

Peptide Syntheses

from chapter(s) _____ in the recommended text

A. Introduction

H-Met-Phe-OH

H-Met-Met-OH

H-Phe-Phe-OH

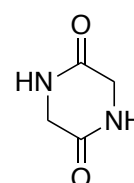
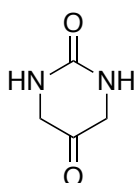
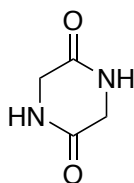
H-Phe-Met-OH

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 Protected Amino Acids

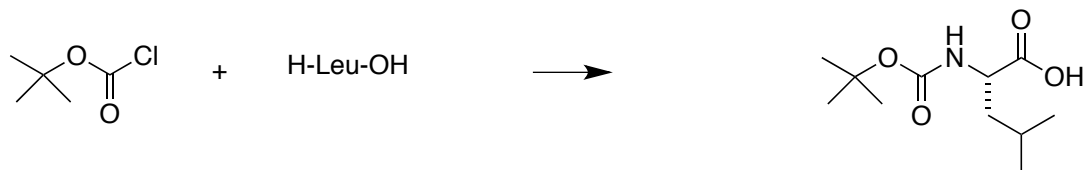
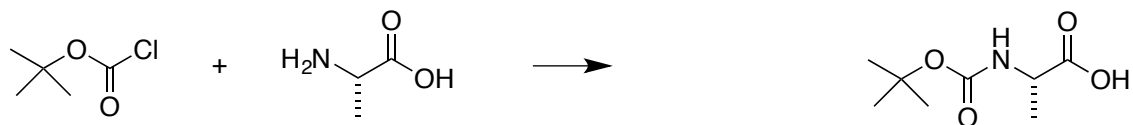


Illustrative Protection: BOC/^tBu

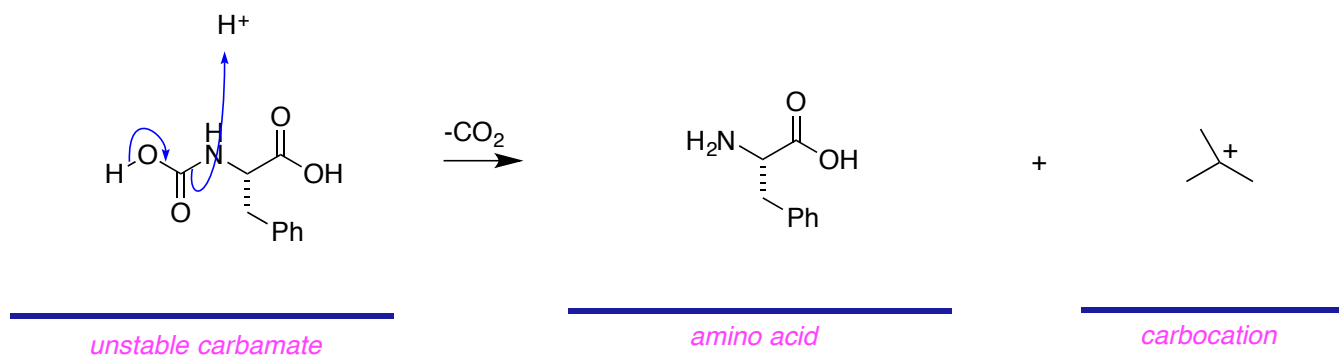
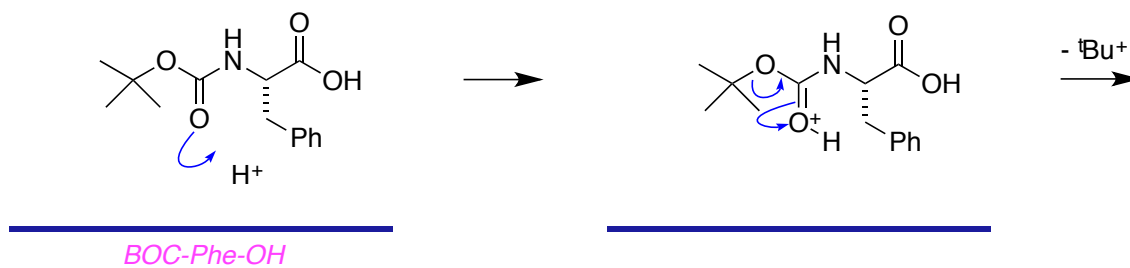
N-BOC Protected Amino Acids

amines

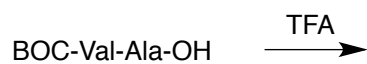
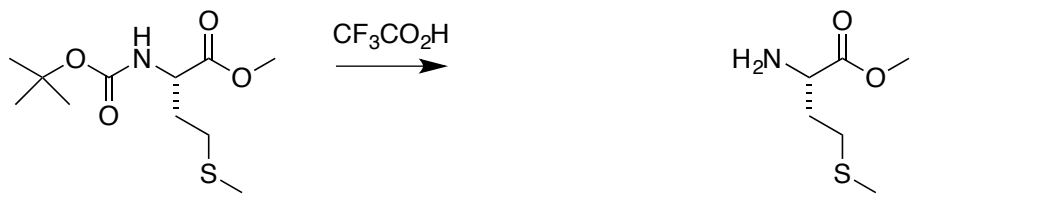
amines.



with *trifluoroacetic (TFA)* acid.

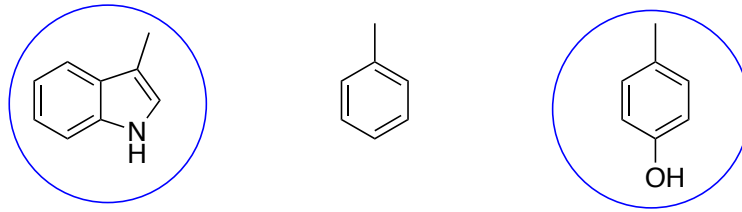
carbon *dioxide*.

Give the products of the following reactions

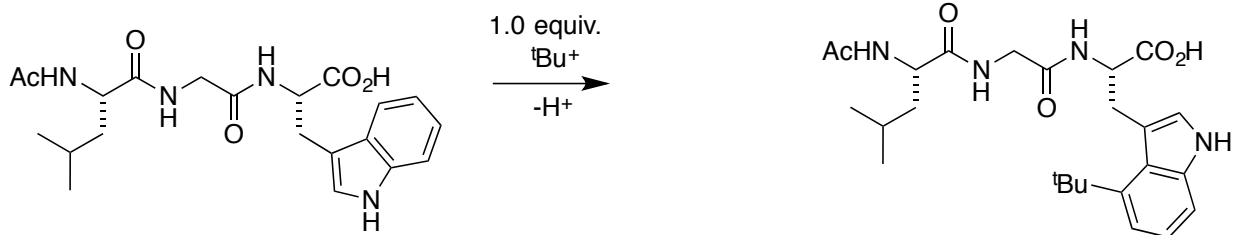
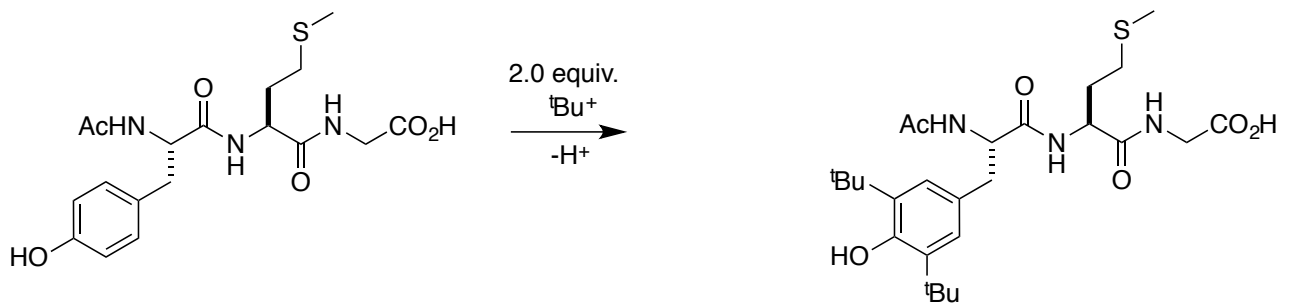


H-Val-Ala-OH

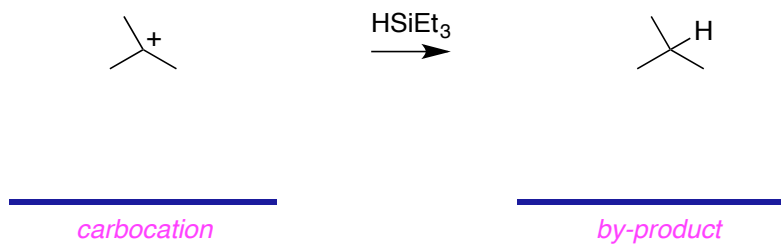
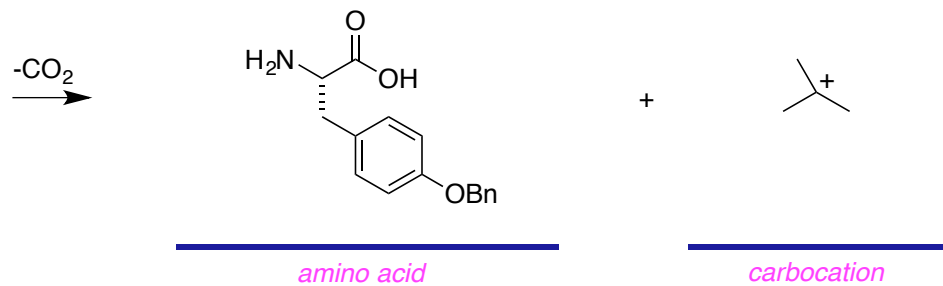
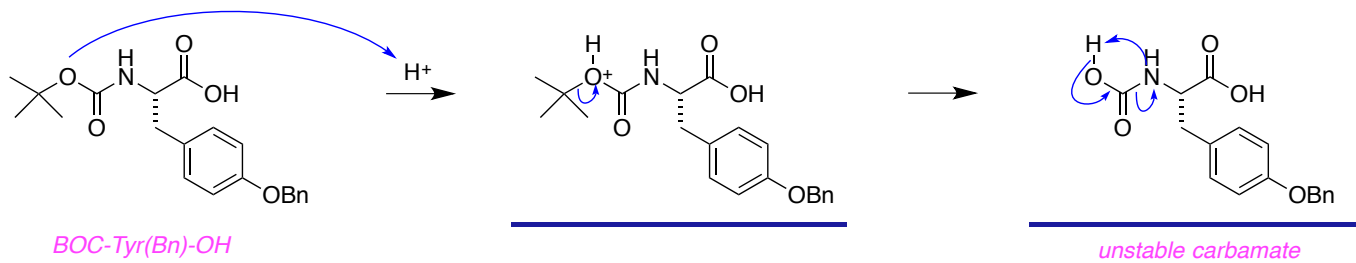
undesirable
 HSiEt_3



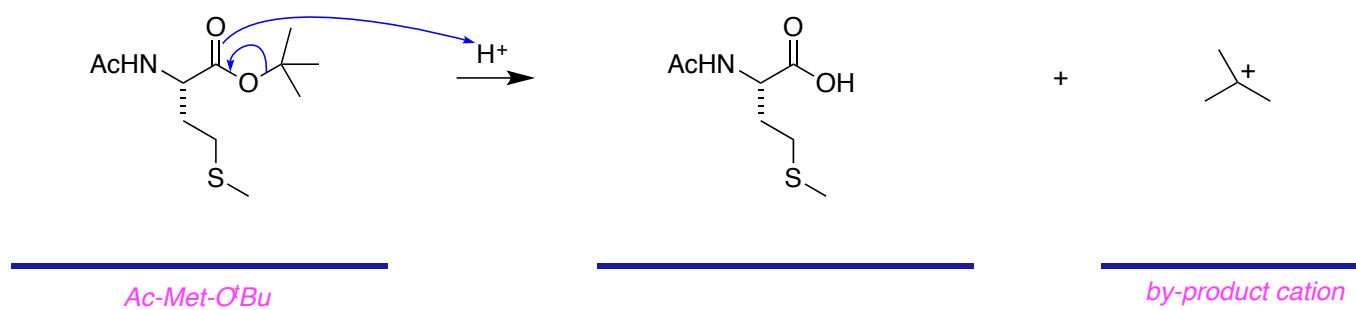
Tyr / Trp



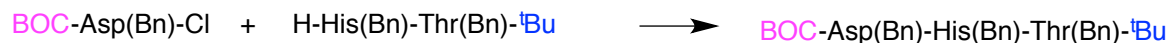
usually



C-Protection Of Amino Acids With ^tBu-Groups



1-Adamantyl esters *cannot*
are



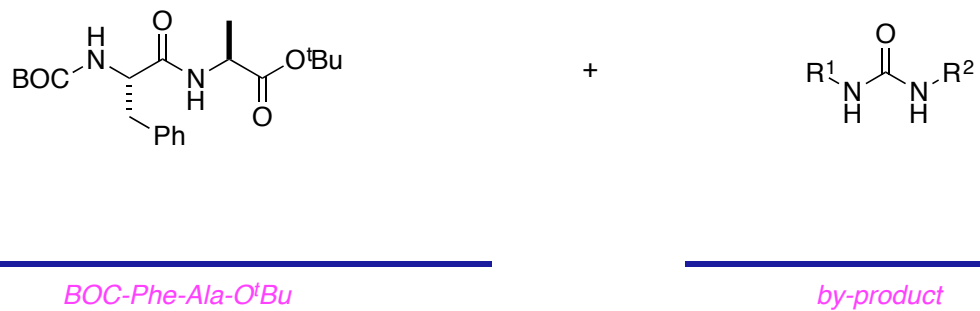
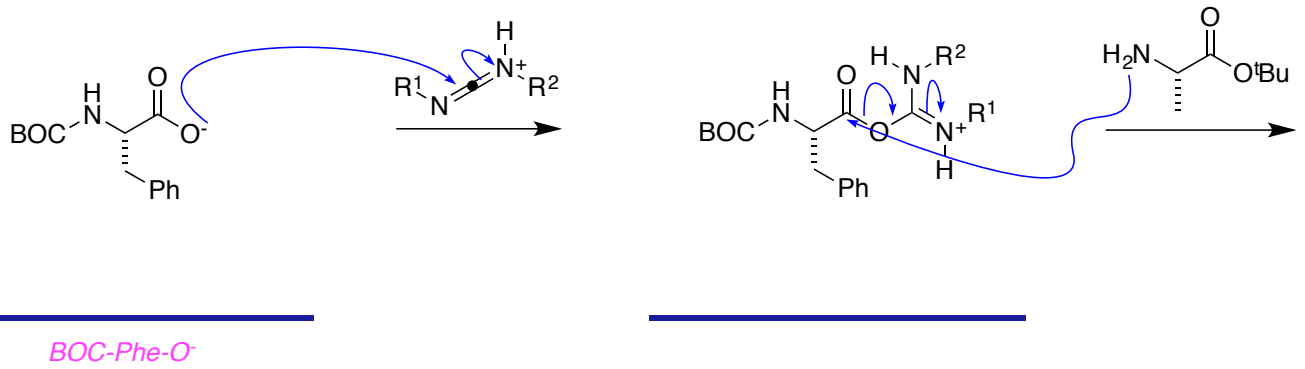
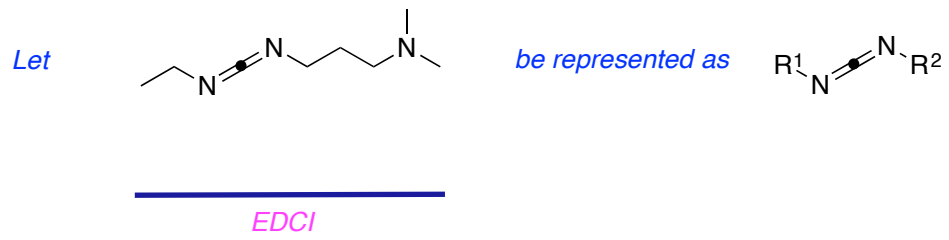
Activation Of *N*-Protected Amino Acids

too *reactive* for

using *carbodiimide* reagents

ie dicyclohexylurea,

because *the by-products can be protonated and are water-soluble.*

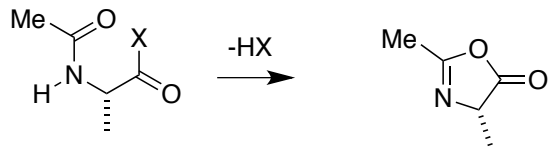


The Epimerization Problem

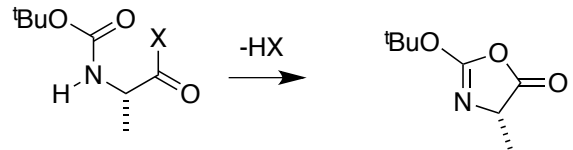
epimerize)
epimeric products.

difficult to separate

azlactone.



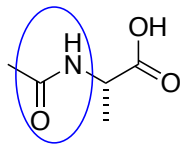
*azlactone
forms rapidly*



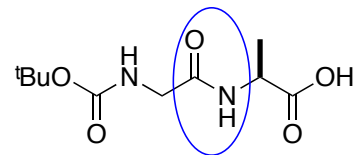
*azlactone
forms slowly*

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

more



Ac-Ala-OH



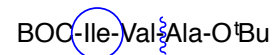
BOC-Gly-Ala-OH

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

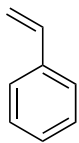
are
C- to N- direction

B. Solid Phase Peptide Syntheses

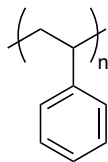
are mixed with
is usually required
easier to purify
advantages of

are not optimally

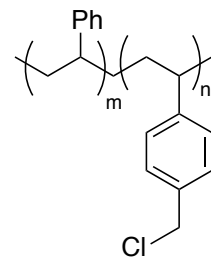
*C-*terminus.



styrene

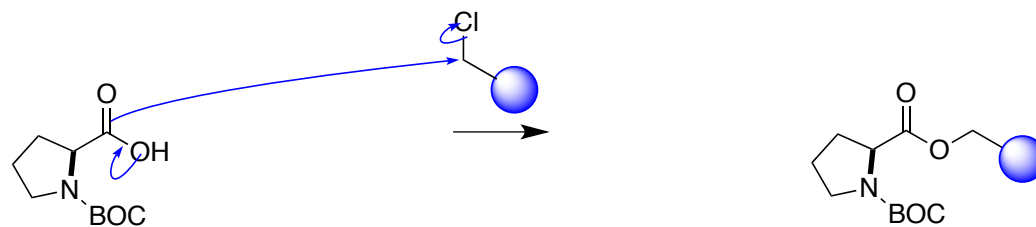


polystyrene



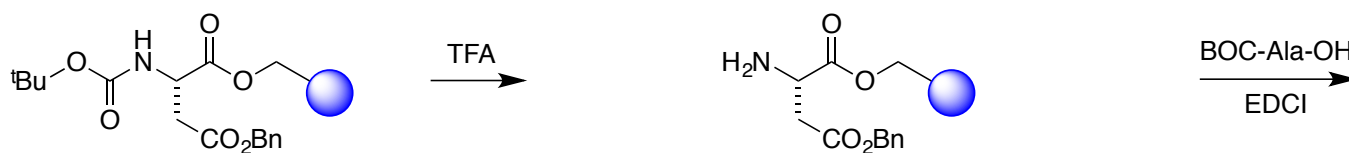
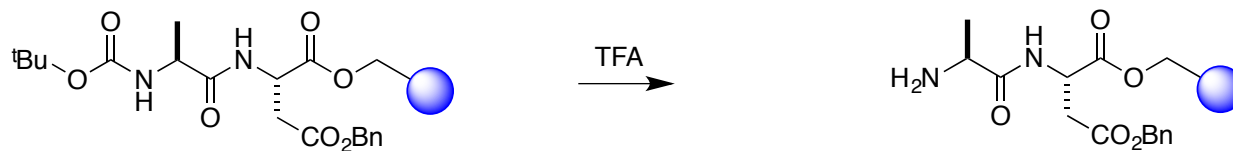
"4-chloromethylpolystyrene"

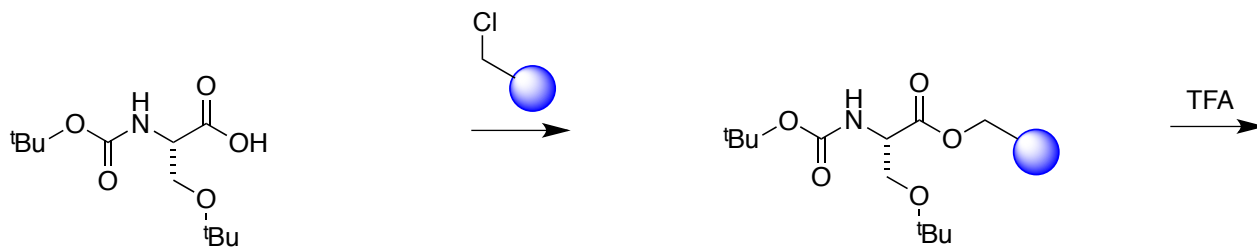
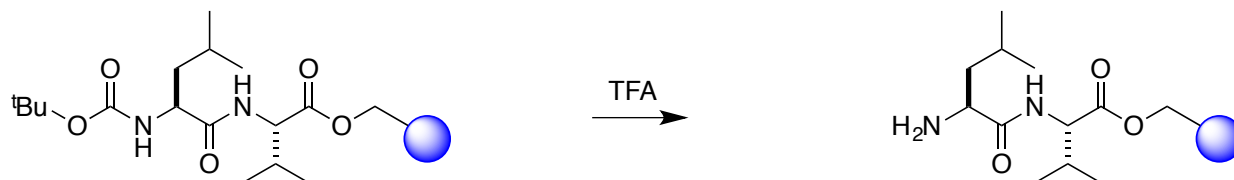
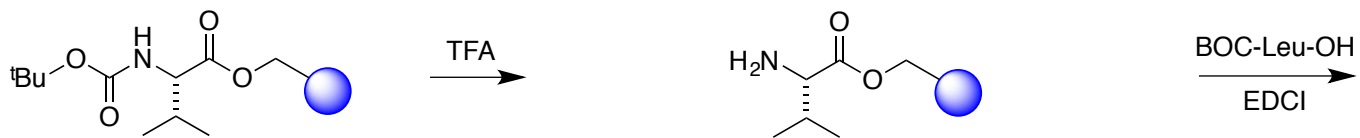
S_N2 reaction

*BOC-Pro-OH*

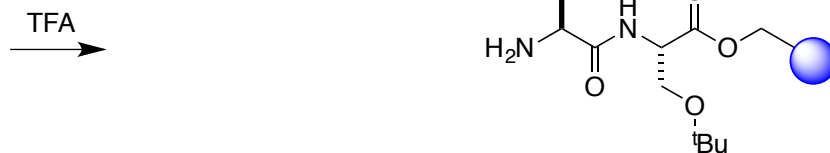
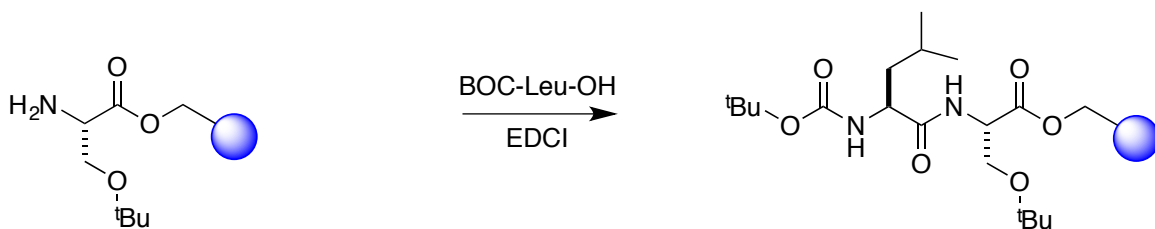
TFA often in the *presence* of a scavenger; this *does not*

N-terminus

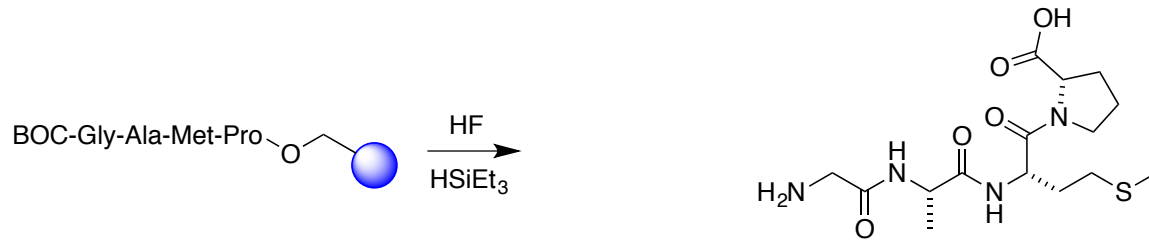
*BOC-Asp(Bn)-support*



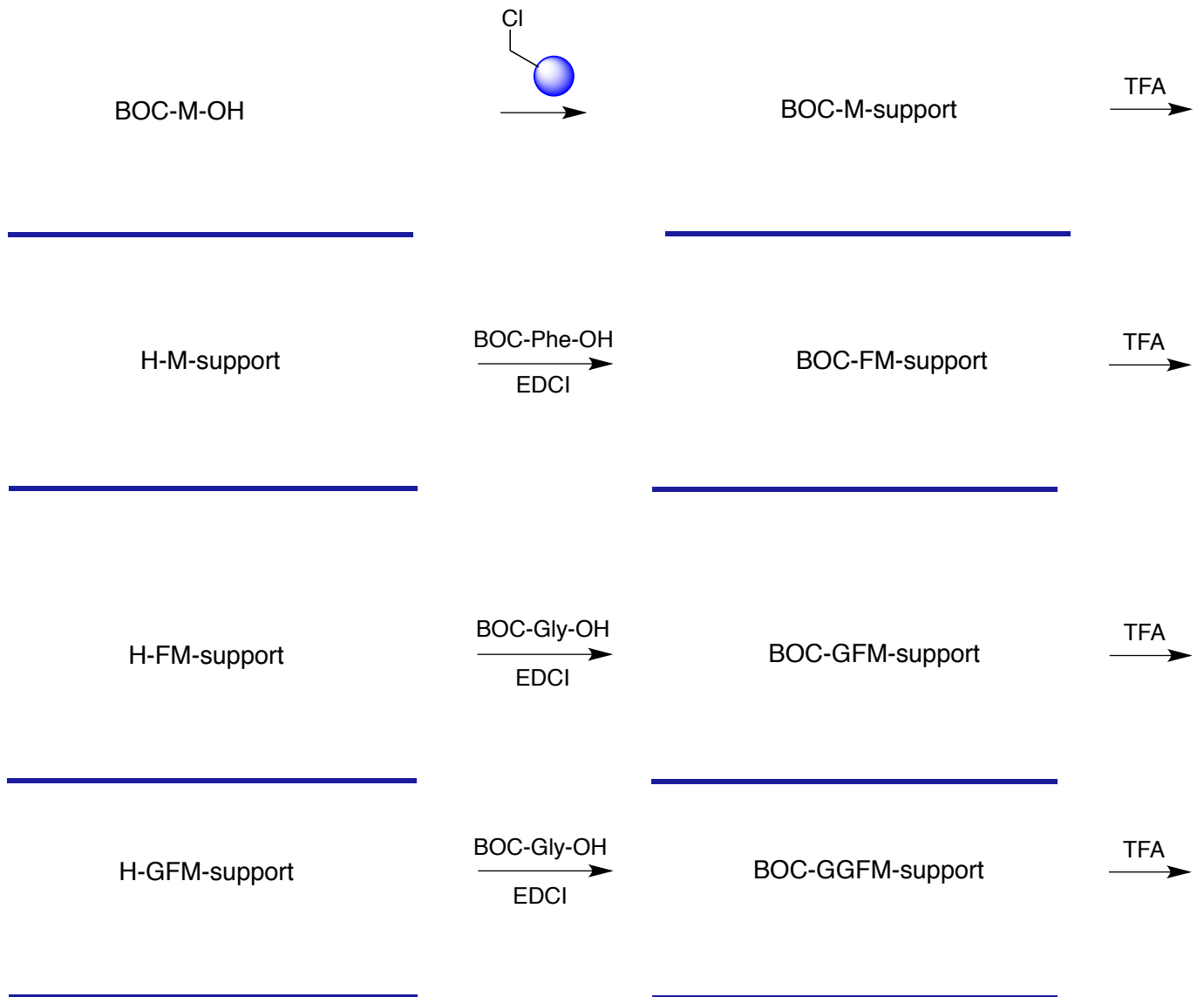
BOC-Ser(O^tBu)-OH

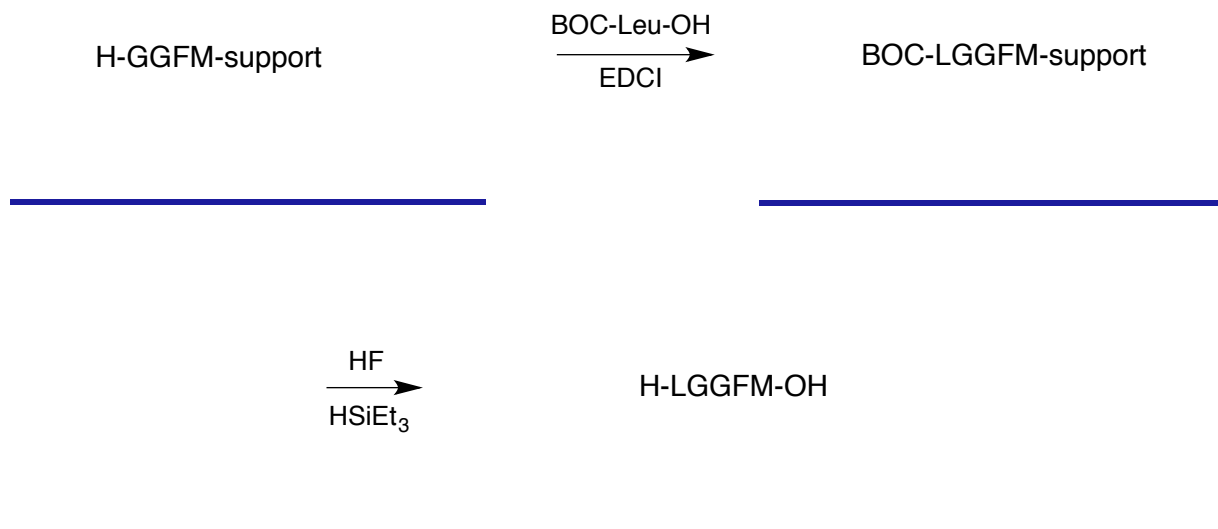


HF and scavengers



draw peptide

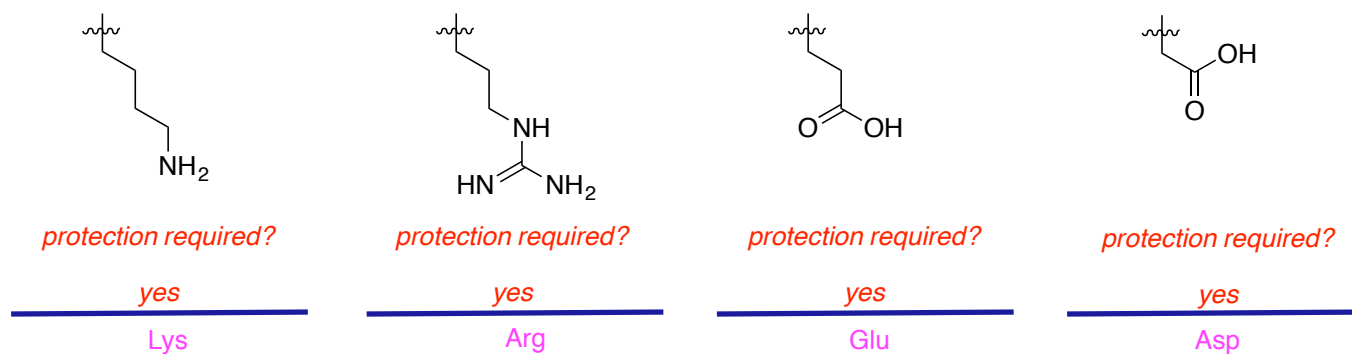


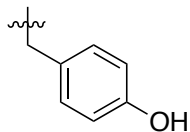


C. Side-chain Protection Of Amino Acids

may
is required.

undesirable
desirable

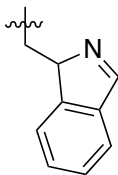




protection required?

yes

Tyr



protection required?

yes

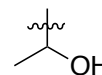
Trp



protection required?

yes

Ser



protection required?

yes

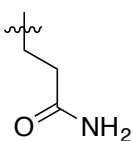
Thr



protection required?

yes

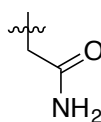
Cys



protection required?

yes

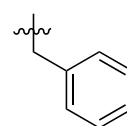
Gln



protection required?

yes

Asn



protection required?

no

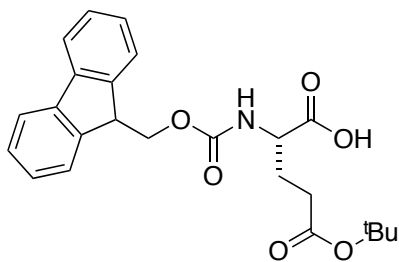
Phe

D. The Fmoc Approach

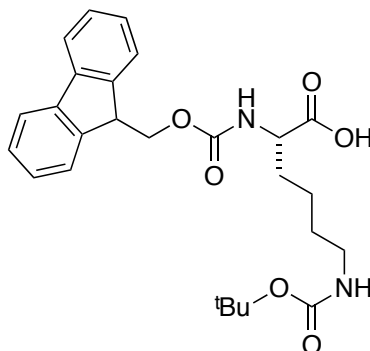
HF

base labile

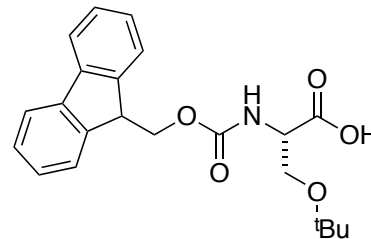
via TFA.



Fmoc-Glu(^tBu)-OH



Fmoc-Lys(BOC)-OH



Fmoc-Ser(^tBu)-OH