

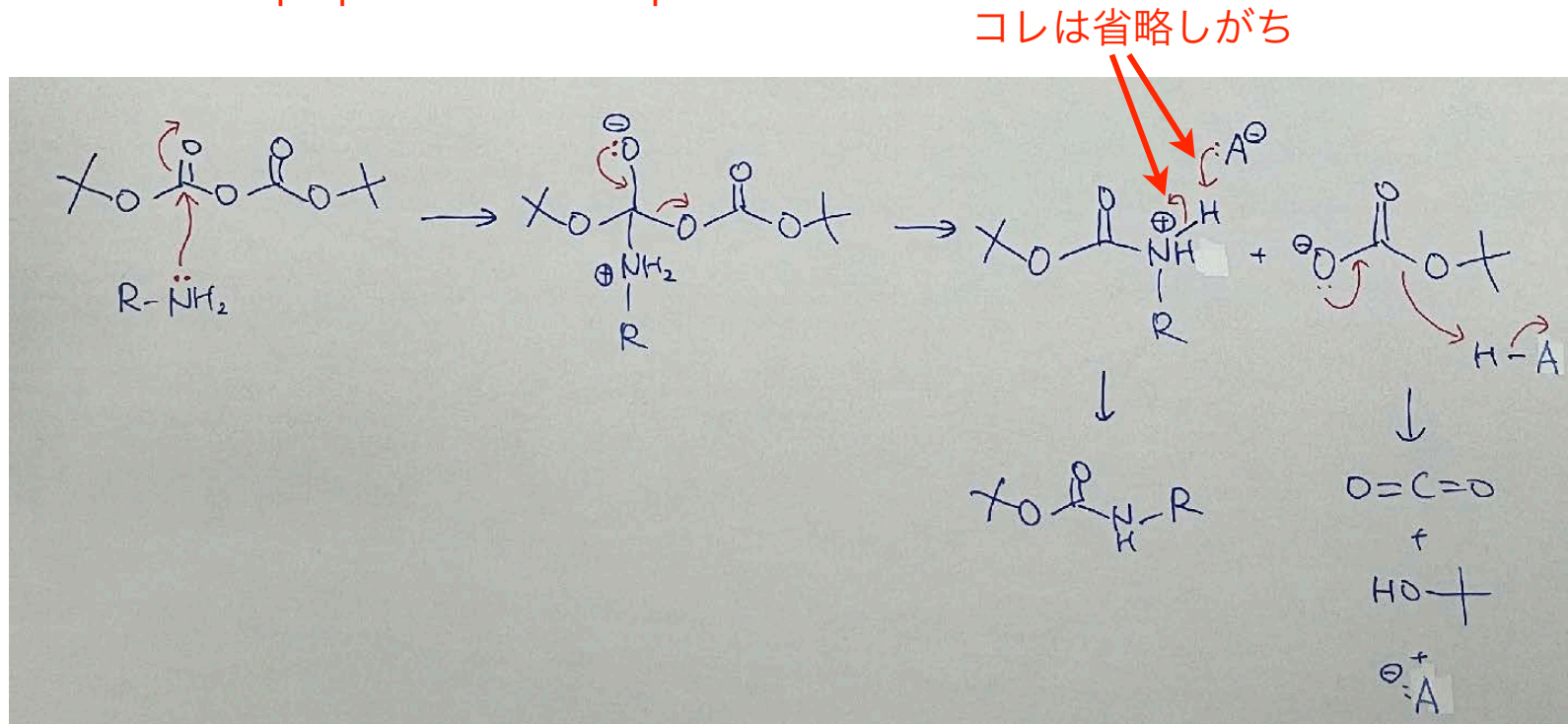
Organic Chemistry III

後藤 佑樹 (Yuki Goto, Bioorganic Chemistry Lab.)

“Organic chemistry of biomolecules”

讀者としての「プロトンの移動をすべて示さなければならないか?」
 正しいか? $\text{B} + \text{OH}^-$ が起こるとは必ずしも思わないが、
 $\text{NH}_3 \leftrightarrow \text{NH}_2^-$ か $\text{COO}^- \leftrightarrow \text{COOH}$ は 4C に
 必要なく、プロトンの移動を省略していいのだろうか?

Strictly speaking, every/each electron movement should be shown for complete representation of the mechanisms.
 But, we often omit simple proton transfer steps.



Why is the product in Q1 Boc-NH-R but not $\text{Boc-N}^-(\text{R})\text{COO}^-$ under basic condition?

★★★ (現時点では)

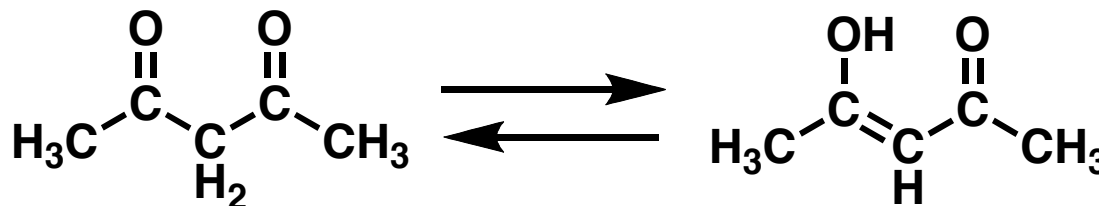
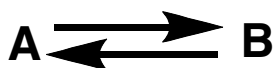
最終的には★★

補足！有機化学でよく使う矢印の種類

・ 構造式間の矢印

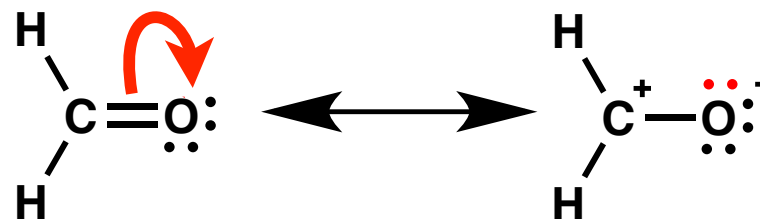
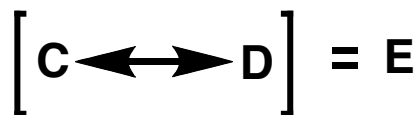
◎ 平衡を示す矢印

2つの異なる
化学種



◎ 共鳴構造を示す矢印

2つの Lewis 構造式
C と D をもつ1つの化
学種 E



ホルムアルデヒド

・ 電子の移動を示す矢印 (巻き矢印)

◎ 電子対 (2電子) の動きを示す矢印  『両羽矢印』

◎ 1電子の動きを示す矢印  『片羽矢印』

★★★ (現時点では)

最終的には★★

電子の矢印の書き方 まとめ

ルールとコツ

- ・ 両羽矢印は電子 2 つ分の移動を示す。
- ・ 非共有電子対だけでなく、結合 1 つ分も電子 2 つと考える。
- ・ 電子が余っているところ → 電子を欲しがっている/受け取れるところ へと描く

・ 矢印のスタートは、**電子対 or 結合**

・ 矢印のゴールは、**原子 or 結合** (or 原子間の空間 【発展】)

スタートが結合の場合 = **結合が解裂 or 結合の多重度が減る**

スタートが原子の場合 = その原子の**電荷が一段階正に**

(スタートは電子対でも結合でも) ゴールが既にある結合の場合 = **結合が一段階多重に**

(スタートは電子対でも結合でも) ゴールがこれまで結合してなかった原子の場合 = **結合が形成**

(スタートが結合で) ゴールが分子内の原子の場合 = その原子の**電荷が一段階負に**

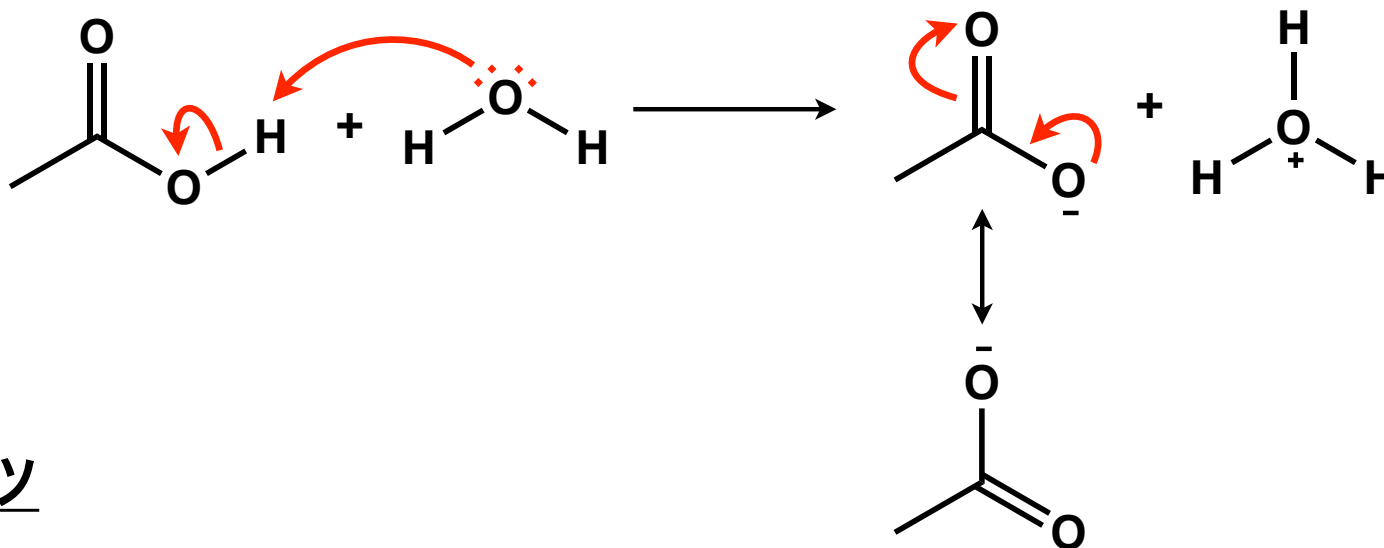
- ・ 矢印を1つ書いてみた後の状態が不自然な場合、さらに次の矢印を書いていく。

★★★ (現時点では)

最終的には★★

電子の矢印の書き方

まとめ



ルールとコツ

・ 矢印のスタートは、**電子対 or 結合**

・ 矢印のゴールは、**原子 or 結合** (or 原子間の空間 【発展】)

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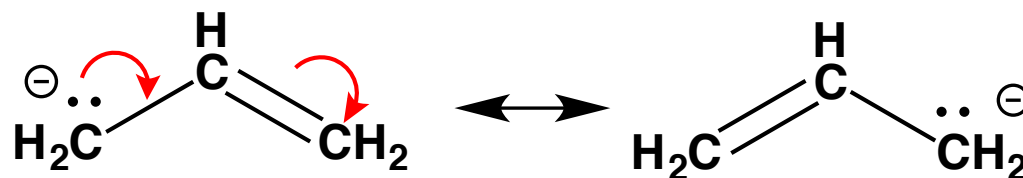
(スタートは電子対でも結合でも) ゴールがこれまで結合してなかった原子の場合 = **結合が形成**

(スタートが結合で) ゴールが分子内の原子の場合 = その原子の**電荷が一段階負に**

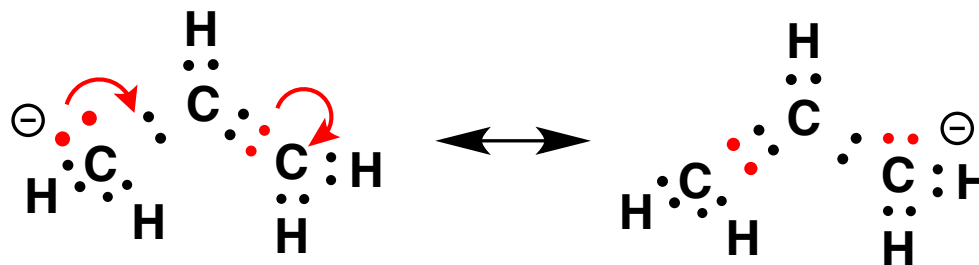
・ 矢印を1つ書いてみた後の状態が不自然な場合、さらに次の矢印を書いていく。

共鳴構造式の書き方

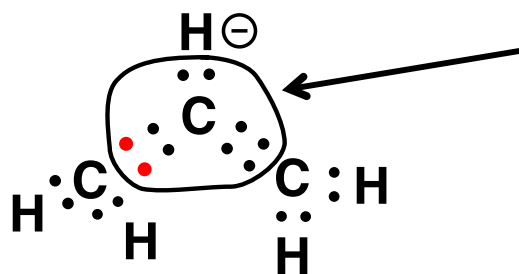
- 注1 不自然な形式電荷をもつLewis構造式は除く (eg. +2や-2の電荷等)
- 注2 Lewis構造式を描く場合、オクテット則をオーバーしないように
- 注3 原子を無くしたり、追加したりしたらダメ (化学種が変わる)
- 注4 原子の繋がりパターンを変えたらダメ (化学種が変わる)



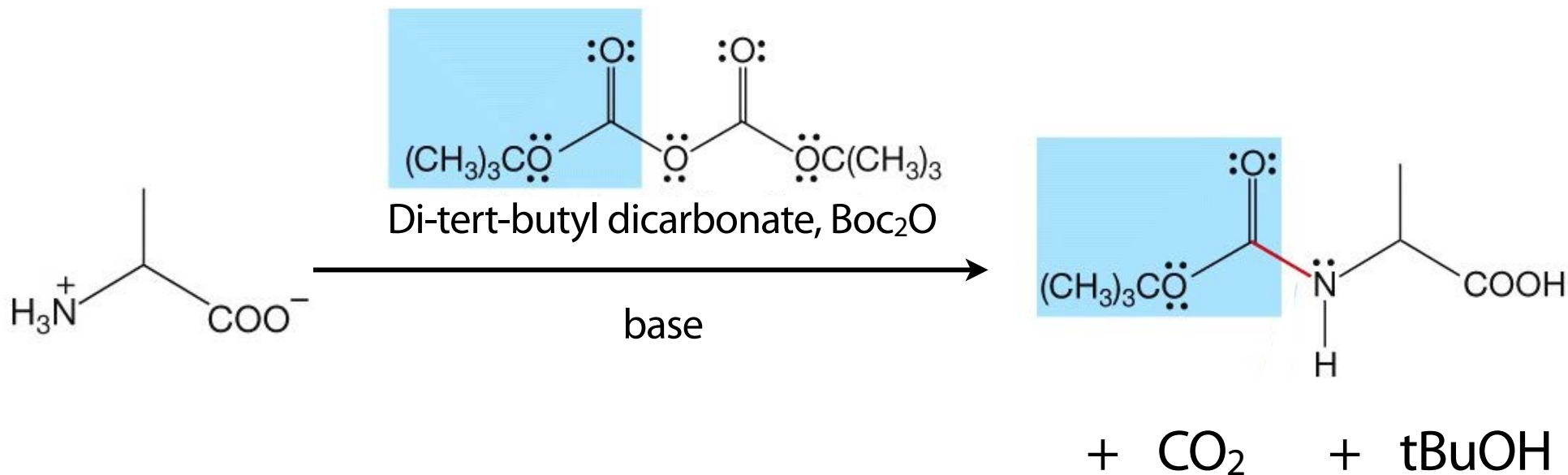
電子式で書くと...



途中で止めてしまうと...



オクテット則をオーバー
(最外殻に10個の電子)
→存在し得ない状態

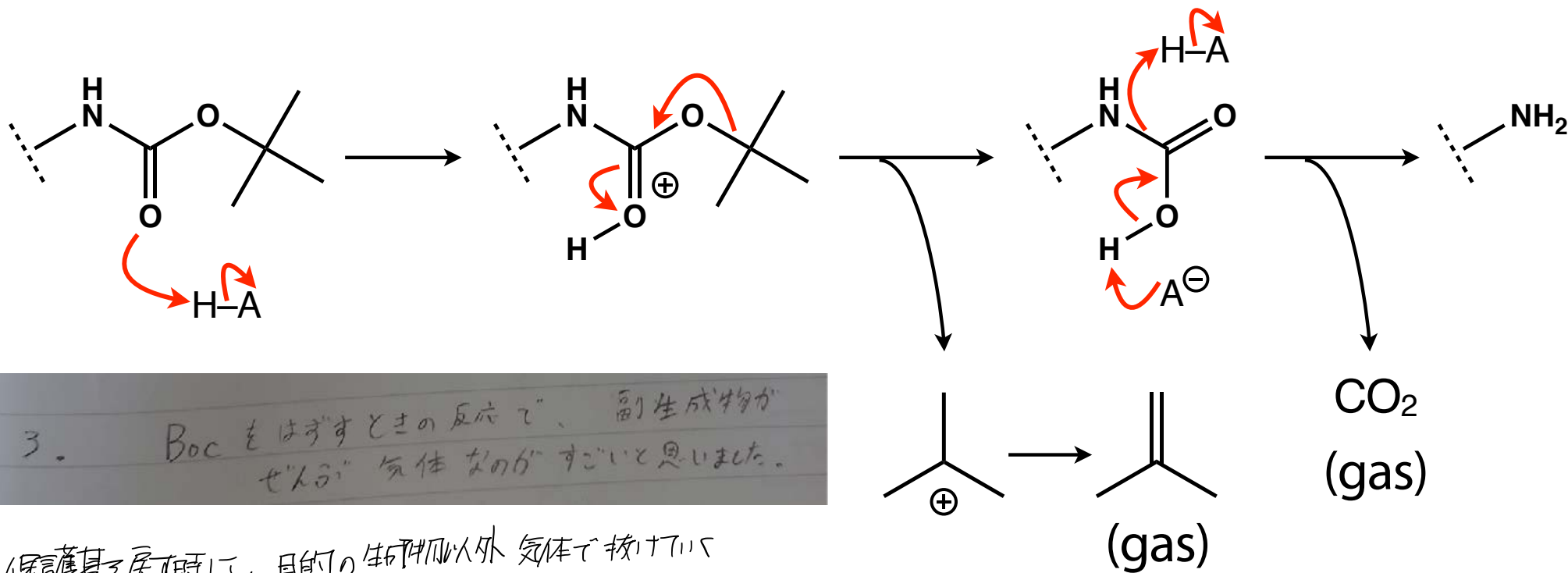


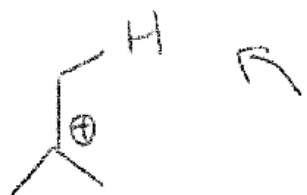
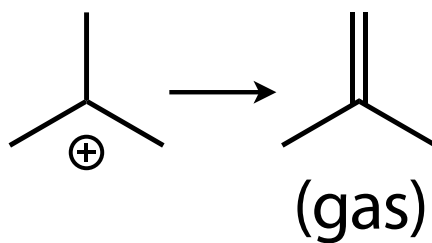
Practice quiz: Reaction mechanism?

Why is the product in Q1 $\text{Boc}-\text{N}(\text{H})-\text{CH}(\text{CH}_3)-\text{COOH}$ but not $\text{Boc}-\text{N}(\text{H})-\text{CH}(\text{CH}_3)-\text{COO}^-$ under basic condition?

You are right. After the reaction finishes, the product exist as its carboxylate form in the reaction mixture.

1. In the subsequent purification step, the product will be neutralized for isolation.
2. By convention, we generally provide chemical structures as their neutral form in reaction schemes unless a specific charged form is relevant in the reaction.

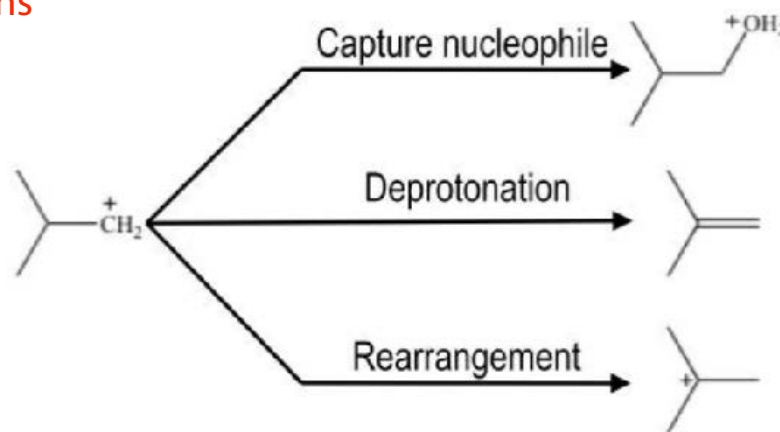


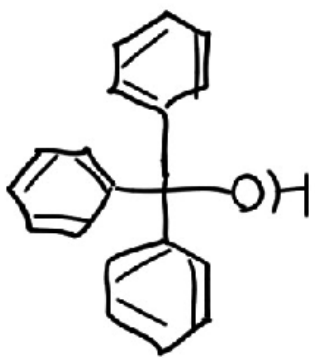


Is pKa of this proton
 low enough to form CC(C)=C
 in acidic condition?

This step is an equilibrium reaction (i.e., isobutene can be protonated to regenerate the carbocation under the acidic conditions).
 And, the pKa is not very low enough to efficiently generate isobutene.
 But, the product isobutene can be liberated from the reaction mixture, so most of the carbocation species will be eventually converted to isobutene.

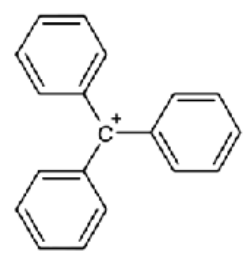
Review; fate of carbocations





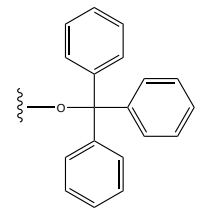
を Bu-OH の代わりに使うことはあまりないのでは
しょうか？

Yes!

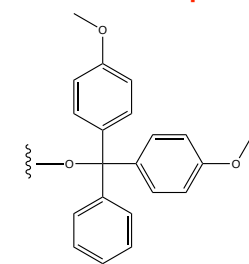


is very stable cation, so it can be used for acid labile protective group.

triphenylmethyl;
trityl (Trt)
トリチル基



-OTrt



-ODMT

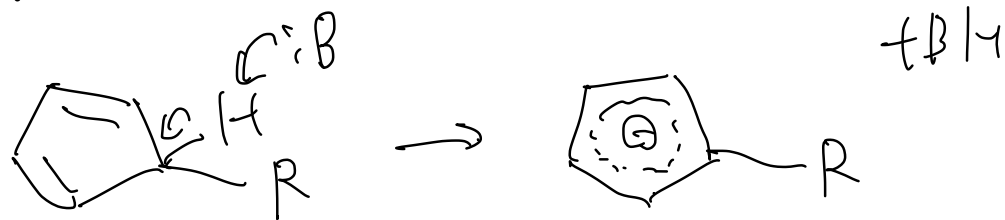
-OMe → -OH はできない
-Ot → -OH はできるという話に興味深かったです。

ということで、さらに外し易い版がTrt基です↑

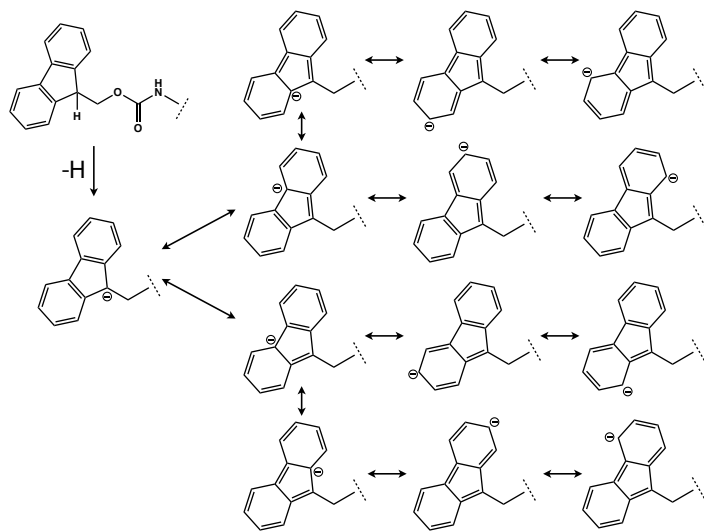
3、良く考えられて、
有機化学者って
すごいなーって思いました。
(語いカ)

僕も昔の偉い先生ありがとうっていつも思ってます。(語いカ)

Fmoc基のアリール環がなくとも、シクロペンタジエニルが芳香族に分子を駆動力にして脱プロトン化で異なる気がしました。

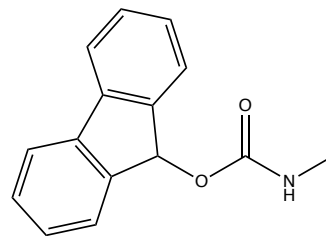


Good thinking!



Actually, this is also aromatization upon deprotonation.

(14 π)



Structure Match

- As Drawn (1)
- Substructure (335)
- Similarity (274)
- Analyze Structure Precision

Chemscape Analysis

Visually explore structure similarity with a powerful new tool. Learn more about Chemscape.

Create Chemscape Analysis

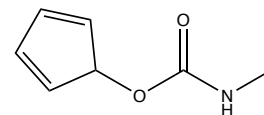
1 Result

1

61518-14-7

C₁₅H₁₃NO₂
9H-Fluoren-9-yl, 3-(N-methyl)carbamate

1 Reference 0 Reactions 2 Suppliers



Structure Match

- As Drawn (0)
- Substructure (0)
- Similarity (280)

Chemscape Analysis

Visually explore structure similarity with a powerful new tool. Learn more about Chemscape.

Create Chemscape Analysis

Filter Behavior

Filter by Exclude

Filtering: Number of Components: 1

271 Results

1

1943-79-9

C₈H₉NO₂
Phenyl methylcarbamate

330 References 143 Reactions 45 Suppliers 7 Refe

有機実験としていて分からないと困る感じたの。それはそれと
分からないことが多くて。復習 ちゃんとしてます。

有機化学は「分からないに 対して 学ぶ までか
長〜の で 突いてる...

「アジ、とか「無水物の acidity」とかを忘れていた。有機はよく使うので、
アジ→アジ 字が直ぐうと覚えました。

る。アジノ基と無水物の反応機構はまるっきり忘れていました。

有機化学はいまある学問の中でもかなり体系だって理解/勉強できる分野になっていると個人的には思います。

(「天才的」な理解や「センス」はそんなに必要ない)

なので頑張ってください。

今までの quiz の 答えを まとめて載せて頂けると
ありがたいです。

シケタイよろ。各ハンドアウトの最後にまとまっています。

英語で" コメントしたら

だれか" しつもんしたのかバツるので

はずかいです... (てか今もひろかな
は「かりで... 分かりやすい...)

質問

日本語、とっても上手!

③

いつも何を飲まれているのかを見るのが楽しみです。

照れるやん。。。

6/8 (Wed) **Goto** sugar #1
6/10 (Fri) **Goto** sugar #2
6/15 (Wed) **Goto** sugar #3 & amino acids #1
6/17 (Fri) **Goto** amino acids #2 & peptides #1
6/22 (Wed) **Goto** peptides #2
6/29 (Wed) **Goto** peptides #3

6/24 (Fri) no class!

7/1 (Fri) **Suga** carbonyl #4
7/6 (Wed) **Suga** carbonyl #5
7/8 (Fri) **Suga** ribosomal synthesis of peptides
engineering of translation

7/13 (Wed) or 7/15 (Fri) **no class!**

7/22 (Fri) **Final exam**

Final Exam

July 22nd (Fri) 10:25~11:55

on-site (Chemistry main bldg., 3F lecture room)

guidelines

- There will be a 15-minute "cheating time" during 10:55–11:10. During this time, you may see the textbook, lecture handouts, notes, memos, etc. that you brought.
- However, viewing/using electronic devices such as PCs, tablets, and cell phones is prohibited.
- Consultation/discussion with other students is also prohibited.
- 開始30分後からの15分間、「cheating time」を設けます。この間は、持参した教科書・講義資料・ノート・メモ等を参照しても構いません。
- ただし、PC・タブレット・携帯などの電子デバイスの閲覧/使用は禁止。
- 他の人との相談も禁止。

Topics

- **synthesis of peptides**

- protection of amino group
 - Boc group
 - Fmoc group

done

-
- activation of carboxyl group
 - condensation agents
 - additives
 - solid phase peptide synthesis
 - condensation agents
 - additives

- **structure of peptides**

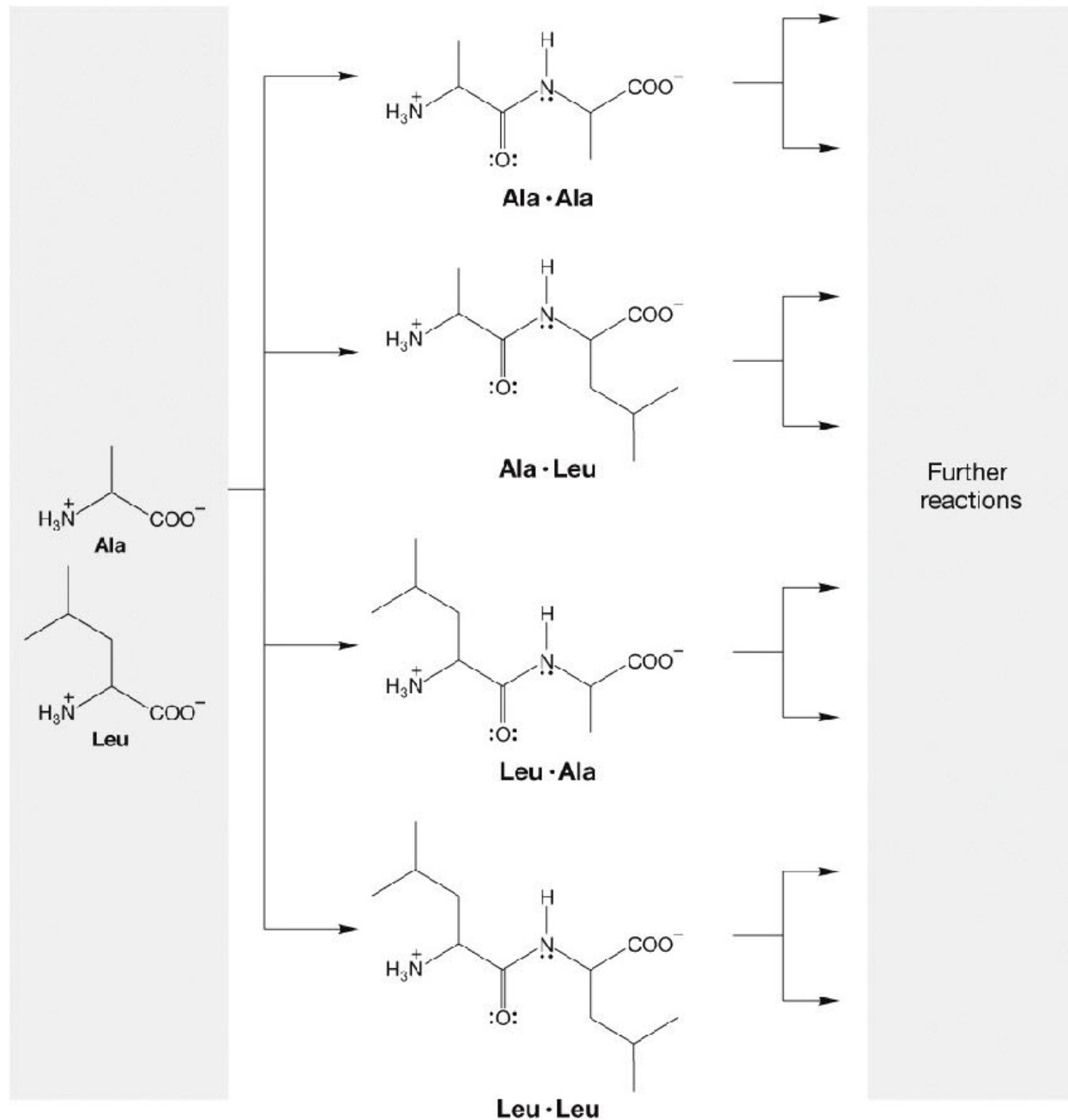
- properties of amide bonds
- secondary and tertiary structures of peptides

- **reactions of peptides**

- Edman degradation
- cleavage by CNBr

Chemical synthesis of peptides

If you try to synthesize H-Ala-Leu-OH by condensation of Ala and Leu...

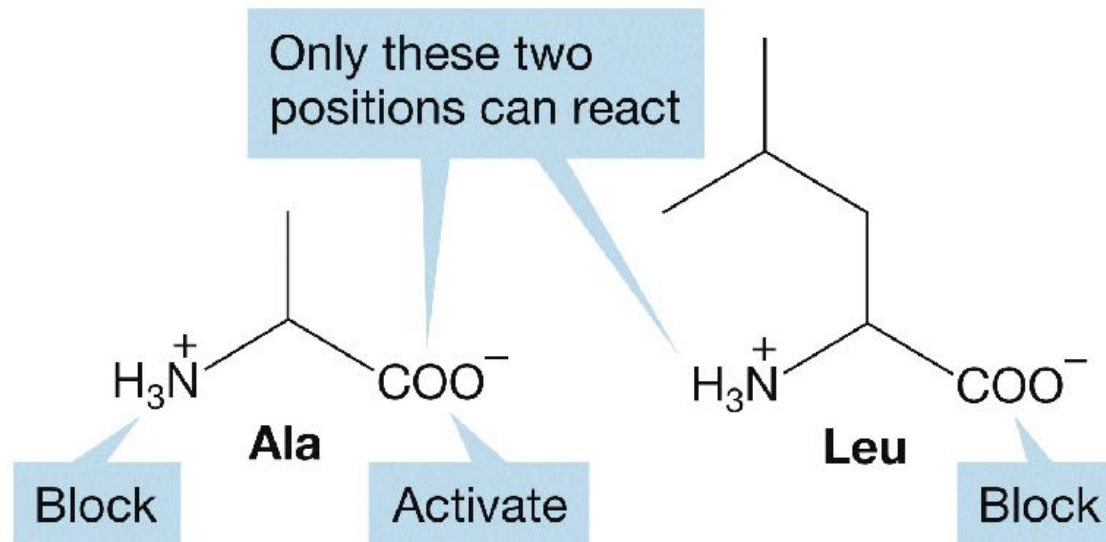


Chemical synthesis of peptides

To selectively and efficiently obtain H-Ala-Leu-OH,

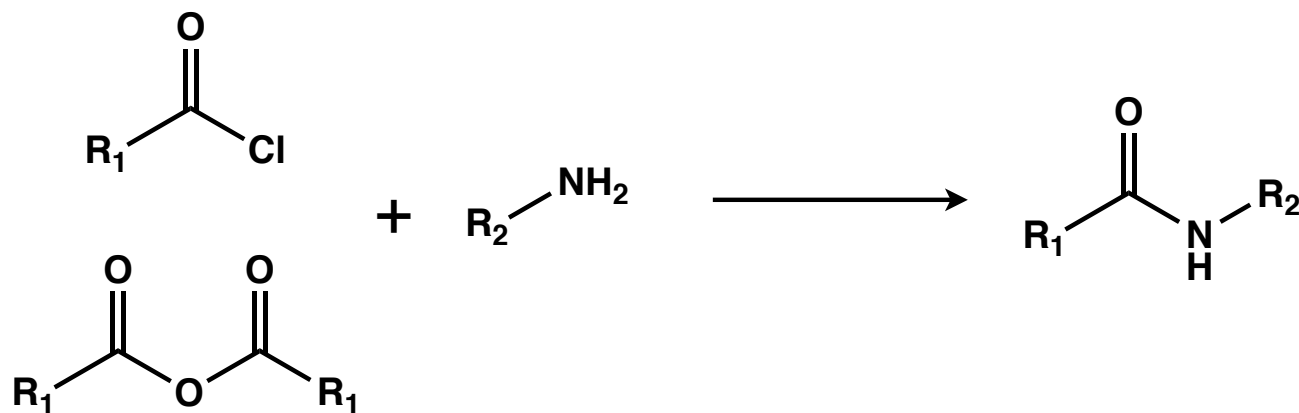
- 1. Protection of amino group**
- 2. Activation of carboxyl group**

are required.

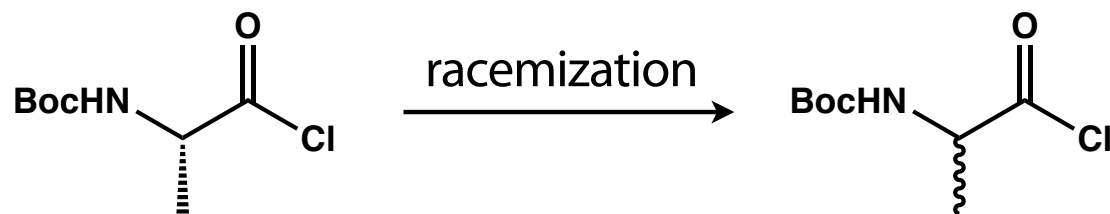


Activation of carboxyl groups in peptide synthesis

In general organic chemistry, acid chlorides and acid anhydrides are often used for amide formation.



But, acid chlorides and acid anhydrides are not generally used in peptide synthesis.

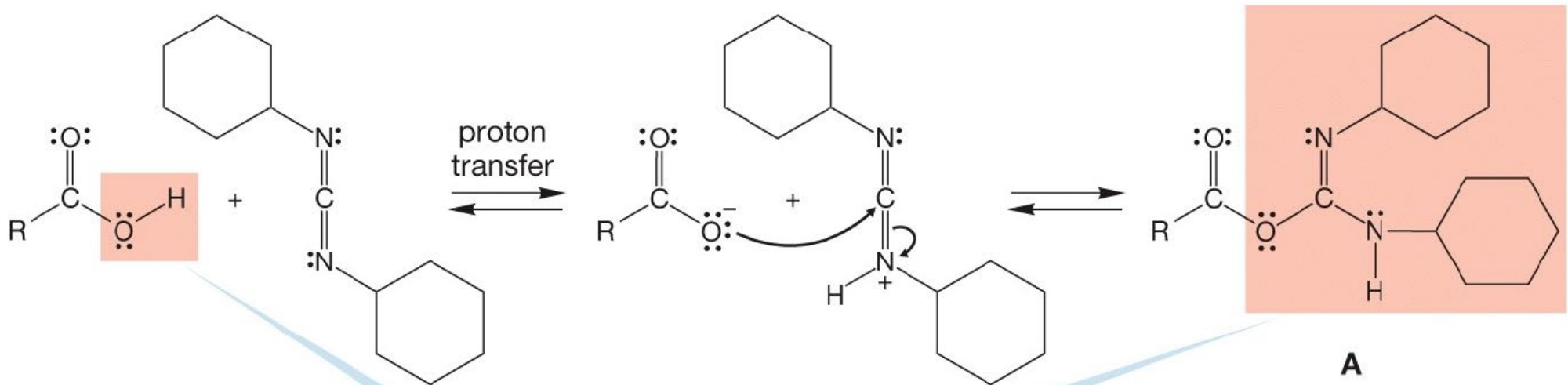
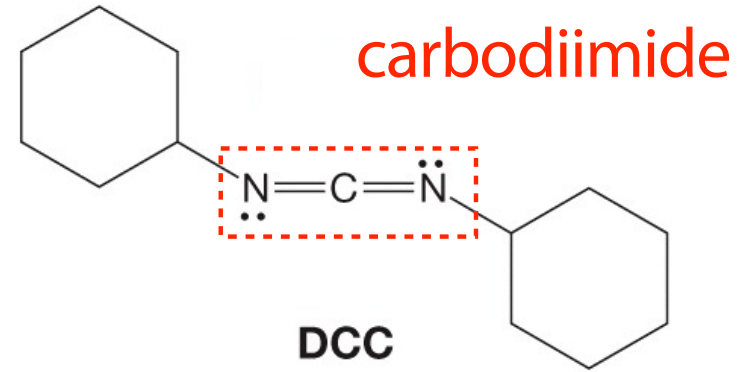


(Also, reaction conditions to prepare acid chlorides are generally harsh.)

Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

N,N'-Dicyclohexylcarbodiimide (DCC)

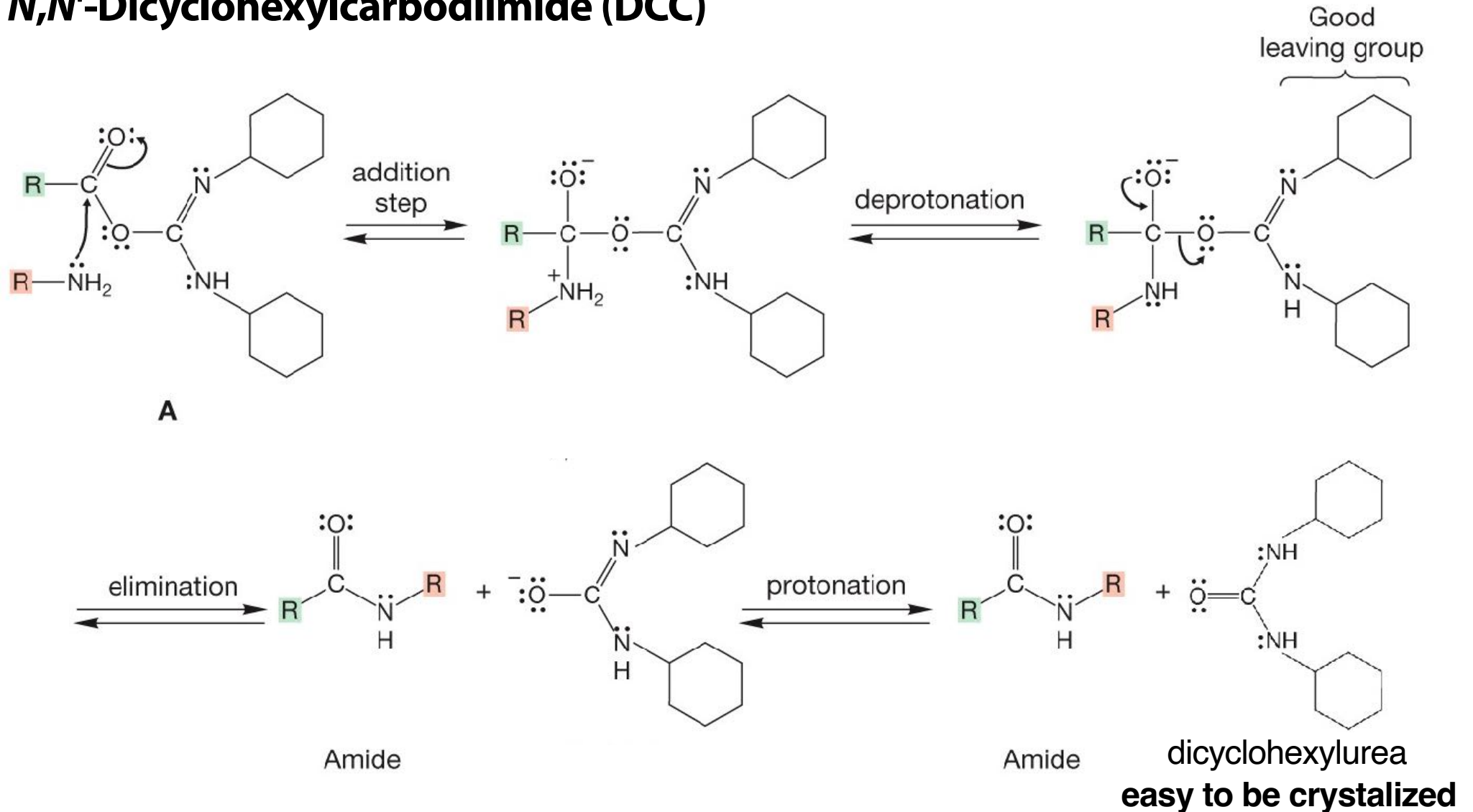


Overall change; better leaving group formed

Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

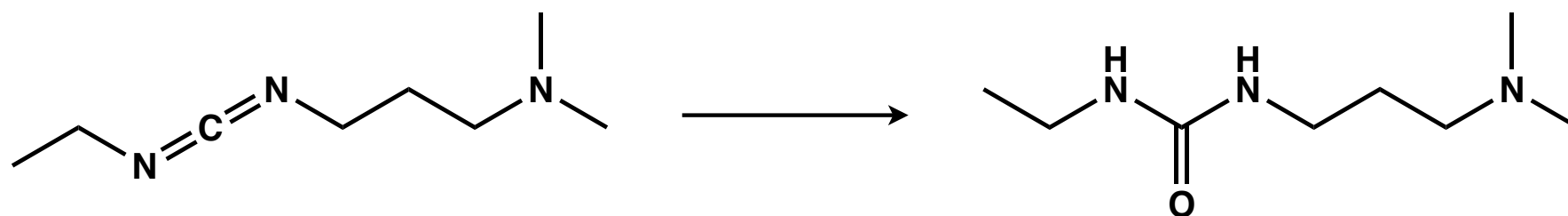
N,N'-Dicyclohexylcarbodiimide (DCC)



Activation of carboxyl groups in peptide synthesis

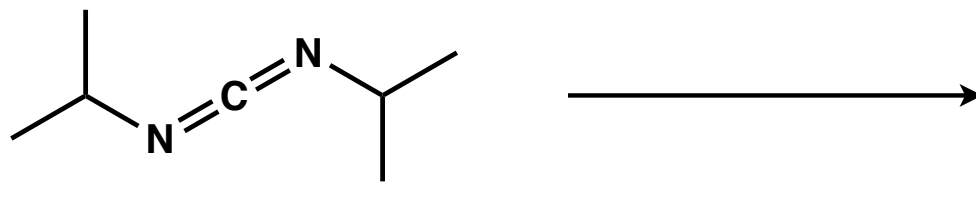
other carbodiimides

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)



residual urea
removable by extraction

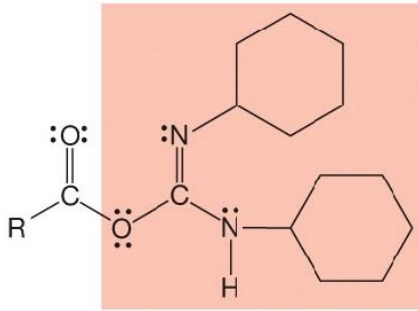
N,N'-Diisopropylcarbodiimide (DIC)



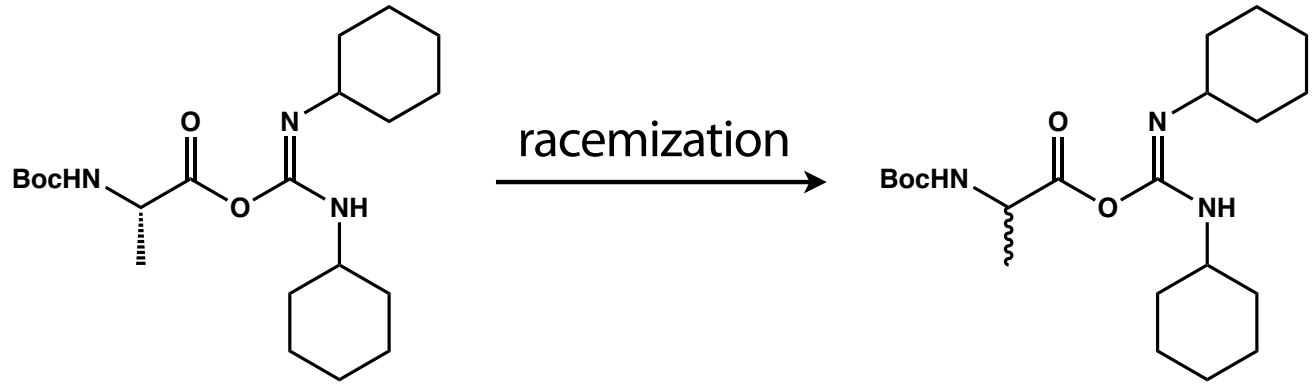
residual urea
soluble in organic solvents

Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

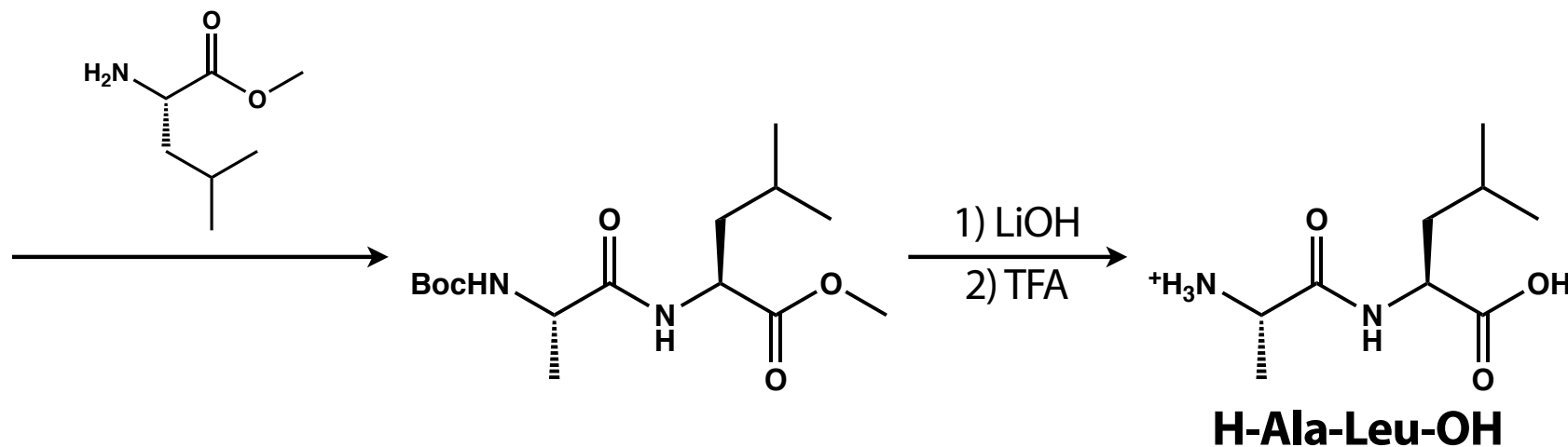
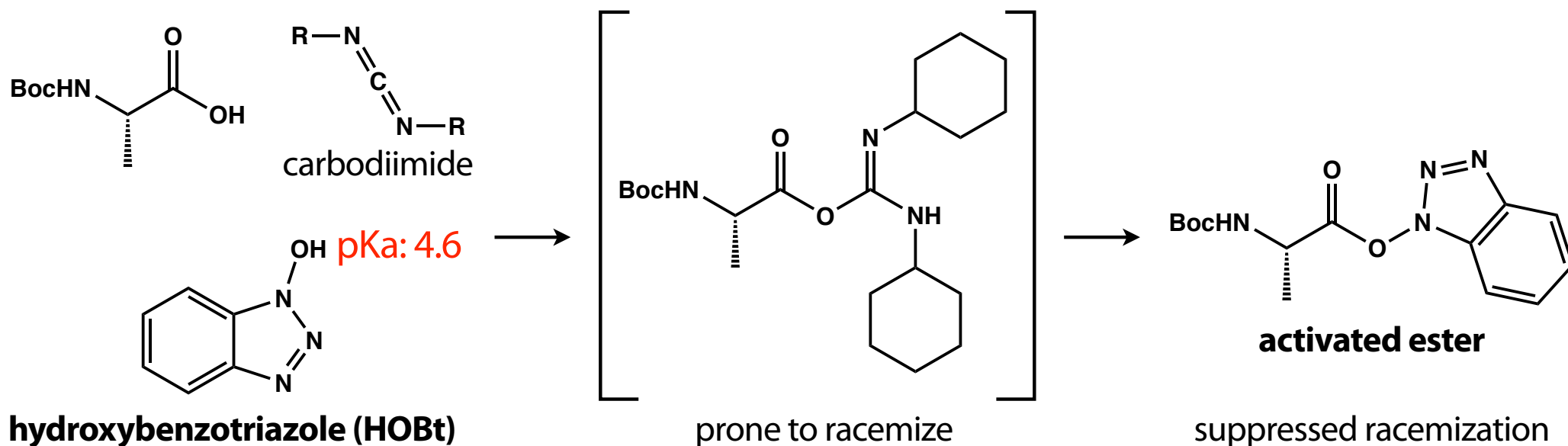


prone to racemize



Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤) and **additives to generate activated esters**



Efficient and facile solid phase peptide synthesis (固相合成)

Efficiency and facility are critical in peptide synthesis

Even if the yield of one cycle of coupling/deprotection is 90% ...

yield of 10-mer peptide is $0.9^{10} = 35\%$ in 20 steps

yield of 20-mer peptide is $0.9^{20} = 12\%$ in 40 steps

yield of 30-mer peptide is $0.9^{30} = 4\%$ in 60 steps



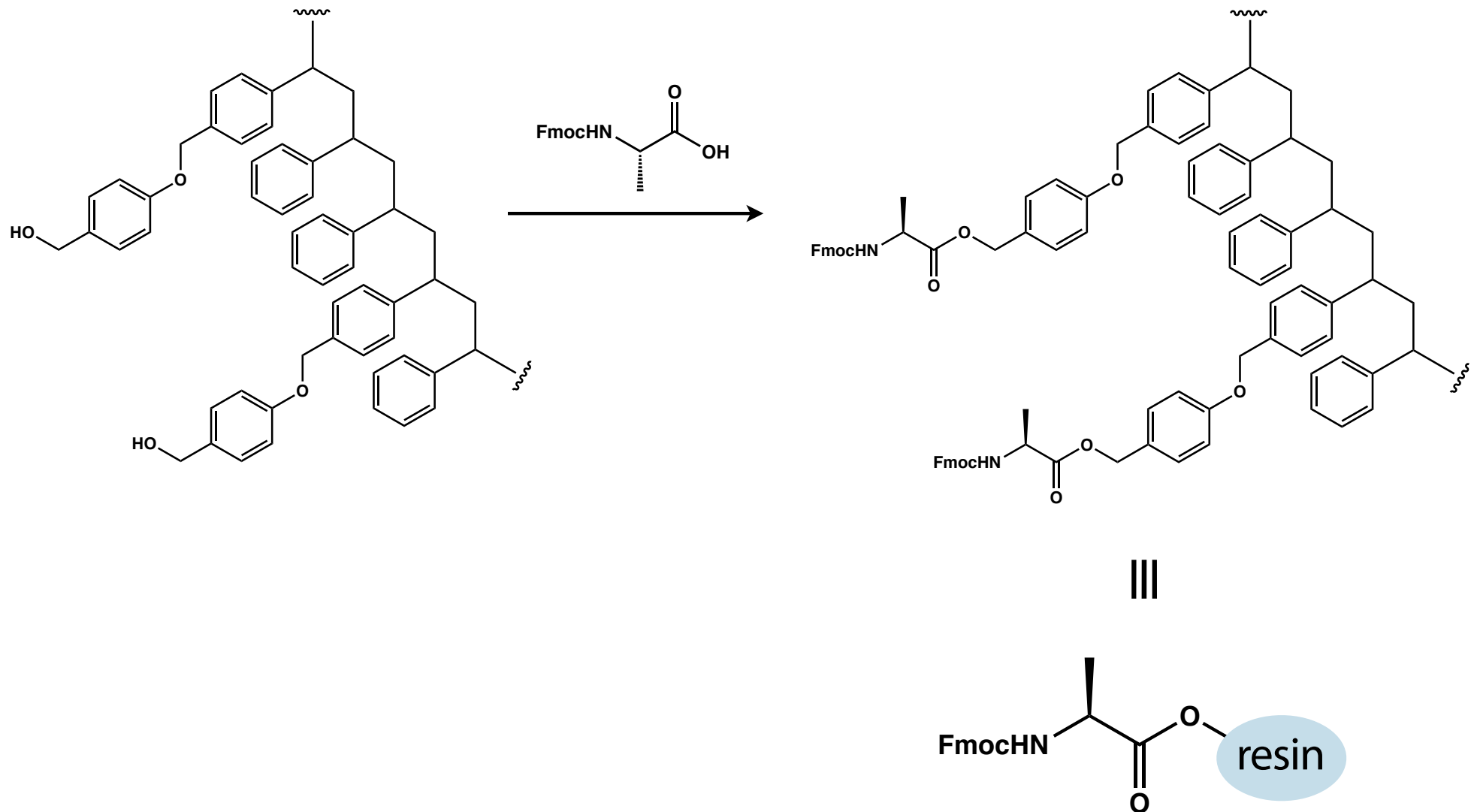
Robert Bruce Merrifield

Nobel Prize in Chemistry (1984)

"for his development of methodology for chemical synthesis on a solid matrix"

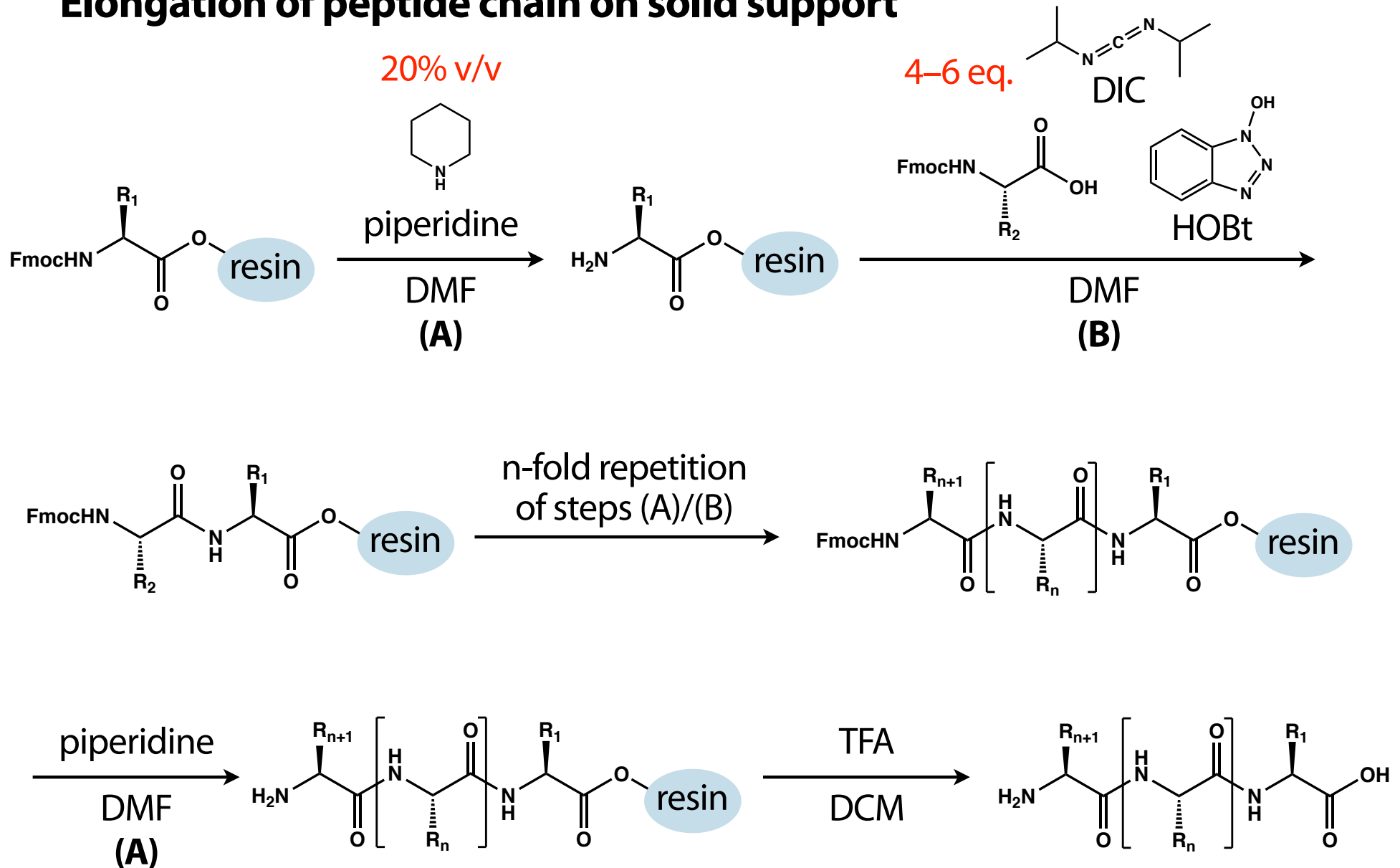
Efficient and facile solid phase peptide synthesis (固相合成)

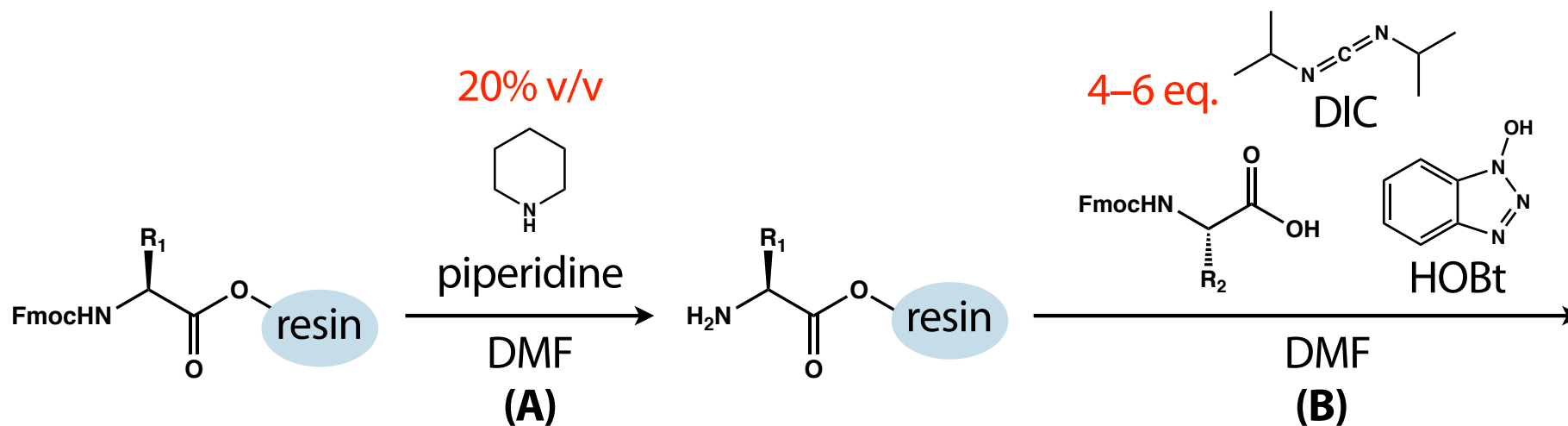
Loading an amino acid onto solid support (resin)



Efficient and facile solid phase peptide synthesis (固相合成)

Elongation of peptide chain on solid support



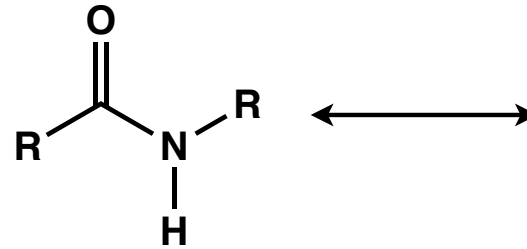


Automated solid phase peptide synthesis



Properties of backbone amide linkages

resonance structure of amide

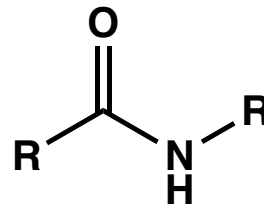


- Thus,
- the C–N bond has a partial double bond character
 - the amide oxygen has (weak but significant) nucleophilicity

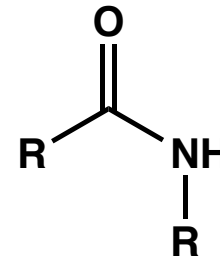
isomers of amide bond

Review point

conformation of conjugated dienes



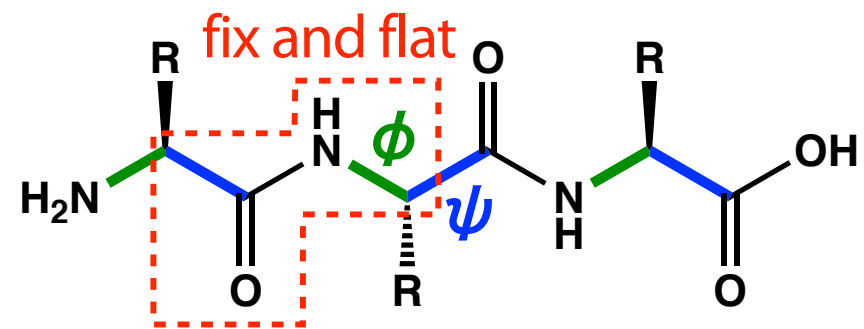
s-trans



s-cis

rigidity of peptide chain

only two rotatable bonds
in each residue

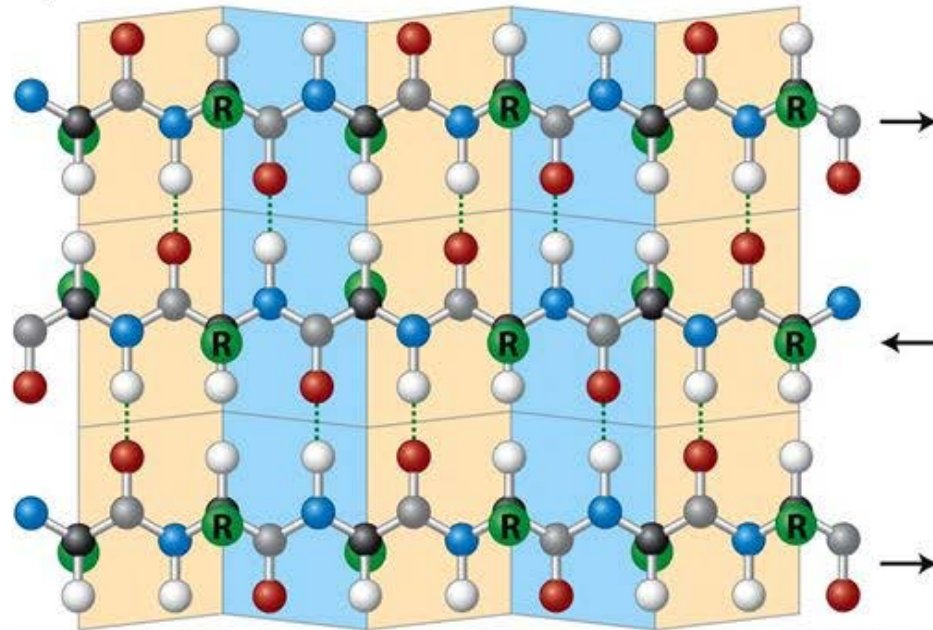


Structure of peptides

Secondary structures

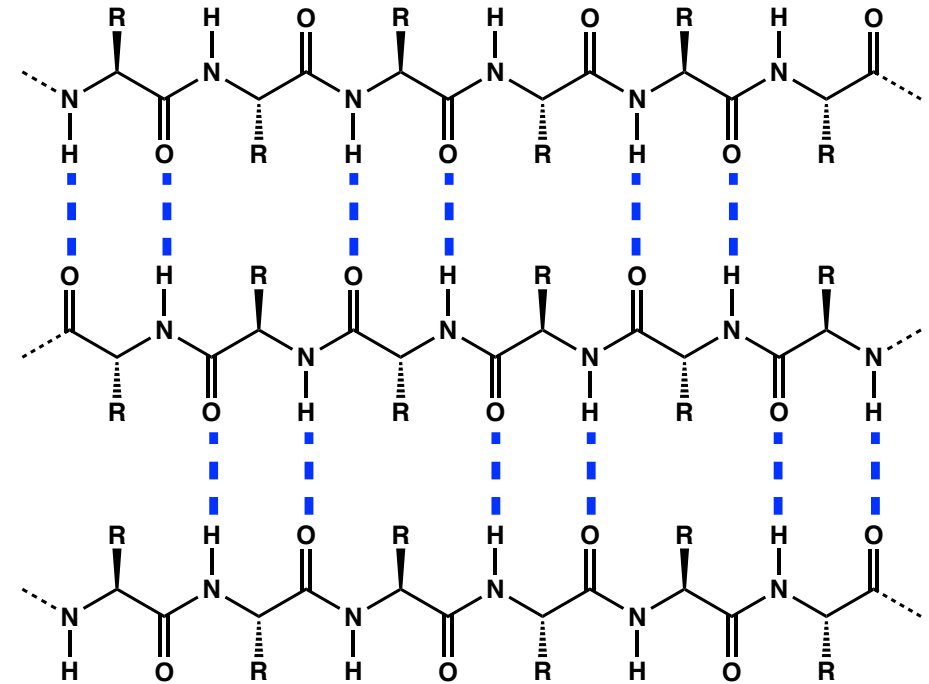
β -sheet

(a) Top view

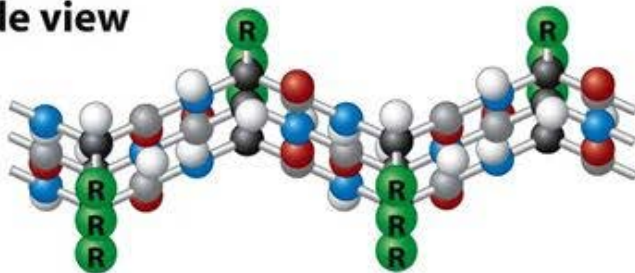


Amino
terminus

Carboxyl
terminus



(b) Side view



polypeptide backbone is extended and flat

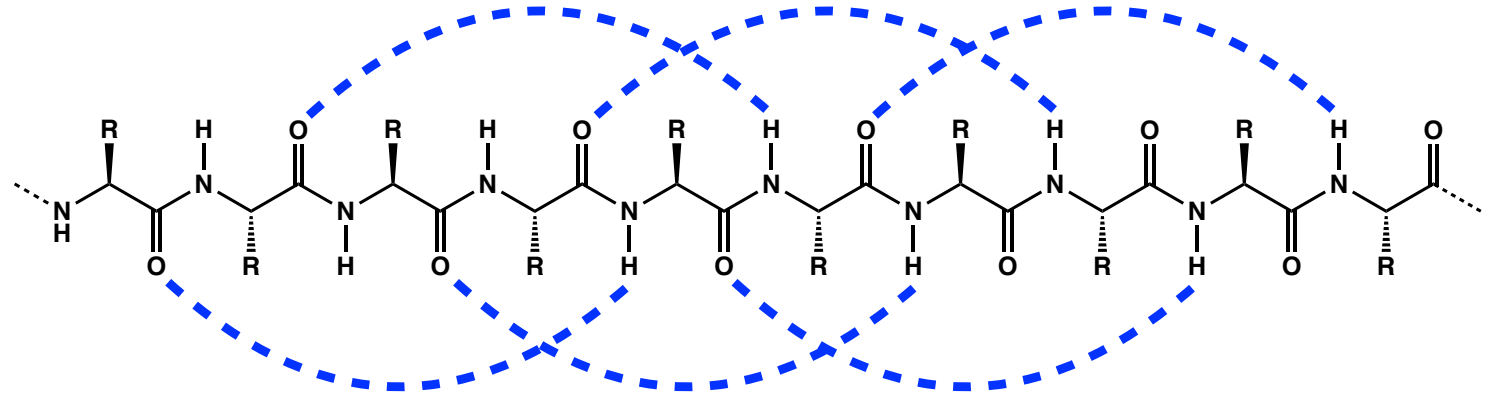
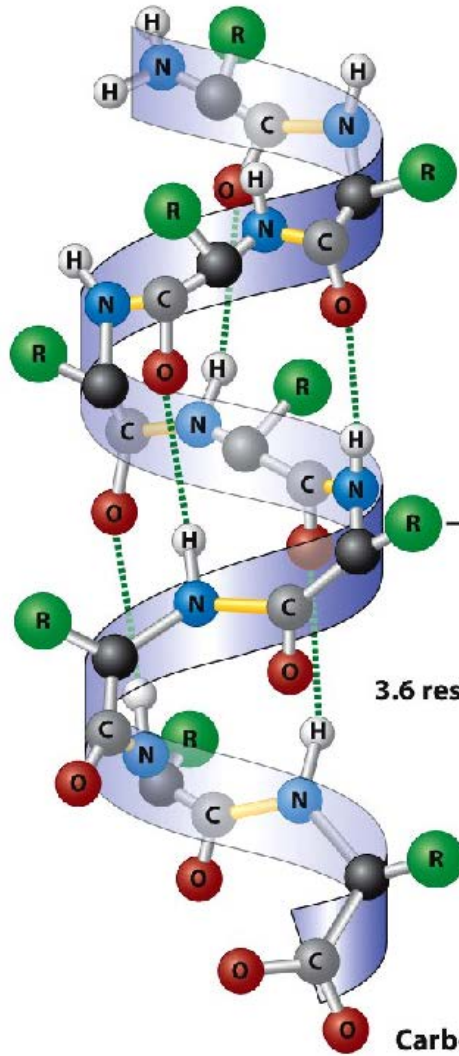
side chains alternately extend into
opposite sides of the sheet

Structure of peptides

Secondary structures

α -helix

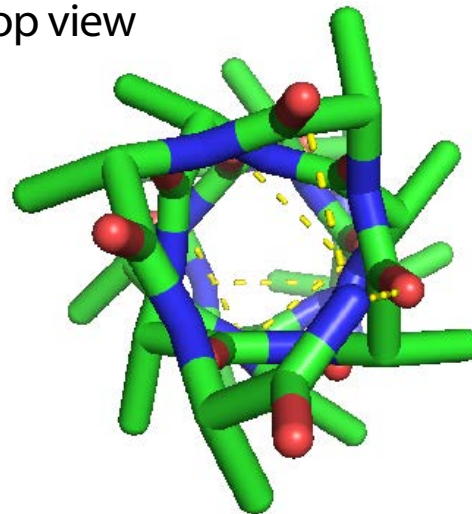
Amino terminus



hydrogen bonds

between $\text{C}=\text{O}$ of n th residue
and $\text{N}-\text{H}$ of $(n+4)$ th residue

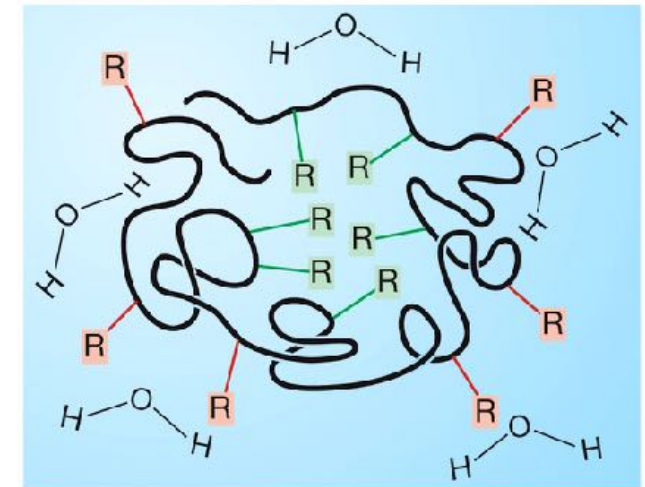
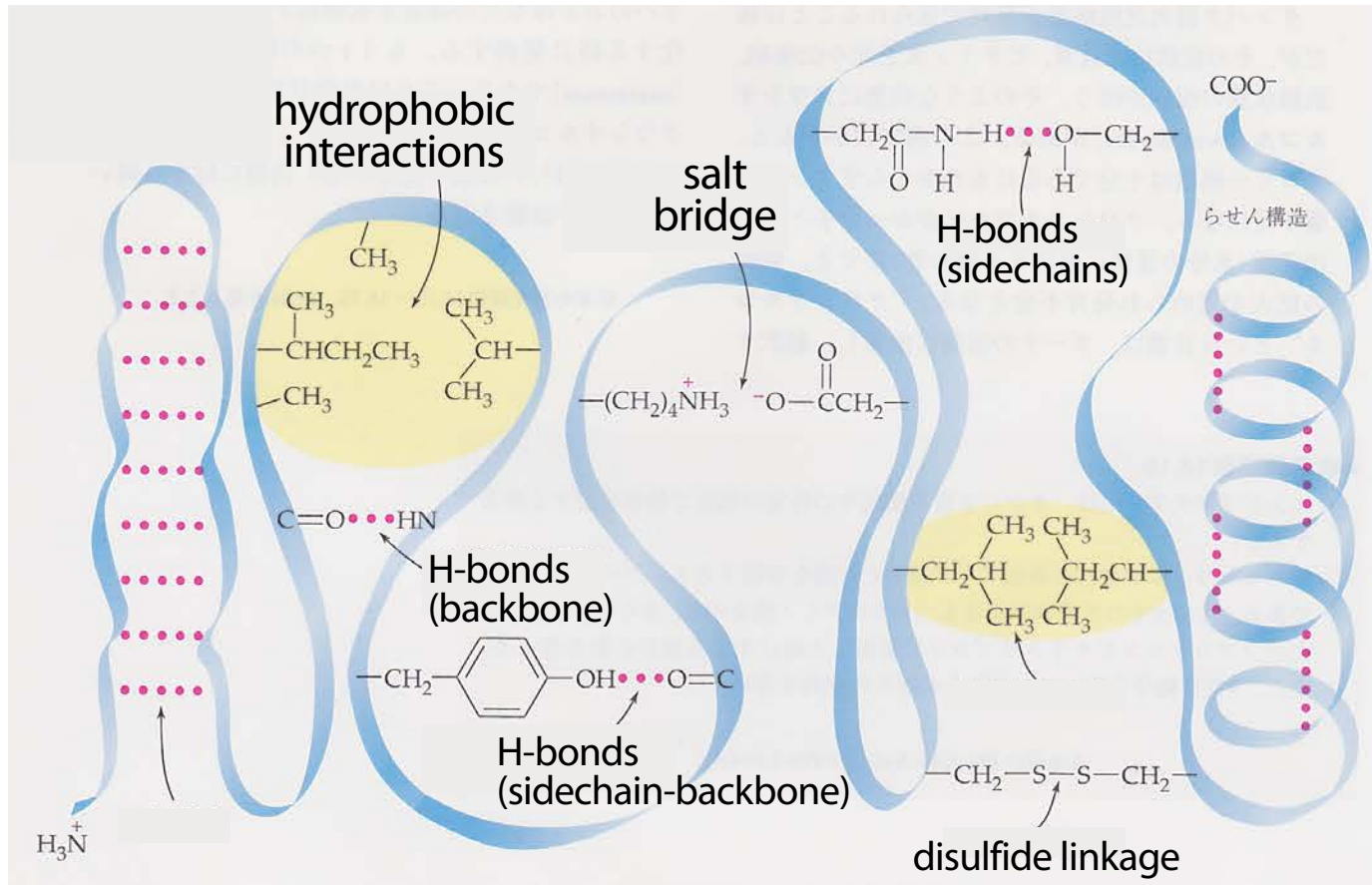
top view



side chains extend into
outside of the helix
with various directions

Structure of proteins

Tertiary structures



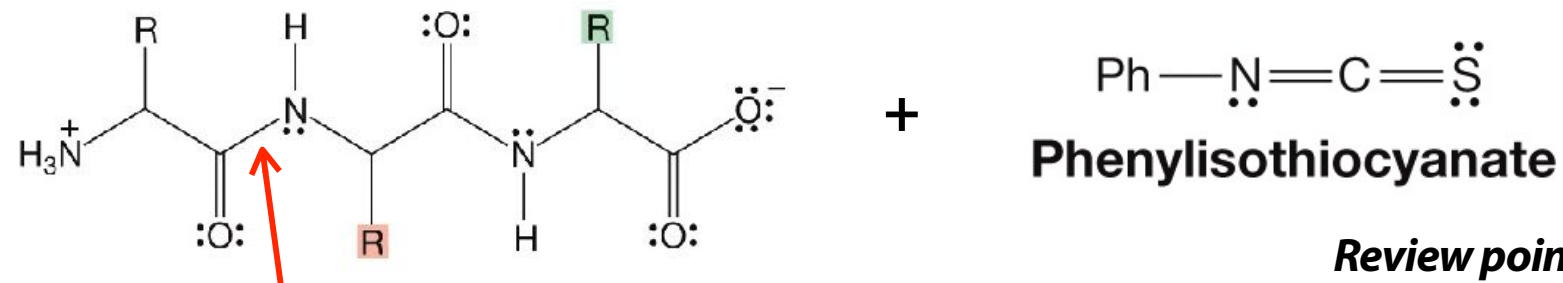
R = Hydrocarbon-like, nonpolar side chains
R = Polar side chains

Organic reactions of peptides

Amide bonds are chemically stable, but there are some reactions to cleave them

Edman degradation

overall reaction

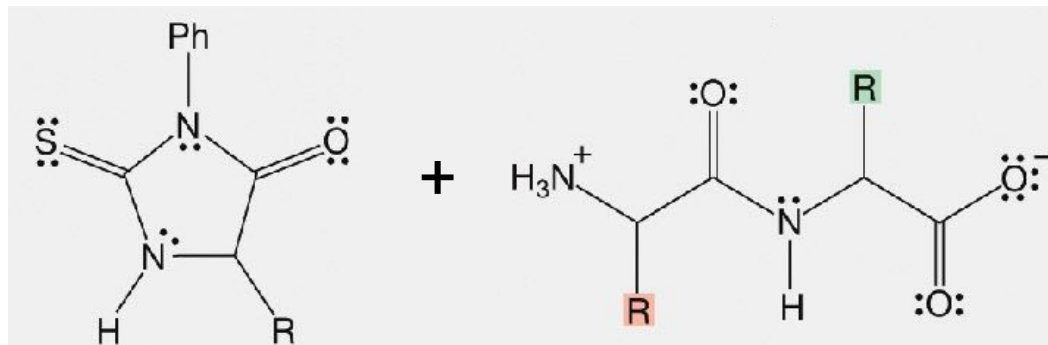


Phenylisothiocyanate

Review point

isocyanates generated
by Curtius rearrangement

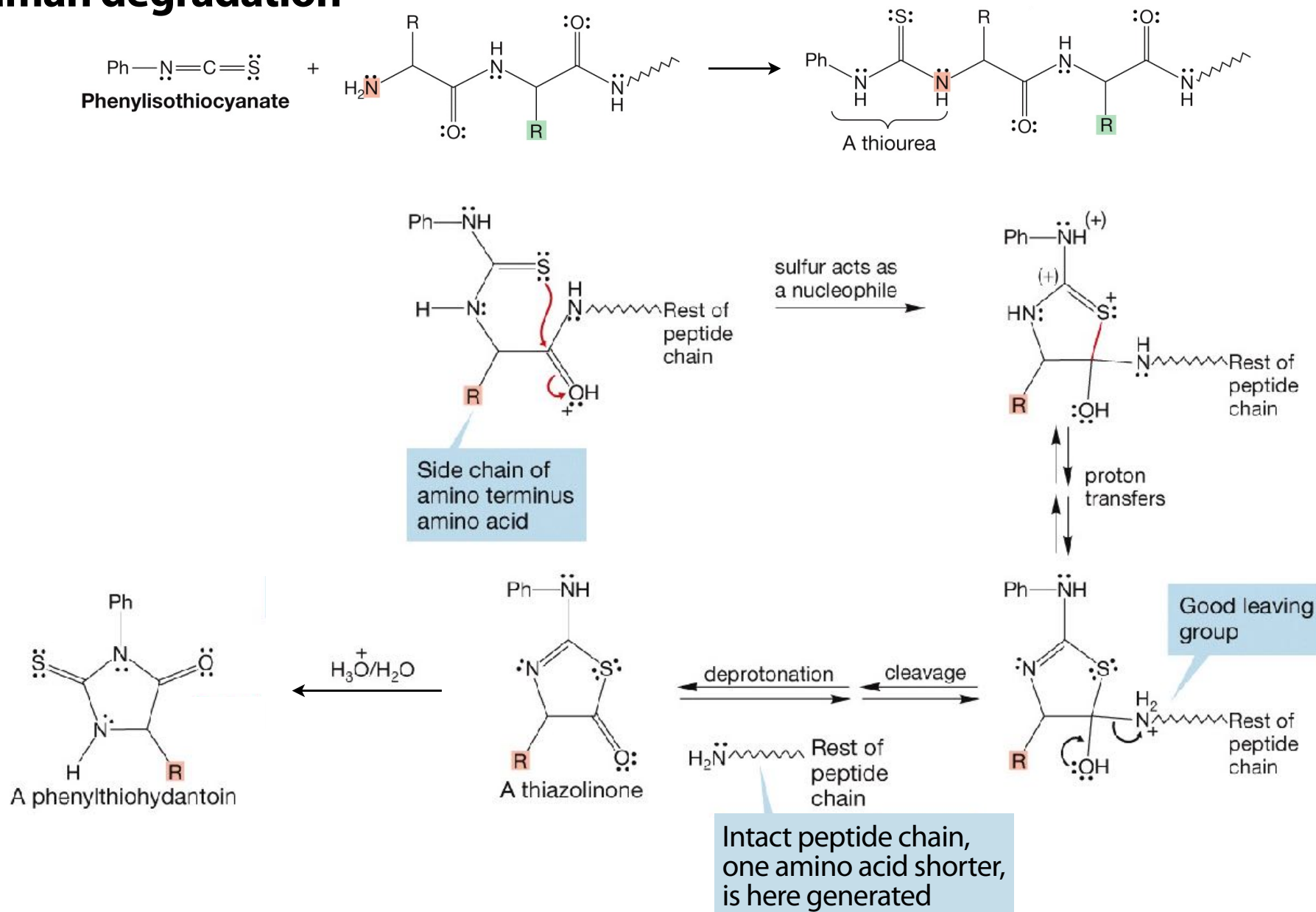
cleaved



Organic reactions of peptides

Amide bonds are chemically stable, but there are some reactions to cleave them

Edman degradation

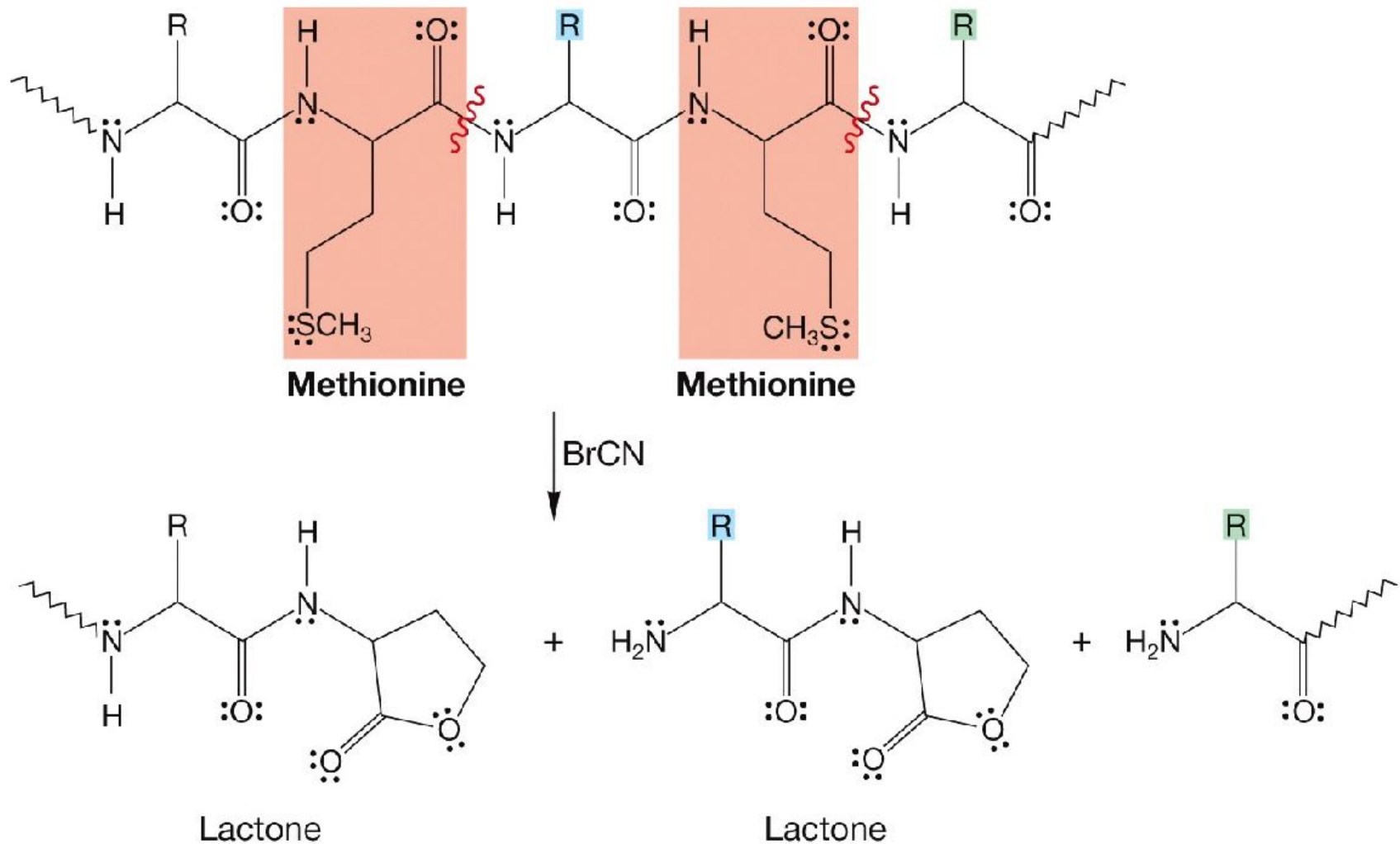


Organic reactions of peptides

Amide bonds are chemically stable, but there are some reactions to cleave them

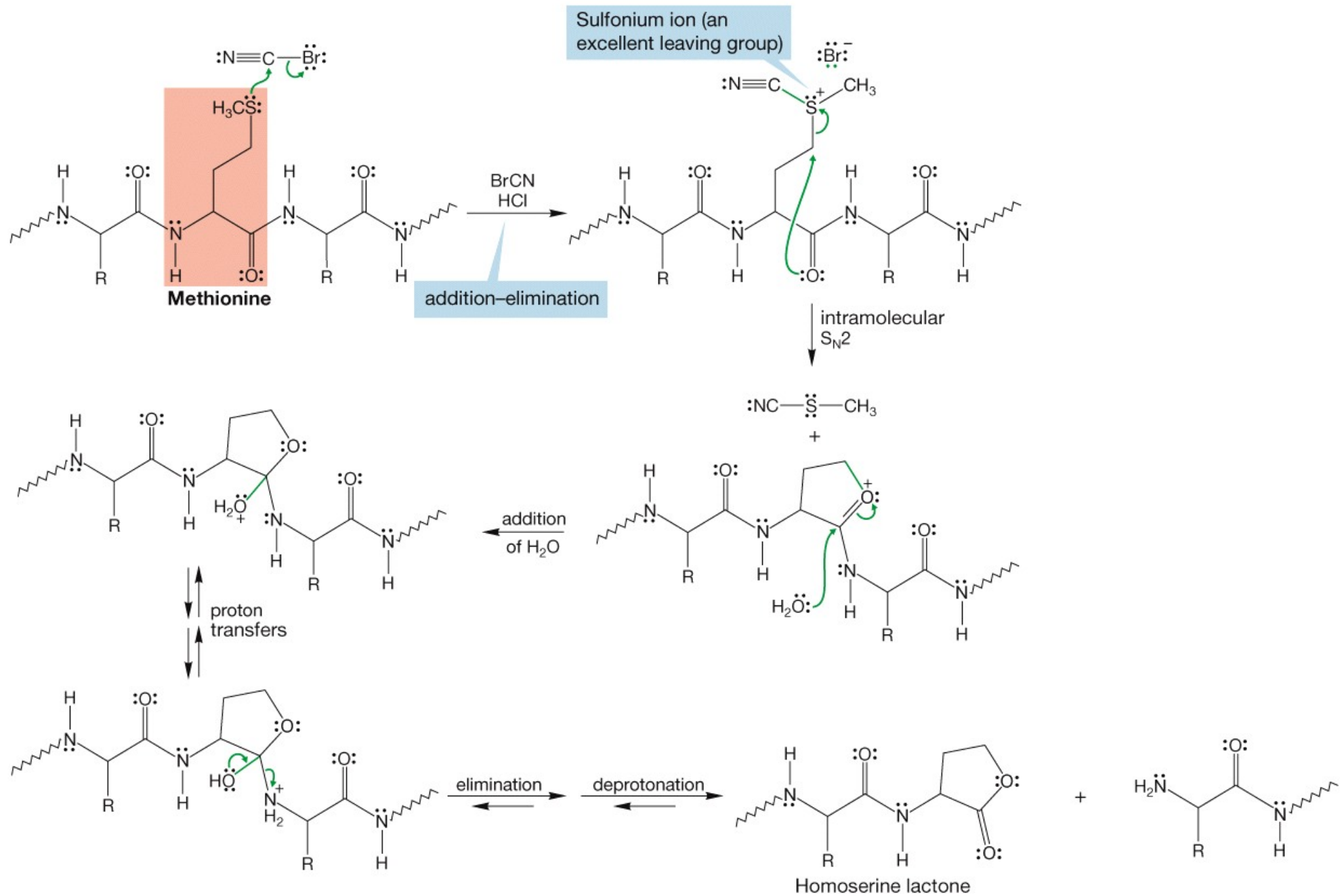
selective cleavage of Met sites by CNBr

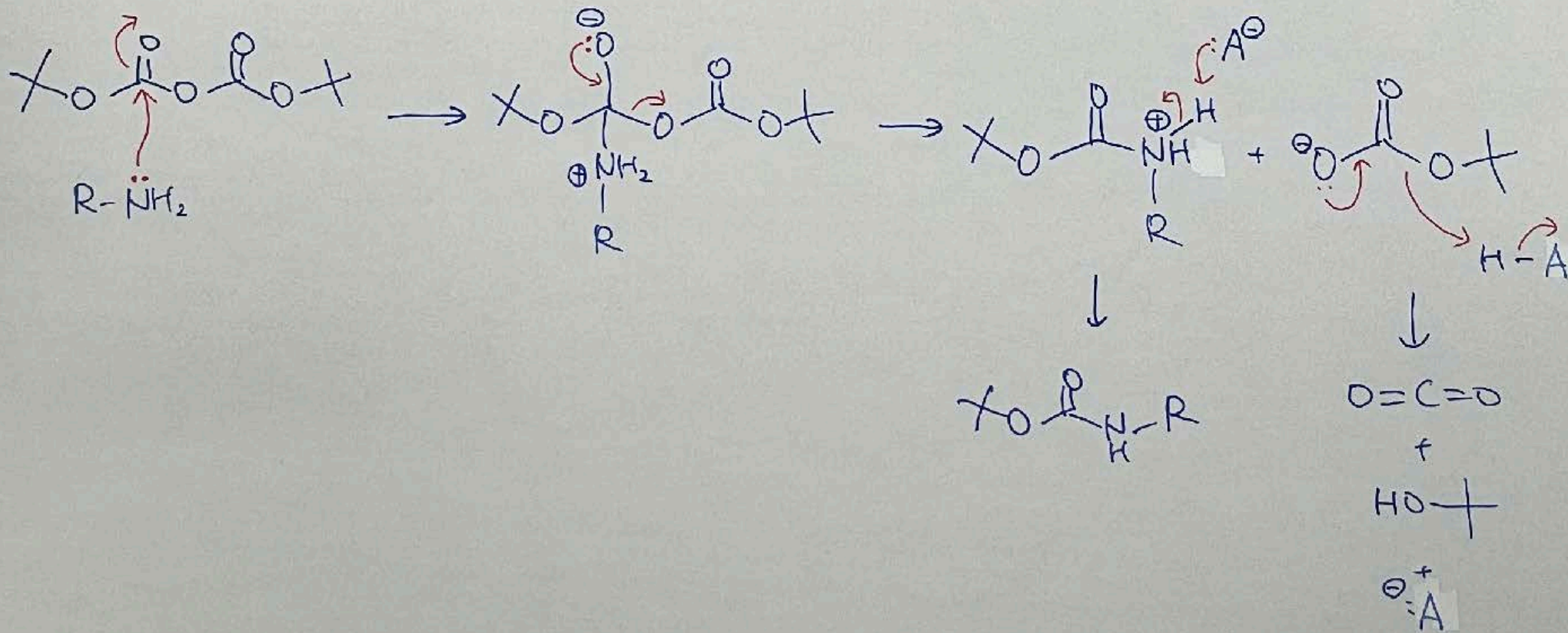
overall reaction



Organic reactions of peptides

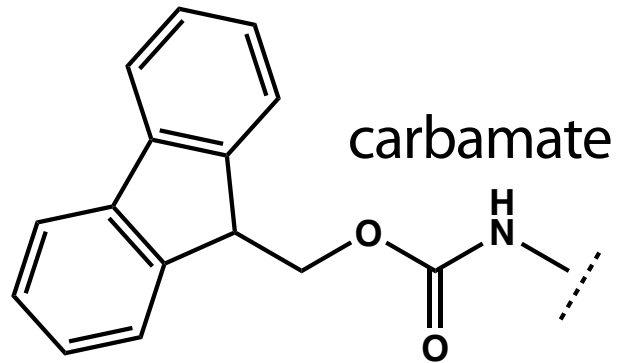
selective cleavage of Met sites by CNBr



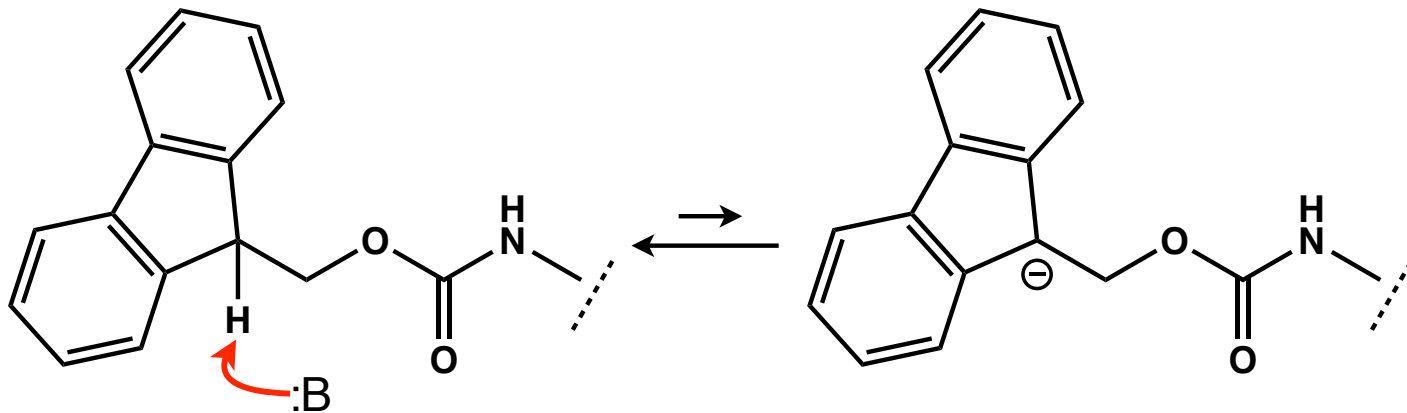


Protective group of amines in peptide synthesis

2. 9-fluorenylmethoxycarbonyl (Fmoc)

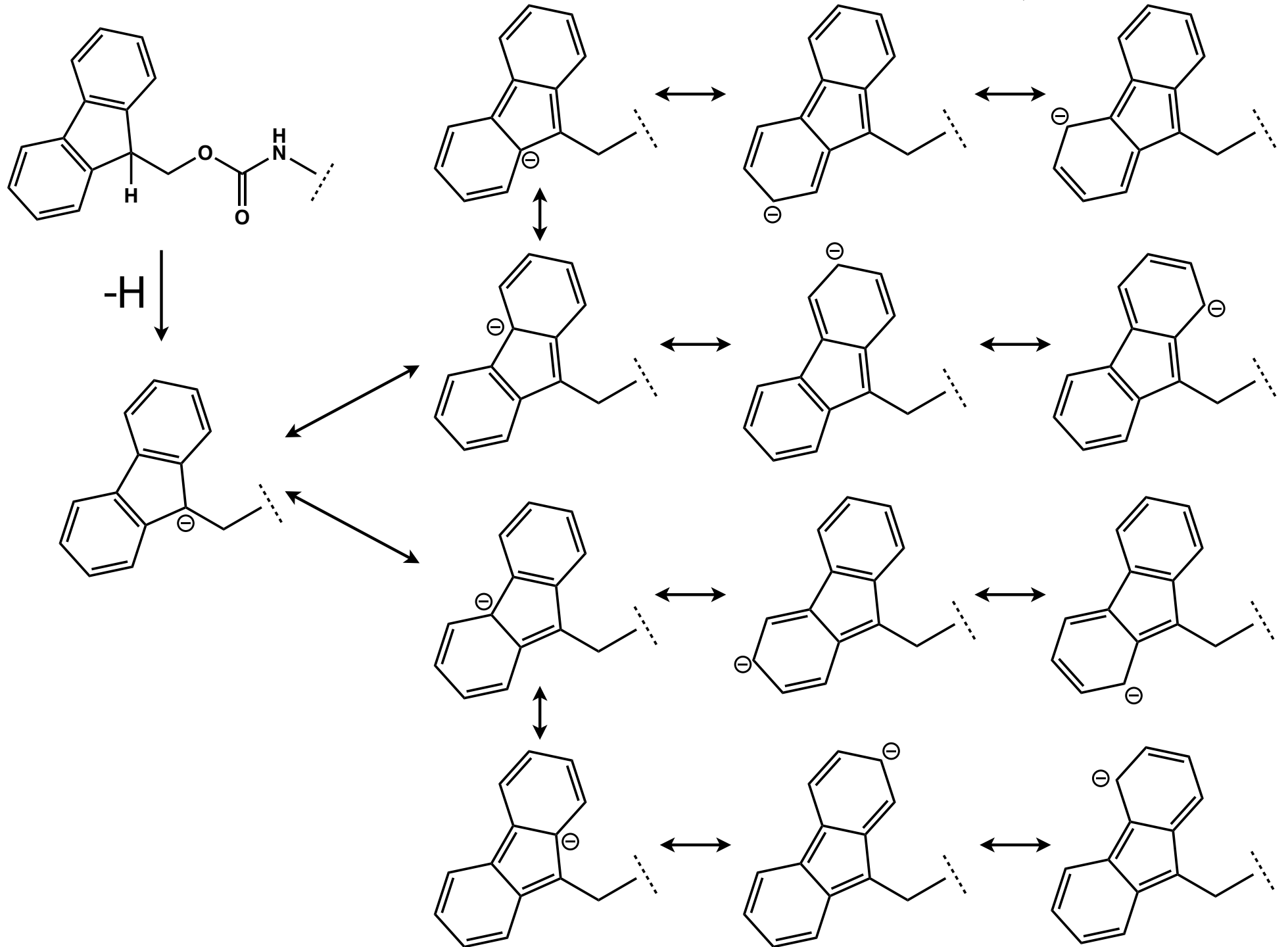


Deprotected under basic conditions (secondary amines such as piperidine)



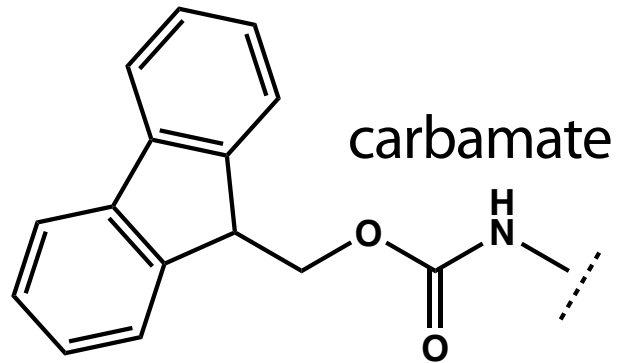
Practice quiz: Which proton in Fmoc group is the most acidic? Answer with your reason.

Protective group of amines in peptide synthesis



Protective group of amines in peptide synthesis

2. 9-fluorenylmethoxycarbonyl (Fmoc)



Deprotected under basic conditions (secondary amines such as piperidine)

