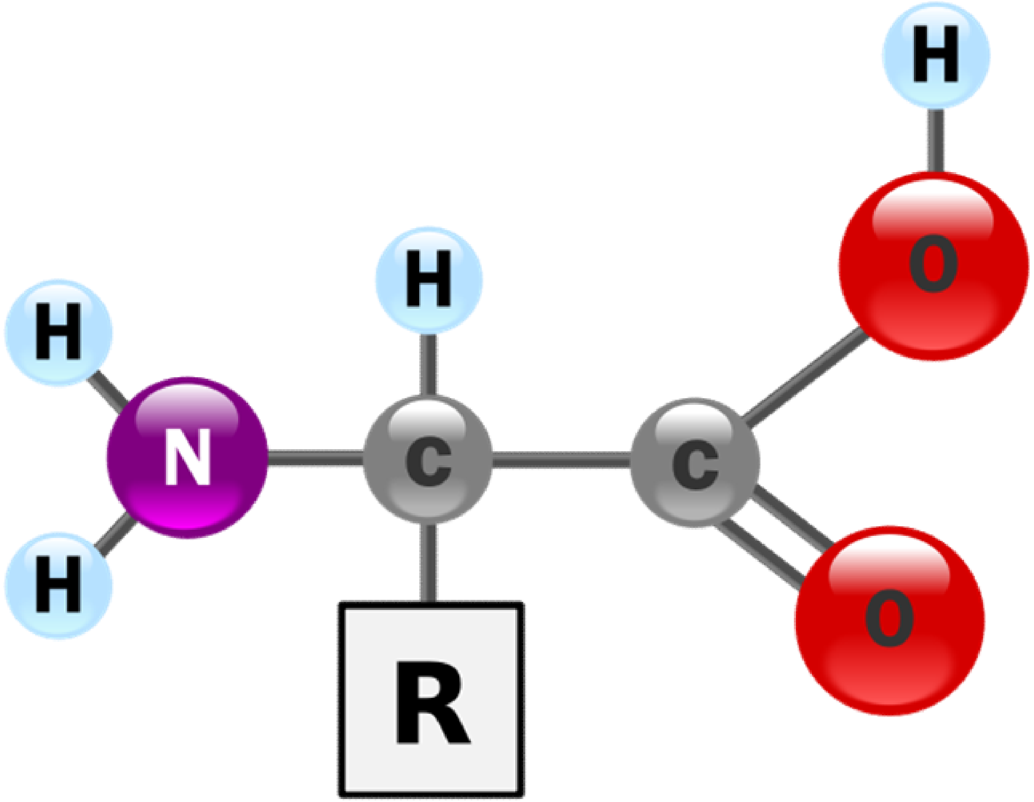
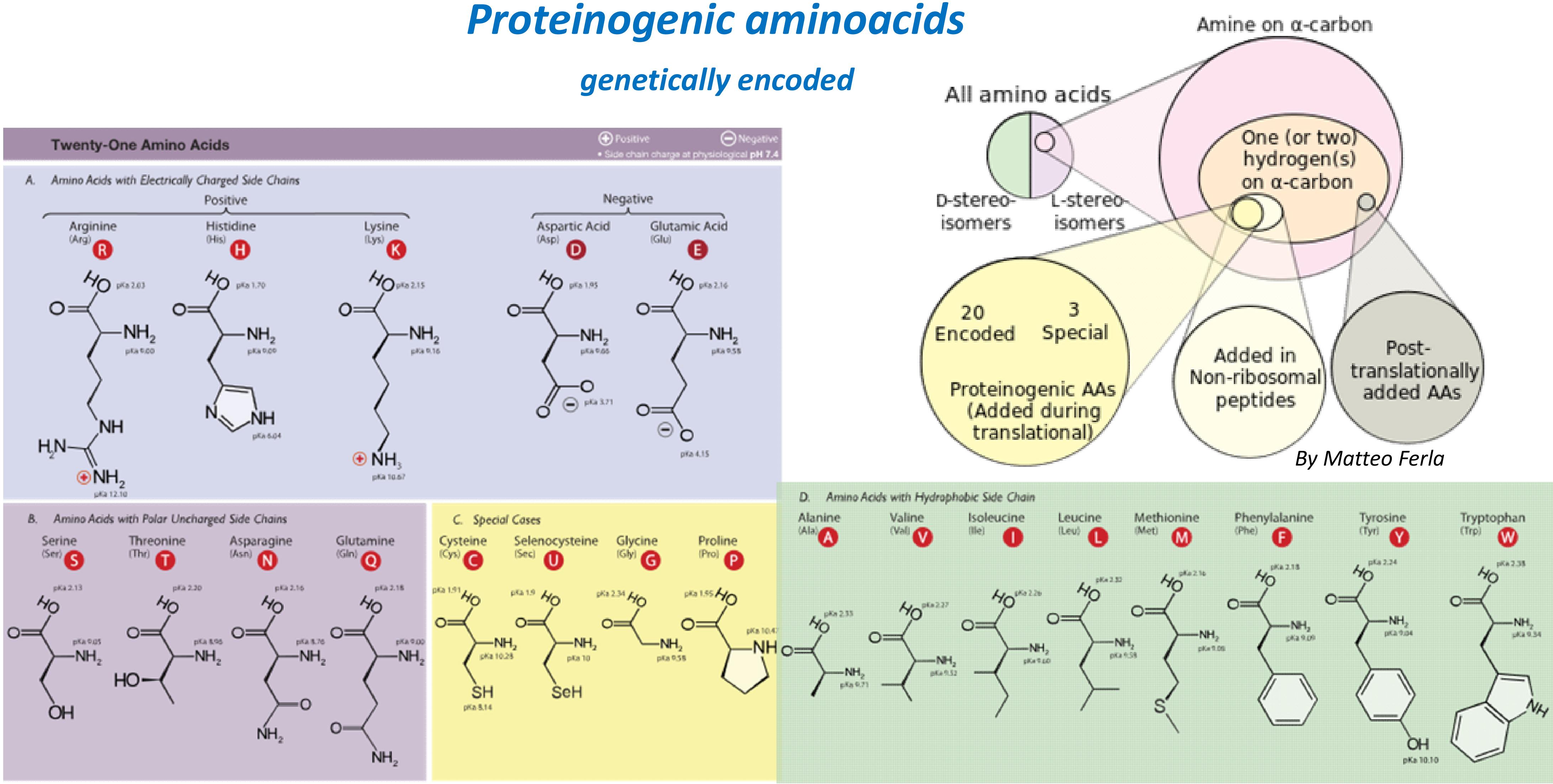
Aminoacids

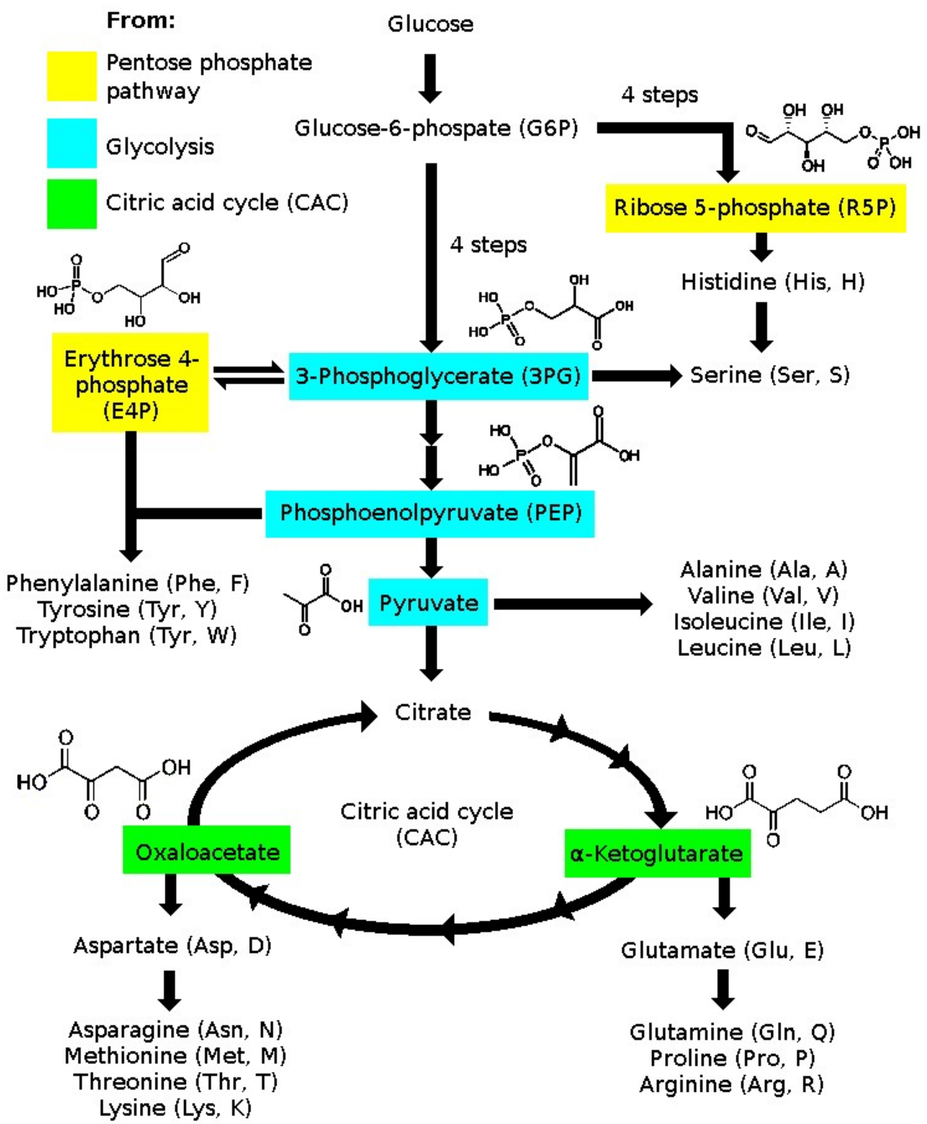


Proteinogenic aminoacids

genetically encoded



Biosynthesis of biogenic aminoacids



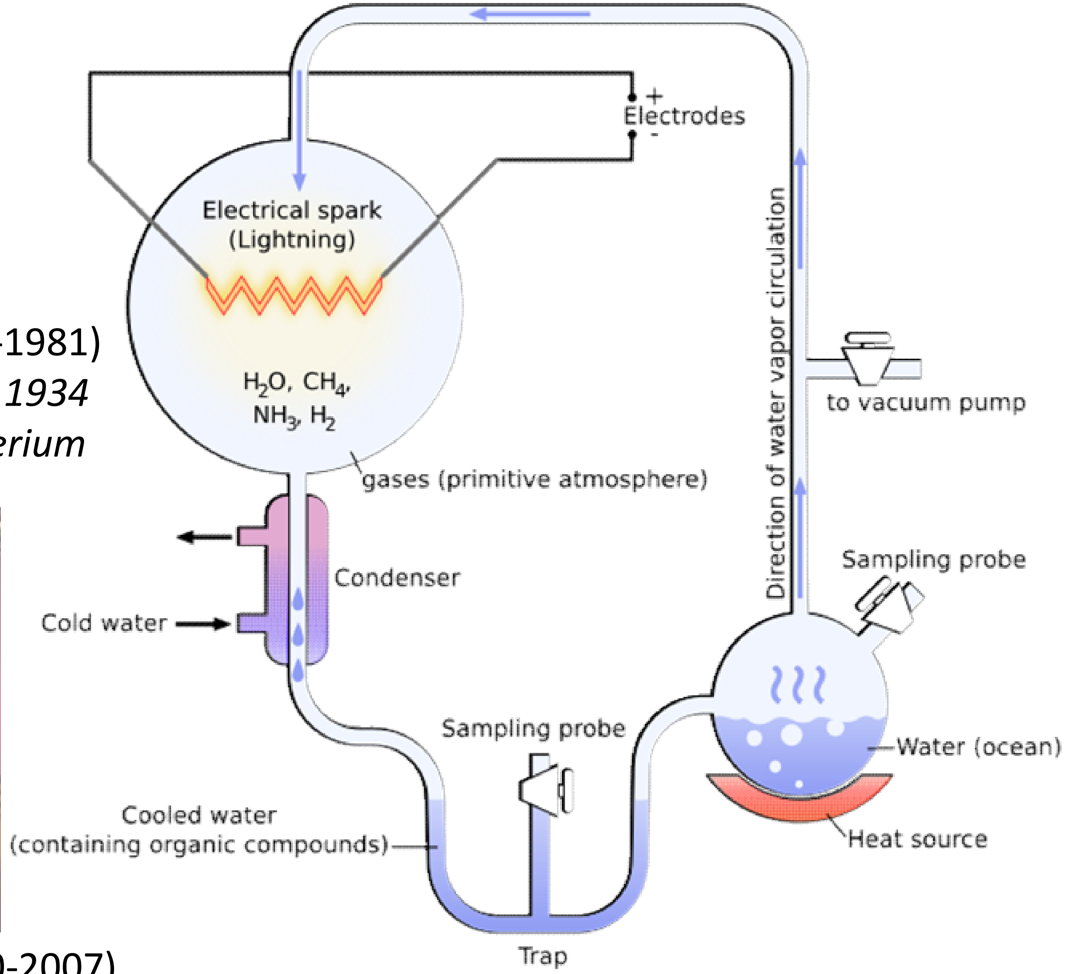
Atmosphere composition for young terrestrial planets

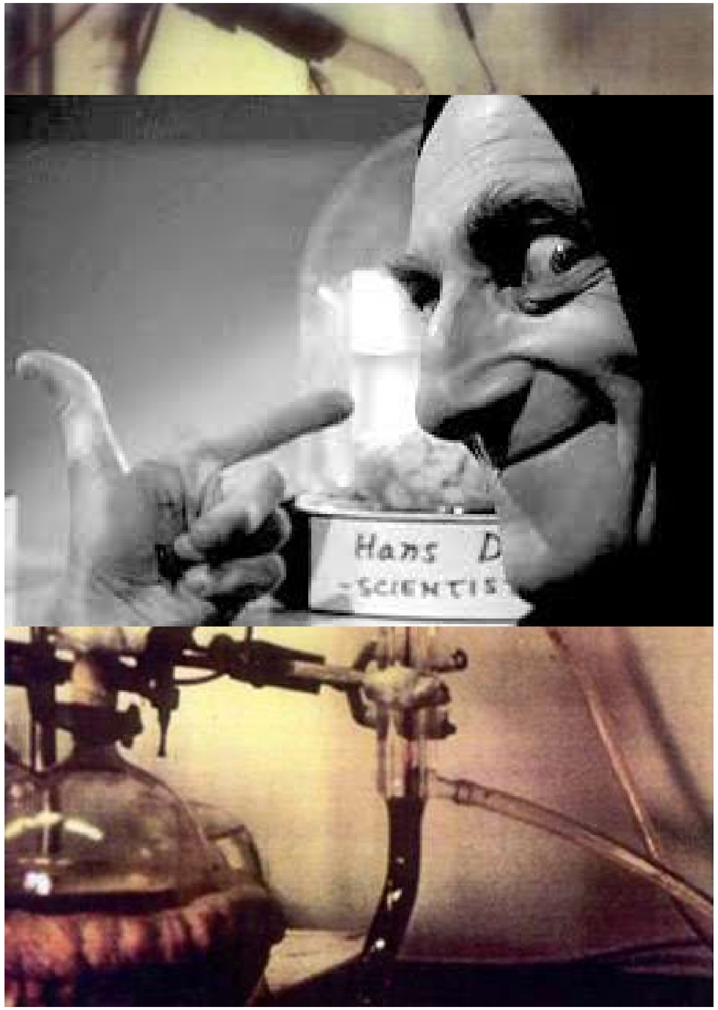
	Reduced	Neutral	Oxic
Carbon (C)	CH_4	CO, CO_2	CO_2
Nitrogen (N)	NH_3	N_2	N_2
Oxygen (O)	H_2O	H_2O, CO, CO_2	O_2
Hydrogen (H)	H_2, CH_4, NH_3, H_2O	H_2O	H_2O

Miller-Urey experiment - 1952

Harold Urey (1893-1981)
UCSD, Nobel prize 1934
Discovery of deuterium

Stanley Miller (1930-2007)
UCSD San Diego, CA, USA





Products of the Miller-Urey experiment

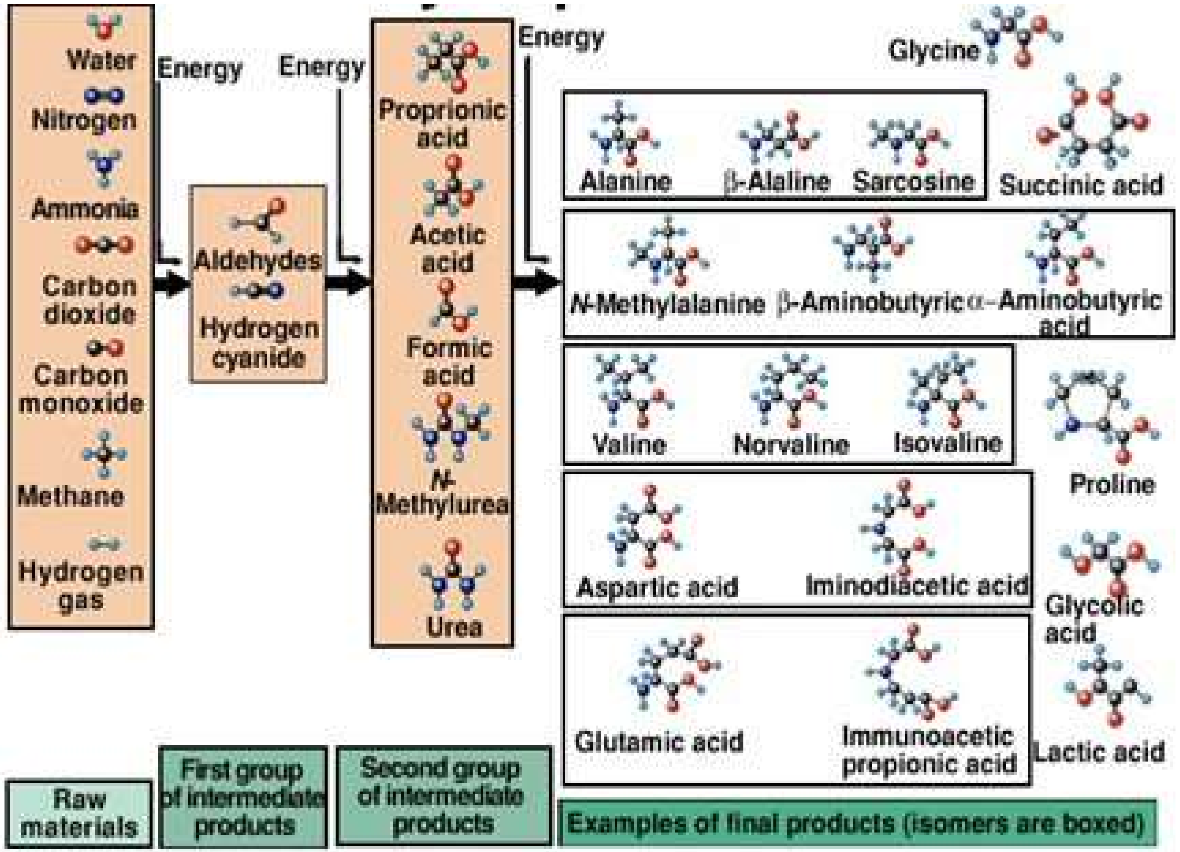


TABLE 4.2
Typical Miller-Urey reaction products formed under reducing conditions

Compound	Yield (% total fixed carbon)	Compound	Yield (% total fixed carbon)
Formic acid	4.0	Succinic acid	0.27
Glycine	2.1	Sarcosine	0.25
Glycolic acid	1.9	Iminoacetic propionic acid	0.13
Alanine	1.7	*N*-methylalanine	0.07
Lactic acid	1.6	Glutamic acid	0.05
β-Alanine	0.76	*N*-methylurea	0.05
Propionic acid	0.66	Urea	0.03
Acetic acid	0.51	Aspartic acid	0.02
Iminodiacetic acid	0.37	α-Aminoisobutyric acid	0.01
α-Hydroxybutyric acid	0.34		
α-Amino-*n*-butyric acid	0.34	Total	15

Cysteine and methionine also present, when H_2S is added to the reaction mixture

Generation of radicals

$$H_2 \xrightarrow{\text{High-energy electrons or UV light}} 2\ H^\bullet$$

$$H_2O \longrightarrow H^\bullet + HO^\bullet$$

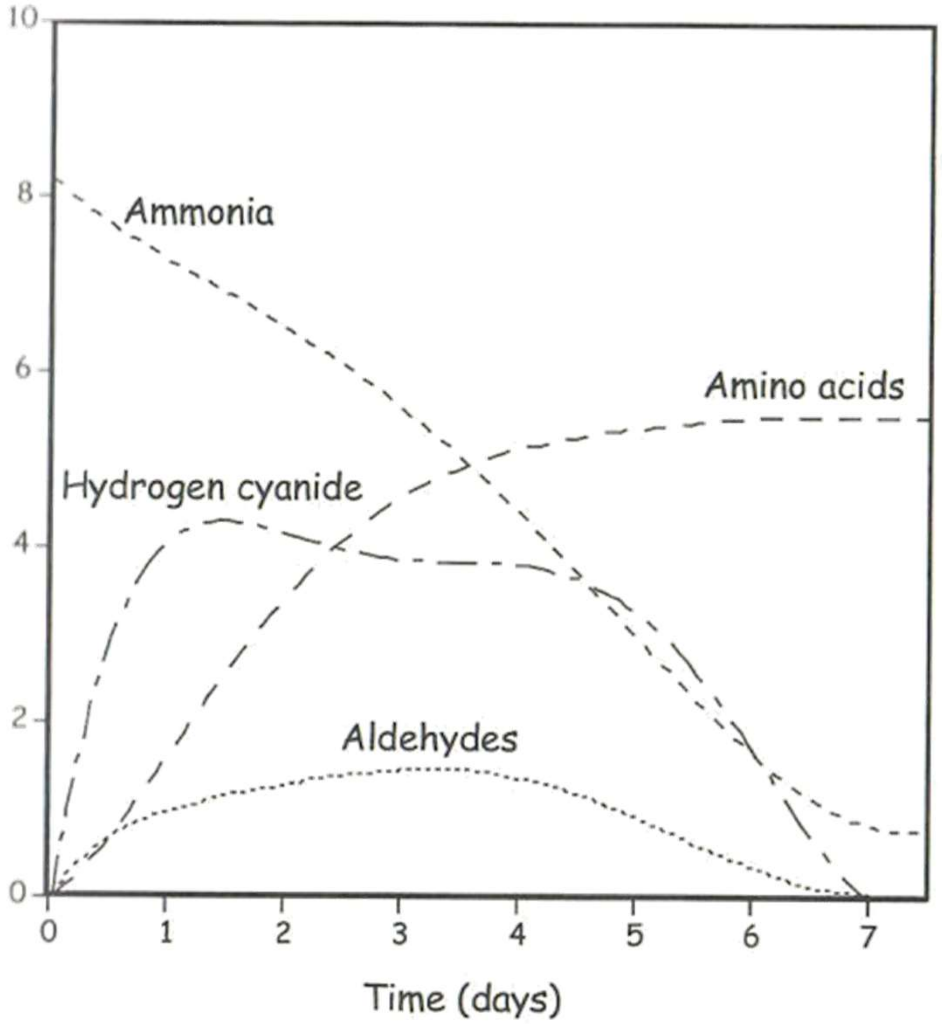
$$CH_4 \longrightarrow {}^\bullet CH_3 + {}^\bullet H$$

Radical reactions

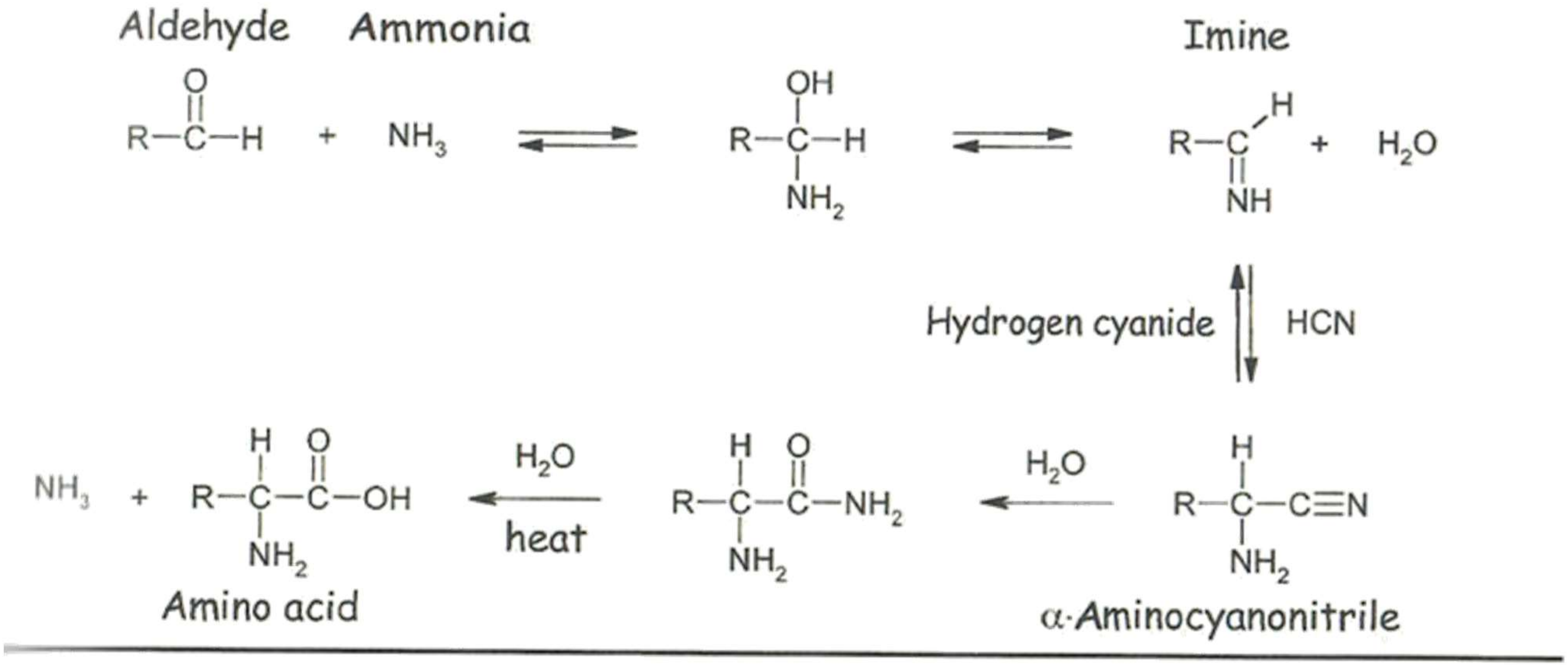
$$^\bullet CH_3 + H_2O \longrightarrow H_3C{-}O^\bullet + H_2$$

$$H_3C{-}O^\bullet + H^\bullet \longrightarrow \underset{\text{Formaldehyde}}{H_2C{=}O} + H_2$$

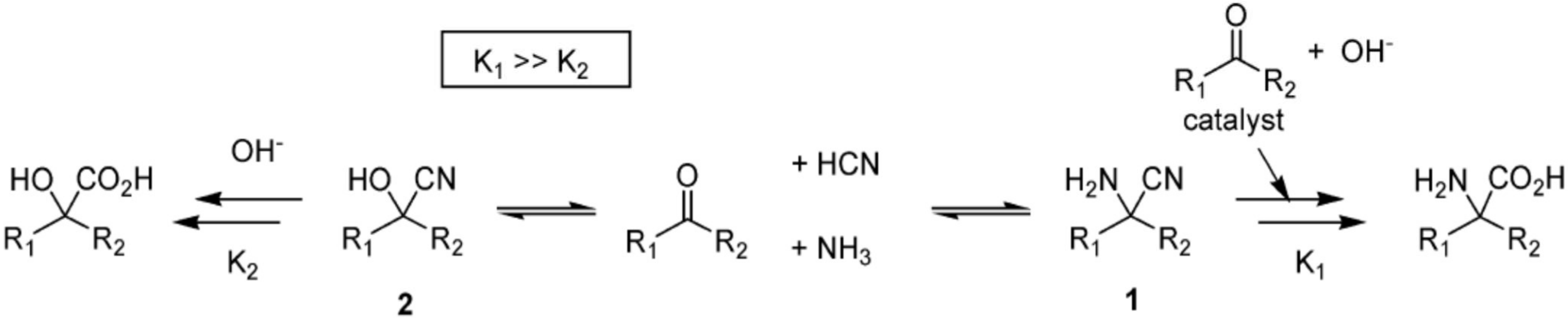
$$^\bullet CH_3 + {}^\bullet CH_3 \longrightarrow \underset{\text{Ethane}}{H_3C{-}CH_3}$$



Strecker reaction



Scheme 1. Synthesis of α-Amino Acids through the Strecker Reaction



α-Aminoacid production in the Miller-Urey experiment

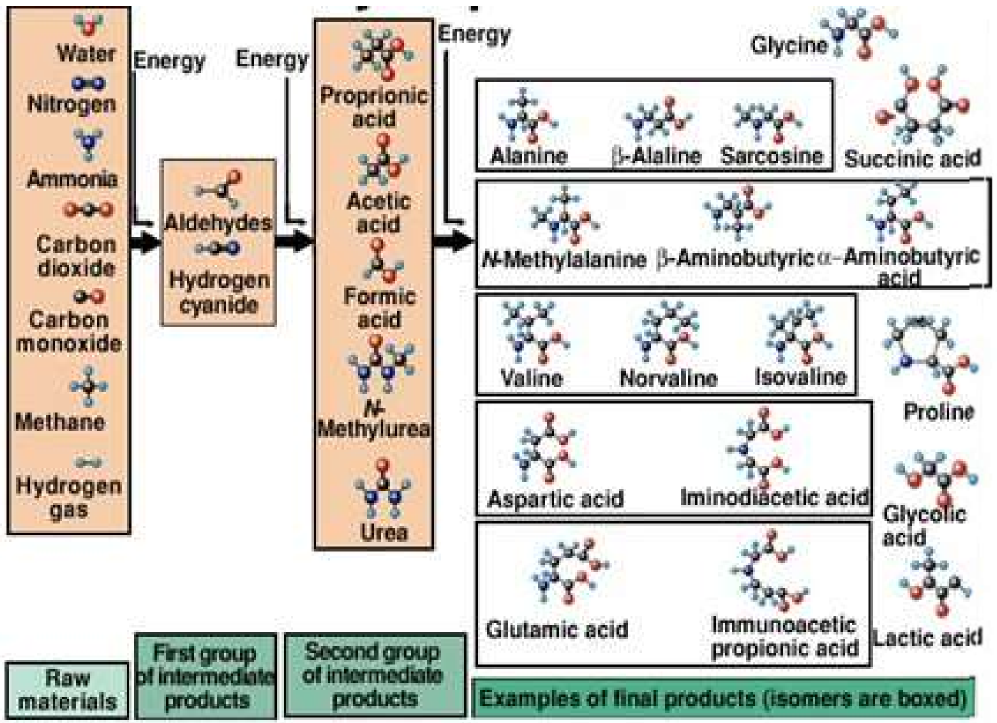


TABLE 4.3

Yields of the α-amino acids in the Miller-Urey experiment

Amino acid	Yield (µM)	Amino Acid	Yield (µM)
Glycine	440	Norleucine	6
Alanine	790	**Isoleucine**	5
α-Aminobutyric acid	270	**Serine**	5
Norvaline	61	Alloisoleucine	5
Aspartate	34	Isovaline	5
α-Aminoisobutyric acid	30	**Proline**	2
Valine	20	**Threonine**	1
Leucine	11	Allothreonine	1
Glutamate	8	*Tert*-Leucine	0.02

Note: Proteogenic amino acids in bold type.

Aminoacid production under hydrothermal conditions

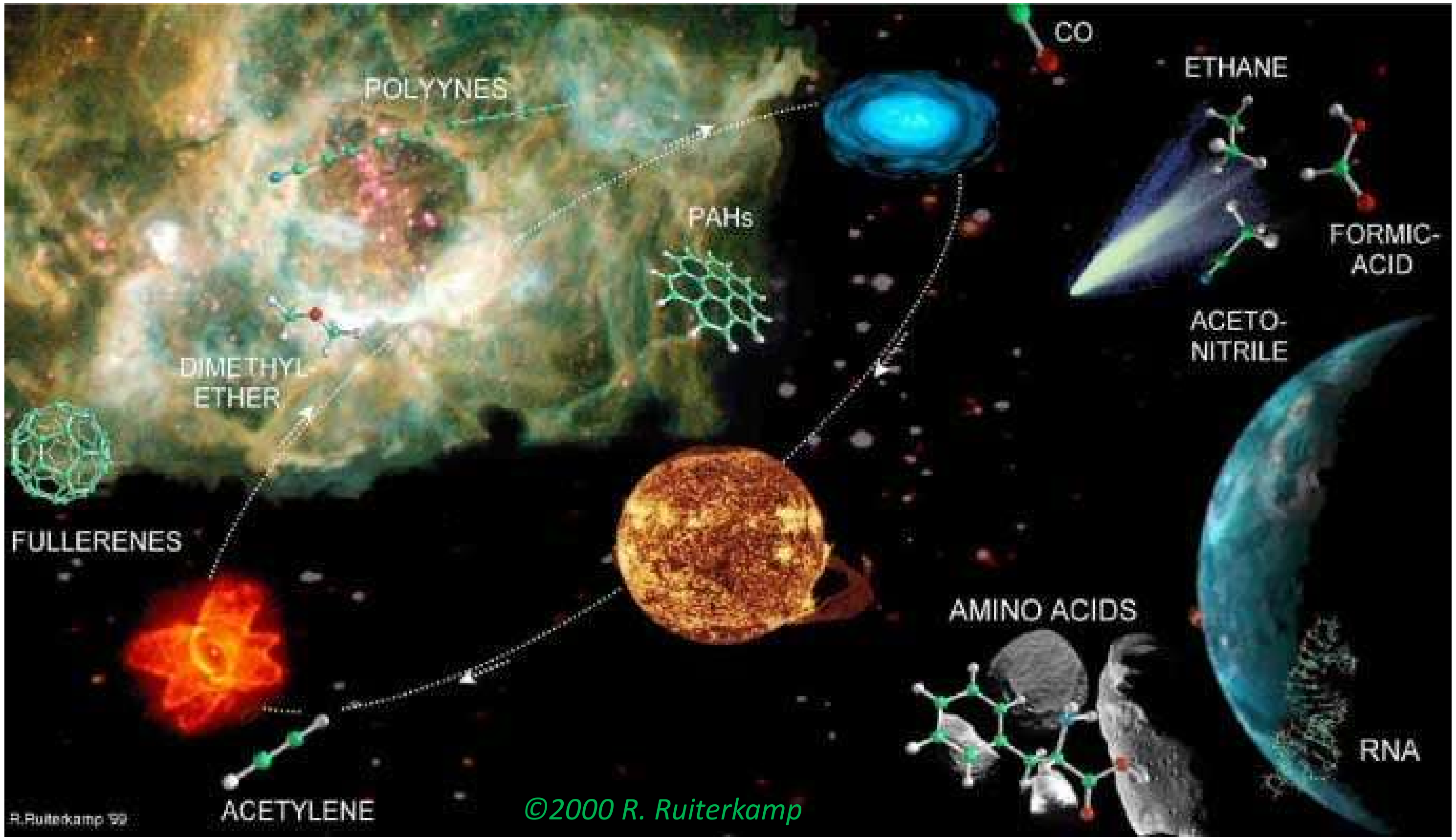
$Ni(OH)_2/KCN/CO$ in alkaline aqueous conditions (80-120^{0}C) → α-amino and α-hydroxyacids

Huber, C.; Wächtershäuser, G. *Science* **2006**, *314*, 630–632

$Ca(OH)_2/NiSO_4/KCN/CO$ in alkaline (pH 9.1-12.9) aqueous conditions (145-280^{0}C) → α-amino and α-hydroxyacids (higher yields): glycine, alanine, serine, glycolate, lactate, glycerate

Huber, C.; Eisenreich, H.; Wächtershäuser, G. *Tetrahedron Lett.* **2010**, *51*, 1069-1071

Extraterrestrial origin of biomolecules



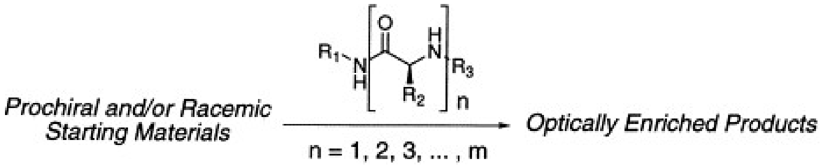
Extraterrestrial origin of biomolecules

Murchison meteorite
chondrite

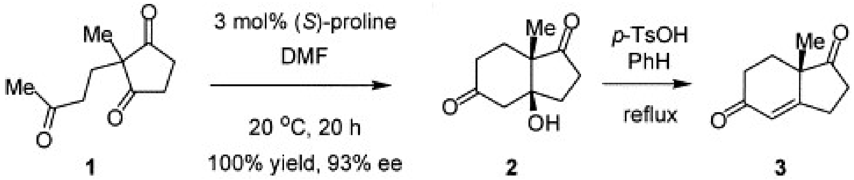
Table 1. Soluble Organic Compounds in the Murchison Meteorite[a]

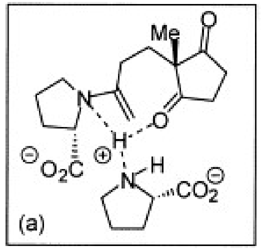
class of compounds	parts per million	n[b]
aliphatic hydrocarbons	>35	140
aromatic hydrocarbons	15–28	87
polar hydrocarbons	<120	10[d]
carboxylic acids	>300	48[d]
amino acids	60	75[d]
imino acids	nd[c]	10
hydroxy acids	15	7
dicarboxylic acids	>30	17[d]
dicarboximides	>50	2
pyridinecarboxylic acids	>7	7
sulfonic acids	67	4
phosphonic acids	2	4
N-heterocycles	7	31
amines	13	20[d]
amides	nd[c]	27
polyols	30	19

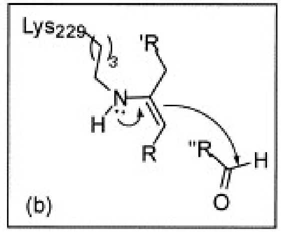
Catalytic properties of aminoacids - organocatalysis



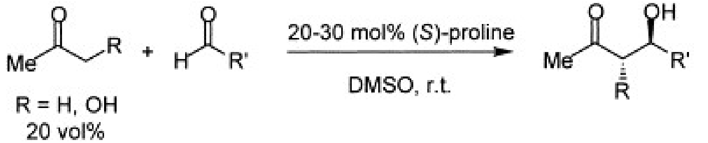
Robinson annulation

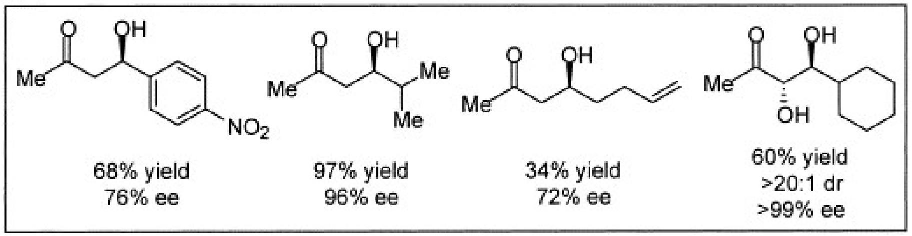


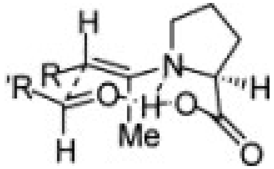




aldol reaction



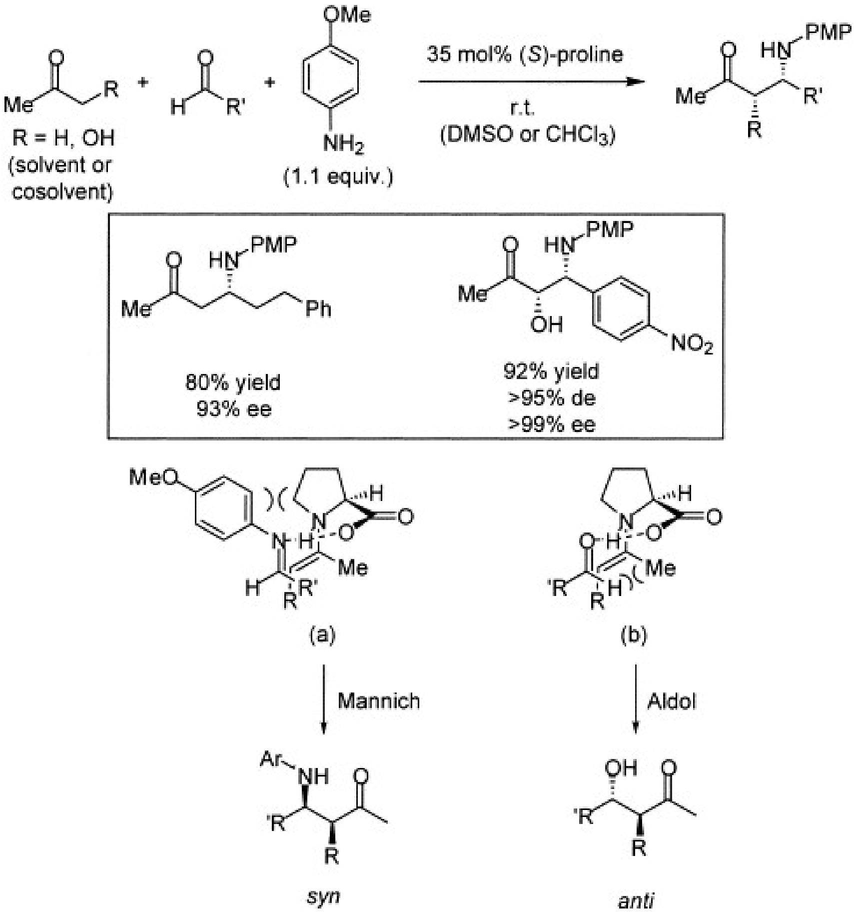




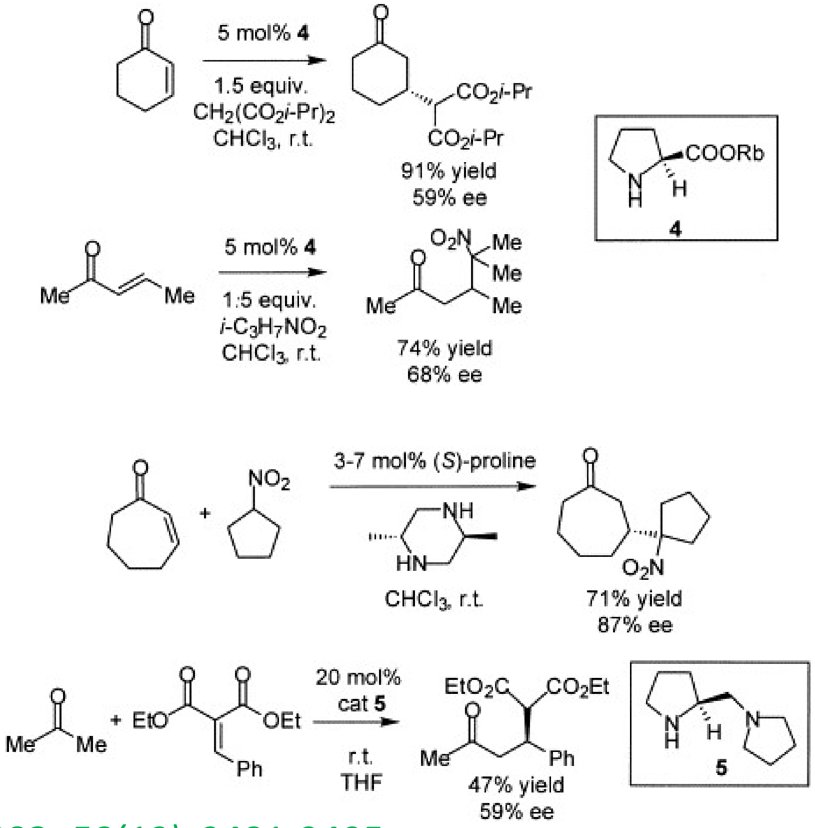
Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

Catalytic properties of aminoacids - organocatalysis

Mannich reaction



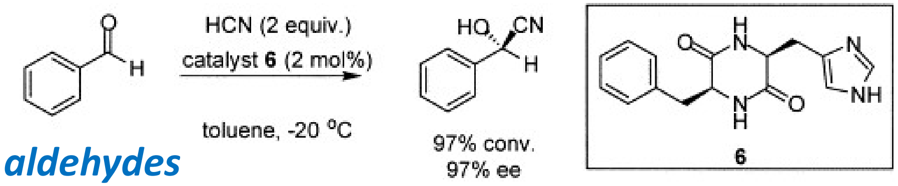
Michael addition



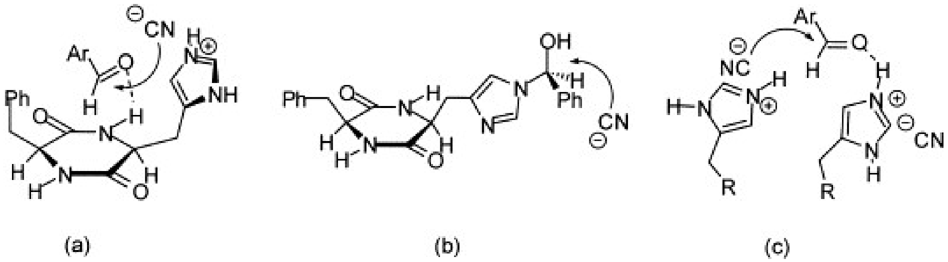
Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

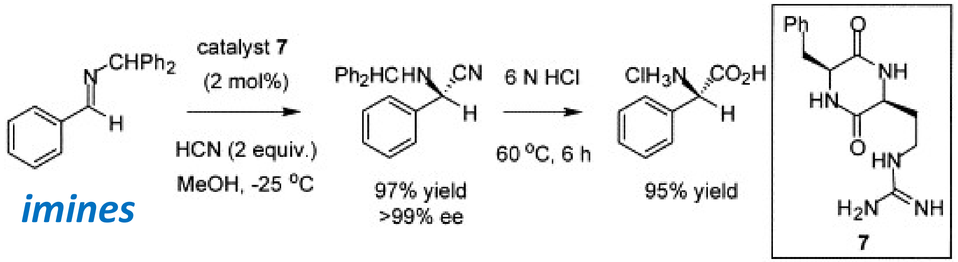
Catalytic properties of aminoacids - organocatalysis

Hydrocyanation



aldehydes



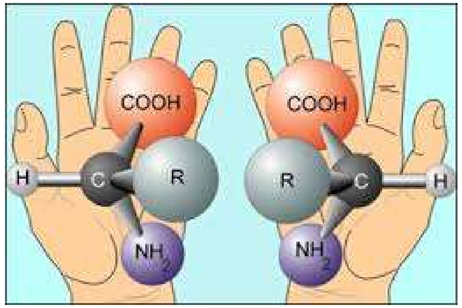


imines

assymetric Strecker reaction!!!

Jarvo, E. R., Miller, S. J. *Tetrahedron* **2002**, *58(13)*, 2481-2495.

The origins of homochirality



Currently known biopolymers are homochiral

Structural propensity and catalytic activity strongly depends on the enantopurity
→ Homochirality must have been involved early in the process of life formation
→ Chiral monomers could be only partially enantioenriched

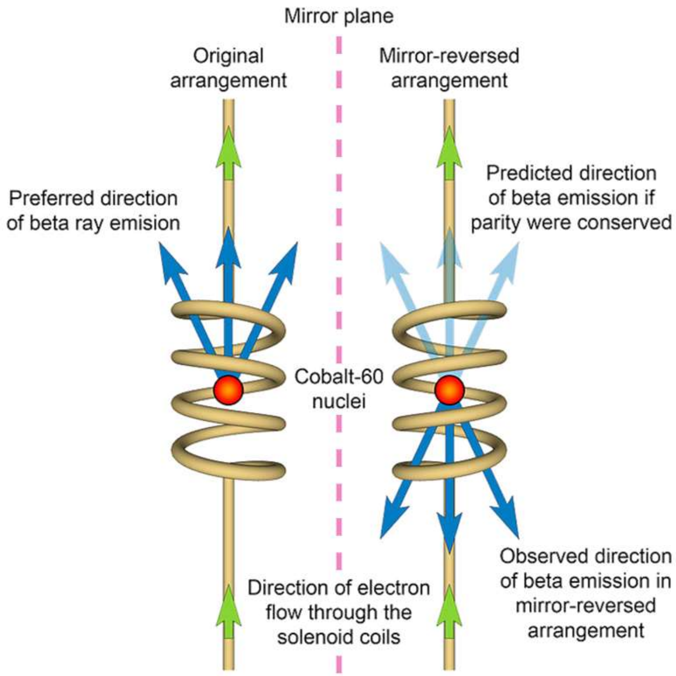
General cause of homochirality:
the initial symmetry breaking + subsequent assymetry amplification:

- ***The pairity violation***
- ***Stochastic symmetry disturbances***

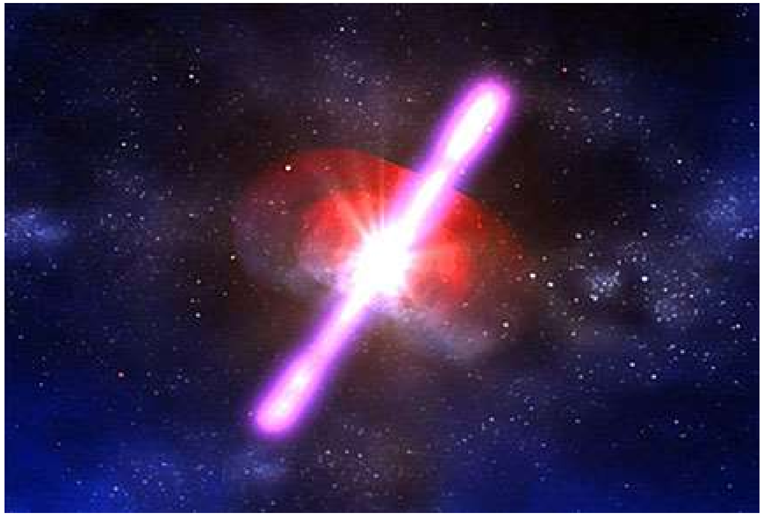
Electroweak interactions and the pairity violation principle cause *L*-aminoacids and *D*-sugars to be SLIGHTLY MORE STABLE than their enantiomers

Differentiation in left and right handedness is inherent property of weak interactions

Chien-Shiung Wu (1956) – experiment on ^{60}Co decay

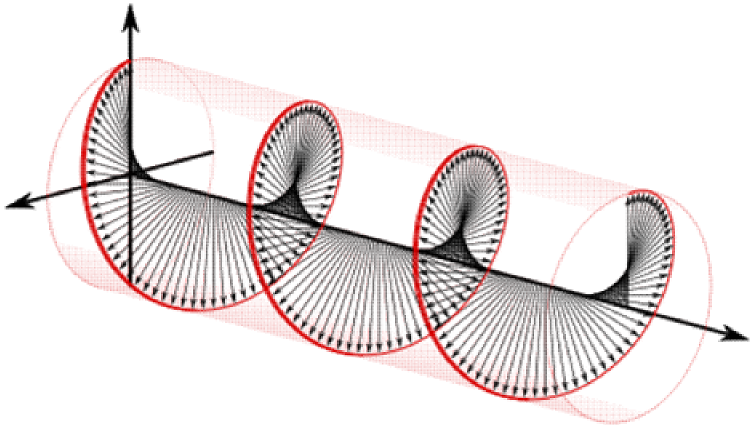


The origins of homochirality



K. Wiersema et al., *Nature* **509** 201, 2014

Circularly polarized light (CPL) from gamma ray bursts

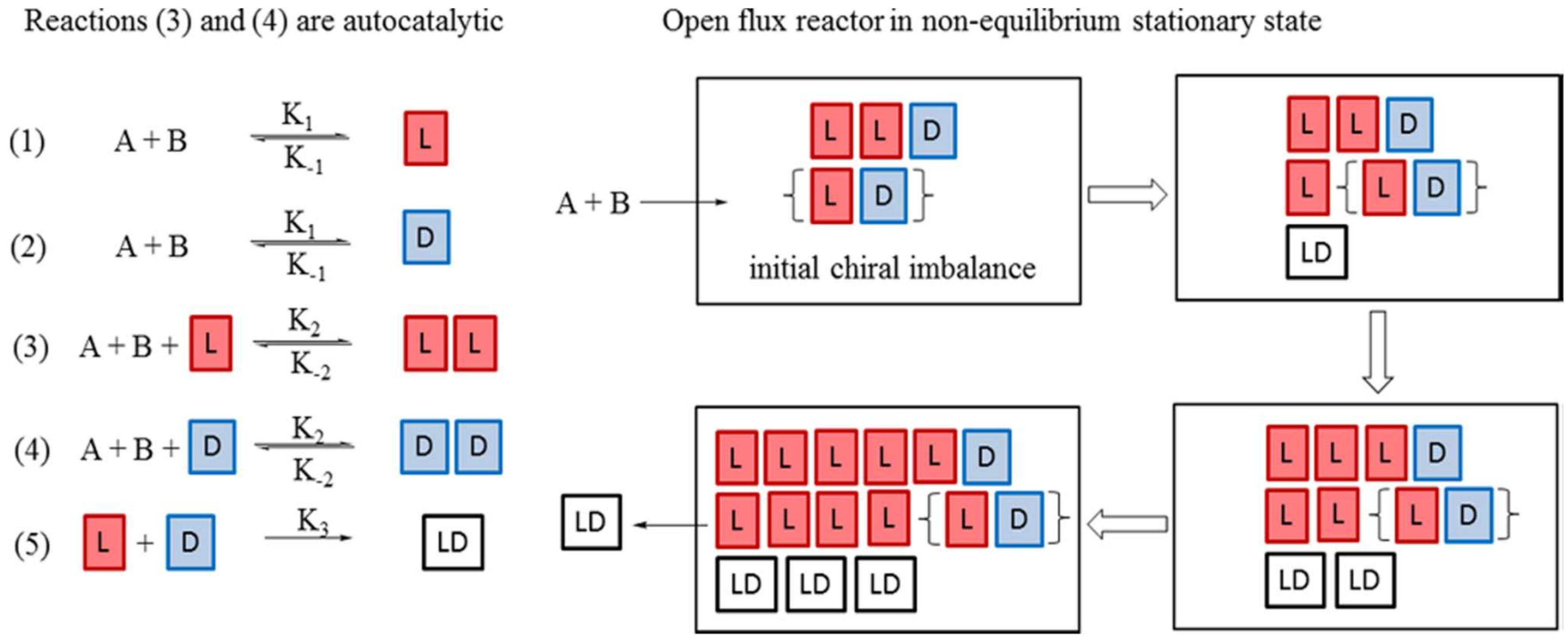


Small enantiomeric excess can be obtained by enantioselective degradation of aminoacids with CPL

Up to 2.6% ee

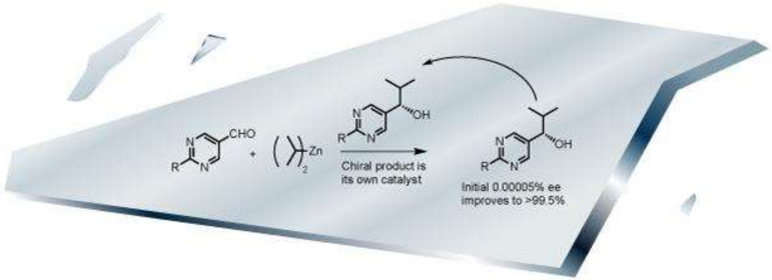
Meierhenrich, U. J.; Nahon, L.; Alcaraz, C.; Bredehoft, J. H.; Hoffmann, S. V.; Barbier, B.; Brack, A. Angew. Chem., Int. Ed. 2005, 44, 5630

Stochastic induction of assymetry – Frank model



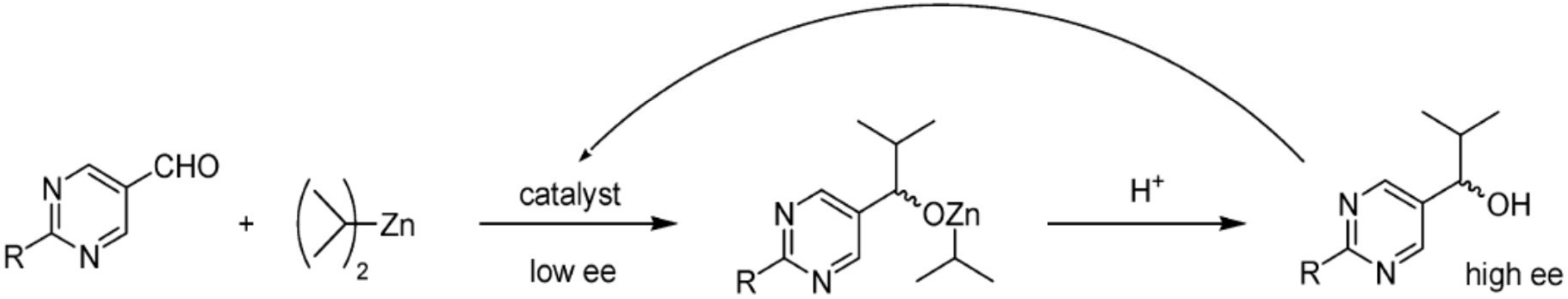
If a chiral dissipative structure catalyzes its own formation and inhibits formation of the opposite enantiomer, any stochastic symmetry breaking in the system will be amplified

autocatalytic Soai reaction – extreme chirality amplification



Organometallic reaction
- NOT prebiotic

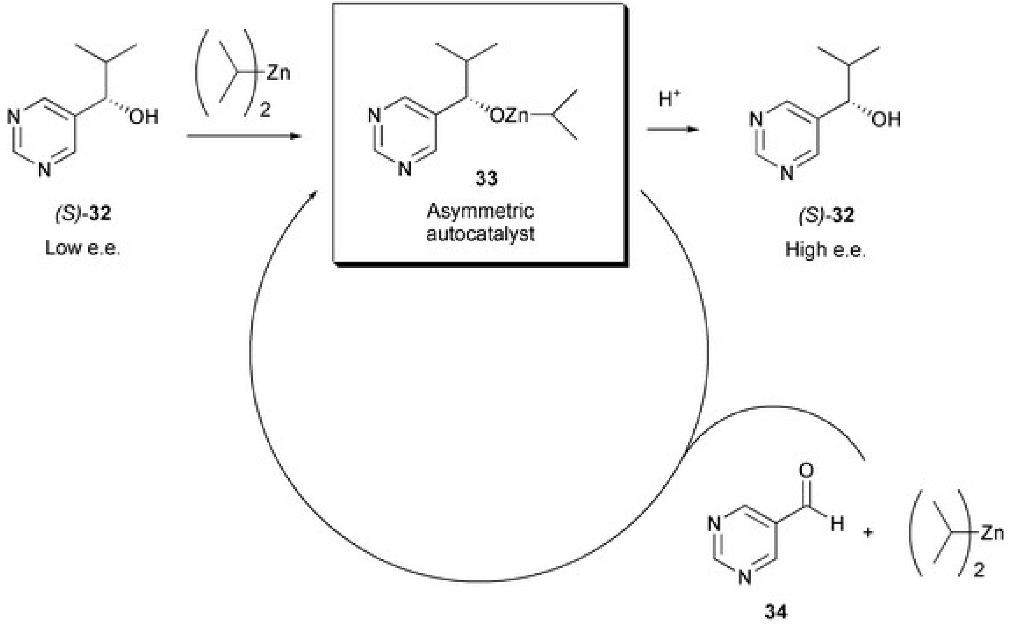
Scheme 9. Soai Autocatalytic Reaction

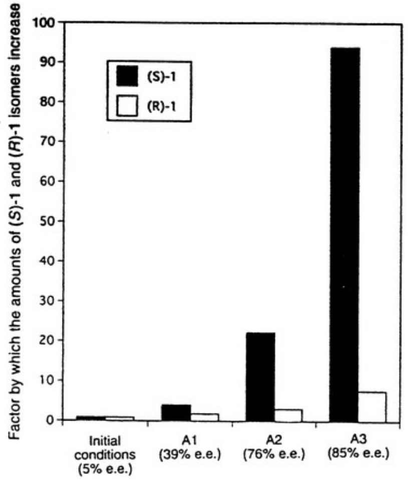


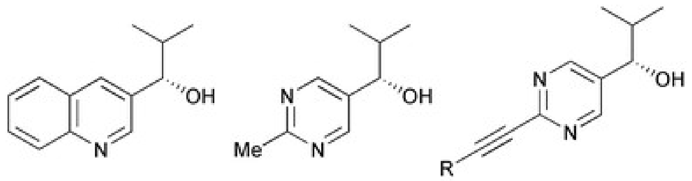
CPL
Aminoacids
$^{12}C/^{13}C$-enantiomers!

Extremelly sensitive
chirality detector

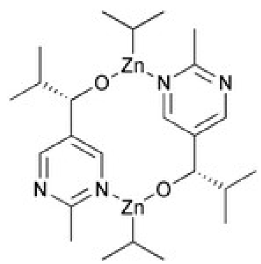
autocatalytic Soai reaction – extreme chirality amplification







35 36 37



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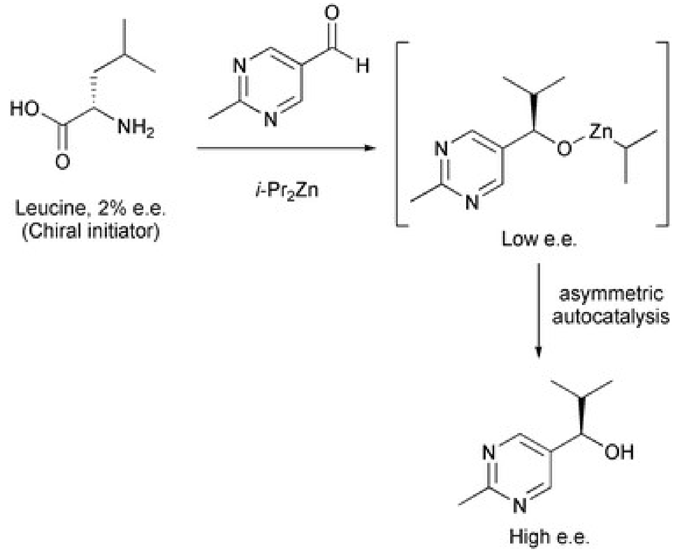
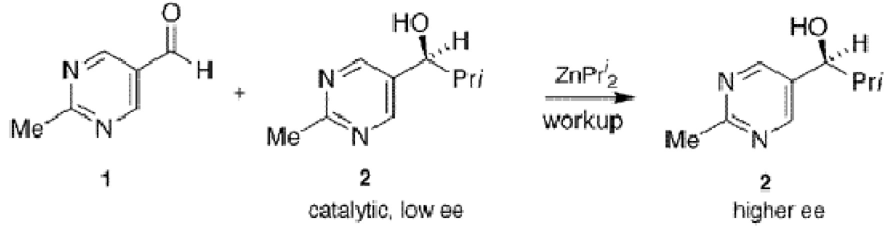
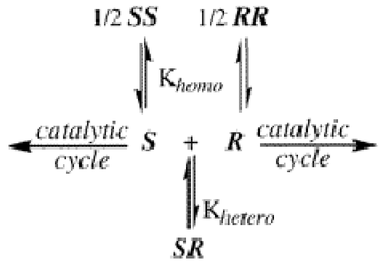
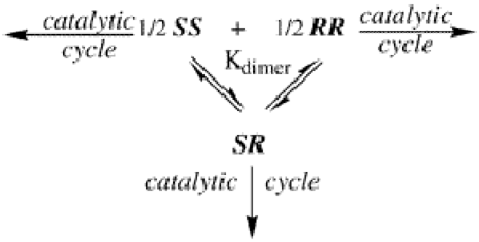


autocatalytic Soai reaction – extreme chirality amplification





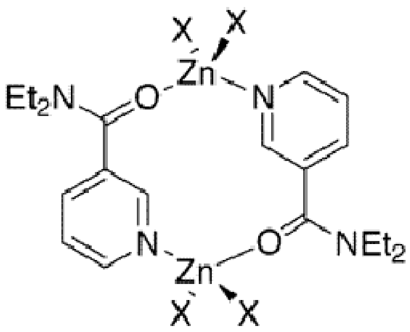
a



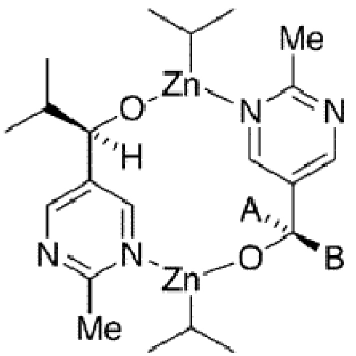
b

$$g = \frac{\text{activity of } [SR]}{\text{activity of } [RR]} \quad \beta = \frac{[SR]}{[RR] + [SS]} \quad K = \frac{([SR])^2}{([RR])([SS])}$$

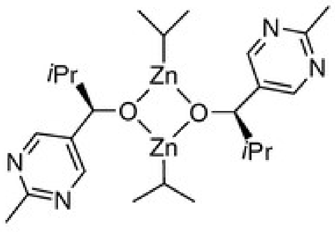
$$ee_{dx} = \frac{[RR] - [SS]}{[RR] + [SS] + g[SR]} \quad ee_{x+dx} = \frac{ee_x[\mathbf{2}] + ee_{dx}\frac{dx}{2}[\mathbf{1}]_0}{[\mathbf{2}] + \frac{dx}{2}[\mathbf{1}]_0} \qquad (2)$$



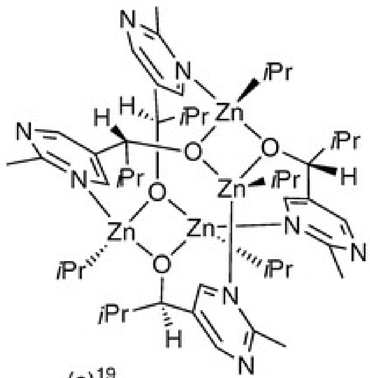
7a, X = Cl,
7b, X = SCN



***(S,S)*-8** A = H, B = Pr^i
***(R,S)*-8** A = Pr^i, B = H



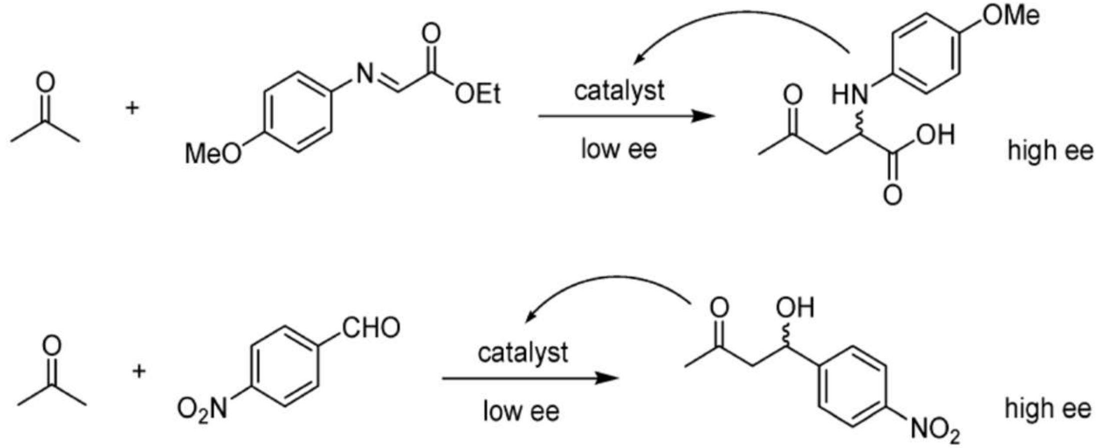
(b)[19]



(c)[19]

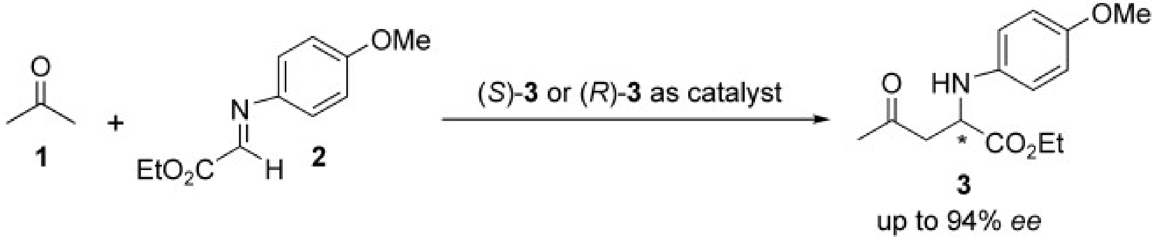
autocatalytic organic reactions

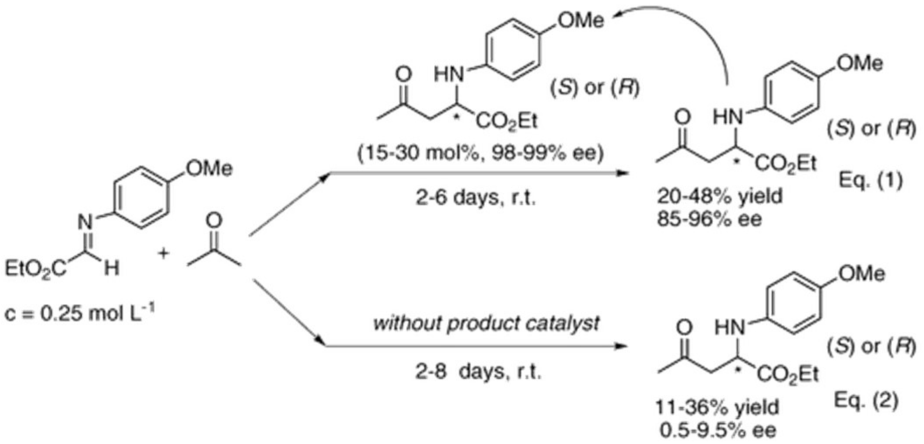
Scheme 10. Mannich and Aldol Autocatalytic Reactions[a]

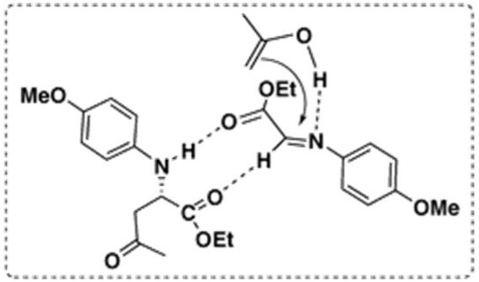


Meaningful transformations for the prebiotic syntheses of aminoacids and sugars

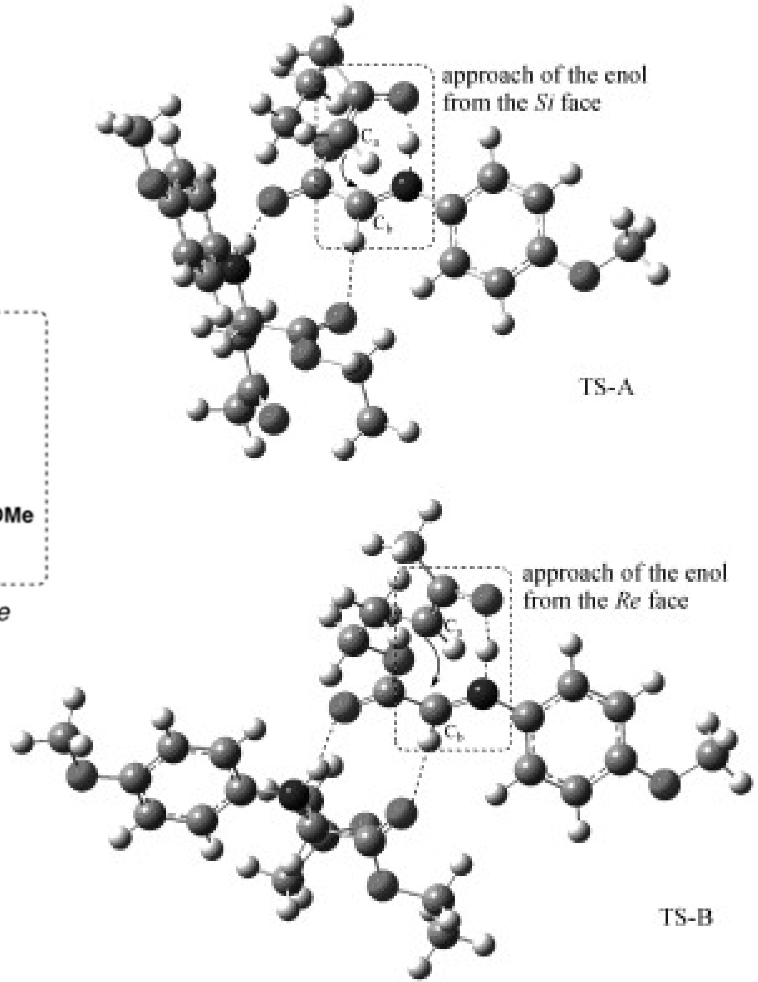
autocatalytic organic reactions







proposed transition-state structure



Organocatalysis – the origin of homochirality

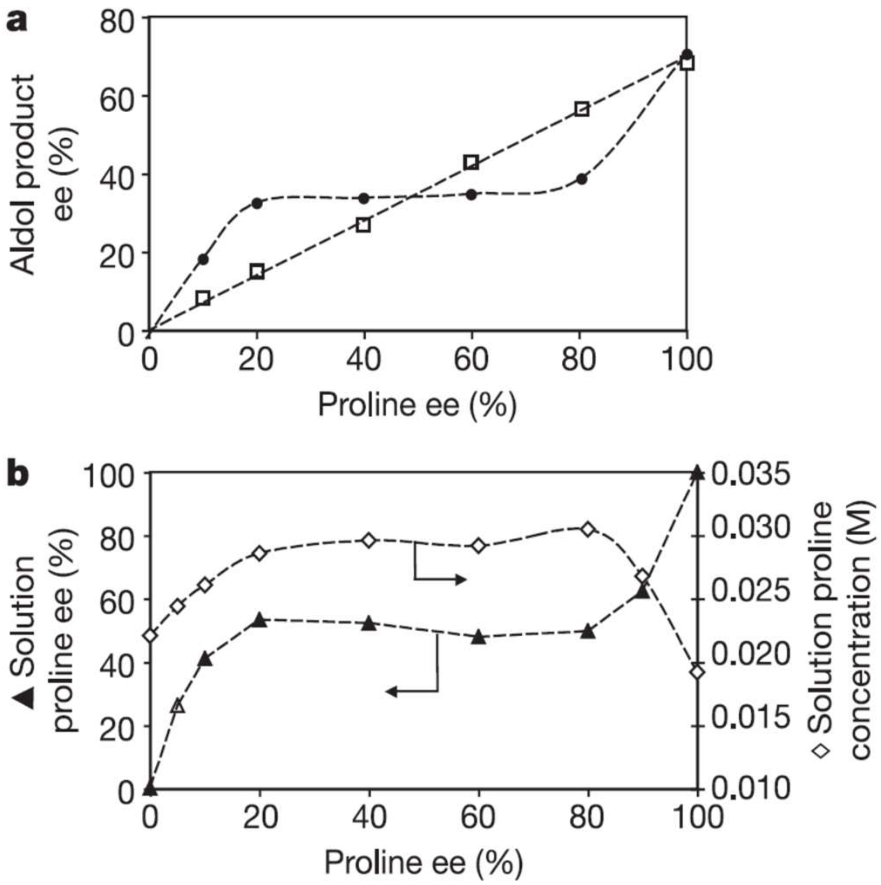
Table 1. Enantiomeric concentration amplification of phenylalanine after two crystallizations from water

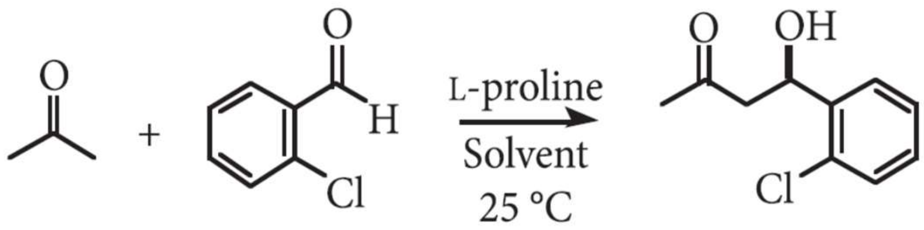
Component	Initial ee, %	Final ee, %
D	10	90.0 ± 3.7
	5	91.7 ± 1.5
	1	87.2 ± 2.0
L	10	88.3 ± 1.1
	5	88.6 ± 0.9
	1	90.9 ± 0.3

Solutions with as little as 1% enantiomeric excess (ee) of D- or L-phenylalanine are amplified to 90% ee (a 95/5 ratio) by two successive evaporations to precipitate the racemate. Such a process on the prebiotic earth could lead to a mechanism by which meteoritic chiral α-alkyl amino acids could form solutions with high ee values that were needed for the beginning of biology.

Breslow, R., Levine, M. Proc. Natl. Acad. Sci. USA **2006,** *103(35),* 12979-12980

Chirality amplification in biphasic systems





Reaction and solution behaviour as a function of the overall proline enantiomeric excess.

a, Product enantiomeric excess versus proline enantiomeric excess for the aldol reaction of equation

b, Solution proline enantiomeric excess (left axis, triangles) and solution proline concentration (right axis, diamonds) as a function of the overall enantiomeric excess for proline at 0.1 M

Klussmann, M., et al. Nature **2006,** *441,* 621-623

Chirality amplification in biphasic systems

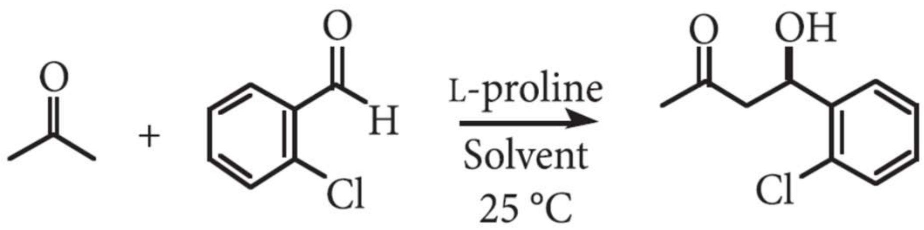
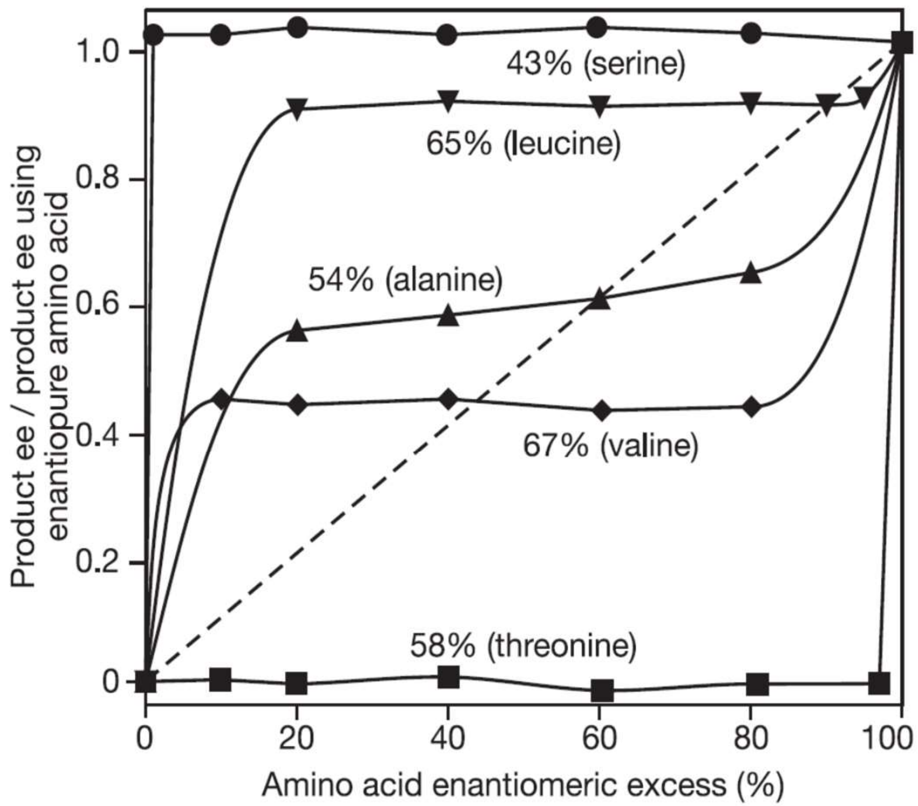


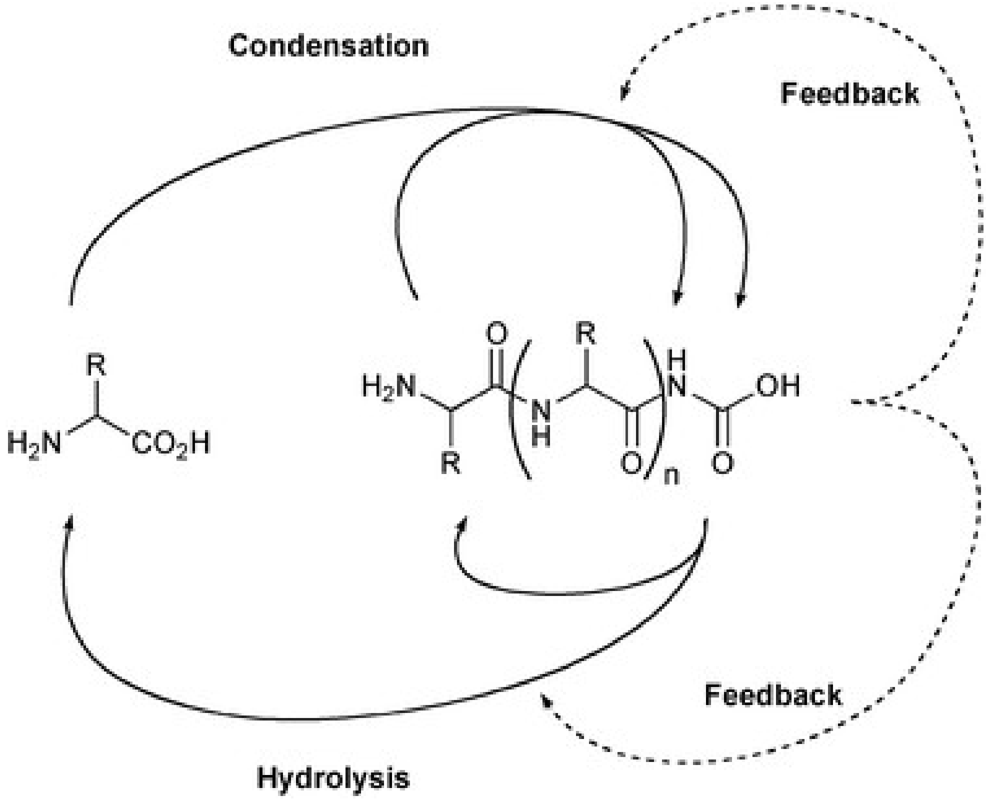
Table 1 | Solution enantiomeric excess at the eutectic point in water at 25 °C for selected amino acids

Amino acid	ee of solution at eutectic (%)	Amino acid	ee of solution at eutectic (%)
Threonine	0	Methionine	85
Valine	46	Leucine	87
Alanine	60	Histidine	93
Phenylalanine	83	Serine	>99

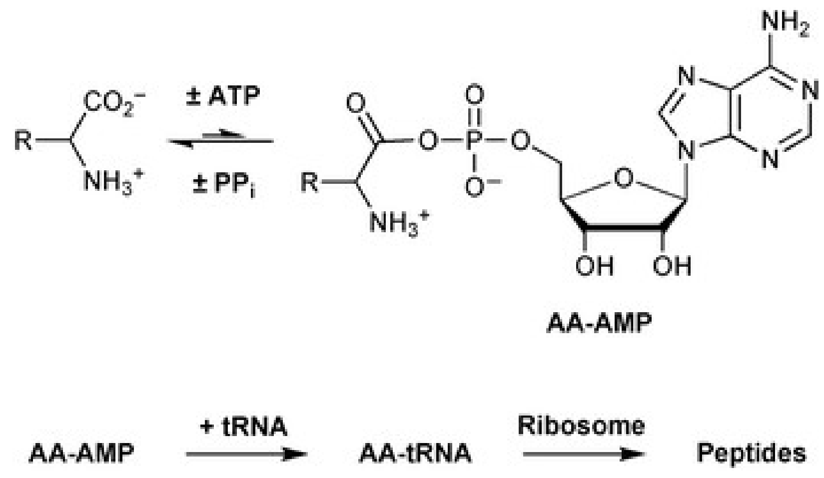


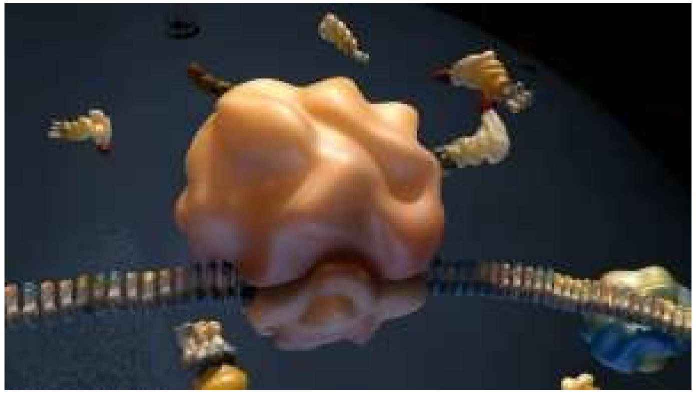
Klussmann, M., et al. Nature **2006,** *441*, 621-623

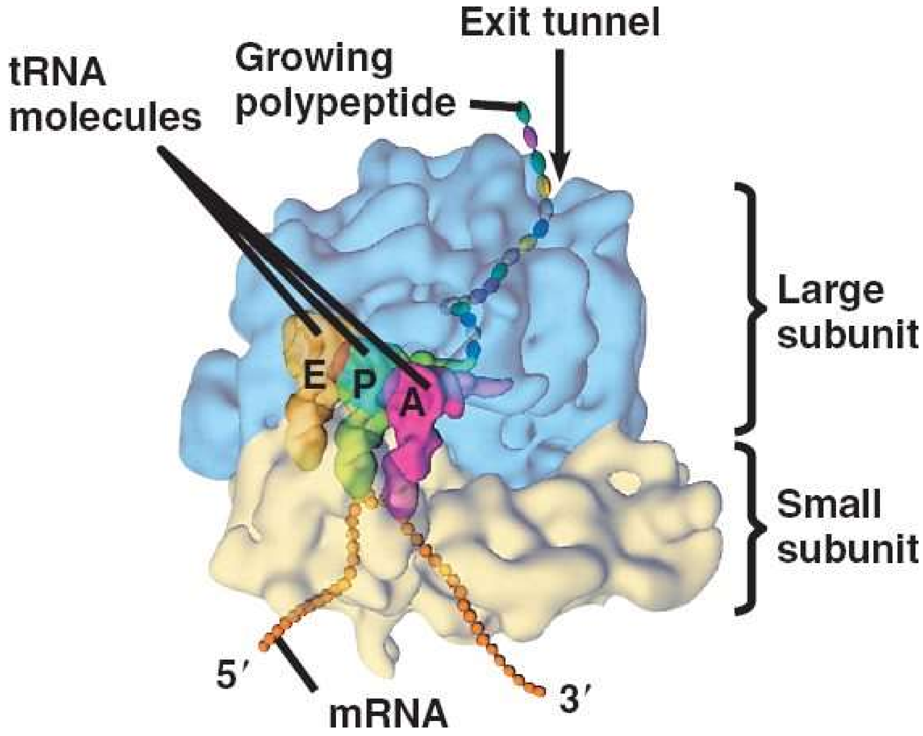
Condensation of aminoacids into peptides



Biochemical condensation of aminoacids into peptides





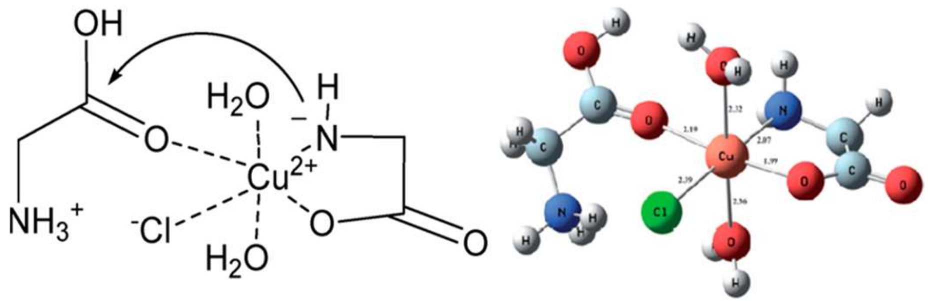


Nature Publishing Group, www.nature.com/nrg/multimedia

Prebiotically relevant peptide condensation agents

Entry	Activating agent	Hydrolysis/ hydration product	$\Delta G^{o\prime}$/ kJ mol^{-1}
1	NH_2CONH_2	$CO_2 + NH_3$	−16[a]
2	COS (g)	$CO_2 + H_2S$	−17[a]
3	Pyrophosphate	Phosphate	−19[b]
4	CO (g)	HCO_2H	−16[a]
5	HNCO	$CO_2 + NH_3$	−54[a]
6	HCN	$HCO_2H + NH_3$	−75[a]
7	RCN	$RCO_2H + NH_3$	−80[c]
8	NH_2CN	Isourea	−83[d]
9	HNCNH	Isourea	−97[d]
10	HCCH (g)	CH_3CHO	−112[a]

Danger, G.; Plasson, R.; Pascal, R. *Chem. Soc. Rev.* **2012**, *41*, 5416.

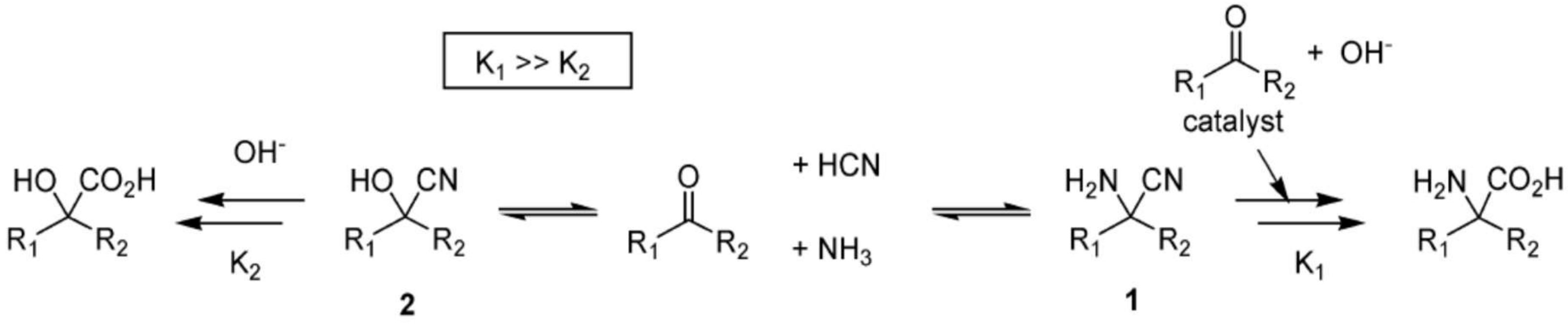


SIPF copper complex geometry with two glycine ligands, optimized by ab initio Hartree−Fock calculations.

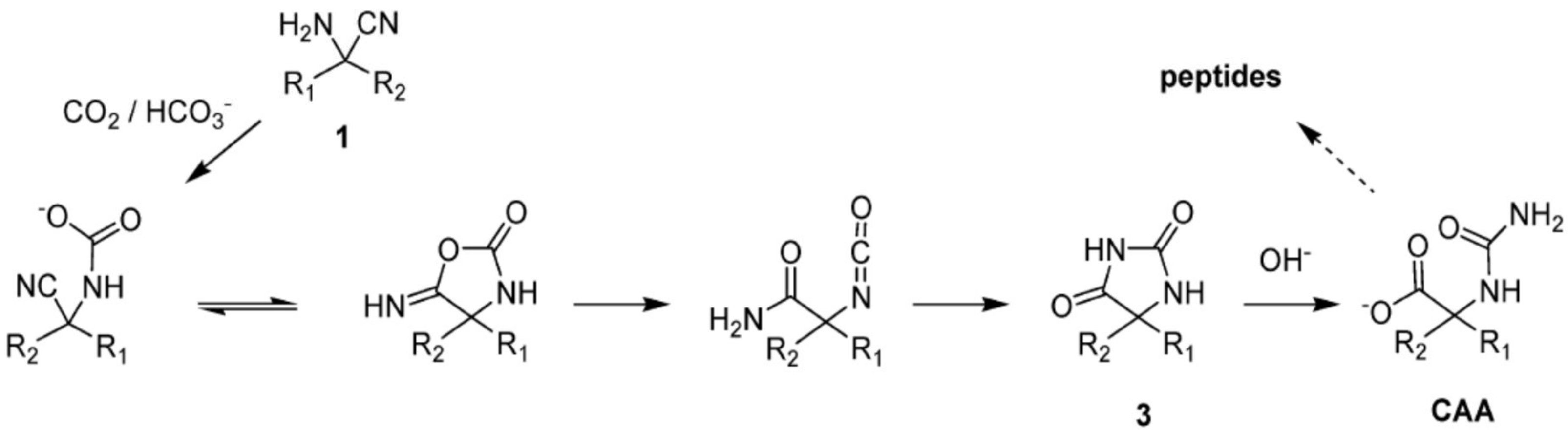
Rode, B. M.; Fitz, D.; Jakschitz, T. Chem. *Biodiversity* **2007**, *4*,2674.

Condensation of aminoacids into peptides

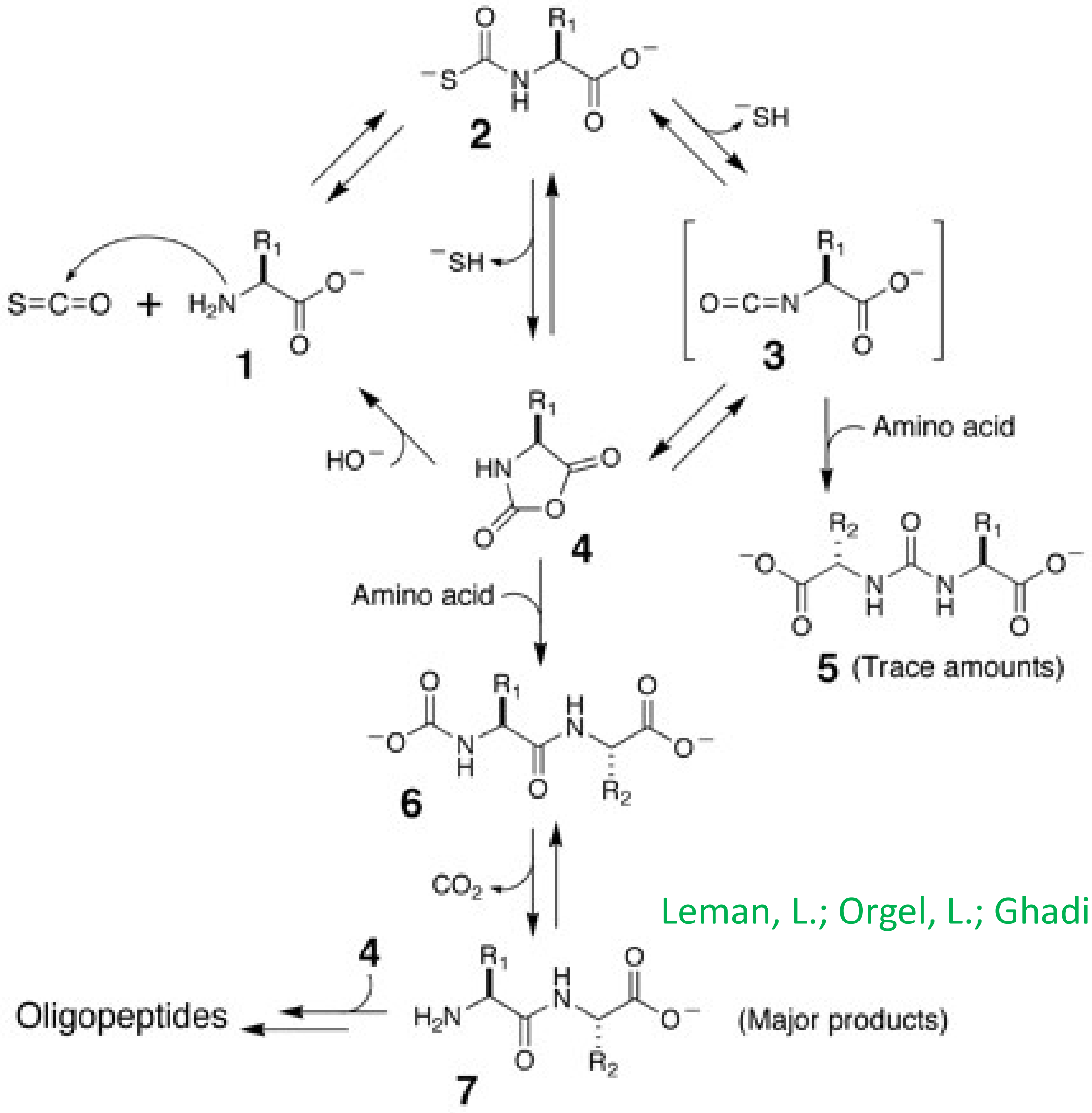
Scheme 1. Synthesis of α-Amino Acids through the Strecker Reaction



Scheme 2. Bücherer–Bergs Hydrolysis of α-Aminonitriles



Carbonyl sulfide – condensing agent



Leman, L.; Orgel, L.; Ghadiri, M. R. *Science* **2004**, *306*, 283-286.

Carbonyl sulfide – condensing agent

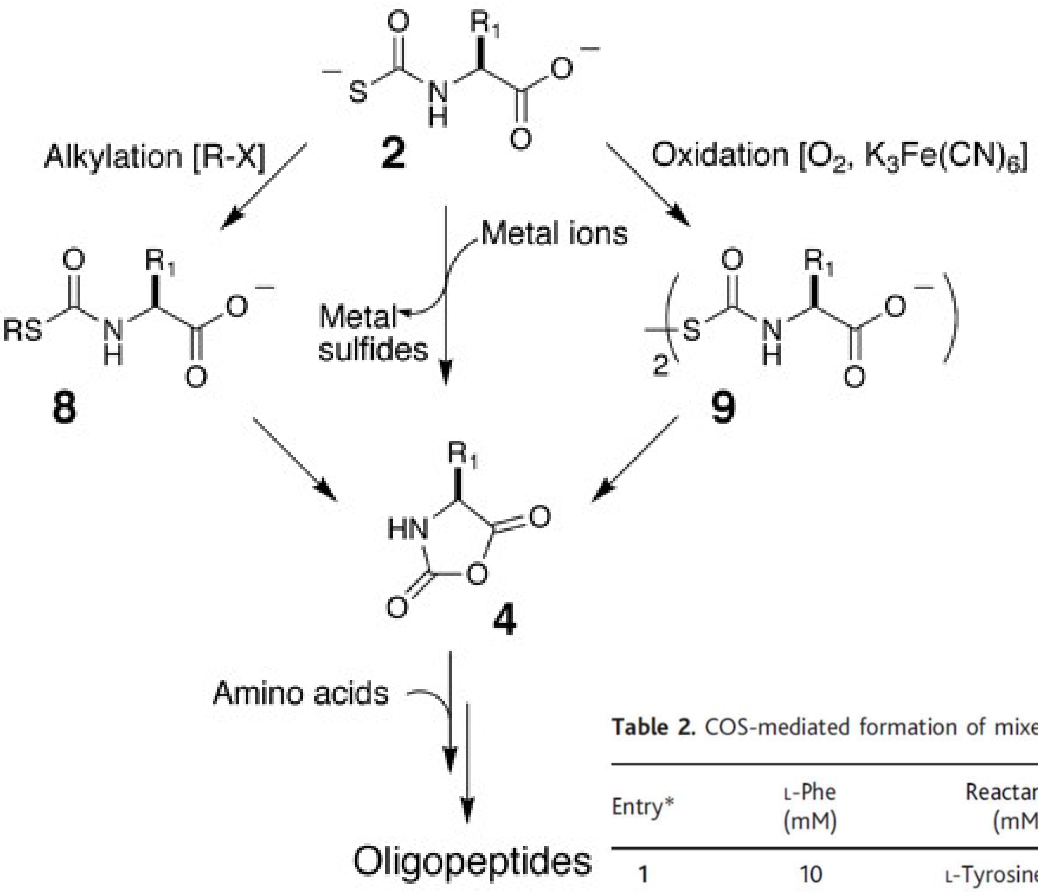


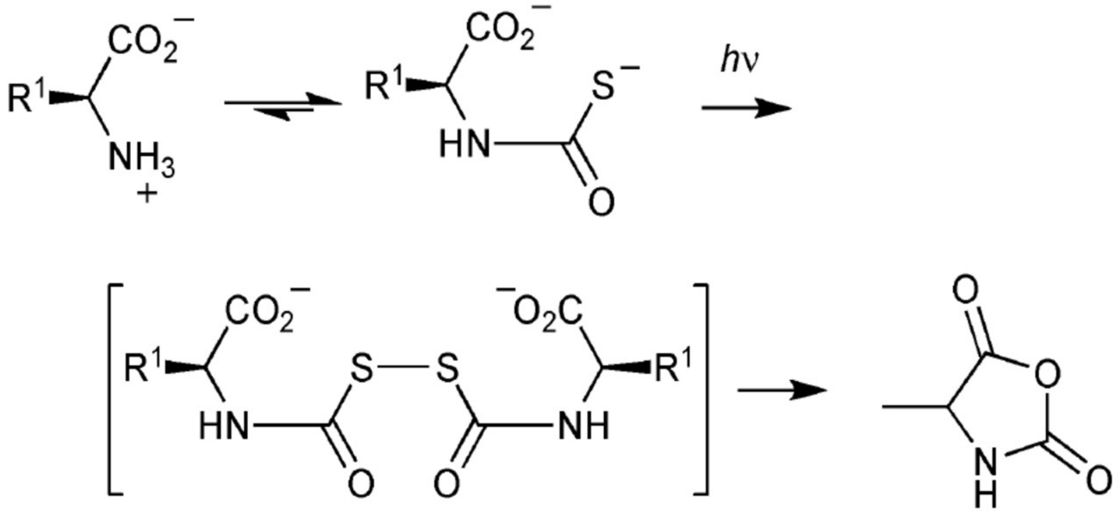
Table 2. COS-mediated formation of mixed peptides. Abbreviations for the amino acid residues: A, Ala; F, Phe; L, Leu; S, Ser; Y, Tyr.

Entry*	L-Phe (mM)	Reactant 2 (mM)	$PbCl_2$ (mM)	Final pH	Time (hours)	Observed dipeptides†	Observed tripeptides†
1	10	L-Tyrosine (10)	20	7.2	3	FF, YY, (YF), (FY)	YYY, (YYF), (YFF), FFF
2	25	L-Leucine (25)	50	7.1	3	FF, LL, (FL)	(LLF), (LFF), FFF
3	25	L-Alanine (25)	50	5.9	3	FF, (AF)	(AAF), (AFF), FFF
4	25	L-Serine (25)	50	6.3	3	SS, FF, SF, FS	SSS, (SFF), FFF

*Each experiment was initiated by admitting ~20 ml of COS gas to an argon-purged reaction vessel containing 2 ml of the reaction mixture indicated dissolved in 500 mM Me_3N buffer, at an initial pH of 9.1. Peptide products were identified by LCMS after quenching the reaction at 3 hours. †Peptides for which product masses were observed but primary amino acid sequences which were not determined are indicated in parentheses.

Leman, L.; Orgel, L.; Ghadiri, M. R. *Science* **2004**, *306*, 283-286.

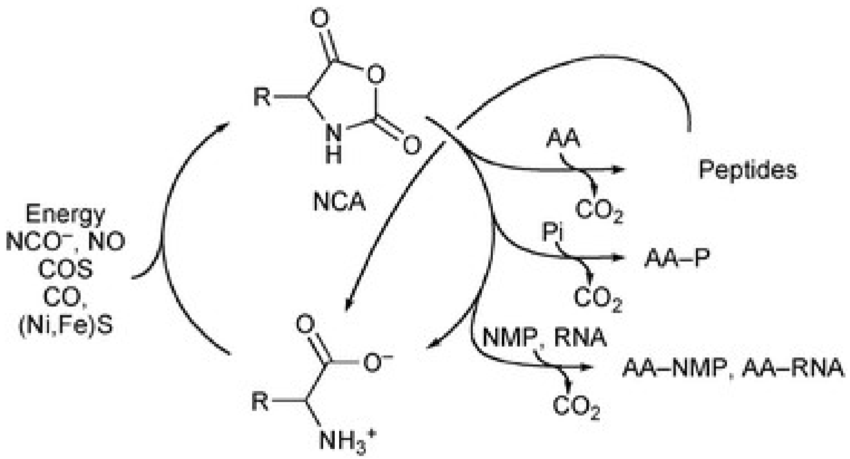
Carbonyl sulfide – photochemical activation



A slow formation of NCAs from free amino acids and COS in the absence of oxidizing or alkylating agents has been reported and studied through theoretical chemistry investigations. However, it seems unlikely that COS (ΔG_0 = 16.9 kJ/mol) could be able to generate NCA (ΔG_0 = 60 kJ/mol) in spite of its cyclic structure.

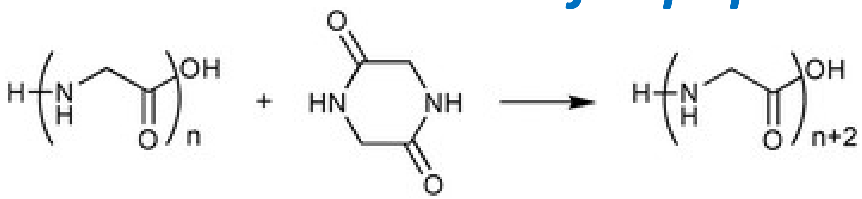
A photochemical activation of thiocarbamate that could take place in a way similar to that of thioacetate in aqueous solution may provide an explanation to this observation. This potential photochemical reaction may also constitute an efficient pathway for the prebiotic formation of NCAs.

Carbonyl sulfide – photochemical activation

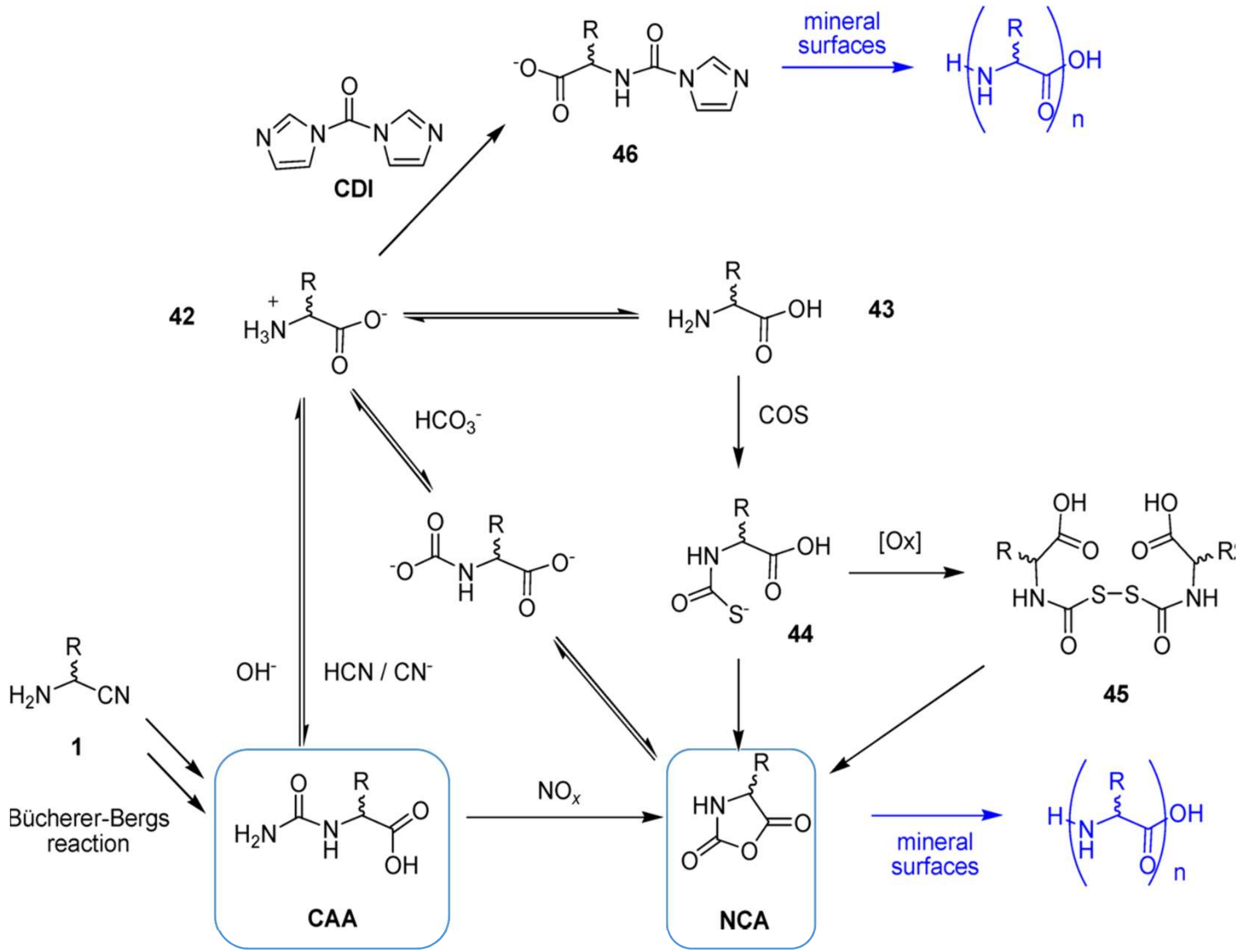


Pathways for the formation of NCAs and
further reactions including polymerization and interactions
with inorganic phosphate (Pi), nucleotides (NMP), and RNA.

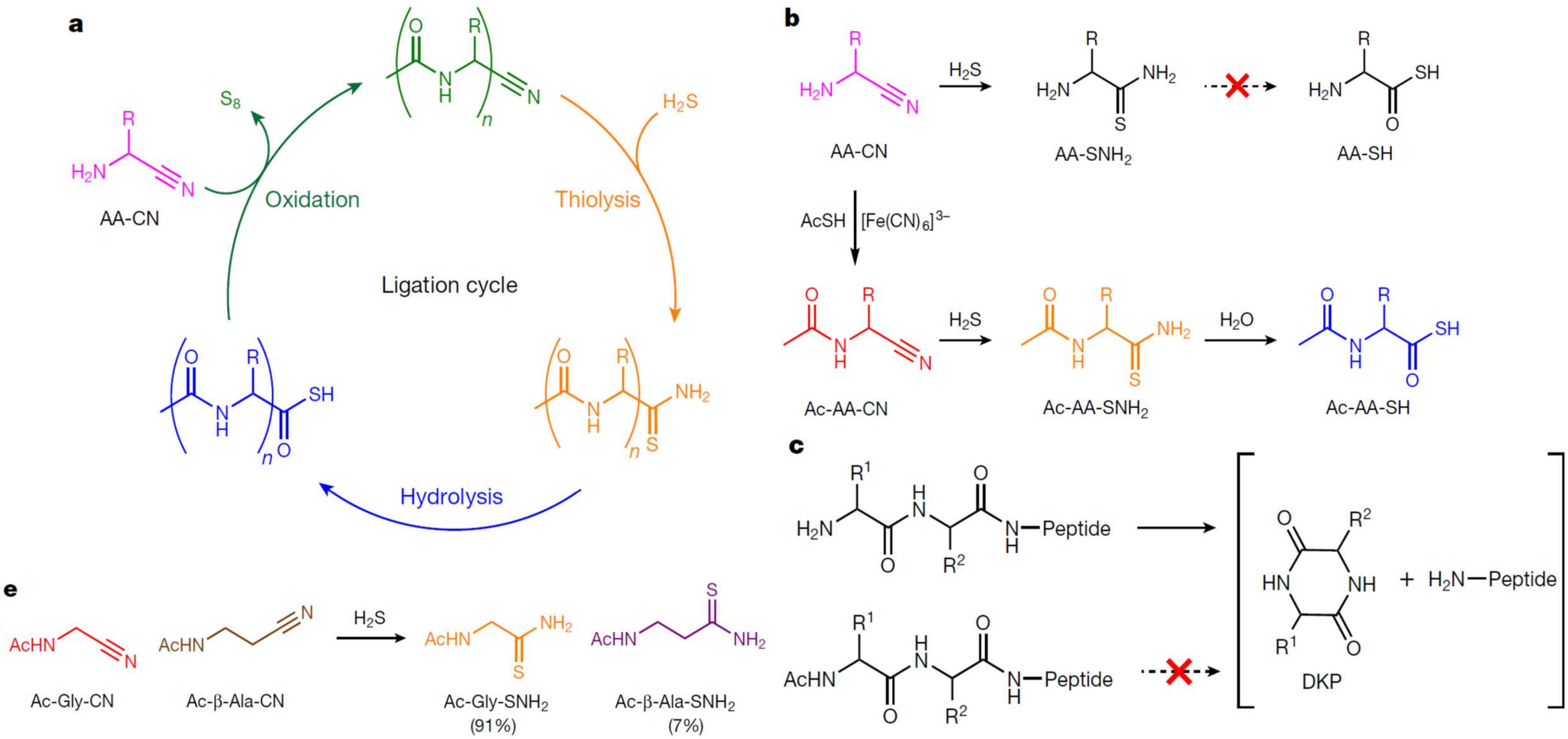
Diketopiperazines as intermediates for peptide condensation



Condensation of aminoacids into peptides

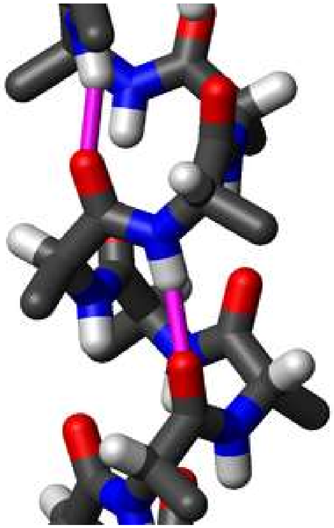


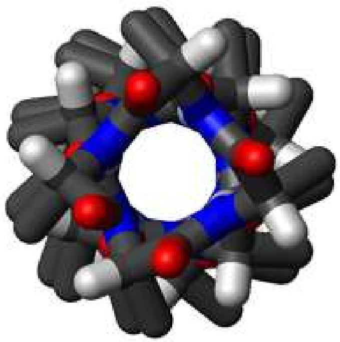
Prebiotic peptide condensation in water



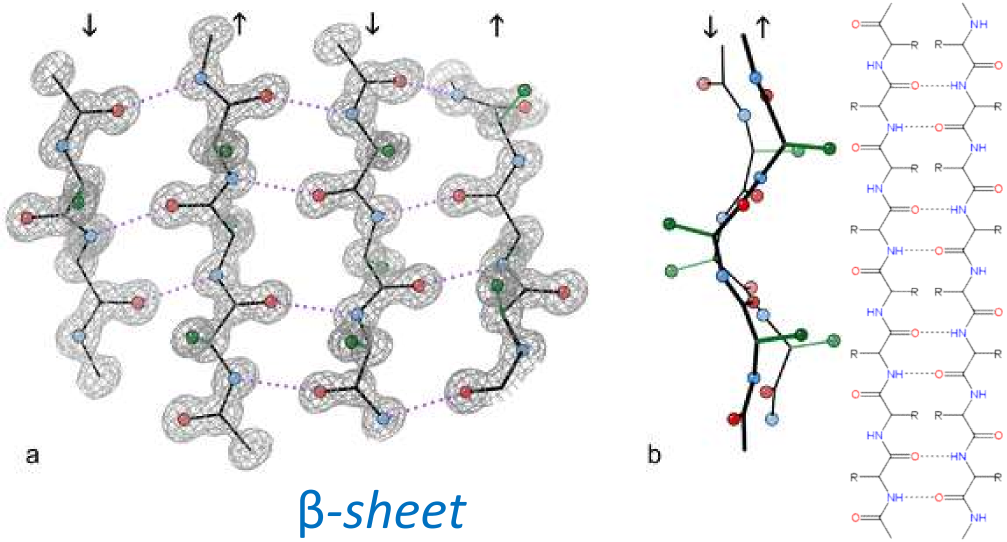
P. Canavelli, S. Islam & M. W. Powner *Nature* **2019**, *571*, 546-549.

GADV-protein world

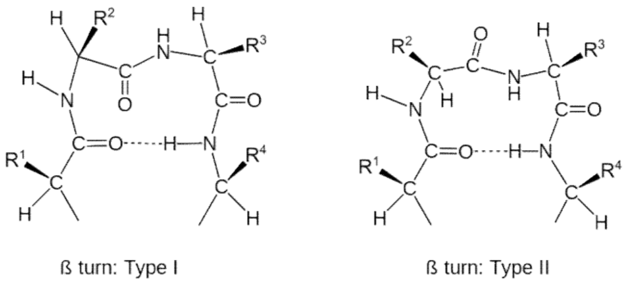




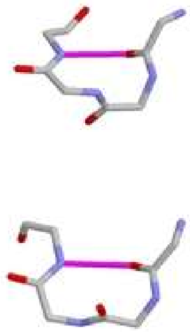
α-helix
(Ala)



β-sheet
(Val)



β-turn (coil)
(Gly)



hydrophilic
and
hydrophobic
structures

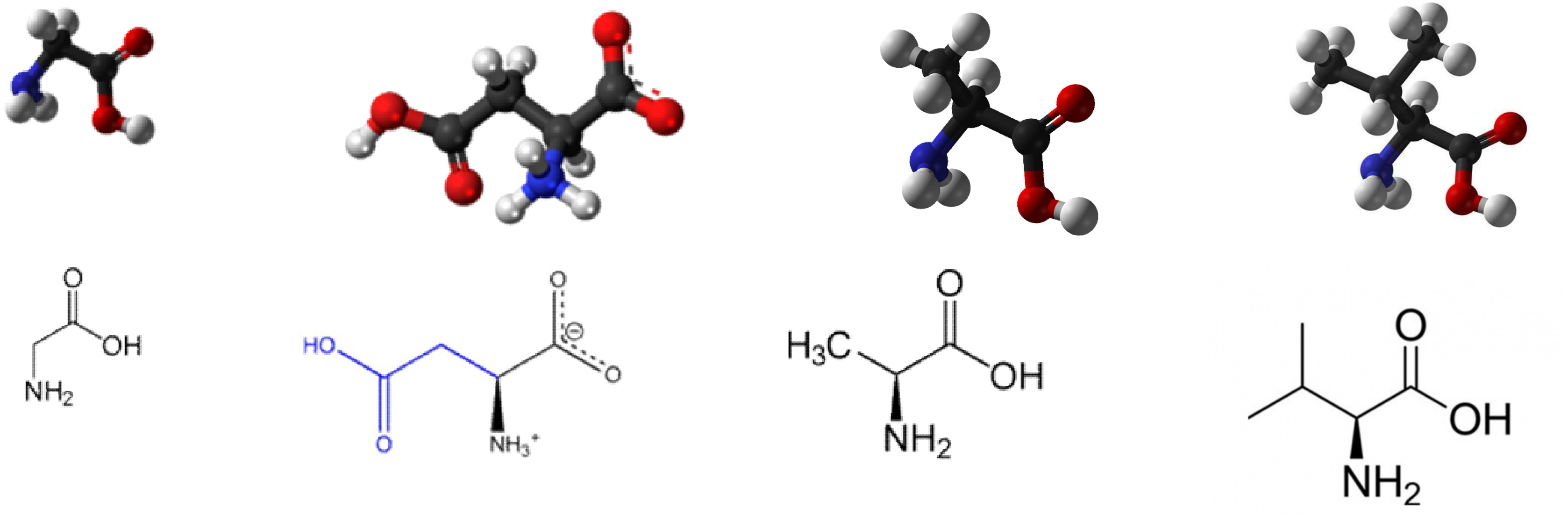
globular
structures

catalytic
activity
(Asp)

Basic aminoacids for primitive genetic code?

Primordial genetic code might have involved only 4 „GNC” codons:

- *GGC for glycine*
- *GCC for alanine*
- *GAC for aspartic acid*
- *GUC for valine*

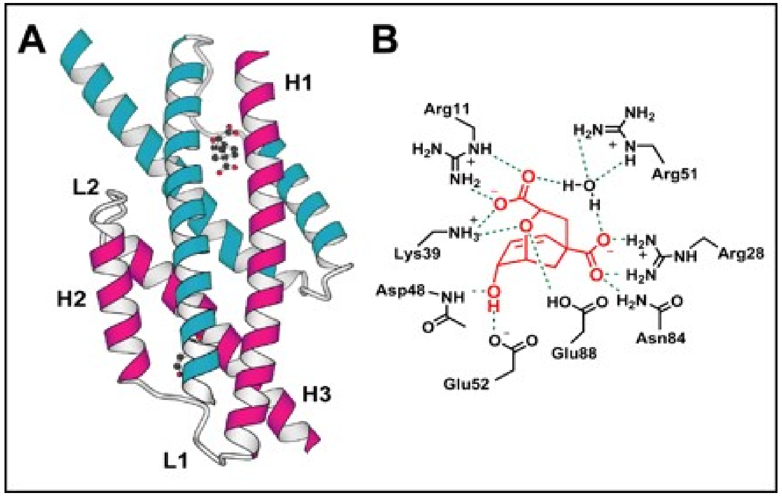


Later, the ‚GNC’ code probably evolved into ‚SNS’ code (S = G/C, N = A, U, G, C) – 16 codons encoding 10 basic aminoacids (Gly, Ala, Asp, Val, Glu, Leu, Pro, His, Glu, Arg)

Reduced aminoacid alphabet

9-aminoacid alphabet is sufficient to construct functional enzymes

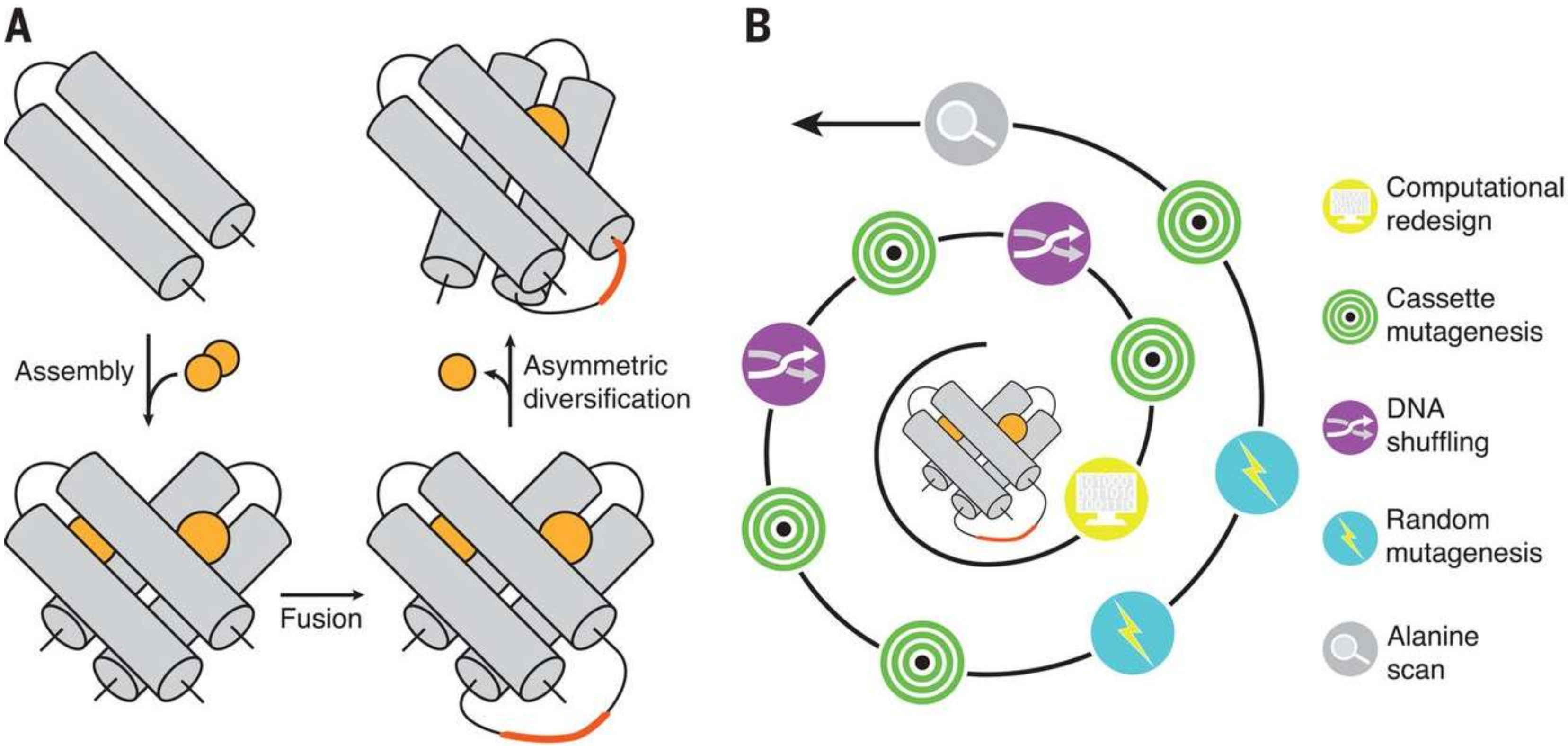
Aminoacids: Asp, Glu, Asn, Lys, Phe, Ile, Leu, Met, Arg



AroQ structure and active site. *A*, the homodimeric EcCM is shown with a transition state analog inhibitor bound at its active sites; the two identical polypeptide chains are colored *blue* and *pink* for clarity. *B*, proposed interactions between residues in the evolved active site of the simplified enzyme and the transition state analog inhibitor, compound **1** (*red*), based on the x-ray structure of EcCM. Residues Gln^{88} and Ser^{84} in EcCM are substituted with Glu^{88} and Asn^{84} in the 9-amino acid enzyme. Residue numbers are referenced to EcCM.

Walter, K. U., Vamvaca, K., Hilvert, D. *J. Biol. Chem.* **2005**, *280*,37742-37749.

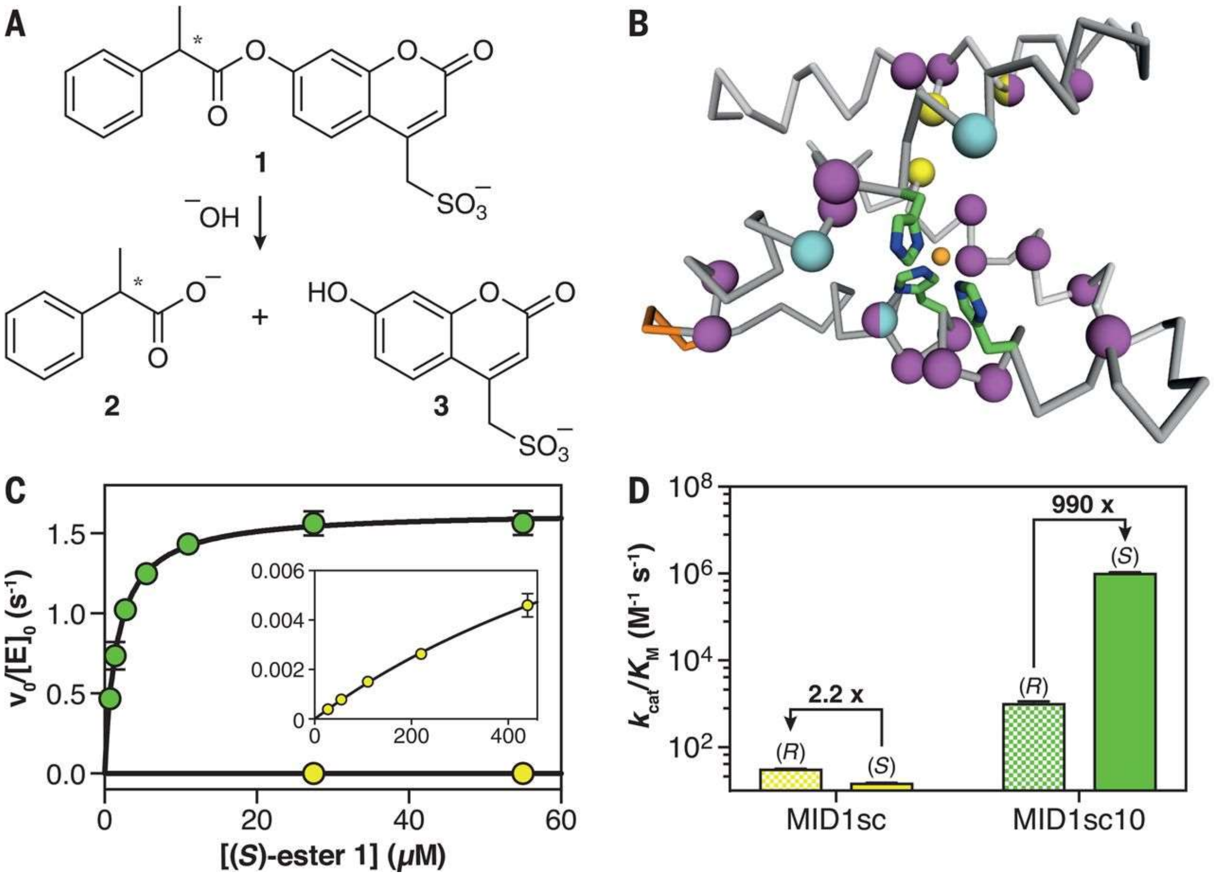
Evolution of a metalloenzyme from short peptides



Zinc-mediated assembly of helix-turn-helix fragments, followed by fusion and asymmetric diversification, afforded MID1sc10, an efficient metalloesterase.

S. Studer, D.A. Hansen, Z. Pianowski, P.R.E. Mittl, A. Debon, S.L. Guffy, B.S. Der, B. Kuhlman, D. Hilvert *Science,* **2018**, *362,* 1285-1288

Evolution of a metalloenzyme from short peptides



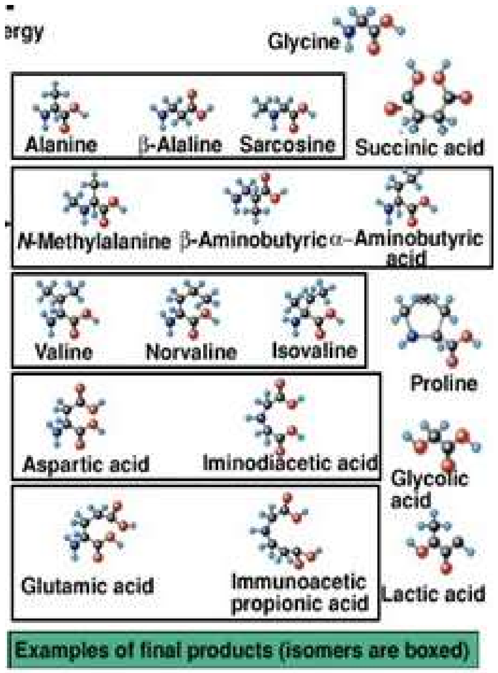
Crystal structure of MID1sc10
zinc ion - orange sphere,
coordinating histidines - green sticks
linkage of two polypeptides – orange sticks
beneficial mutations - magenta spheres,
residues replaced to prevent competitive zinc binding modes - cyan spheres).

The evolved variant MID1sc10 is highly enantioselective as a consequence of a 2200-fold specificity switch from the modestly (R)-selective starting catalyst MID1sc

Michaelis-Menten plots for **MID1sc** (yellow and inset) and **MID1sc10** (green) show a 70,000-fold improvement in hydrolysis efficiency for (S)-configured **1** after optimization.

S. Studer, D.A. Hansen, Z. Pianowski, P.R.E. Mittl, A. Debon, S.L. Guffy, B.S. Der, B. Kuhlman, D. Hilvert *Science,* **2018**, *362,* 1285-1288

Aminoacids - Summary



Prebiotic generation plausible – variants of the Miller-Urey experiment
Strecker-type of chemistry likely

Aminoacids are good catalysts, can perform various chemical transformations

The origin of homochirality in the Universe caused by the pairity violation and stochastic fluctuations

Chirality amplification possible in numerous chemical reactions

Aminoacids can catalyse their own formation with chirality amplification and undergo physical enantioenrichment processes

Condensation of aminoacids into peptides plausible under prebiotic conditions using condensing agents

Simple peptides can exhibit broad structural variety,
catalytically active enzymes can be constructed with reduced aminoacid alphabet