Organic Chemistry III

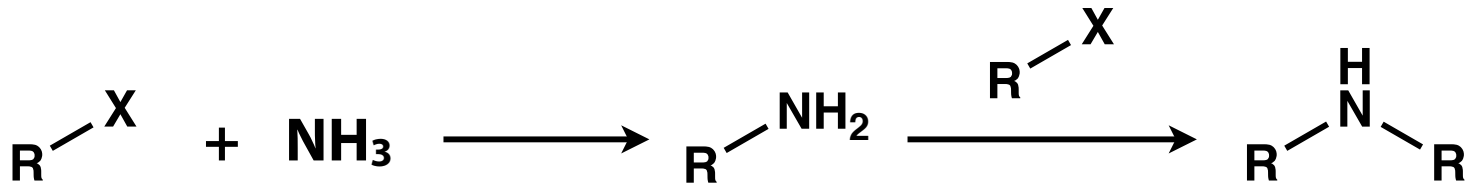
後藤 佑樹 (Yuki Goto, Bioorganic Chemistry Lab.)

“Organic chemistry of biomolecules”

Q and A

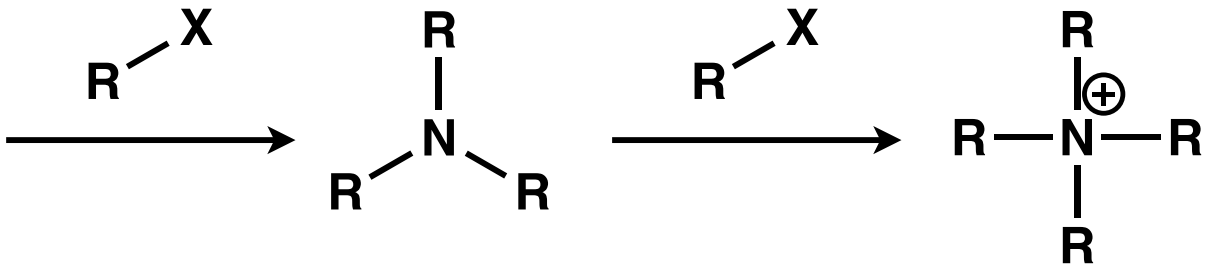
3. トリエチルアミンはなぜジエチルアミンよりも塩基性が弱いのですか？

Why is Et3N less basic than EtNH?



pKaH: (R = Et)

9.21 10.63 10.98



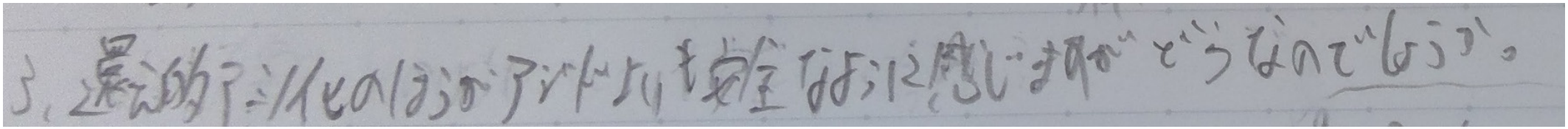
10.75

Good question!

We need to consider both

- delocalization of the positive charge by the electron donating alkyl groups
- stabilization of the ion by solvation

Note that steric hinderance is not the issue.

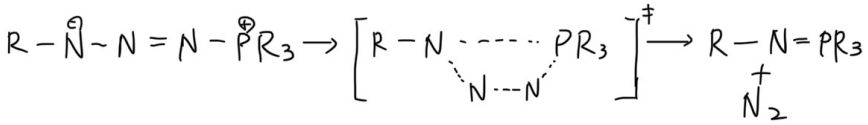


This student feels that the reductive amination is safer than the method using azide.

I would say sodium azide is not necessarily an extraordinarily dangerous reagent.
Similarly, NaCNBH3 used for reductive amination should be handled with care.
Nevertheless, sodium azide is certainly explosive, so we would refrain from using this in a large scale synthesis. But, we definitely use this reagent routinely for lab-scale synthesis.

アジド、金属スプーンはダメ！

3. シュタウディンガー反応のアジドの還元の反応機構を調べたのですが、

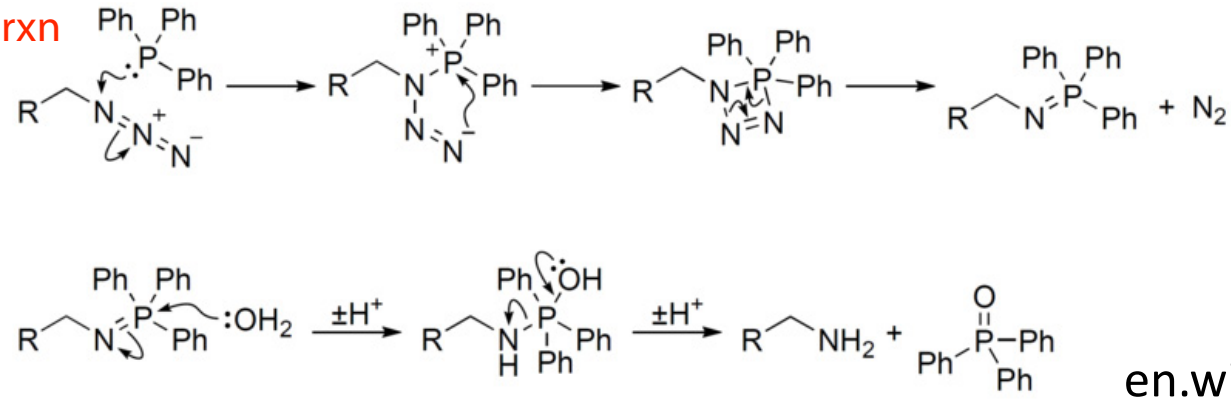


みたいな過程が出てきて、あんまり見ない機構だなーと思いました。

This student thinks that the mechanism of the Staudinger reaction is somewhat unusual.

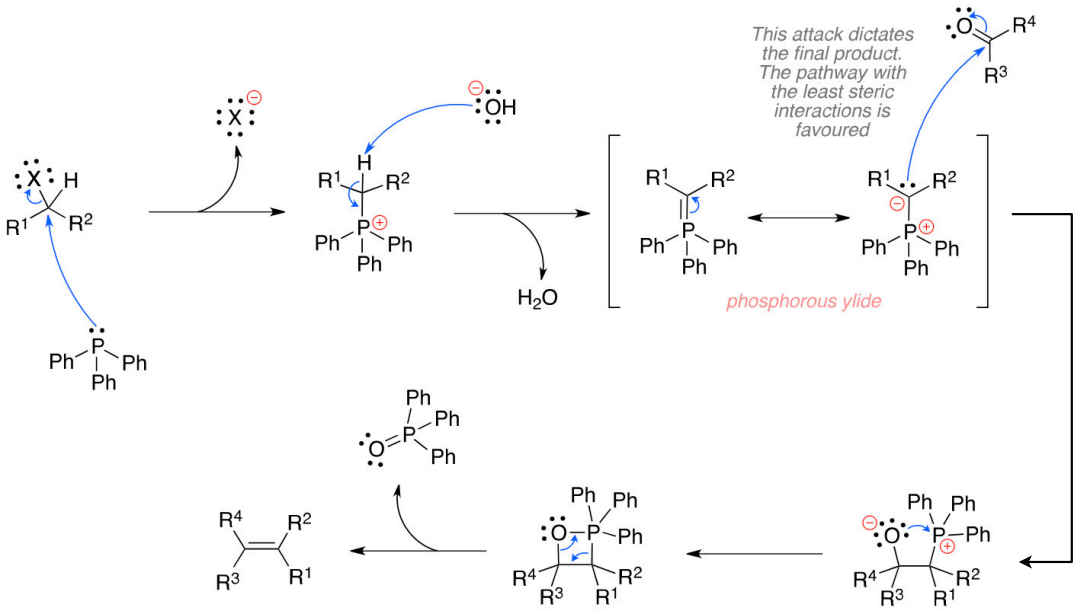
Good self-study, and good thought.
The full mechanism is shown below.
Agree that the mechanism might be little tricky, but please note that it is analogous to the mechanism of the Wittig reaction.

Staudinger rxn



en.wikipedia.org

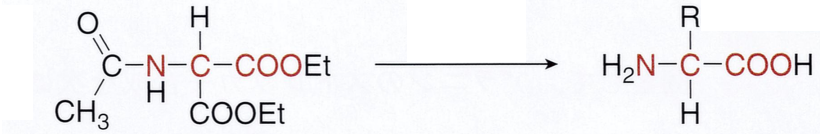
Wittig rxn



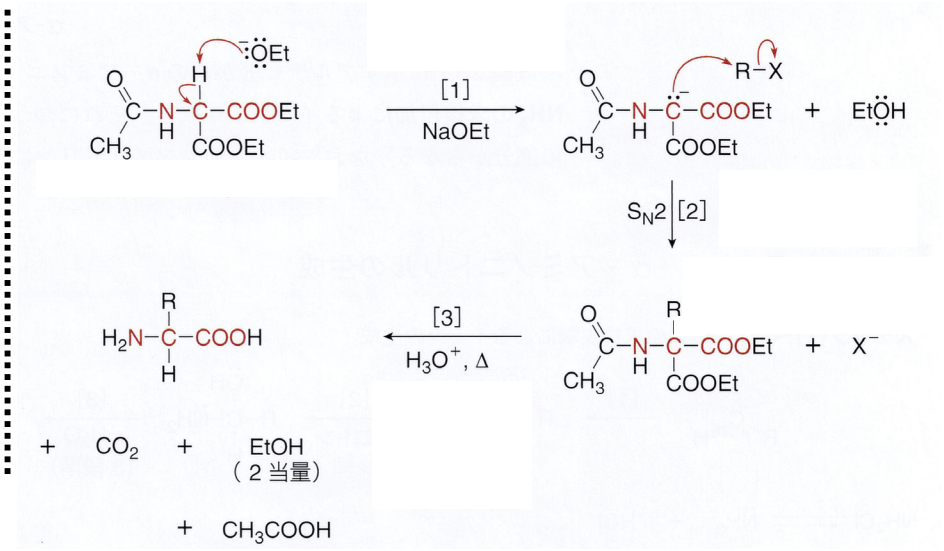
name-reaction.com

Advance study suggestion:
Check the mechanism of the “aza-Wittig reaction”

• Alkylation of acetamidomalonate



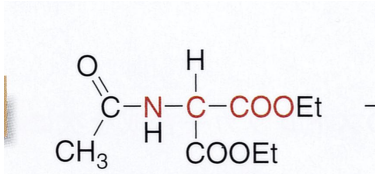
アセトアミドマロン酸ジエチル
(diethyl acetamidomalonate)



Malonate を使ったアミノ酸合成で裸のアミノ基ではなくアセトアミドを窒素源として使うのは、

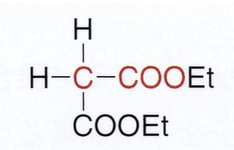
1. 弱い電子供与性で malonate のアルファ位の pKa を下げる効果
2. 窒素のローンペアを抑えて RX への窒素からの求核攻撃を抑える効果

があるという理解でよろしいですか？



アセトアミドマロン酸ジエチル
(diethyl acetamidomalonate)

predicted pKa: 11.93



マロン酸ジエチル
(diethyl malonate)

predicted pKa: 11.84

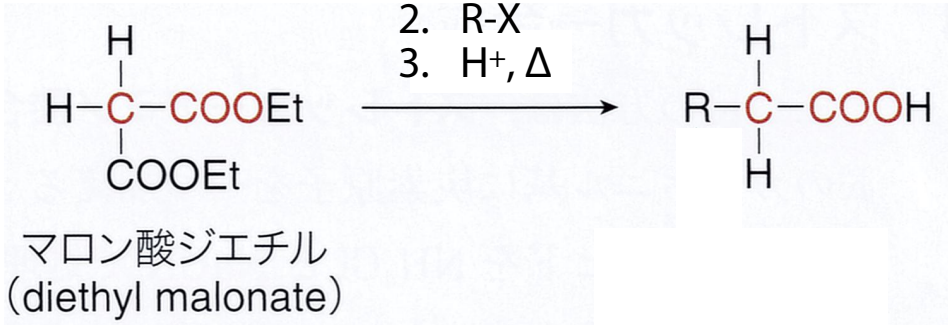
Why this synthesis use the N-acetylated derivative rather than N-free aminomalonate?

1. The weak electron donating AcNH- group can increase the acidity of the α-hydrogen?

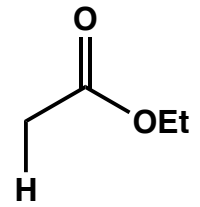
   Good try, but not correct.
   An adjacent electron donating group actually decrease the acidity of the α-hydrogen.
   See above.

2. The Ac group can mask the amino group and suppress its undesirable reaction with R-X?

   Yes, the acetyl group can be regarded as a protective group.
   And, free amino group would drastically increase the acidity of the α-hydrogen.



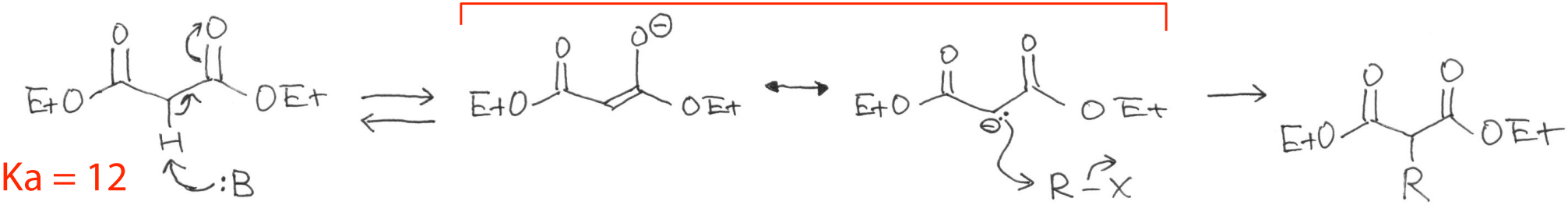
cf. ethyl acetate



pKa = 25

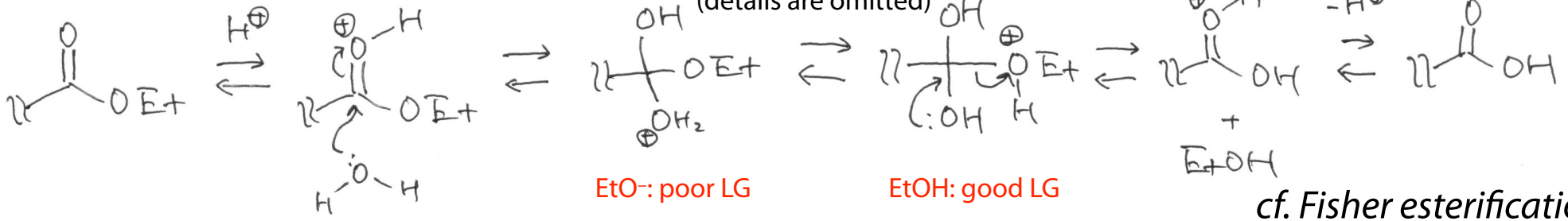
1st & 2nd steps

resonance-stabilized enolate



pKa = 12

acid-catalyzed hydrolysis

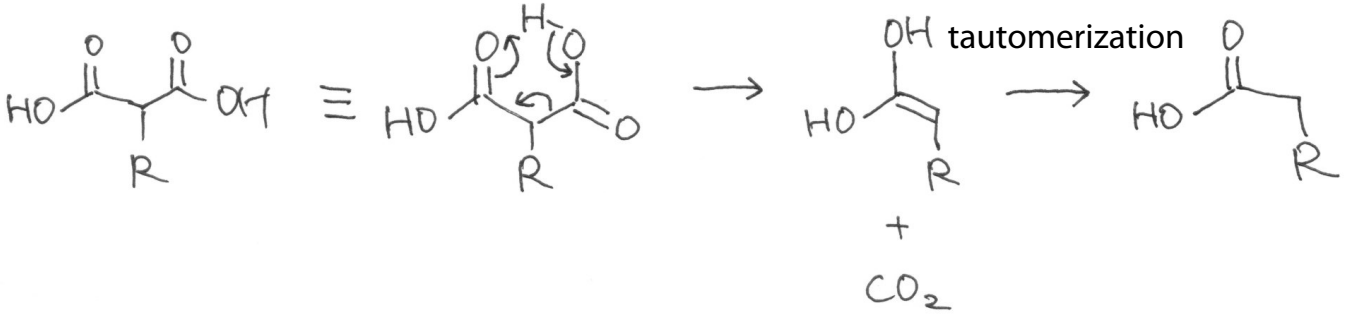


EtO⁻: poor LG

EtOH: good LG

cf. Fisher esterification

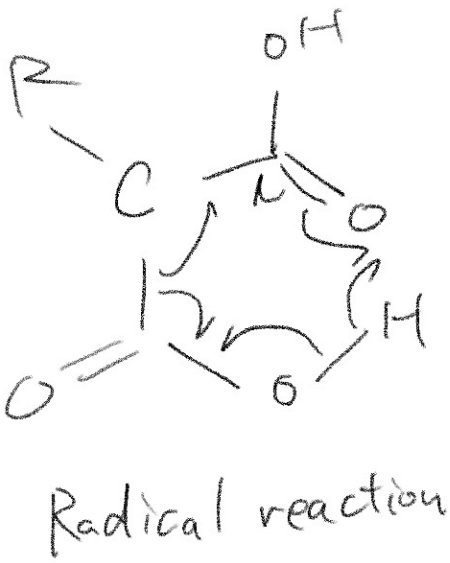
decarboxylation



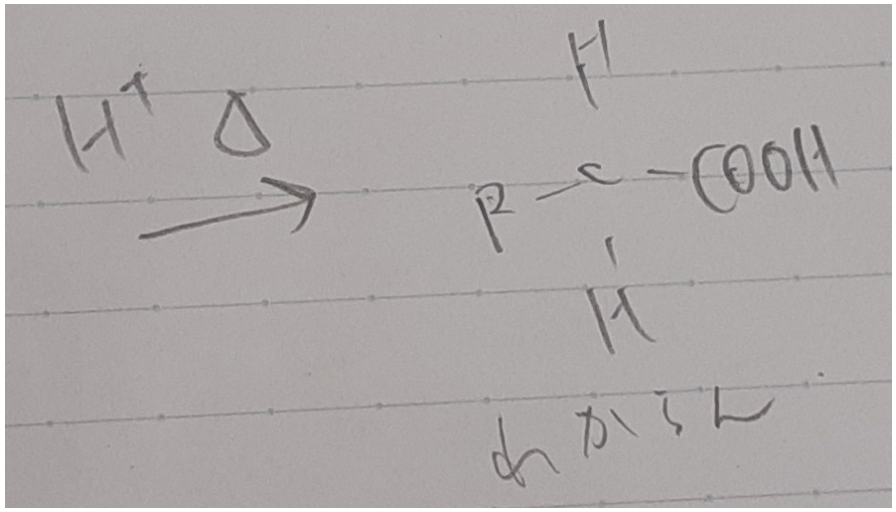
脱炭酸反応がわかりなかったので、
授業で出てくるのを楽しみにしてます。

3-
decarboxylationの反応機構が
よくわからなかったです

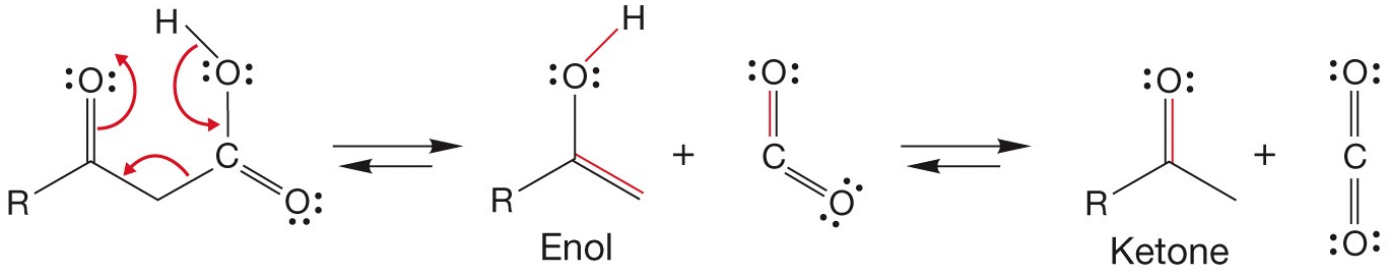
問3 脱炭酸の反応機構の書きたがよく分かりませんでした…！



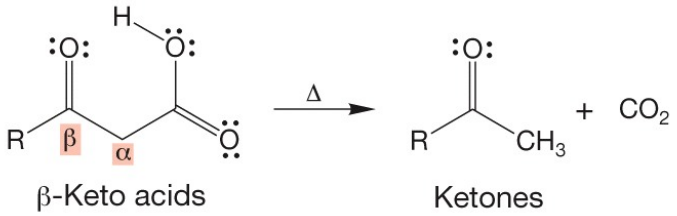
Radical reaction?

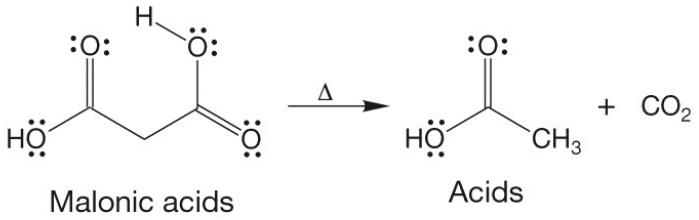


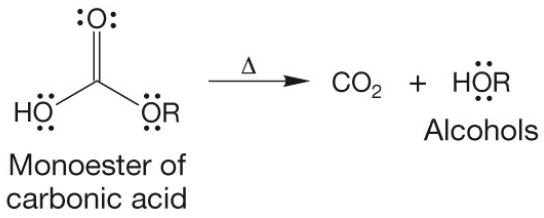
Many questions about the mechanism of decarboxylation.
Sorry, I guess you have not yet learned the mechanism in the previous classes.

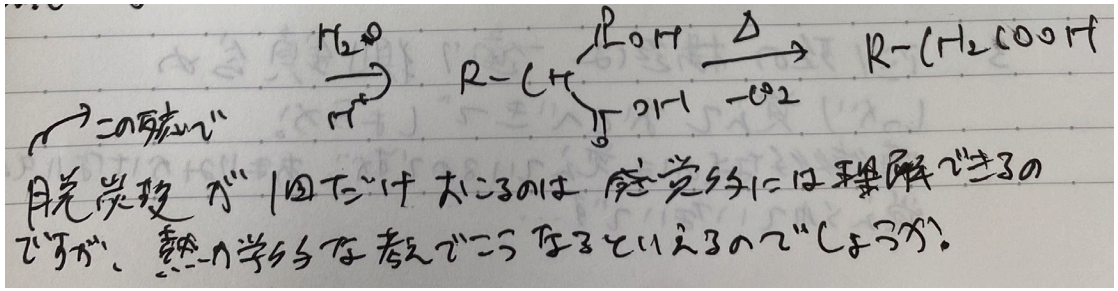


GENERAL REACTIONS









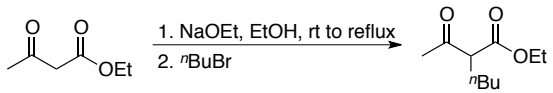
Why the second COOH does not undergo decarboxylation?

As the mechanism suggests, the decarboxylation of a COOH group is assisted by the other COOH moiety.
So the remaining COOH does not undergo the decarboxylation.

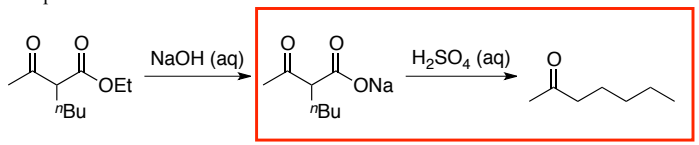
Note that similar decarboxylation can happen (not only in malonate derivatives) in β-keto acids as well, yielding ketones.
And, you will perform this reaction THIS WEEK!!!
Recognize that the reaction can be used as a versatile synthetic strategy for various substituted ketones by changing R-X.

3. β-ケトエステルの反応と Wittig 反応

3－1　Ethyl 2-acetylhexanoate



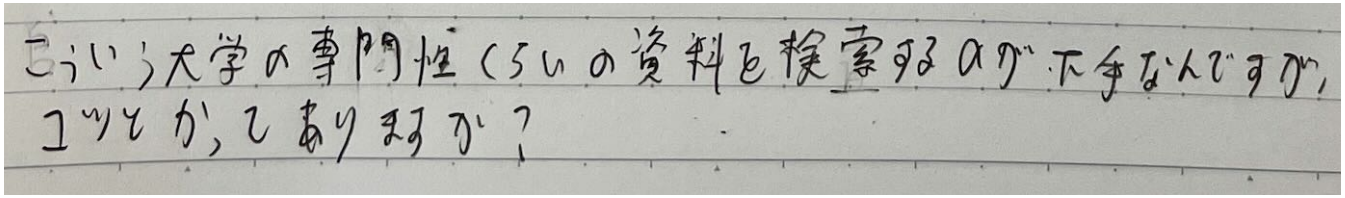
3－2　2-Heptanone



今日提出の無機化学のレポートのヒントがあって
ラッキーの気持ちです。🥹

3. ラセミ体の分離法のところで、無機実験でCo錯体のラセミ体の分離法を行ったことを思い出した。

無機実験のテキスト見ました。
あれはキラルなCo錯体をそのまま再結晶化で分けてるので、ちょっと違いますが、
光学分割という点では同じですね。



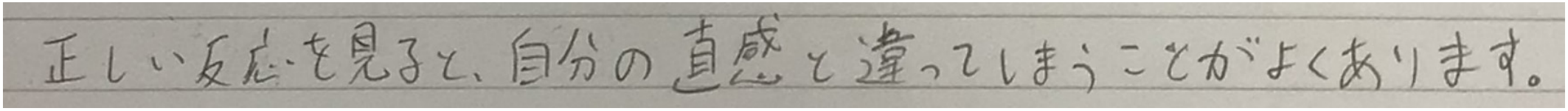
英語でも検索するのが良いかなぁ。
いずれにせよ、適切なtermで検索するだけの知識は必要な気がする。
あと、画像検索も使うとか？

3.ふと思いついたのですが、試験に分子模型を持ち込むのはいいのでしょうか？

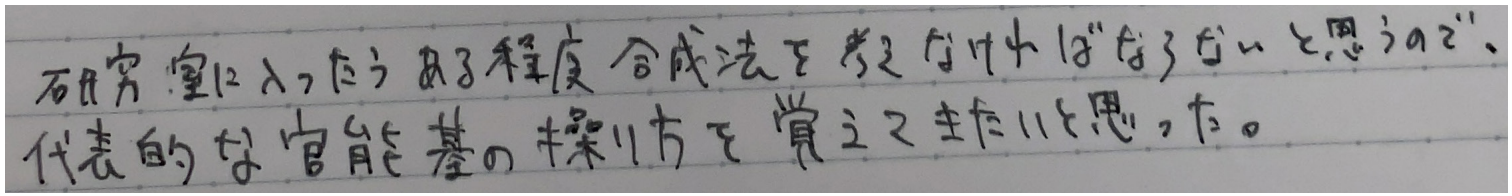
うーん、無しってことにしようと思うけど、いかが？

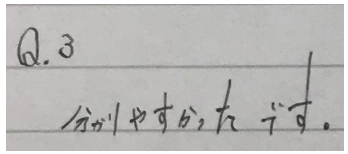
感想・質問

有機は不得意なので復習して下さるのは助かります。



3, 有機1で学んだ反応で合成を理解できるのが楽しいです。





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）
なので頑張って下さい。

化学館は本郷2丁目から近くて有難いので
その授業も化学館で行ってほしいです…

むしろ遠いと思ってるのだけど、どうだろう。

Final Exam

July 22nd (Fri)10:25〜11:55

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

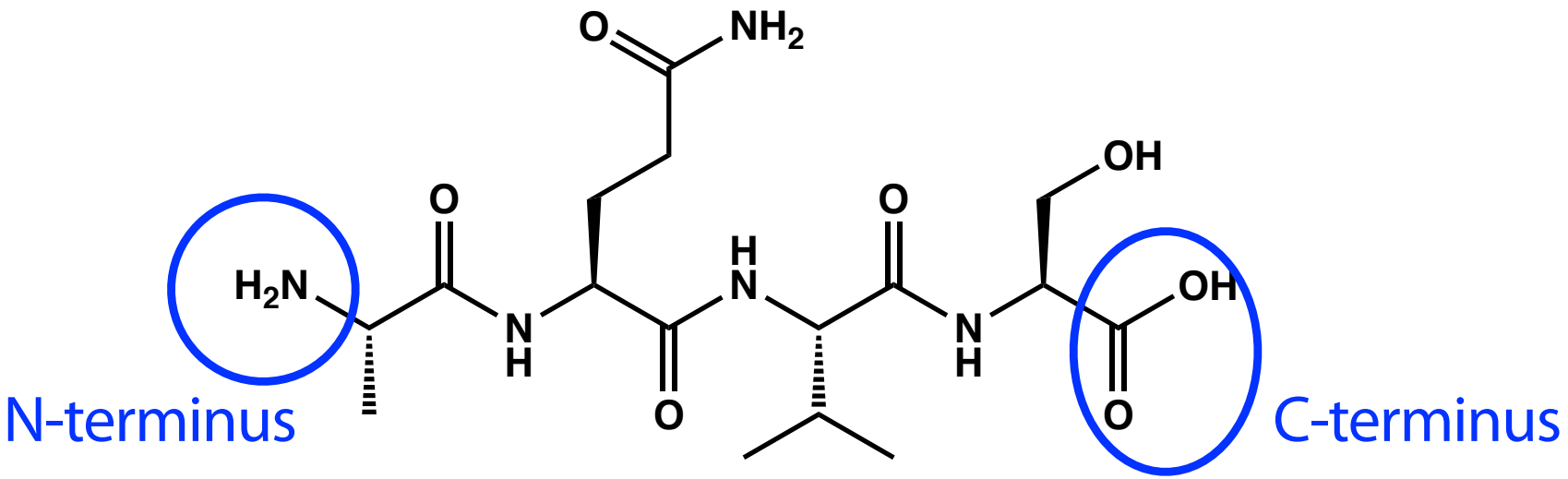
guidelines

- 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.

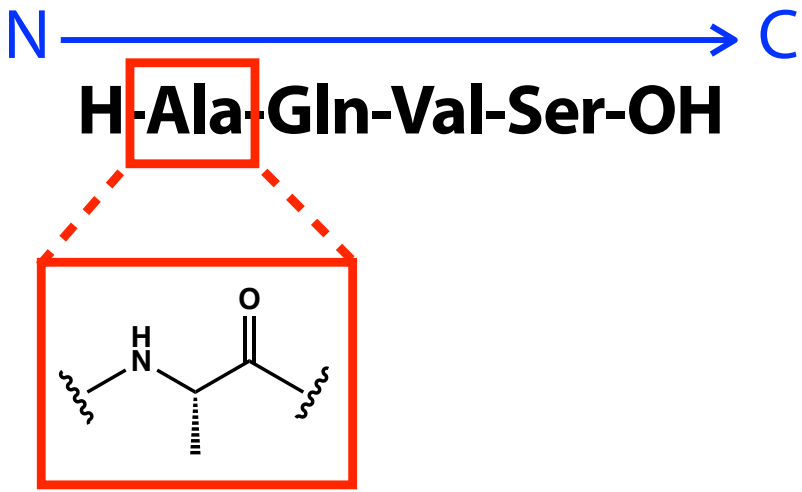
- 開始30分後からの15分間、「cheating time」を設けます。この間は、持参した教科書・講義資料・ノート・メモ等を参照しても構いません。
- ただし、PC・タブレット・携帯などの電子デバイスの閲覧/使用は禁止。
- 他の人との相談も禁止。

Peptides

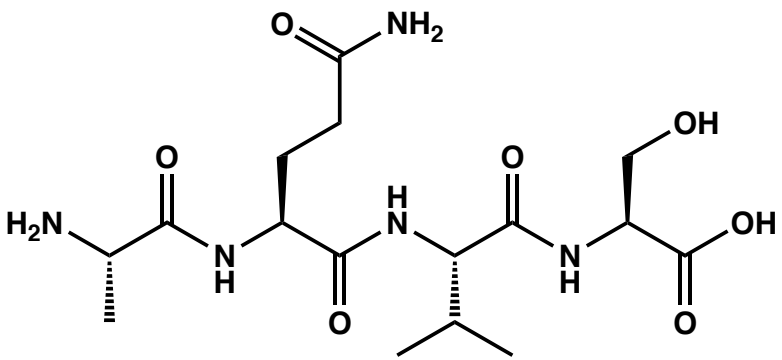
Representation of peptides

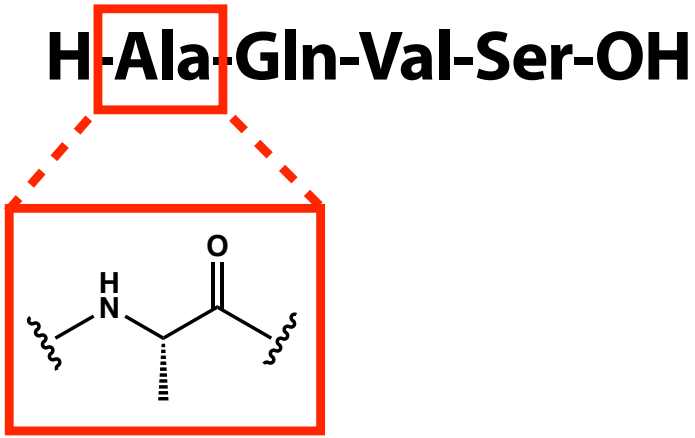


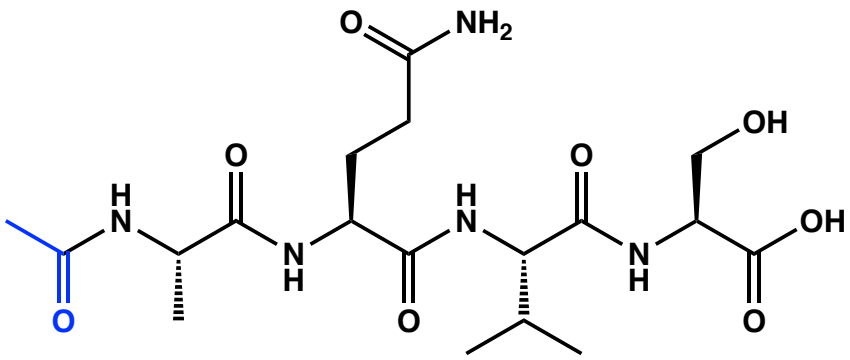
AQVS

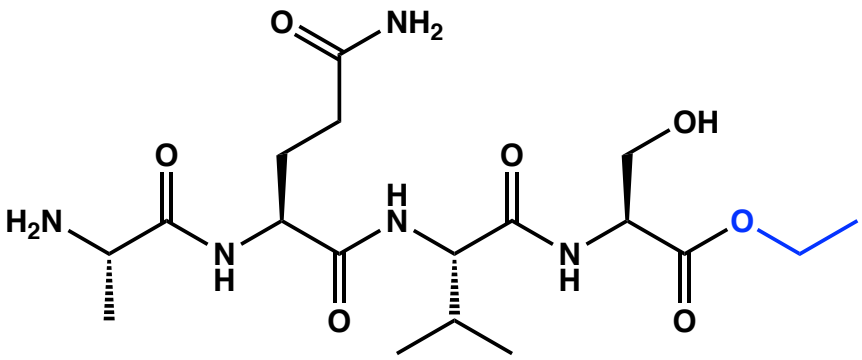


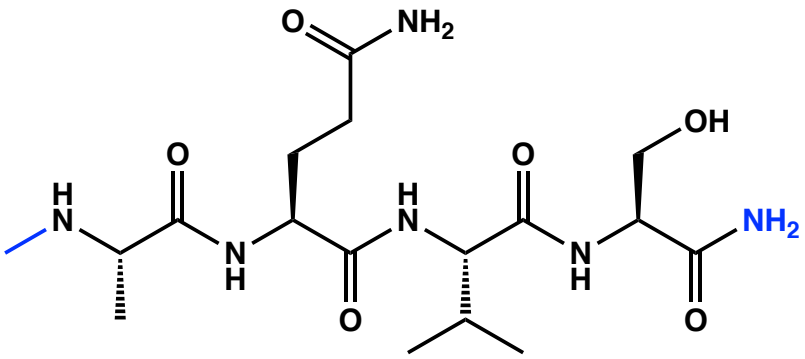
Representation of peptides









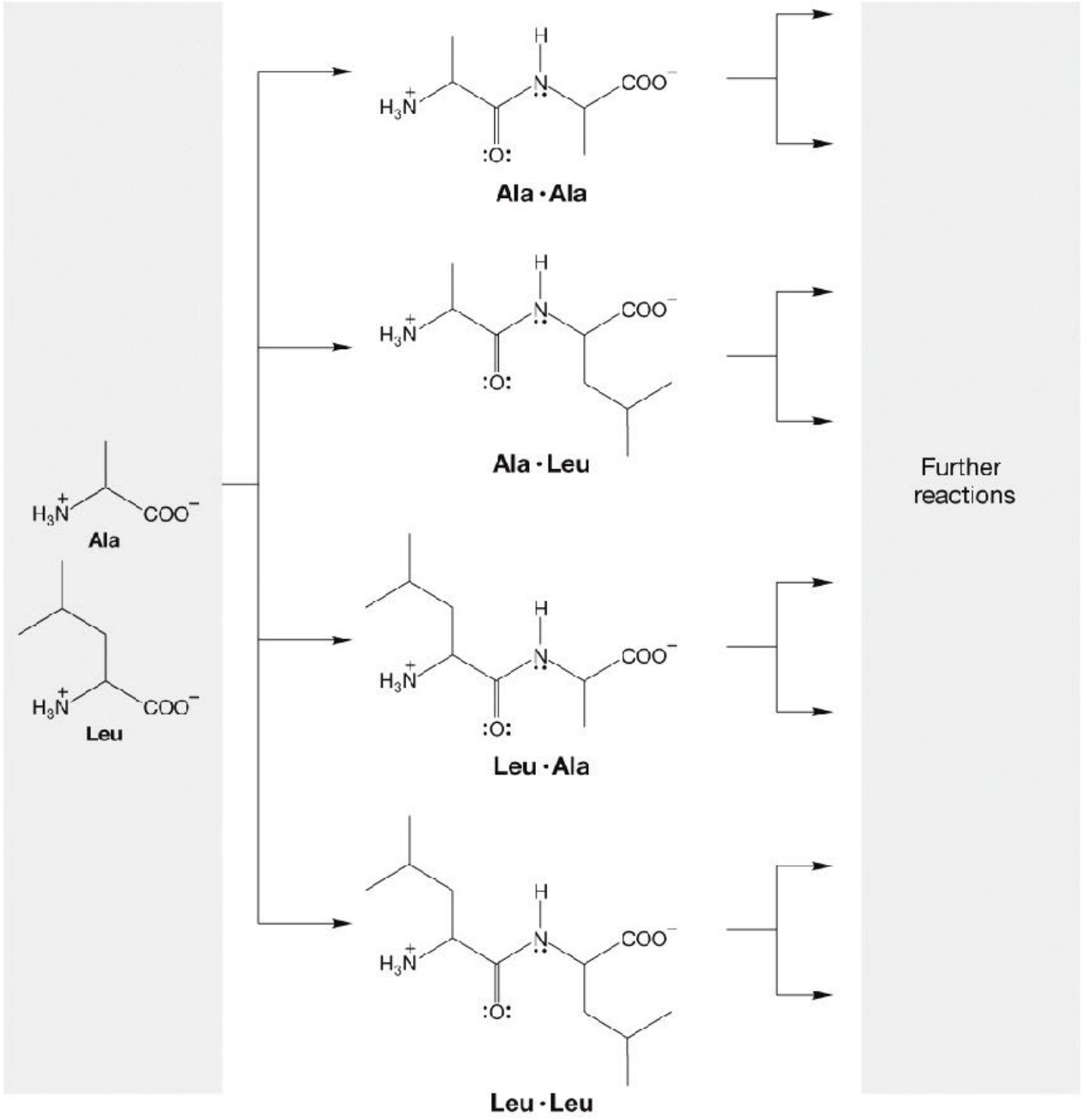


Topics

- **synthesis of peptides**
    - protection of amino group
        - Boc group
        - Fmoc group
    - 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…

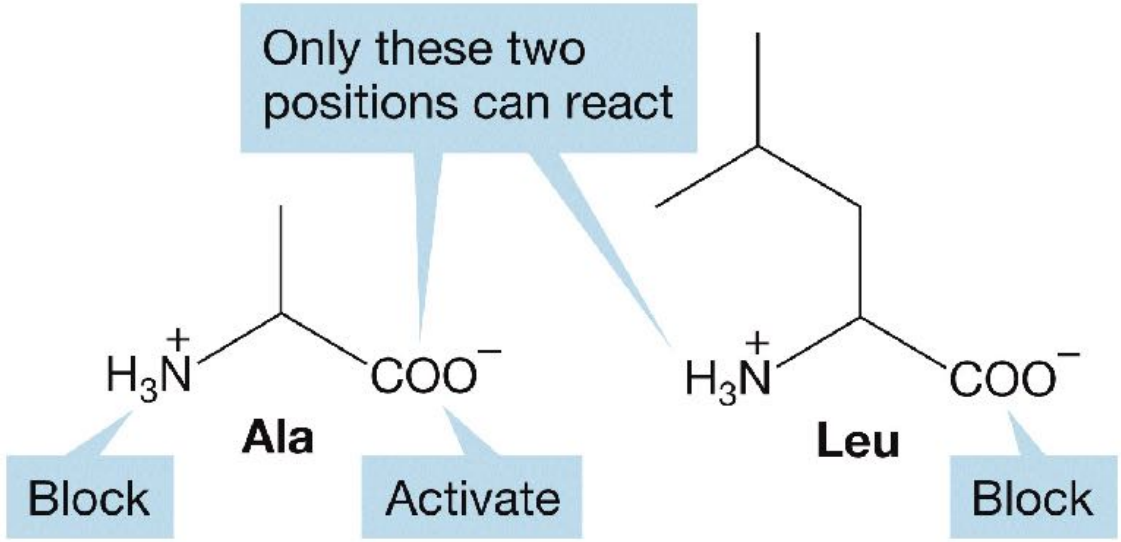


Chemical synthesis of peptides

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

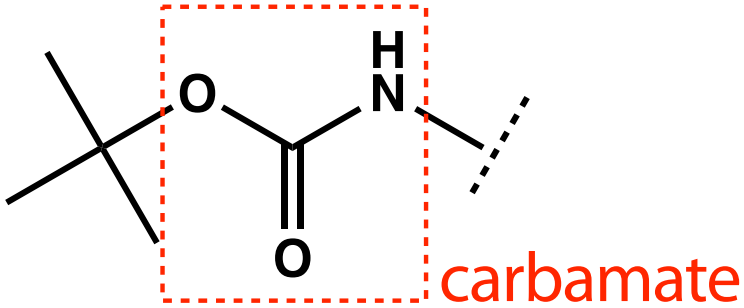
1. **Protection of amino group**
2. **Activation of carboxyl group**

are required.

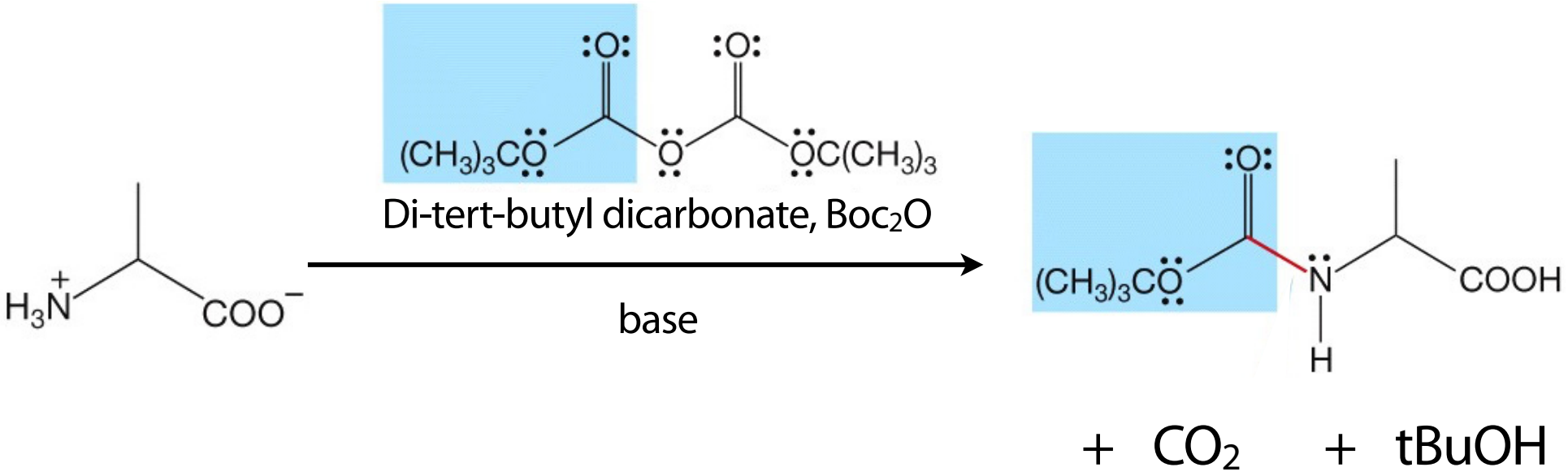


Protective group of amines in peptide synthesis

1. *t*-butoxycarbonyl (tBoc, Boc)



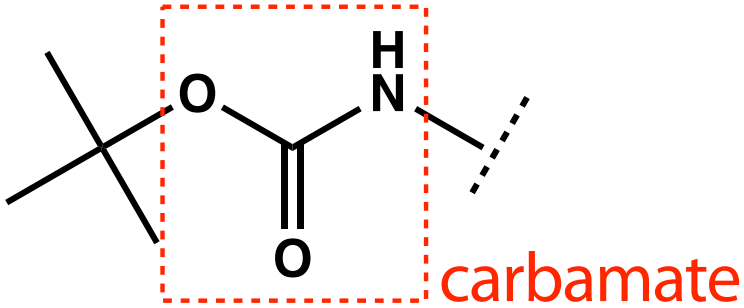
Protection



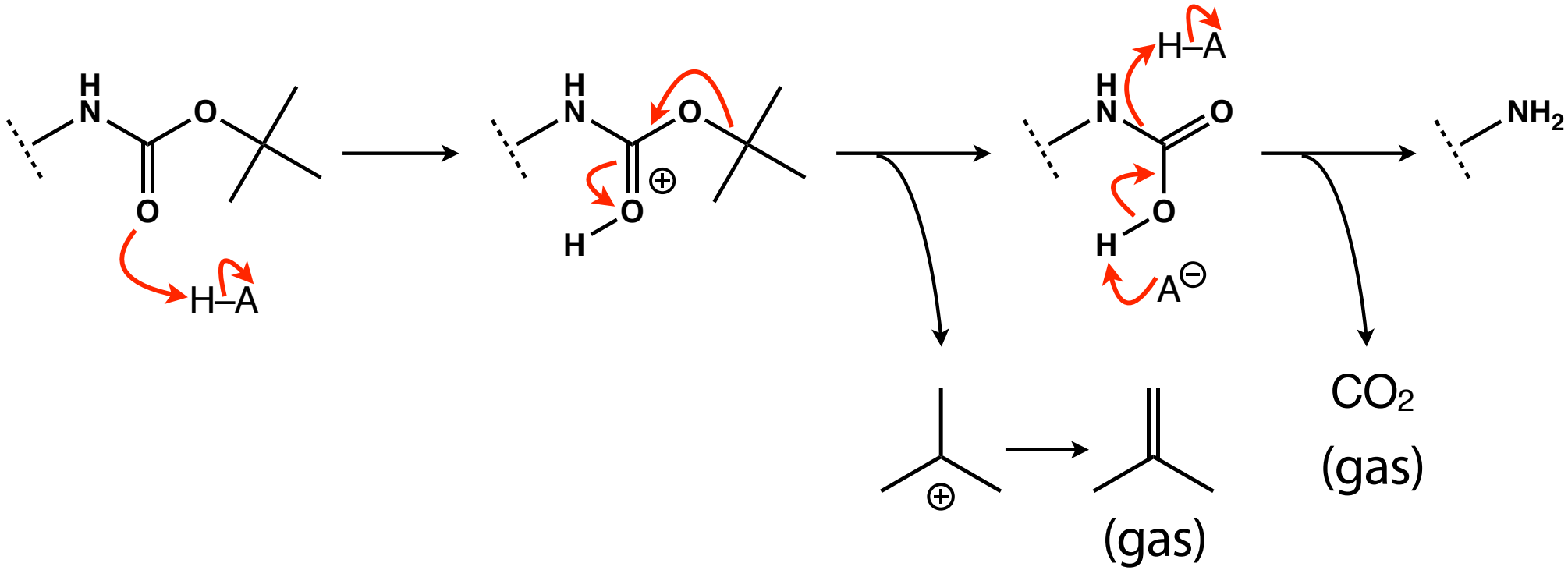
Practice quiz: Reaction mechanism?

Protective group of amines in peptide synthesis

1. *t*-butoxycarbonyl (tBoc, Boc)

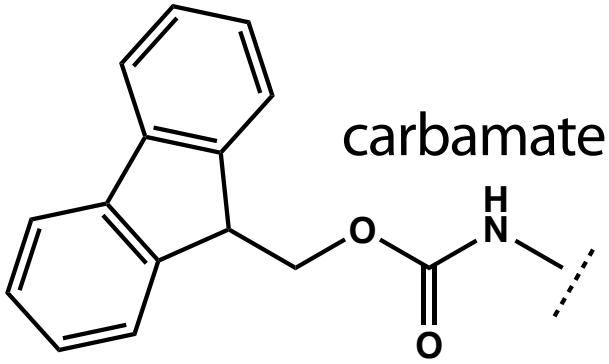


Deprotected under acidic conditions (e.g. HCl, TFA)

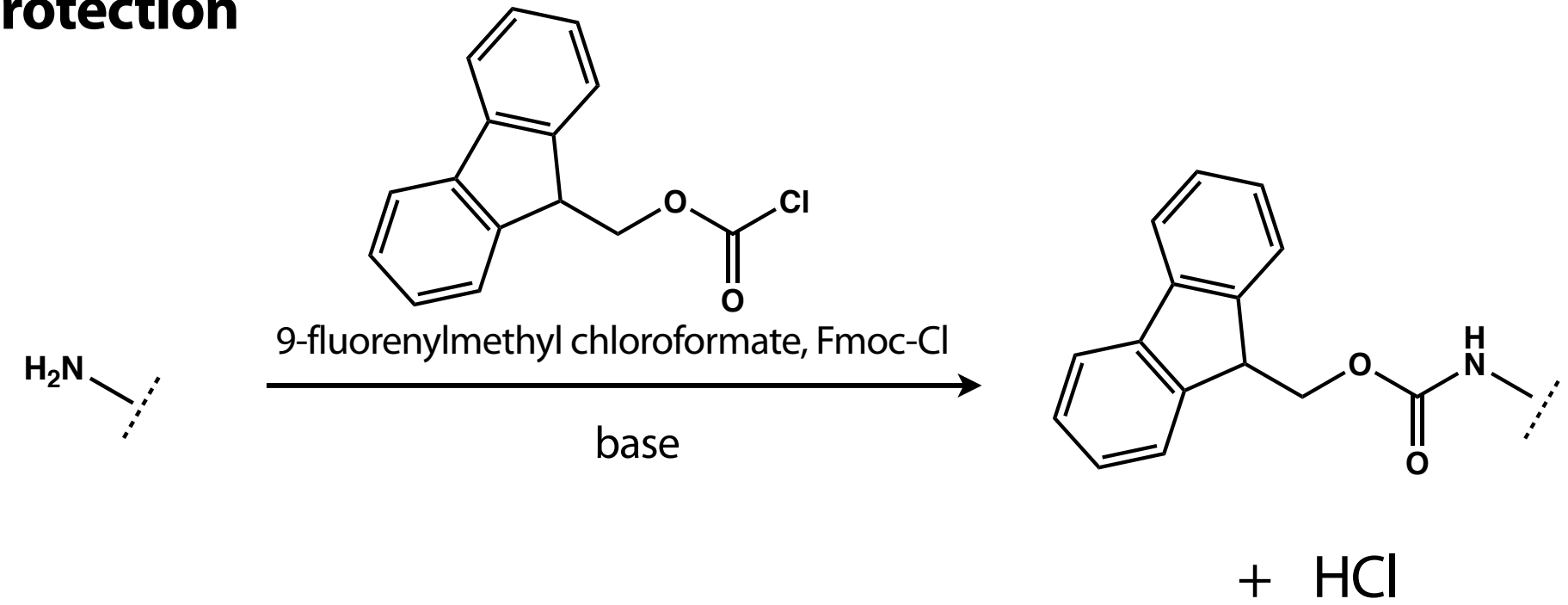


Protective group of amines in peptide synthesis

2. 9-fluorenylmethoxycarbonyl (Fmoc)

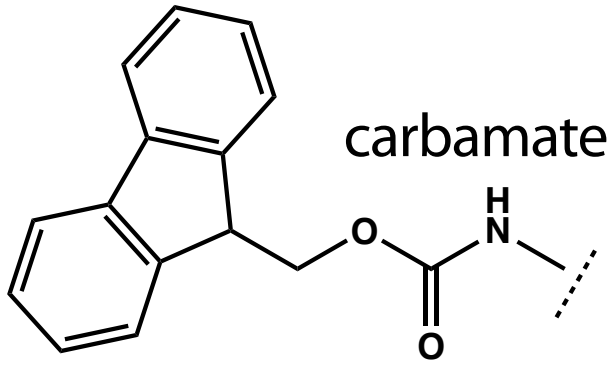


Protection

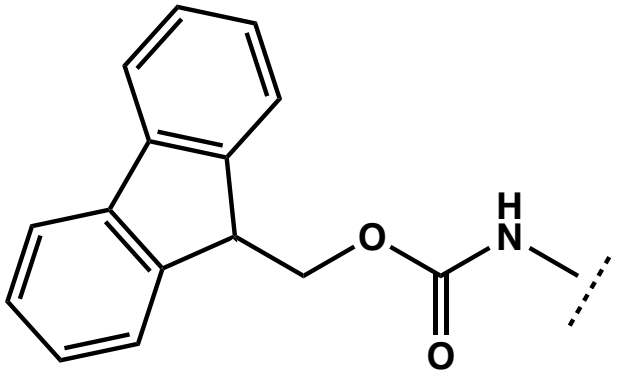


Protective group of amines in peptide synthesis

2. 9-fluorenylmethoxycarbonyl (Fmoc)



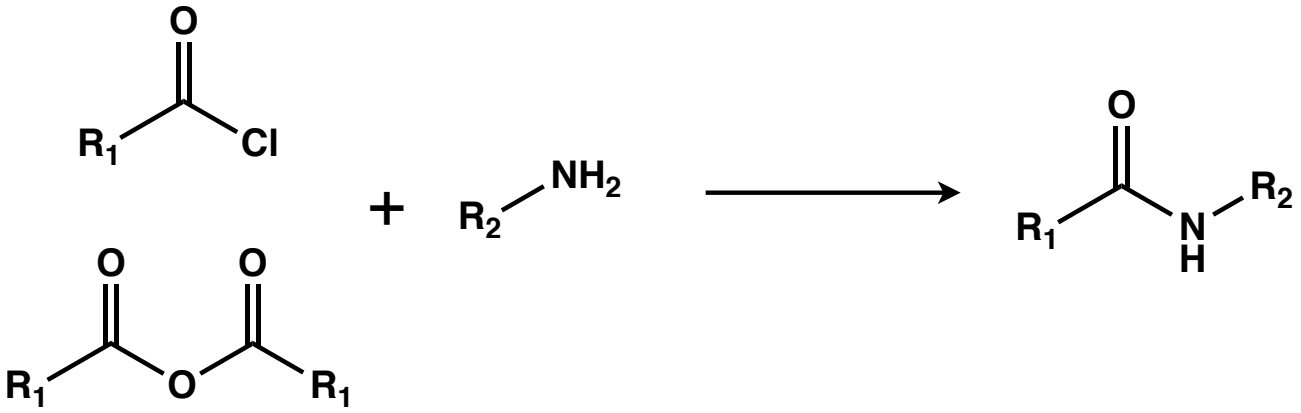
Deprotected under basic conditions (secondary amines such as piperidine)



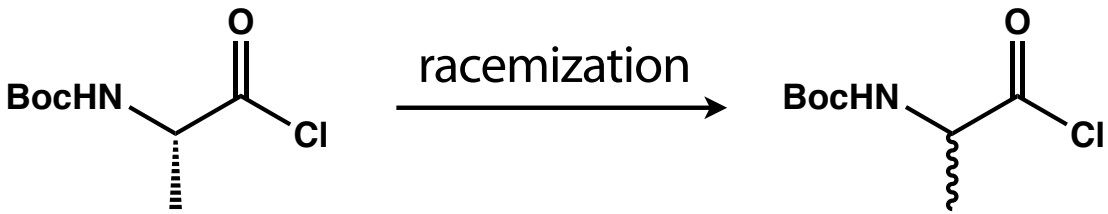
Practice quiz: Which proton in Fmoc group is the most acidic? Answer with your reason.

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.

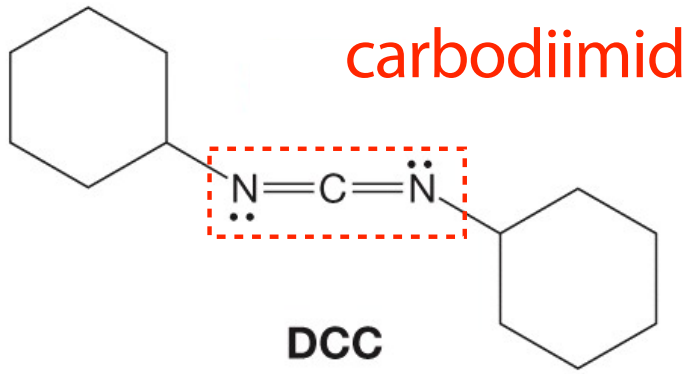


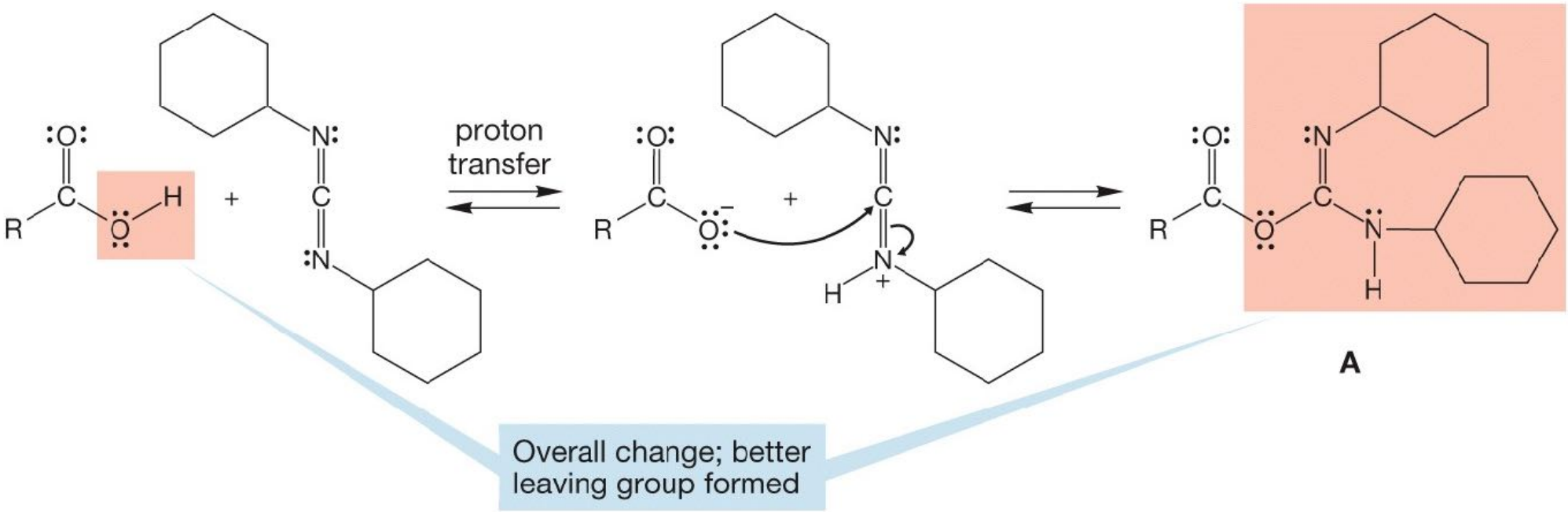
(Also, reaction conditions to prepare acid chlorides are generally harsh.)

Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

***N,N'*-Dicyclohexylcarbodiimide (DCC)**

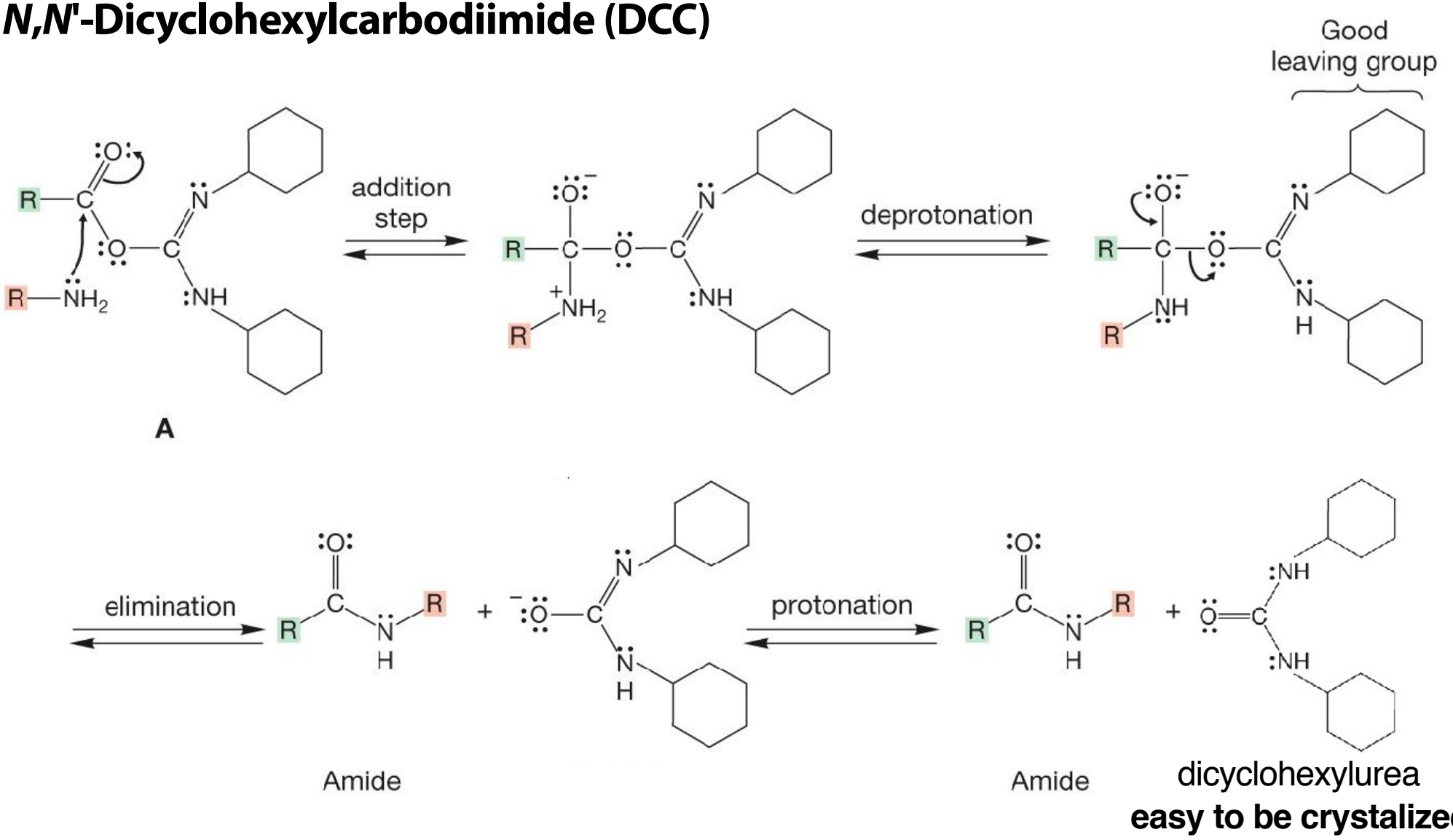




Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

N,N'-Dicyclohexylcarbodiimide (DCC)

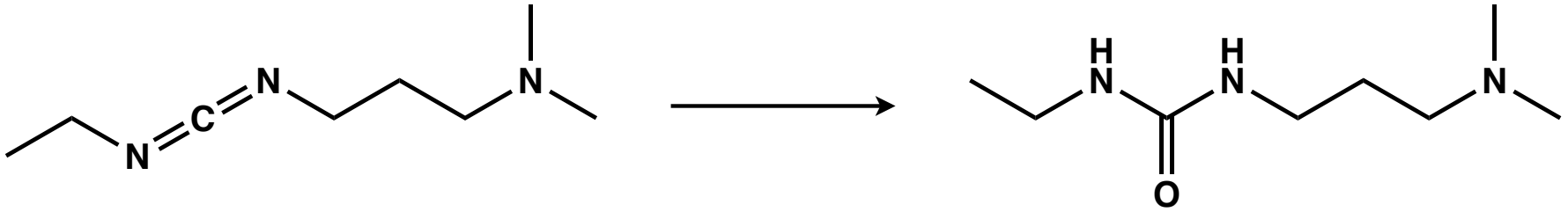


easy to be crystalized

Activation of carboxyl groups in peptide synthesis

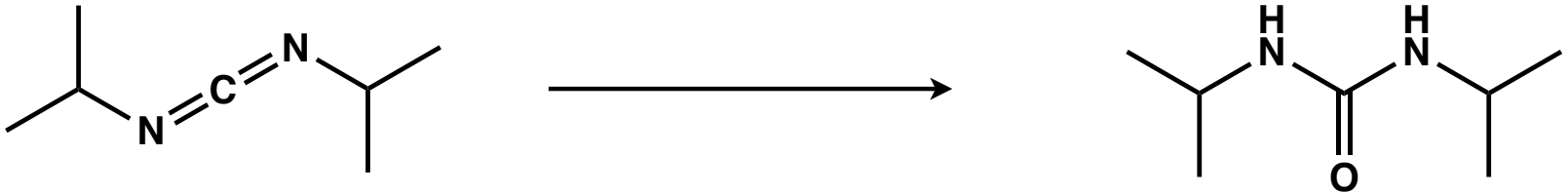
other carbodiimides

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



residual urea
removable by extraction

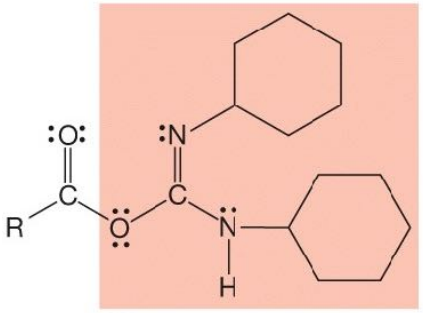
N,N'-Diisopropylcarbodiimide (DIC)



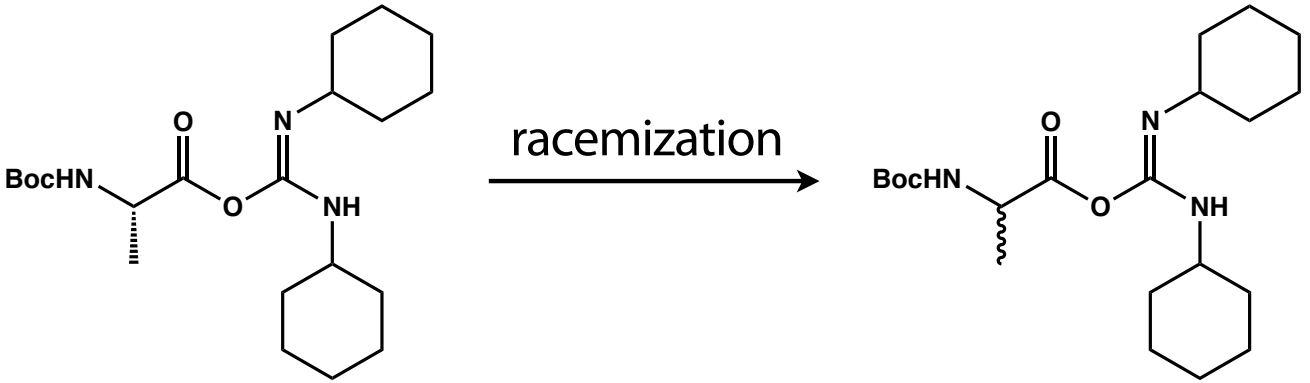
residual urea
soluble in organic solvents

Activation of carboxyl groups in peptide synthesis

Use of condensation agent (縮合剤)

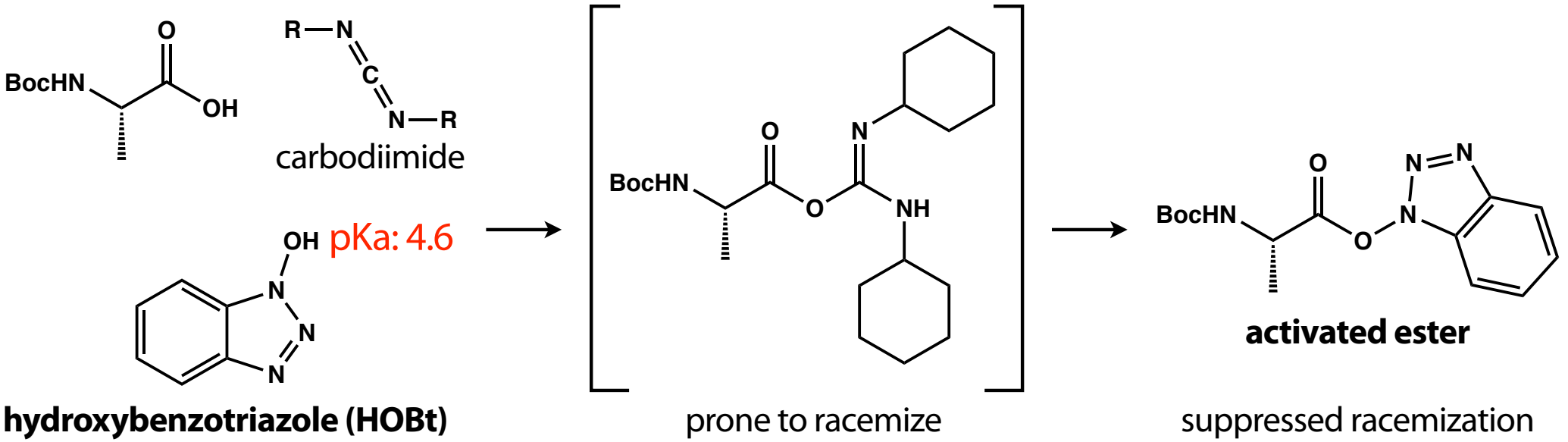


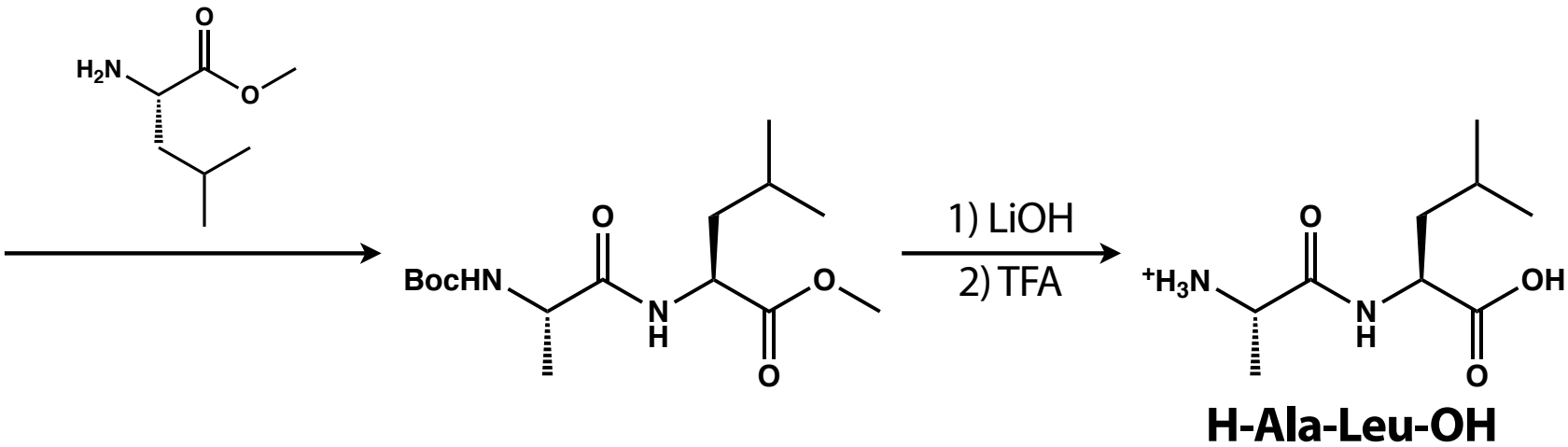
prone to racemize



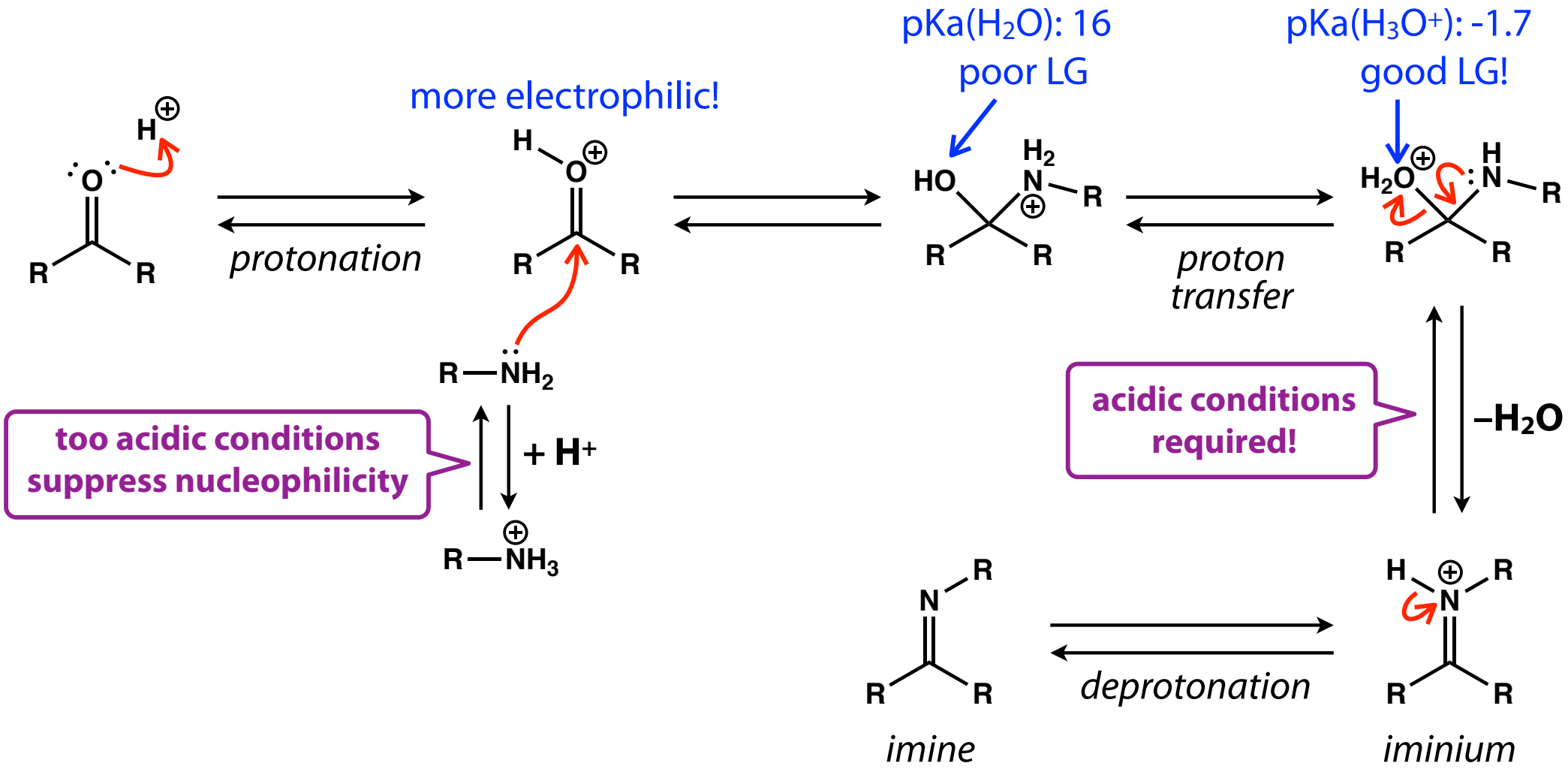
Activation of carboxyl groups in peptide synthesis

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

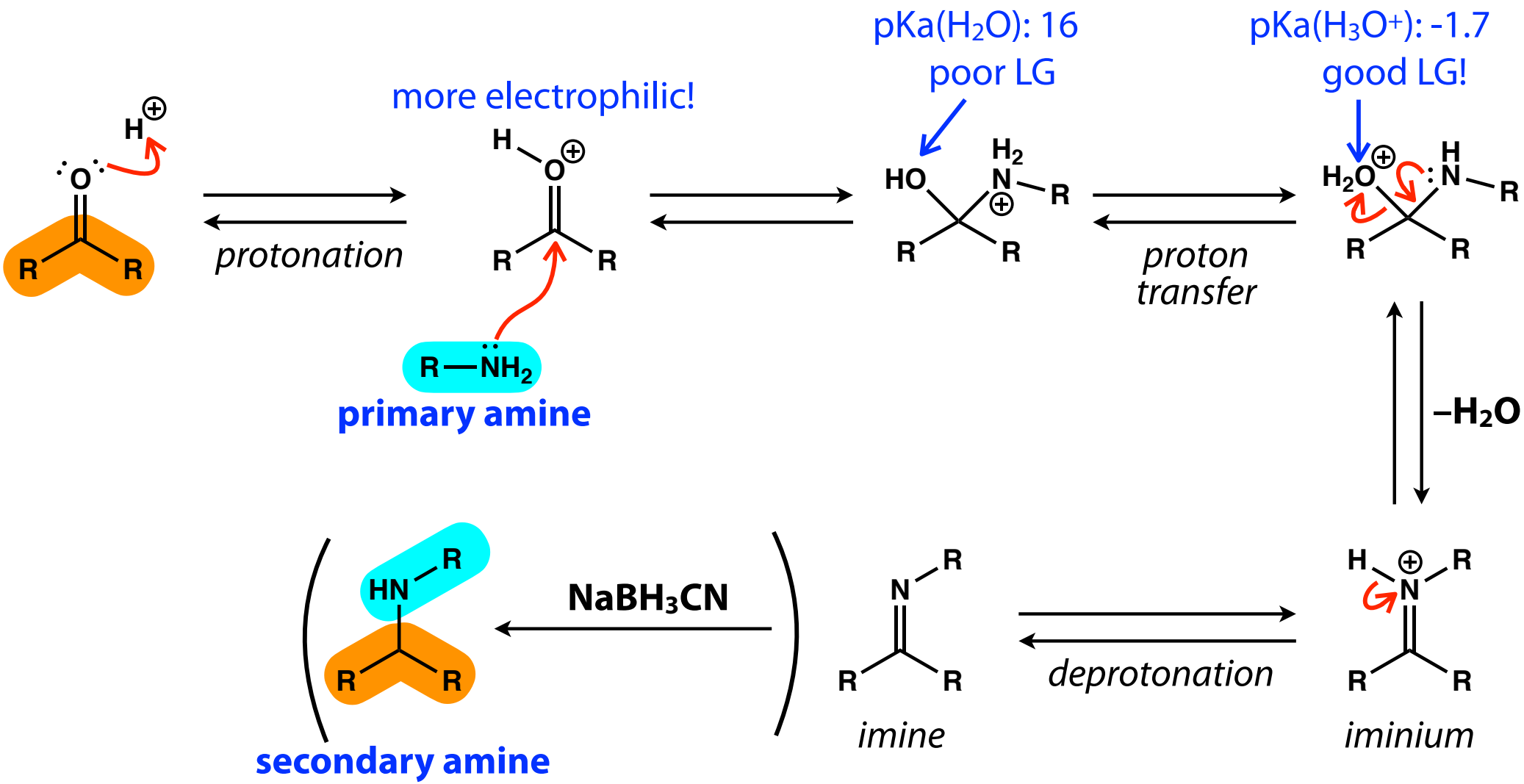




1. Show the mechanism of imine formation and explain why imine formation is often performed in weak acidic conditions.



Summary of reductive amination



ammonia -> primary amine
primary amine -> secondary amine
secondary amine -> tertiary amine