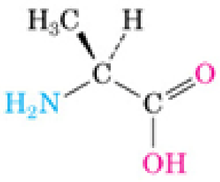
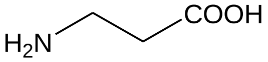
Amminoacidi

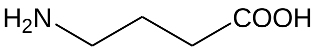
Sono molecole che contengono un gruppo amminico e un’acido carbossilico. Sono stati identificati più di 700 AA diversi. Vengono classificati in funzione della posizione relativa della funzione amminica e di quella acida: α, β, γ, etc. Hanno ruoli biologici molto diversi.



alanina: α-amminoacido proteinogenico

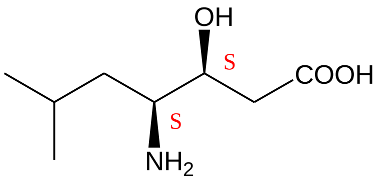


β-alanina



acido γ-amminobutirrico

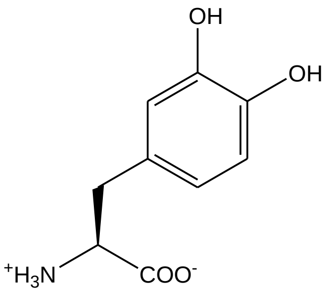
GABA



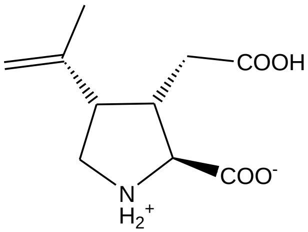
statina

β-alanina: unità strutturale presente nel CoA.
GABA: neurotrasmettitore ad azione inibitrice; ha azione ipertensiva
statina: componente di un pentapeptide che inibisce l'azione di una proteasi, la pepsina

Aminoacidi non proteinogenici

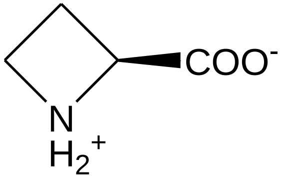


L-Dopa
(anti-Parkinson's)



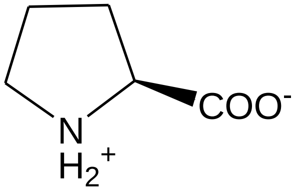
Acido kainico
Eccitante (funghi)

Aminoacidi non proteinogenici incorporati in proteine

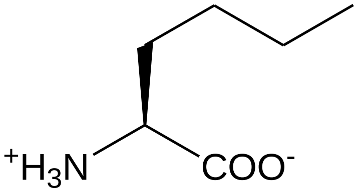


Ac. Azetidin-2-carbossilico

per

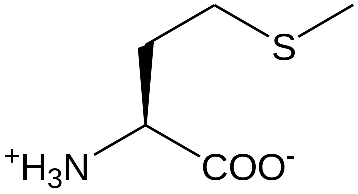


Pro



Norleucina

per



Met

Twenty-One Amino Acids

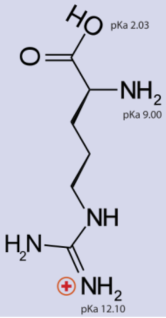
⊕ Positive ⊖ Negative

• Side chain charge at physiological pH 7.4

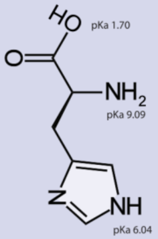
A. *Amino Acids with Electricaly Charged Side Chains*

Positive

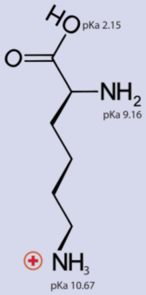
Arginine (Arg) **R**



Histidine (His) **H**

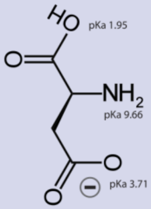


Lysine (Lys) **K**

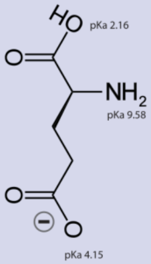


Negative

Aspartic Acid (Asp) **D**

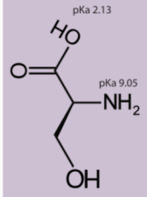


Glutamic Acid (Glu) **E**

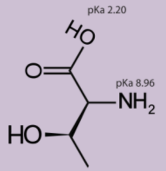


B. *Amino Acids with Polar Uncharged Side Chains*

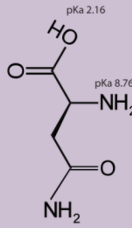
Serine (Ser) **S**



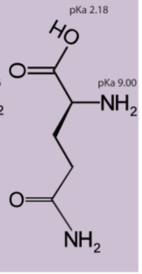
Threonine (Thr) **T**



Asparagine (Asn) **N**

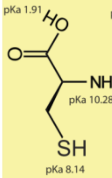


Glutamine (Gln) **Q**

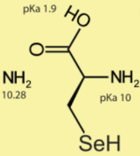


C. *Special Cases*

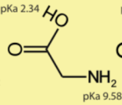
Cysteine (Cys) **C**



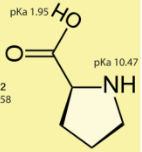
Selenocysteine (Sec) **U**



Glycine (Gly) **G**

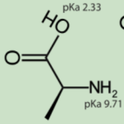


Proline (Pro) **P**

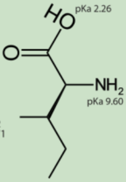


D. *Amino Acids with Hydrophobic Side Chain*

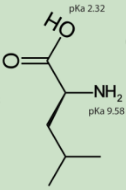
Alanine (Ala) **A**



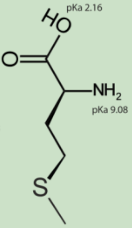
Isoleucine (Ile) **I**



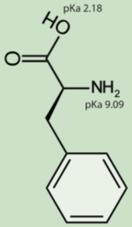
Leucine (Leu) **L**



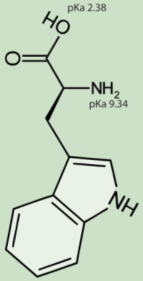
Methionine (Met) **M**



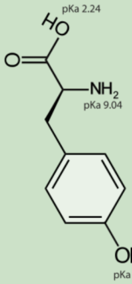
Phenylalanine (Phe) **F**



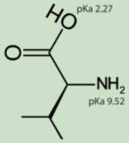
Tryptophan (Trp) **W**



Tyrosine (Tyr) **Y**



Valine (Val) **V**



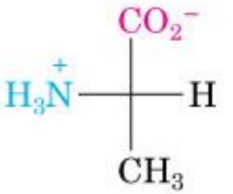
pKa Data: CRC Handbook of Chemistry, v.2010

Dan Cojocari, Department of Medical Biophysics, **University of Toronto**, 2010

Aminoacidi

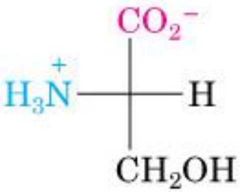
A parte la glicina tutti gli amminoacidi proteinogenici sono chirali e, negli organismi superiori, le proteine sono formate solo da amminoacidi della serie L.

Negli organismi inferiori (batteri) si trovano anche amminoacidi della serie D e amminoacidi non chirali come l'Aib (acido α-amminoisobutirrico)



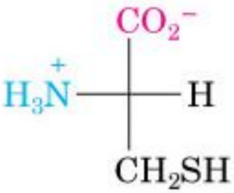
$$\begin{array}{c} CO_2^- \\ H_3\overset{+}{N} - C - H \\ CH_3 \end{array}$$

L-Alanina
(*S*)-Alanina



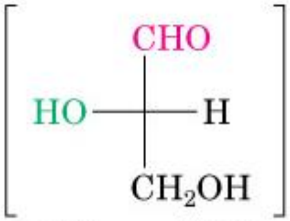
$$\begin{array}{c} CO_2^- \\ H_3\overset{+}{N} - C - H \\ CH_2OH \end{array}$$

L-Serina
(*S*)-Serina



$$\begin{array}{c} CO_2^- \\ H_3\overset{+}{N} - C - H \\ CH_2SH \end{array}$$

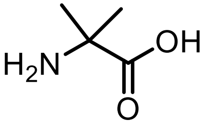
L-Cisteina
(*R*)-Cisteina



$$\left[\begin{array}{c} CHO \\ HO - C - H \\ CH_2OH \end{array}\right]$$

L-Gliceraldeide

(L)A-(L)A-(L)A-(L)A-(L)A-(L)A
(D)A-(L)A-(L)A-(L)A-(L)A-(L)A
(L)A-(D)A-(L)A-(L)A-(L)A-(L)A
etc, etc ….



Aib

Aminoacidi

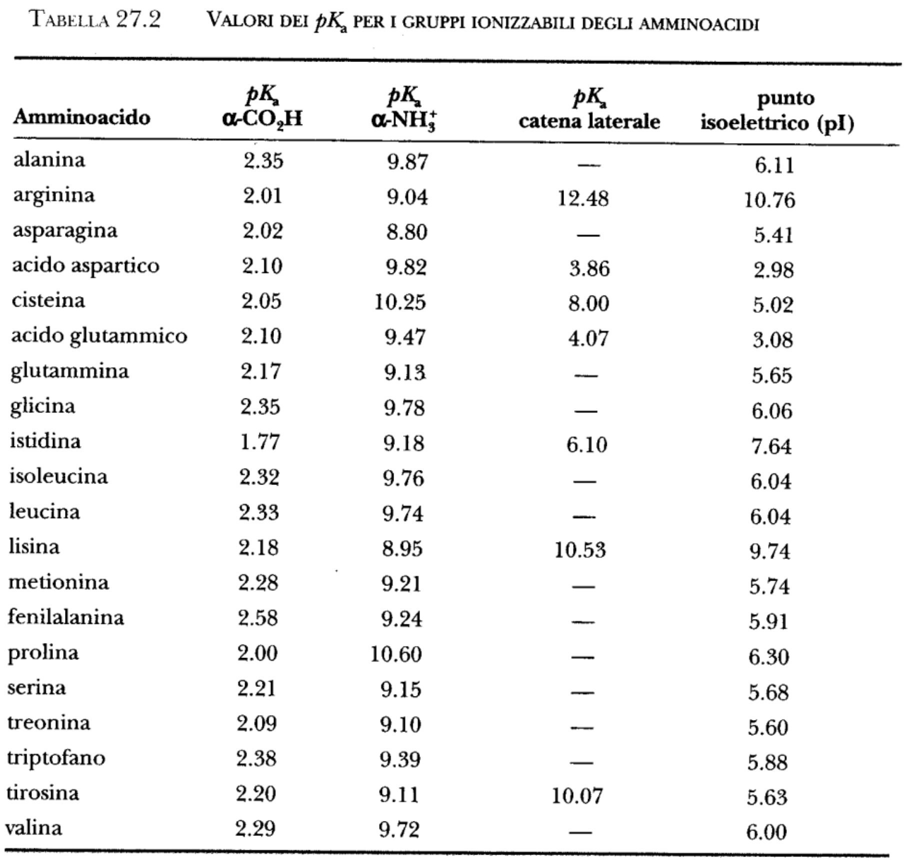
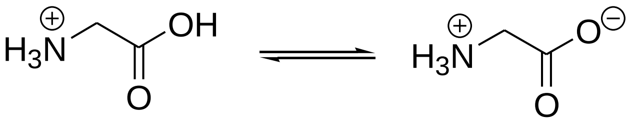
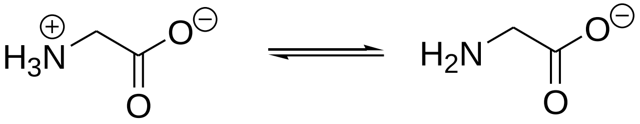


TABELLA 27.2 VALORI DEI pK_a PER I GRUPPI IONIZZABILI DEGLI AMMINOACIDI

Amminoacido	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a catena laterale	punto isoelettrico (pI)
alanina	2.35	9.87	—	6.11
arginina	2.01	9.04	12.48	10.76
asparagina	2.02	8.80	—	5.41
acido aspartico	2.10	9.82	3.86	2.98
cisteina	2.05	10.25	8.00	5.02
acido glutammico	2.10	9.47	4.07	3.08
glutammina	2.17	9.13	—	5.65
glicina	2.35	9.78	—	6.06
istidina	1.77	9.18	6.10	7.64
isoleucina	2.32	9.76	—	6.04
leucina	2.33	9.74	—	6.04
lisina	2.18	8.95	10.53	9.74
metionina	2.28	9.21	—	5.74
fenilalanina	2.58	9.24	—	5.91
prolina	2.00	10.60	—	6.30
serina	2.21	9.15	—	5.68
treonina	2.09	9.10	—	5.60
triptofano	2.38	9.39	—	5.88
tirosina	2.20	9.11	10.07	5.63
valina	2.29	9.72	—	6.00



pK_a = 2.35 (4.76 HAc)



pK_a = 9.78 (10.7 RNH_3^+)

Punto Isoelettrico (pI)

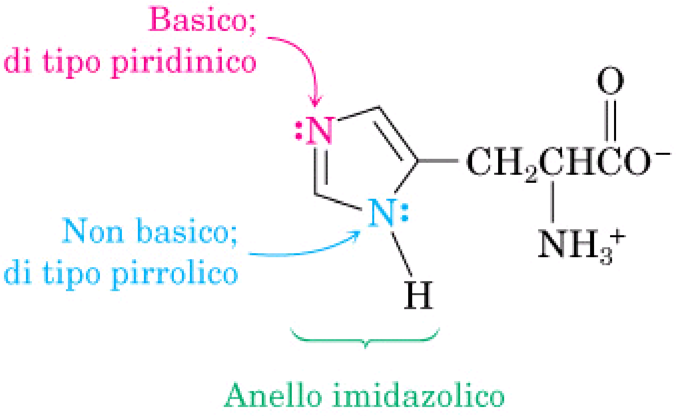
E’ il valore di pH al quale la carica netta di una certa specie elementare è zero.

Il pI è la media dei valori di p*K*a dei gruppi carbossilico e ammonio.

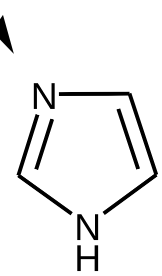
(9.78+2.35)/2 = 6.06

Aminoacidi: istidina e arginina

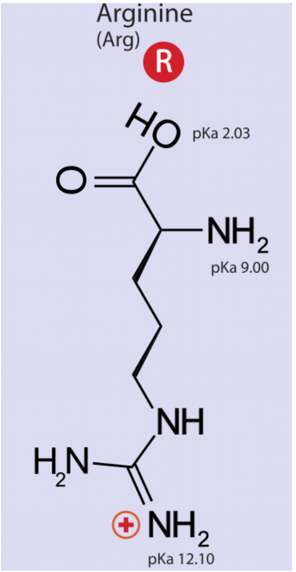
pKa = 6.10

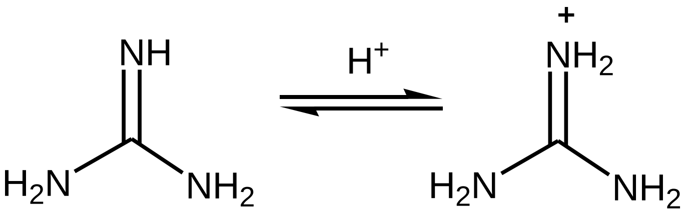


pKa = 6.95



imidazolo

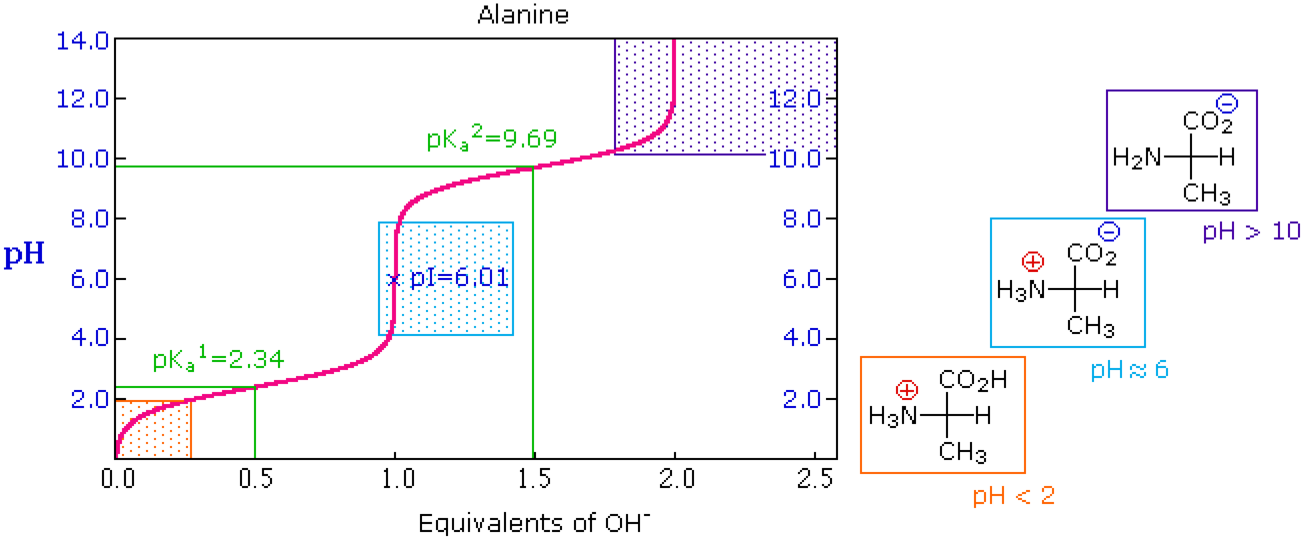


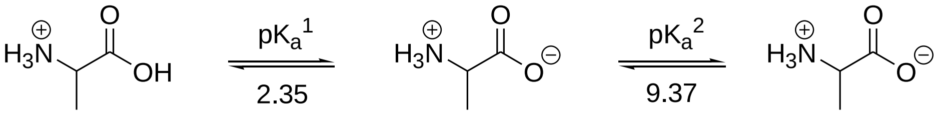


pKa = 13.6

TEA pKa = 10.75

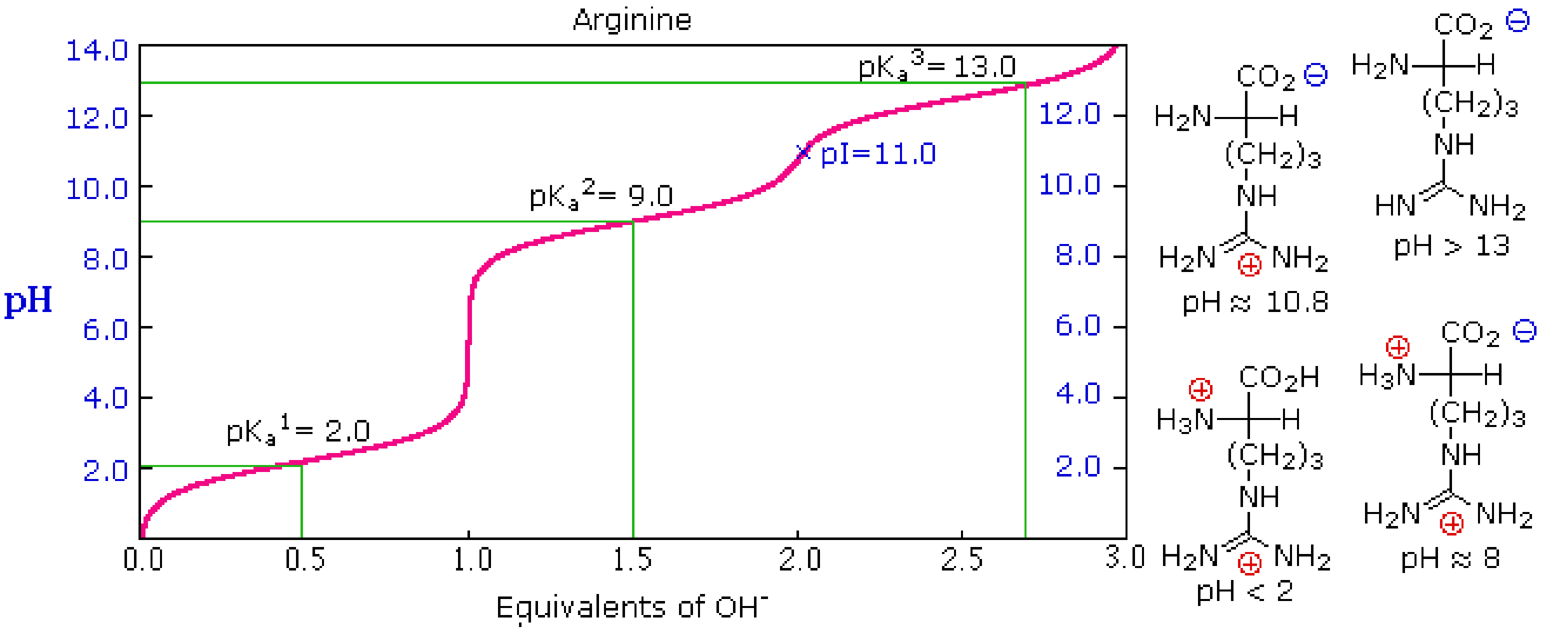
Titolazioni di amminoacidi: ALANINA

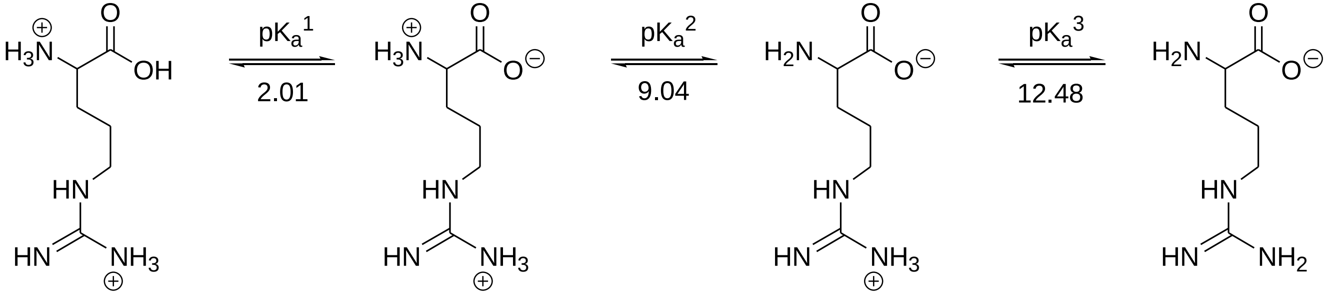




pI = 6.11

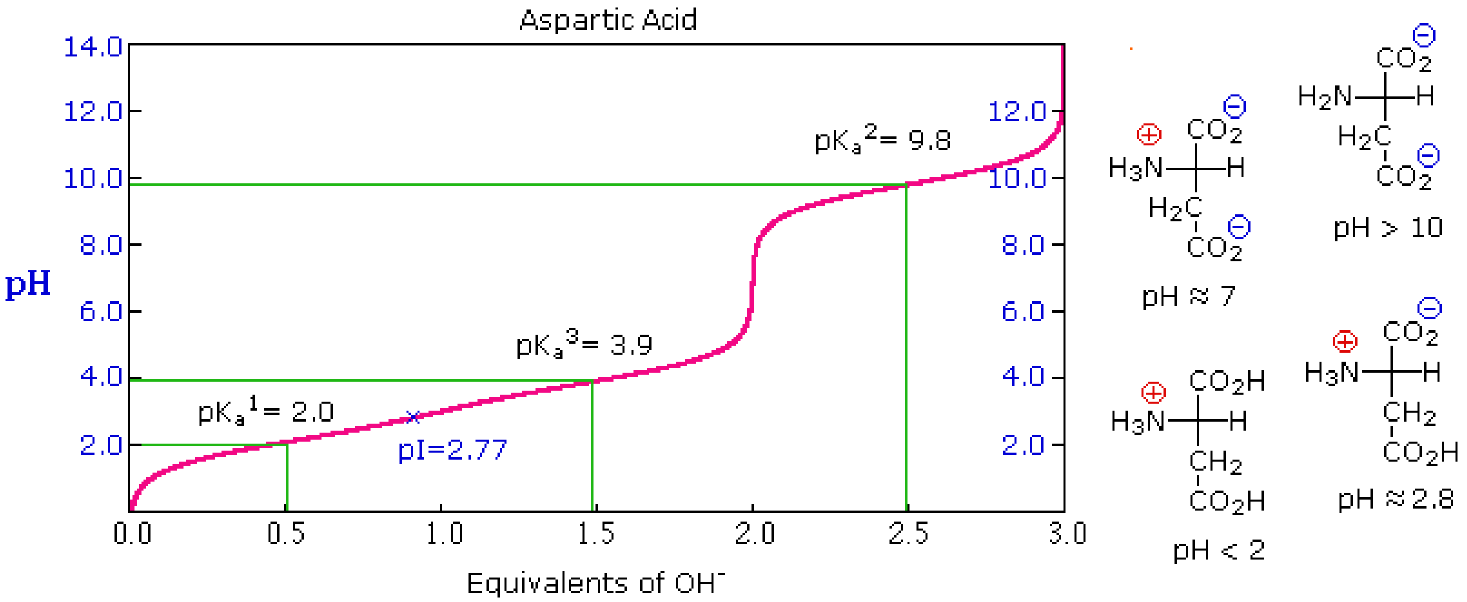
Titolazioni di amminoacidi: Arginina

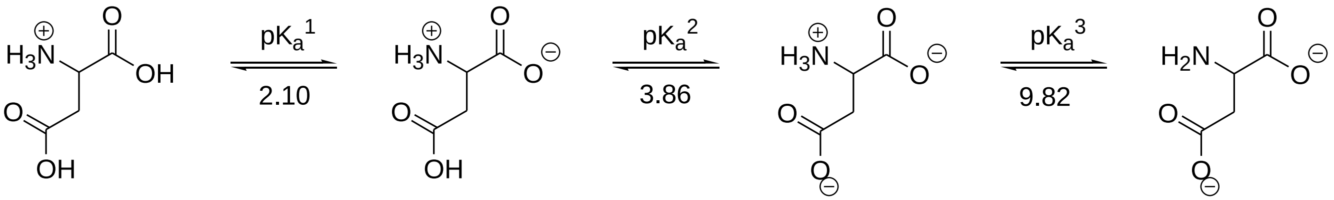




pI = 10.7

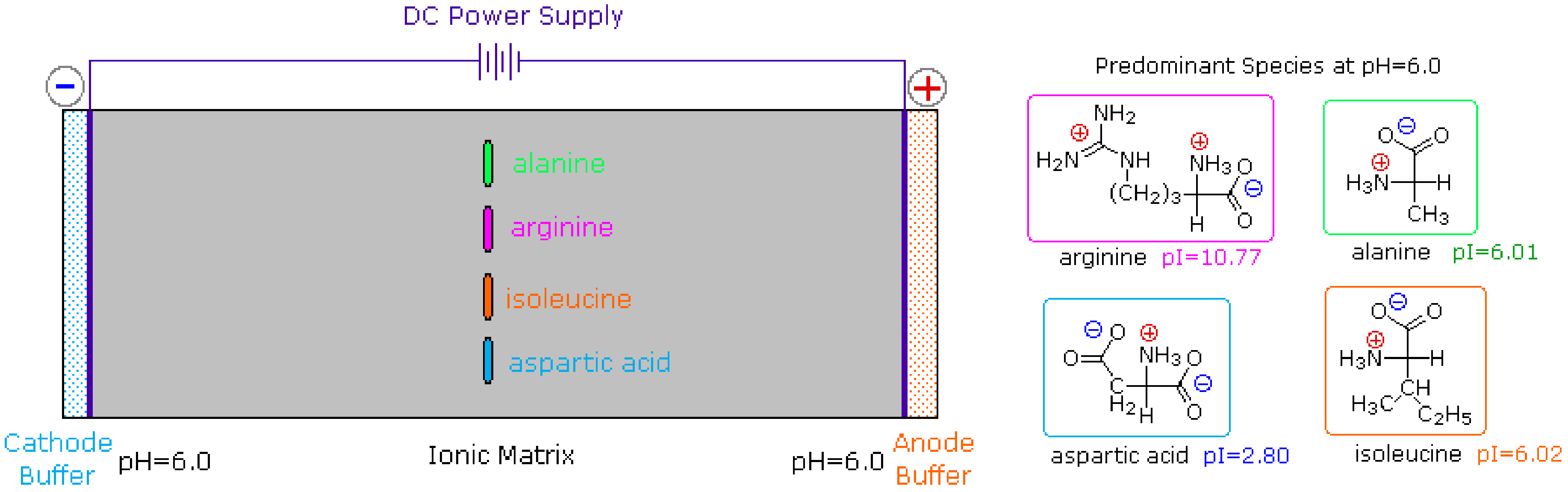
Titolazioni di amminoacidi: Acido Aspartico





pI = 2.98

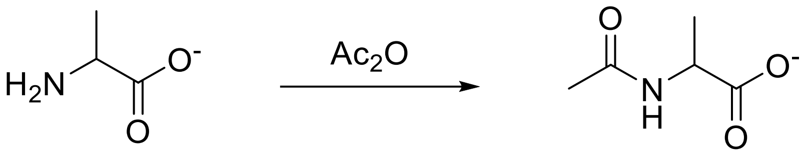
Elettroforesi



Amminoacidi: reazioni

Reazioni del gruppo amminico:

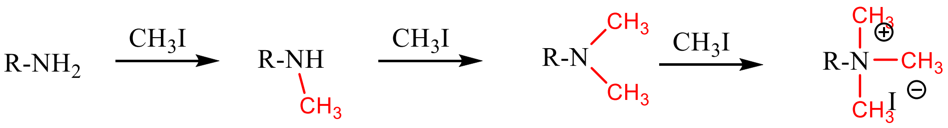
acilazione



alchilazione

$$H_2N\text{-}CHR\text{-}COO^- \xrightarrow[\text{(eccesso)}]{CH_3I} (H_3C)_3\overset{+}{N}\text{-}CHR\text{-}COO^-$$

betaina



$$R\text{-}NH_2 \xrightarrow{CH_3I} R\text{-}NH\text{-}CH_3 \xrightarrow{CH_3I} R\text{-}N(CH_3)_2 \xrightarrow{CH_3I} R\text{-}\overset{\oplus}{N}(CH_3)_3\ I^{\ominus}$$

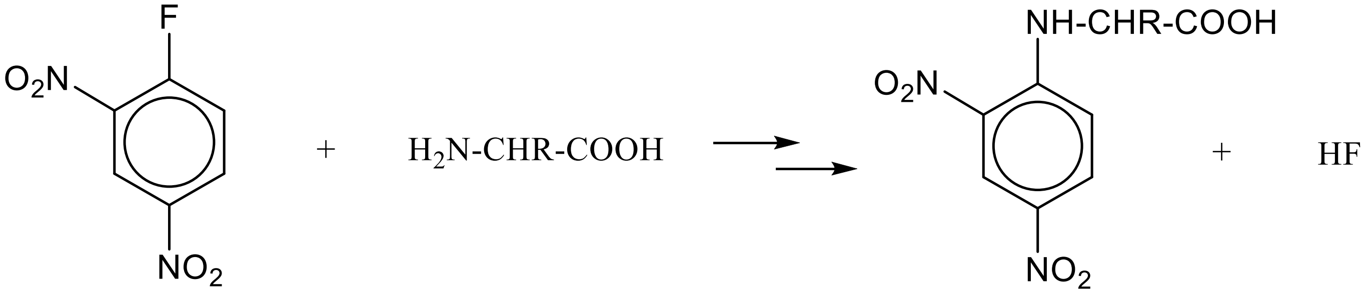
$$(H_3C)_3\overset{+}{N}\text{-}CHR\text{-}COO^- \overset{CH_3I}{\nrightarrow} (H_3C)_3\overset{+}{N}\text{-}CHR\text{-}COOMe$$

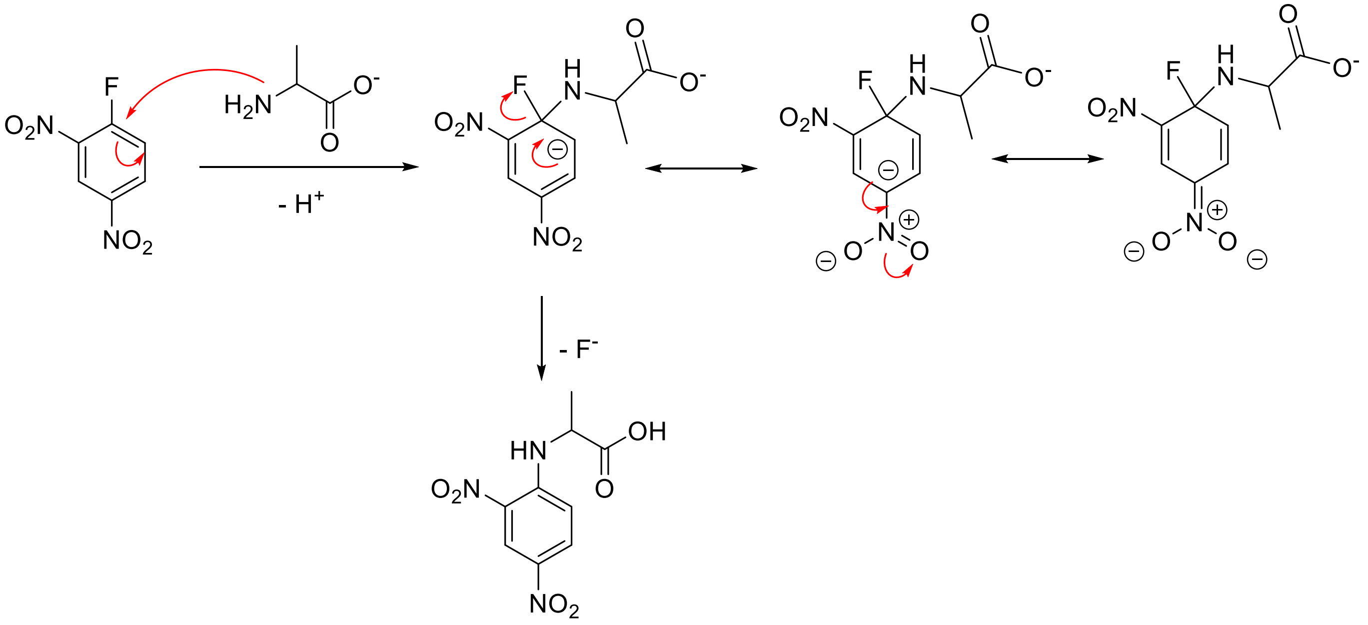
Amminoacidi: reazioni

Reazioni del gruppo amminico:

alchilazione

- reazione di Sanger





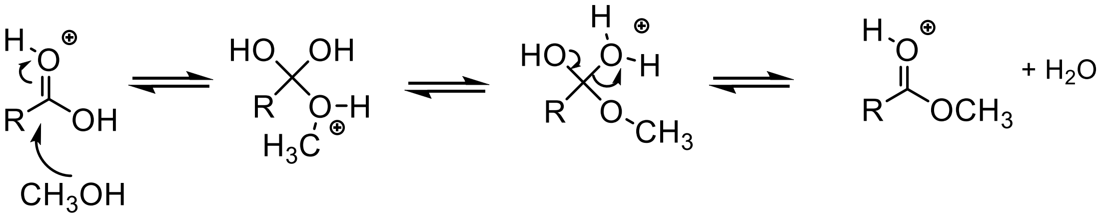
Amminoacidi: reazioni

Reazioni del gruppo carbossilico:

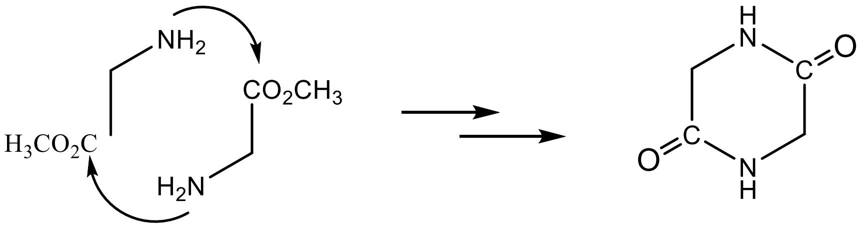
Formazione di esteri:

$$H_2N\text{-}CHR\text{-}COOH \xrightarrow[HCl]{CH_3OH} \left[\begin{matrix} H_3\overset{+}{N}\text{-}CHR\text{-}COOH \\ Cl^- \end{matrix} \right] \xrightarrow[HCl]{CH_3OH} \begin{matrix} H_3\overset{+}{N}\text{-}CHR\text{-}COOCH_3 \\ Cl^- \end{matrix}$$

$$\xrightarrow[H_2O]{NaHCO_3} H_2N\text{-}CHR\text{-}COOCH_3$$



NB: gli esteri degli α-amminoacidi sono instabili. Più stabili i loro cloridrati.



+ 2 CH_3OH

2,5-dichetopiperazina

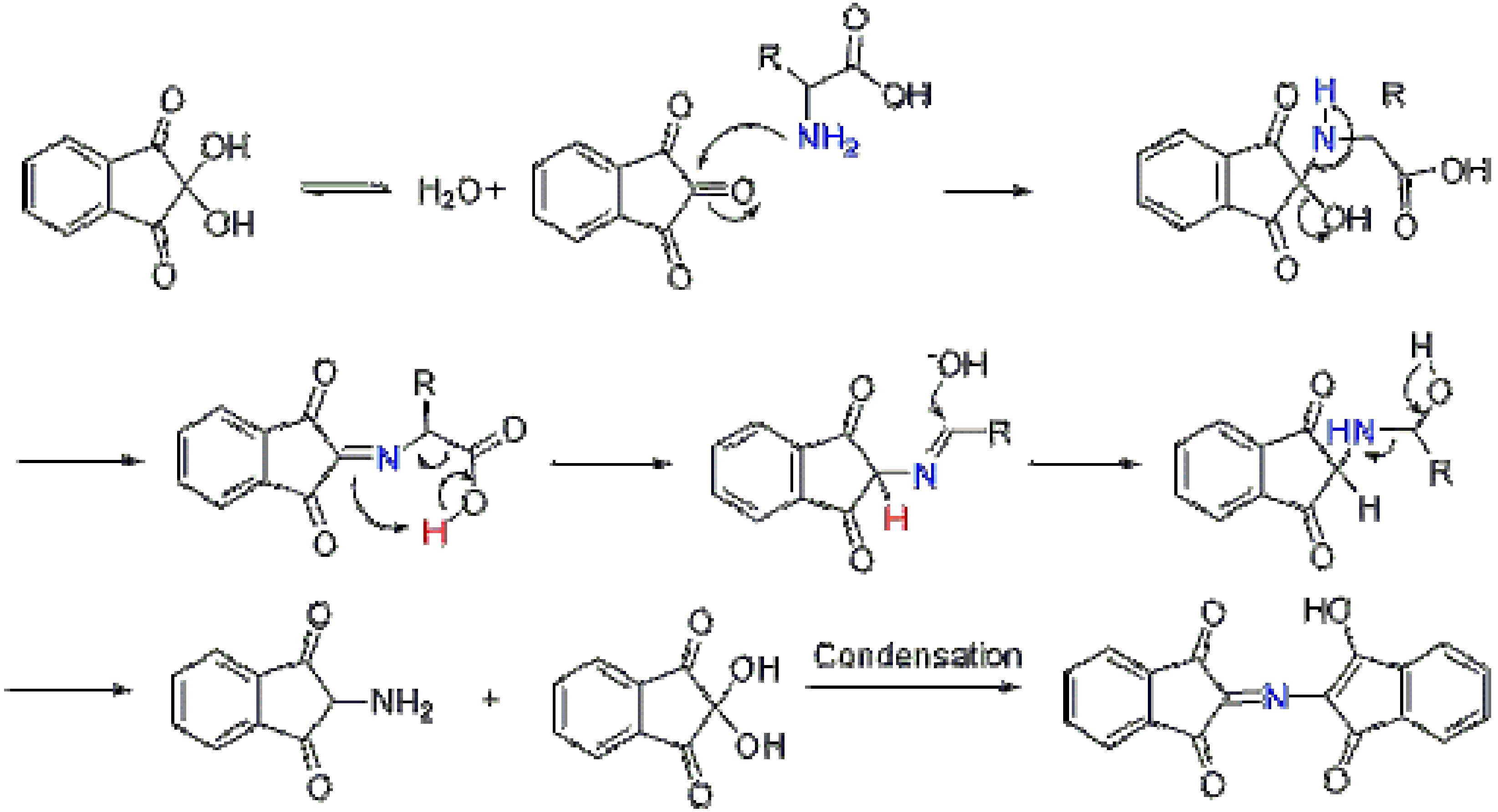
Riduzione del gruppo estereo:

$$H_2N\text{-}CHR\text{-}COOCH_3 \xrightarrow[\text{dietiletere}]{LiAlH_4} H_2N\text{-}CHR\text{-}CH_2OH + CH_3OH$$

β-amminoalcol

Amminoacidi: reazioni

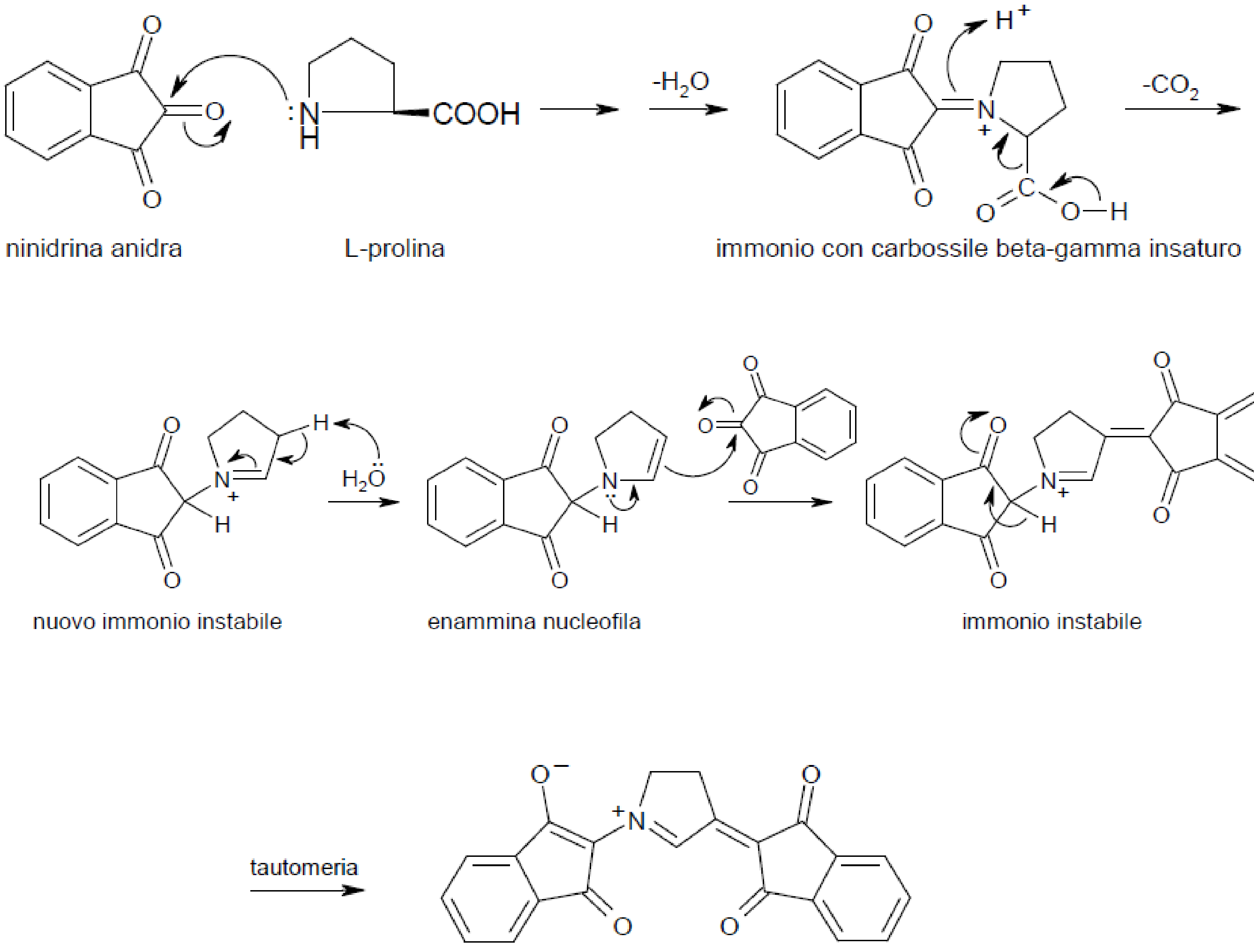
Reazione con la ninidrina



blu magenta assorbe a 570 nm

Amminoacidi: reazioni

Reazione con la ninidrina



ninidrina anidra

L-prolina

immonio con carbossile beta-gamma insaturo

nuovo immonio instabile

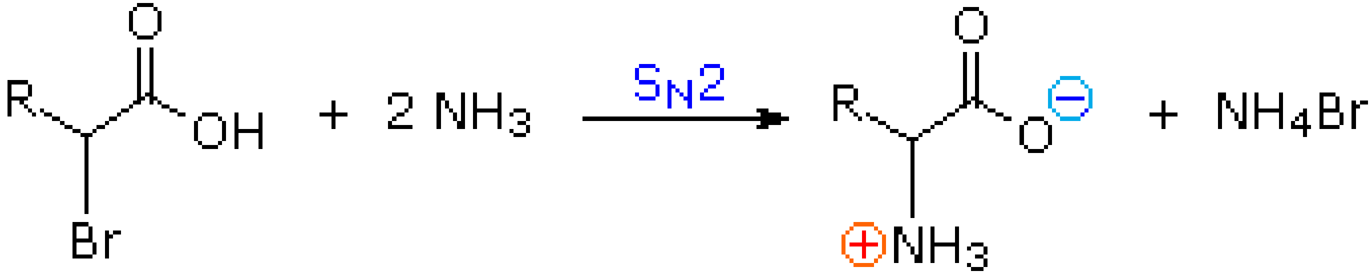
enammina nucleofila

immonio instabile

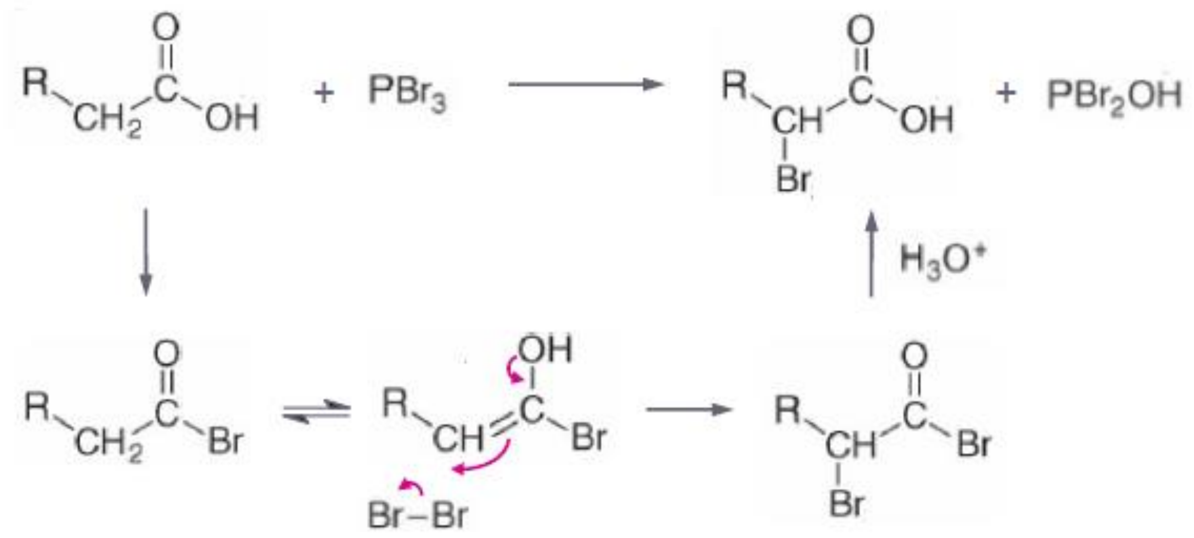
giallo, assorbe a 440 nm

Amminoacidi: sintesi

Ammonolisi di acidi α-bromocarbossilici

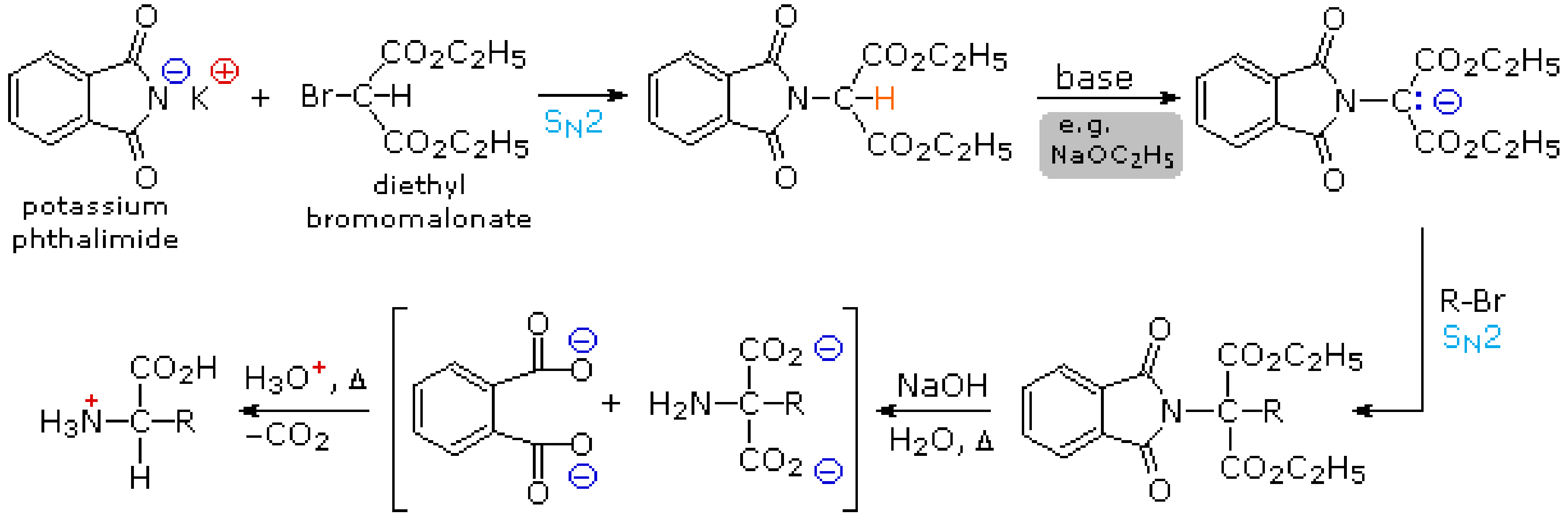


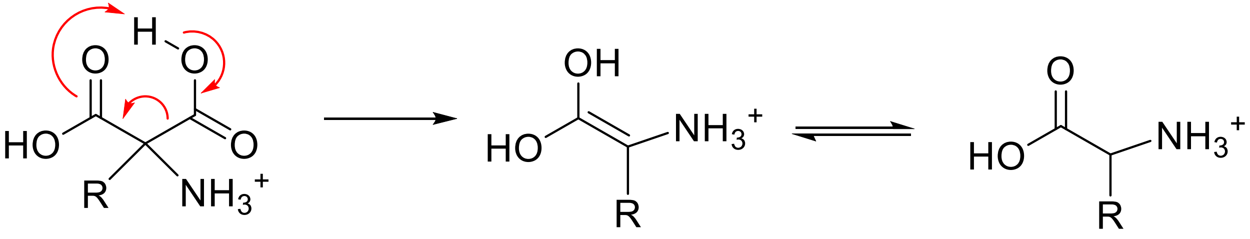
$$2P + 3\,Br_2 \rightarrow 2PBr_3$$



Amminoacidi: sintesi

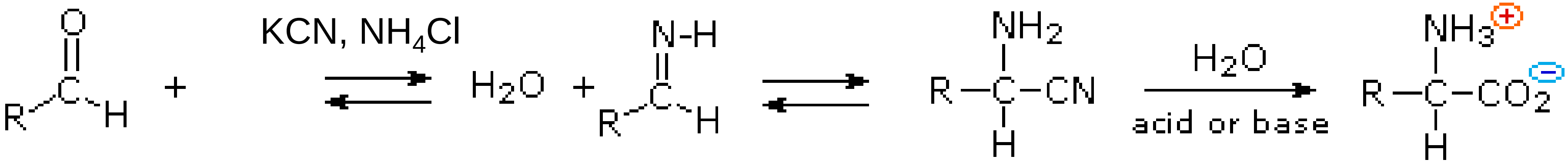
Sintesi di Gabriel

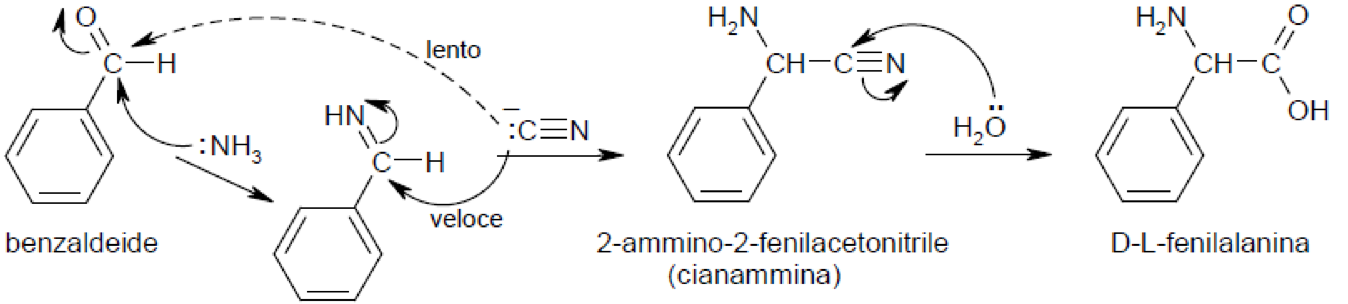




Amminoacidi: sintesi

Sintesi di Strecker



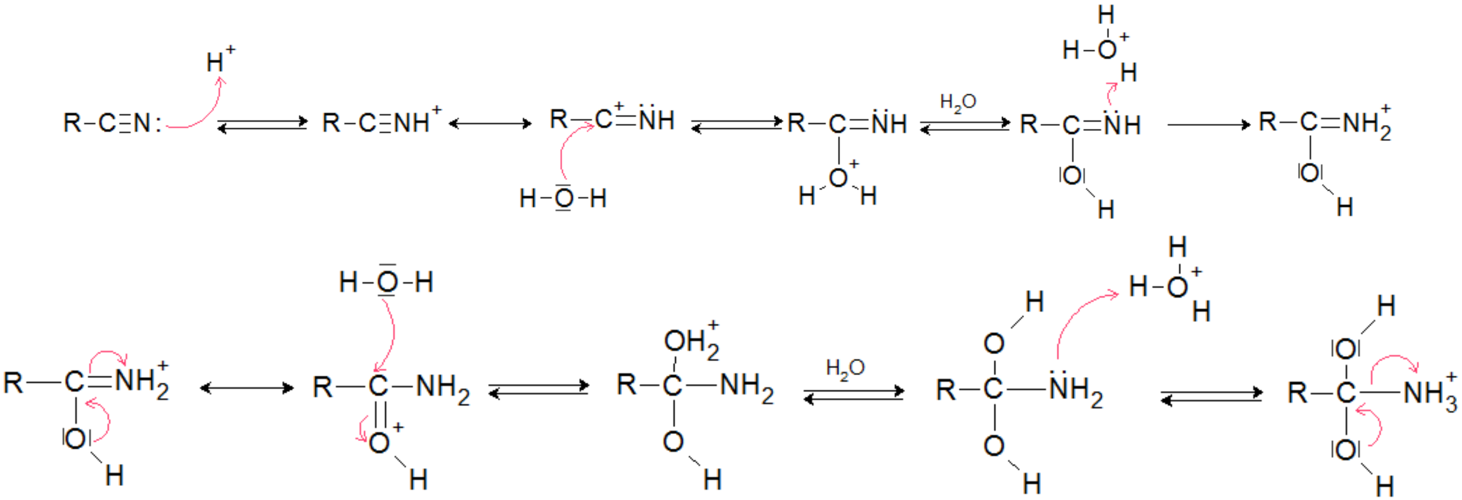


benzaldeide

1-fenilmetanimmina reattiva

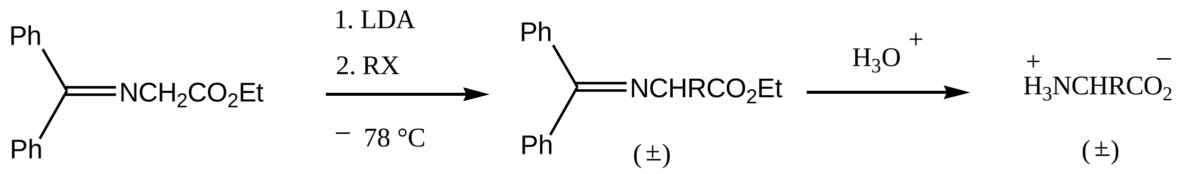
2-ammino-2-fenilacetonitrile (cianammina)

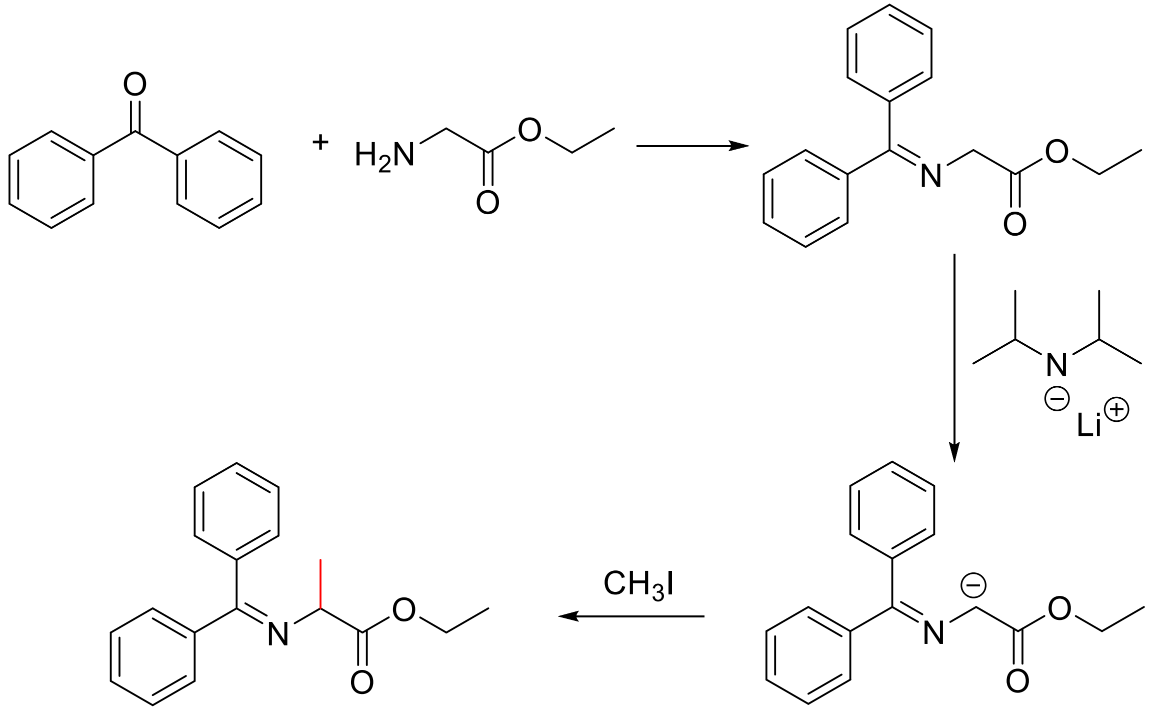
D-L-fenilalanina



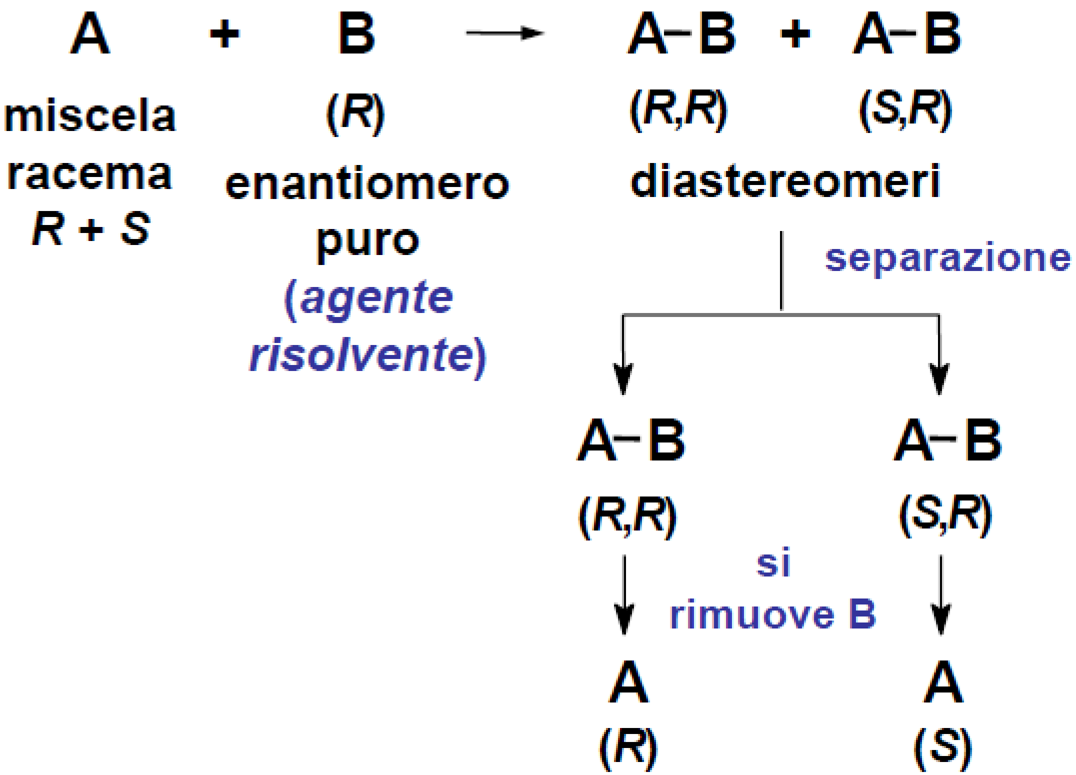
Amminoacidi: sintesi

Alchilazione della glicina N-funzionalizzata





Risoluzione di Enantiomeri



A + B → A–B + A–B

miscela racema *R* + *S*

(*R*) enantiomero puro (*agente risolvente*)

(*R*,*R*) (*S*,*R*) diastereomeri

separazione

A–B (*R*,*R*)

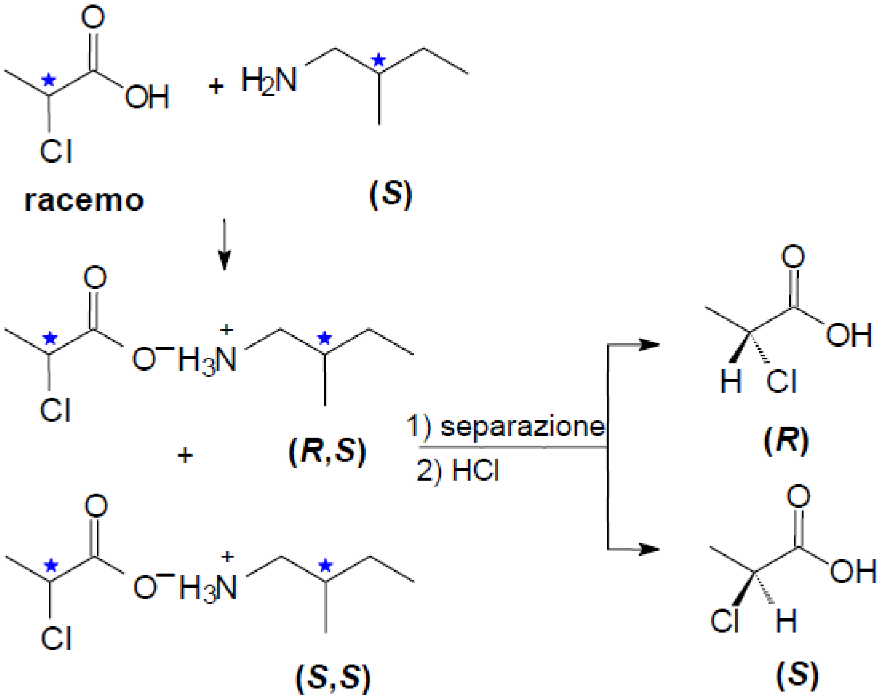
A–B (*S*,*R*)

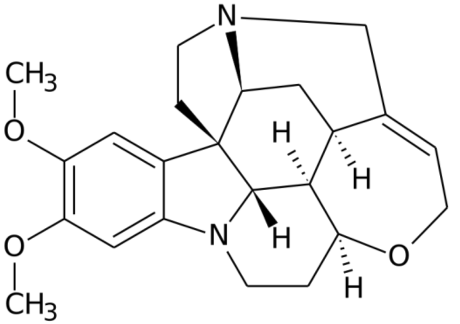
si rimuove B

A (*R*)

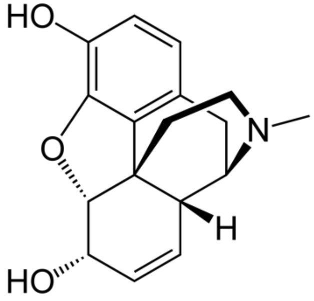
A (*S*)

Risoluzione di Enantiomeri



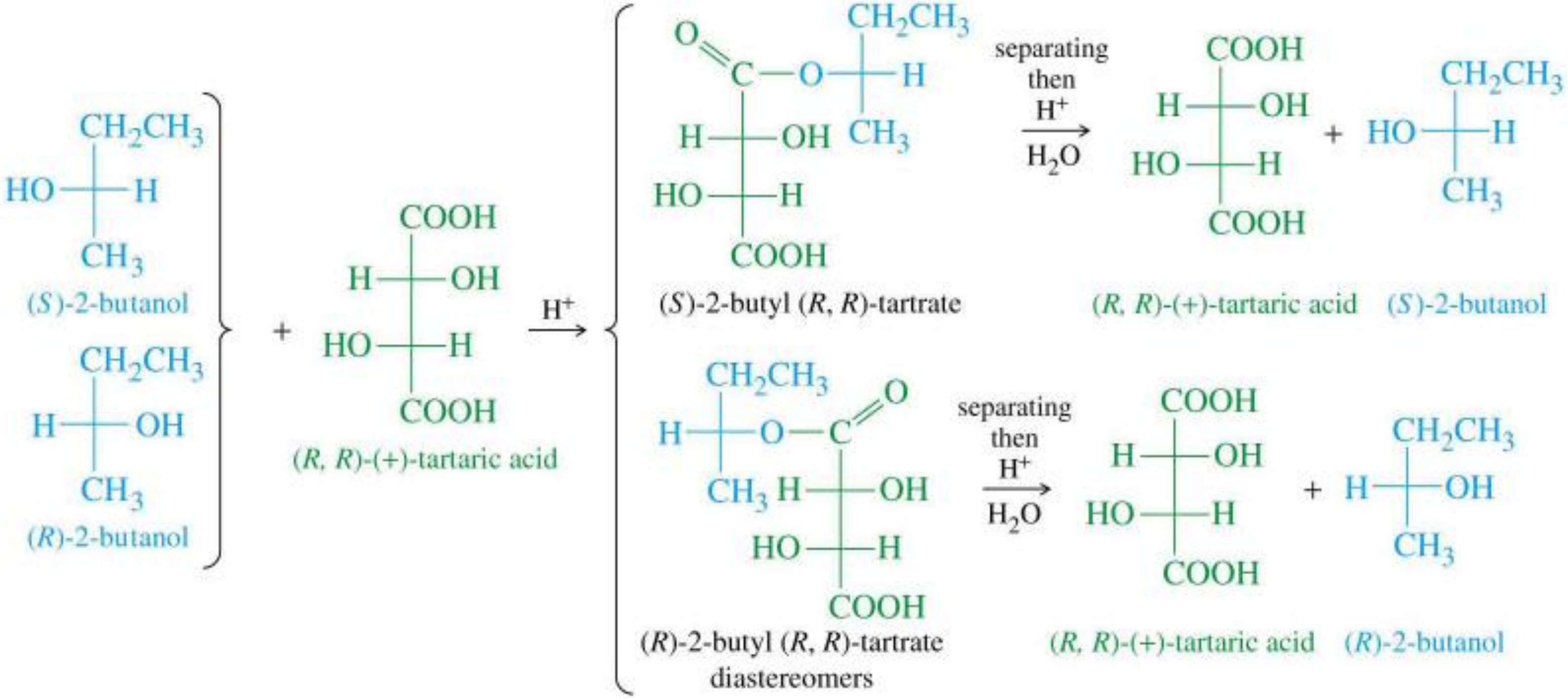


Brucina (2,3-dimetossistricnina)

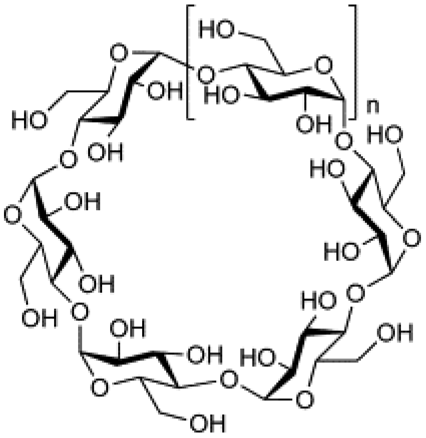


morfina

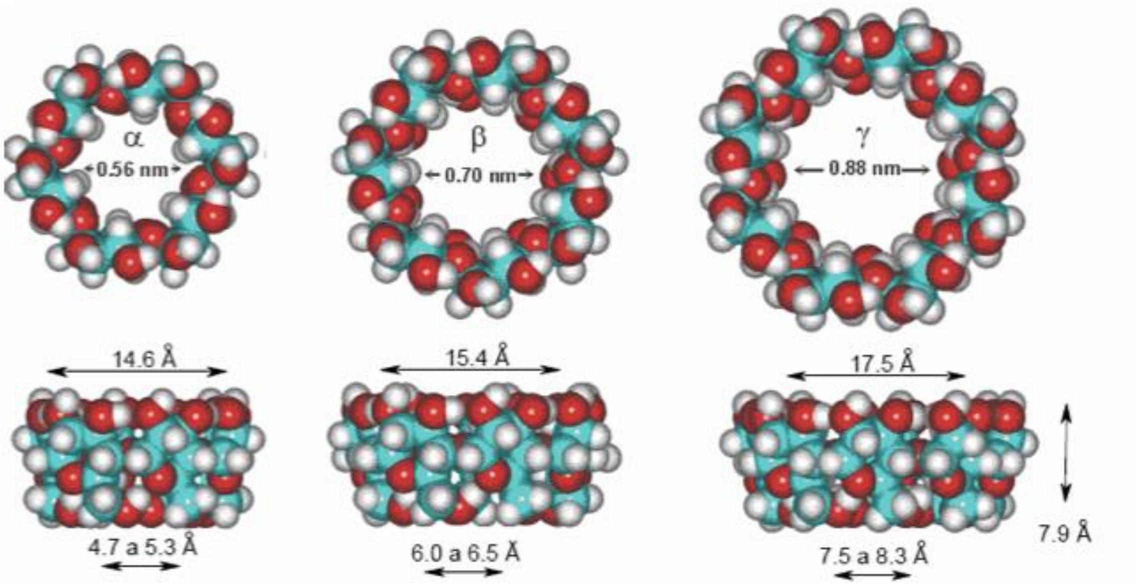
Risoluzione di Enantiomeri

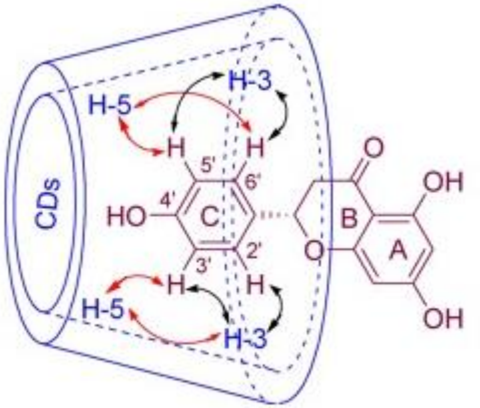


Ciclodestrina

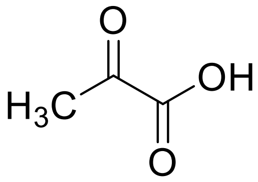


n = 1, α-cyclodextrin
n = 2, β-cyclodextrin
n = 3, γ-cyclodextrin

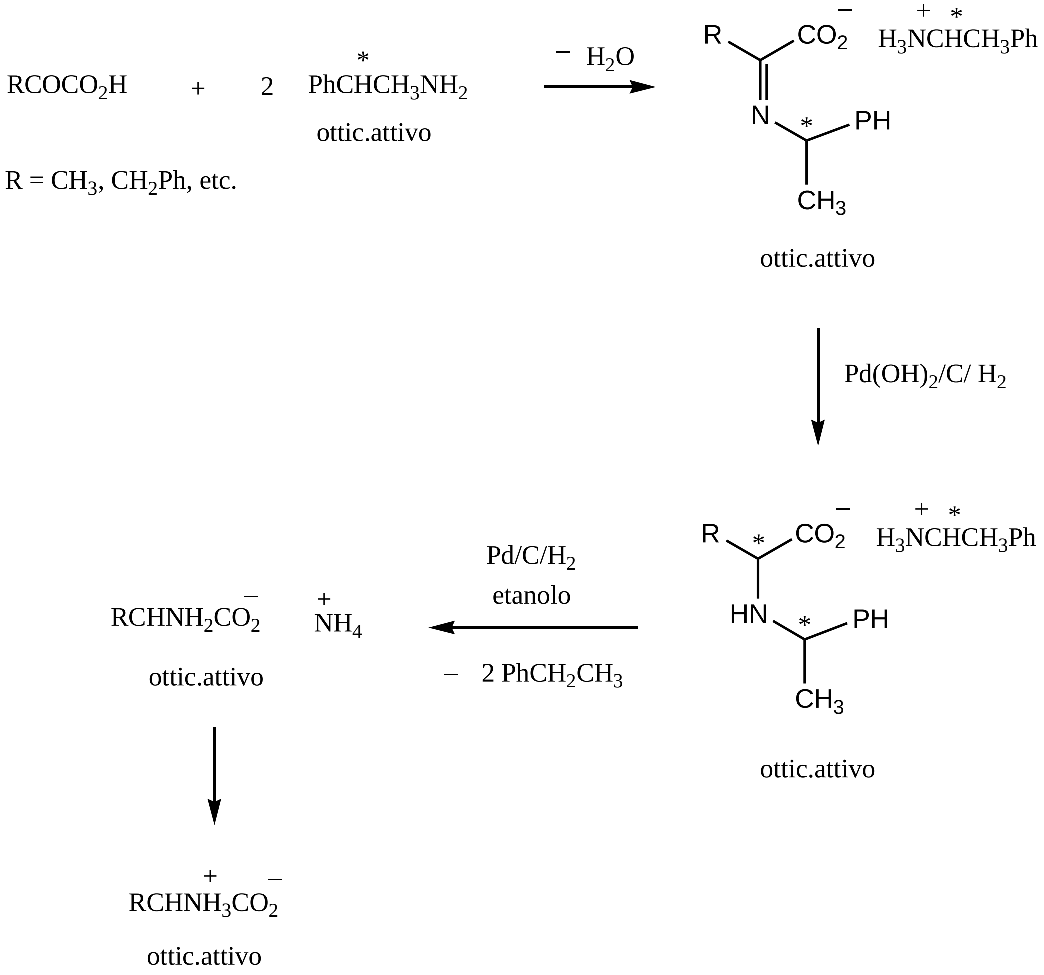




Amminoacidi: sintesi enantioselettiva



acido piruvico



$RCOCO_2H$ + 2 $\overset{*}{Ph}CHCH_3NH_2$ $\xrightarrow{-\ H_2O}$

ottic.attivo

R = CH_3, CH_2Ph, etc.

ottic.attivo

Pd(OH)$_2$/C/ H_2

ottic.attivo

Pd/C/H_2

etanolo

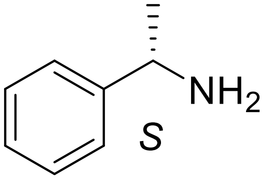
– 2 $PhCH_2CH_3$

$RCHNH_2CO_2^-$ $\overset{+}{N}H_4$

ottic.attivo

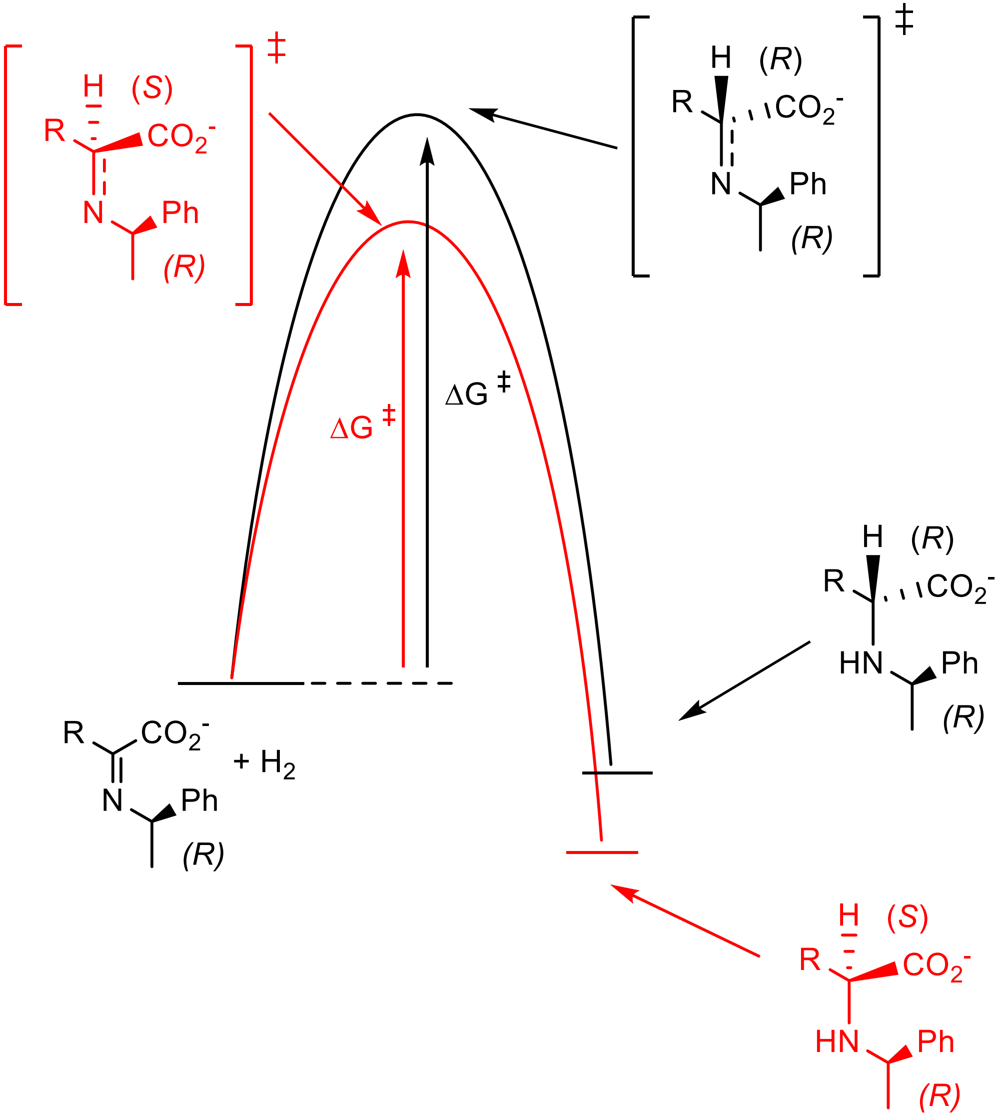
$RCH\overset{+}{N}H_3CO_2^-$

ottic.attivo

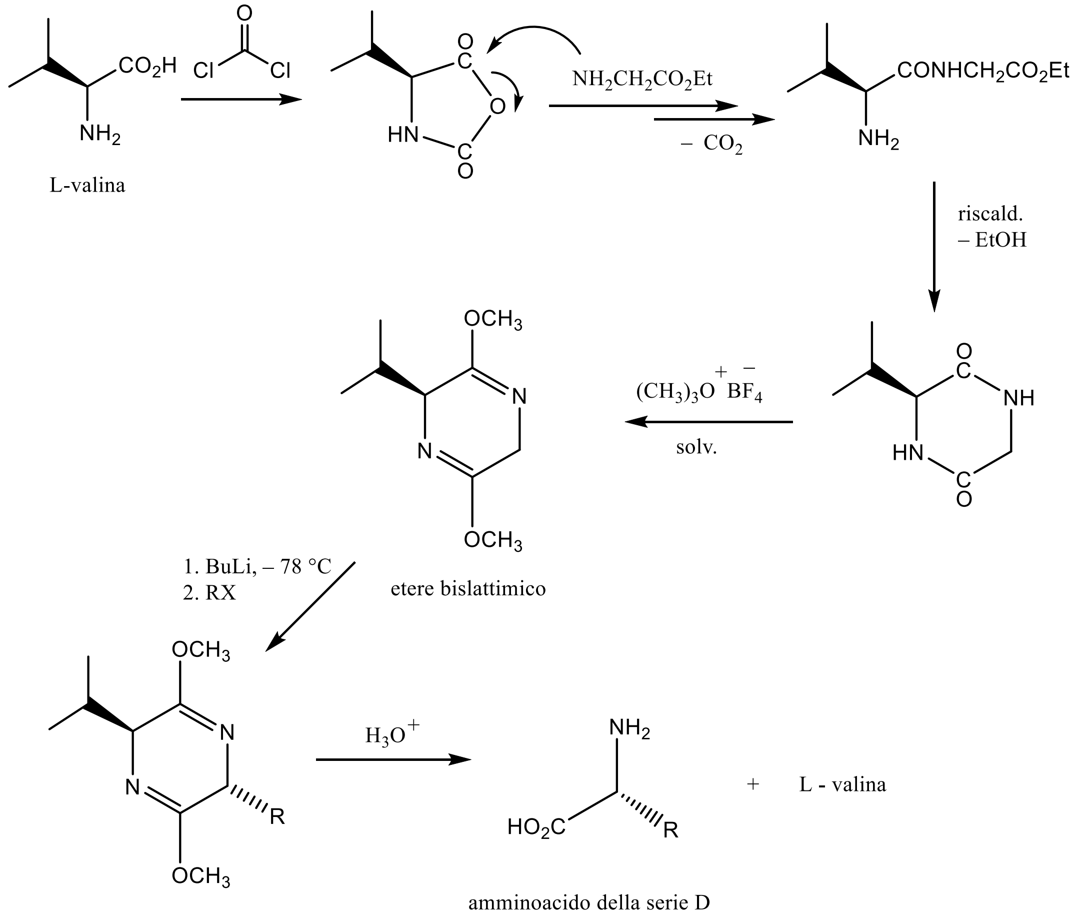


Ad es. utilizzando la (*S*)-(–)-1-fenetilammina, dopo l'idrogenazione del doppio legame imminico, si ottengono due diastereomeri salini in proporzioni diverse che possono essere separati per cristallizzazione frazionata, sottoposti ad idrogenolisi per dare l'amminoacido che sarà otticamente attivo.

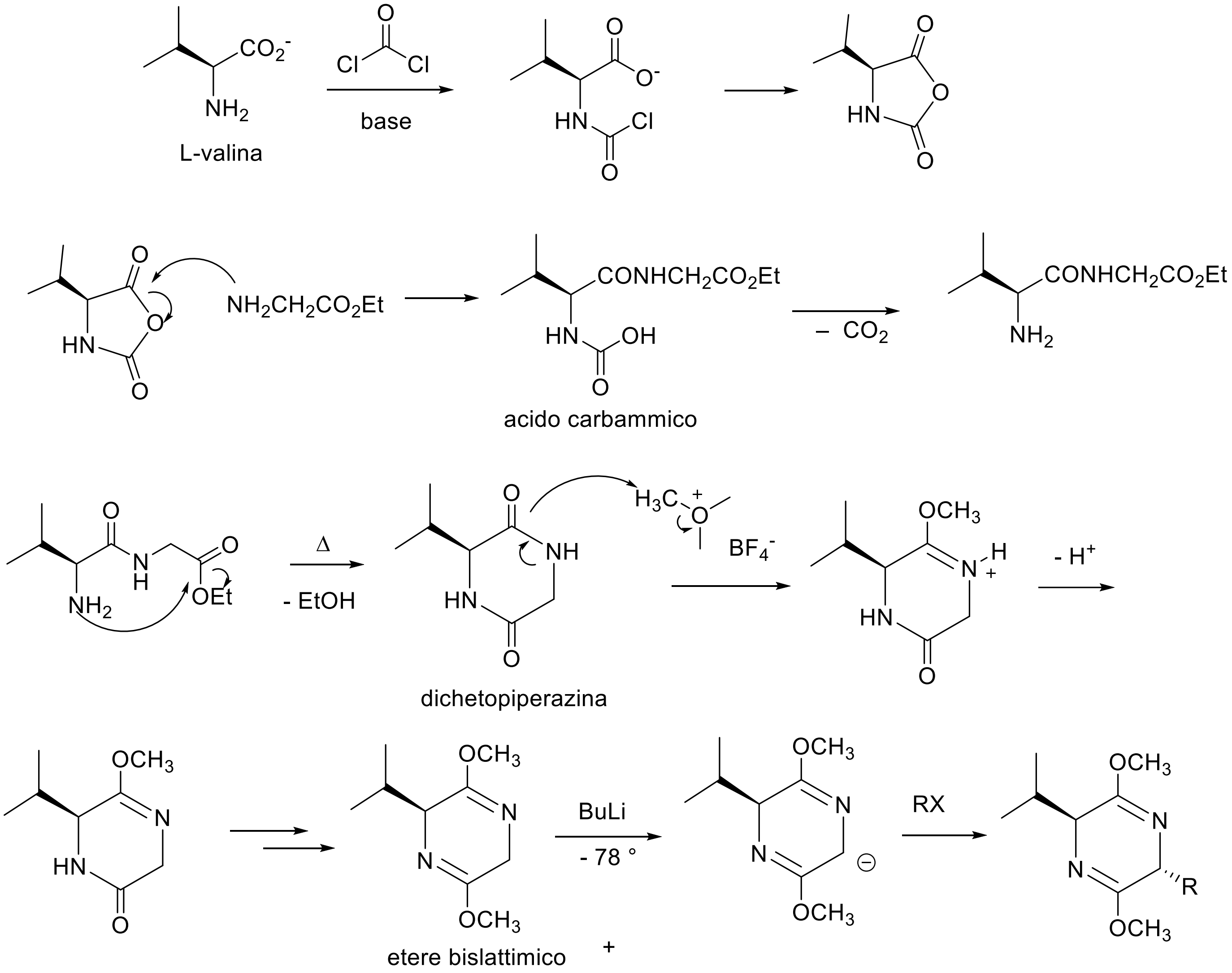
Amminoacidi: sintesi enantioselettiva



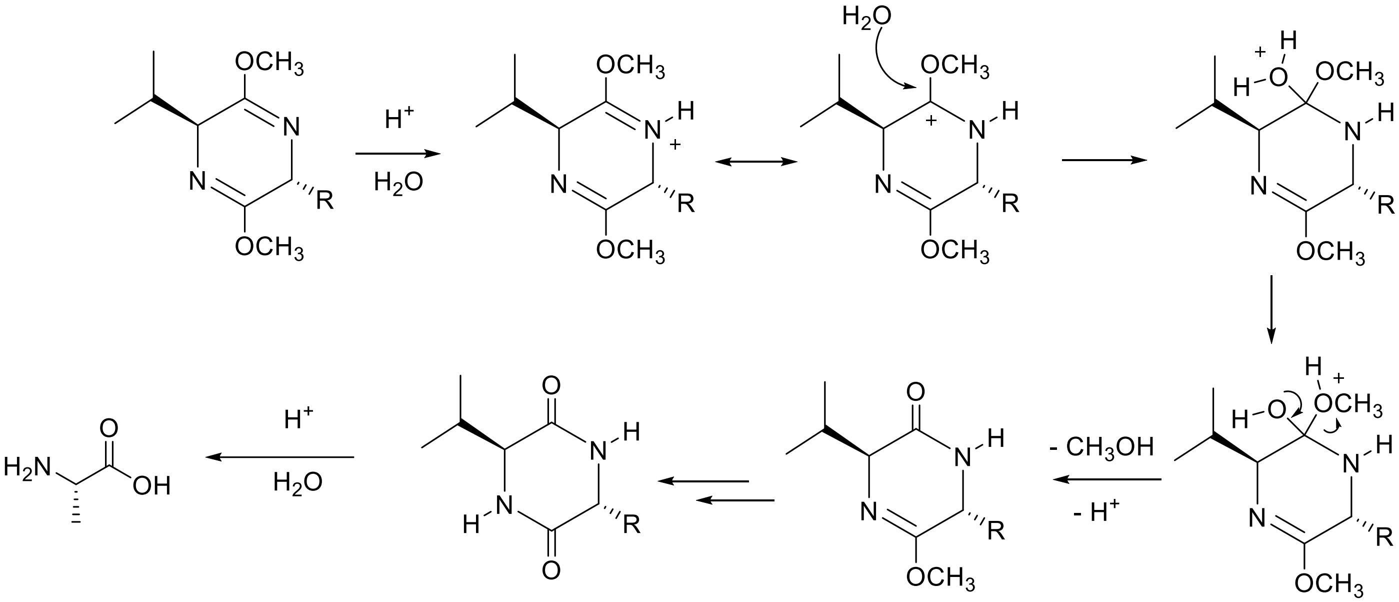
Amminoacidi: sintesi enantioselettiva



Amminoacidi: sintesi enantioselettiva

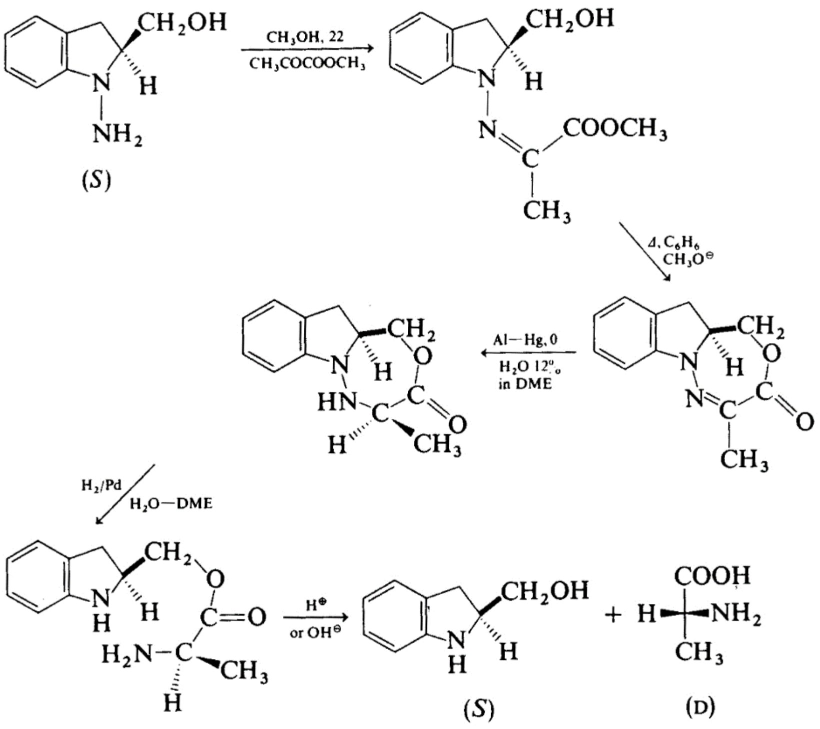


Amminoacidi: sintesi enantioselettiva

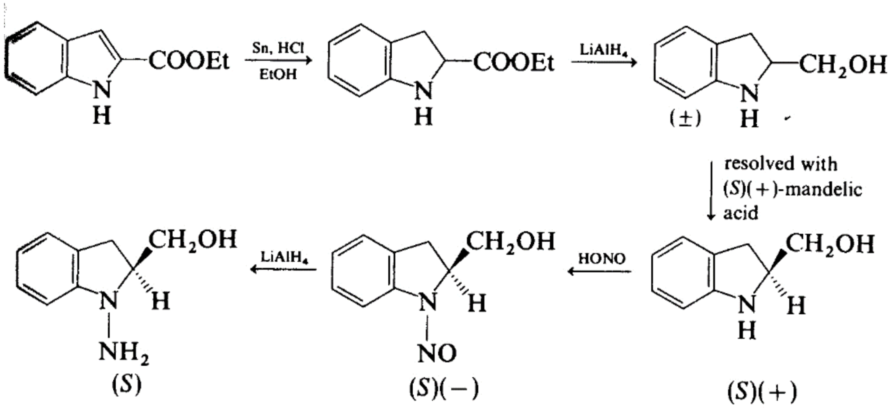


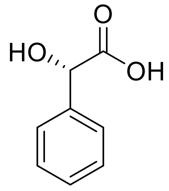
Amminoacidi: sintesi enantioselettiva

Sintesi di E.J. Corey

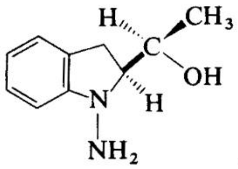


e.e. 80 %





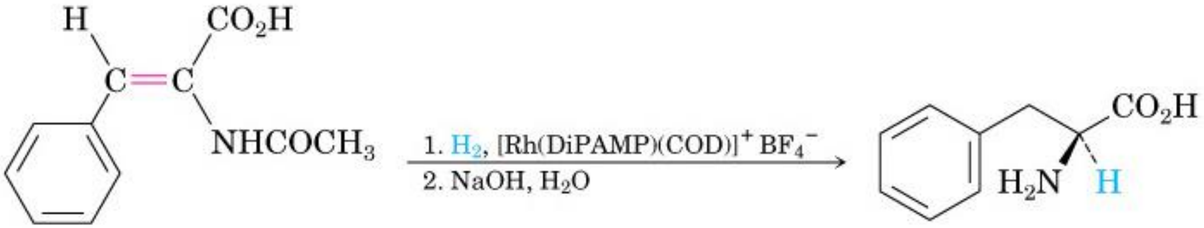
(S)-Mandelic acid



e.e. 96 %

Amminoacidi: sintesi enantioselettiva

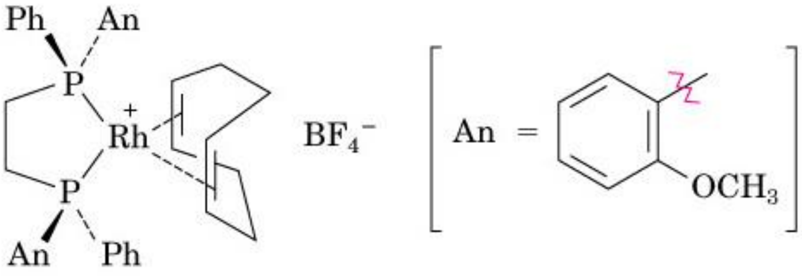
Sintesi di W. S. Knowles



Enammido acido *Z*

(*S*)-Fenilalanina

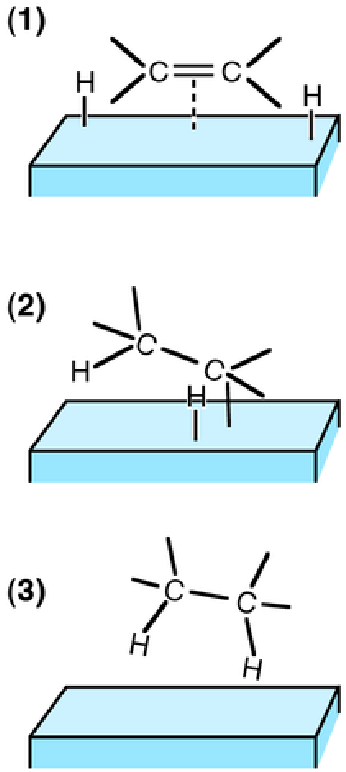
e.e. 99 %



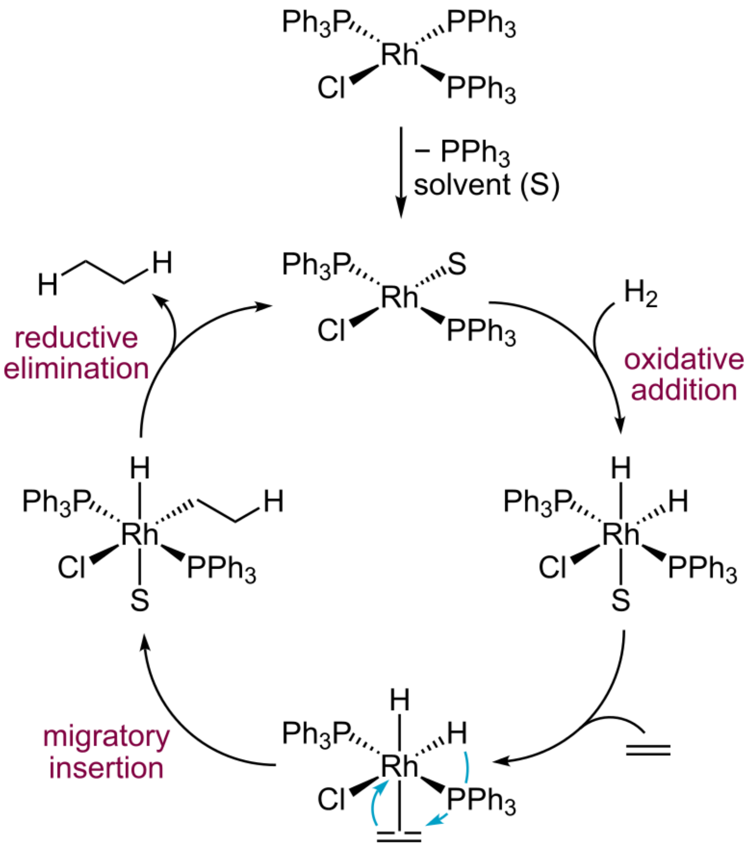
[Rh(*R*,*R*-DiPAMP)(COD)]$^+$ BF$_4^-$

Idrogenazione catalitica

Catalisi eterogenea



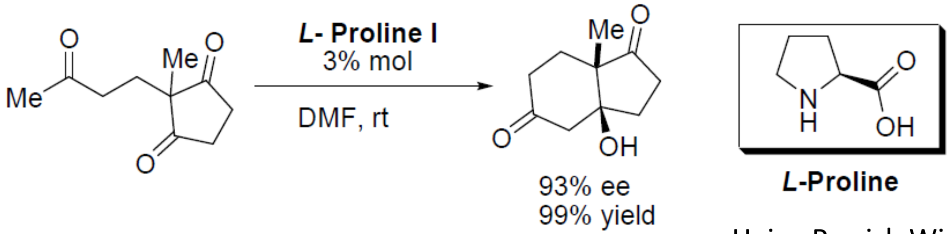
Catalisi omogenea



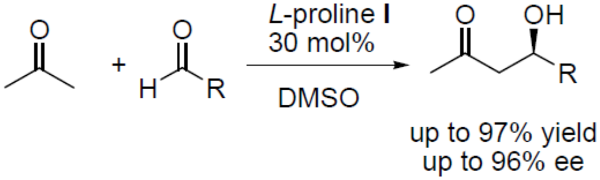
Catalizzatore di Wilkinson

Organocatalisi

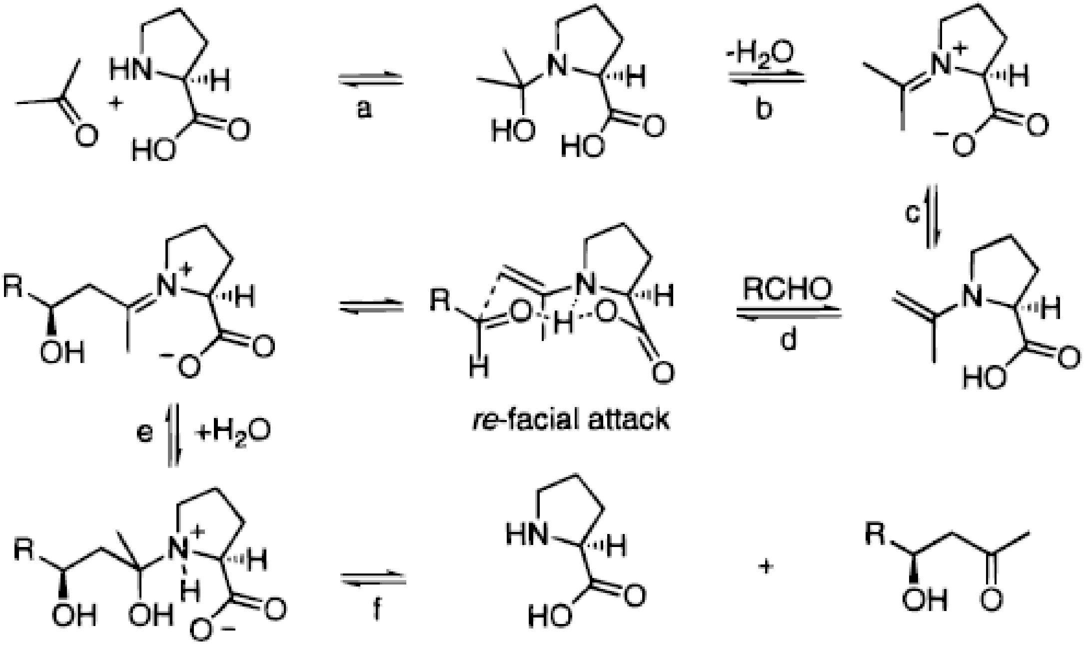
Ammino catalisi



Hajos Parrish Wiechert, Eder, and Sauer, **1971**

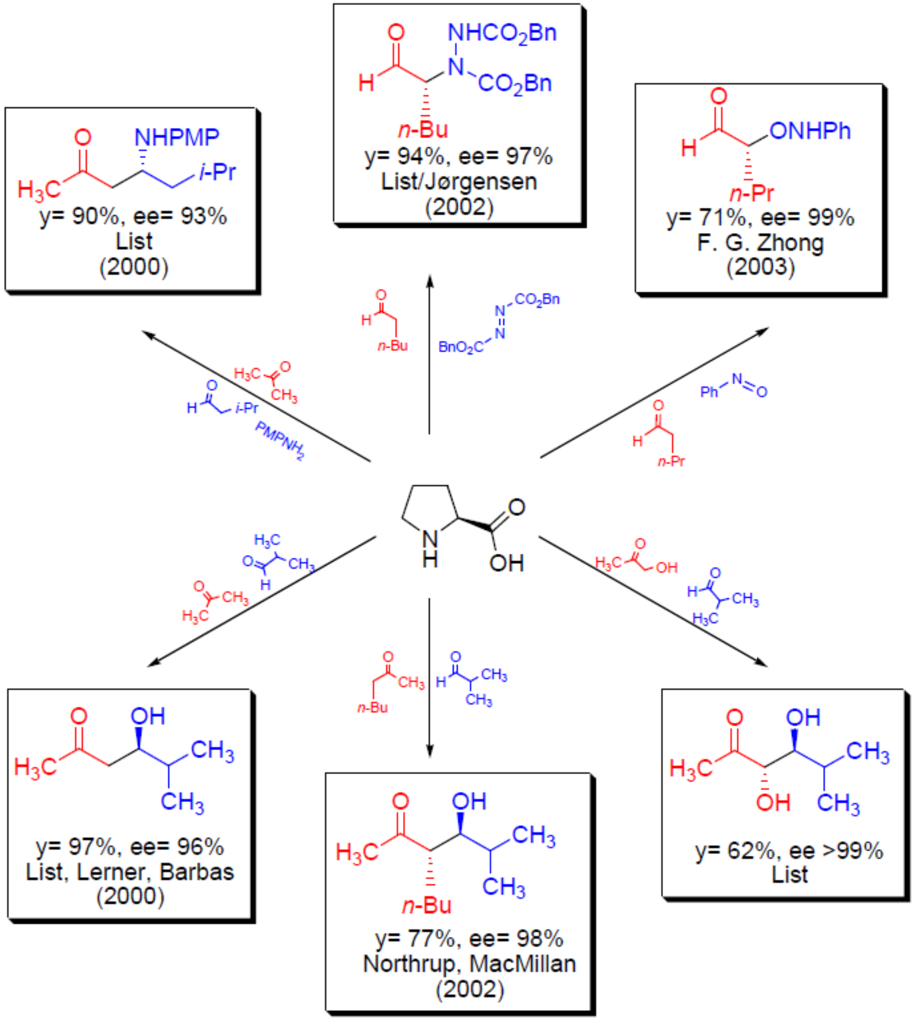


B.List, R. A. Lerner, F. C. Barbas III *J. Am. Chem. Soc.* **2000**,*122*, 2395.



Organocatalisi

Ammino catalisi



y= 90%, ee= 93%
List
(2000)

y= 94%, ee= 97%
List/Jørgensen
(2002)

y= 71%, ee= 99%
F. G. Zhong
(2003)

y= 97%, ee= 96%
List, Lerner, Barbas
(2000)

y= 77%, ee= 98%
Northrup, MacMillan
(2002)

y= 62%, ee >99%
List