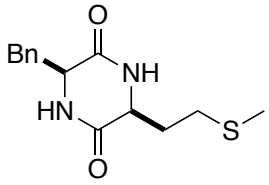
diketopiperazine



symmetrical



symmetrical

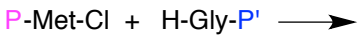


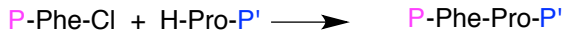
unsymmetrical

Polymeric materials *would* also be produced in this reaction.
Overall, this route would be a(n) *impractical*

To solve this problem it is necessary to *N*-protect one of the fragments and *C*-protect the other.

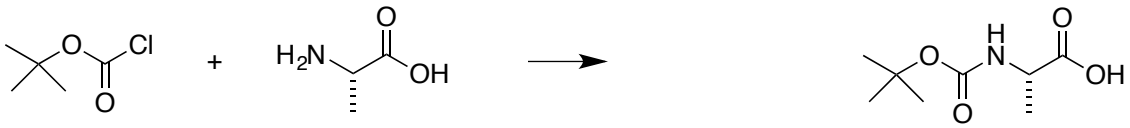
Reactions Of Protected Amino Acids

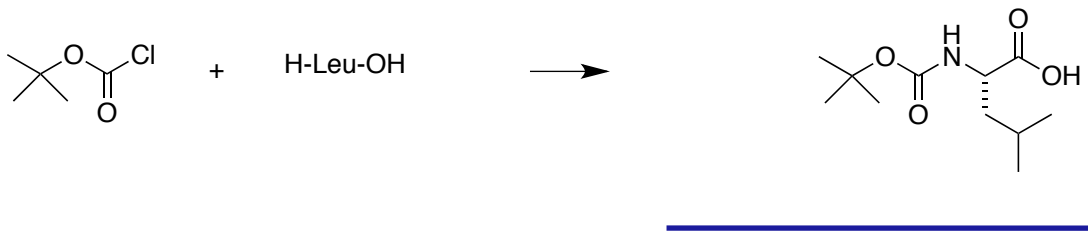




Illustrative Protection: BOC/^{t}Bu

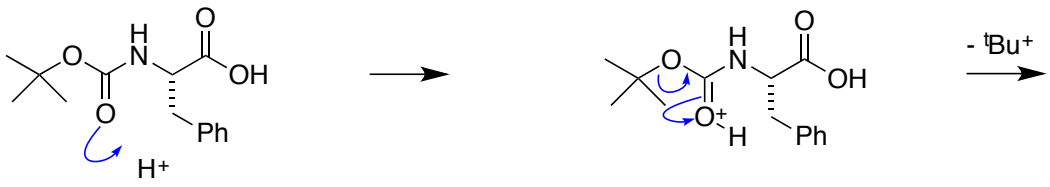
N-BOC Protected Amino Acids
amines
amines.



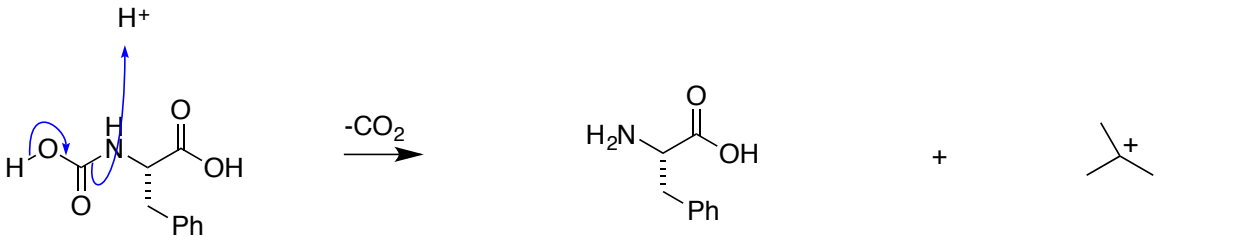


with *trifluoroacetic (TFA)* acid.

carbon *dioxide*.



BOC-Phe-OH

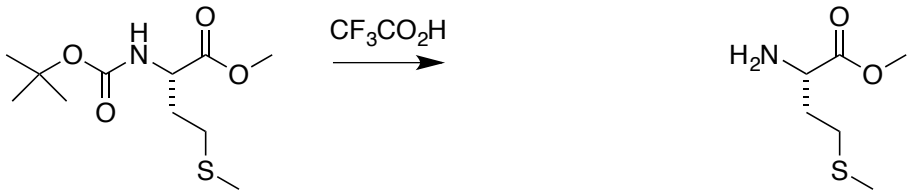


unstable carbamate

amino acid

carbocation

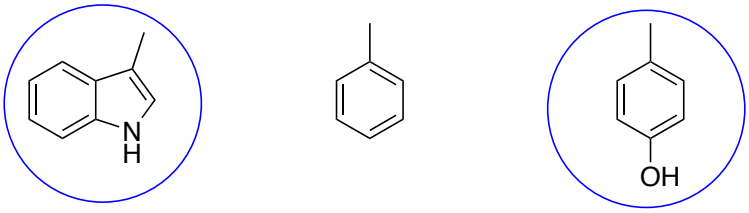
Give the products of the following reactions



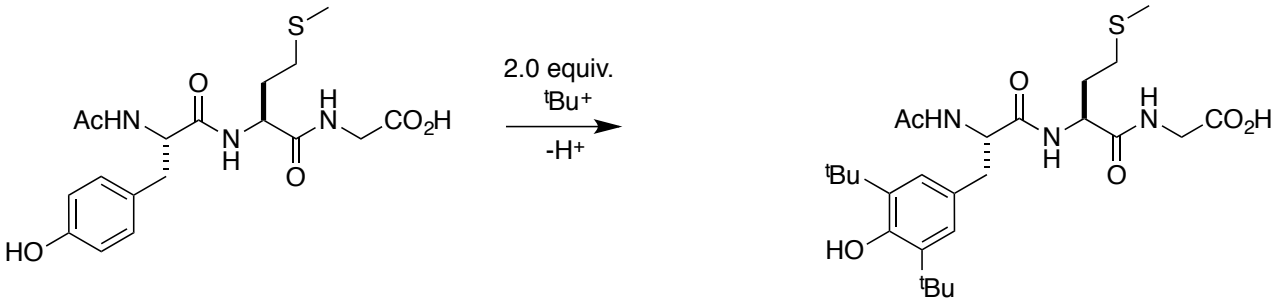
BOC-Val-Ala-OH $\xrightarrow{\text{TFA}}$ H-Val-Ala-OH

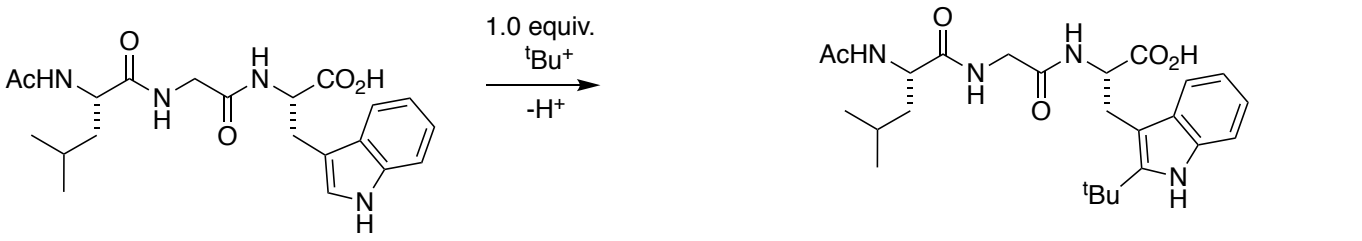
undesirable

$HSiEt_3$

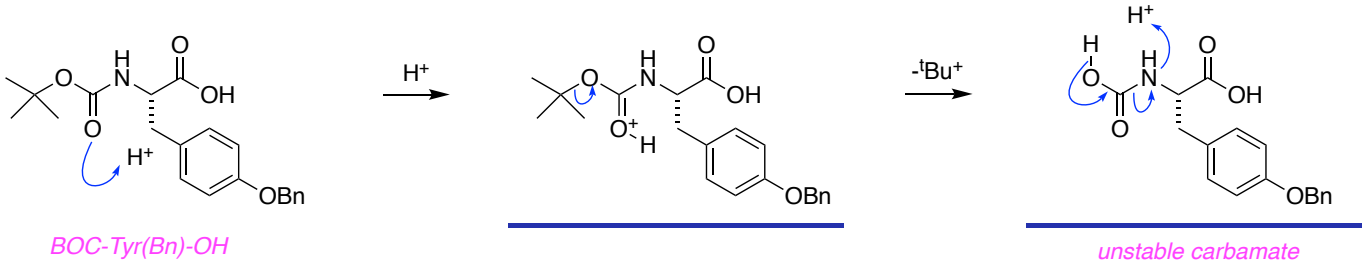


Tyr / Trp



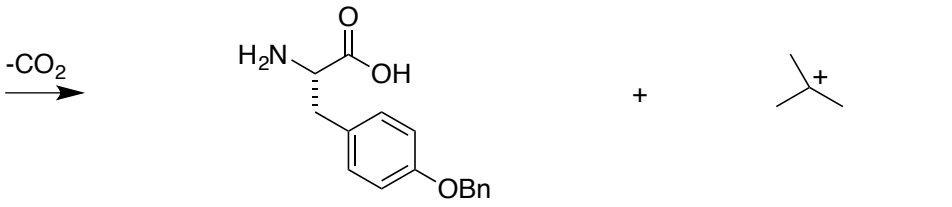


usually



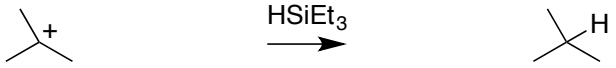
BOC-Tyr(Bn)-OH

unstable carbamate



amino acid

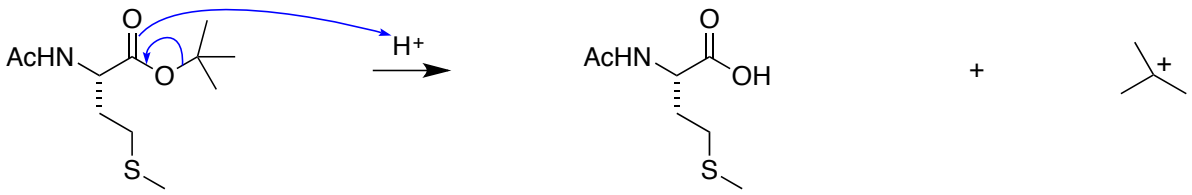
carbocation



carbocation

by-product

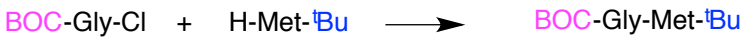
C-Protection Of Amino Acids With ^{t}Bu-Groups

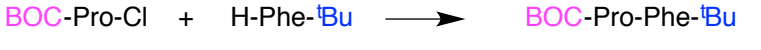


Ac-Met-O^{t}Bu

by-product cation

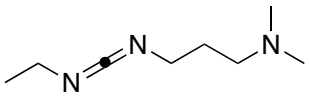
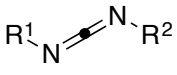
1-Adamantyl esters *cannot*
are



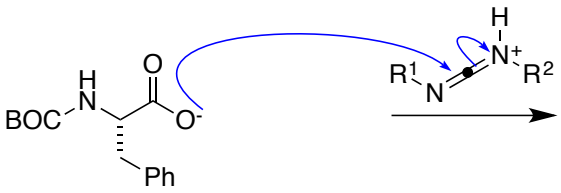


Activation Of *N*-Protected Amino Acids

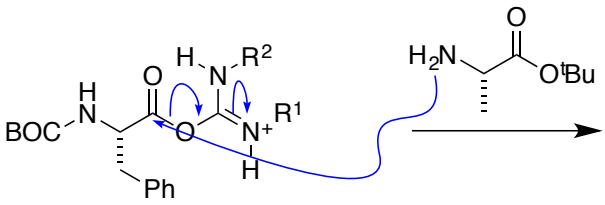
too *reactive* for
using *carbodiimide* reagents
ie dicyclohexylurea,
because *the by-products can be protonated and are water-soluble*.

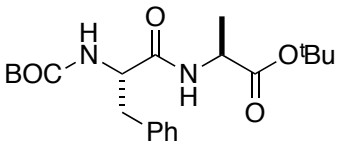
Let  *be represented as* 

EDCI

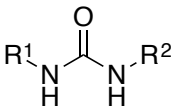


BOC-Phe-O⁻





BOC-Phe-Ala-O^{t}Bu

\+ 

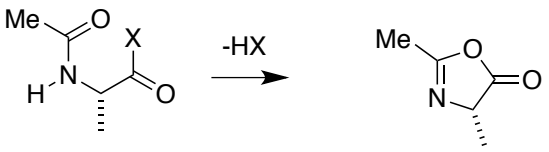
by-product

The Epimerization Problem

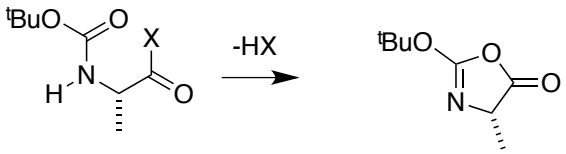
epimerize)
epimeric products.

difficult to separate

azlactone.



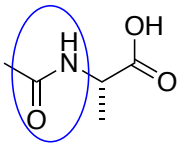
azlactone forms rapidly



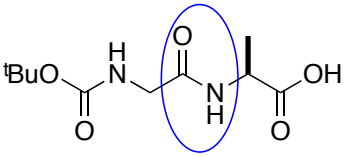
azlactone forms slowly

is driven by aromatic stabilization in the product and simultaneous *loss carbamate*.

more



Ac-Ala-OH



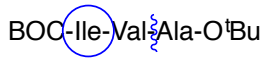
BOC-Gly-Ala-OH

Strategies In Solution Phase Syntheses That Avoid Epimerization

will

will tend to

less prone to racemization



more prone to racemization

circle the one amino acid in one of these structures that is most vulnerable to epimerization

are

C- to N- direction

B. Solid Phase Peptide Syntheses

are mixed with

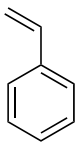
is usually required

easier to purify

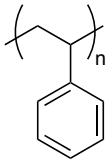
advantages of

are not optimally

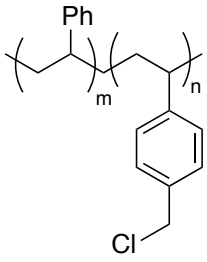
C-terminus.



styrene

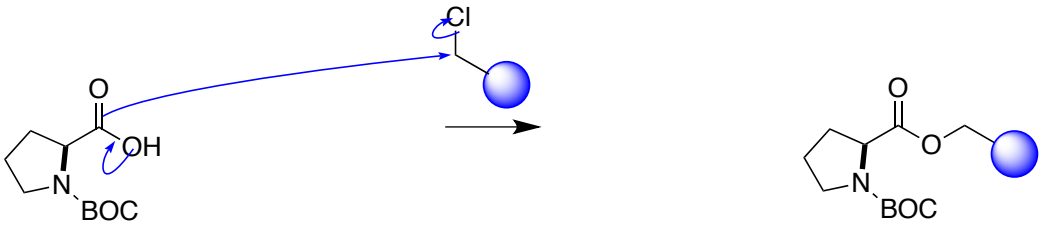


polystyrene



"4-chloromethylpolystyrene"

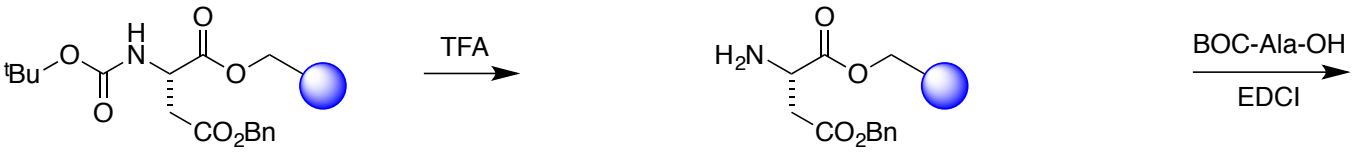
S_N2 reaction



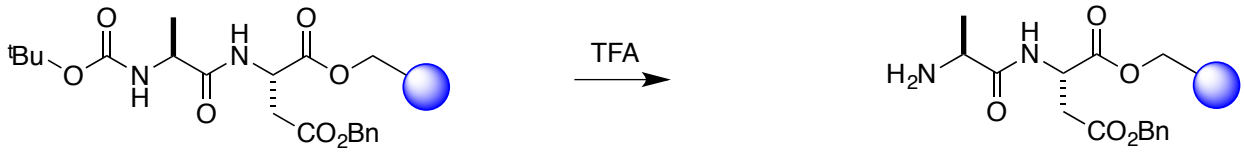
BOC-Pro-OH

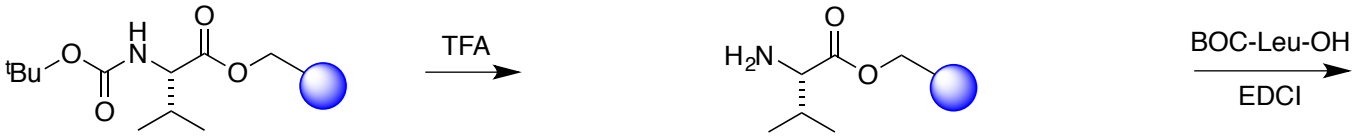
TFA often in the *presence* of a scavenger; this *does not*

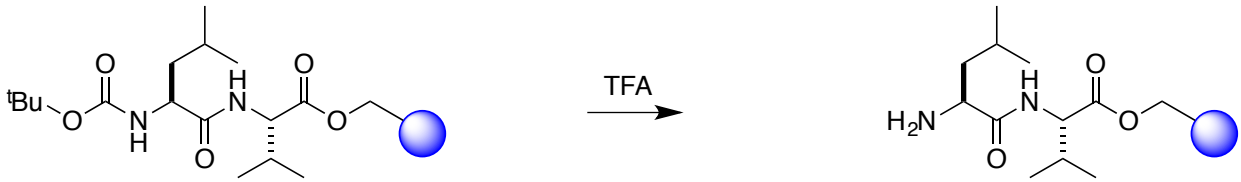
N-terminus

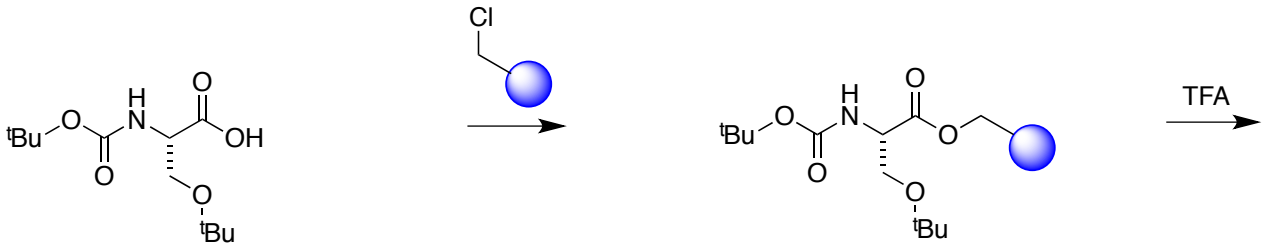


BOC-Asp(Bn)-support

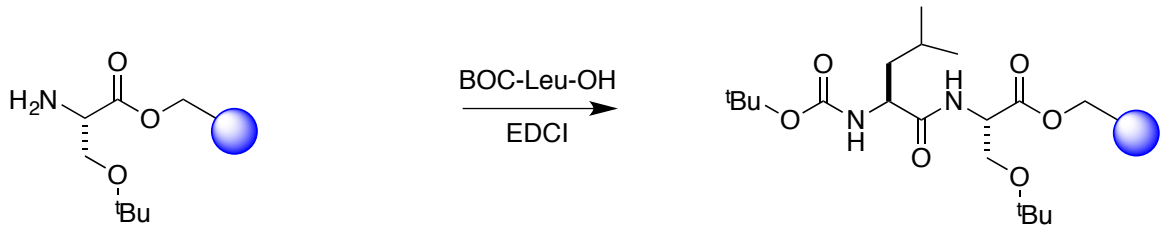


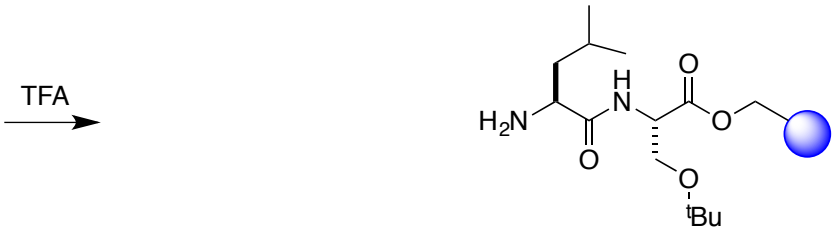




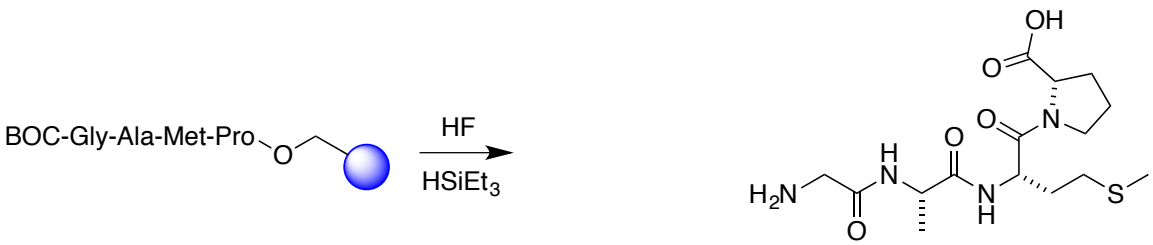


BOC-Ser(O^{t}Bu)-OH

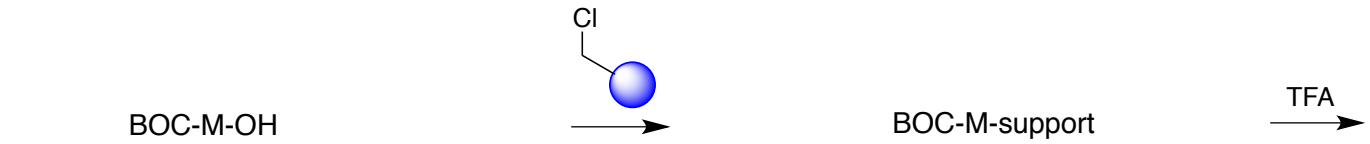


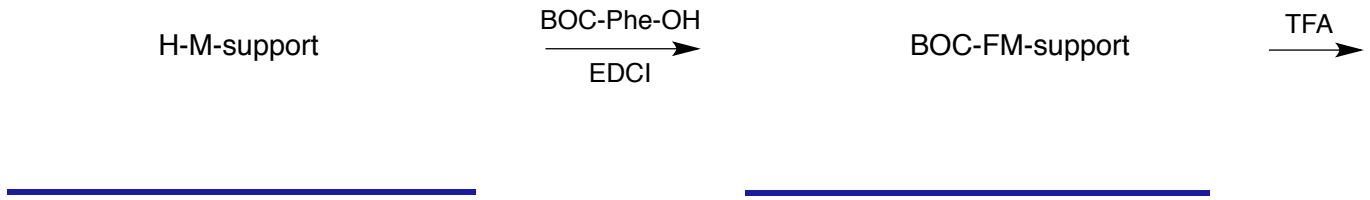


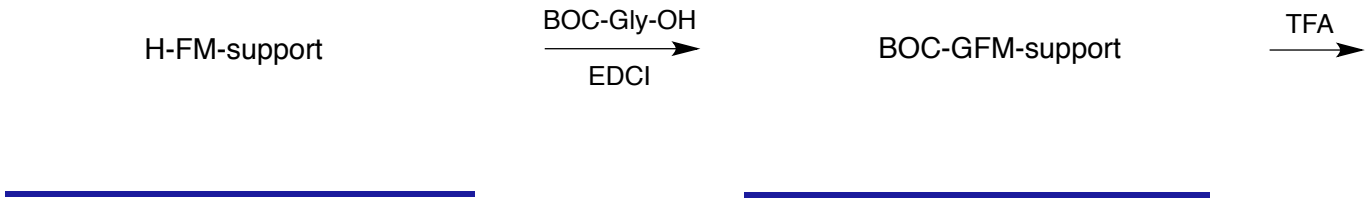
HF and scavengers

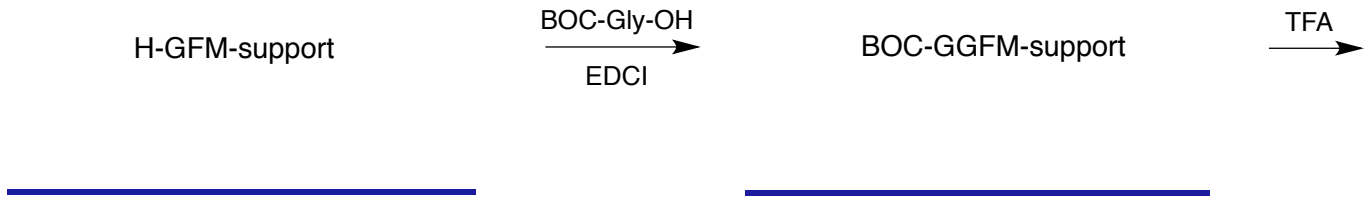


draw peptide





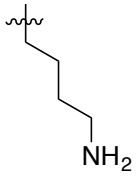




C. Side-chain Protection Of Amino Acids

may
is required.

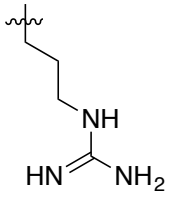
undesirable
desirable



protection required?

yes

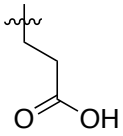
Lys



protection required?

yes

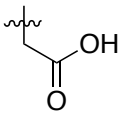
Arg



protection required?

yes

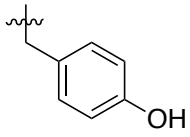
Glu



protection required?

yes

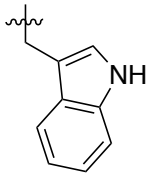
Asp



protection required?

yes

Tyr



protection required?

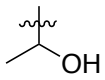
yes

Trp

protection required?

yes

Ser



protection required?

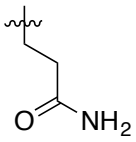
yes

Thr

protection required?

yes

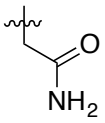
Cys



protection required?

yes

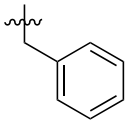
Gln



protection required?

yes

Asn



protection required?

no

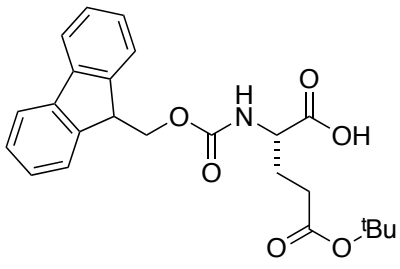
Phe

D. The FMOC Approach

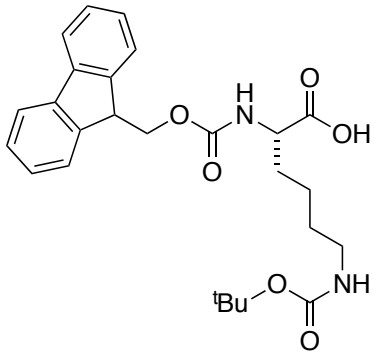
HF

base labile

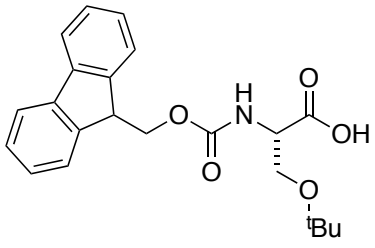
via *TFA*.



FMOC-Glu(^{t}Bu)-OH



FMOC-Lys(BOC)-OH



FMOC-Ser(^{t}Bu)-OH