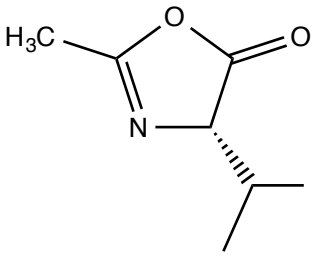
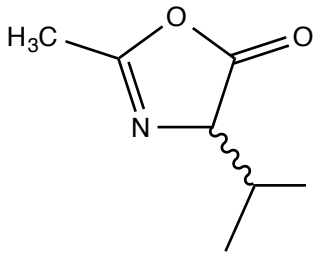
Peptide quiz 1 (5 questions for 10 minutes) ***10 points max***

1. Draw the structure of oxazolone formed upon activation of N-Acetylvaline

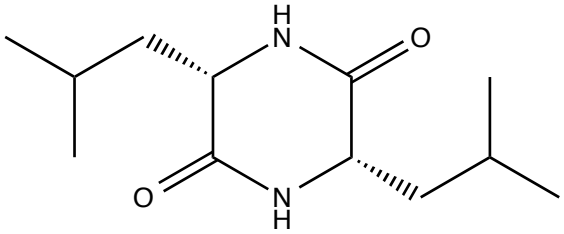


OR



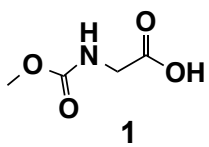
2. The following DKP (**1**) is prepared by cyclisation of dipeptide **H-Leu-Leu-OH** (fill the missing amino acid residues in, *three-letter code*).

Is **1** chiral? (Explain your answer in no more than 15 words):
Answer: Compound **1** is chiral. *Explanation:* Contains two asymmetric carbons, but has neither mirror plane nor center of symmetry.

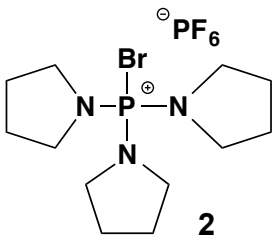


1

3. Carboxyl group in **1** was activated with the phosphonium reagent PyBrop (**2**) (in presence of DIPEA) Draw <u>one</u> of "secondary" activated species derived from **1** that could be be detected in the reaction mixture.



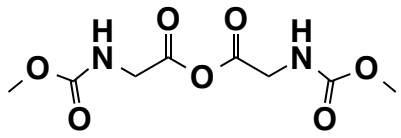
1

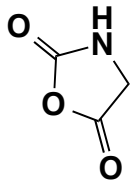


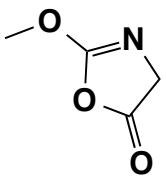
2

Answer:

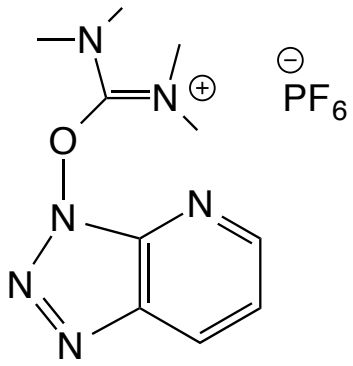
Full credits for one of the following:







4. Draw the structure of HATU



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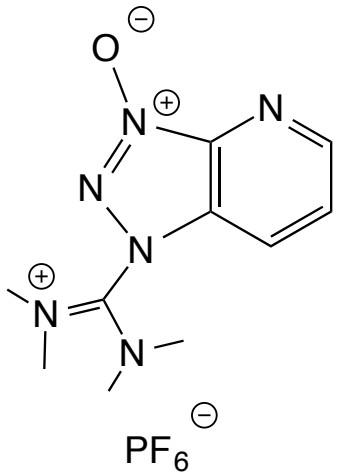
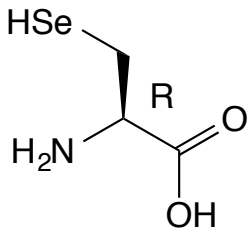
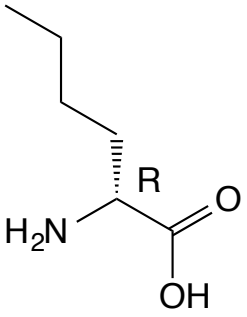


5. Determine the stereochemistry (*R* or *S*) of the chiral centers in the following amino acids

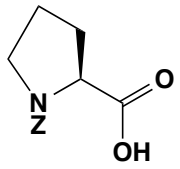


selenocysteine

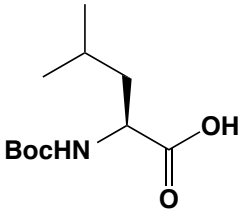


norleucine

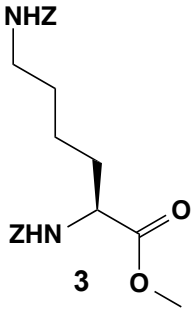
6. The following building blocks (**1**, **2** and **3**) were tried for the synthesis of tripeptide H-Pro-Ile-Lys-OH in solution. The synthesis failed. Suggest correct building blocks.



1

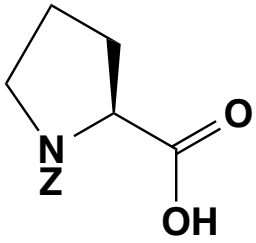


2

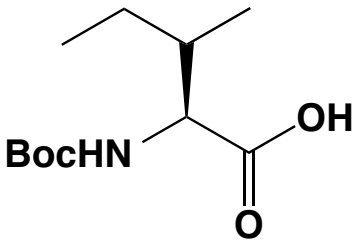


3

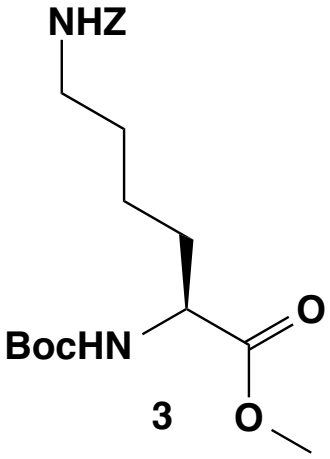
Answer:



1



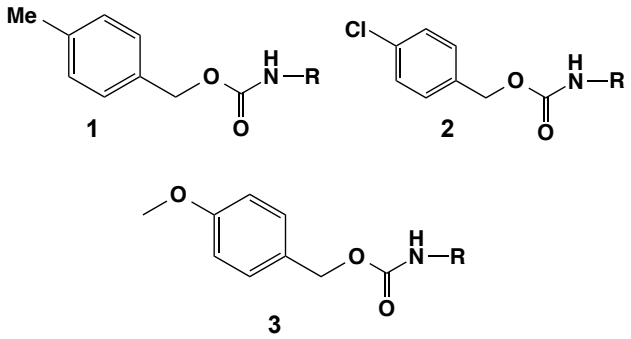
2-Ile



3

In the Lys and Ile building blocks (**3** and **2-Ile**) the alpha amino groups have to be protected orthogonally to that of the side chain of the Lys residue and to the alpha-carboxyl of Lys. The given Boc-amino acid (**2**) is not Ile but Leu.

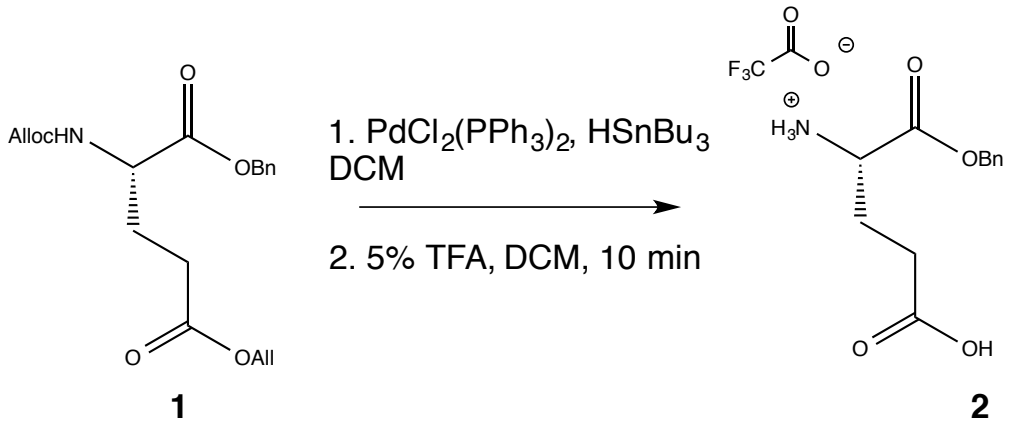
7. Position the following Z-group derivatives in the order of <u>decreasing</u> acid <u>sensitivity</u>. Justify your answer (maximum 15 words).



Answer: The order of the decreasing acid sensitivity is: **3** (more sensitive than) **1** (more sensitive than) **2.**

Justification: Due to decrease of benzylic carbocation stability (OMe- resonance stabilization, Me - hyperconjugative stabilization, Cl – electron withdrawing)

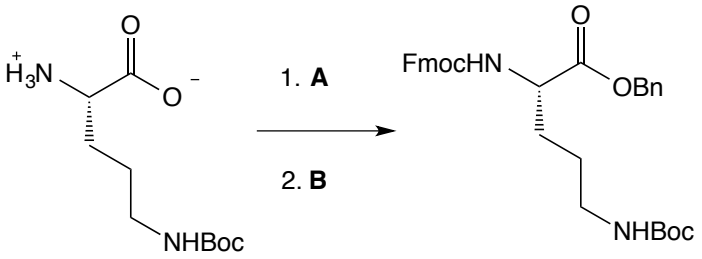
8. The deprotection sequence below have been applied to the protected amino acid **1**. Draw the structure of the product **2** thus obtained.



1 **2**

(*Bn-ester is obviosly stable to dilute TFA for just 10 min, the amino group gets protonated*)

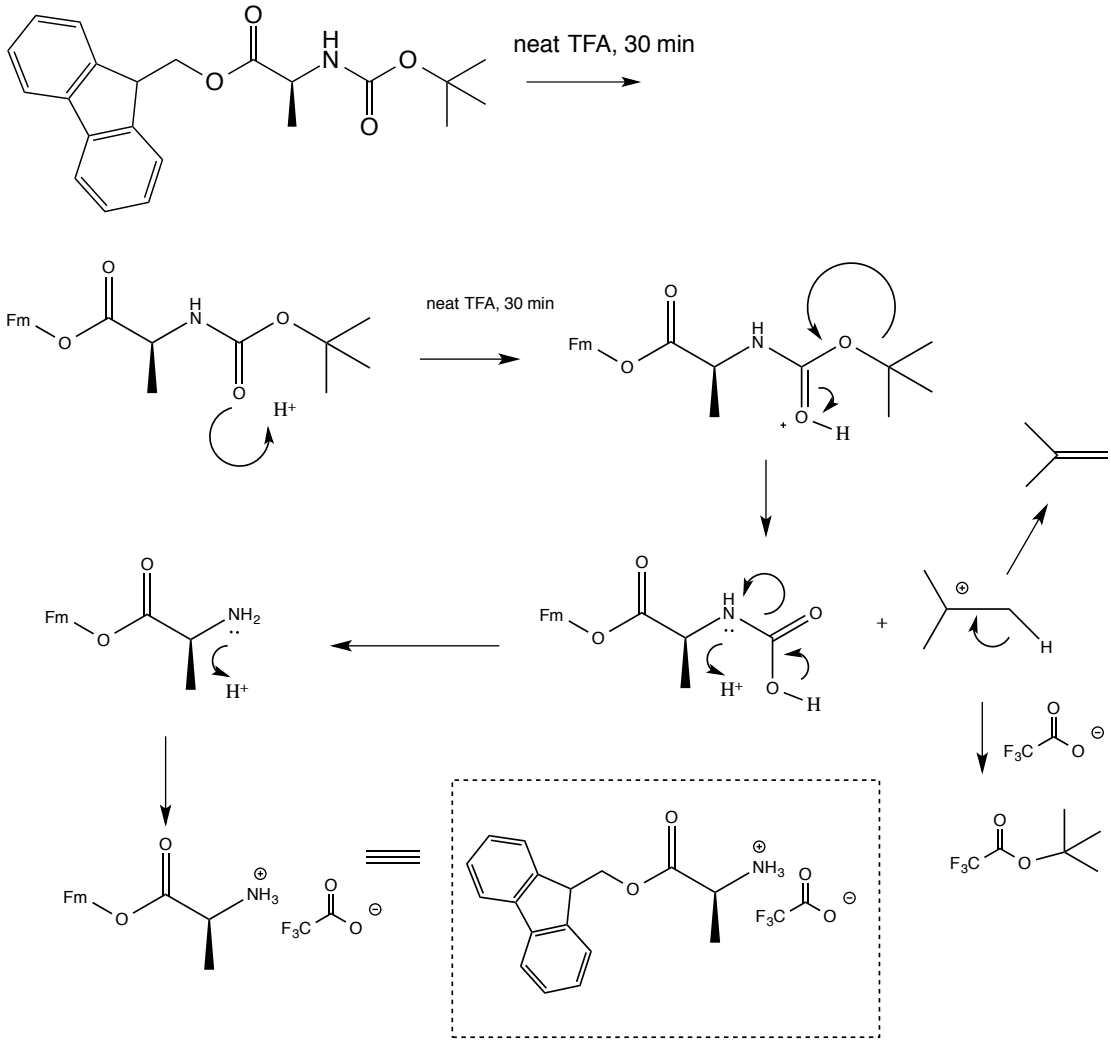
9 Give the reagent mixtures **A** and **B** that are suitable to effect the following transformation:



A: Fmoc-OSu, H_2O/dioxane, $NaHCO_3$ B: Ag_2CO_3, BnBr, DMF

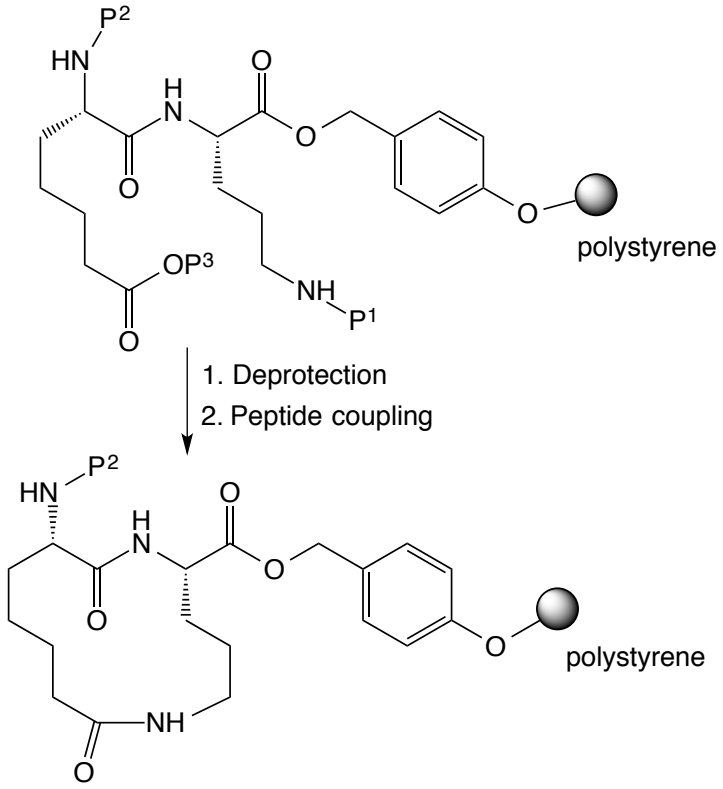
(*for other viable options see the lecture materials*)

10. Draw the product and the mechanism of the following deprotection reaction.



(*note that the product is neccesary a TFA-salt*)

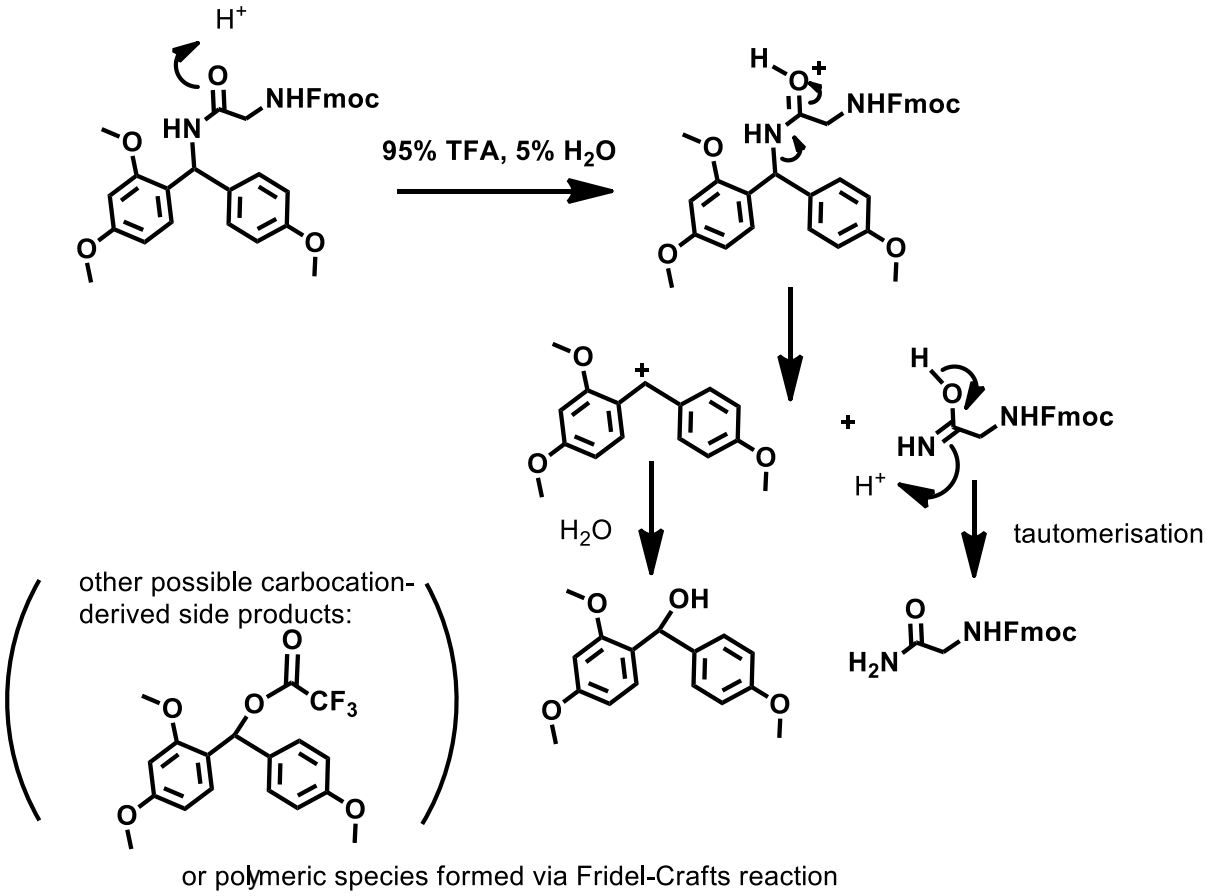
11. Suggest the protective groups P^1, P^2, P^3 that can be applied in the following synthetic plan:



For example: P^1- Alloc, P^3- All, P^2- Boc (P^2 can be other urethane-based protection except of Alloc)

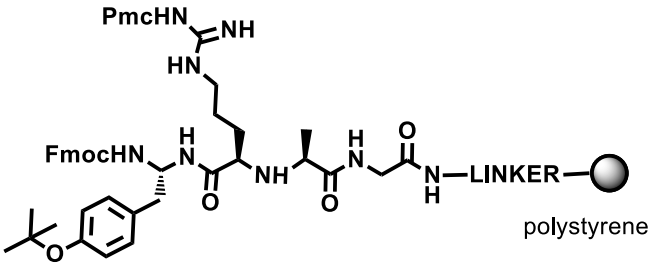
(*note that the linker(Wang) is TFA sensitive, therefore P1= Boc and/or P2 =Bu^t is NOT an option here*)

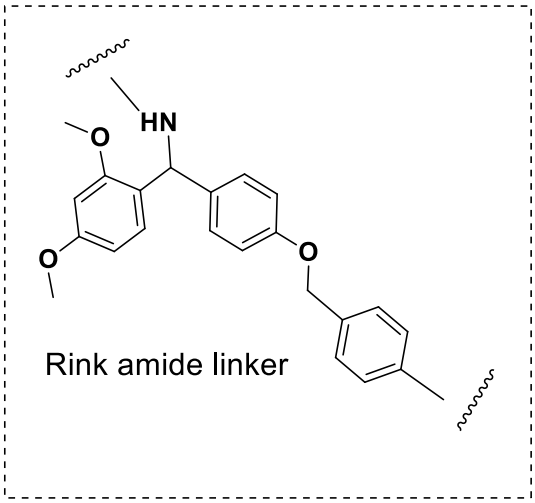
12. Draw the products and the mechanism of the following reaction:



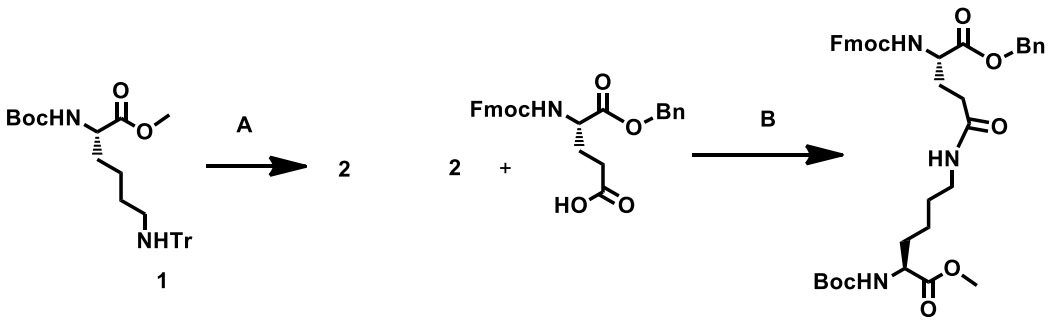
(*variants of this mechanism that start with the protonation of the amide nitrogen are also approved. Both Fmoc-cleavage and amide hydrolysis are excluded under specified conditions)*

13. The protected peptide in the scheme below has been assembled via Fmoc-chemistry. Draw the structure of a suitable linker.





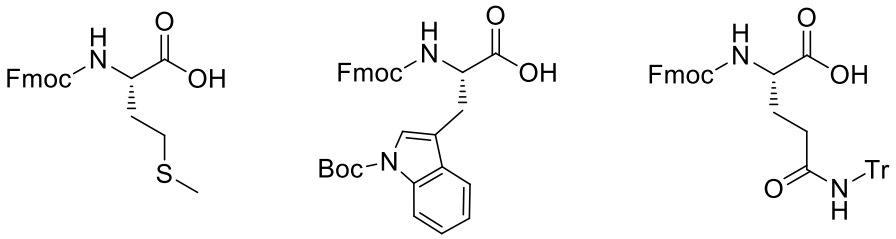
14. Suggest the reagents and conditions (**A** , **B**) for the following sequence of transformations.



(*A: 1-2% TFA in DCM to cleave Tr selectively in the presence of Boc; B: BOP, DIPEA (3 eq), DMF or any other sensible peptide coupling reagent in combination with organic base)*

15. Draw the structures of the appropriately protected amino acid building blocks suitable for a Fmoc-based solid phase synthesis of the following peptide:

H-Met-Trp-Gln-OH



(*Note that you have been asked for the amino acid building blocks for solid phase synthesis*)