# The molecular origins of life

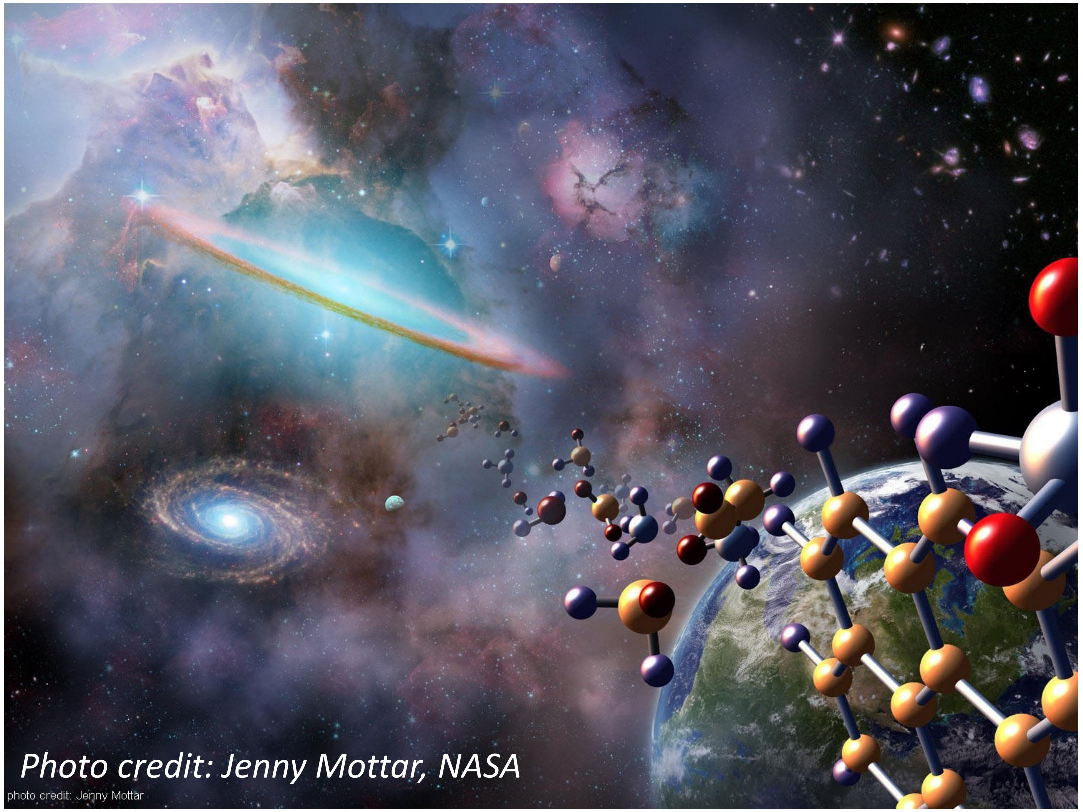


*Photo credit: Jenny Mottar, NASA*

L2 SoSe 2019 HD

Zbigniew Pianowski

# *General references*

**K. W. Plaxco, M. Gross** ***Astrobiology. A brief introduction.*** **2nd Ed.**
(EN, The Jonh Hopkins Univ. Press)
***Astrobiologie für Einsteiger*** (DE, Wiley-VCH)

**K. Ruiz-Mirazo, C. Briones, A. Escosura** ***Prebiotic Systems Chemistry: New Perspectives for the Origins of Life.***
*Chemical Reviews, 2014, 114, pp. 285-366*

**A. Pross** ***What is Life? How Chemistry Becomes Biology.***
*(Oxford Univ. Press)*

# *Overview of the course*

*Origin of the Universe – stars, planets, elements*

*Origin of biorelevant monomers – primordial soup*

*Complex chemical processes on the way to living systems*

*Protocells and LUCA*

# *Overview of the course*

| | |
|---|---|
| ***Topic 1*** | *Introduction to life* |
| ***Topic 2*** | *The primordial soup: Aminoacids, Lipids, Sugars, Nucleobases* |
| ***Topic 3*** | *Systems chemistry: cyanosulfidic chemistry* |
| ***Topic 4*** | *Oligomerization, Self-assembly of biopolymers* |
| ***Topic 5*** | *RNA world* |
| ***Topic 6*** | *Metabolism, protocells* |
| ***Topic 7*** | *LUCA, extremophilic organisms, extraterrestrial life* |

# *Definitions of life*

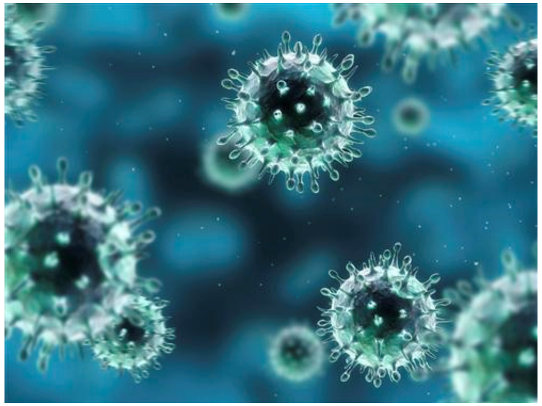
Life is a self-replicating chemical system capable of evolution (NASA, 2009)

Self-replicating: copies itself
Chemical system: based on assembly of molecules
Evolvable: adapt to the surroundings

*Mules*

*Infertile or old animals*

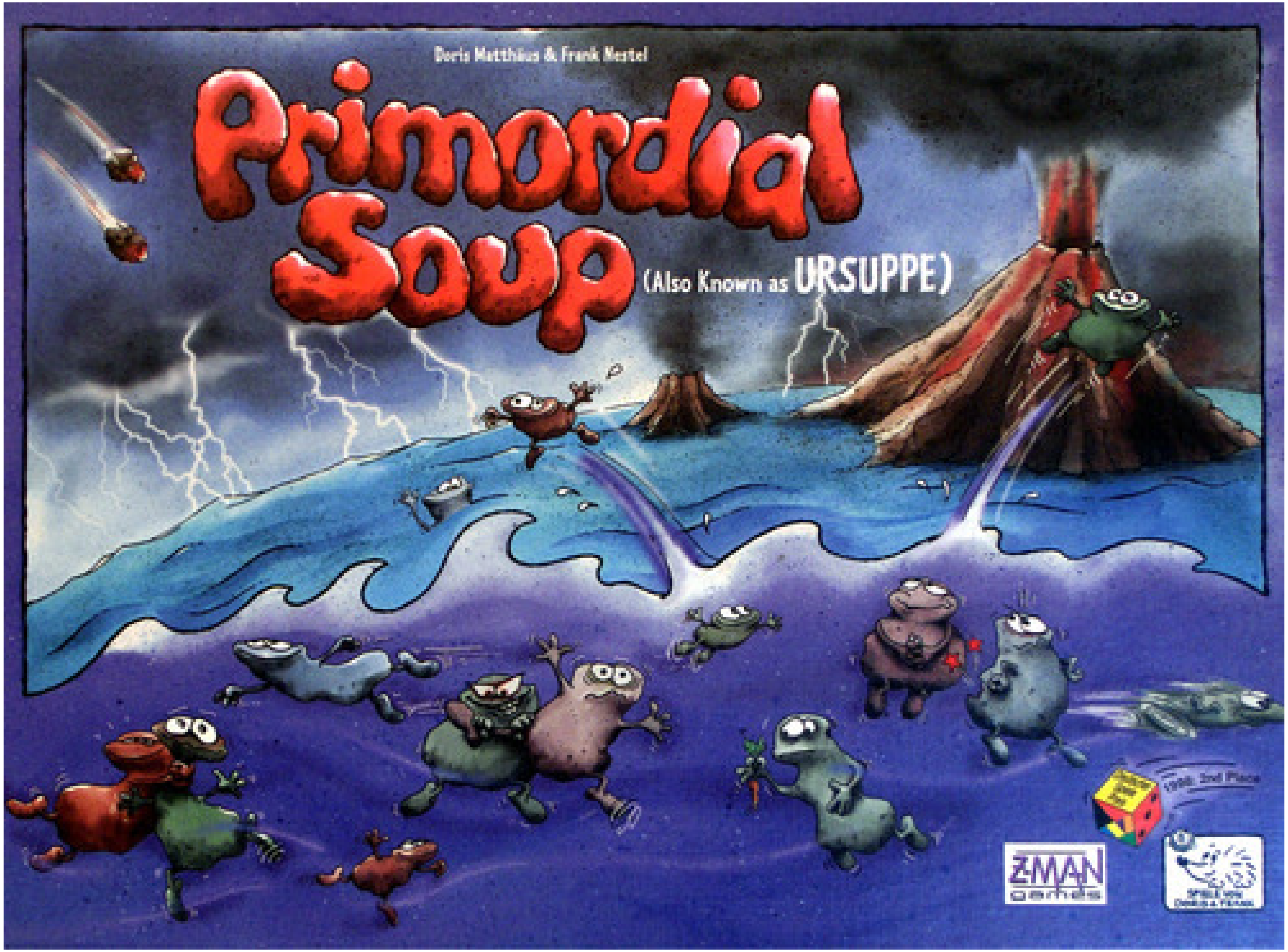
*Viruses*



The definition covers all species, not necessarily individuals

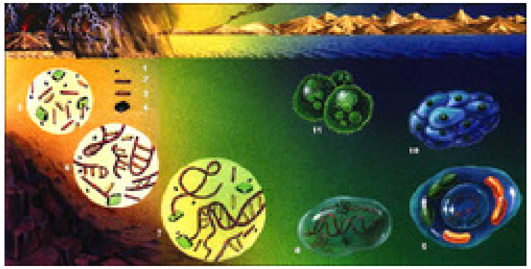
## *Origins of a habitable planet - conclusions*

Earth formed in the inner region of the solar nebula
Predominantly composed of refractory metals and silicates – non-biogenic materials
Jupiter provided proto-Earth with icy, volatile-rich material, and allowed cleanup of the Solar System from planetasimales, so no more big, planet-sterilizing impact possible anymore.
Earth is optimally positioned (0.95-1.15 AU) to maintain the acquired water as liquid, and stable surface temperature over billions years.


Doris Matthäus & Frank Nestel
Primordial Soup
(Also Known as URSUPPE)
1998 2nd Place
Z-MAN games
SPIELE VON DORIS & FRANK

# *The origin of biorelevant molecules on Earth*

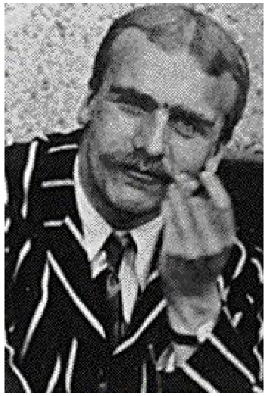
Alexander Oparin
(USSR, 1894-1980)



„atmospheric oxygen prevents the synthesis of certain organic compounds that are necessary building blocks for the evolution of life”

*1.The early Earth had a chemically reducing atmosphere.*
*2.This atmosphere, exposed to energy in various forms, produced simple organic compounds ("monomers").*
*3.These compounds accumulated in a "soup" that may have concentrated at various locations (shorelines, oceanic vents etc.).*
*4.By further transformation, more complex organic polymers - and ultimately life - developed in the soup.*

John B. S. Haldane
(UK, India, 1892-1964)

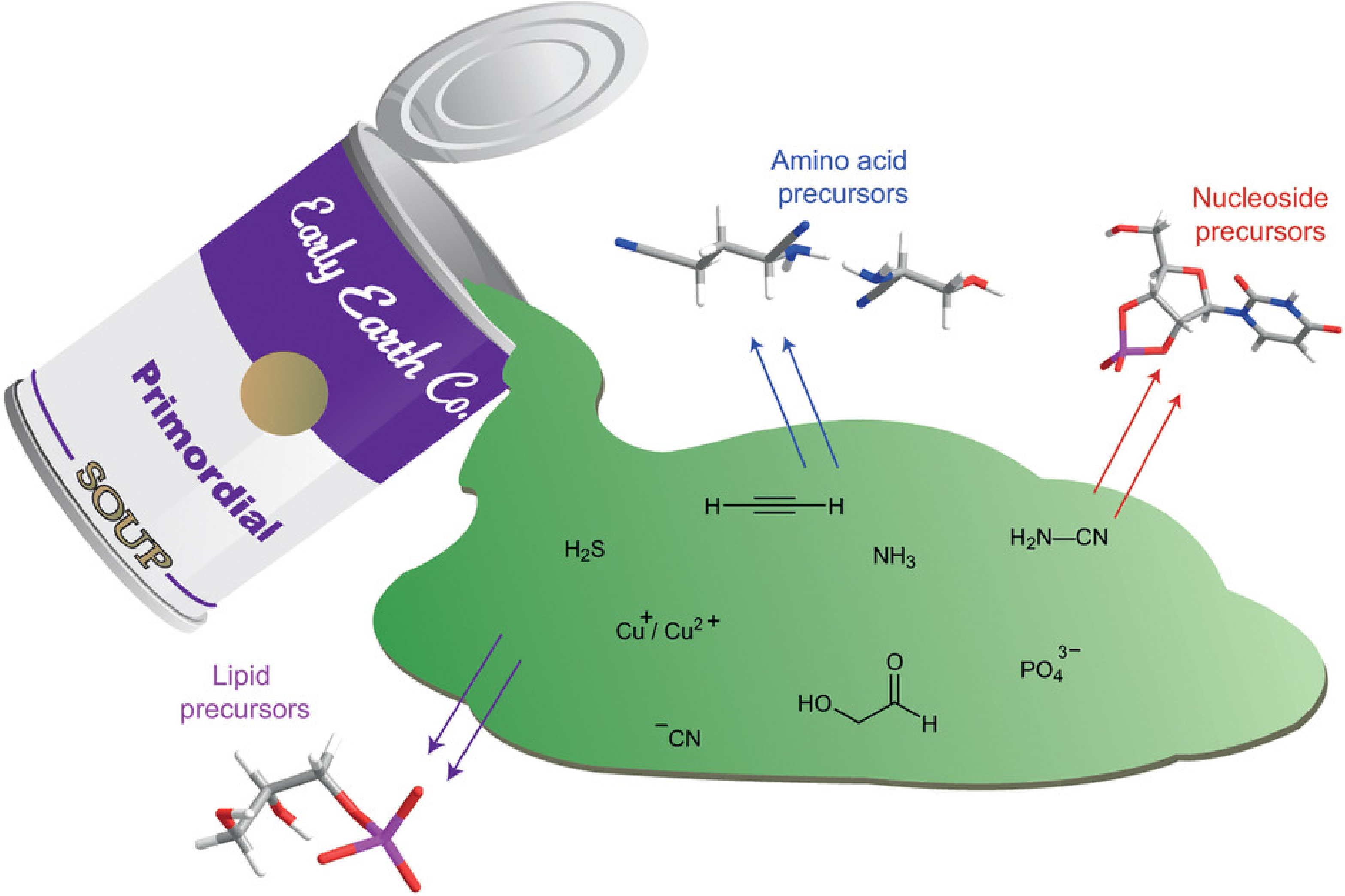


„Primordial soup”

„Biopoeiesis” – prebiotic oceans as „hot diluted soup” under anoxic conditions: e.g. $CO_2$, $NH_3$, $H_2O$

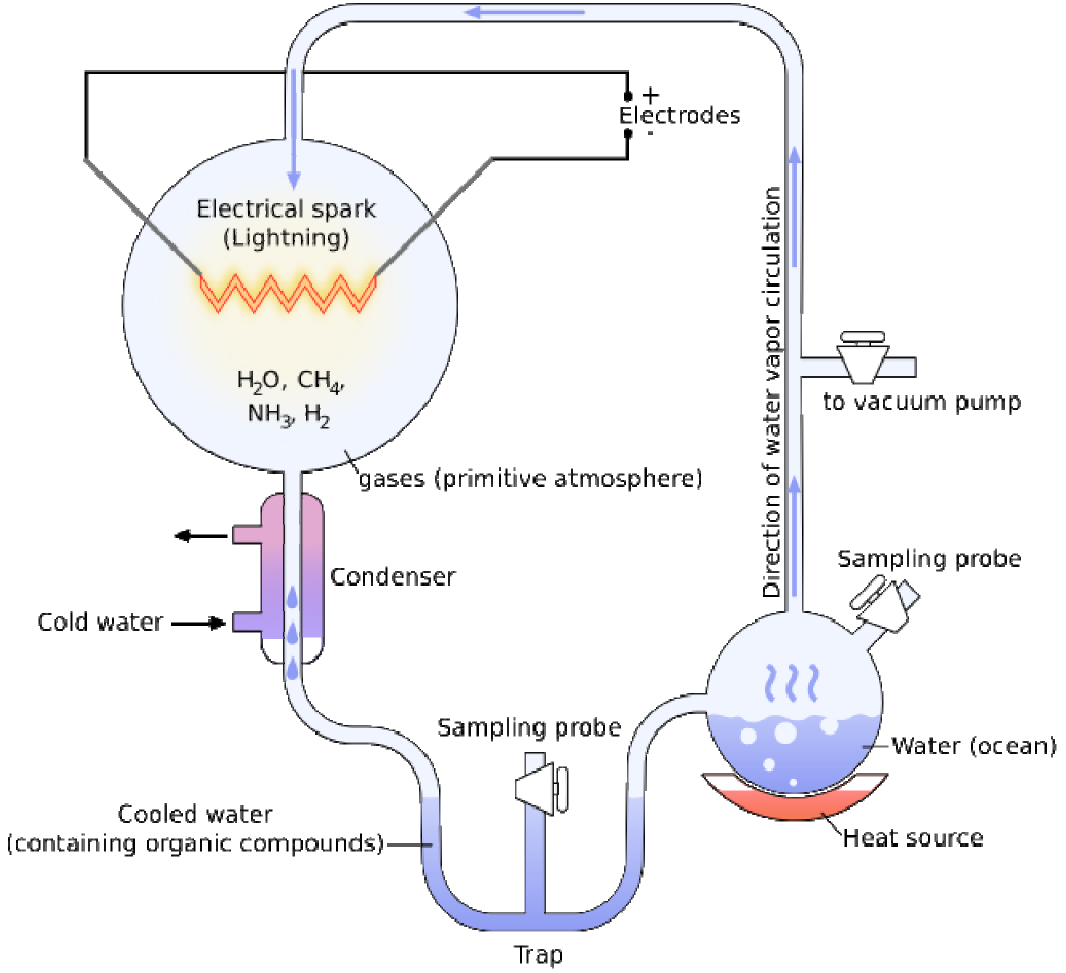
„Life arose through the slow evolution of chemical systems of increasing complexity”

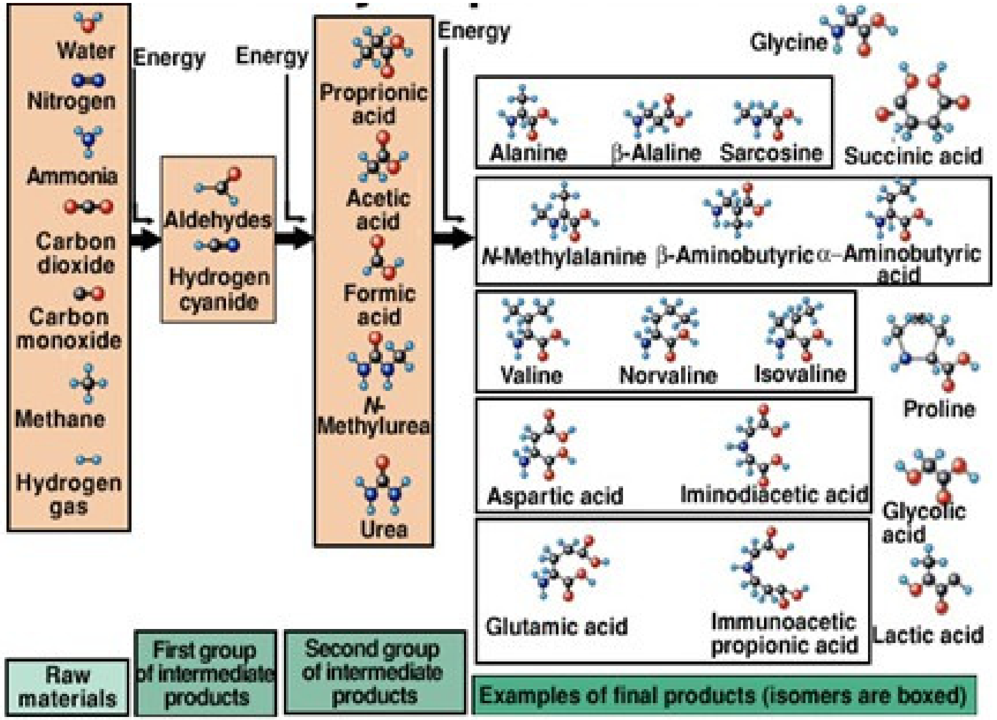
# *Basic classes of biomolecules*

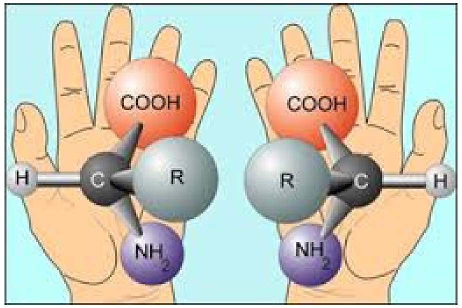


- Aminoacids
- Lipids
- Carbohydrates (sugars)
- Nucleotides
- Nucleosides (sugar+nucleotide)

# *Miller-Urey experiment - 1952*



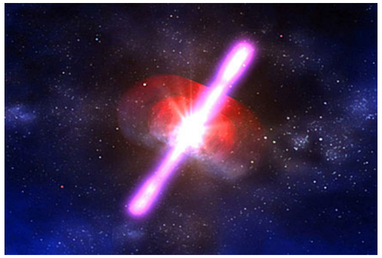


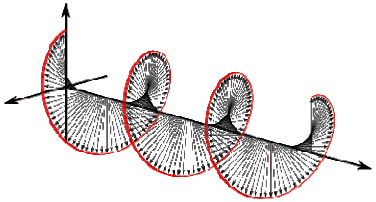


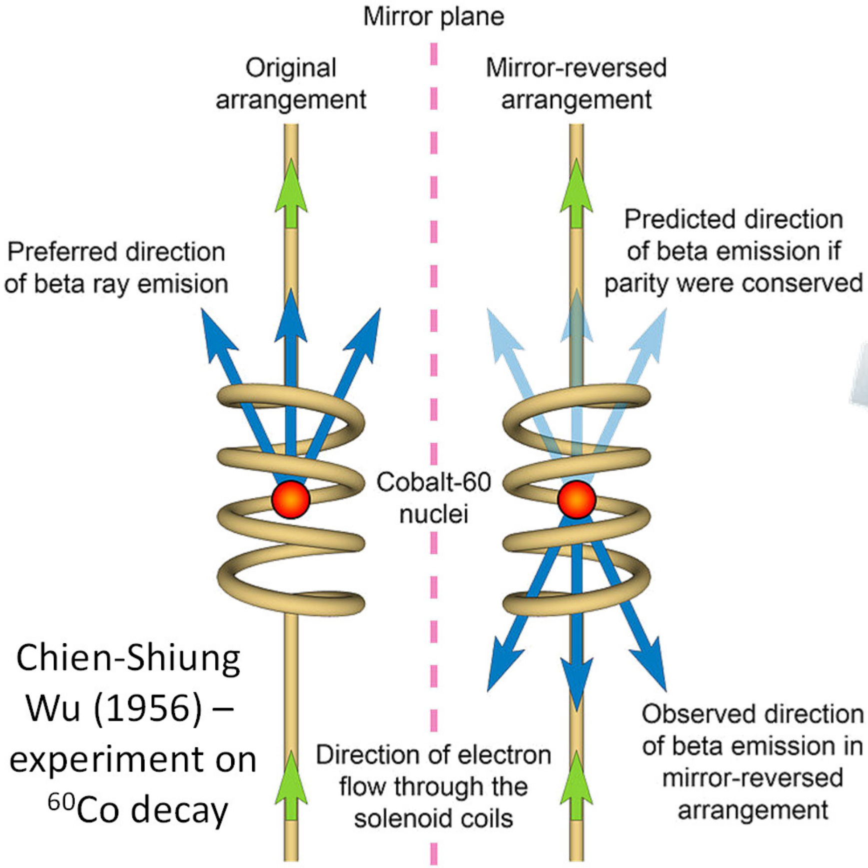
# *The origins of homochirality*

*The pairity violation*

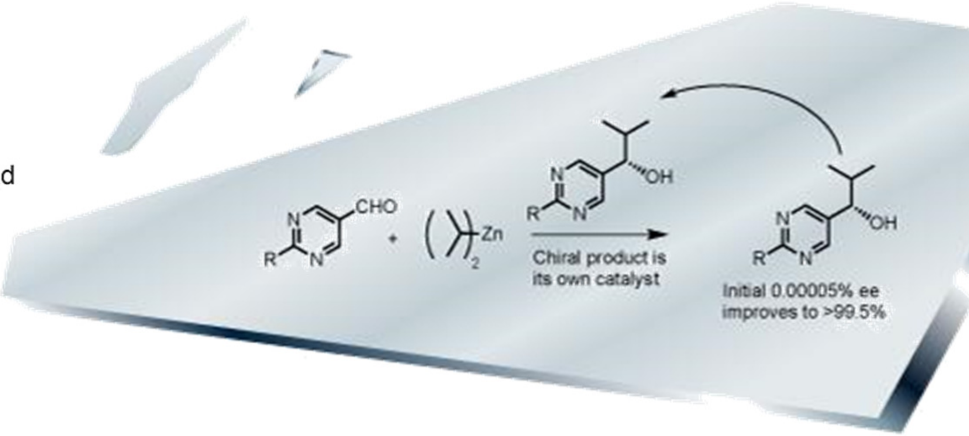
*Stochastic symmetry disturbances*

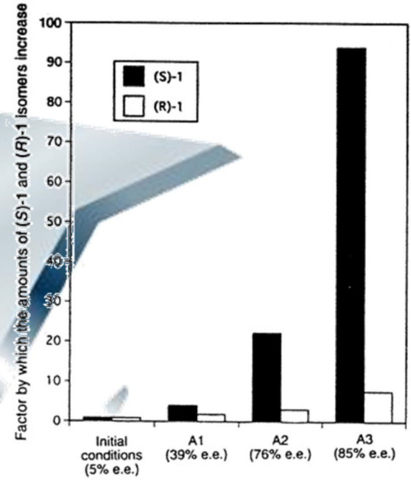


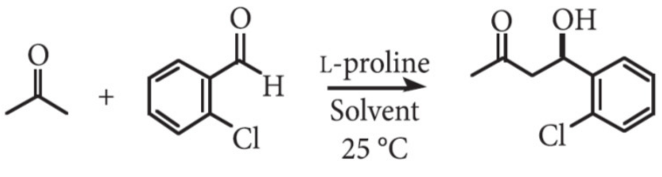


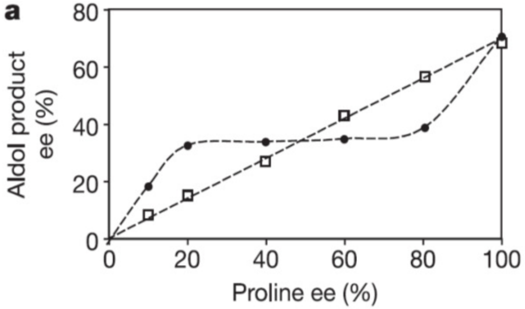


Chien-Shiung Wu (1956) – experiment on $^{60}$Co decay

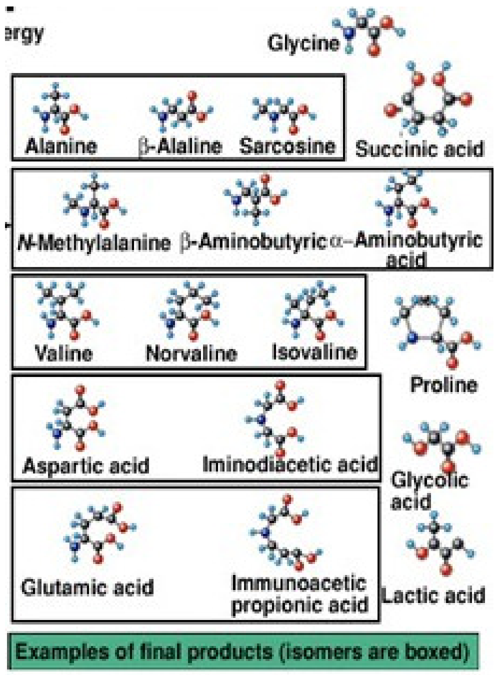








# *Aminoacids - Summary*



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

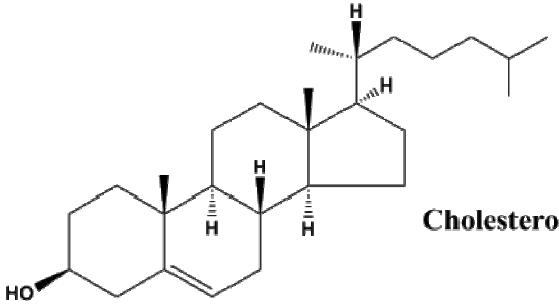
Chirality amplification possible in numerous chemical reactions

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

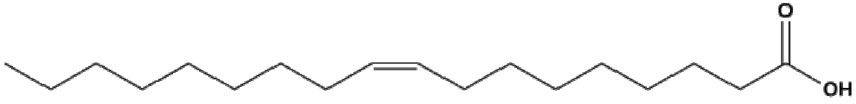
Condensation of aminoacids into peptides plausible under prebiotic conditions using condensing agents

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

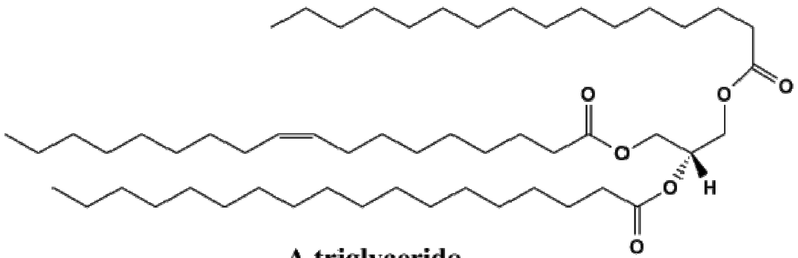
# *Lipids*



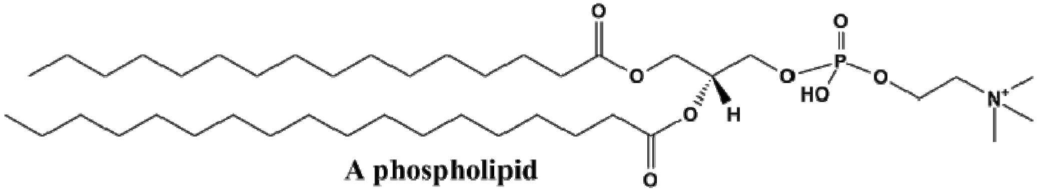
**Cholesterol**



**A free fatty acid**

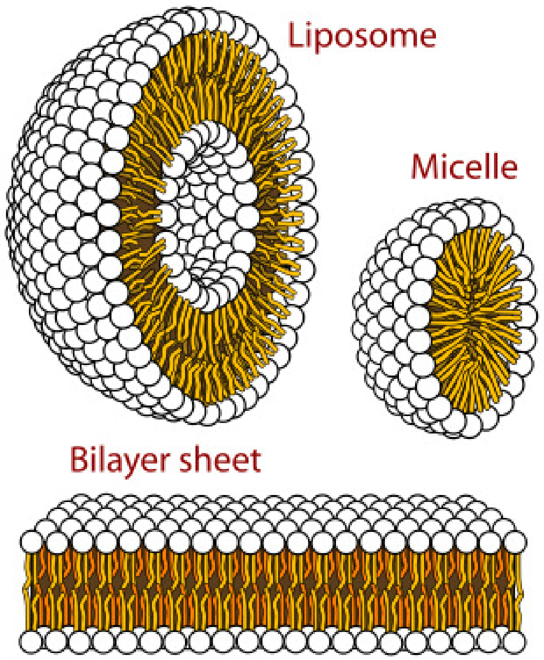


**A triglyceride**



**A phospholipid**

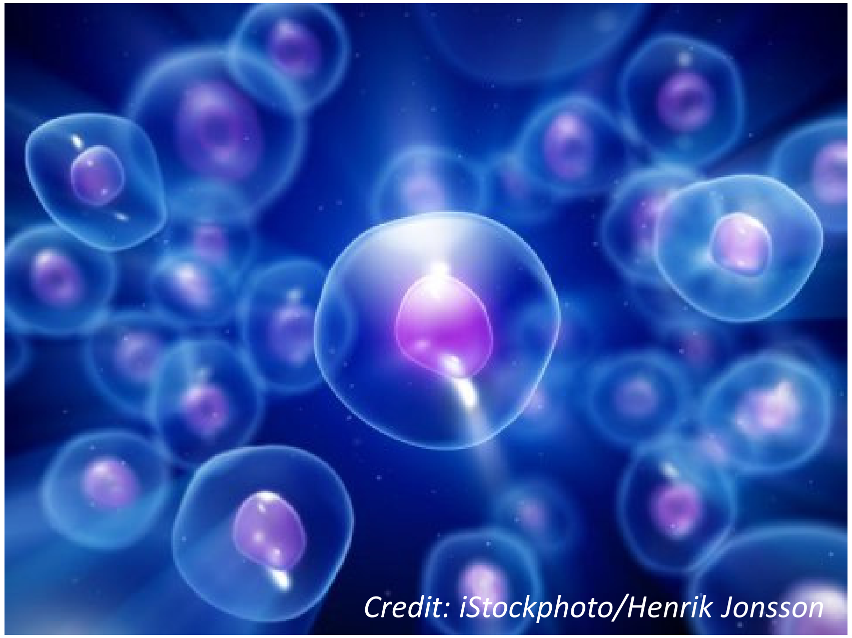
*By Lmaps*



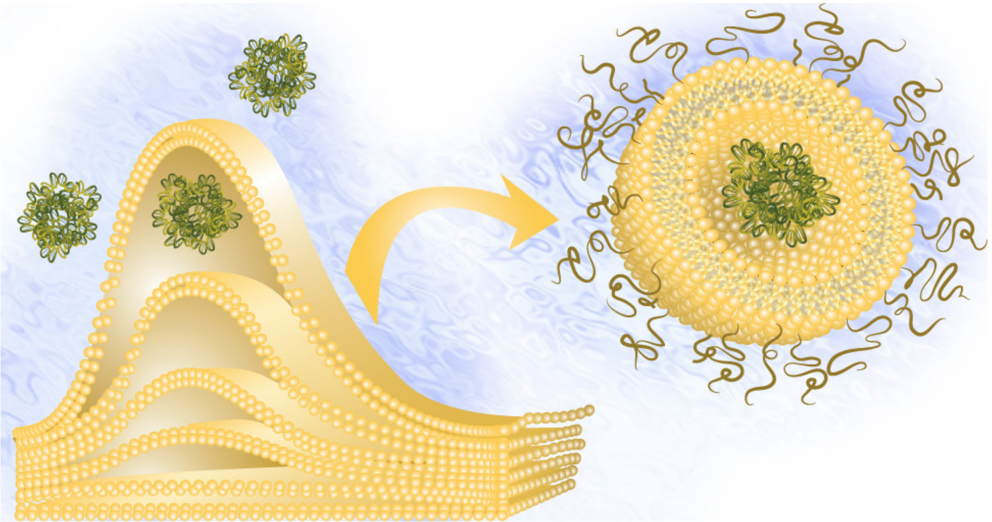
*By Mariana Ruiz Villarreal*

# *Encapsulation – essential for life*

Evolving chemical systems require compartments for Darwinian evolution – to compete, to store information and to concentrate reactants/metabolites



*Credit: iStockphoto/Henrik Jonsson*



*Levine, R.M., Pearce, T.R., Adil, M., Kokkoli, E. Langmuir, 2013, 29 (29): 9208–9215.*

Encapsulation into membranes is considered an early stage in prebiotic chemical evolution and essential requirement for the emergence of life

# *Fischer-Tropsch synthesis*

Long hydrocarbon chains from CO + $H_2$ in presence of metal catalysts and high pressure, fatty acids and alcohols are minor by-products

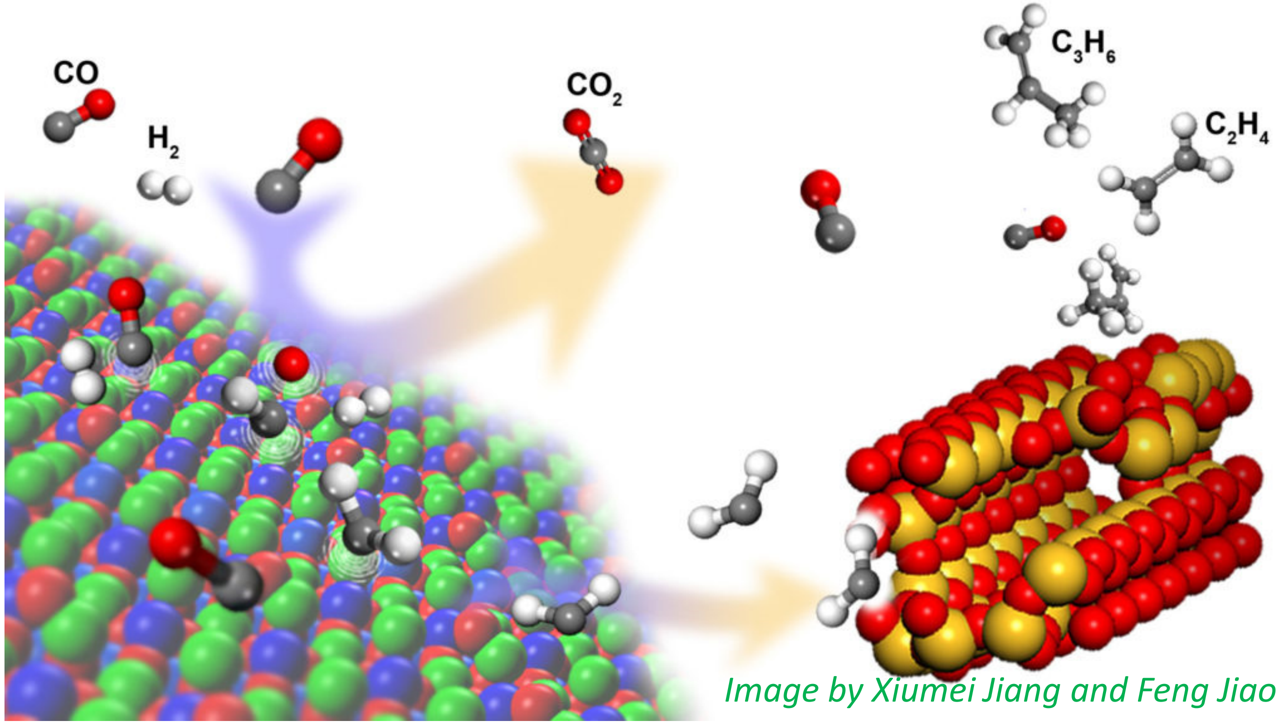


*Image by Xiumei Jiang and Feng Jiao*

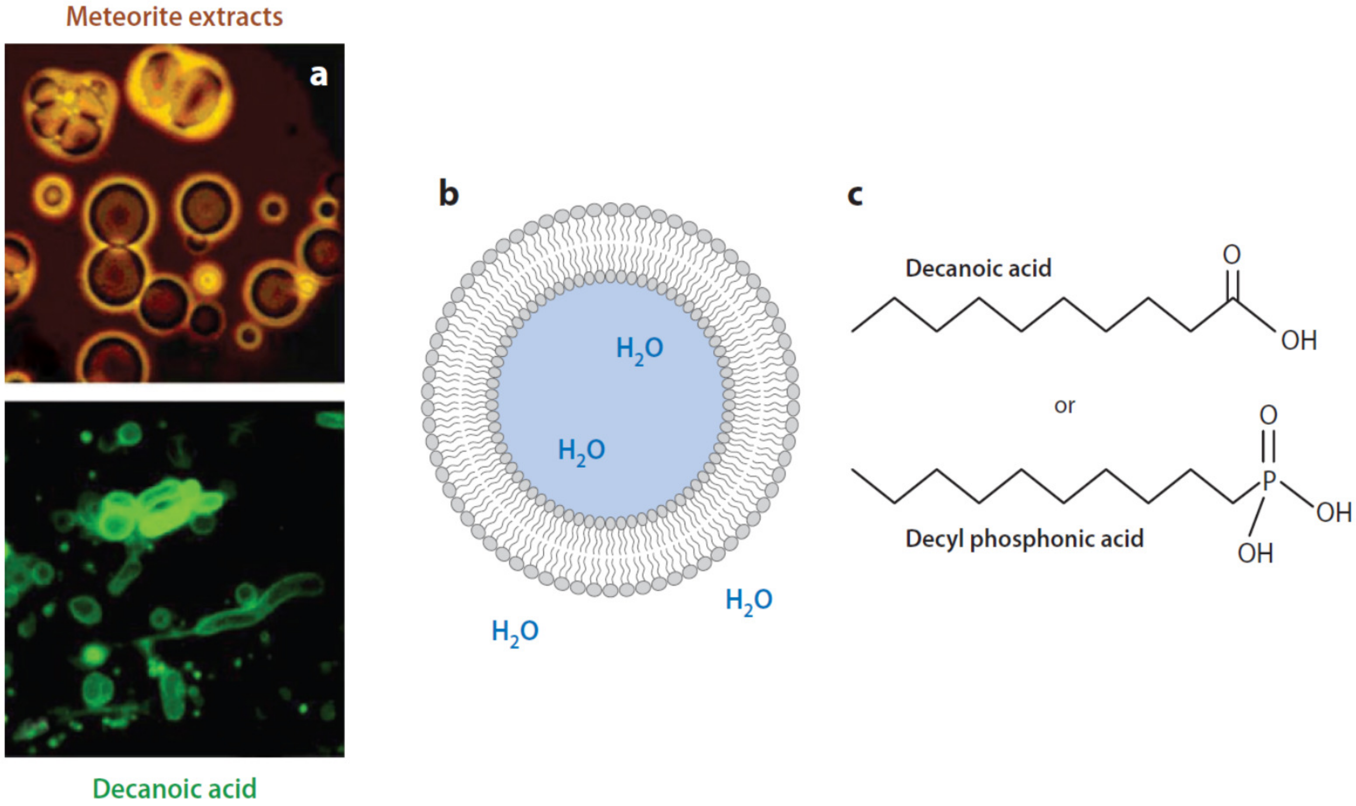
The mixture of $D_2$ and CO over meteoritic iron or iron ore produced alkanes and n-fatty acids

*Oro, J. et al. Geochim. Cosmochim. Acta* **1976**, *40,* 915-924.

# *Encapsulation – essential for life*

Fatty acids have been found in meteorites – plausible prebiotic synthesis pathways existed in the early Solar System

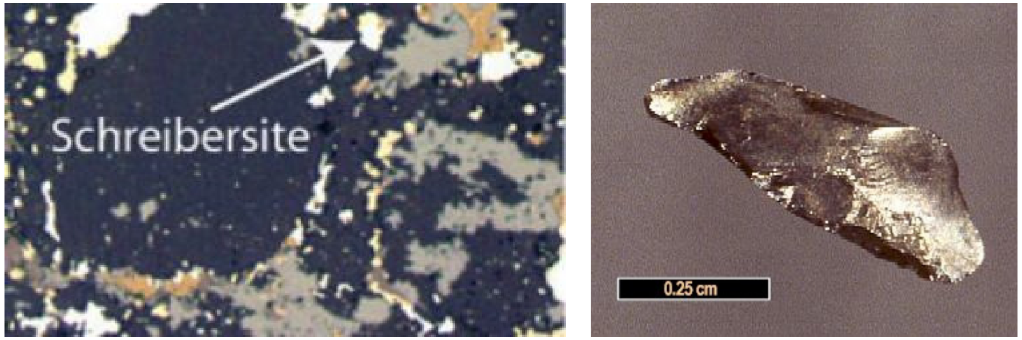
Murchison meteorite
*chondrite*



Extracts of meteorites containing these compounds spontaneously form vescicles when hydrated

# *Phosphates and phospholipids*

*Source: Google Images*



*Virginia Smith, UA Lunar & Planetary Laboratory*

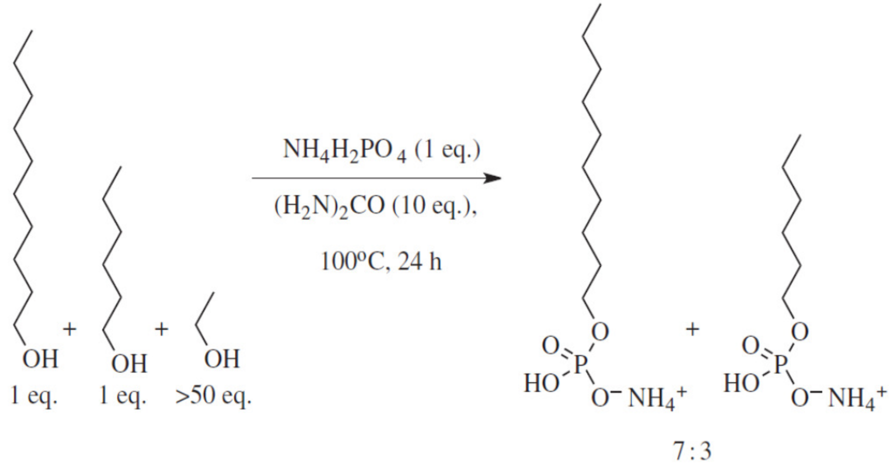
Image of schreibersite grain present in a thin-section of the enstatite meteorite, KLE 98300.

**Schreibersite** is generally a rare iron-nickel phosphide mineral, $(Fe,Ni)_3P$, though common in iron-nickel meteorites

Acidic schreibersite corrosion under anaerobic conditions (10% aq. $HCl/N_2$) → soluble forms of phosphorus

$$(Fe,Ni)_3P + HCl_{aq} \rightarrow H_2PO_3^- \rightarrow H_2P_2O_5^{2-}$$

T. P. Kee *et al.Geochimica et Cosmochimica Acta.* ***2013*** *109,* 90-112



M. Powner, J. Sutherland *Phil. Trans. R. Soc. B* **2011**, *366*, 2870–2877

# *Lipids - summary*

Many amphiphilic organic compounds spontaneously form vesicles in water at sufficiently high concentrations

Current phospholipid membranes likely evolved late. Protocells probably encapsulated by fatty acids, fatty alcohols, prenyl oligomers, or phosphorylated alcohols

Nucleolipids are proposed as intermediates in templated oligonucleotide replication

Phosphorus was accessible upon corrosion of meteorite materials and could be incorporated into lipids

# *The origin of small reactive intermediates*


***vivianite***

*Wikimedia , Carles Millan*

**Schreibersite** $(Fe,Ni)_3P$, from iron-nickel meteorites: source of phosphorus, iron and nickel

Under more neutral conditions phosphates recombine with iron → $Fe_3(PO_4)_2$ (**vivianite**)

It should be re-solubilized to become accessible for following chemical transformations

HCN – the crucial reactive intermediate – burning of carbon-rich chondrite meteorites into redox-neutral atmosphere containing $N_2$ and water

$$Fe_3(PO_4)_2 + 18CN^-{}_{aq} \rightarrow 2PO_4^{3-} + 3[Fe(CN)_6]^{4-}$$

Two important functions: solubilization of phosphates and concentration of atmospheric HCN deposited as salts of mono- and divalent cations (Na, K, Mg, Ca)

Similar reactions take place with insoluble copper and nickel sulfides deposited by iron-nickel meteorite impacts (same occurence as schreibersite, rich mining sources of these metals until today)

$$NiS + H_2O + 6CN^- \rightarrow [Ni(CN)_6]^{4-} + HS^- + OH^-$$

$$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$$

# The origin of small reactive intermediates

Thermal decomposition of cyanoferrates (volcanic):

$$(\mathrm{Na,K})_4[\mathrm{Fe(CN)_6}] \xrightarrow{700^\circ\mathrm{C}} 4(\mathbf{Na/K})\mathbf{CN} + \mathrm{Fe(CN)_2}$$

$$3\mathrm{Fe(CN)_2} \xrightarrow{700^\circ\mathrm{C}} \mathrm{Fe_3C} + 5\mathrm{C} + 3\mathrm{N_2}$$

$$\mathrm{Fe(CN)_2} \xrightarrow{700^\circ\mathrm{C}} \mathrm{Fe} + 2\mathrm{C} + \mathrm{N_2}$$

$$\mathrm{Ca_2[Fe(CN)_6]} \xrightarrow{660^\circ\mathrm{C}} 2\mathrm{Ca(CN)_2} + \mathrm{Fe(CN)_2}$$

$$\mathrm{Ca(CN)_2} \xrightarrow{660^\circ\mathrm{C}} \mathbf{CaNCN} + \mathrm{C} \xrightleftharpoons{1000^\circ\mathrm{C}} \mathbf{CaC_2} + \mathrm{N_2}$$

$$\mathrm{Mg_2[Fe(CN)_6]} \xrightarrow{315^\circ\mathrm{C}} 2\mathrm{Mg(CN)_2} + \mathrm{Fe(CN)_2}$$

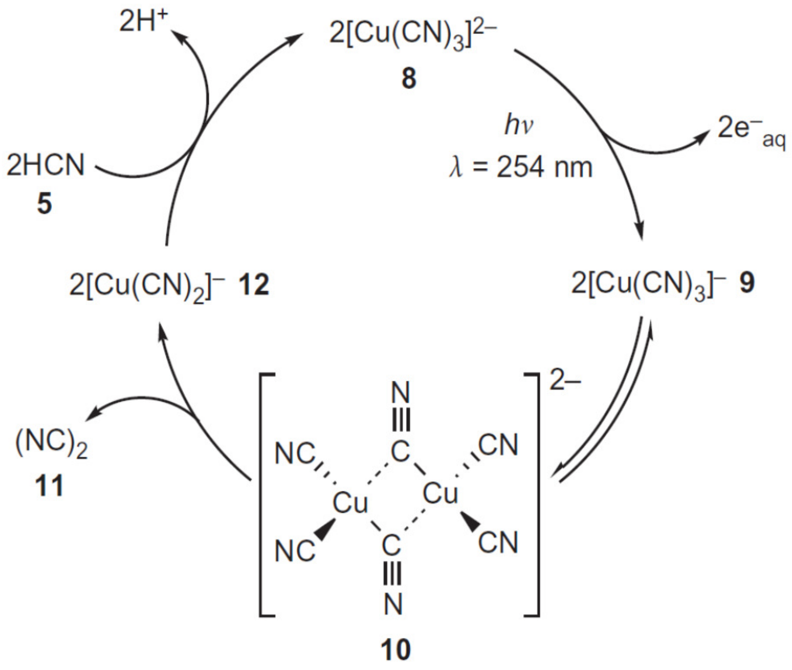
$$\mathrm{Mg(CN)_2} \xrightarrow{395^\circ\mathrm{C}} \mathrm{MgCN_2} + \mathrm{C}$$

$$3\mathrm{MgCN_2} \xrightarrow{420^\circ\mathrm{C}} \mathbf{Mg_3N_2} + 3\mathrm{C} + 2\mathrm{N_2}$$

$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$

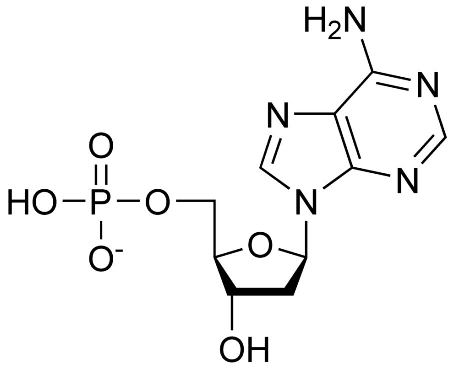
cyanocuprates and $HS^-$ are delivered by this process

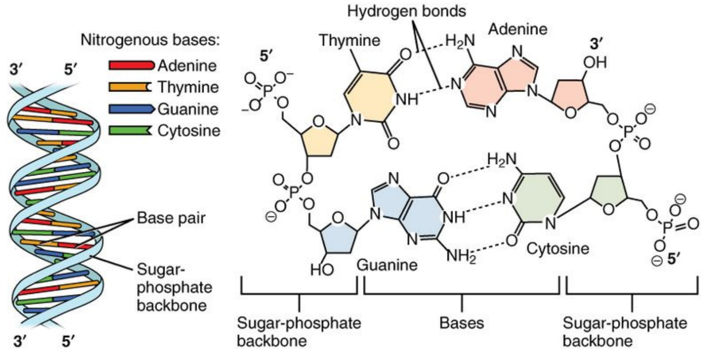
Photoredox cycle based on cyanocuprates may convert HCN into cyanogen

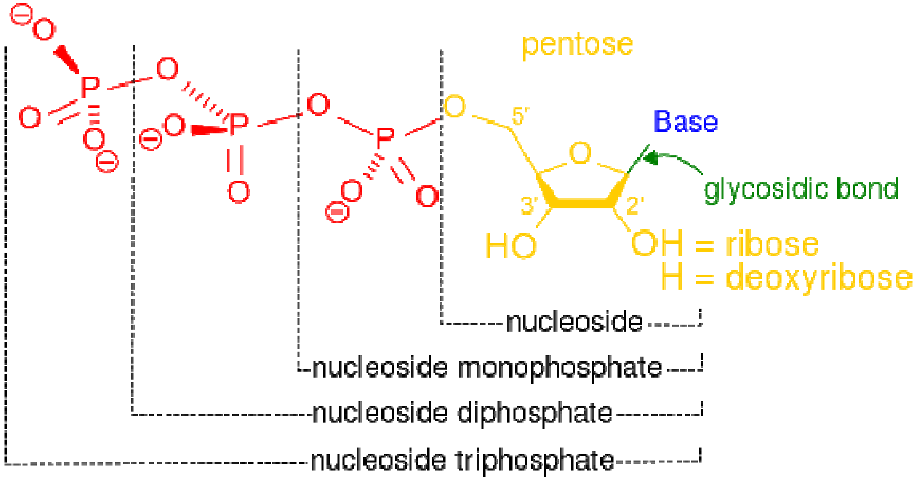


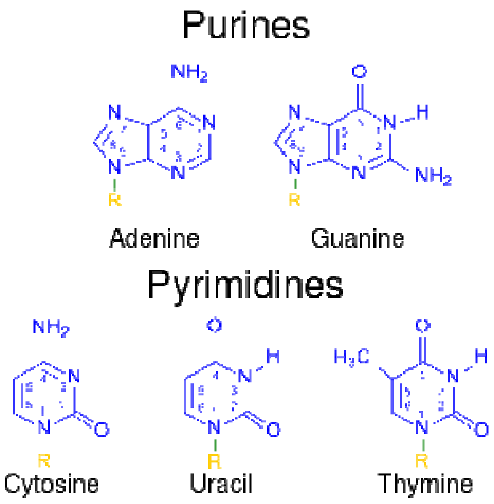
Action of water (bufferred to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from $CaC_2$) + ammonia (from $Mg_3N_2$)

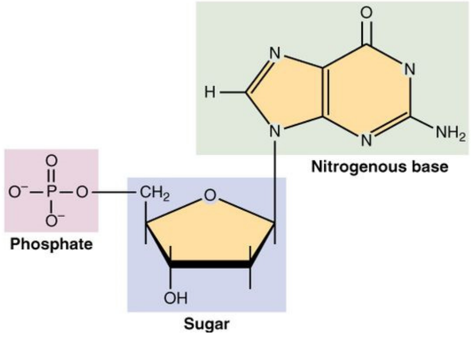
# *Nucleotides - components*



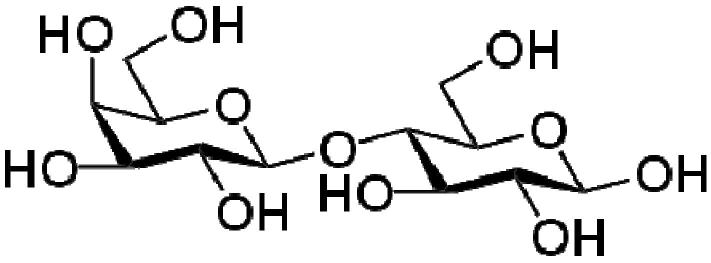


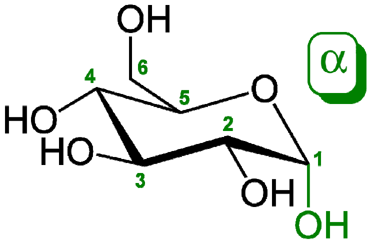


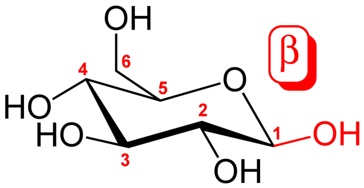




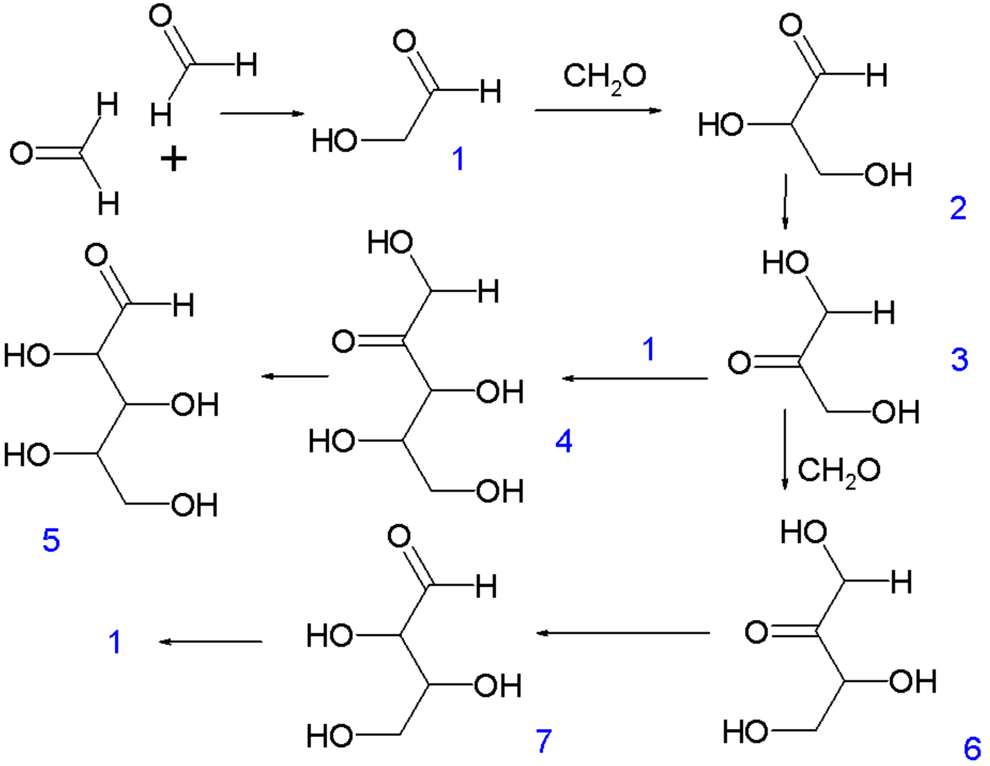
# *Carbohydrates*







# *Formose reaction*

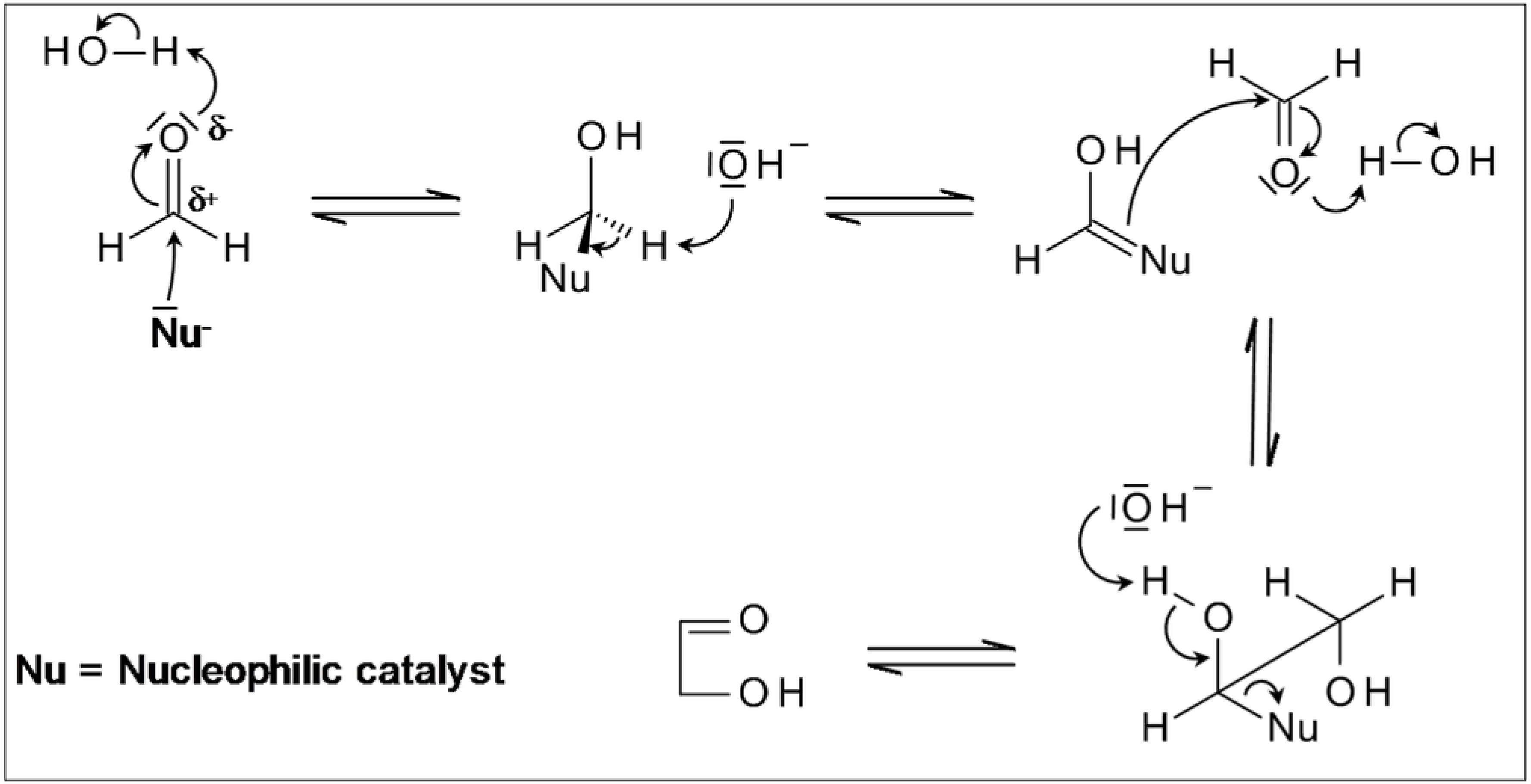


Alexander Butlerov (1828-1886)
*St. Petersburg, Kazan, Russia*

Ronald Breslow (1931-)
*Columbia University, USA*

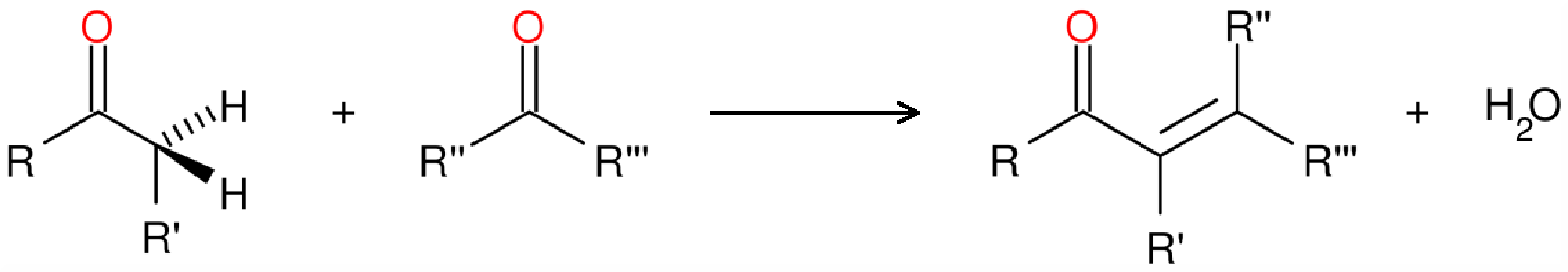
The reaction begins with two formaldehyde molecules condensing to make glycolaldehyde **1** which further reacts in an aldol reaction with another equivalent of formaldehyde to make glyceraldehyde **2**. An aldose-ketose isomerization of **2** forms dihydroxyacetone **3** which can react with **1** to form ribulose **4**, and through another isomerization ribose **5**. Molecule **3** also can react with formaldehyde to produce tetrulose **6** and then aldoltetrose **7**. Molecule **7** can split into **2** in a retro-aldol reaction.

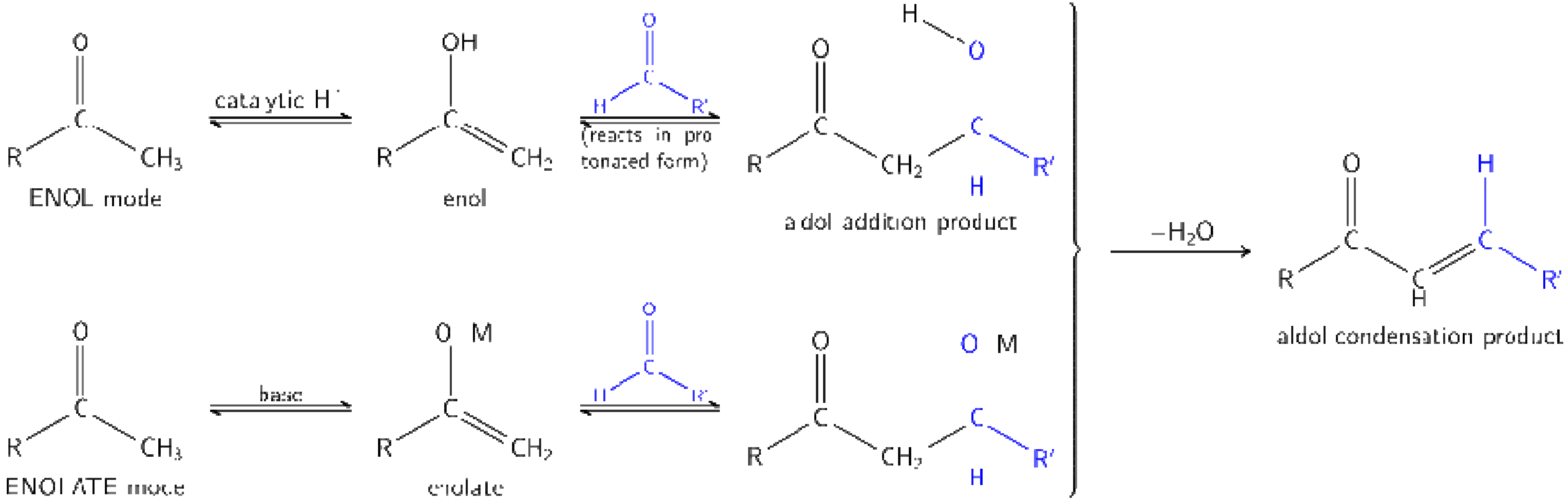
# *Formaldehyde condensation*



Nu = Nucleophilic catalyst

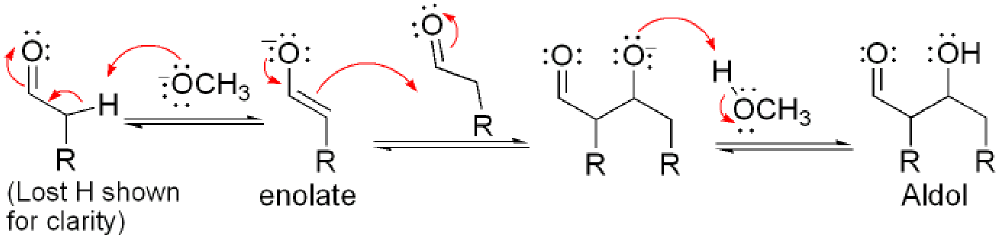
# Aldol reaction



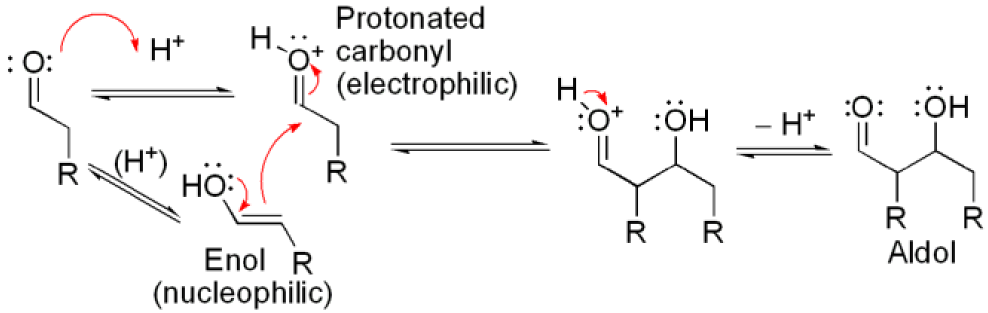


# *Aldol reaction*

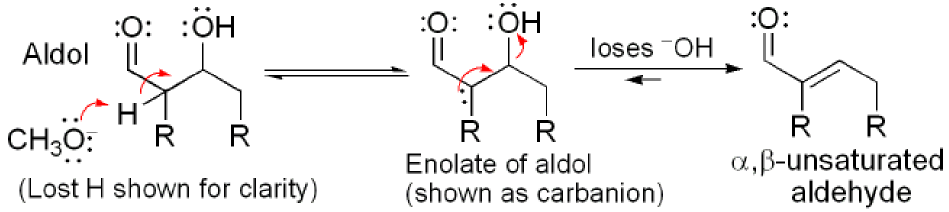
Base catalyzed aldol reaction (shown using $^{-}OCH_3$ as base)



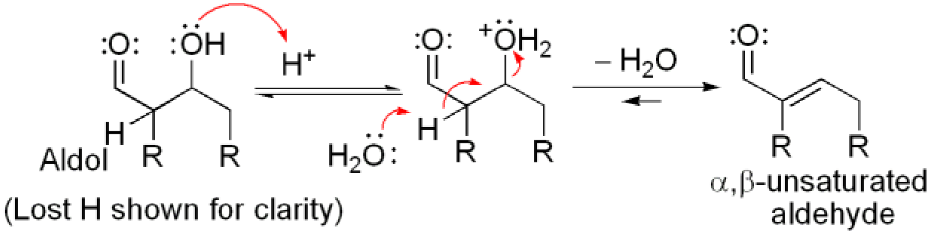
Acid catalyzed aldol reaction



Base catalyzed dehydration (sometimes written as a single step)



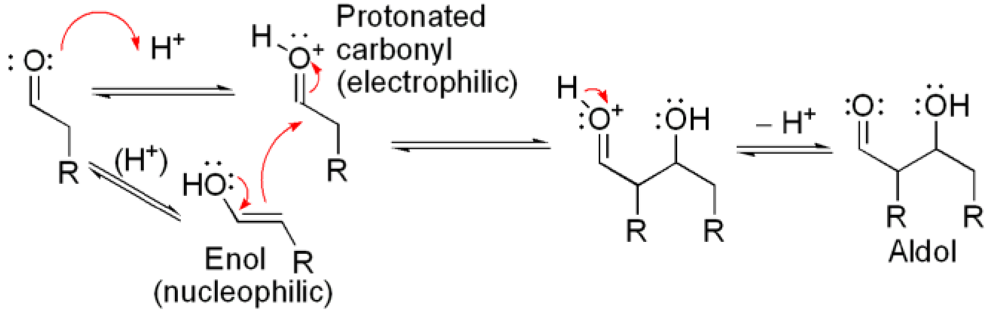
Acid catalyzed dehydration



Reversible process

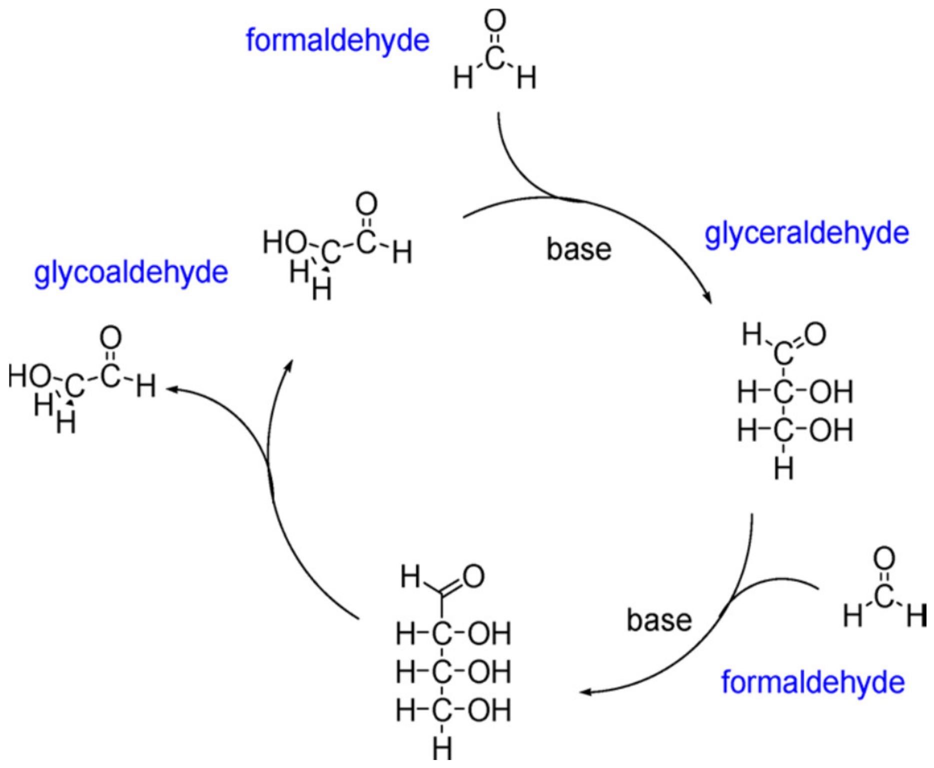
→ retro-aldol reaction

Acid catalyzed aldol reaction



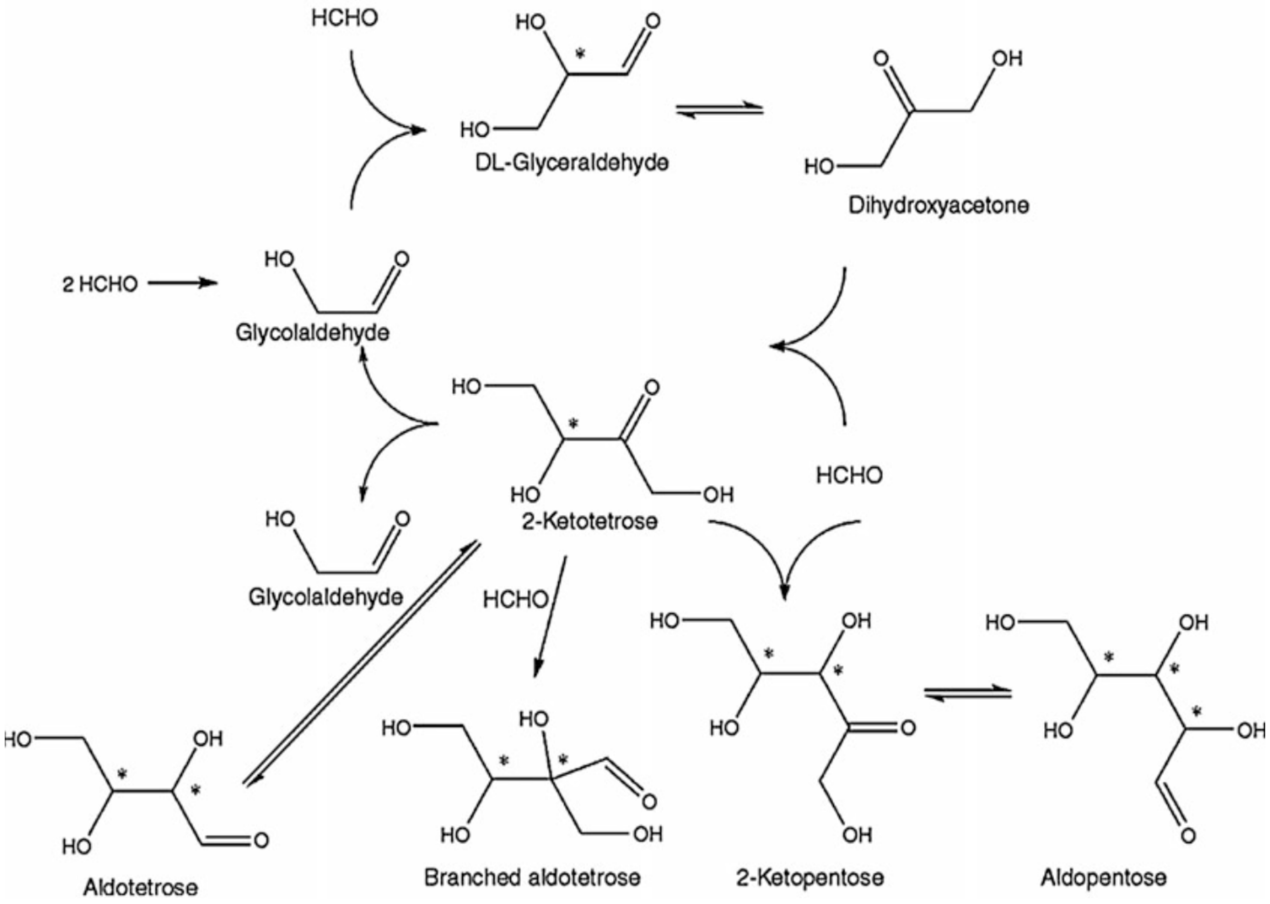
# *Formose reaction as an autocatalytic process*

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde
alkali are typically calcium, magnesium or lead



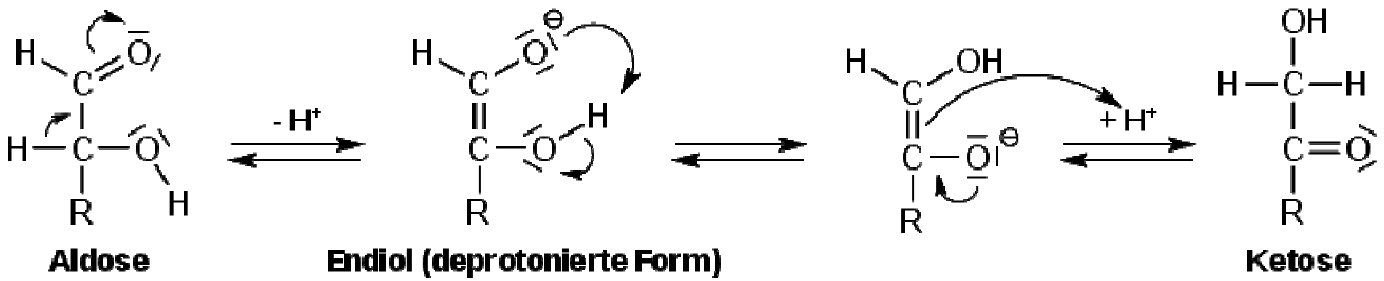
# *Detailed conditions for the formose reaction*

Formose reaction starts in concentrated alkaline aqueous solutions of formaldehyde
alkali are typically calcium, magnesium or lead

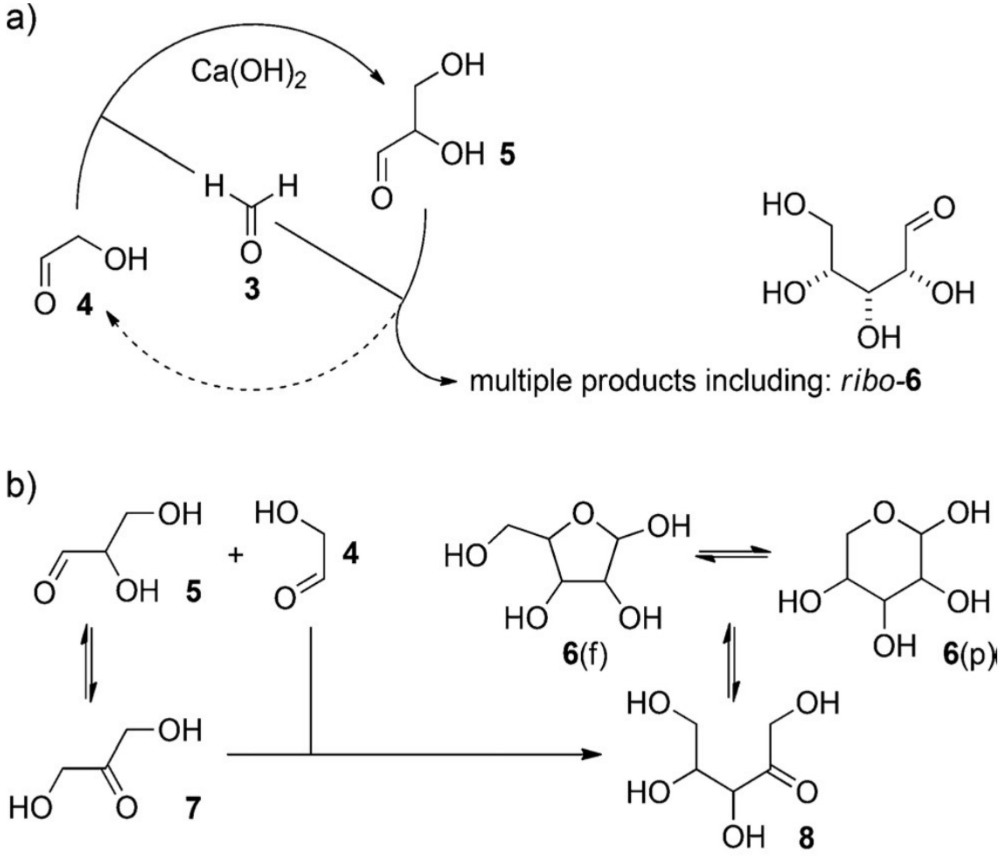


## ***Aldose-ketose isomerization***

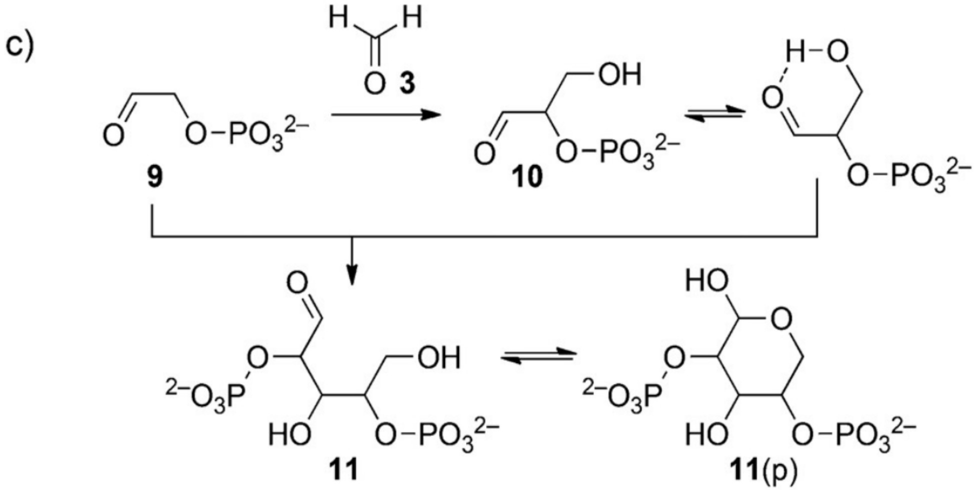
*Lobry de Bruyn(–Alberda)-van Ekenstein transformation*



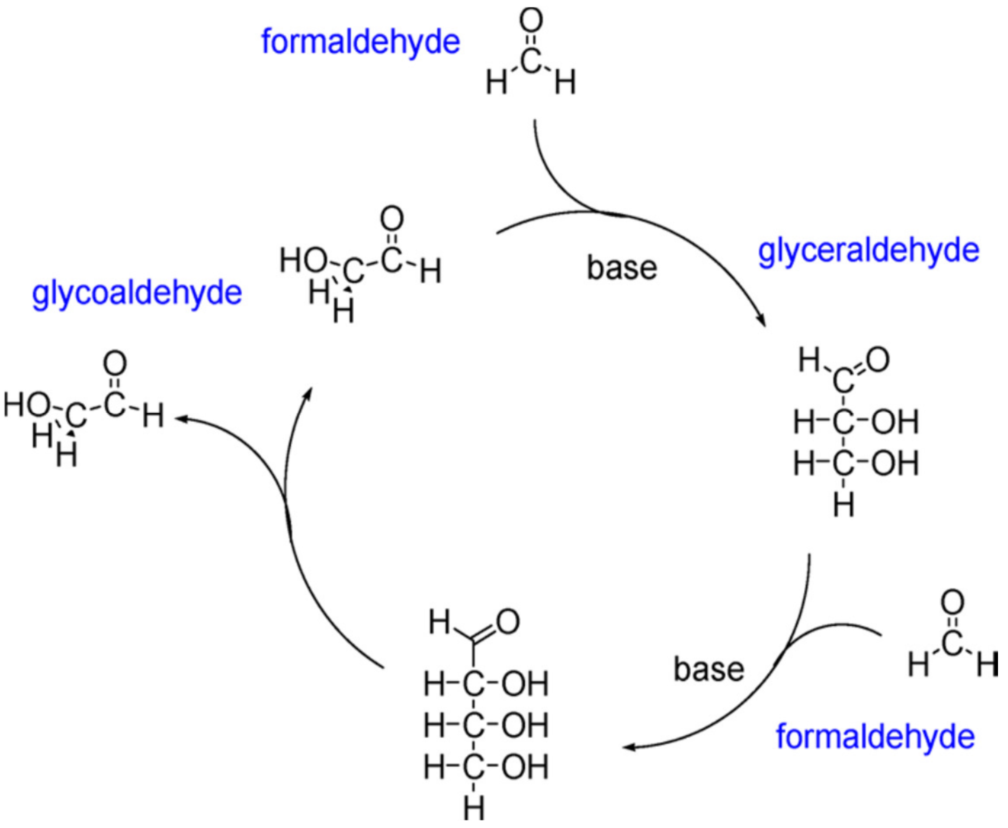
# *Formose reaction – substrate modifications*

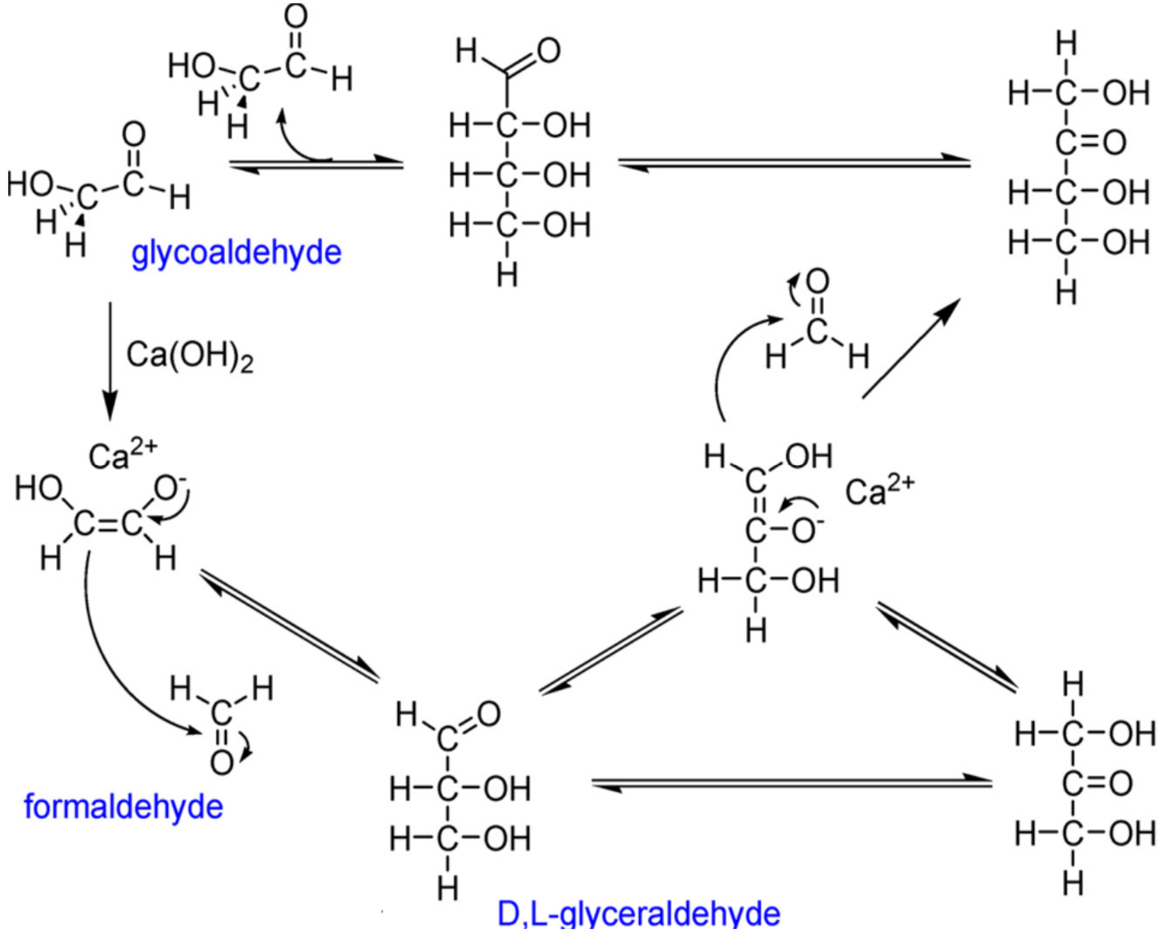


# *Formose reaction – substrate modifications*



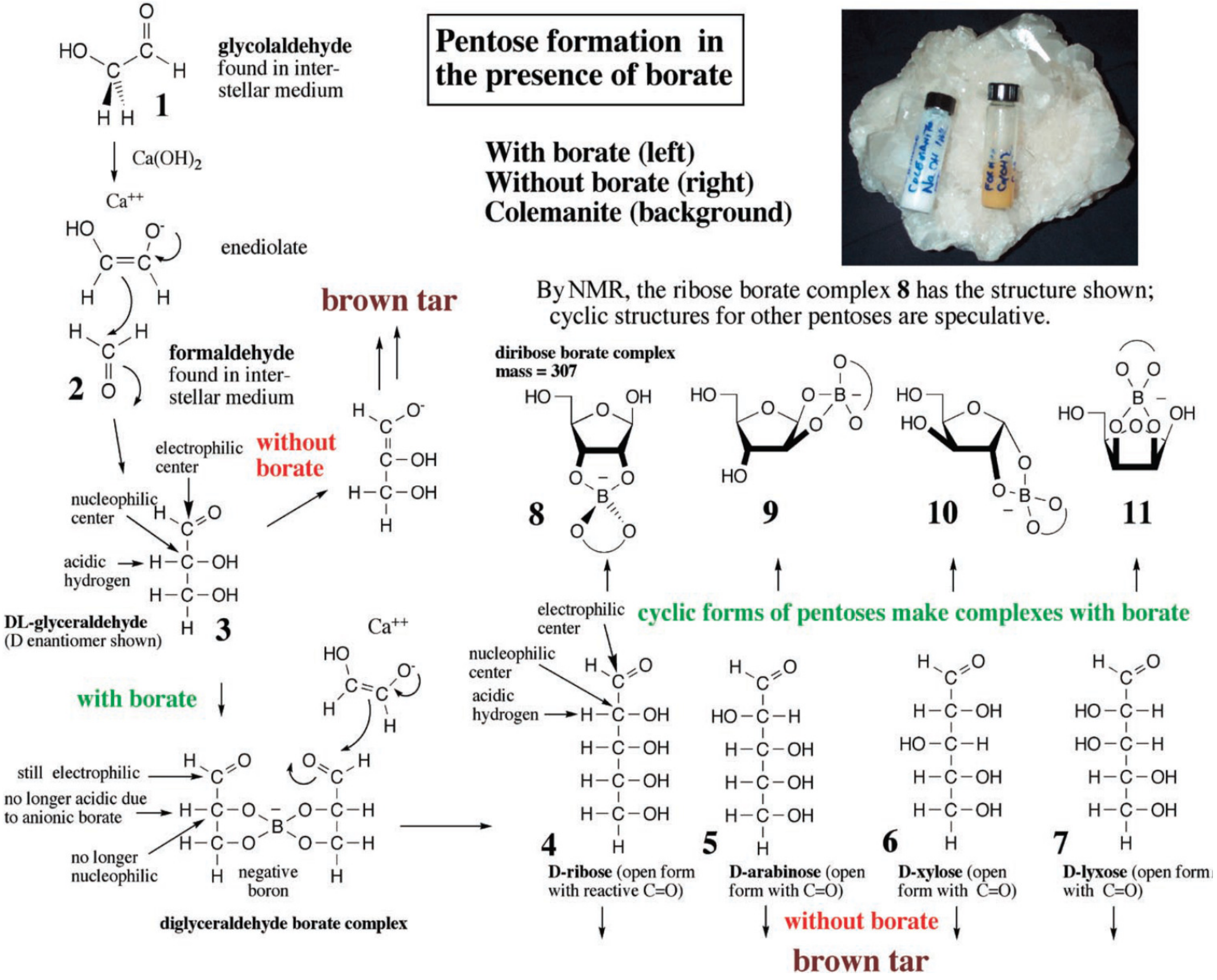
# *Formose reaction under standard basic catalysis*





*Escosura*

# *Formose reaction in presence of borates*



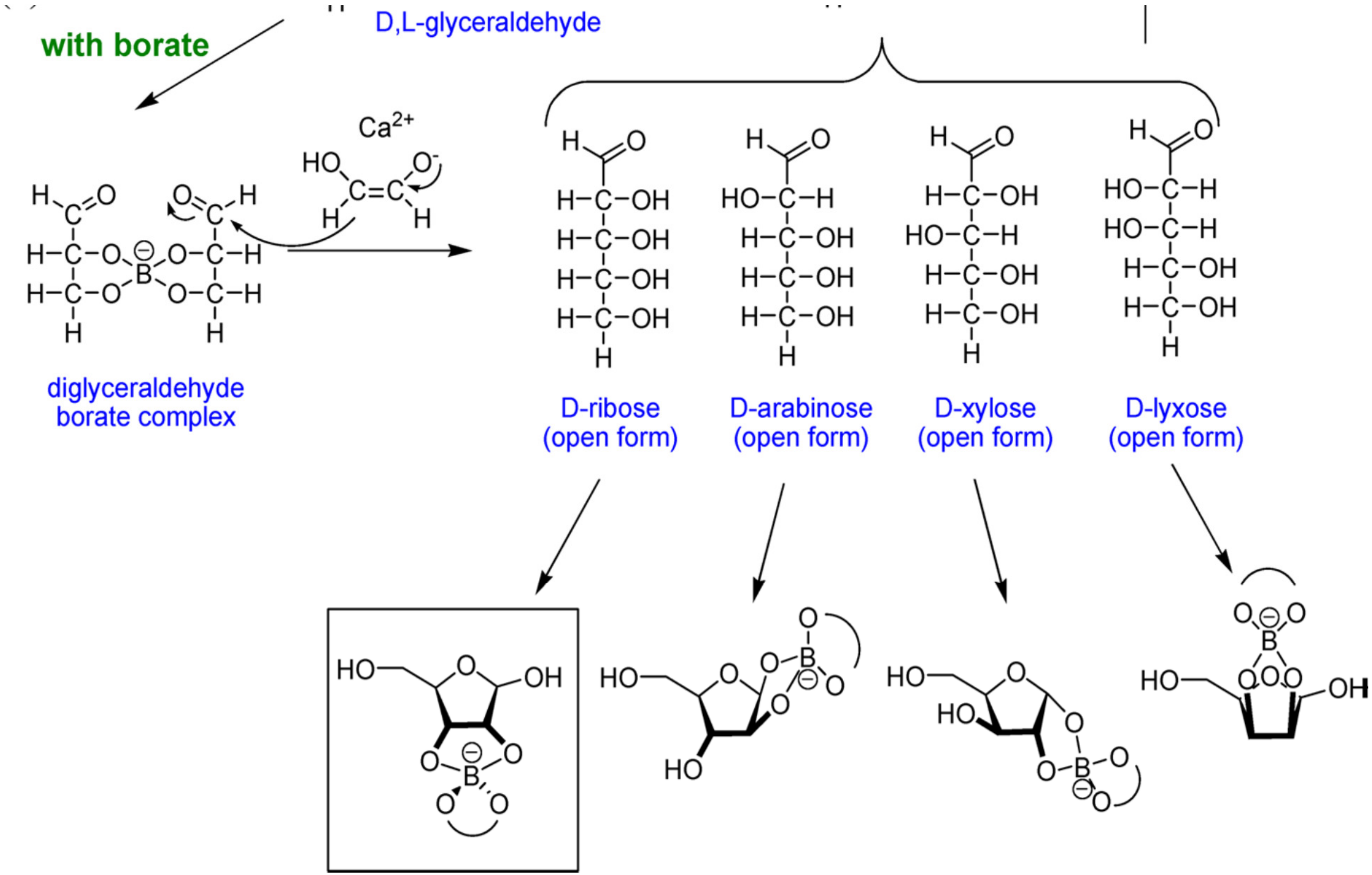
**Pentose formation in the presence of borate**

**With borate (left)**
**Without borate (right)**
**Colemanite (background)**

By NMR, the ribose borate complex **8** has the structure shown; cyclic structures for other pentoses are speculative.

A. Ricardo, M. A. Carrigan, A. N. Olcott, S. A. Benner *Science* **2004**, *303*, 196

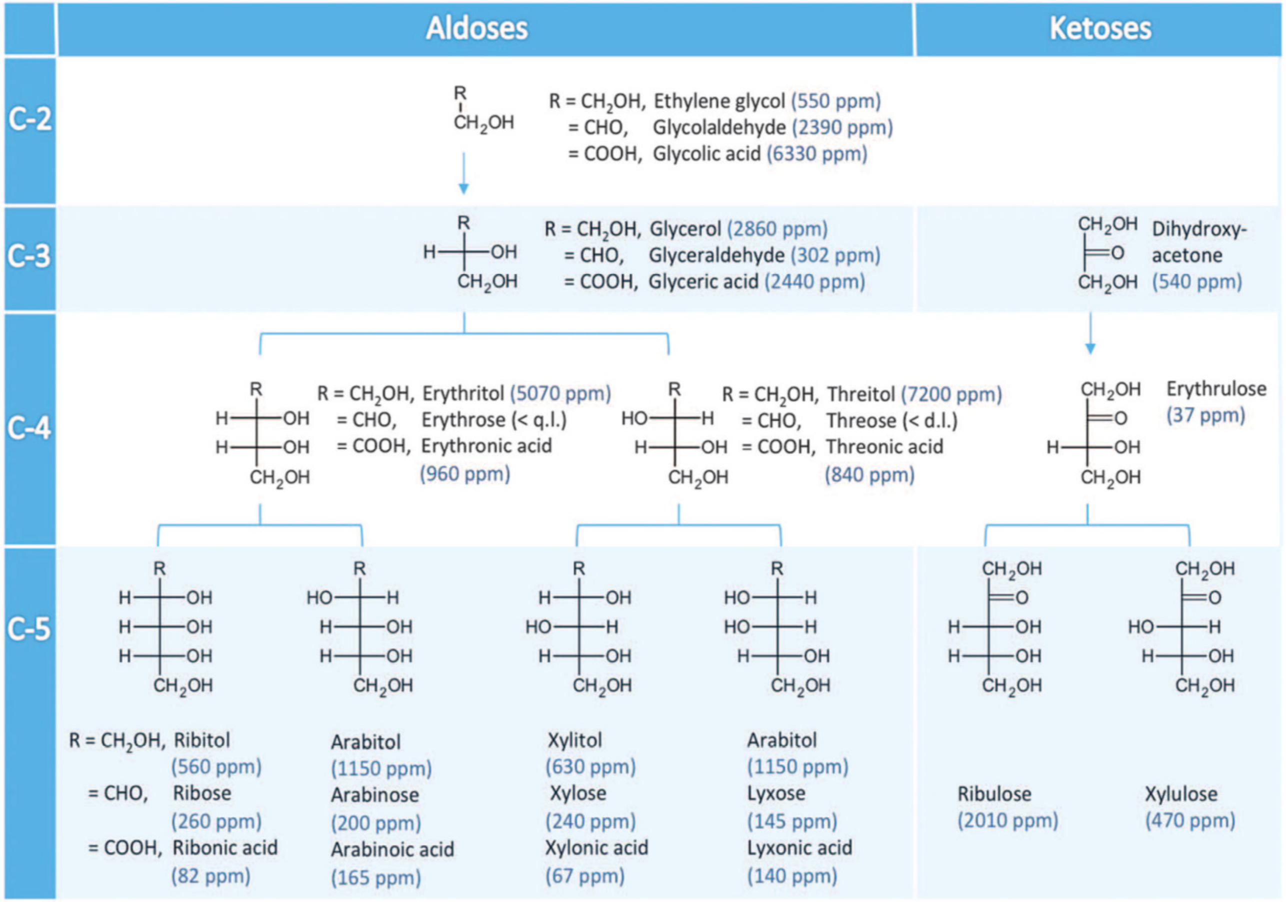
# *Formose reaction in presence of borates*



*Escosura*

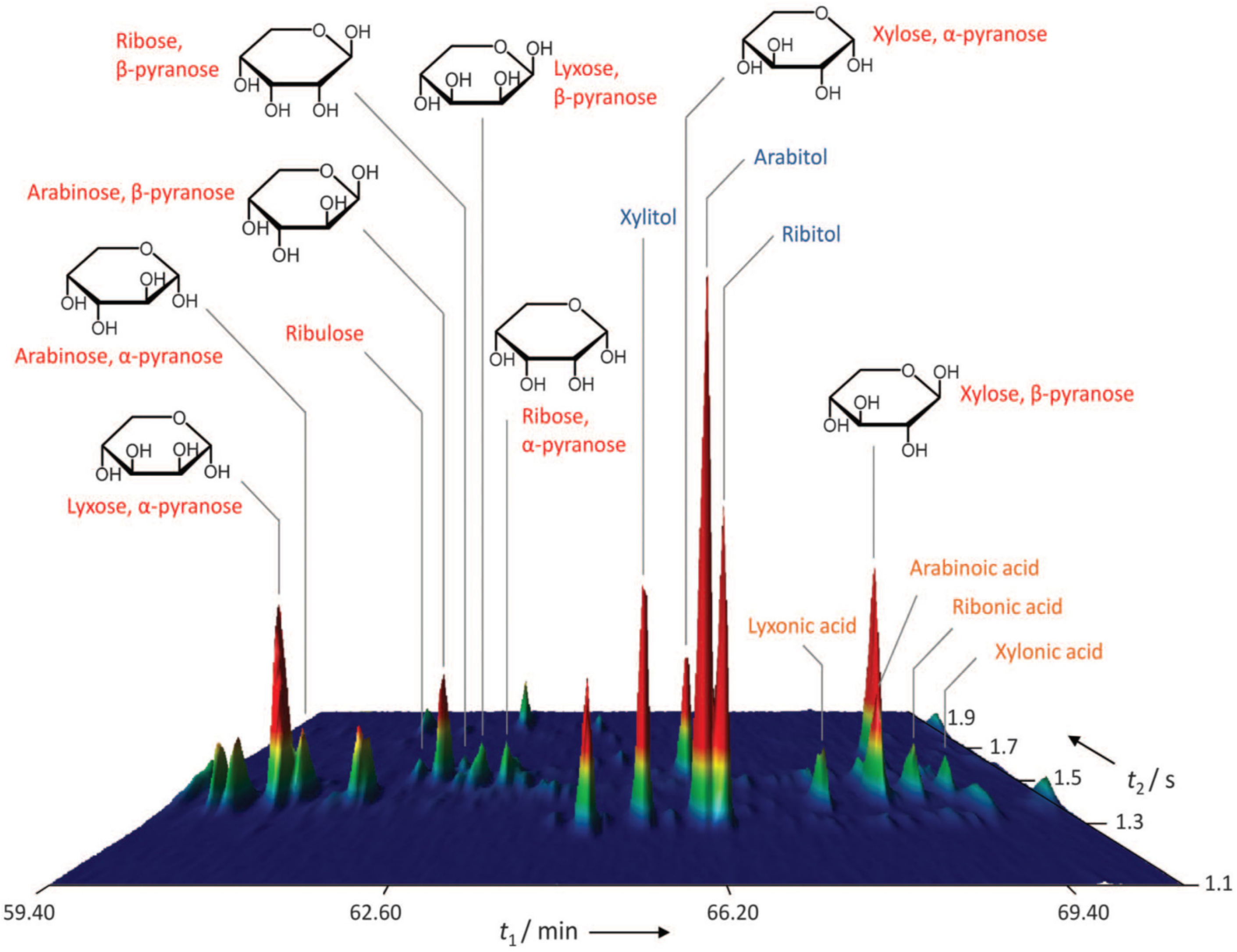
# *Interstellar origin of carbohydrates*

Simulations of photo- and thermochemistry of interstellar ice (silicate/carbon grains surrounded by ice $H_2O$, $CH_3OH$ and $NH_3$) exposed on UV light, low pressure ($10^{-7}$ bar) and temperature (78K) delivers a mixture of sugars



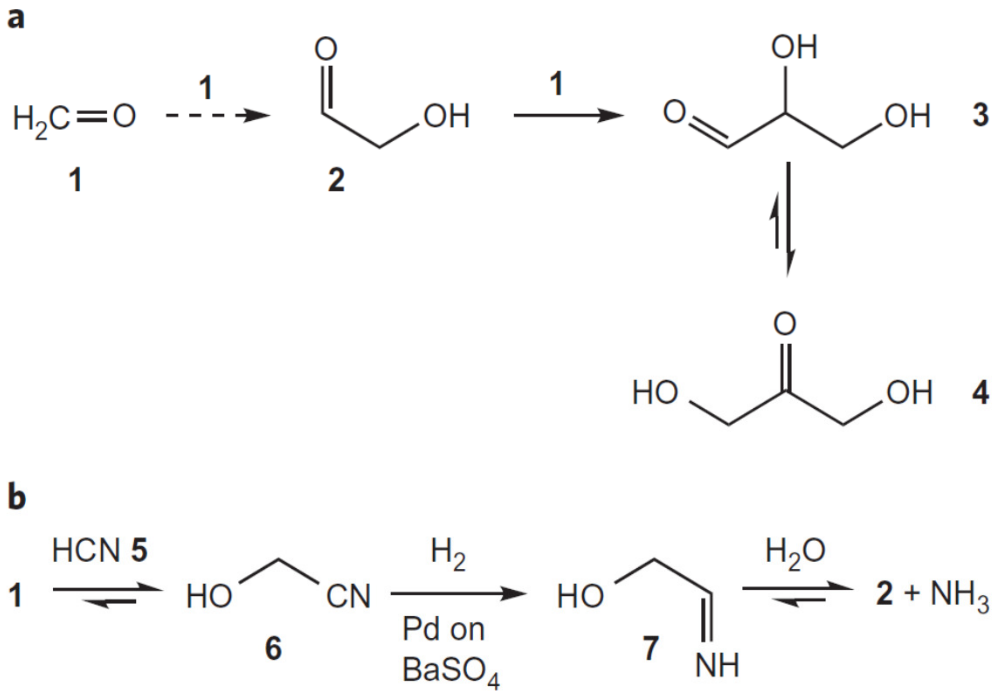
U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

# *Interstellar origin of carbohydrates*



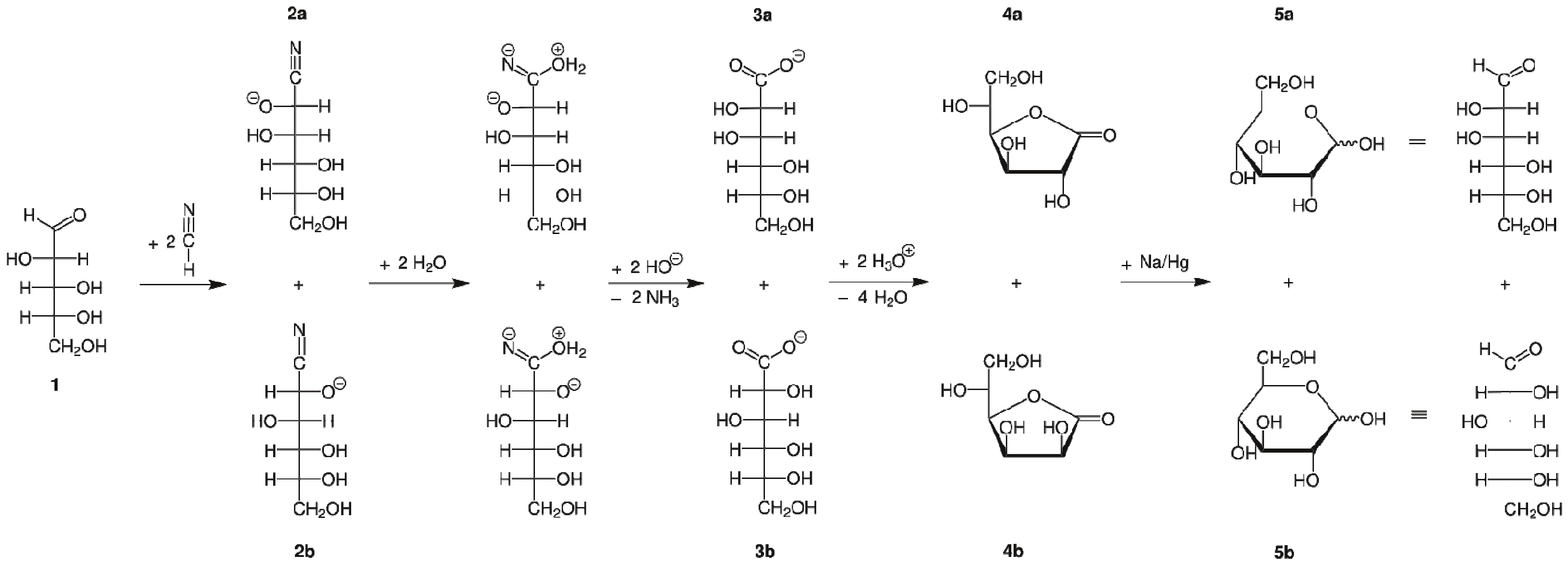
U. Meierhenrich, *et al. Science* **2016**, *352(6282)*, 208-212

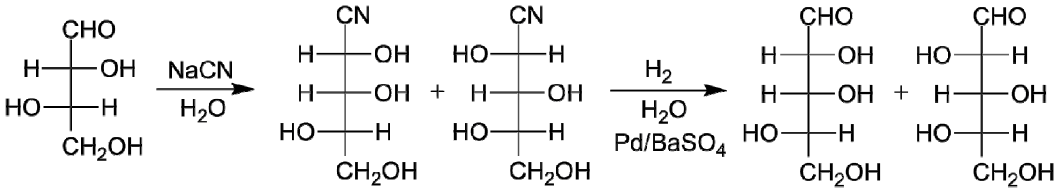
# *Prebiotically plausible alternatives to formose process*



Homologation routes to simple sugars from formaldehyde **1**.
a, Direct homologation of formaldehyde **1** is problematic, because the first dimerization step (dashed) requires umpolung, and because the trimer is more stable as the ketose **4** than the aldose **3** under conditions where **3** can be formed from **1** and **2**. b, Kiliani–Fischer homologation of **1** in conventional synthetic chemistry involves favourable formation of the cyanohydrin **6** by reaction of **1** with hydrogen cyanide **5**, followed by the selective reduction of **6** using very specific conditions.

# *Kiliani-Fischer homologation*

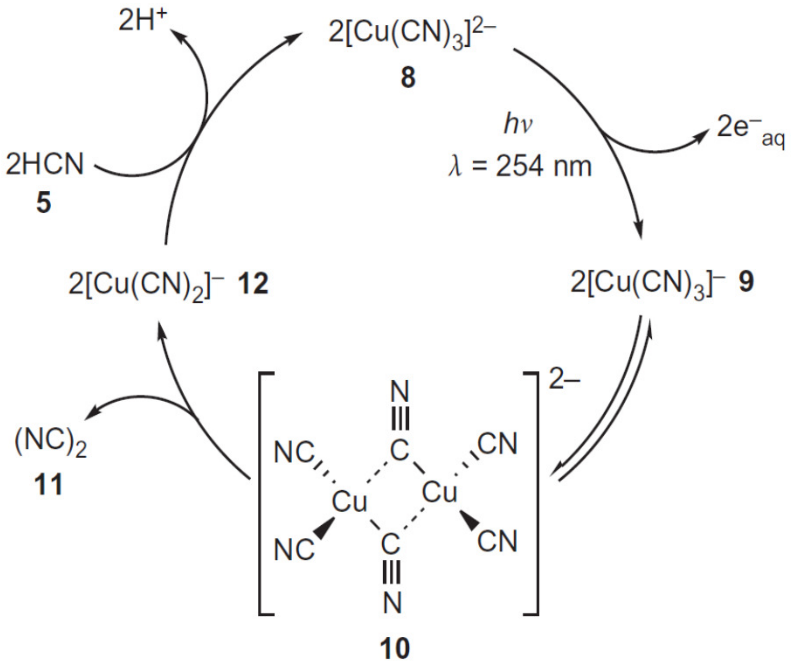


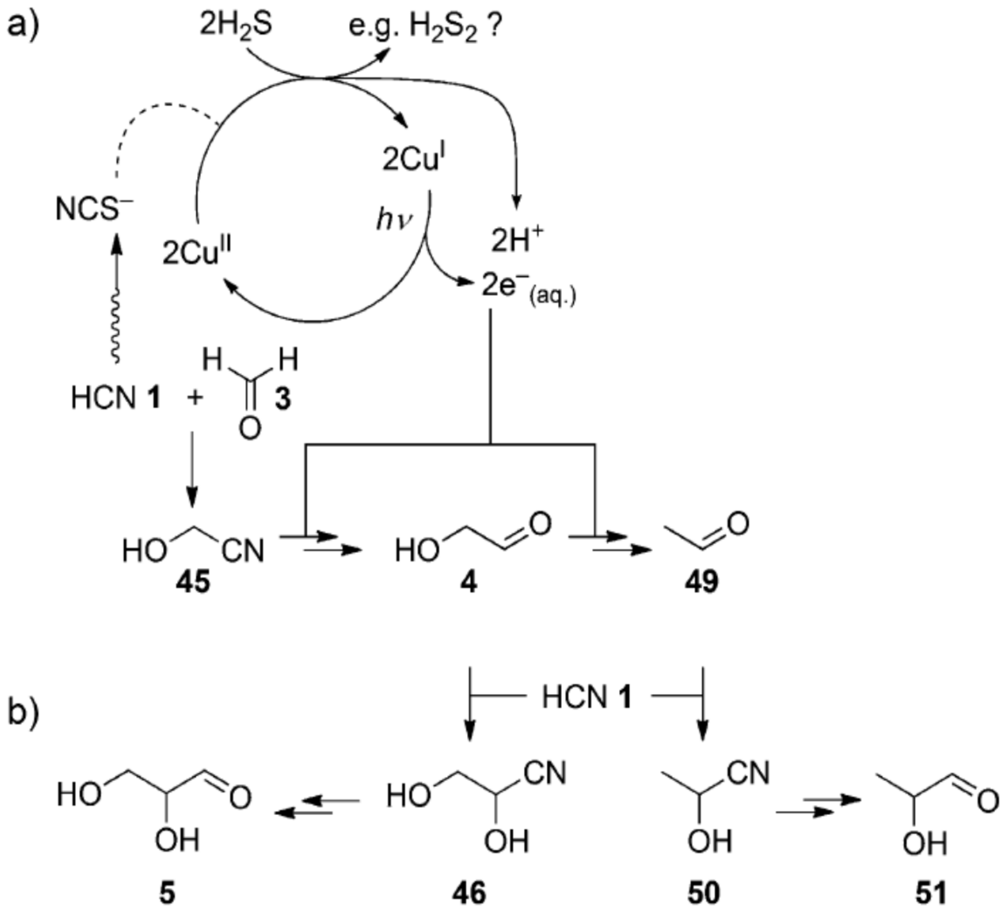


# *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*

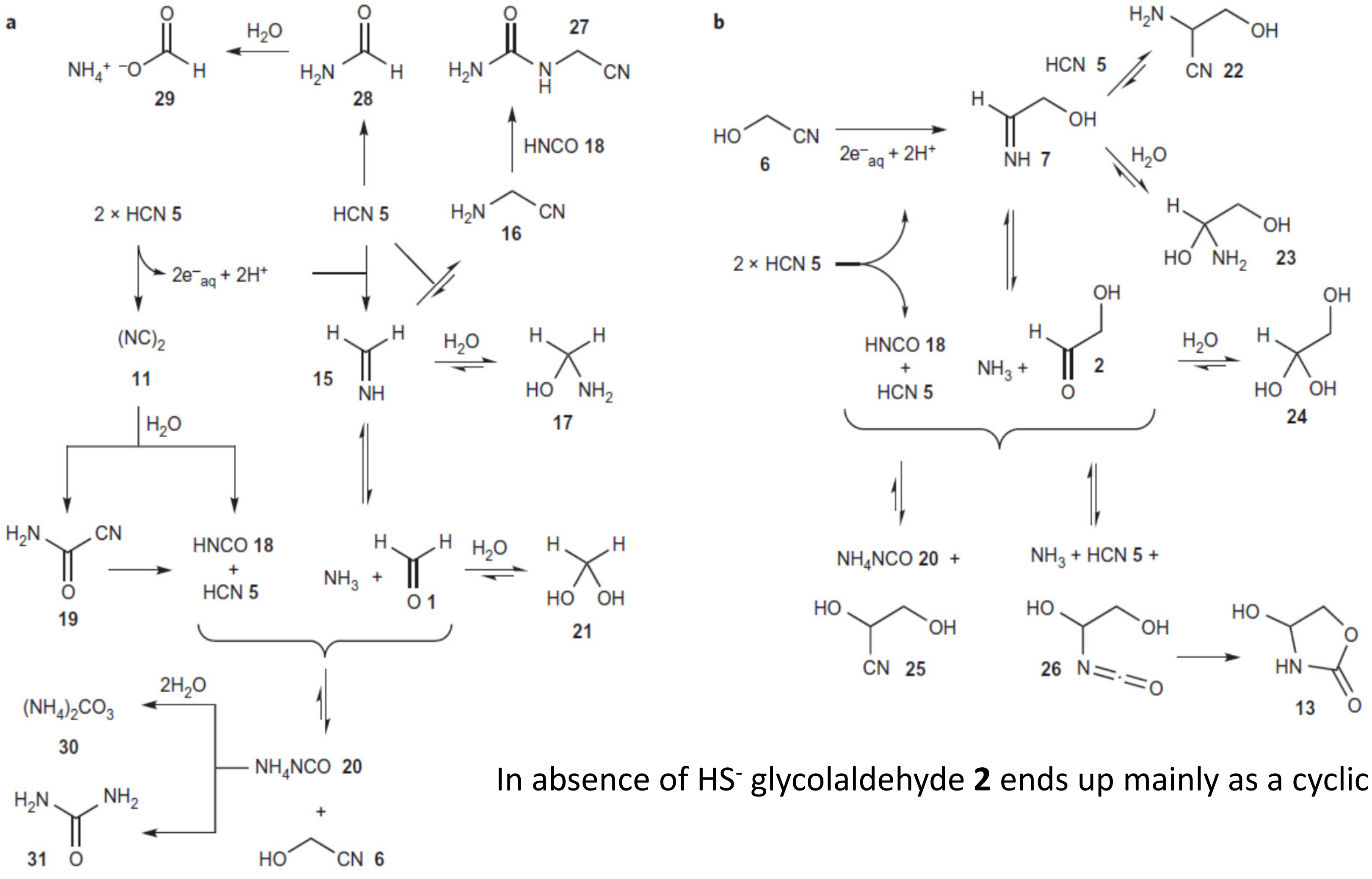
$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen



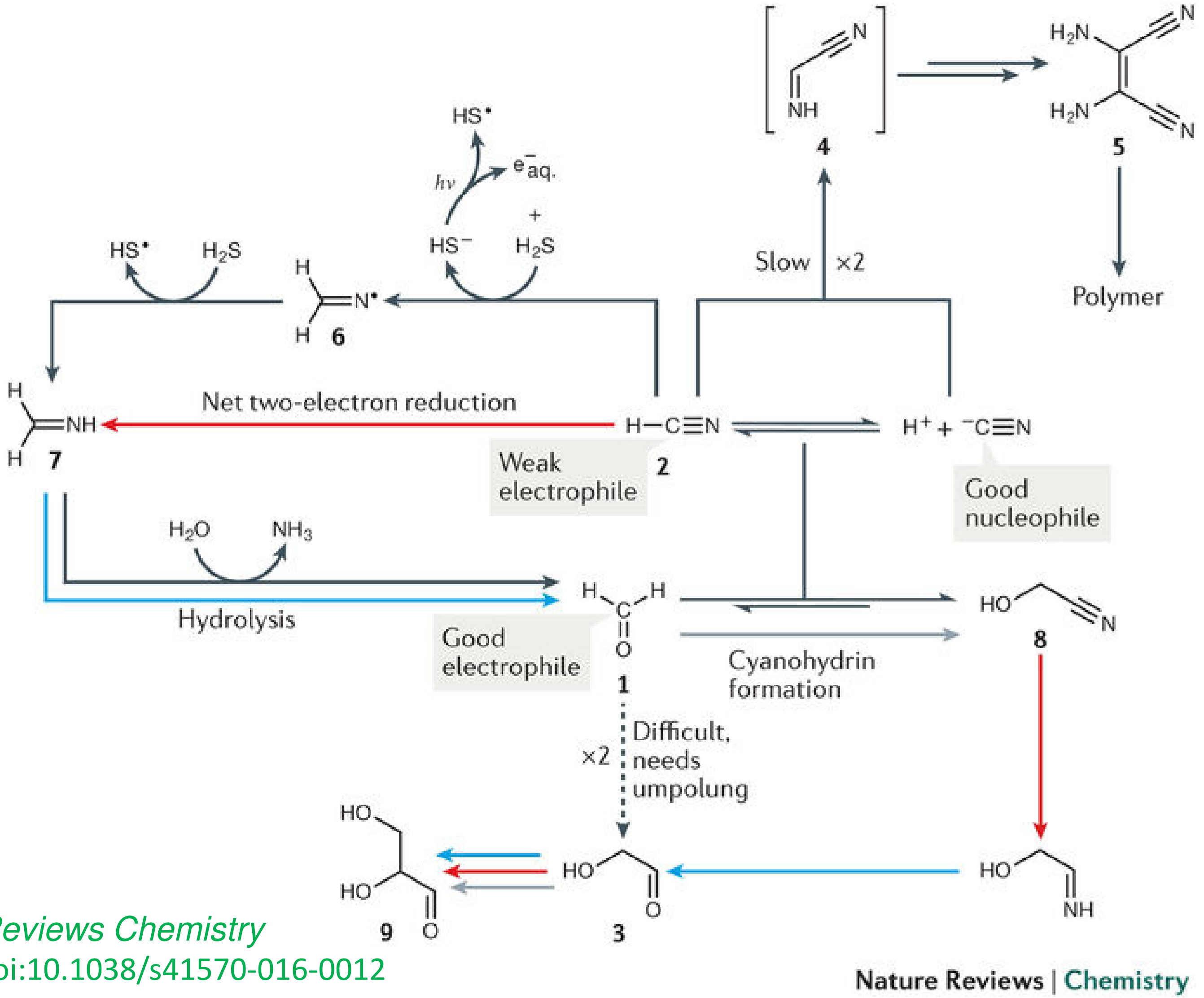


# *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*



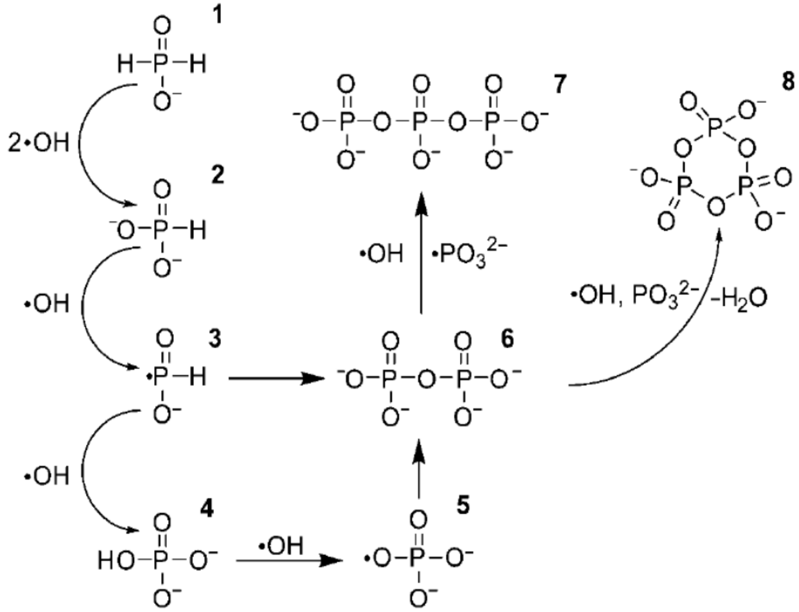
In absence of HS$^-$ glycolaldehyde **2** ends up mainly as a cyclic derivative **13**

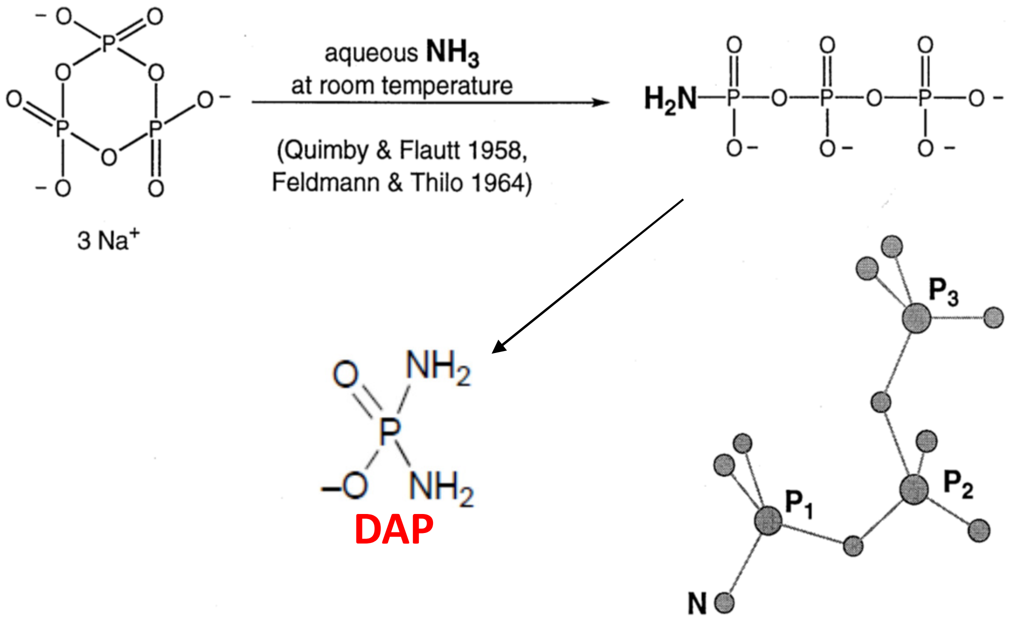
# *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*



J. Sutherland, *Nature Reviews Chemistry*
**2017**, *1*, Article 0012, doi:10.1038/s41570-016-0012

# *Phosphorylation reagents*

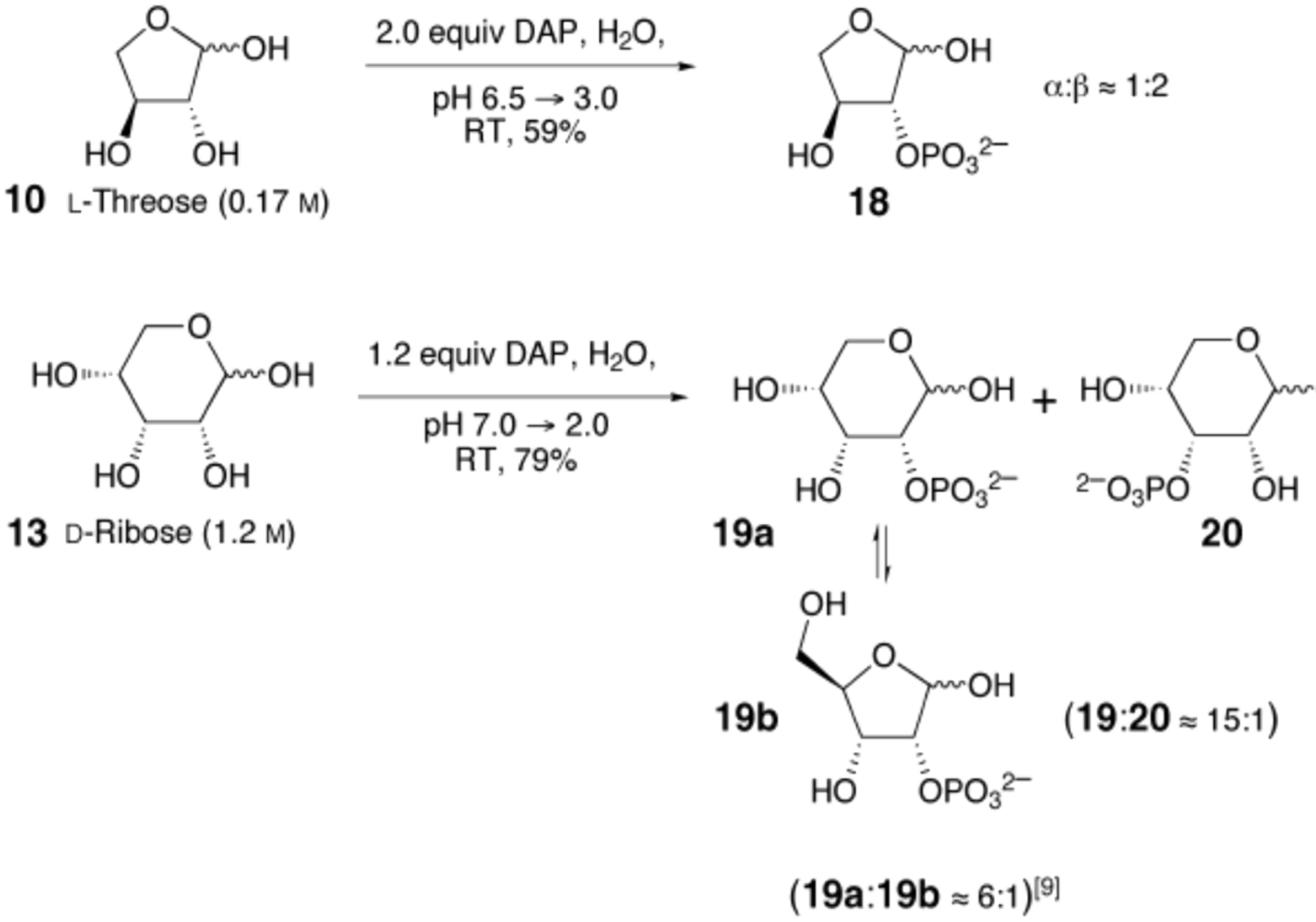


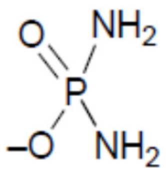


x-ray structure of $K_4(P_3O_9NH_2)$ (Hilmer, 1965)

M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920     A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

# *Phosphorylation reagents*

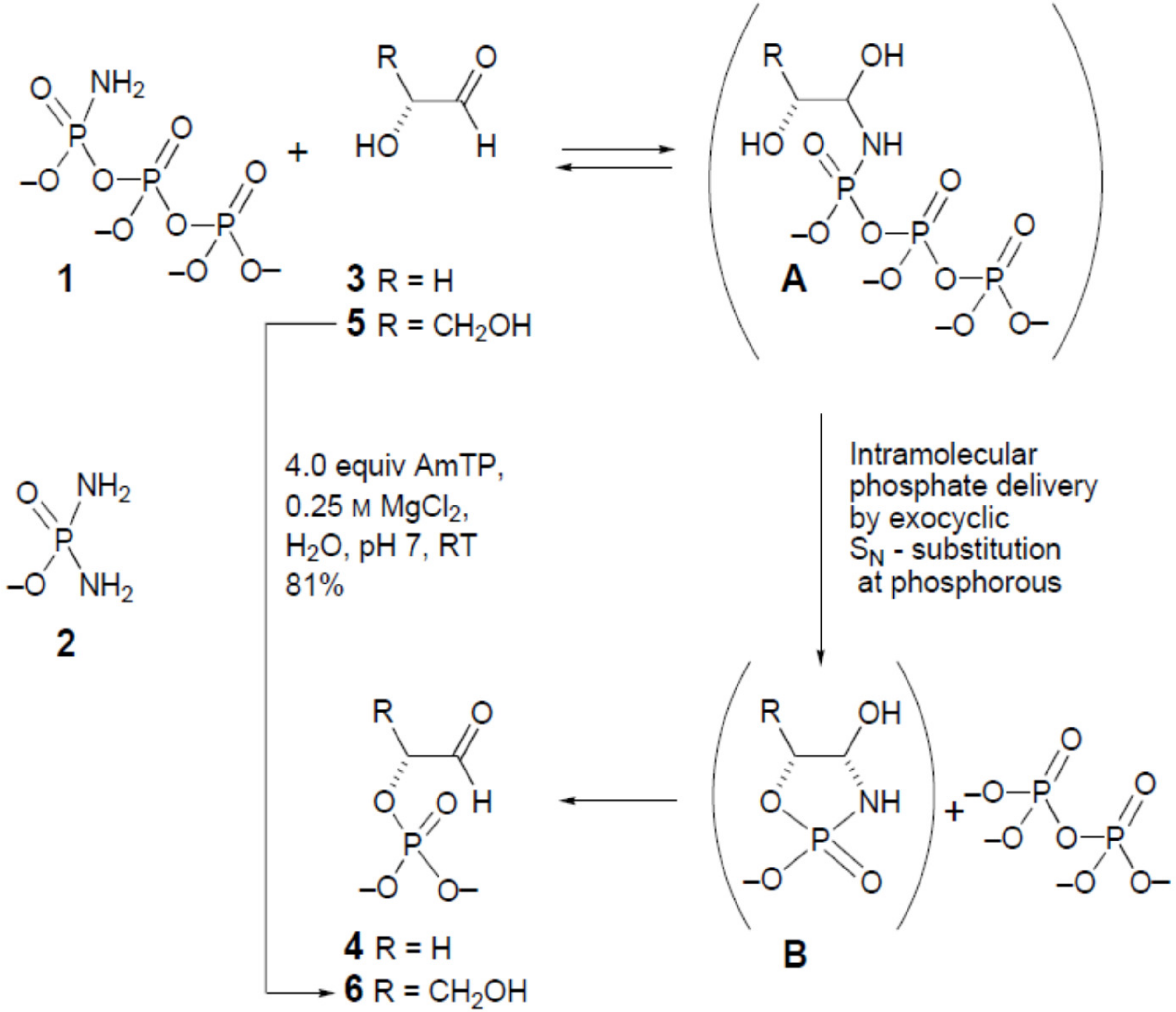




**DAP**

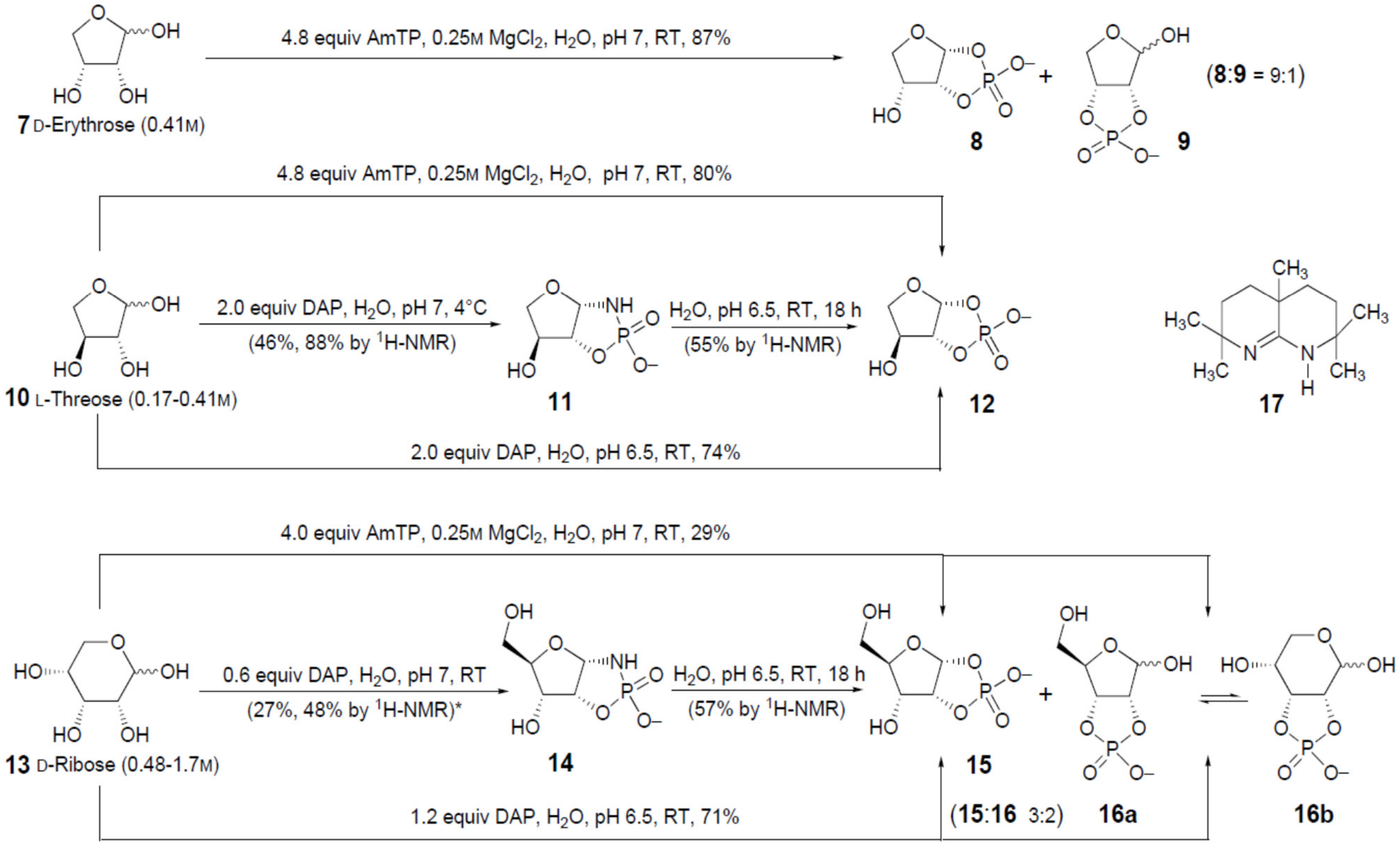
M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920  A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

# *Phosphorylation of sugars*



A. Eschenmoser, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2281-2285

# *Phosphorylation of sugars*



A. Eschenmoser, *et al. Angew. Chem. Int. Ed.* **2000**, *39*, 2281-2285

# *Carbohydrates - summary*

Formose reaction gives access to numerous $C_2$-$C_5$ and higher carbohydrates, but is difficult to direct towards particular outcome, and ultimately turns into polymeric tar if overcooked

In presence of borates, the formose reaction tends to deliver protected pentoses in high yields and stable form

Although formaldehyde is the simplest starting material, the reaction is autocatalytic in glycolaldehyde and without it long incubation period is required

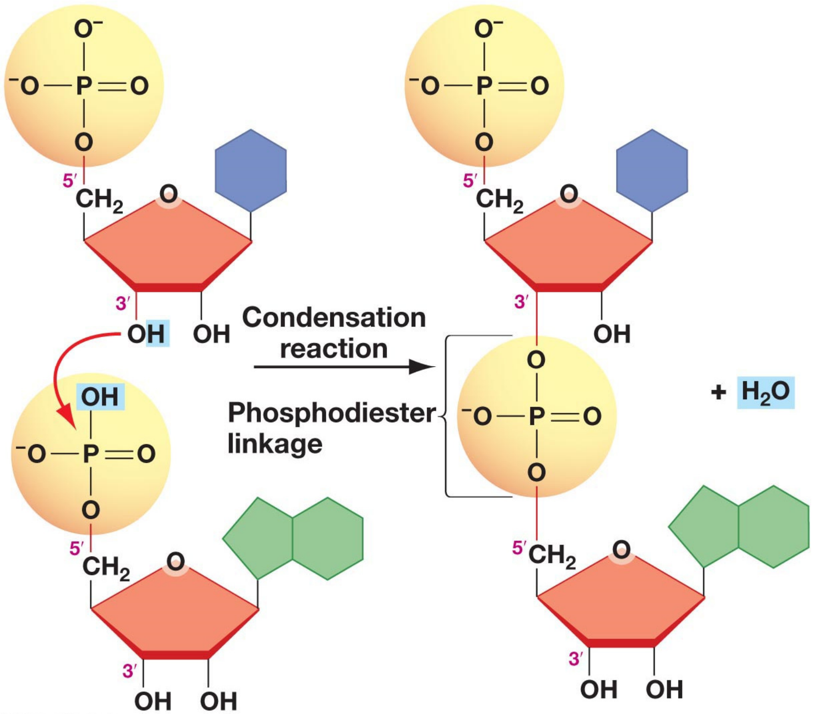
Carbohydrate synthesis can also occur under simulated extraterrestrial conditions – by UV-light irradiation of cometary ice

Alternative prebiotic synthesis of simple carbohydrates involves Kiliani-Fischer homologation process based on HCN in presence of copper ions and hydrosulfides – all accessible by the meteorite-derived cyanide-metal chemistry

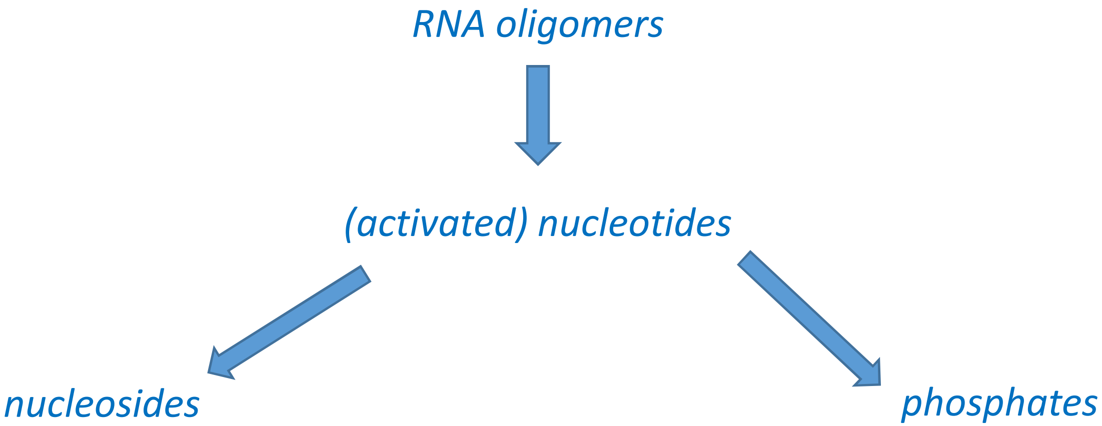
The same type of chemistry can also deliver a set of reactive intermediates like cyanogen, acetylene, ammonia, and activated forms of phosphate – the latest can derivatize sugars and, after redox processes, deliver numerous building blocks present in currently known metabolic cycles

# *Nucleotide polymerization*

*Regioselective formation of 3’-5’ phosphodiester bonds between nucleotides*



## *RNA oligomers – prebiotic disconnections*



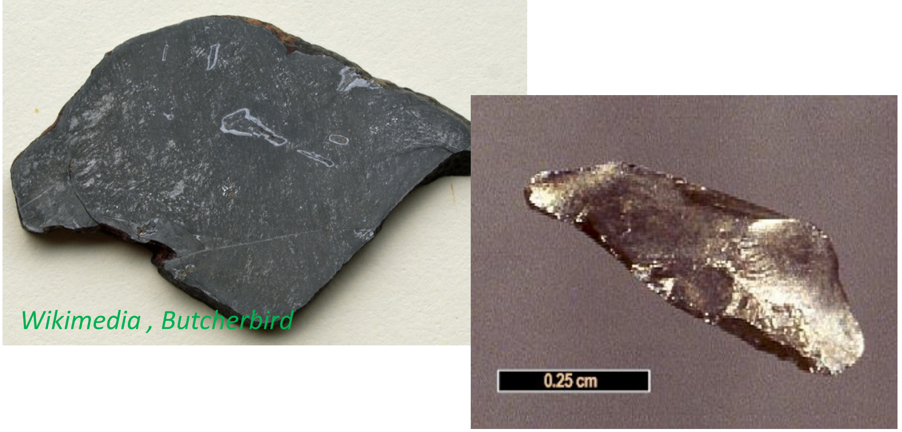
*RNA oligomers*

*(activated) nucleotides*

*nucleosides*

*phosphates*

# Phosphates



Wikimedia , Butcherbird

**Schreibersite** $(Fe,Ni)_3P$, common in iron-nickel meteorites

**HCN** – burning of carbon-rich meteorites into redox-neutral atmosphere ($N_2$ and $H_2O$)

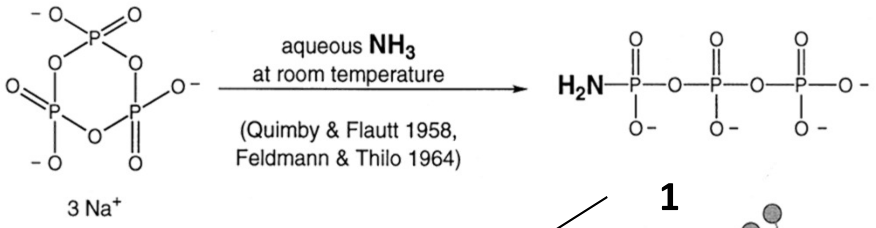
$$(Fe,Ni)_3P + HCl_{aq} \rightarrow H_2PO_3^-$$

$$Fe^{2+} + PO_4^{3-}\ (pH \sim 7) \rightarrow Fe_3(PO_4)_2\ (\textbf{vivianite})$$

***vivianite***

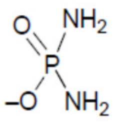
Wikimedia , Carles Millan

$$Fe_3(PO_4)_2 + 18CN^-_{aq} \rightarrow 2PO_4^{3-} + 3[Fe(CN)_6]^{4-}$$

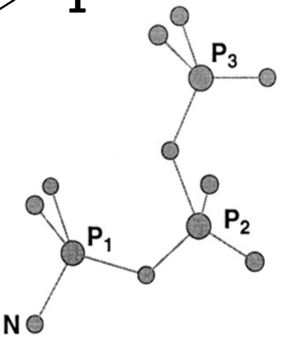


**1**

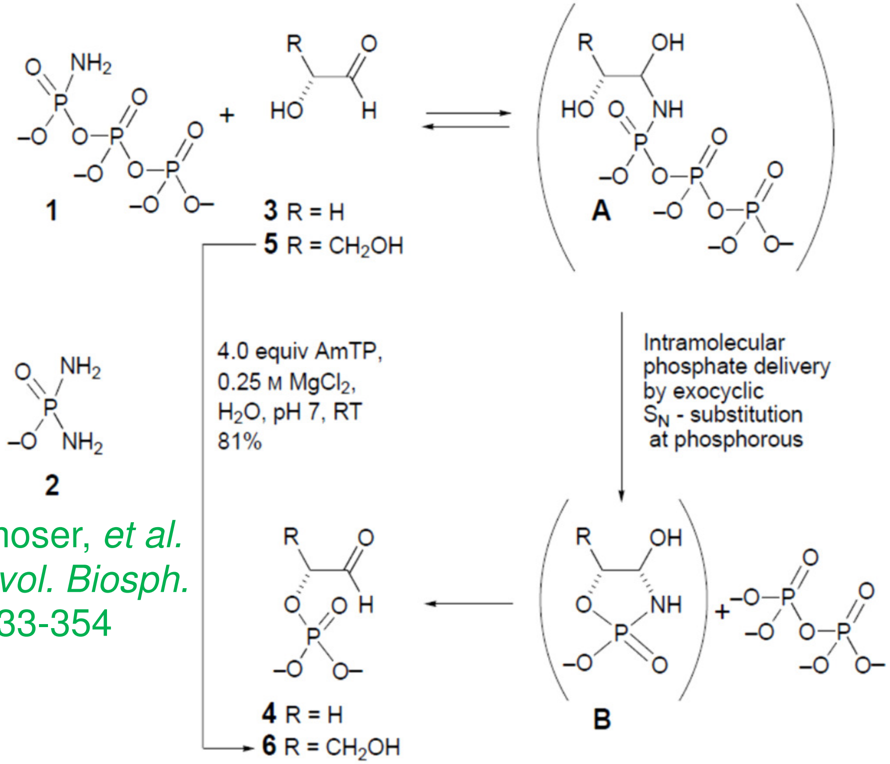
M. A. Pasek, *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 7918-7920



**2**
**DAP**

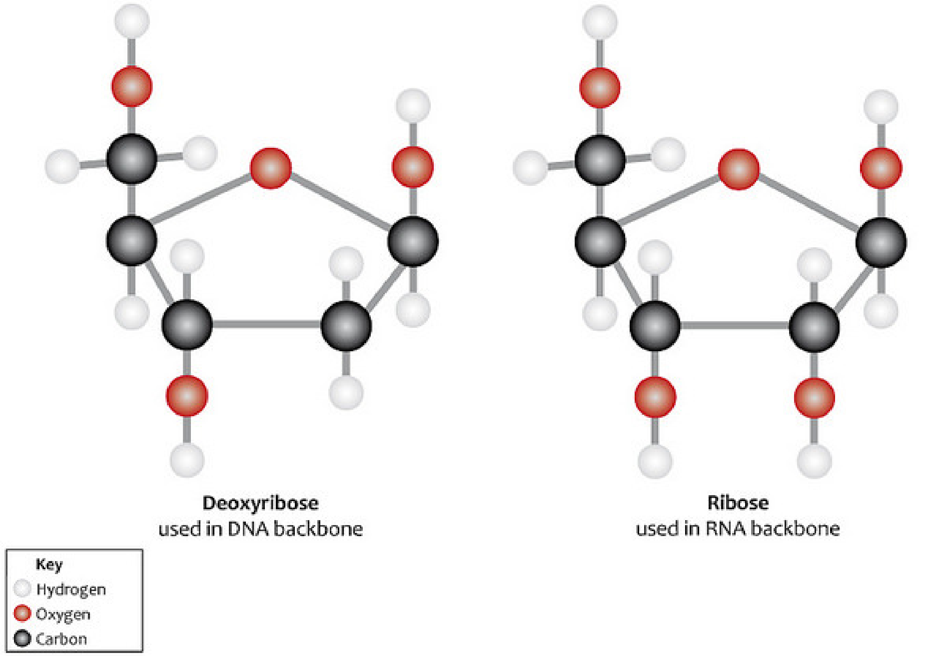


x-ray structure of $K_4(P_3O_9NH_2)$ (Hilmer, 1965)



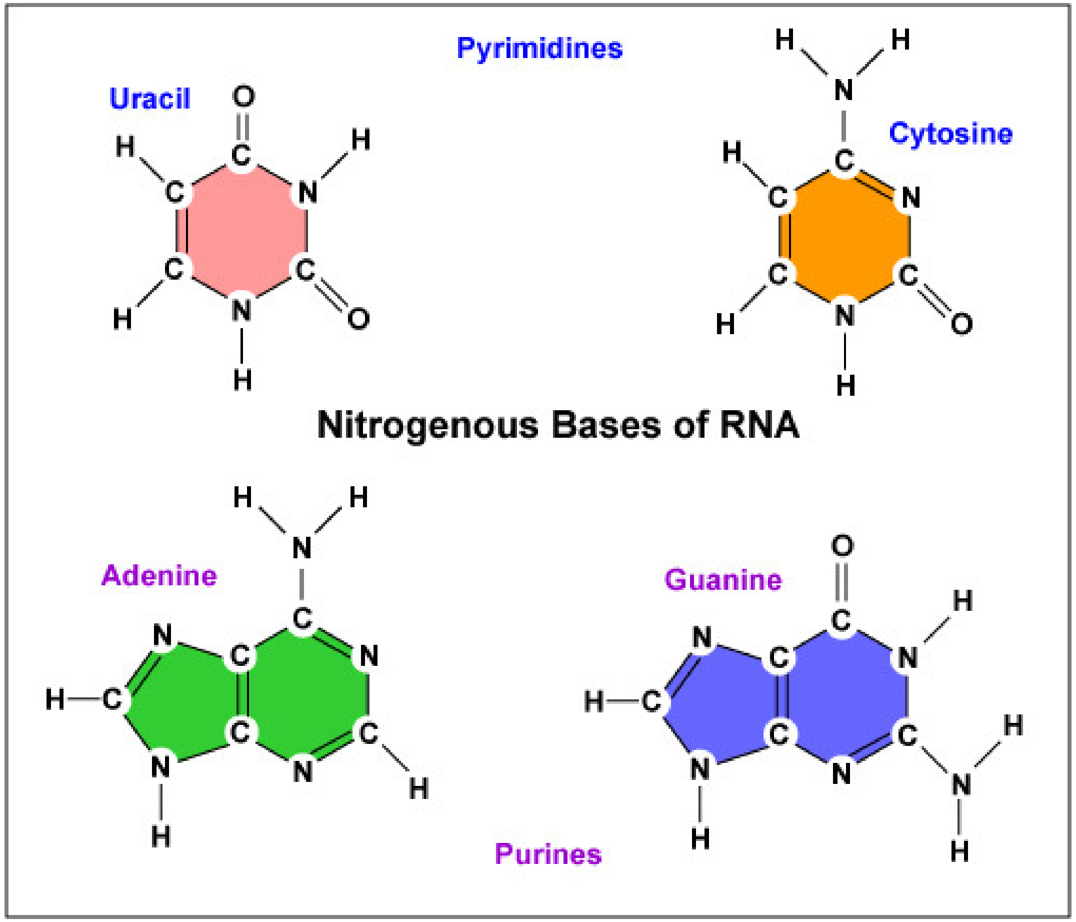
A. Eschenmoser, *et al. Orig. Life Evol. Biosph.* **1999**, *29*, 333-354

# *Nucleosides - nucleobases + sugars*



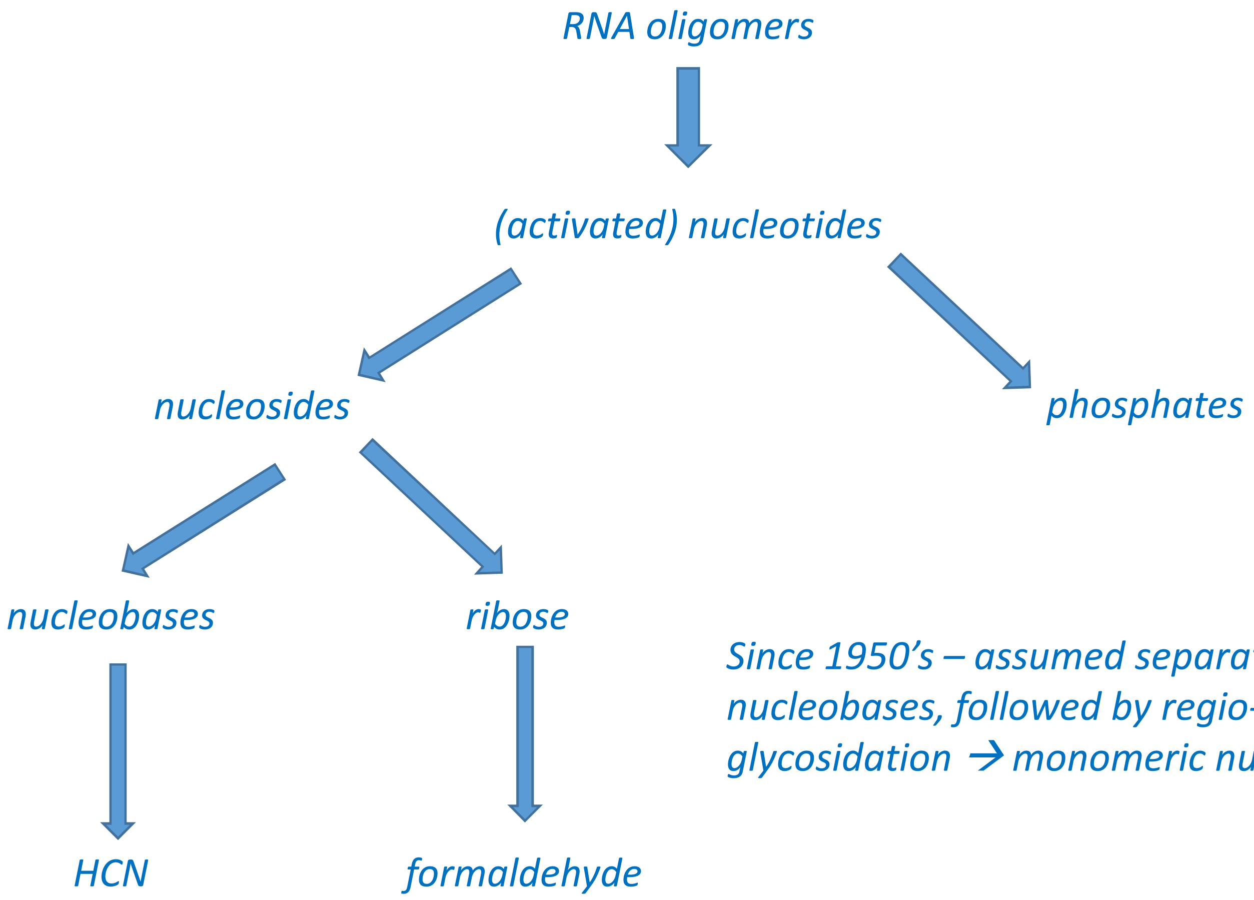
**Deoxyribose**
used in DNA backbone

**Ribose**
used in RNA backbone



*Since 1950's – assumed separate synthesis of sugars and nucleobases, followed by regio- and diastereoselective glycosidation → monomeric nucleotides*

# ***RNA oligomers – prebiotic disconnections***



*RNA oligomers*

*(activated) nucleotides*

*nucleosides*

*phosphates*

*nucleobases*

*ribose*

*HCN*

*formaldehyde*

*Since 1950's – assumed separate synthesis of sugars and nucleobases, followed by regio- and diastereoselective glycosidation → monomeric nucleotides*

# *Literature sources*

J. Oro, *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407–412.

J. D. Sutherland, *Cold Spring Harbor Perspect. Biol.* **2010**, 2, a005439.

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

J. D. Sutherland, *Angew. Chem. Int. Ed.* **2016**, *55*, 104-121.

B. H. Patel, C. Percivalle, D. J. Ritson, C. D. Duffy, J. D. Sutherland, *Nat. Chem*. **2015**, *7*, 301–307.

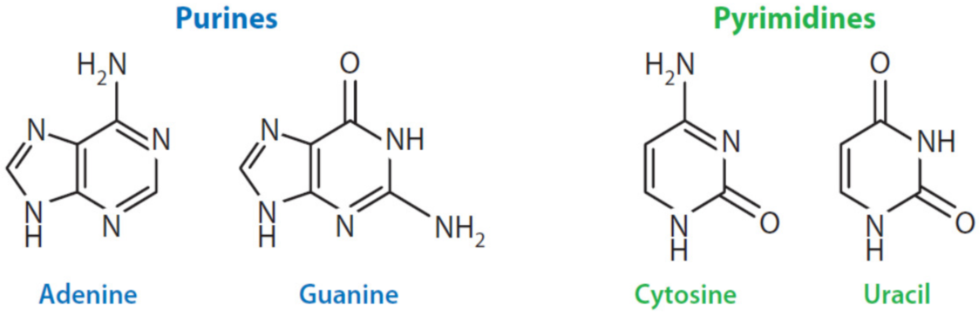
J. D. Sutherland, *et al. Nat. Chem*. **2013**, *5*, 383–389.

L. E. Orgel, *Crit. Rev. Biochem. Mol. Biol.* **2004**, *39*, 99-123.

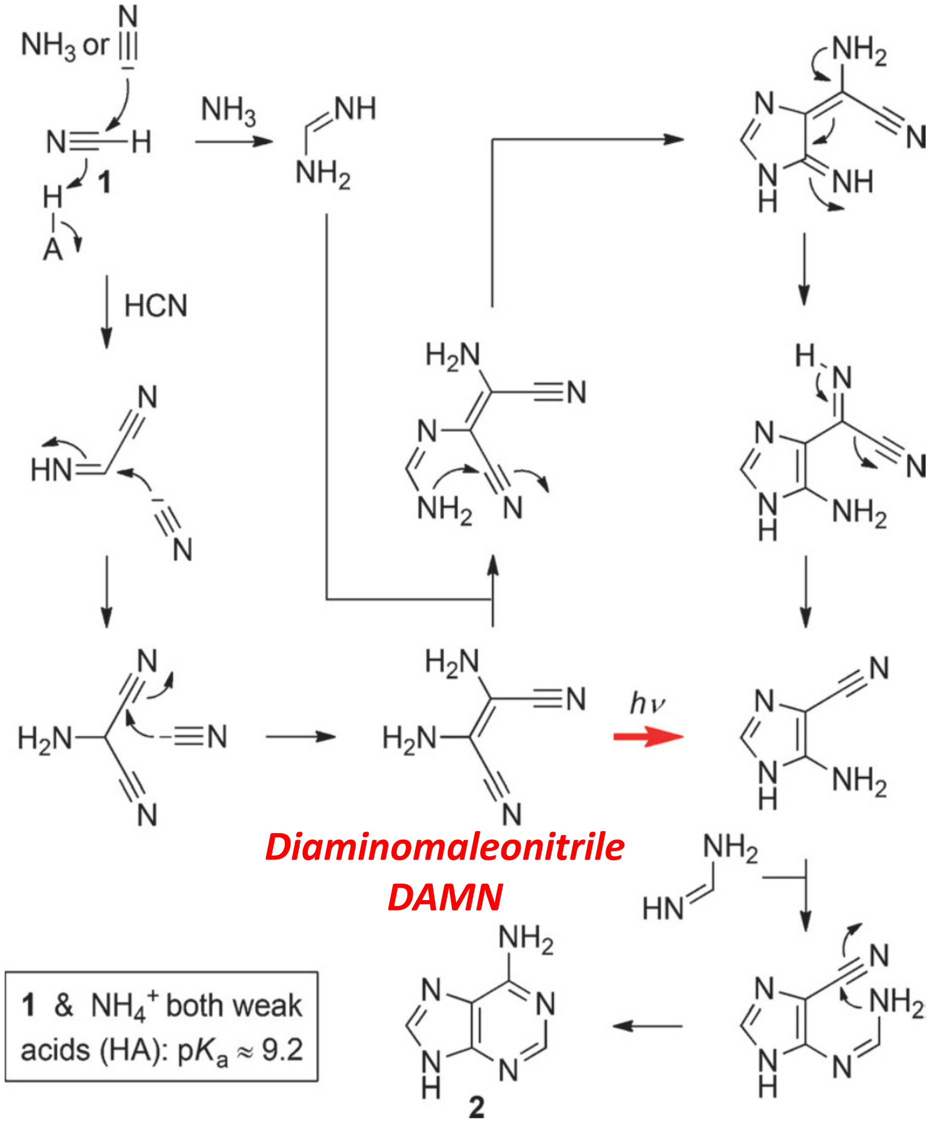
Powner, M. W.; Sutherland, J. D.; Szostak, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 16677

T. Carell, *Nature* **2016**, *352(6287)*, 833-836

# *Prebiotic synthesis of nucleobases*



# *Prebiotic synthesis of adenine – the pentamer of HCN!*



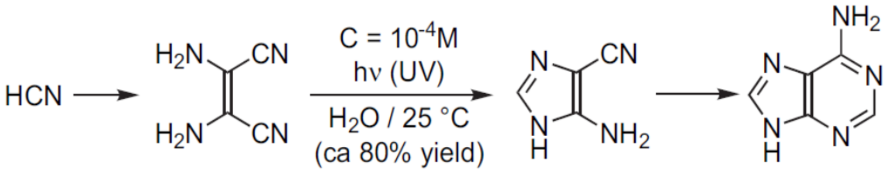
***Diaminomaleonitrile***
***DAMN***

**1** & $NH_4^+$ both weak acids (HA): p$K_a$ ≈ 9.2

1960 - Oró’s synthesis of adenine **2** from hydrogen cyanide **1** and ammonia (general acid–base catalysis, presumed to operate in most steps, is only shown once).
Heating ammonium cyanide at $70^0$C for a few days
→ 0.5% adenine
Heating HCN with liquid ammonia in a sealed tube → 20% adenine

The photochemical shortcut discovered by Ferris and Orgel is shown by the red arrow.
Optimized yields – up to 20% for adenine, 3% for guanine

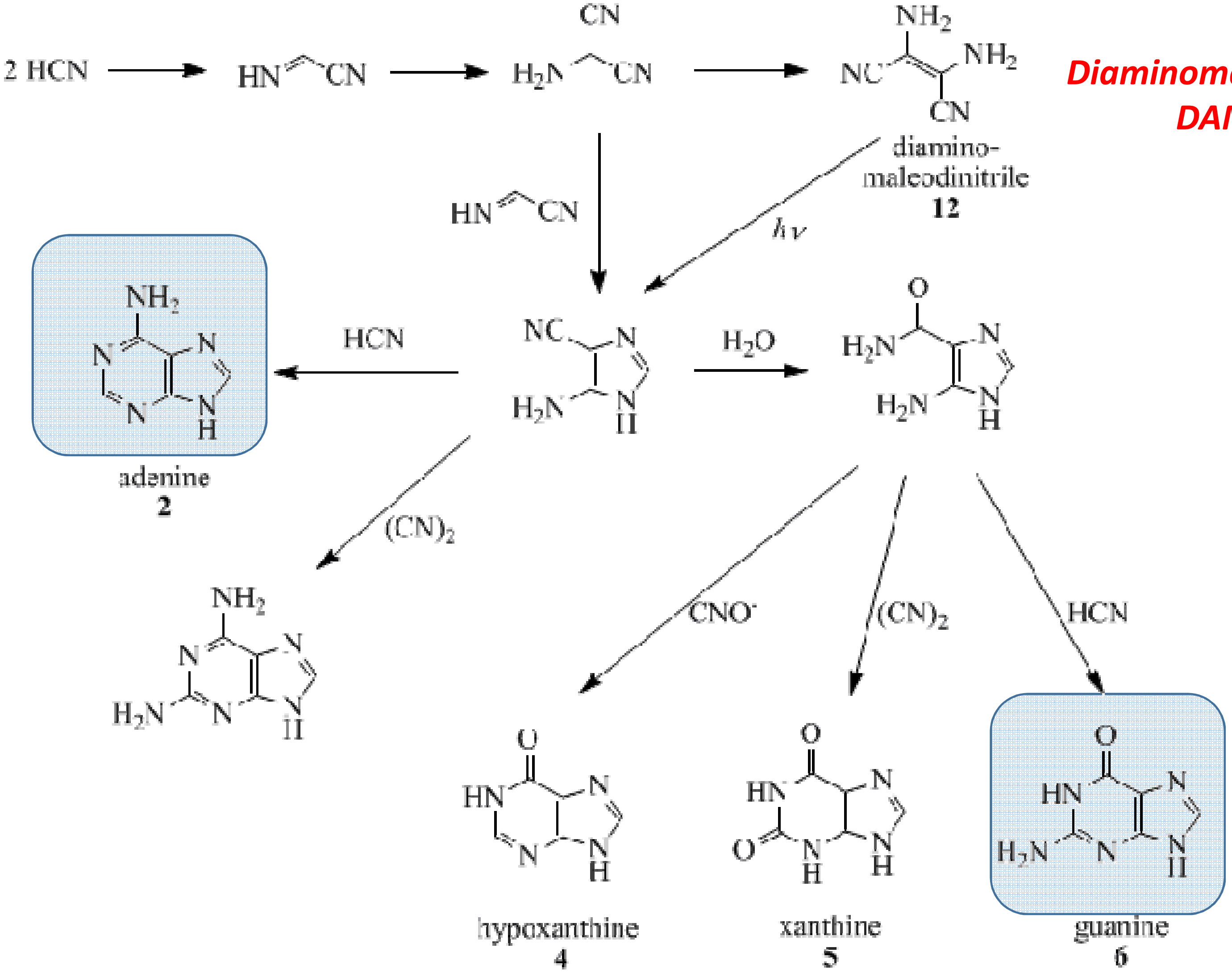
Eutectic freezing ($-20^0$C) increases the yield of DAMN formation by concentrating HCN between pure ice crystals



J. Oro *Biochem. Biophys. Res. Commun.* **1960**, *2*, 407.

J. P. Ferris, L. E. Orgel, *J. Am. Chem. Soc.* **1966**, *88*, 1074

# *Prebiotic synthesis of purines*

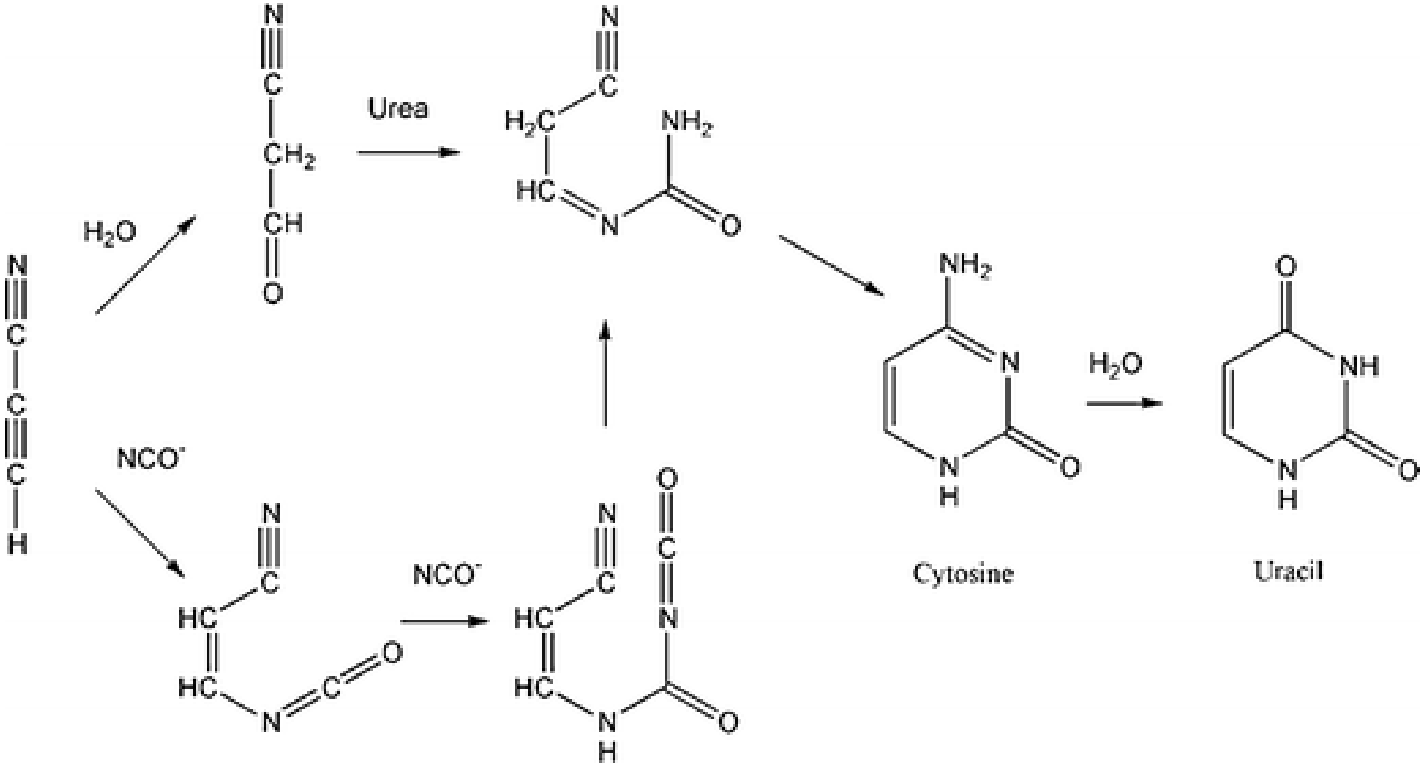


***Diaminomaleonitrile***
***DAMN***

# *Prebiotic synthesis of pyrimidines*

**Cyanoacetylene** is a major product of electric discharges in the mixture of nitrogen and methane

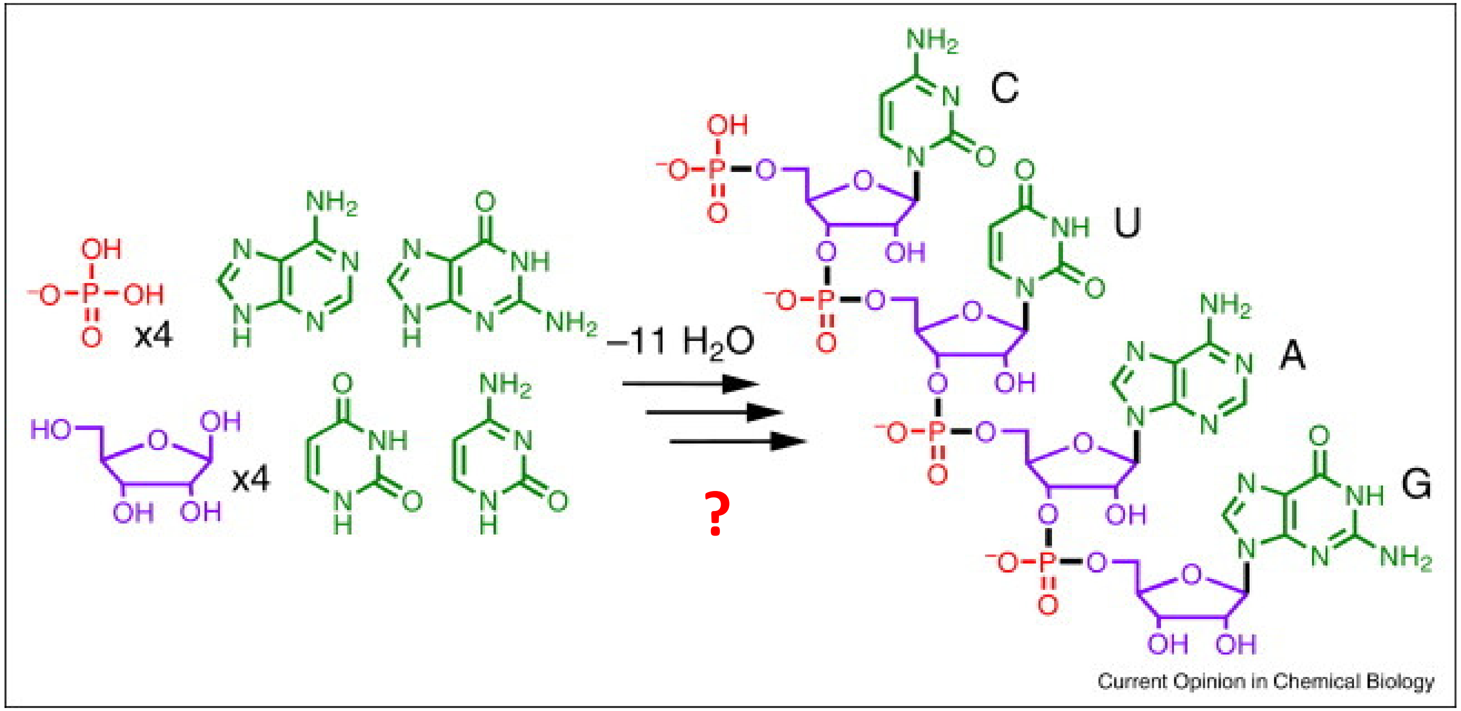
**Cyanoacetylene** can be hydrolysed to cyanoacetaldehyde. That compound can condense with urea to form cytosine



**Cyanoacetylene** incubated with saturated solution of urea yields up to 50% **cytosine**.
Other methods typically yield up to 5% cytosine.It is further converted to uracil by hydrolysis.

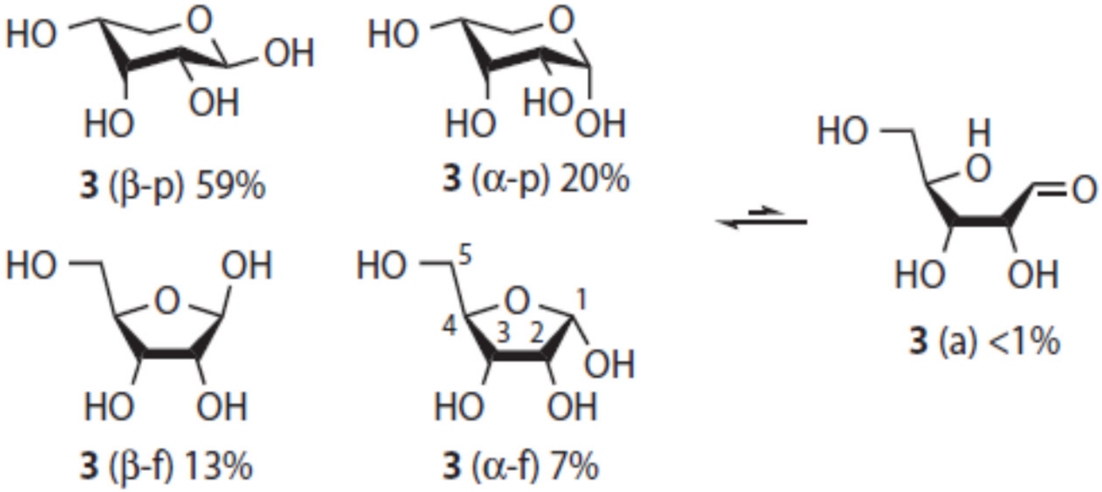
*R. Shapiro PNAS* **1999**, *96,* 4396-4401

# *Prebiotic synthesis of nucleosides, nucleotides and RNA*



Current Opinion in Chemical Biology

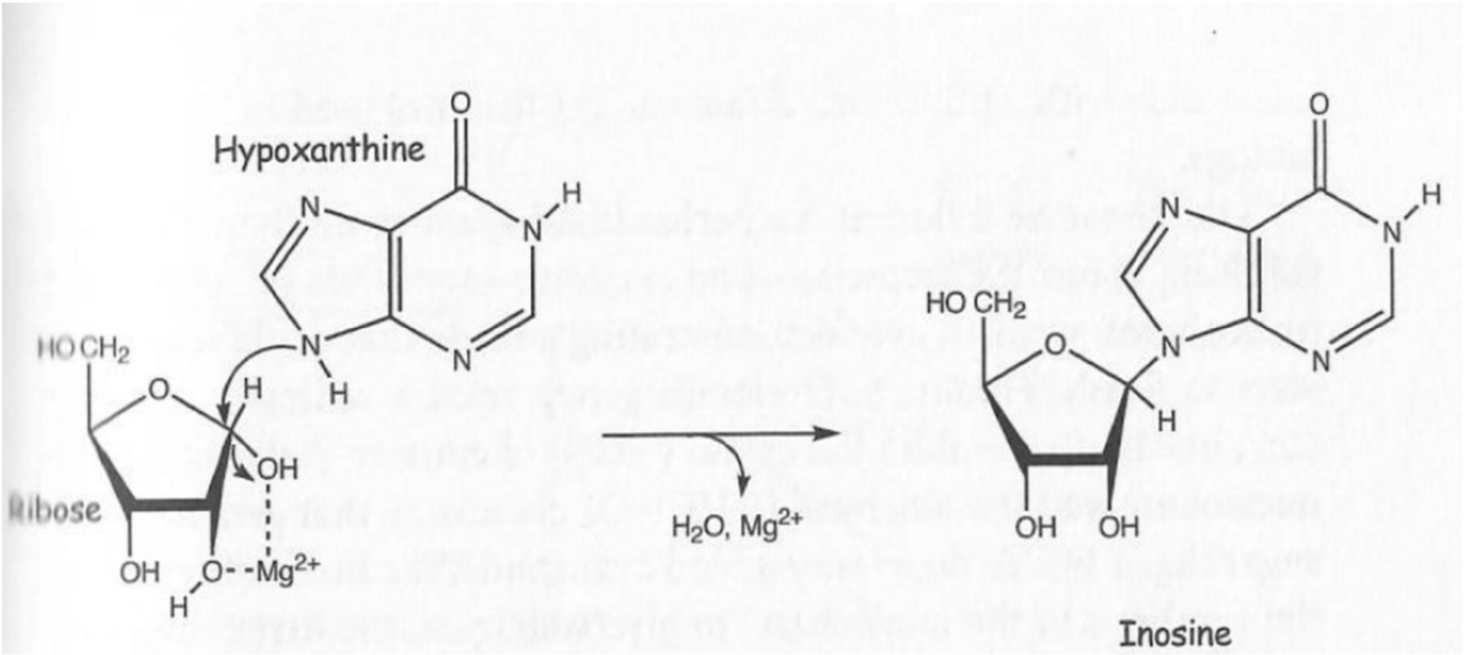
# *Prebiotic synthesis of nucleosides*



The difficulties of assembling beta-ribonucleosides by nucleobase ribosylation:

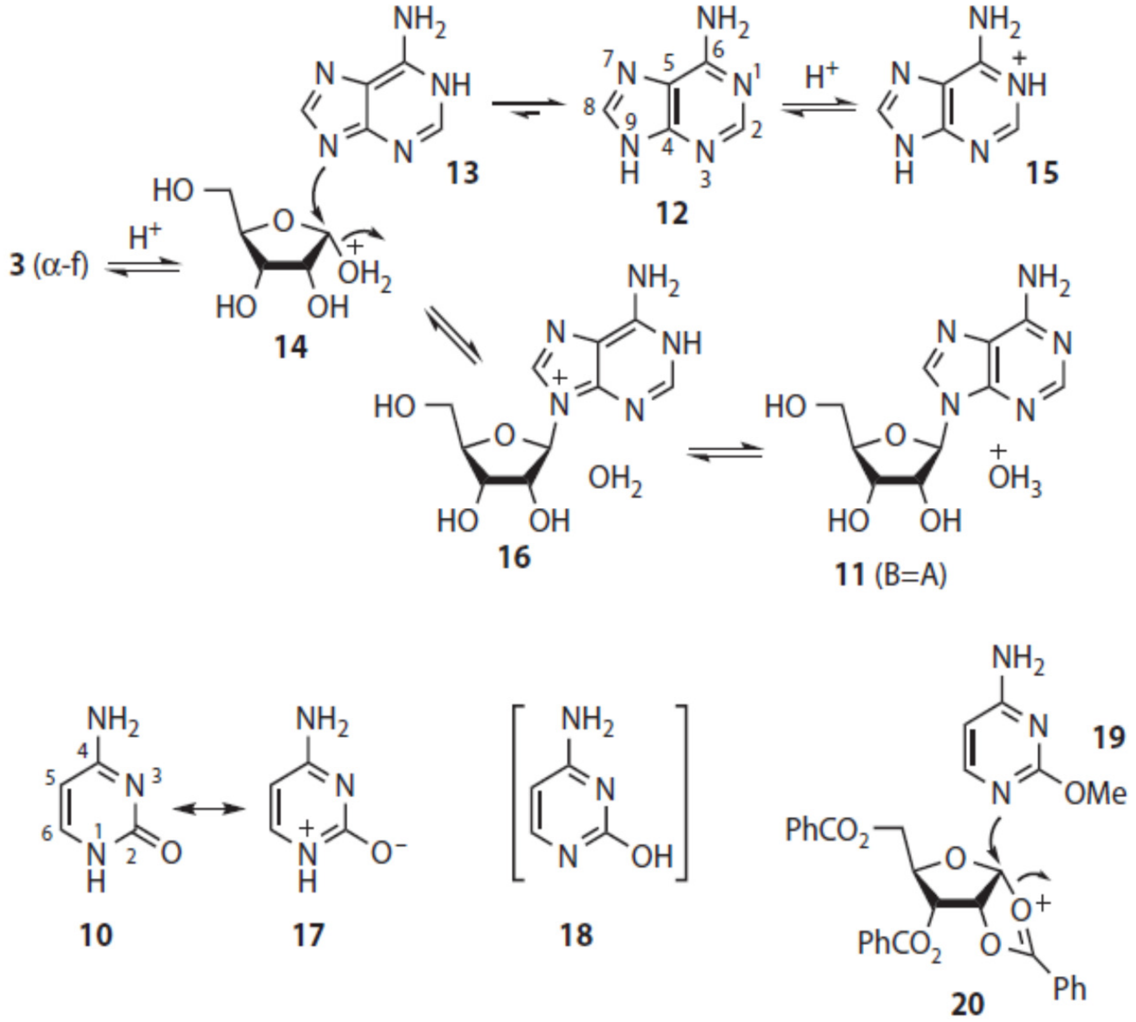
The many different forms of ribose **3** adopted in aqueous solution. The pyranose (p) and furanose (f ) forms interconvert via the open-chain aldehyde (a), which is also in equilibrium with an open-chain aldehyde hydrate (not shown).

# *Prebiotic synthesis of nucleosides*



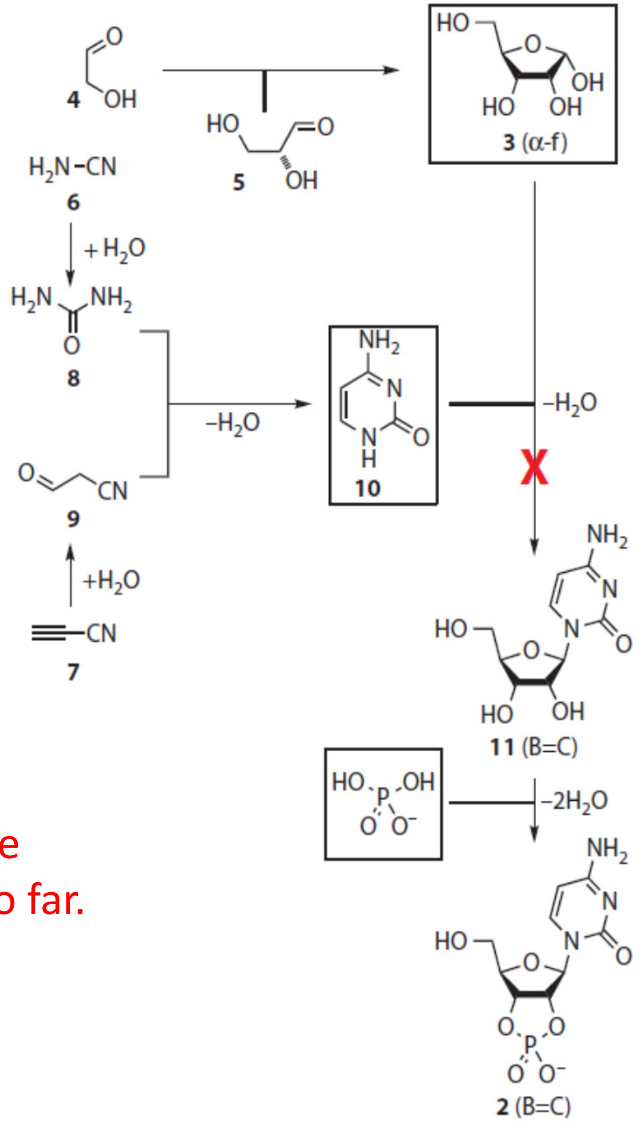
Heating purines with ribose and magnesium salts yields beta-nucleosides, although with low yields
β-inosine – 8%, β-adenosine – 4%, β-guanosine – 9%
Other isomers (e.g. alpha-glycosides) also present.

W. Fuller, R. Sanchez, L. Orgel *J. Mol. Biol.* **1972**, *67, 25-33*



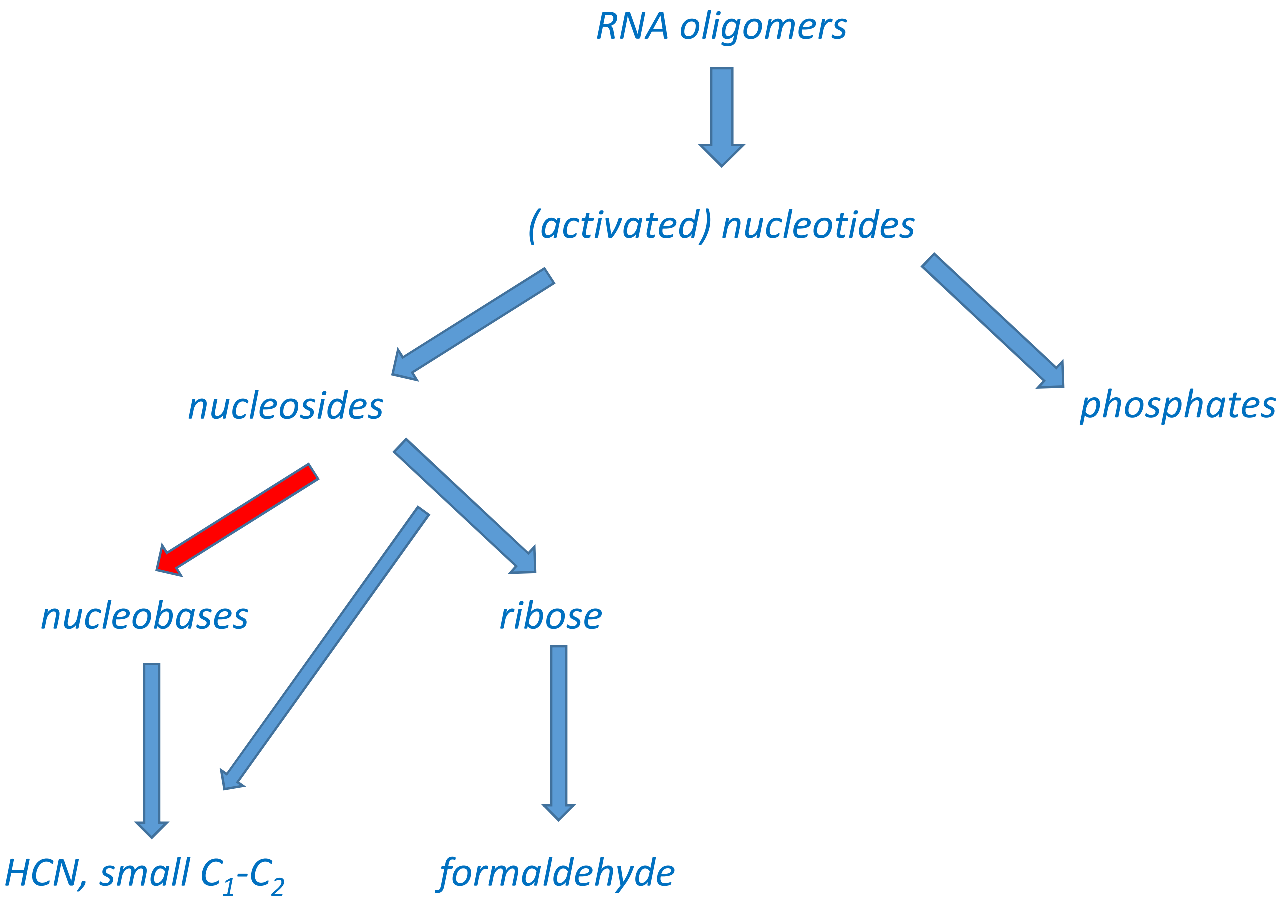
Adenine tautomerism and the ribosylation step necessary to make the adenosine **11** thought to be needed for RNA assembly. The low abundance of the reactive entities **13** and **14** is partly responsible for the low yield of **11**. The reason for the lower nucleophilicity of *N1* of the pyrimidines, and the conventional synthetic chemist's solution to the problems of ribosylation.

# *Prebiotic synthesis of pyrimidine nucleosides*



No direct synthesis of pyrimidine nucleosides from ribose reported so far.

# *RNA oligomers – prebiotic disconnections*



*RNA oligomers*

*(activated) nucleotides*

*nucleosides*

*phosphates*

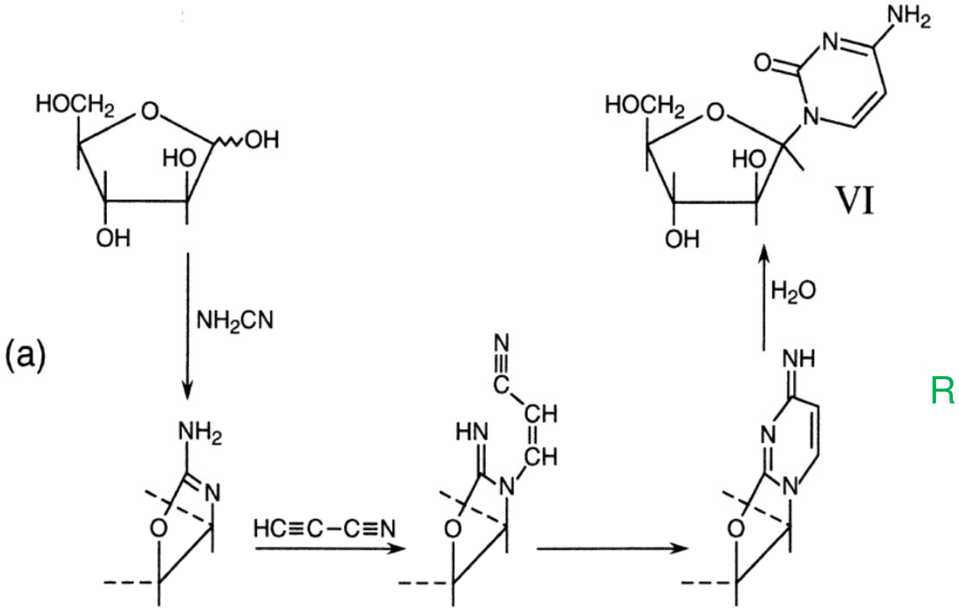
*nucleobases*

*ribose*

*HCN, small $C_1$-$C_2$*

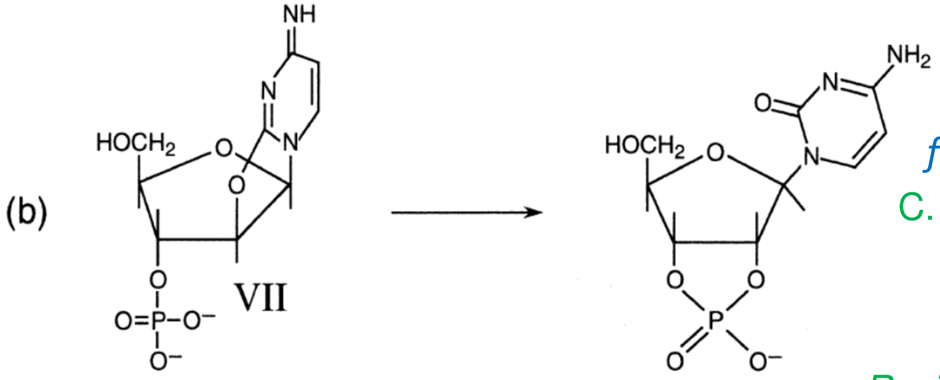
*formaldehyde*

# *Prebiotic synthesis of nucleosides*



*cytosine arabinoside synthesis*

R. Sanchez, L. Orgel *J. Mol. Biol.* **1970**, *47, 531-543*



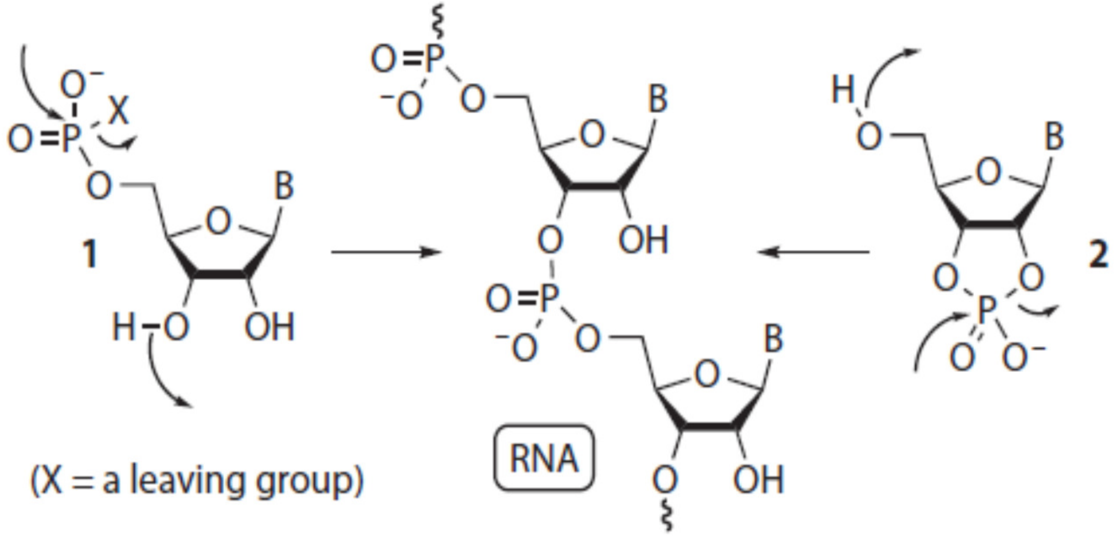
*cytosine riboside (as a cyclic phosphate) is obtained from a phosphorylated substrate*

C. M. Tapiero, J. Nagyvary *Nature* **1971**, *231, 42-43*

*Review*: L. E. Orgel *Crit. Rev. Biochem. Mol. Biol.* **2004**, *39, 99123*

Ara-3'P + $NH_2CN$ + HCC-CN → Cyt-2',3'cP: A. Ingar, R. W. A. Luke, B. R. Hayter, J. D. Sutherland *ChemBioChem* **2003**, *4,* 504-507

# *Prebiotic synthesis of oligonucleotides*

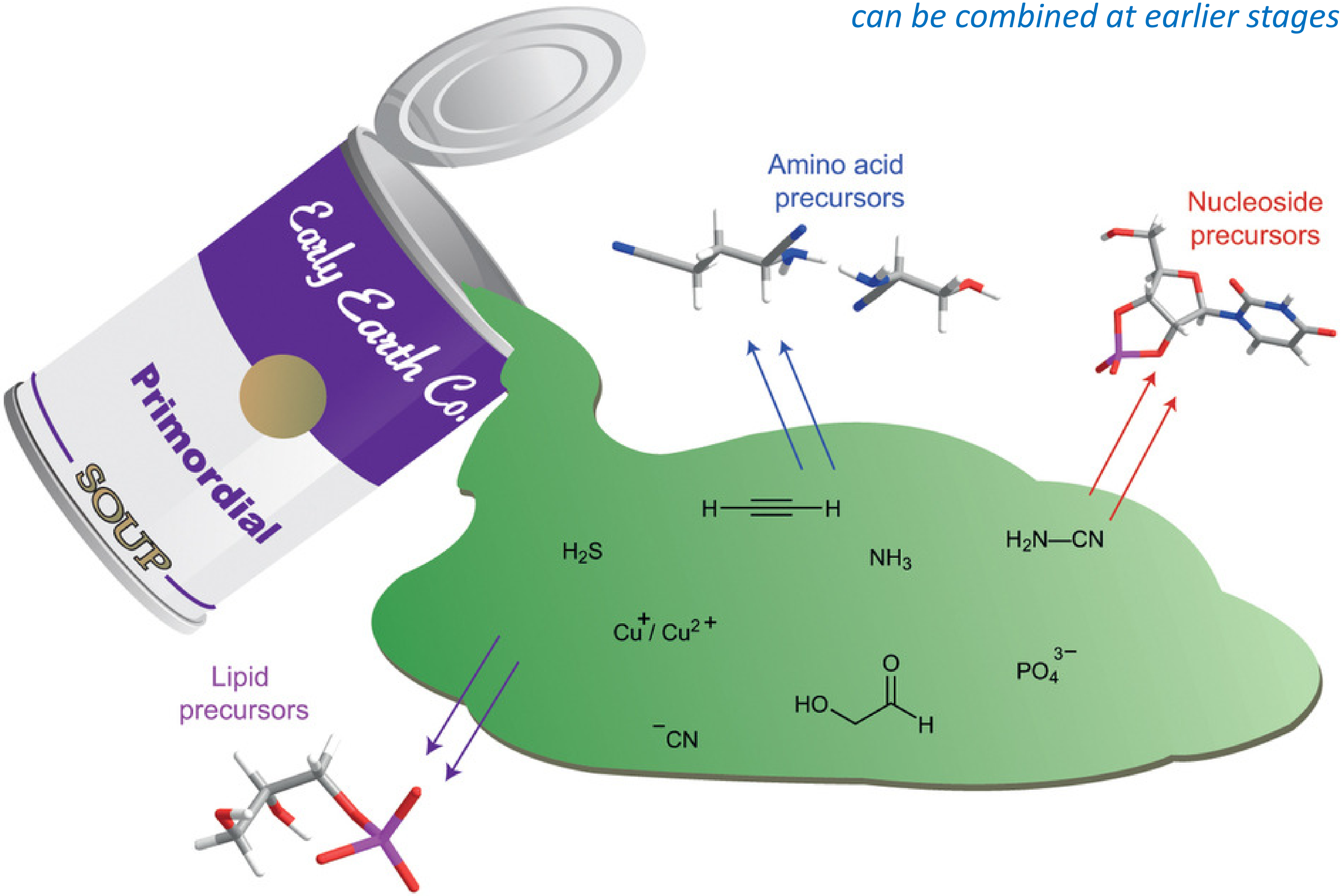


(X = a leaving group)

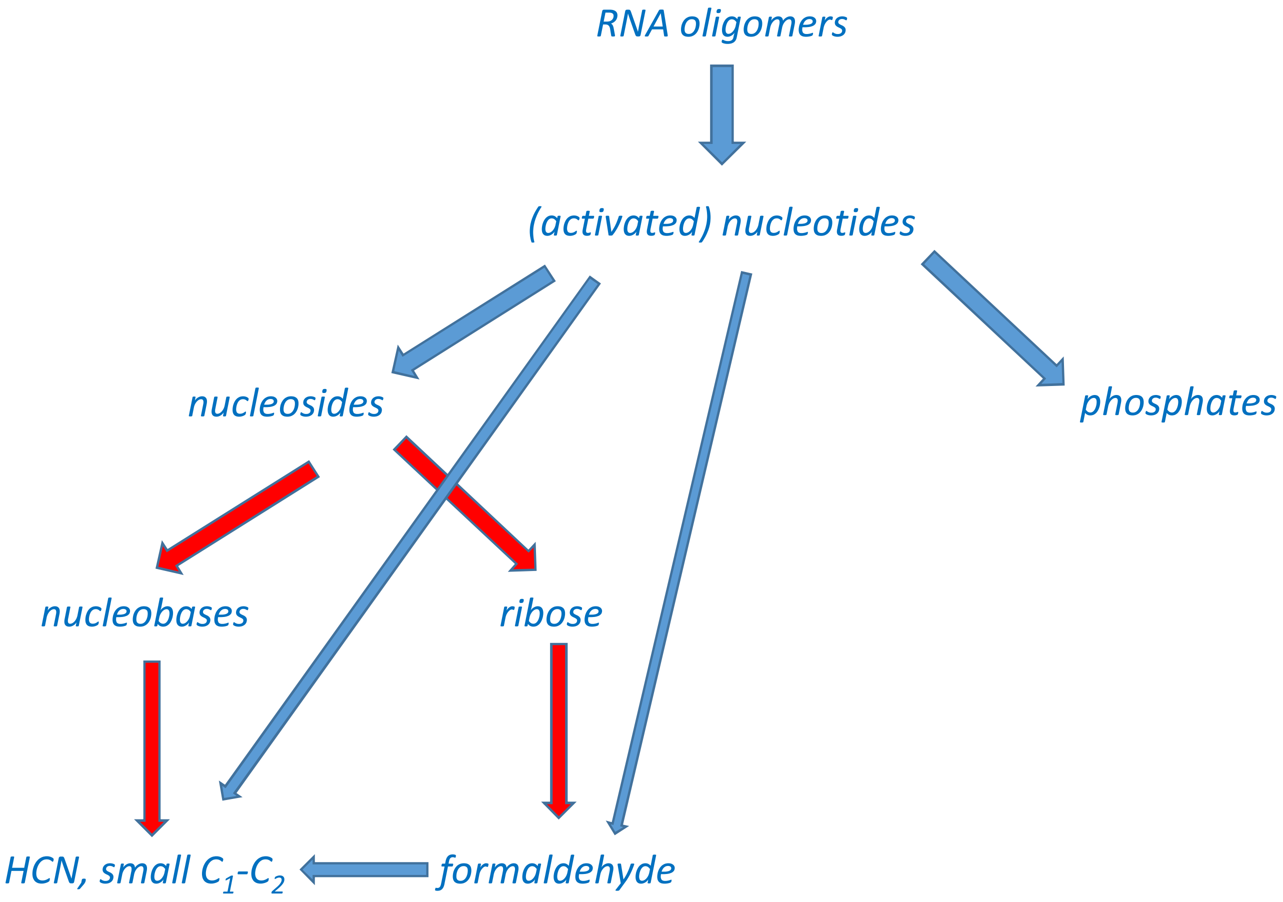
Activated ribonucleotides in the potentially prebiotic assembly of RNA. Potential P–O bond forming polymerization chemistry is indicated by the curved arrows.

# *Cyanosulfidic chemistry*

*The aldol chemistry of sugars and cyanide chemistry of nucleobases can be combined at earlier stages than glycosylation.*



# *RNA oligomers – prebiotic disconnections*



*RNA oligomers*

*(activated) nucleotides*

*nucleosides*

*phosphates*

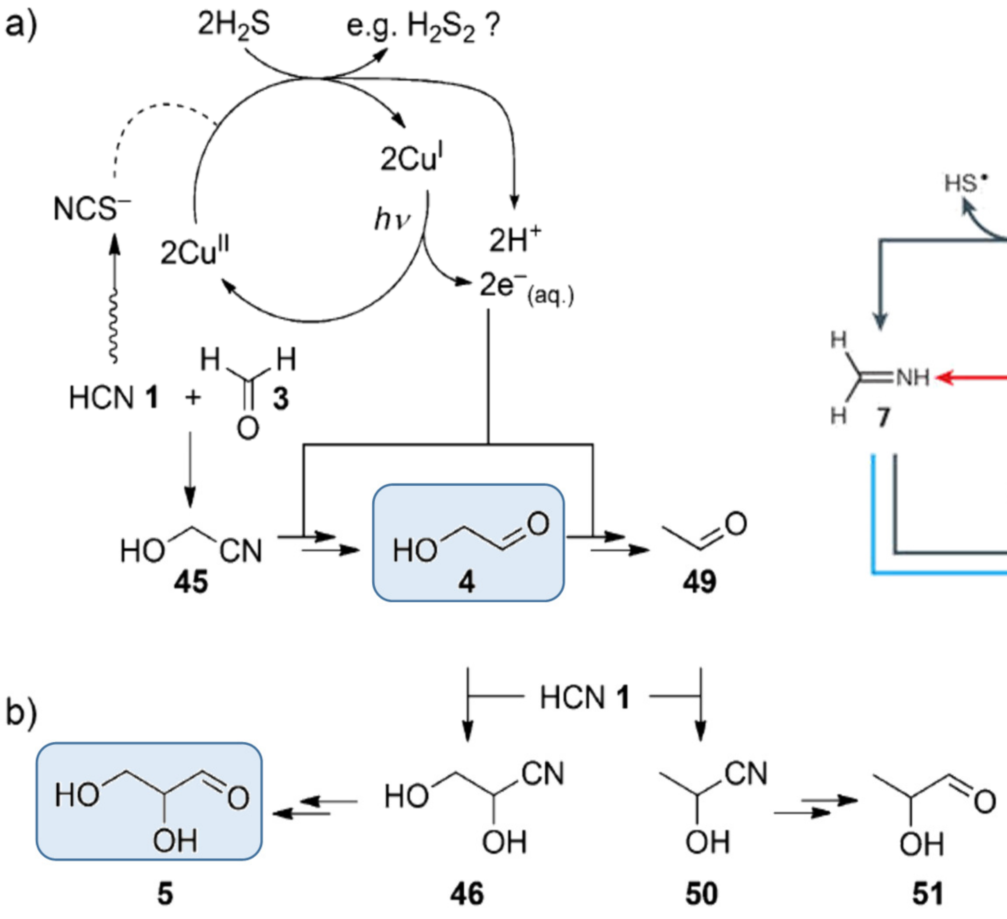
*nucleobases*

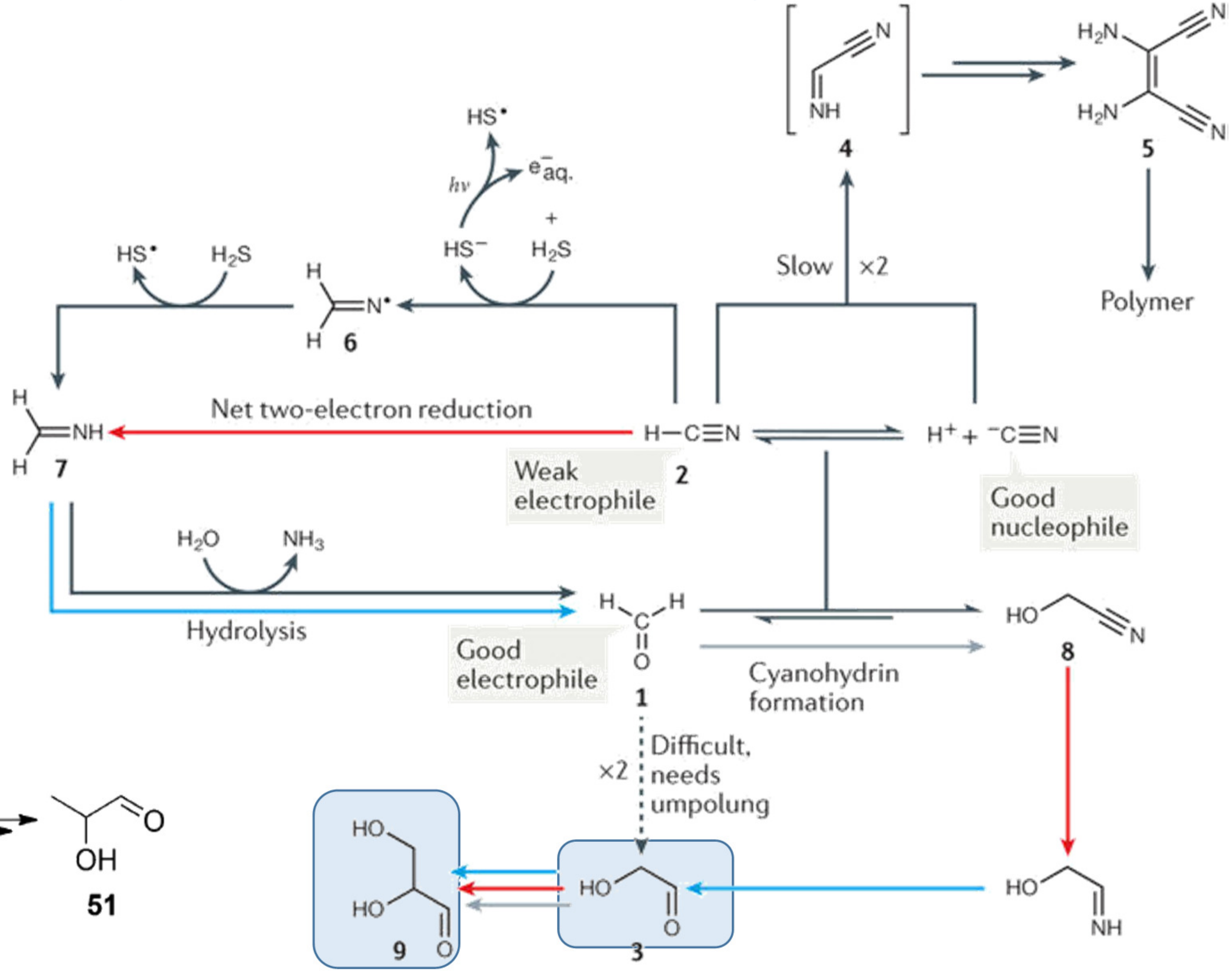
*ribose*

*HCN, small* $C_1$*-*$C_2$

*formaldehyde*

# *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*

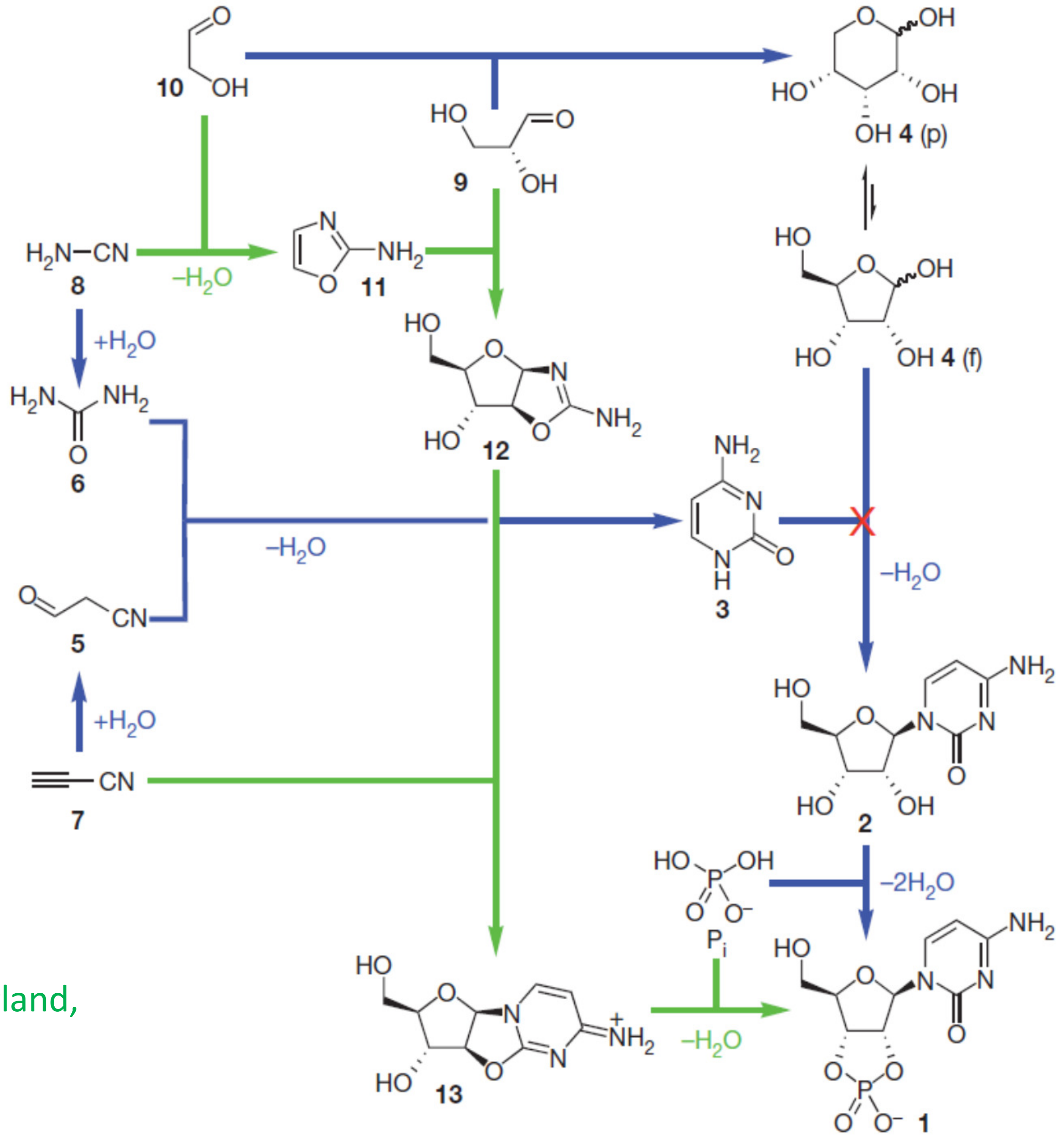




J. Sutherland, *Nature Reviews Chemistry* **2017**, *1*, Article 0012, doi:10.1038/s41570-016-0012

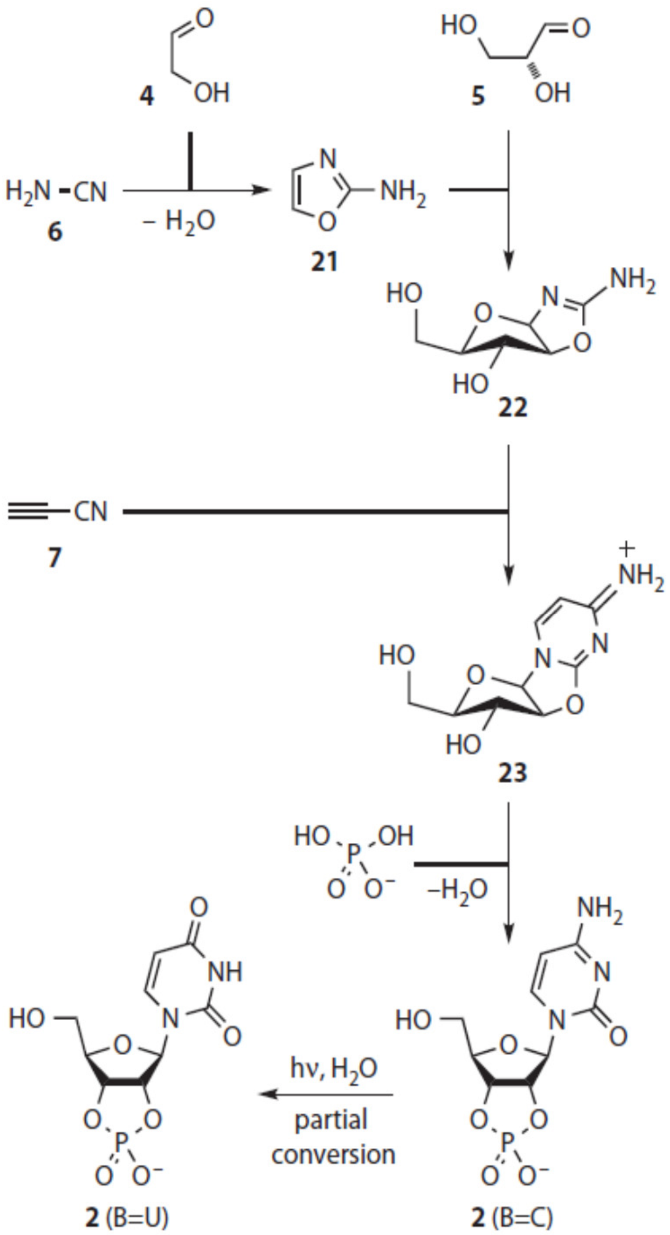
Nature Reviews | Chemistry

## *Cyanosulfidic chemistry*



M. W. Powner, B. Gerland, J. D. Sutherland,
*Nature* **2009**, *459*, 239–242

# *Cyanosulfidic chemistry*

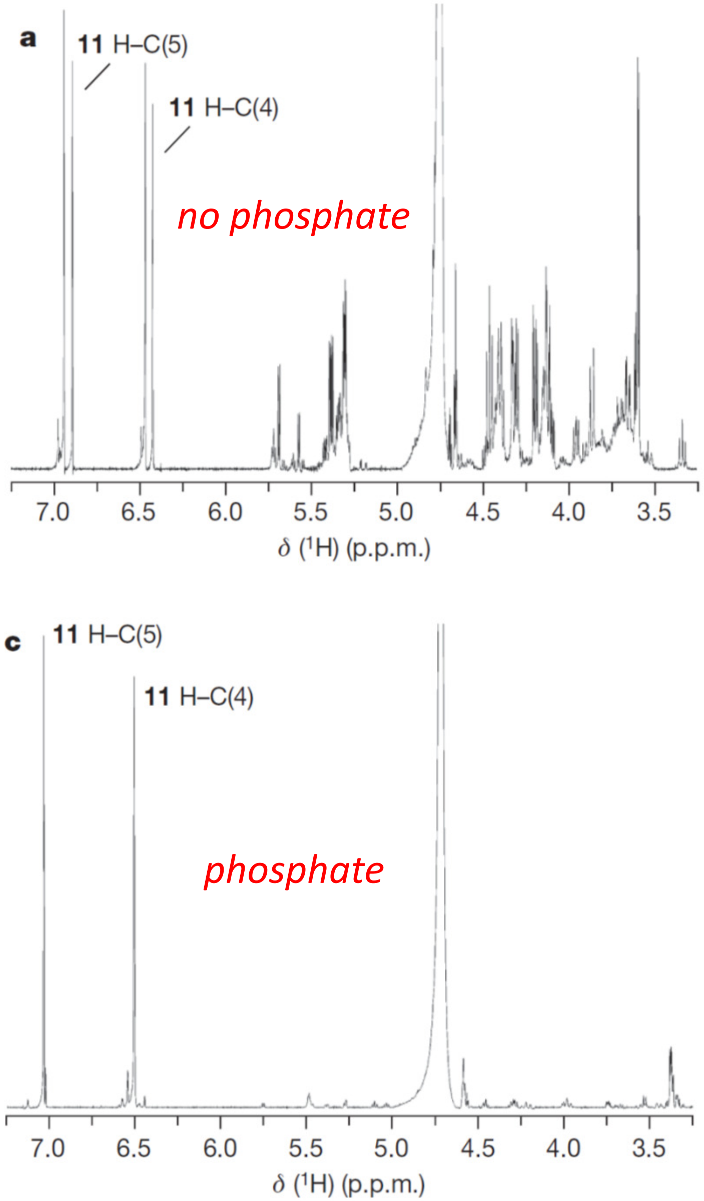


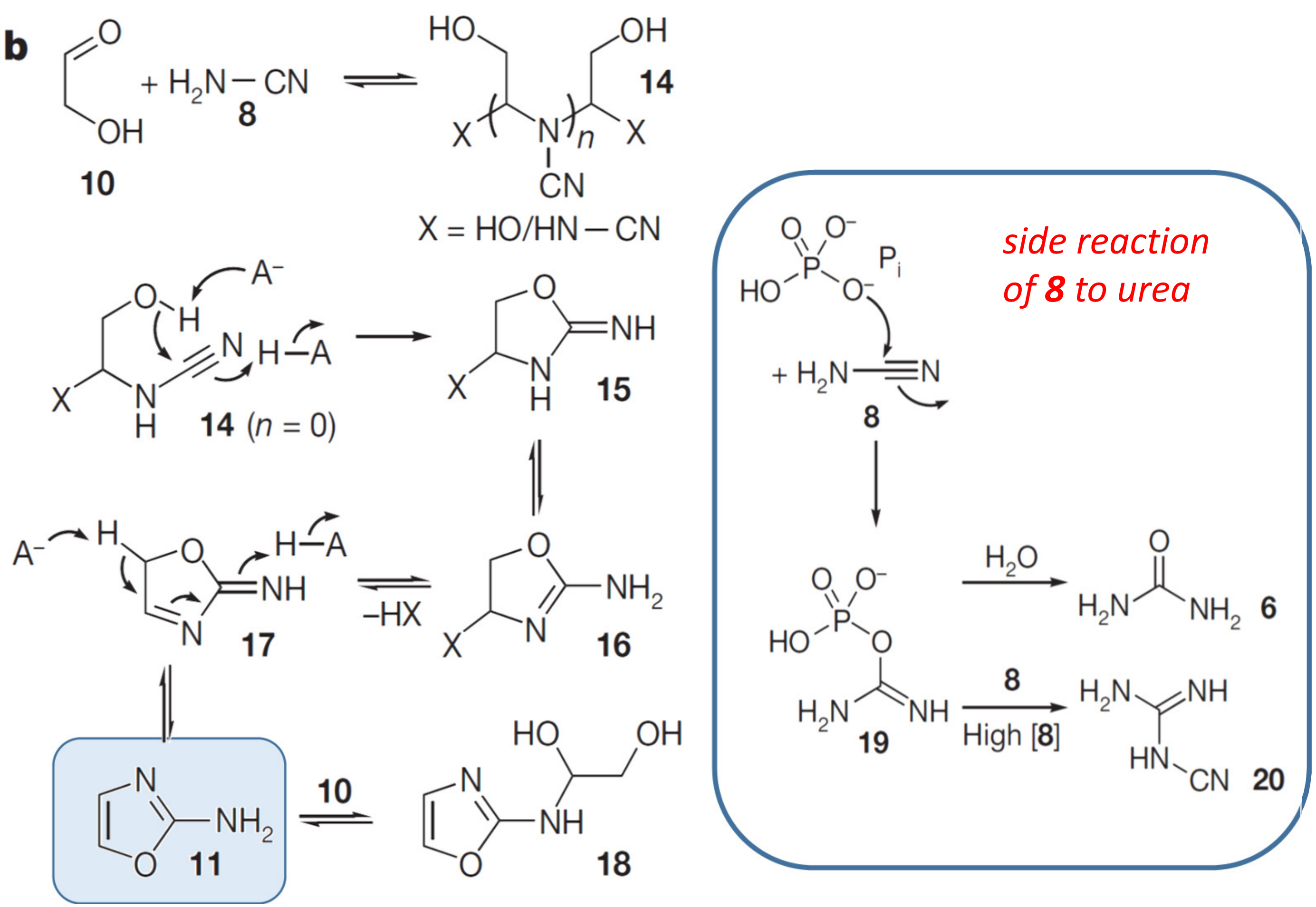
The recently uncovered route to activated pyrimidine nucleotides **2**.

The nucleobase ribosylation problem is circumvented by the assembly proceeding through 2-aminooxazole **21**, which can be thought of as the chimera of half a pentose sugar and half a nucleobase. The second half of the pentose - glyceraldehyde **5** -and the second half of the nucleobase—cyanoacetylene **7**—are then added sequentially to give the anhydronucleoside **23**.

Phosphorylation and rearrangement of **23** then furnishes **2** (B=C), and UV irradiation effects the partial conversion of **2** (B=C) to **2** (B=U).

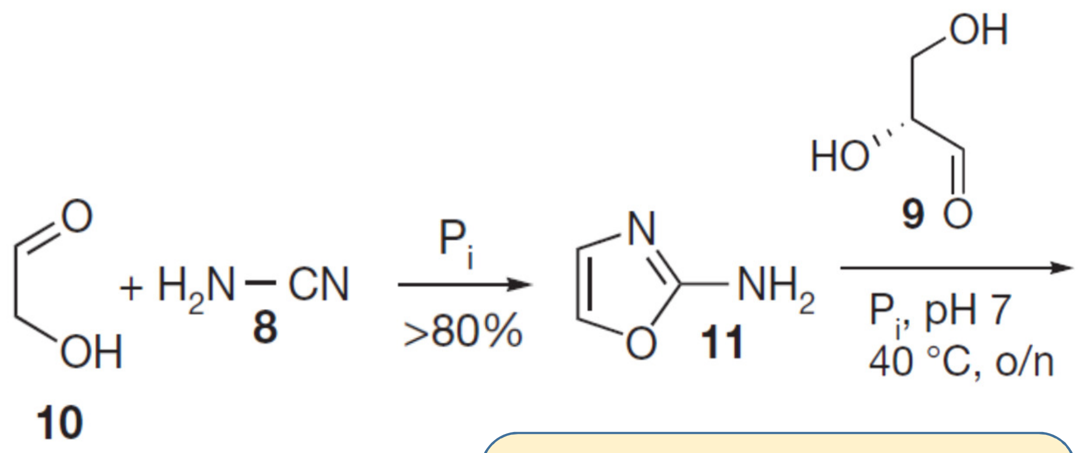
# *Cytosine-2',3'cP – step 1: 2-amino-oxazole*





M. W. Powner, B. Gerland, J. D. Sutherland,
*Nature* **2009**, *459*, 239–242

# *Cytosine-2',3'cP – step 2: pentose-amino-oxazolines*

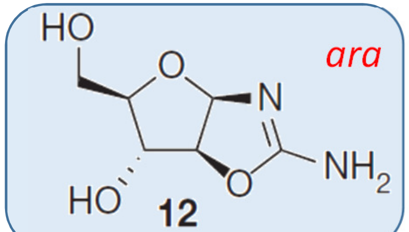


**10** **8** **11** **9**

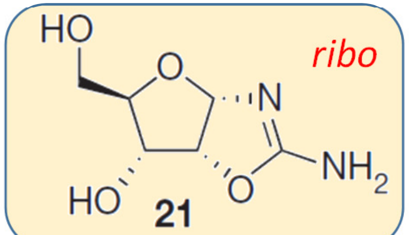
**12** 15%
**21** 25%
**22** 6%
**23** 4%
**24** 11%
**25** 9%

Yields for two steps based on **10**

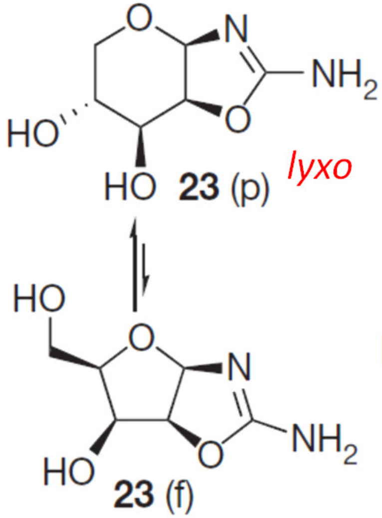
*ribo-**21** – selectively crystallizes on cooling → ara-**12** becomes the main mixture component*



**12**

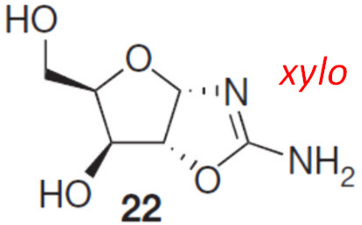


**21**

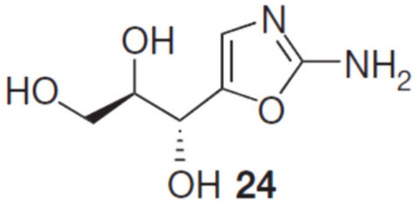


**23** (p)

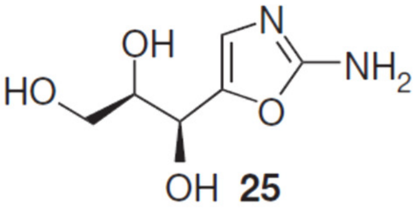
**23** (f)



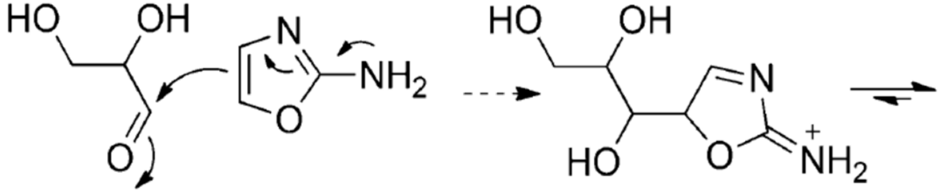
**22**



**24**



**25**

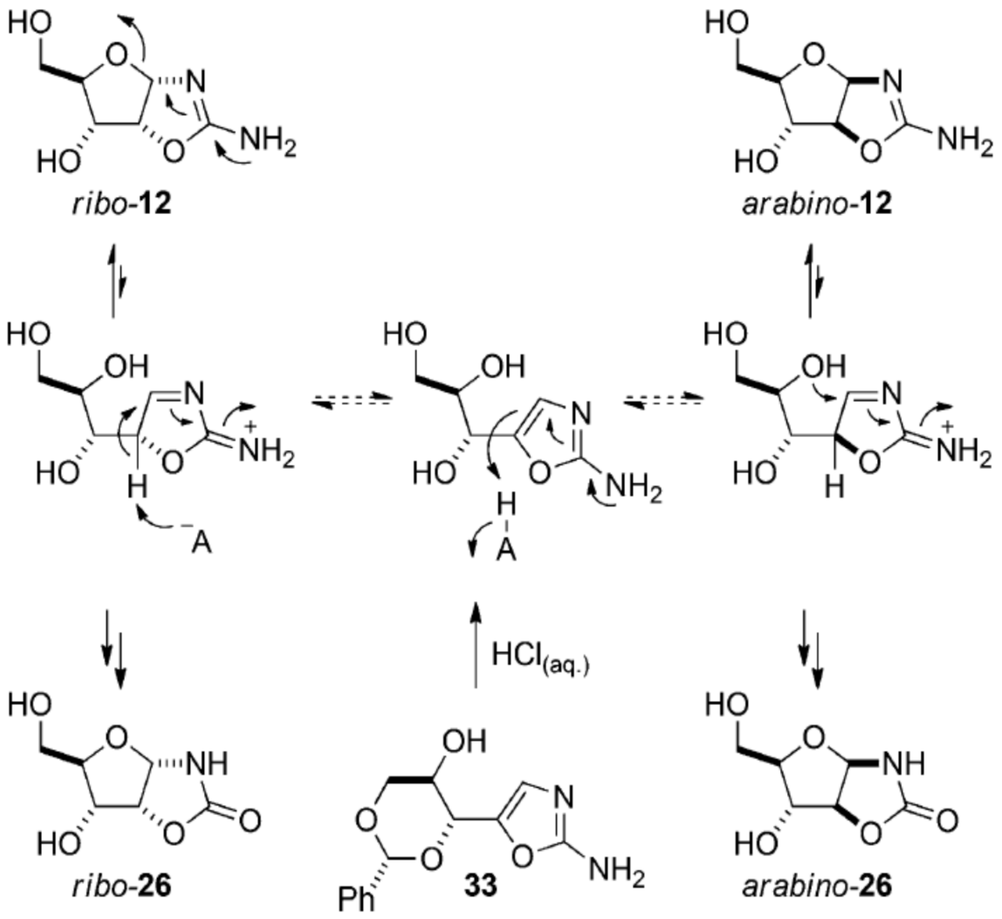


44% *ribo*-**12**
30% *arabino*- **21**
13% *lyxo*- **23**
8% *xylo*- **22**

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

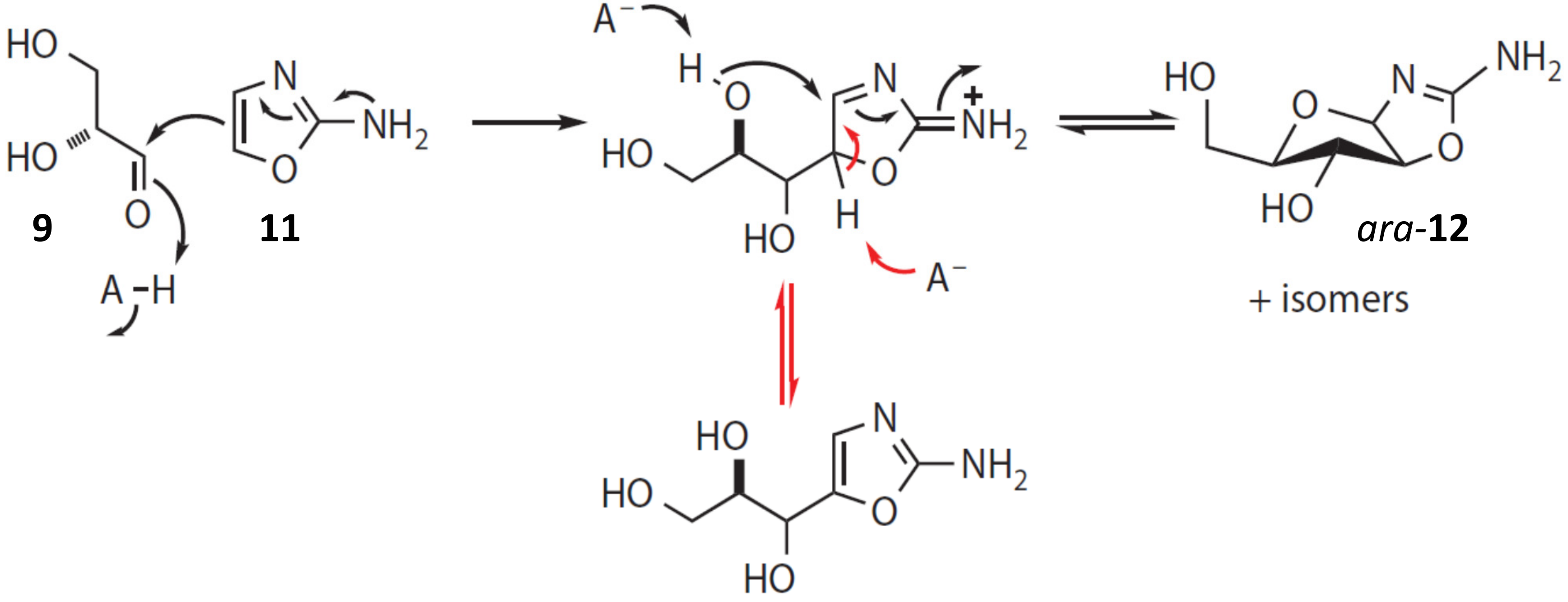
# Cyanosulfidic chemistry

Interconversion of pentose aminooxazoline stereoisomers.

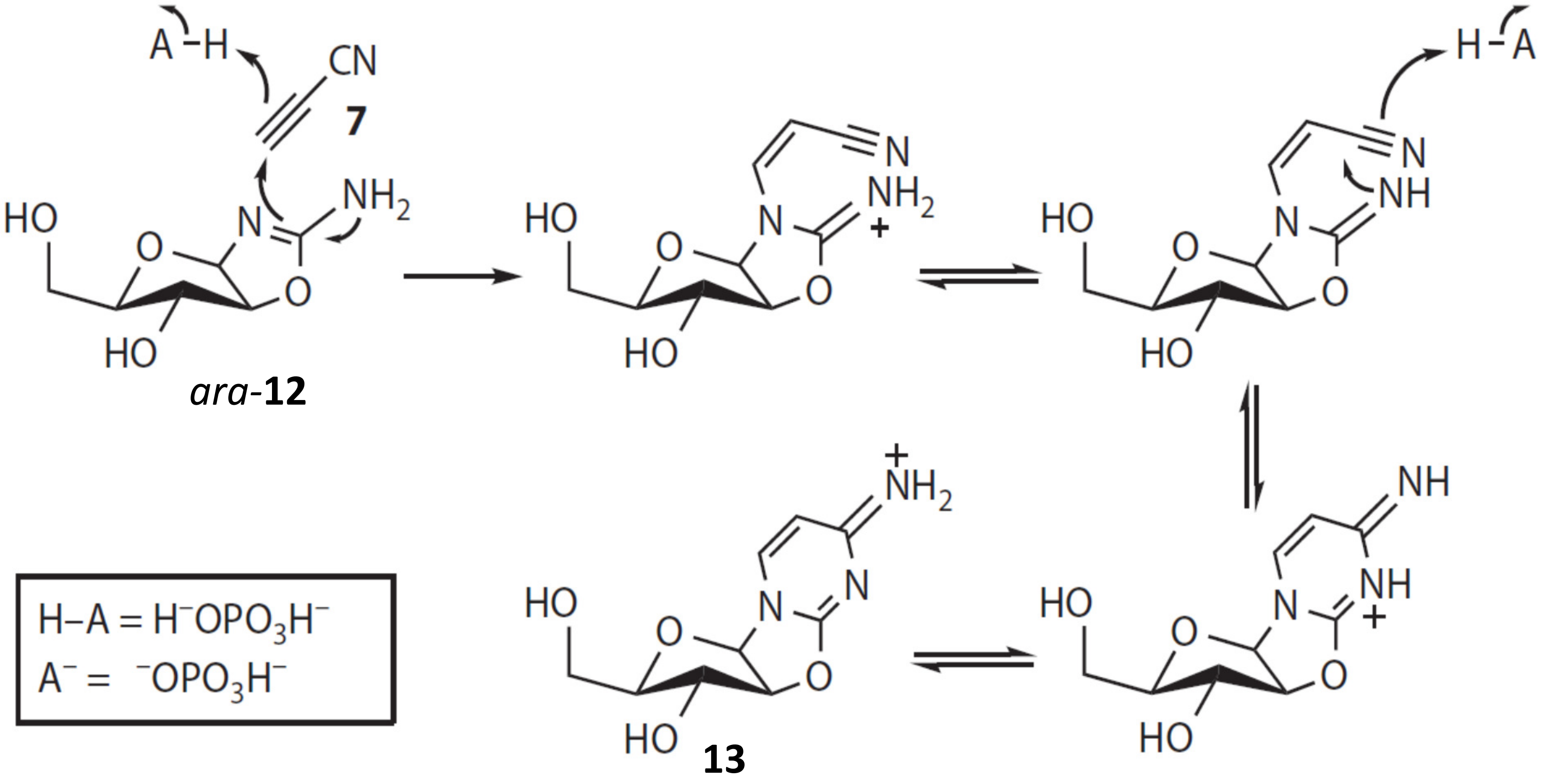


The „side product” *ribo*-**21** can be converted to the expected *arabino*-**12** by general acid-base catalysis in phosphate buffer, although with some decomposition to **26**

# Cytosine-2’,3’cP – step 2: pentose-amino-oxazolines



# Cytosine-2’,3’cP – step 3: arabinose-anhydronucleosides



*ara*-**12**

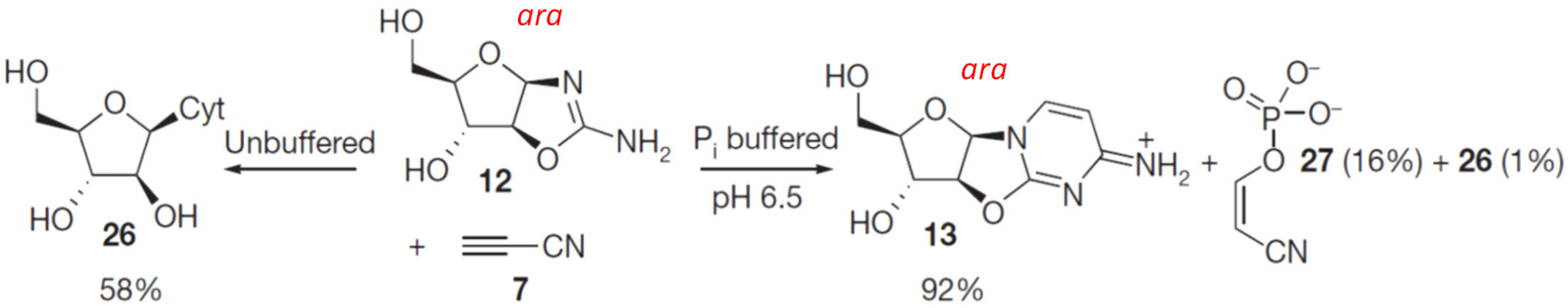
**7**

**13**

$H{-}A = H^{-}OPO_3H^{-}$

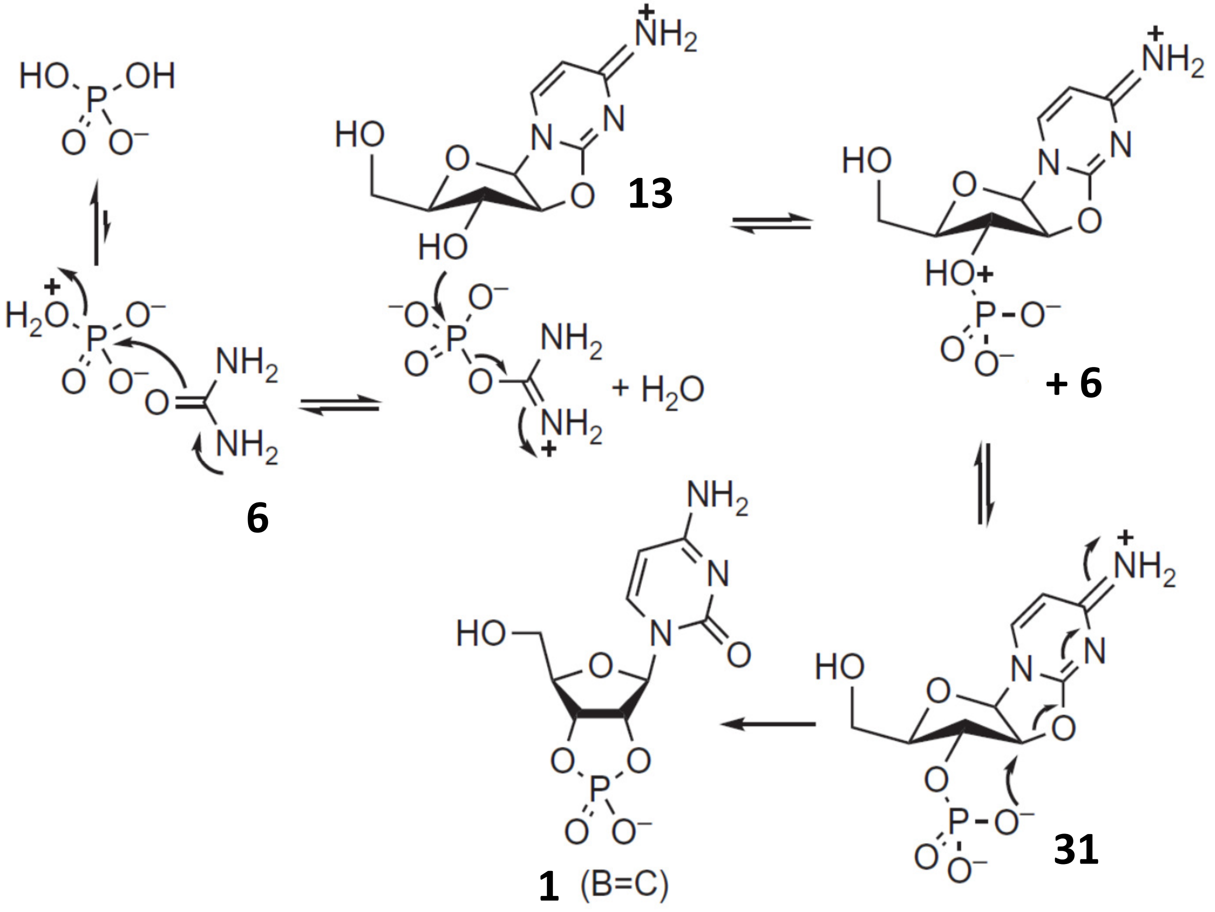
$A^{-} = {}^{-}OPO_3H^{-}$

# *Cytosine-2’,3’cP – step 3: arabinose-anhydronucleosides*



M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

# Cytosine-2',3'cP – step 4: β-ribocytidine-2',3'-cyclic phosphate



**13**

**6**

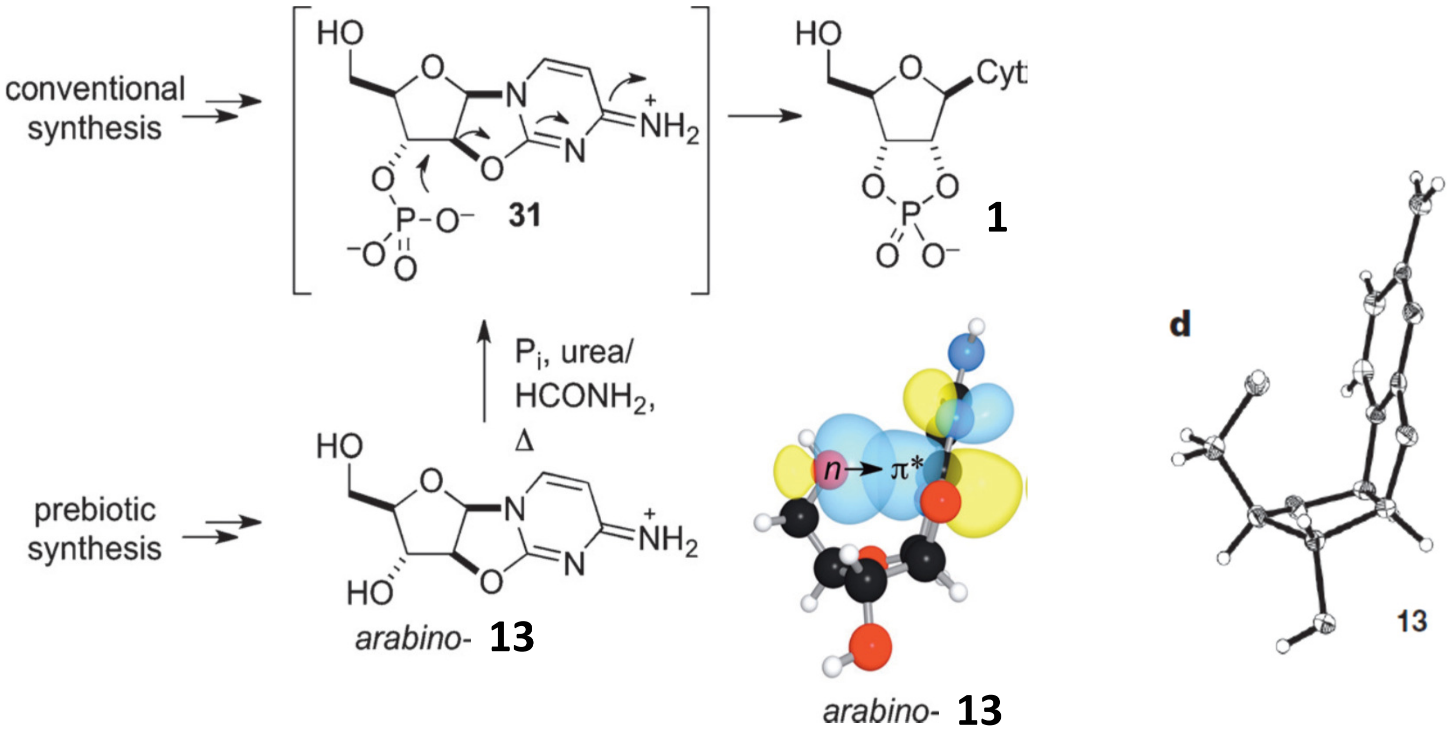
**31**

**1** (B=C)

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

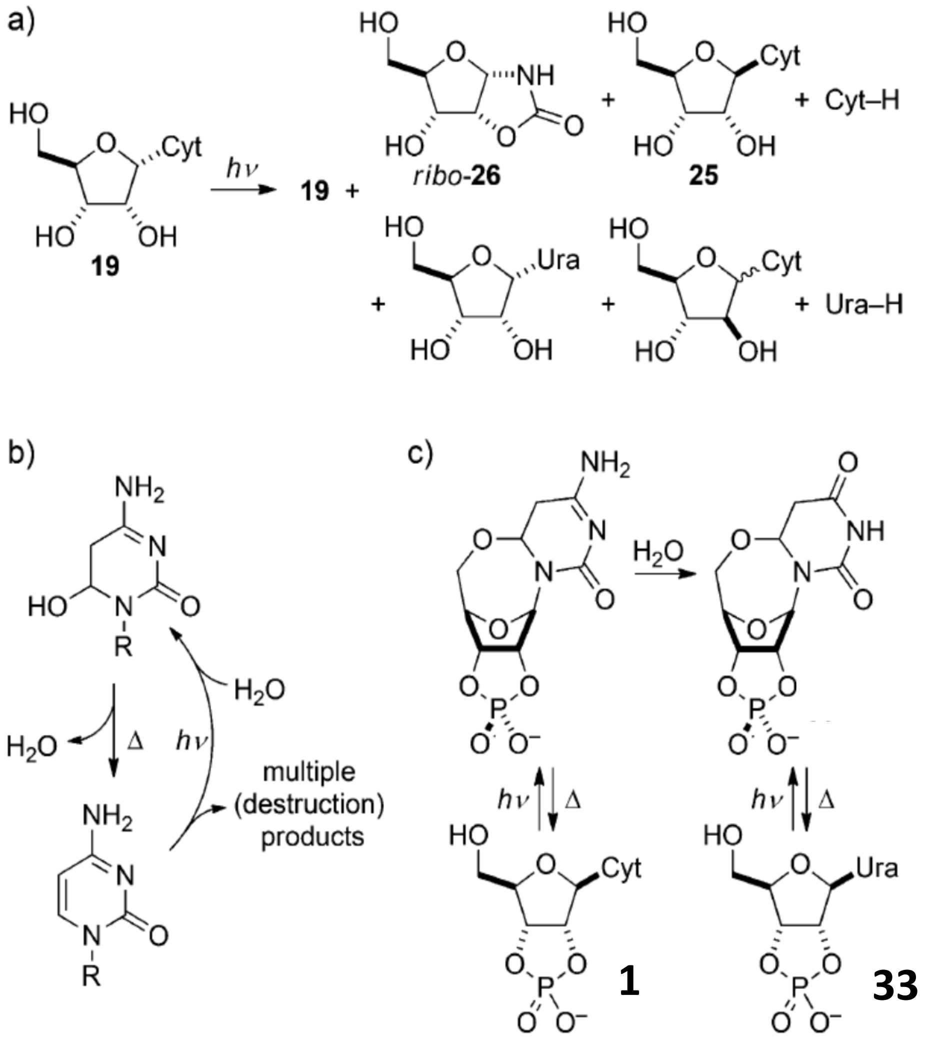
# Cytosine-2’,3’cP – step 4: β-ribocytidine-2’,3’-cyclic phosphate

Rearrangement of **31**, the 3’-phosphate of *arabino*-**13**, to **1** by intramolecular nucleophilic substitution.



M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

# Activated pyrimidine nucleotides – step 5: UV-light induced rearrangement C→U + cleanup of the side products



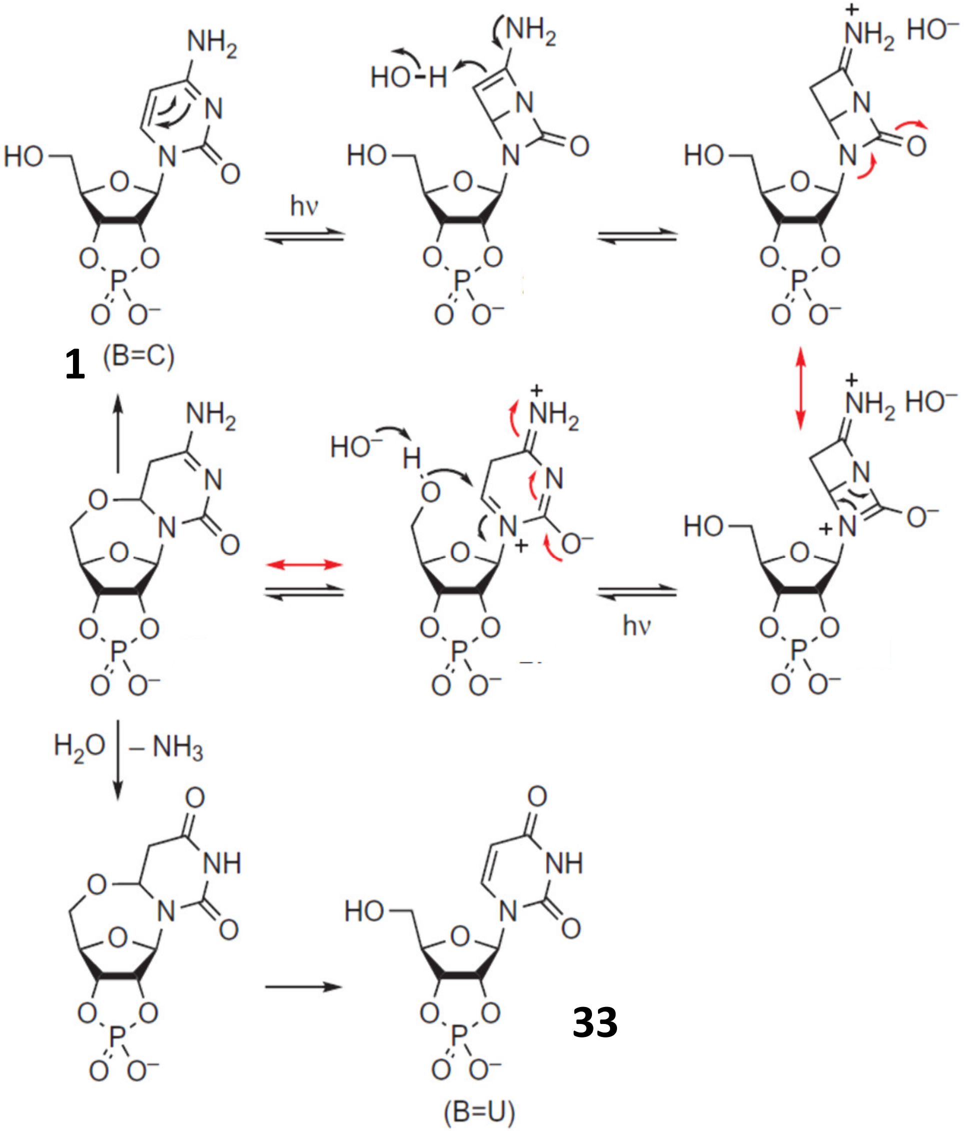
Orgel reported photoanomerization of alpha-cytidine **19** to the beta-anomer **25**, but the reaction was very low-yielding and combined with massive decomposition

R. A. Sanchez, L. E. Orgel, *J. Mol. Biol.* **1970**, *47,* 531-543

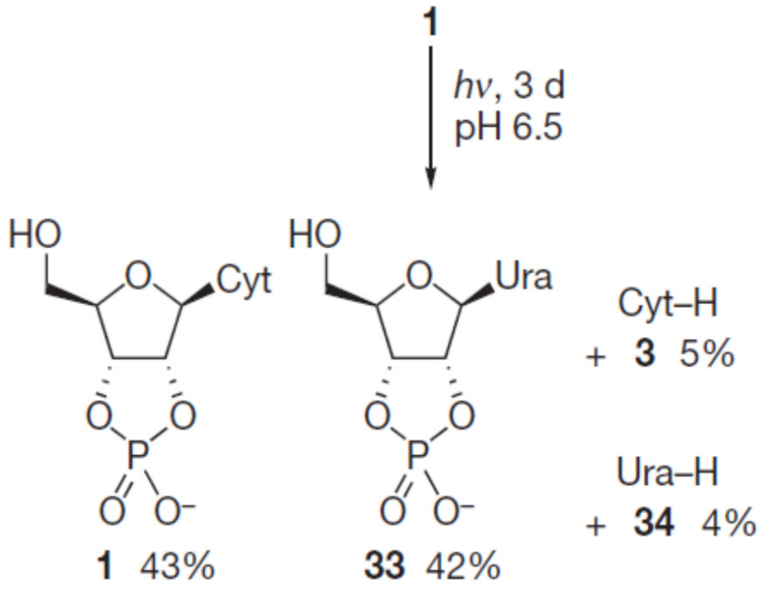
UV light tends to destroy most of phosphorylated cytidine derivatives (by photohydration and followed decomposition).
**EXCEPTION:** beta-cytidine-2',3'-cyclic phosphate **1**
→ Partial conversion to the uridine nucleotide **33**, but both are stable on further irradiation

*Photochemistry of cytidine nucleosides and nucleotides.*

# *step 5: UV-light induced rearrangement C→U + cleanup of the side products*



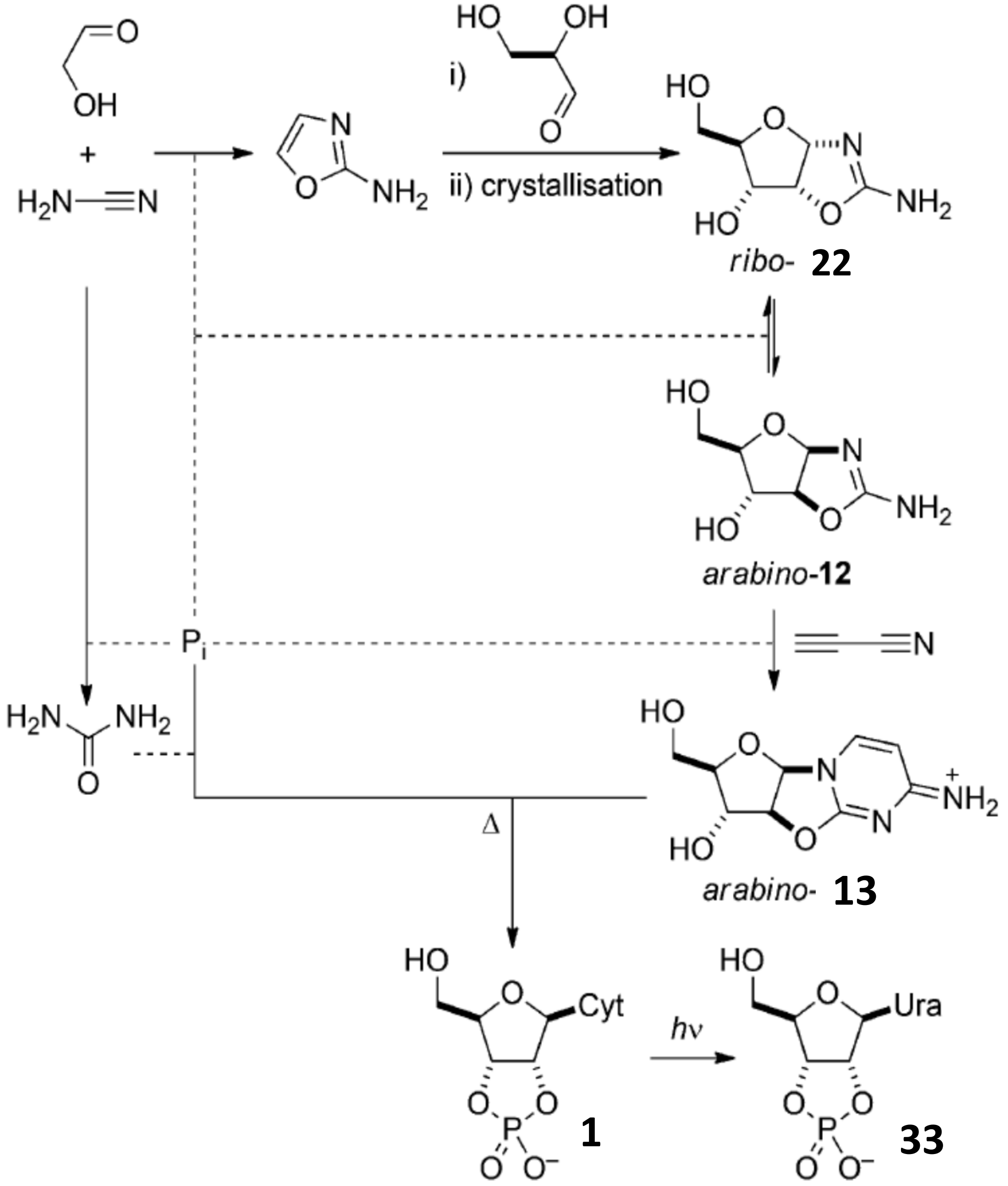
# step 5: UV-light induced rearrangement C→U + cleanup of the side products



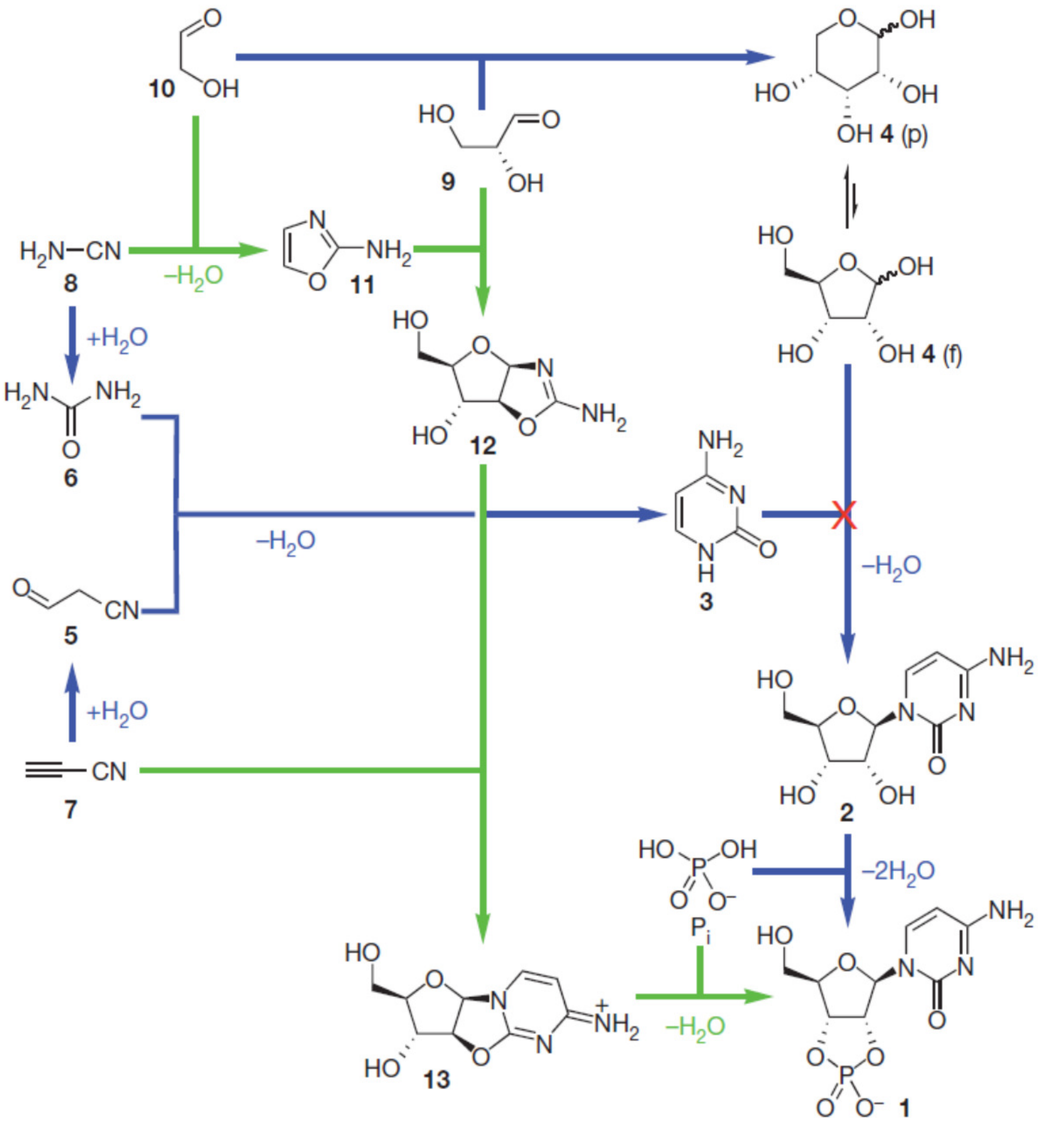
Photochemistry of *beta*-ribocytidine-2’,3’-cyclic phosphate **1**. Under conditions of irradiation that destroy most other pyrimidine nucleosides and nucleotides, **1** undergoes partial hydrolysis and slight nucleobase loss. Ura, N1-linked uracil; Cyt–H, cytosine; Ura–H, uracil.

# *Prebiotic synthesis of activated pyrimidine nucleotides*

Catalysis, and reaction control through pH and chemical buffering, is indicated by dashed lines.



# *Prebiotic route to pyrimidine nucleotides*



**Prof. John Sutherland**
**Laboratory of Chemical Biology**
**Cambridge, UK**

**Dr. Matthew Powner**
**University College London, UK**

# *The origin of small reactive intermediates*

Thermal decomposition of cyanoferrates (volcanic):

$$(Na,K)_4[Fe(CN)_6] \xrightarrow{700^\circ C} 4(\mathbf{Na/K})\mathbf{CN} + Fe(CN)_2$$

$$3Fe(CN)_2 \xrightarrow{700^\circ C} Fe_3C + 5C + 3N_2$$

$$Fe(CN)_2 \xrightarrow{700^\circ C} Fe + 2C + N_2$$

$$Ca_2[Fe(CN)_6] \xrightarrow{660^\circ C} 2Ca(CN)_2 + Fe(CN)_2$$

$$Ca(CN)_2 \xrightarrow{660^\circ C} \mathbf{CaNCN} + C \xrightleftharpoons{1000^\circ C} \mathbf{CaC_2} + N_2$$

$$Mg_2[Fe(CN)_6] \xrightarrow{315^\circ C} 2Mg(CN)_2 + Fe(CN)_2$$

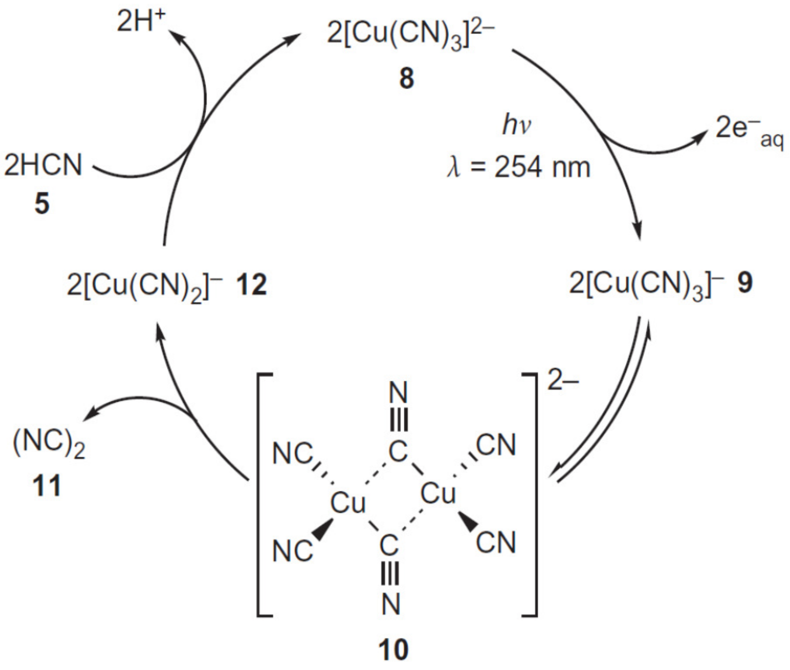
$$Mg(CN)_2 \xrightarrow{395^\circ C} MgCN_2 + C$$

$$3MgCN_2 \xrightarrow{420^\circ C} \mathbf{Mg_3N_2} + 3C + 2N_2$$

$Cu_2S + H_2O + 6CN^- \rightarrow 2[Cu(CN)_3]^{2-} + HS^- + OH^-$

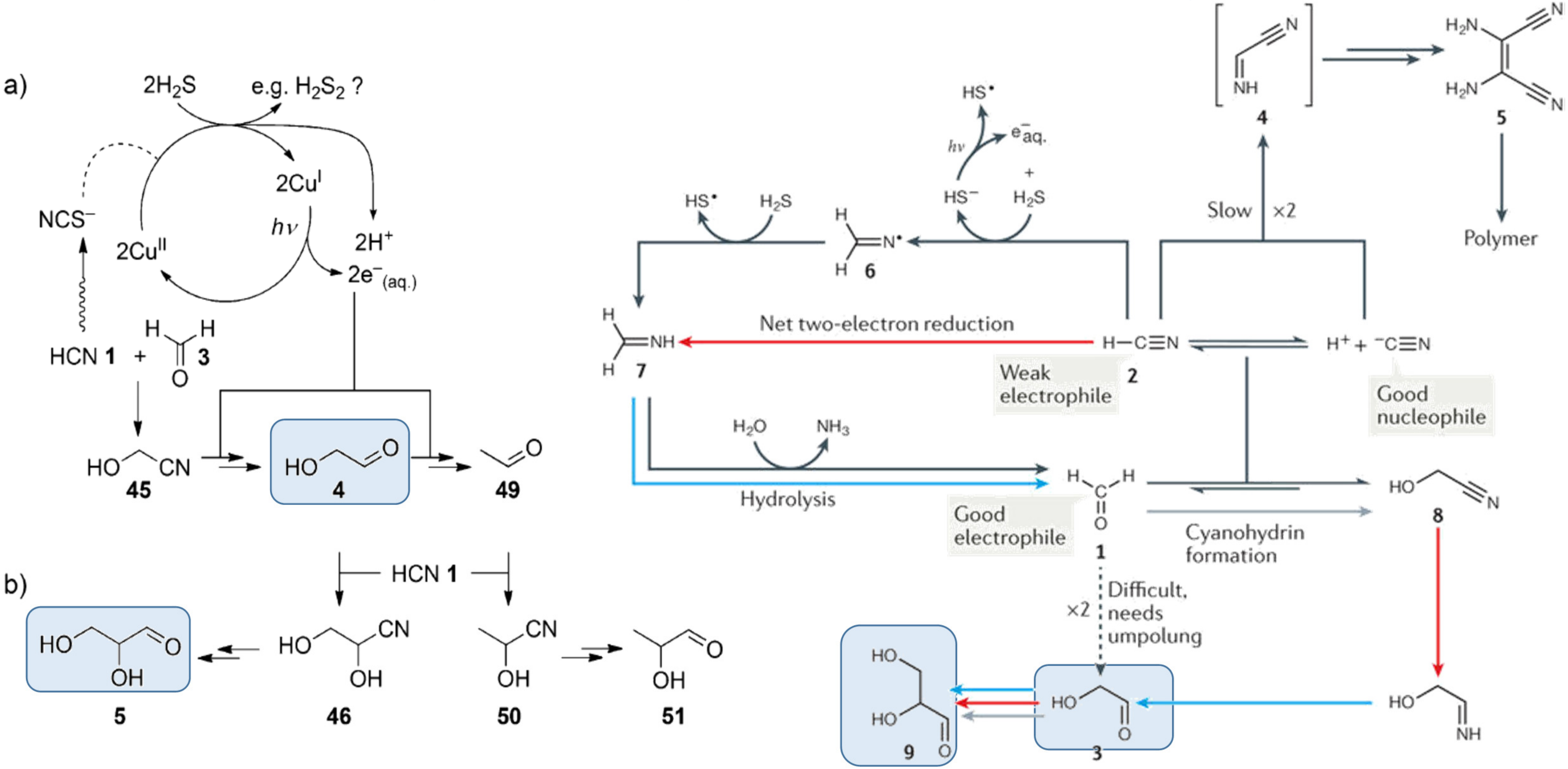
cyanocuprates and $HS^-$ are delivered by this process

Photoredox cycle based on cyanocuprates may convert HCN into cyanogen



Action of water (bufferred to neutral or slightly acidic) on that mixture produced concentrated HCN solution + cyanamide (from CaNCN) + acetylene (from $CaC_2$) + ammonia (from $Mg_3N_2$)

# *Cyanosulfidic chemistry for the Kiliani-Fischer homologation*

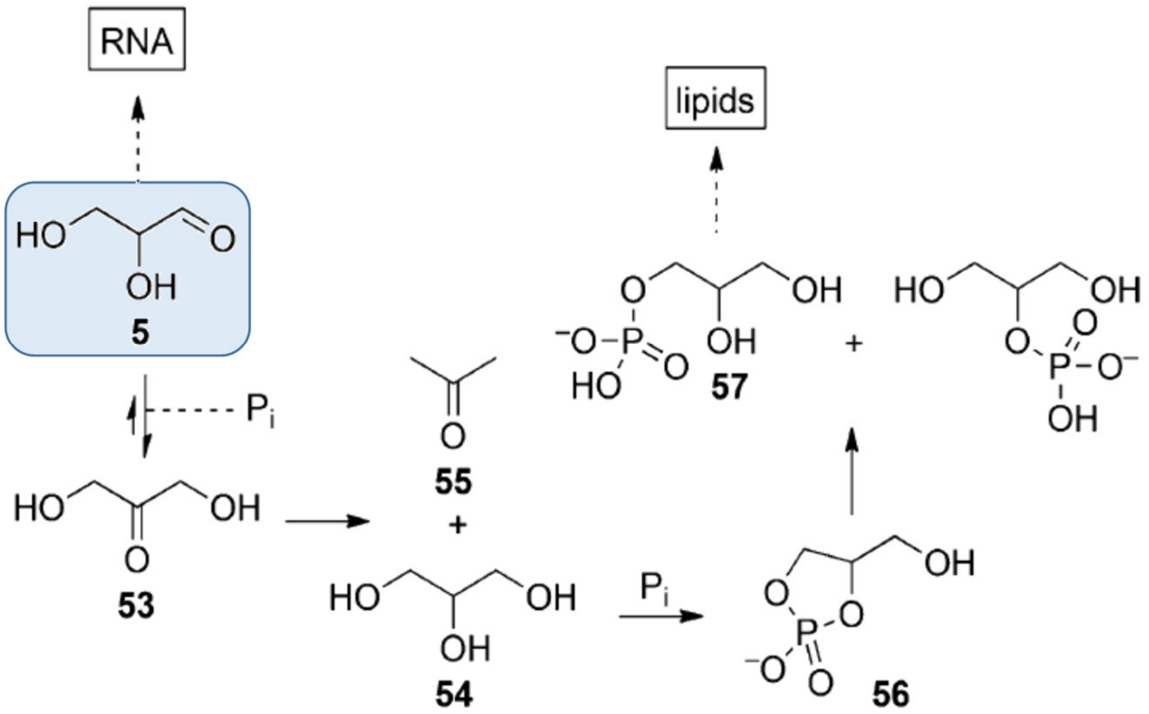


J. Sutherland, *Nature Reviews Chemistry* **2017**, *1*, Article 0012, doi:10.1038/s41570-016-0012

# *Cyanosulfidic chemistry*

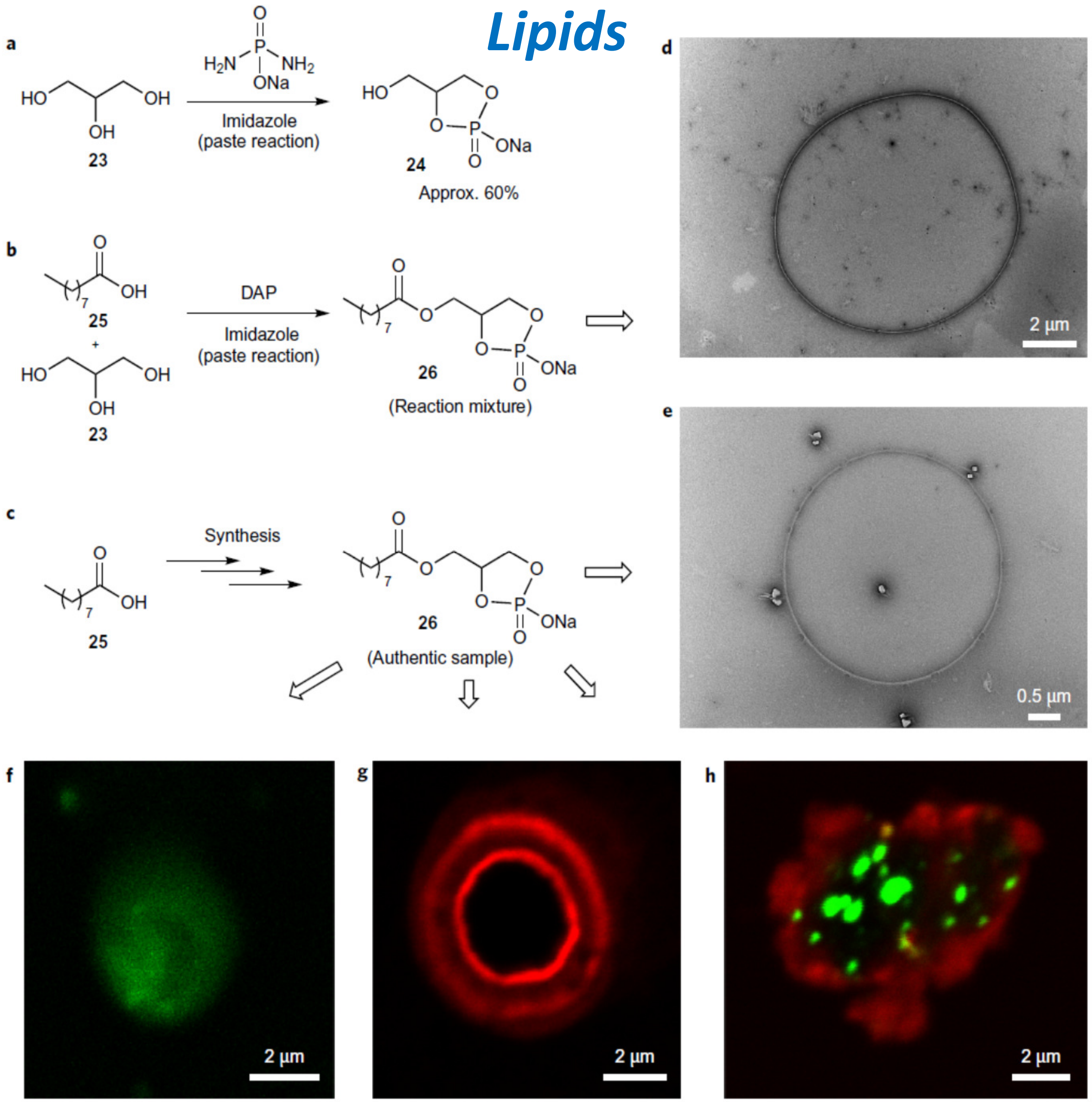
**First signs of a linkage between all subsystems through cyanosulfidic chemistry.**

glyceraldehyde **5** is a precursor of pyrimidine nucleotides (**RNA**), Upon isomerization to **53** and reduction to glycerol **54**, it can be phosphorylated to yield phospho**lipids** (from **56** and **57**)...



J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

# Lipids



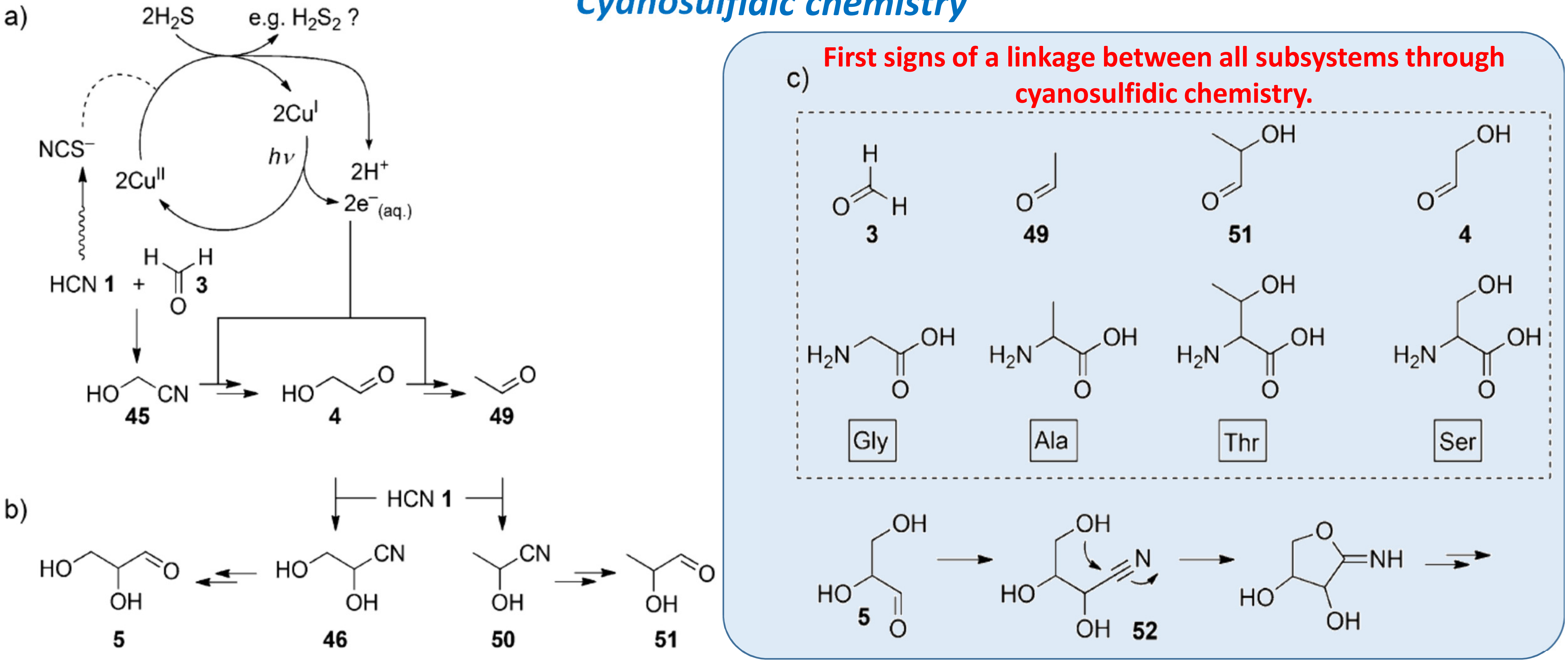
**d**, TEM image of a sample (15 mg in 1 ml water) from the crude reaction in b, showing the formation of vesicle-like structures with a diameter of ~9.2 μm.

**e**, TEM image of a sample (1 mg in 1 ml water) of authentic phospholipid 26 from Fig. 2c showing the formation of vesicle-like structures with a diameter of ~3.5 μm.

**f–h**, Confocal laser scanning microscopy fluorescence images of vesicles prepared with authentic phospholipid **26** (1 mg in 0.1 ml water) with dye encapsulation.

- In **f**, green fluorescence indicates hydrophilic pyranine dye encapsulated within the cavity of the liposome.
- In **g**, red fluorescence indicates rhodamine B dye labelling the bilayer phospholipid membrane of the liposome.
- In **h**, a fluorescence merged image is shown of a phospholipid vesicle prepared with both rhodamine B dye and pyranine dye.

# Cyanosulfidic chemistry

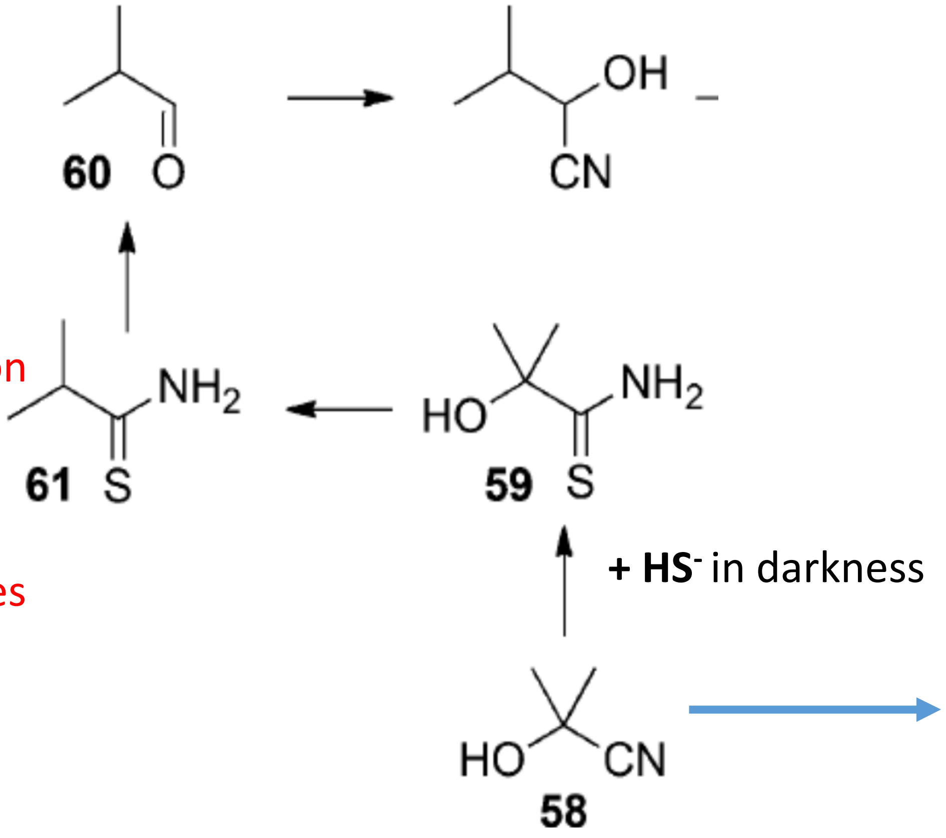


First signs of a linkage between all subsystems through cyanosulfidic chemistry.

Photoredox systems chemistry with hydrosulfide as the stoichiometric reductant. a) (Over-)reduction of glycolonitrile **45** to glycolaldehyde **4** (and acetaldehyde **49**), b) reductive homologation of **4** (and **49**) to **5** (and **51**), c) most of the aldehydes produced by this chemistry as Strecker amino acid precursors (boxed) and the self-destruction (as regards potential Strecker chemistry) of the cyanohydrin **52**.

J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

# *Cyanosulfidic chemistry*



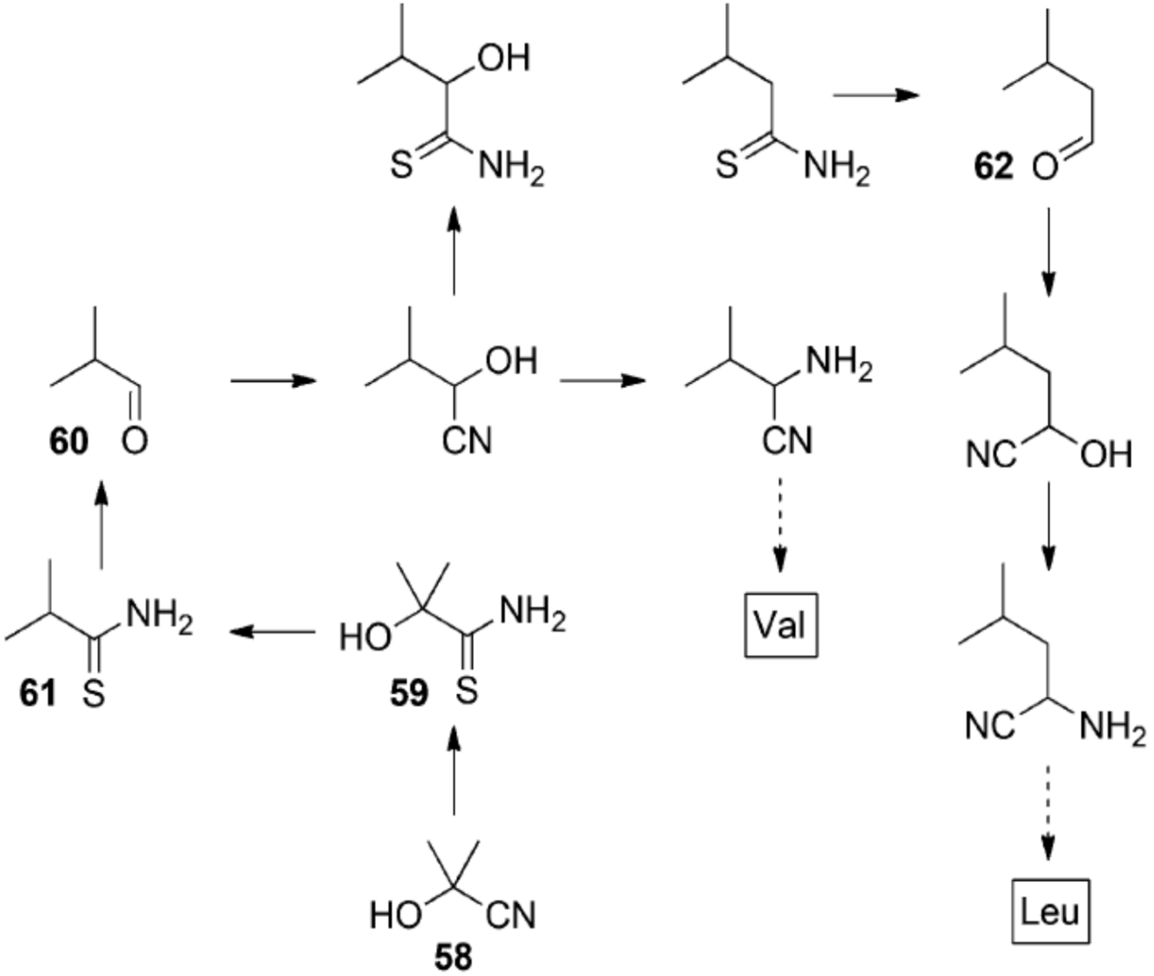
**+ $HS^-$** in darkness

Cyanohydrins undergo photoreduction to α-hydroxyaldehydes. α-hydroxythioamides first undergo photodeoxygenation to thioamides, and then photoreduction to aldehydes

Not reduced under applied conditions

J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

# *Cyanosulfidic chemistry*



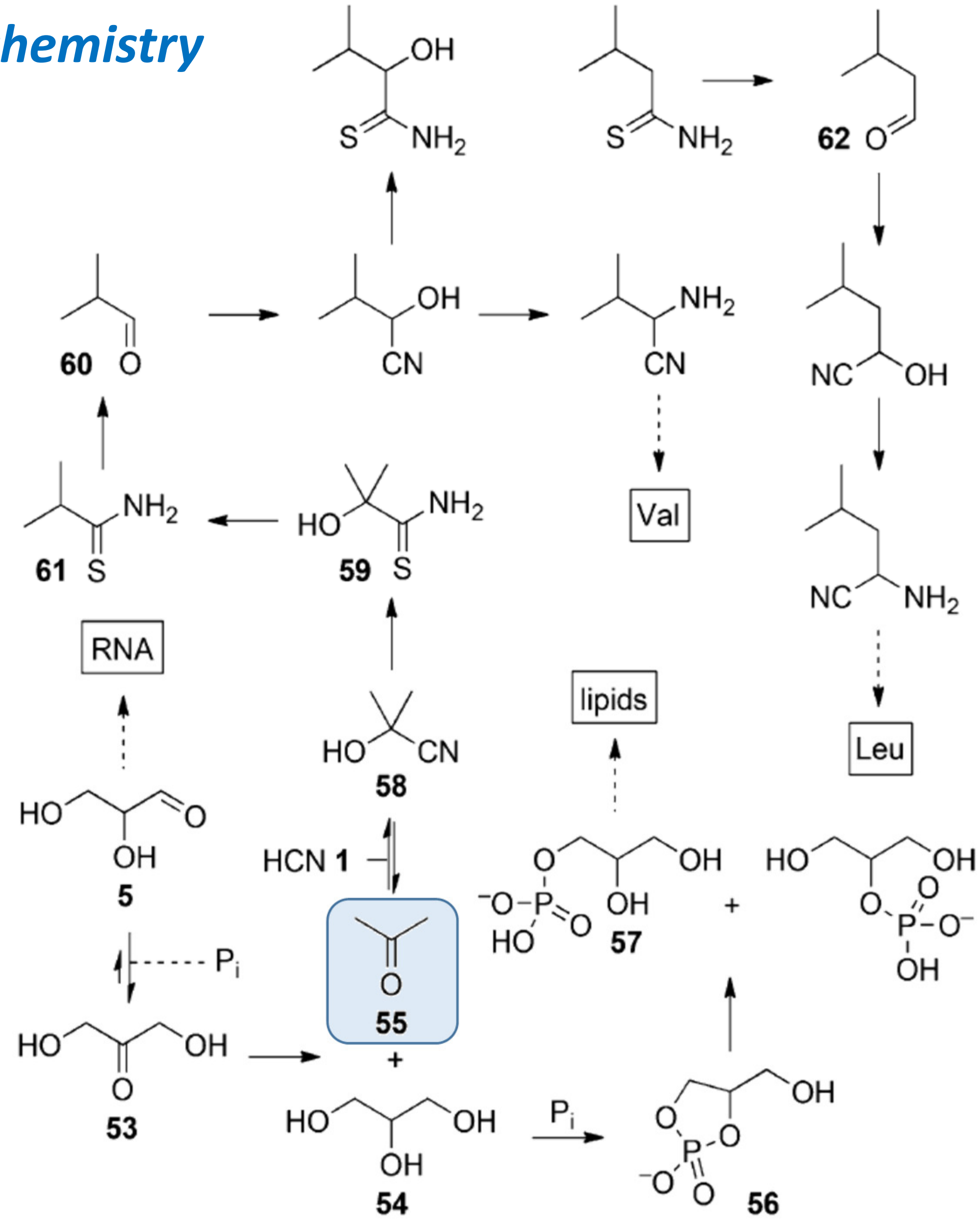
J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

# *Cyanosulfidic chemistry*

First signs of a linkage between all subsystems through cyanosulfidic chemistry.

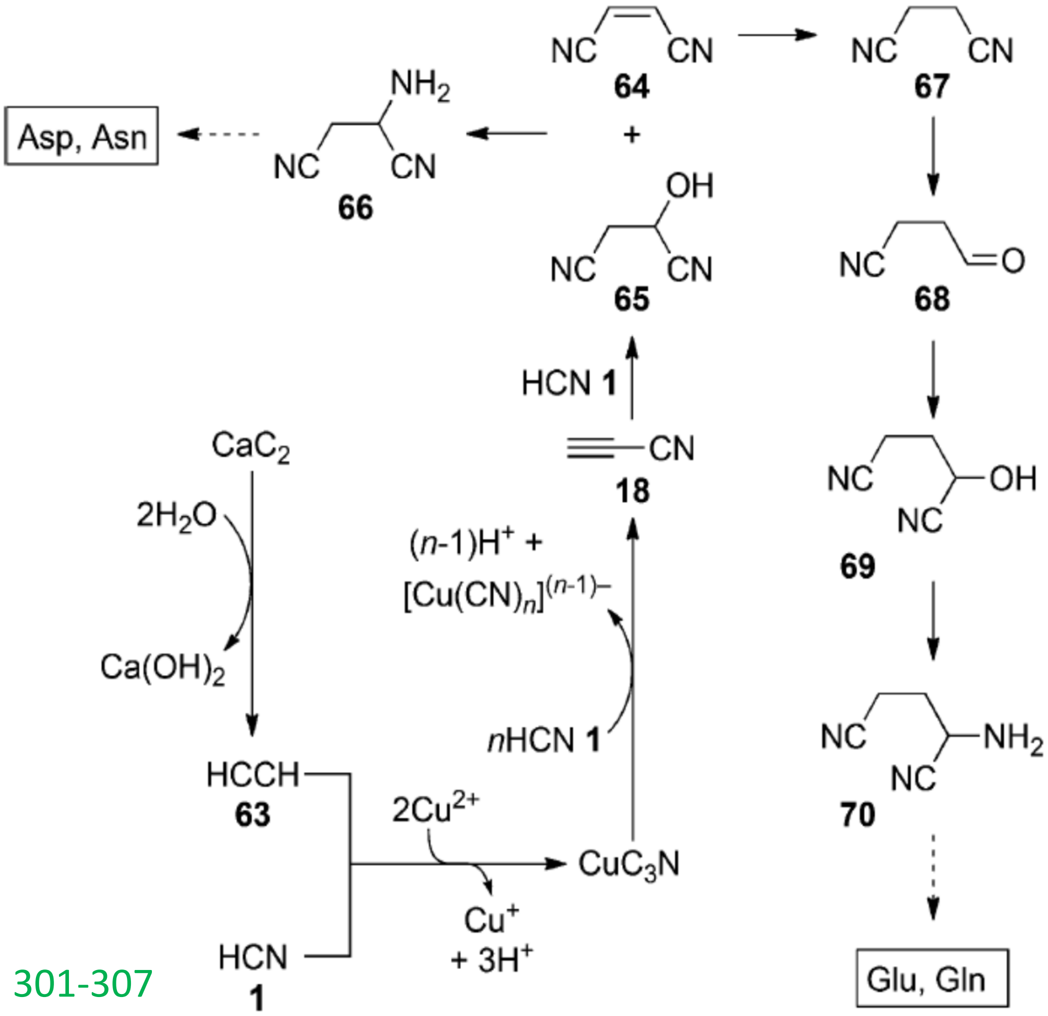
glyceraldehyde **5** is a precursor of pyrimidine nucleotides (**RNA**), Upon isomerization to **53** and reduction to glycerol **54**, it can be phosphorylated to yield phospho**lipids** (from **56** and **57**)...

The side product – acetone **55** – seems to be meaningful in the potentially prebiotic route for branched **aminoacids** Val and Leu



J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

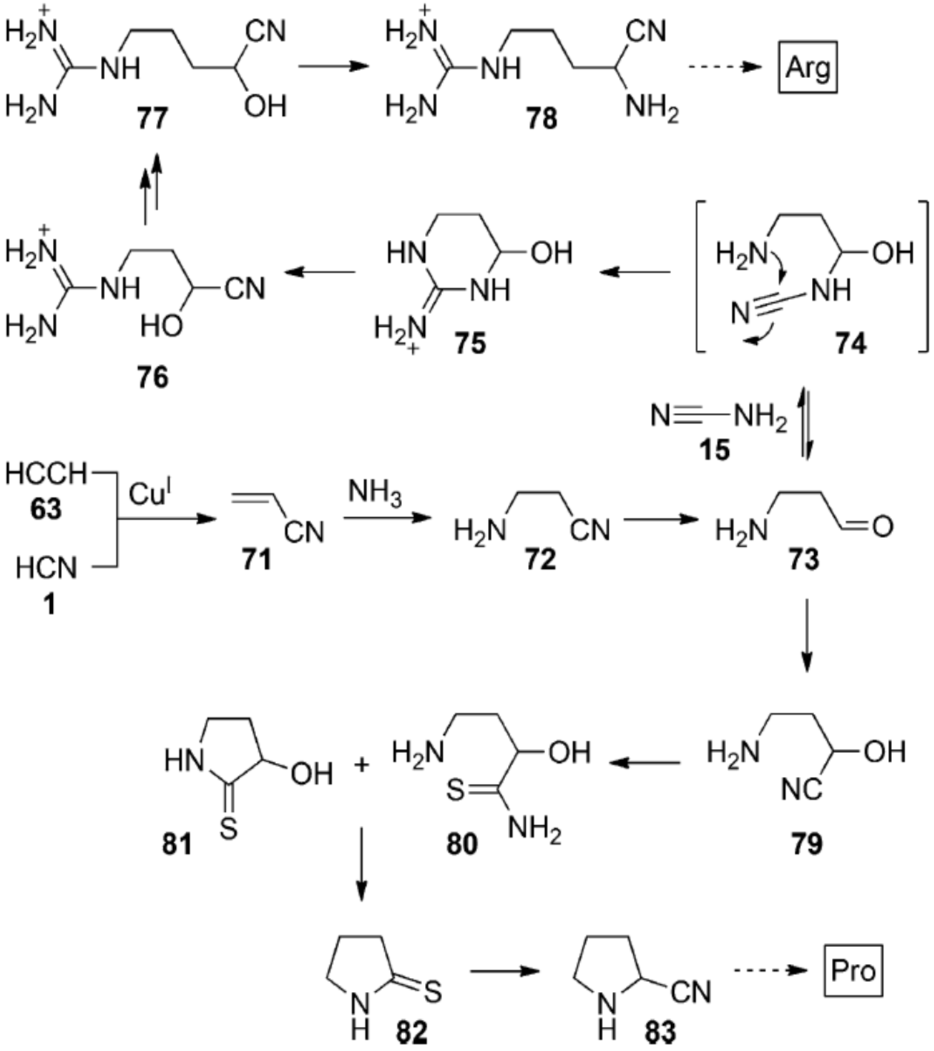
# *Cyanosulfidic chemistry*



J. D. Sutherland, *et al. Nature Chem.* **2015**, *7*, 301-307

Synthesis of cyanoacetylene **18** and reactions leading to amino acid precursors of Asp/Asn and Glu/Gln.

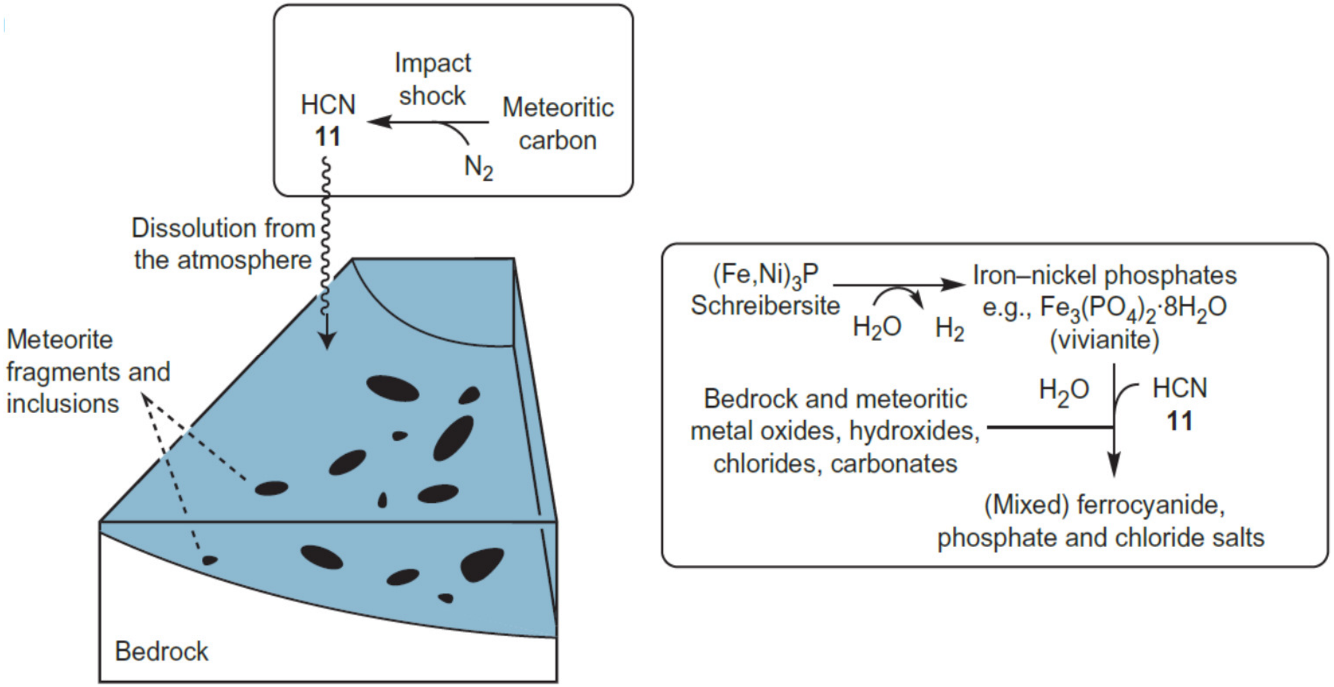
# *Cyanosulfidic chemistry*



Synthesis of acrylonitrile **71** and reactions leading to amino acid precursors therefrom.

# *Cyanosulfidic chemistry*

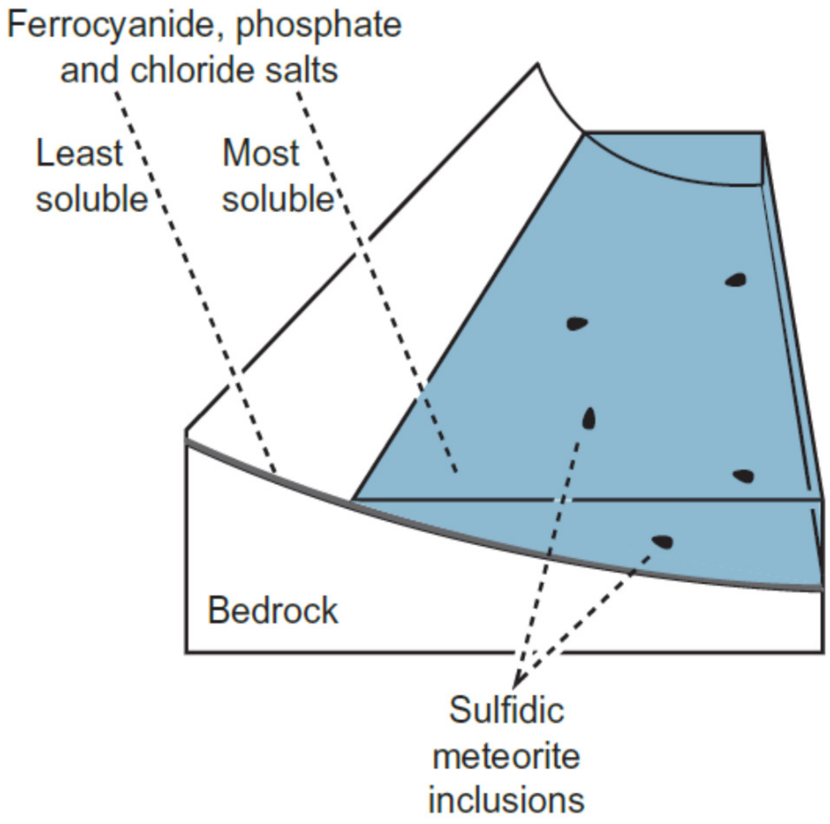
Chemistry in a post-meteoritic-impact scenario.
A series of post-impact environmental events are shown along with the chemistry (boxed) proposed to occur as a consequence of these events.



Dissolution of atmospherically produced hydrogen cyanide results in the conversion of vivianite (the anoxic corrosion product of the meteoritic inclusion schreibersite) into mixed ferrocyanide salts and phosphate salts, with counter cations being provided through neutralization and ion-exchange reactions with bedrock and other meteoritic oxides and salts.

# *Cyanosulfidic chemistry*

Chemistry in a post-meteoritic-impact scenario.
A series of post-impact environmental events are shown along with the chemistry (boxed) proposed to occur as a consequence of these events.



Partial evaporation results in the deposition of the least-soluble salts over a wide area, and further evaporation deposits the most-soluble salts in smaller, lower-lying areas.

# *Cyanosulfidic chemistry*

After complete evaporation, impact or geothermal heating results in thermal metamorphosis of the evaporite layer, and the generation of feedstock precursor salts (in bold).

$$(\mathrm{Na,K})_4[\mathrm{Fe(CN)_6}] \xrightarrow{700\ ^\circ\mathrm{C}} 4(\mathbf{Na/K})\mathbf{CN} + \mathrm{Fe(CN)_2}$$

$$3\mathrm{Fe(CN)_2} \xrightarrow{700\ ^\circ\mathrm{C}} \mathrm{Fe_3C} + 5\mathrm{C} + 3\mathrm{N_2}$$

$$\mathrm{Fe(CN)_2} \xrightarrow{700\ ^\circ\mathrm{C}} \mathrm{Fe} + 2\mathrm{C} + \mathrm{N_2}$$

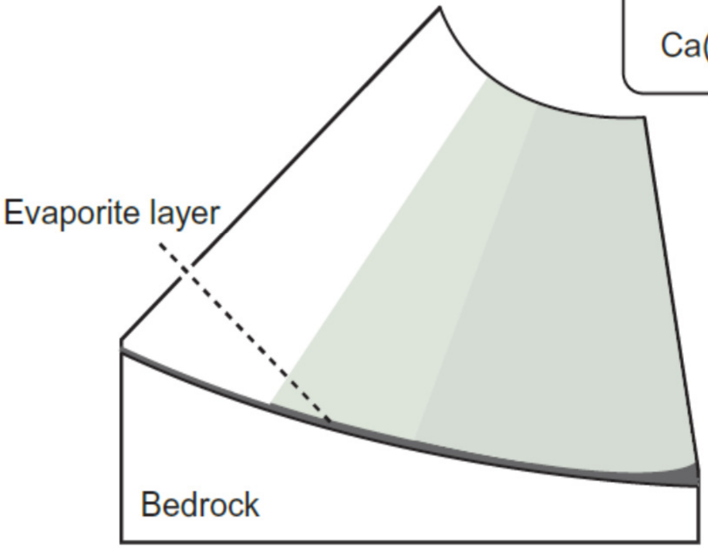
$$\mathrm{Mg_2[Fe(CN)_6]} \xrightarrow{315\ ^\circ\mathrm{C}} 2\mathrm{Mg(CN)_2} + \mathrm{Fe(CN)_2}$$

$$\mathrm{Mg(CN)_2} \xrightarrow{395\ ^\circ\mathrm{C}} \mathrm{MgCN_2} + \mathrm{C}$$

$$3\mathrm{MgCN_2} \xrightarrow{420\ ^\circ\mathrm{C}} \mathbf{Mg_3N_2} + 3\mathrm{C} + 2\mathrm{N_2}$$

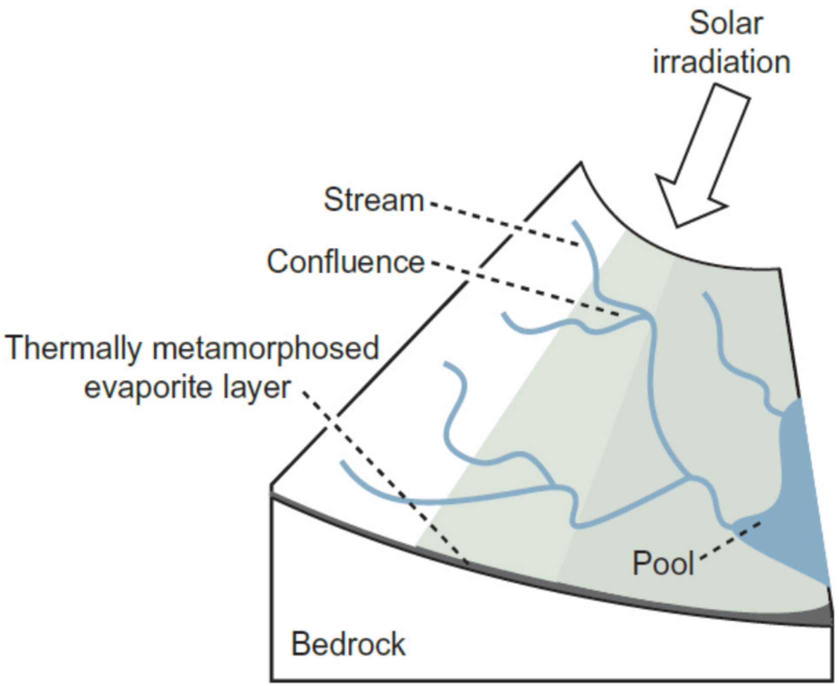
$$\mathrm{Ca_2[Fe(CN)_6]} \xrightarrow{660\ ^\circ\mathrm{C}} 2\mathrm{Ca(CN)_2} + \mathrm{Fe(CN)_2}$$

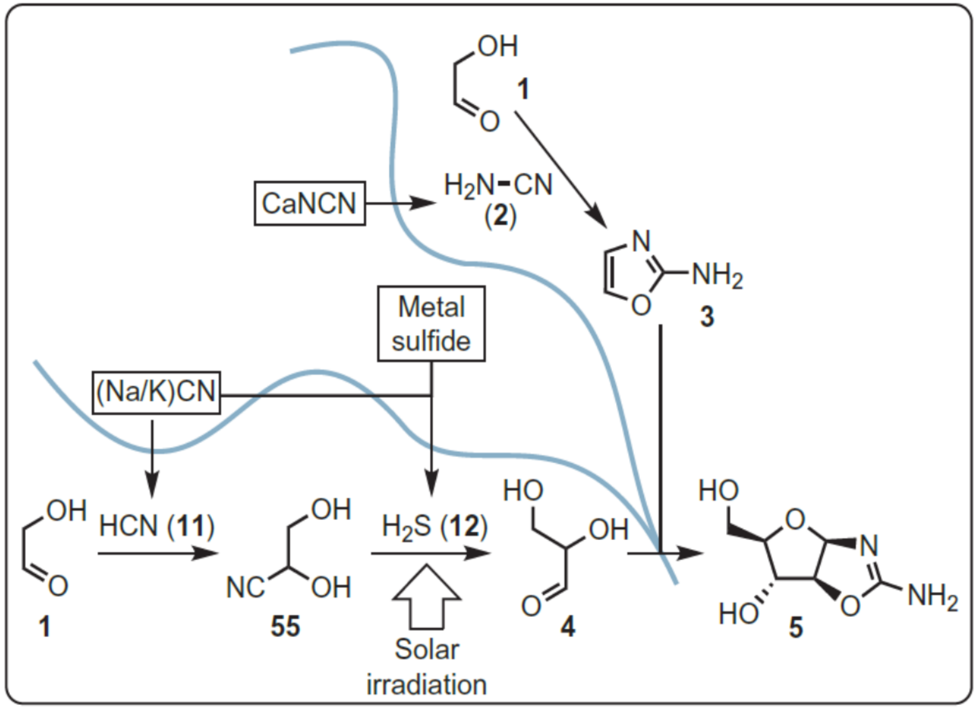
$$\mathrm{Ca(CN)_2} \xrightarrow{660\ ^\circ\mathrm{C}} \mathbf{CaNCN} + \mathrm{C} \overset{1{,}000\ ^\circ\mathrm{C}}{\rightleftharpoons} \mathbf{CaC_2} + \mathrm{N_2}$$



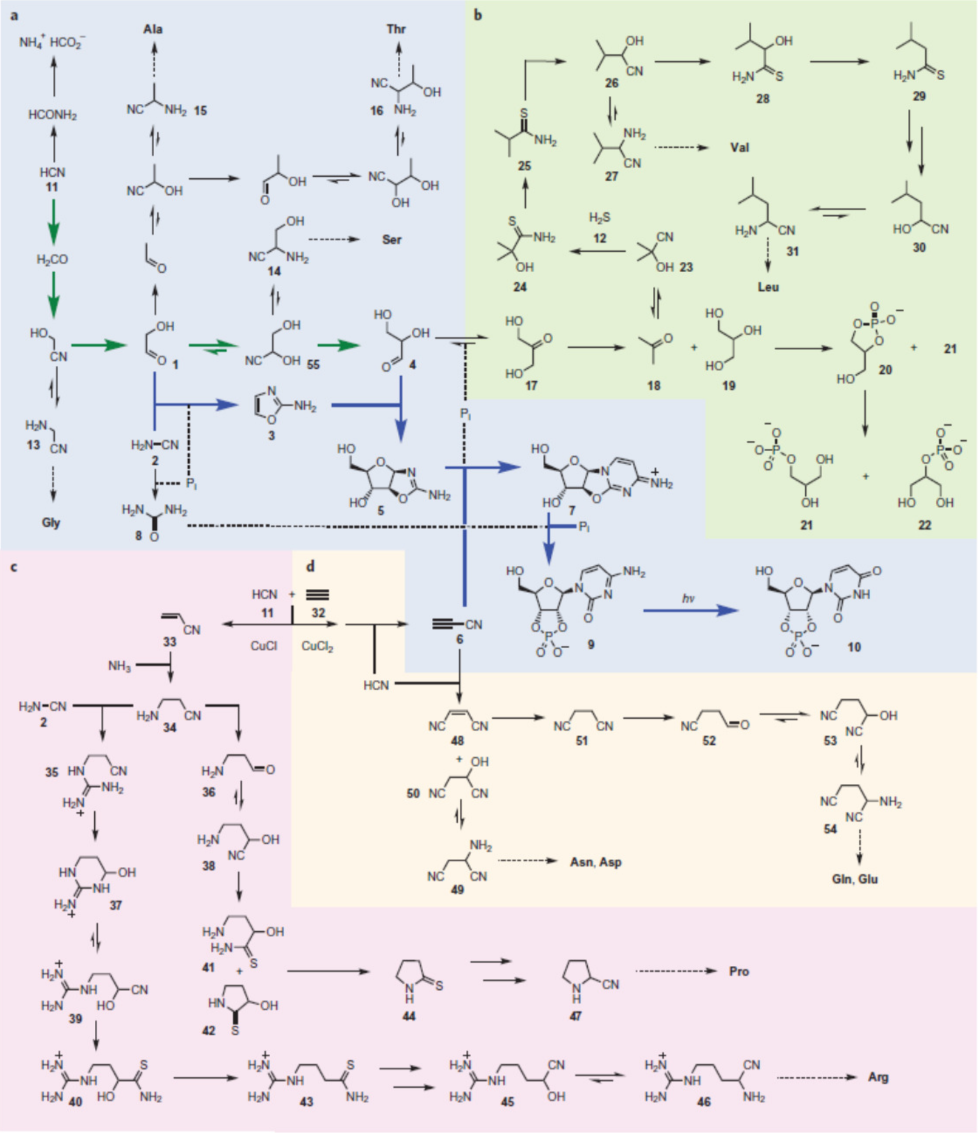
# *Cyanosulfidic chemistry*

Rainfall on higher ground (left) leads to rivulets or streams that flow downhill, sequentially leaching feedstocks from the thermally metamorphosed evaporite layer. Solar irradiation drives photoredox chemistry in the streams. Convergent synthesis can result when streams with different reaction histories merge (right), as illustrated here for the potential synthesis of arabinose aminooxazoline (5) at the confluence of two streams that contained glycolaldehyde (1), and leached different feedstocks before merging.





# *Cyanosulfidic chemistry system*



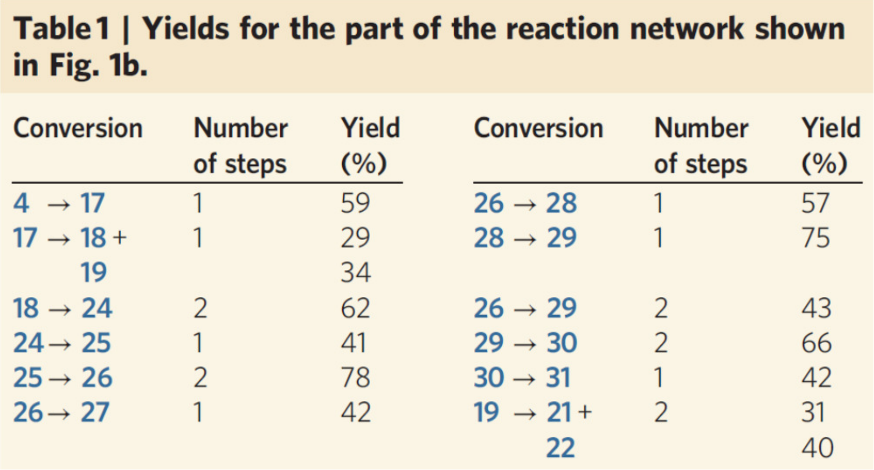


**Table 1 | Yields for the part of the reaction network shown in Fig. 1b.**

| Conversion | Number of steps | Yield (%) | Conversion | Number of steps | Yield (%) |
|---|---|---|---|---|---|
| 4 → 17 | 1 | 59 | 26 → 28 | 1 | 57 |
| 17 → 18 + | 1 | 29 | 28 → 29 | 1 | 75 |
| 19 | | 34 | | | |
| 18 → 24 | 2 | 62 | 26 → 29 | 2 | 43 |
| 24 → 25 | 1 | 41 | 29 → 30 | 2 | 66 |
| 25 → 26 | 2 | 78 | 30 → 31 | 1 | 42 |
| 26 → 27 | 1 | 42 | 19 → 21 + | 2 | 31 |
| | | | 22 | | 40 |

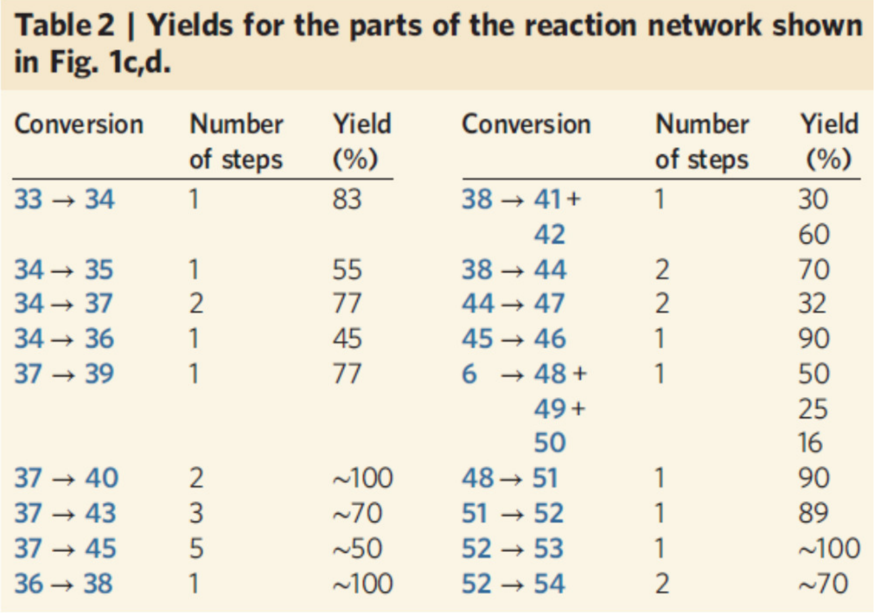
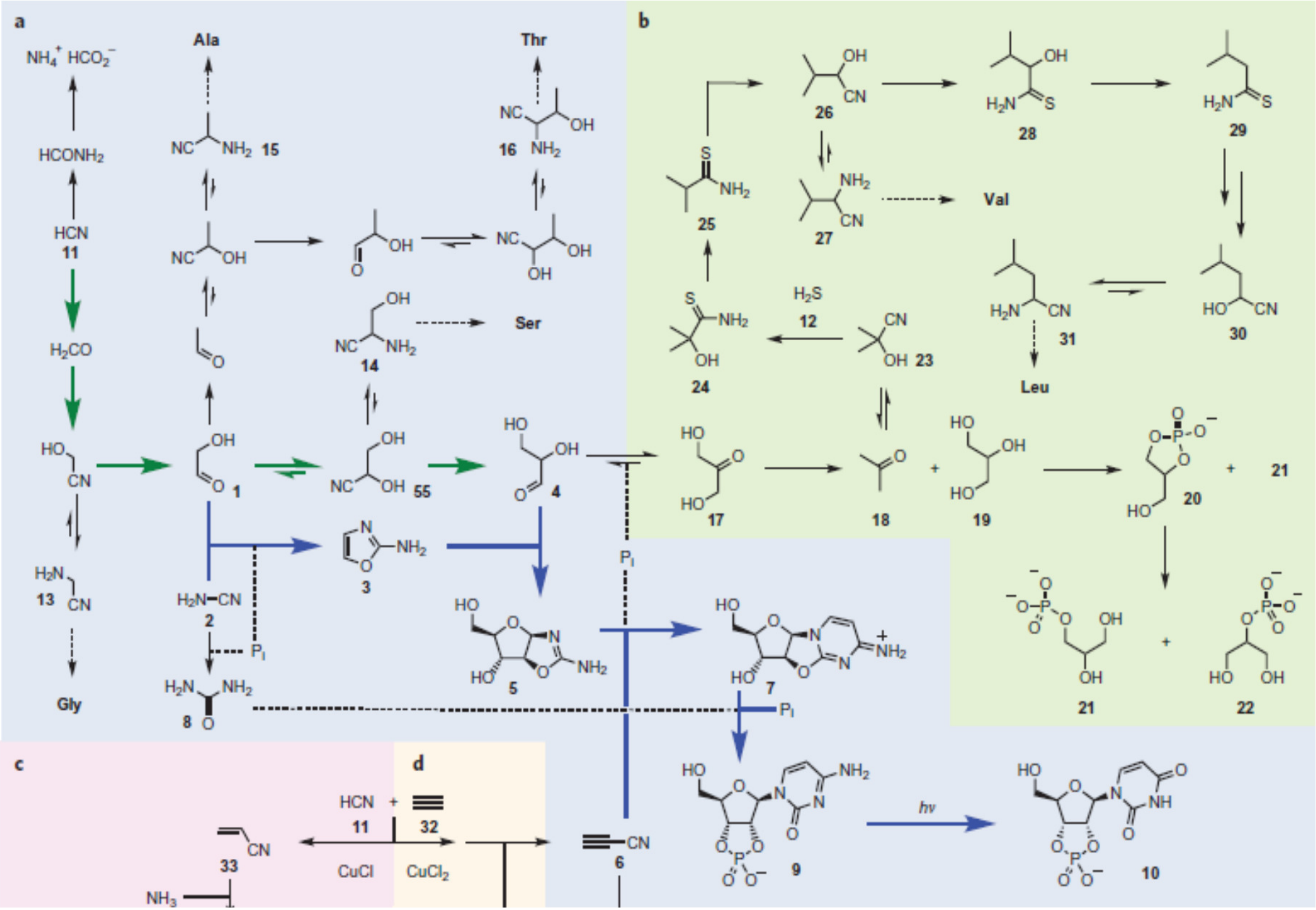


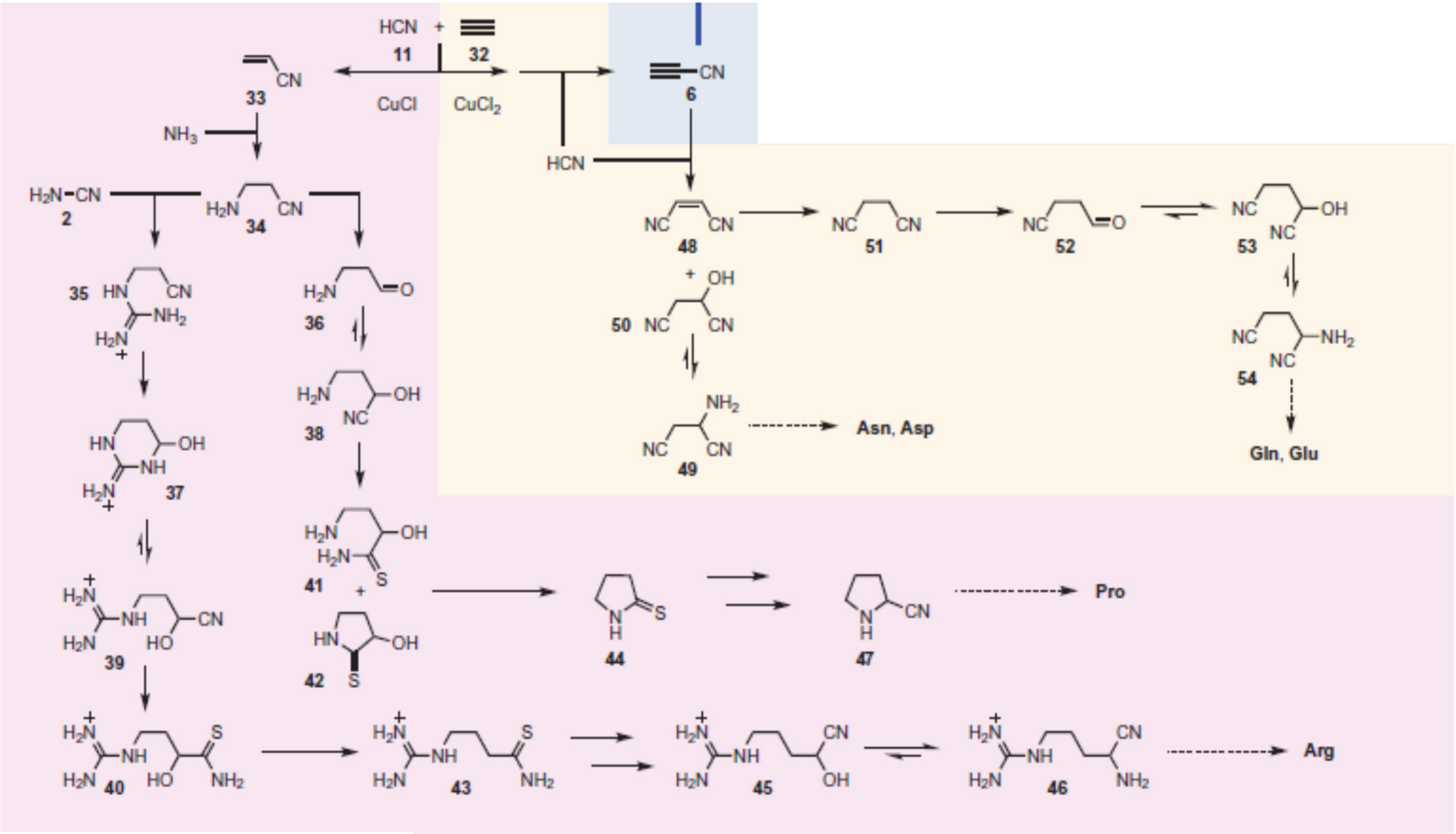
**Table 2 | Yields for the parts of the reaction network shown in Fig. 1c,d.**

| Conversion | Number of steps | Yield (%) | Conversion | Number of steps | Yield (%) |
|---|---|---|---|---|---|
| 33 → 34 | 1 | 83 | 38 → 41 + | 1 | 30 |
| | | | 42 | | 60 |
| 34 → 35 | 1 | 55 | 38 → 44 | 2 | 70 |
| 34 → 37 | 2 | 77 | 44 → 47 | 2 | 32 |
| 34 → 36 | 1 | 45 | 45 → 46 | 1 | 90 |
| 37 → 39 | 1 | 77 | 6 → 48 + | 1 | 50 |
| | | | 49 + | | 25 |
| | | | 50 | | 16 |
| 37 → 40 | 2 | ~100 | 48 → 51 | 1 | 90 |
| 37 → 43 | 3 | ~70 | 51 → 52 | 1 | 89 |
| 37 → 45 | 5 | ~50 | 52 → 53 | 1 | ~100 |
| 36 → 38 | 1 | ~100 | 52 → 54 | 2 | ~70 |

# *Cyanosulfidic chemistry system*



# Cyanosulfidic chemistry system

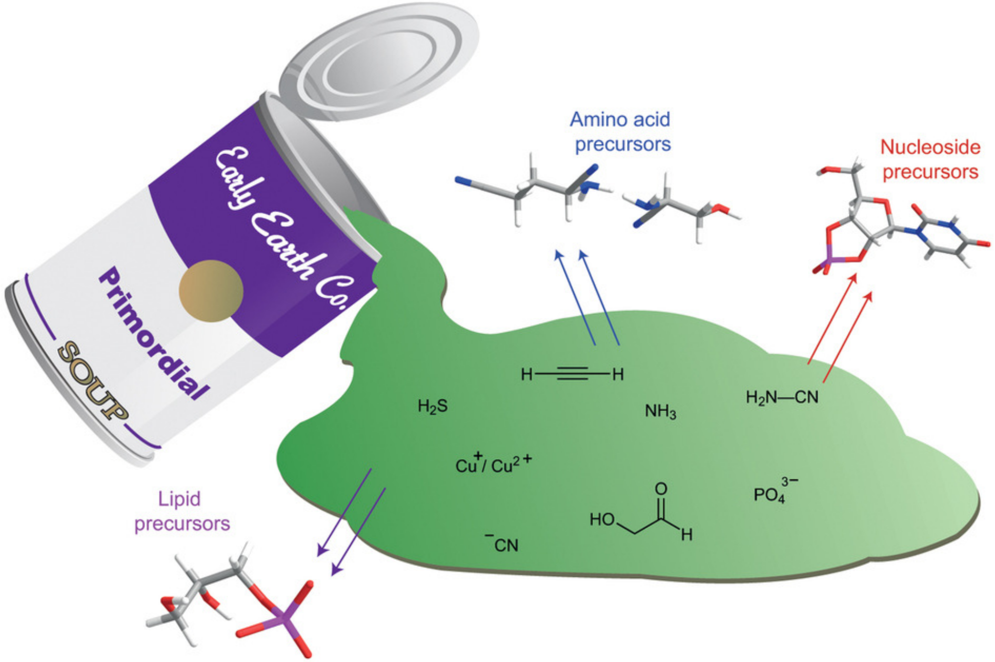


# *Remaining challenges of prebiotic nucleotide synthesis*

Homochirality of currently known biomolecules

Prebiotic synthesis of purine nucleotides and deoxyribonucleotides

Prebiotic polymerization

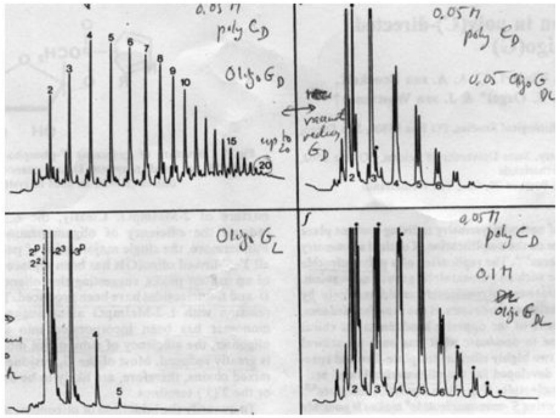


# *Enantiomeric excess in the cyanosulfidic chemistry*

Polymerization of *D*-nucleotides is suppressed in presence of *L*-nucleotides – the problem of „enantiomeric cross-inhibition"

Incorporation of *L*-enantiomers into growing chains of *D*-oligonucleotides → families of diastereomers for each sequence → problematic development of phenotypic RNA properties

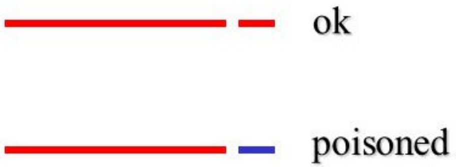
Without access to highly enantioenriched sugars, the nucleotides formed during the ‚cyanosulfidic chemistry' synthesis would not lead to informational polymers capable of establishing a genetic code



template-directed oligomerization
poly ($C_D$) → oligo ($G_D$)

cytosine    guanine

→ Mononucleotides with wrong chirality terminate chain growth



(using HPLC)

→ *enantiomeric cross-inhibition*

G. F. Joyce, G. M. Visser, C. A. A. Van Boeckel, J. H. Van Boom, L. E. Orgel, J. Van Westrenen, *Nature* **1984**, *310*, 602-604

# *Chiral amplification and the origins of homochirality*

Enantioenriched aminoacids present in meteorites (up to 18 % ee *L*-isomers). Further enantioenrichment is possible by manipulation of aminoacid phase behavior:

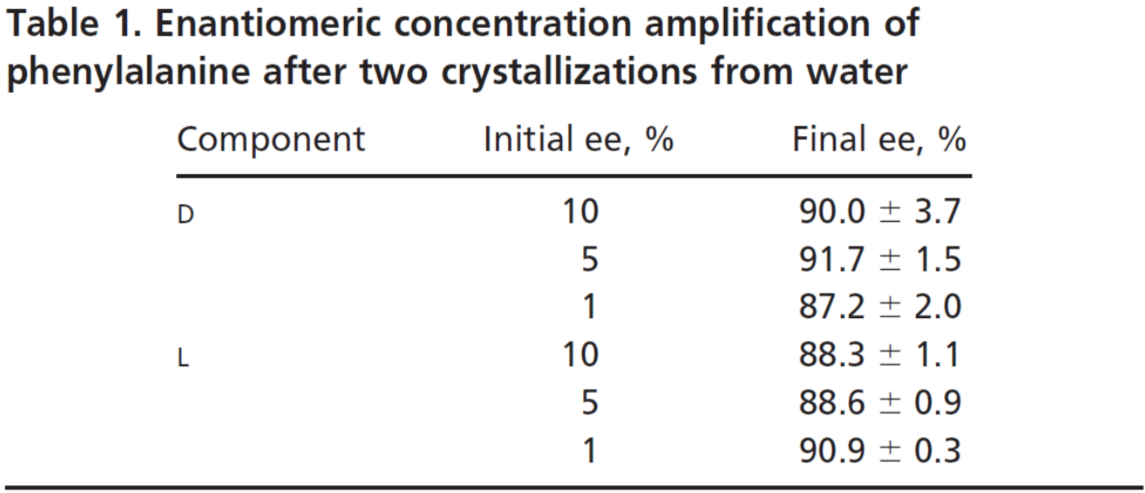
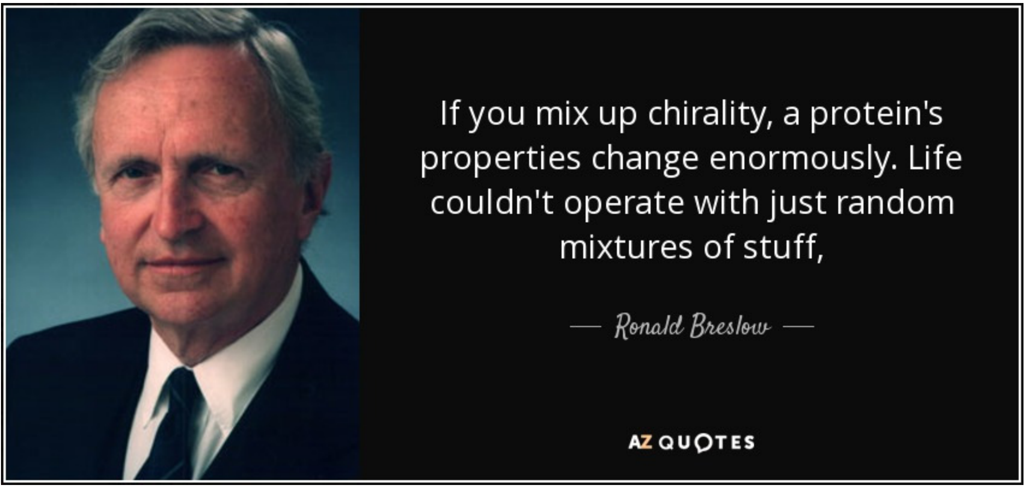


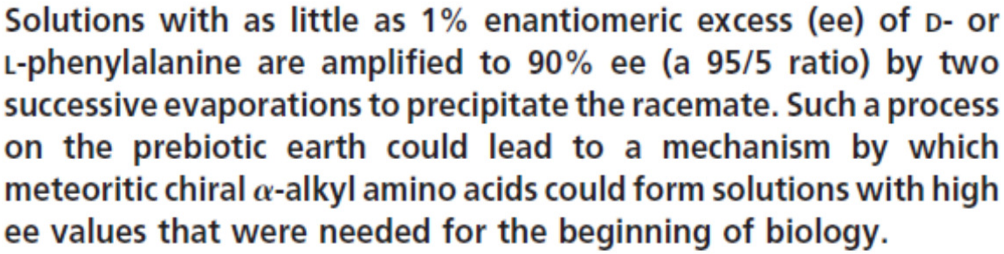
**Table 1. Enantiomeric concentration amplification of phenylalanine after two crystallizations from water**

| 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 |



If you mix up chirality, a protein's properties change enormously. Life couldn't operate with just random mixtures of stuff,

— Ronald Breslow —



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.

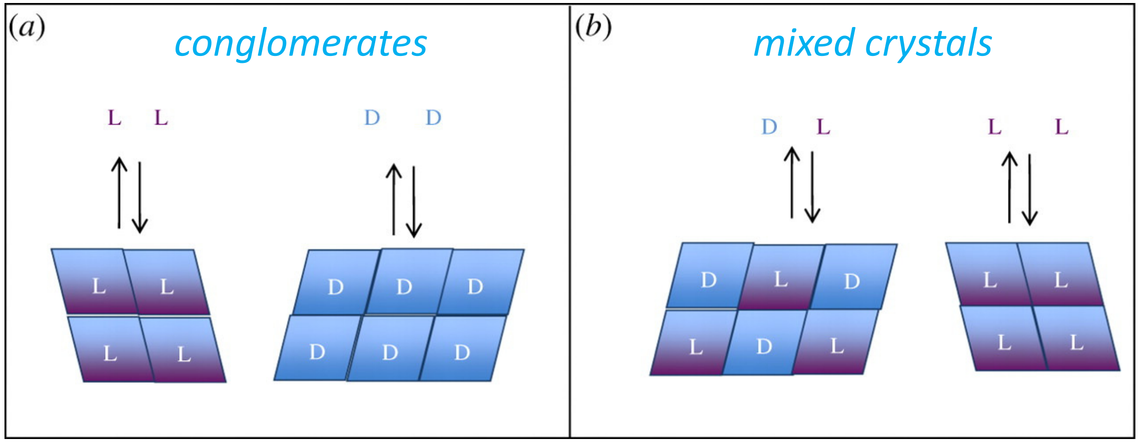
**Prof. Ronald Breslow**
**Columbia University, USA**

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

# *Eutectic solutions over enantioenriched aminoacids*

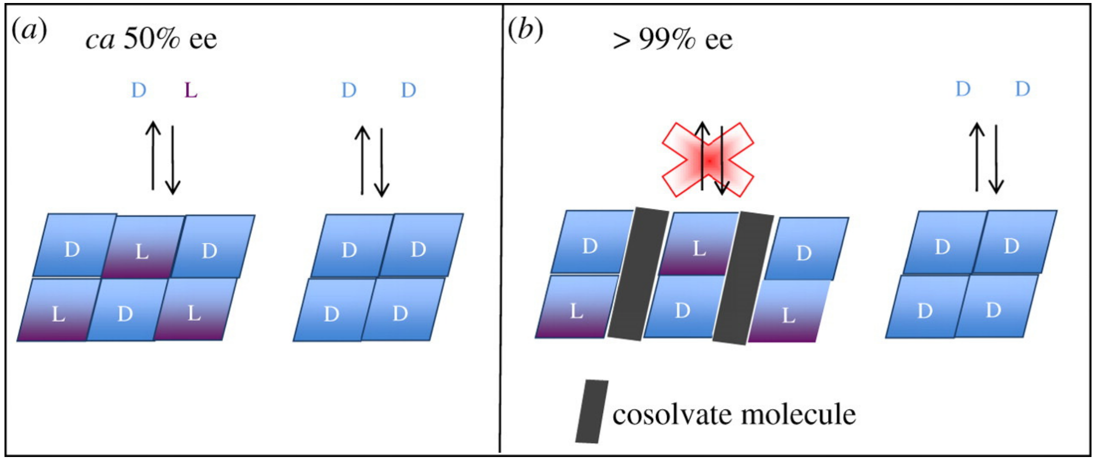
Mixtures of enantiomers can crystallize as conglomerates (a single crystal contains only molecules of one handedness) or racemates (a single crystal is racemic).

Enantioenriched mixtures give mixtures of crystals which would have the same ee value upon re-solubilization



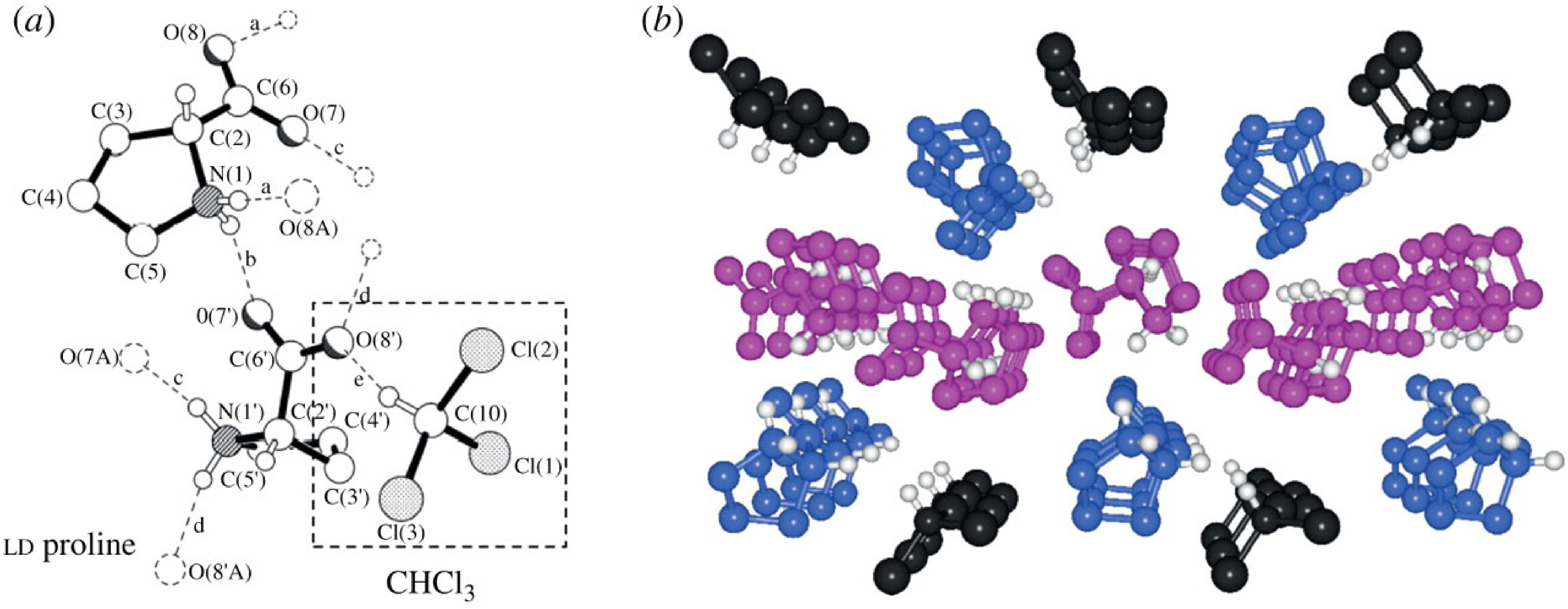
Highly enantioenriched solutions may be obtained from a small initial enantiomeric imbalance for many aminoacids, including proline, via physical amplification processes that sequester the minor enantiomer as racemic solid.

Manipulation of eutectic ee value by formation of a solvate that reduces the solubility of the racemic compound



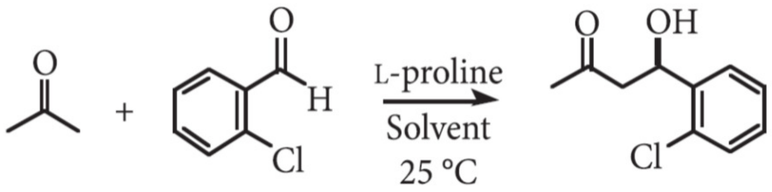
D. Blackmond *Phil. Trans. R. Soc. B* **2011,** *366,* 2878-2884

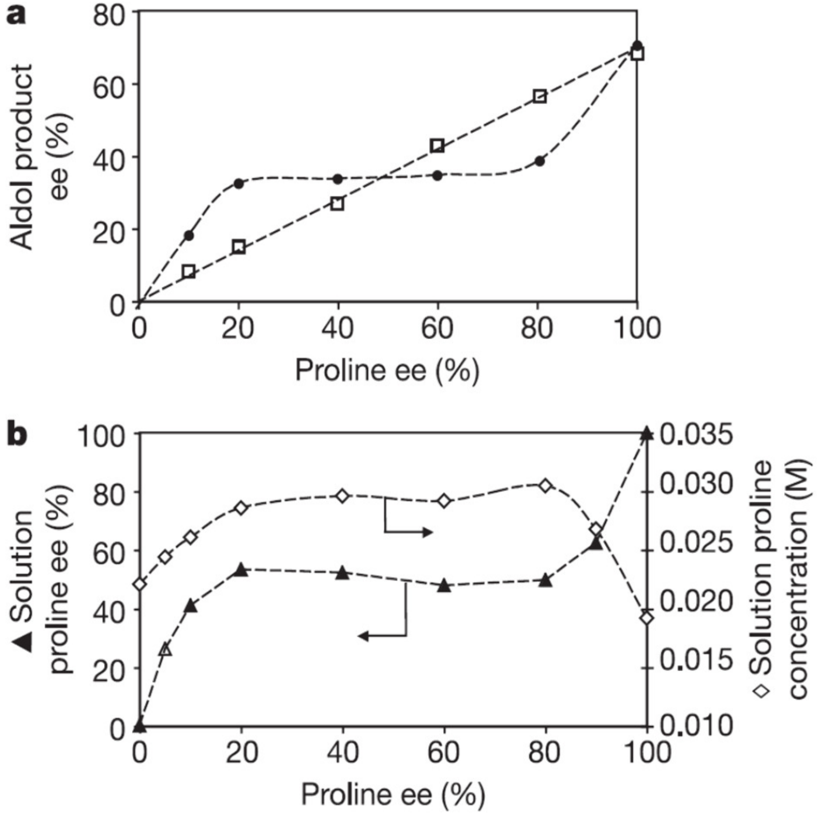
# *Eutectic solutions over enantioenriched aminoacids*



D. Blackmond *Phil. Trans. R. Soc. B* **2011,** *366,* 2878-2884

# *Eutectic solutions over enantioenriched aminoacids*





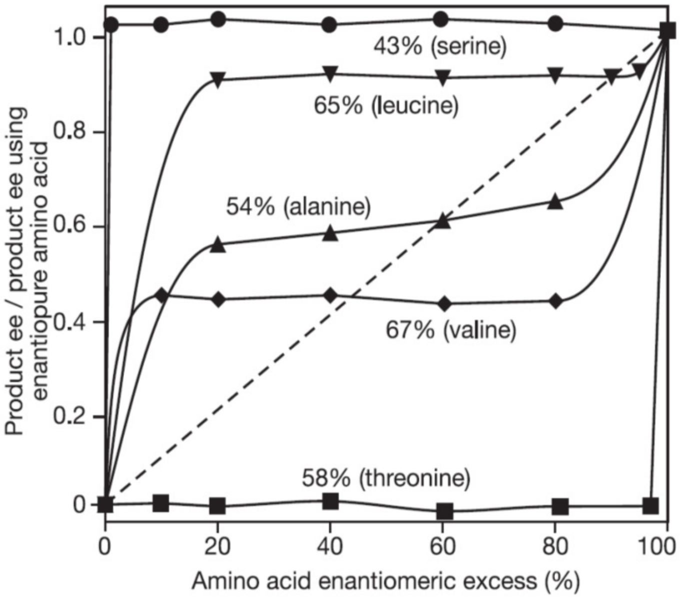
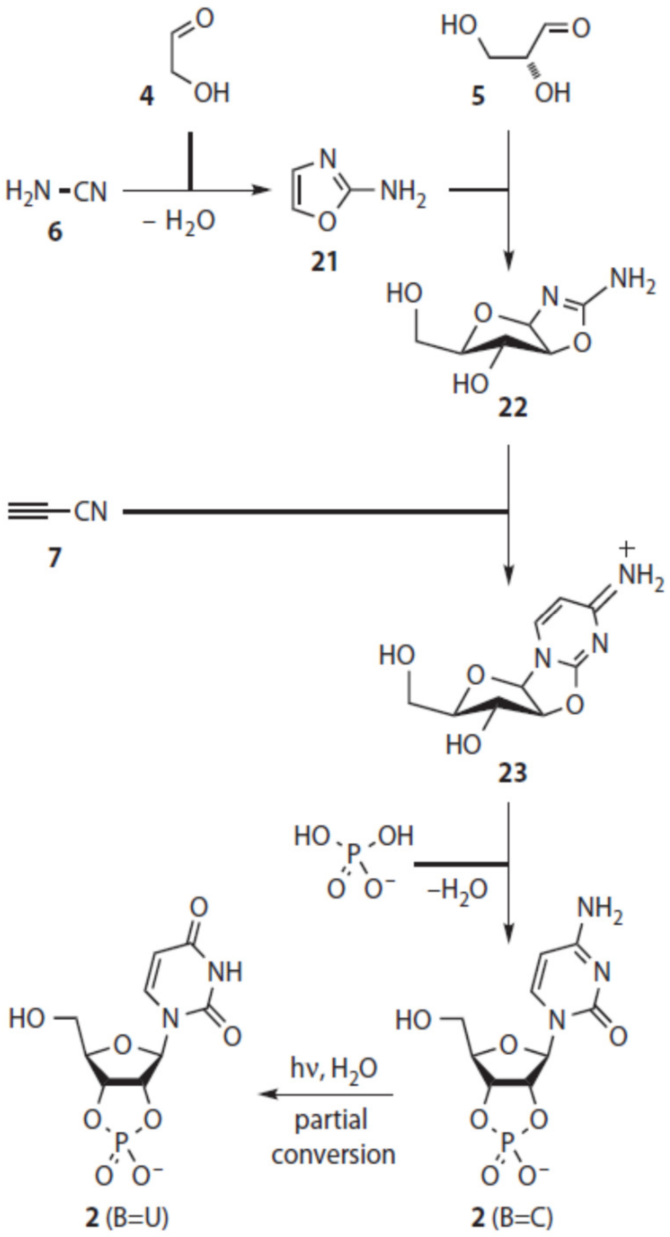


**Table 1** | **Solution enantiomeric excess at the eutectic point in water at 25 °C for selected amino acids**

| 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

# *Cyanosulfidic chemistry*



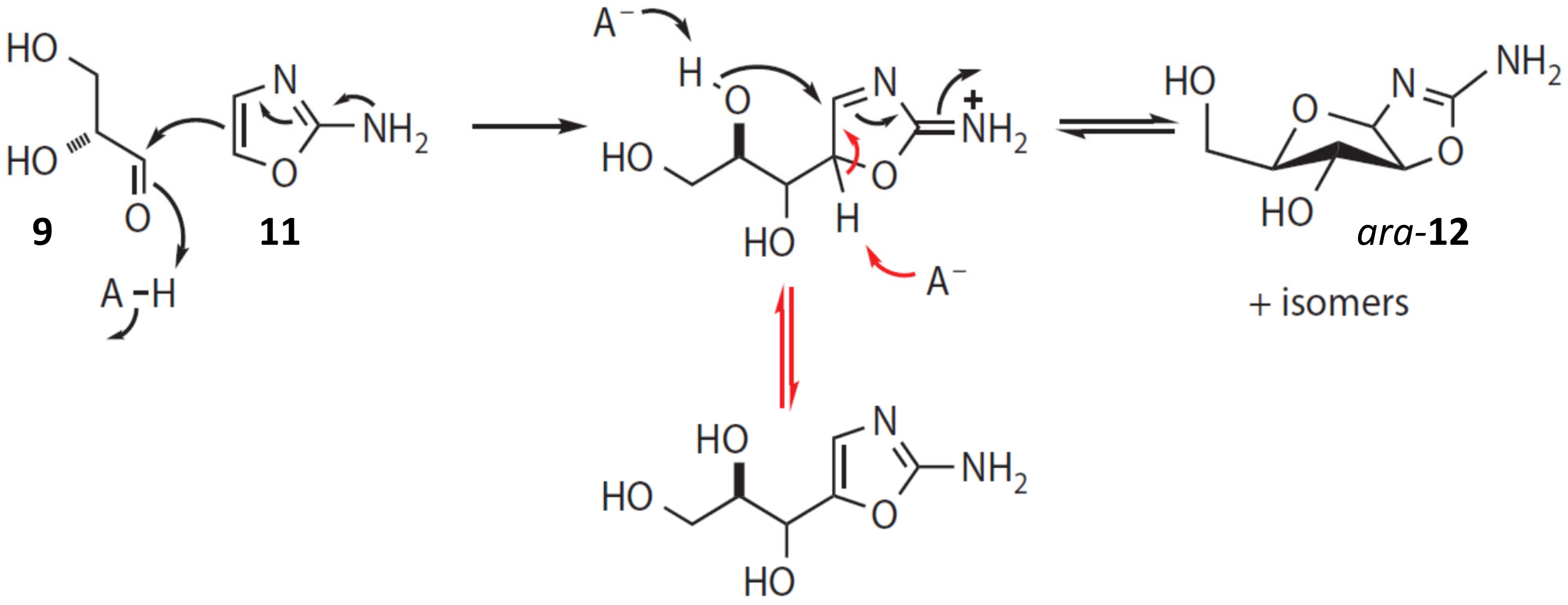
The recently uncovered route to activated pyrimidine nucleotides **2**.

The nucleobase ribosylation problem is circumvented by the assembly proceeding through 2-aminooxazole **21**, which can be thought of as the chimera of half a pentose sugar and half a nucleobase. The second half of the pentose - glyceraldehyde **5** -and the second half of the nucleobase—cyanoacetylene **7**—are then added sequentially to give the anhydronucleoside **23**.

Phosphorylation and rearrangement of **23** then furnishes **2** (B=C), and UV irradiation effects the partial conversion of **2** (B=C) to **2** (B=U).

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

# *Cytosine-2’,3’cP – step 2: pentose-amino-oxazolines*



9

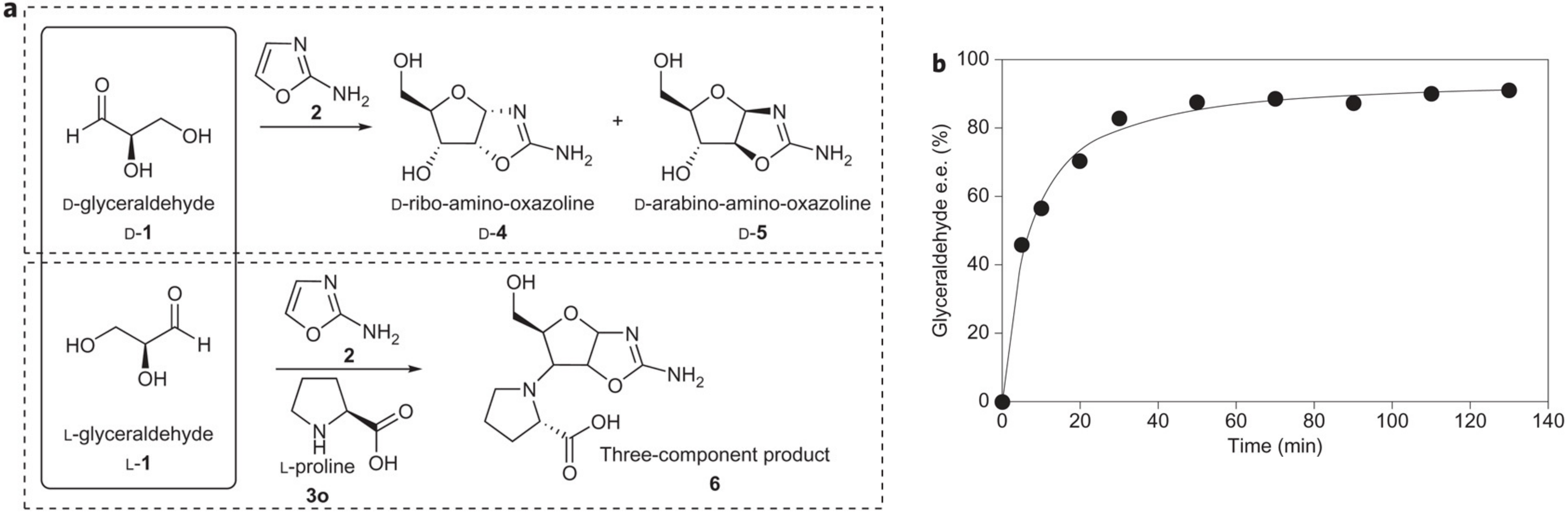
11

*ara*-**12**

+ isomers

M. W. Powner, B. Gerland, J. D. Sutherland, *Nature* **2009**, *459*, 239–242

# *Enantiomeric excess in the cyanosulfidic chemistry*



**a**, In the presence of an enantioenriched L-proline (3o), the diastereoselective formation of a three-component side product (6) effectively sequesters the unnatural L-glyceraldehyde (L-1).

**b**, The side reaction acts as a kinetic resolution of glyceraldehyde, giving enantiorichment of greater than 90% e.e. D-1, which reacts with 2 to form the enantioenriched amino-oxazoline RNA precursors D-4 and D-5. e.e. values are ±2%.

J. E. Hein, E. Tse, D. G. Blackmond, *Nature Chem.*, **2011**, *3*, 704-706

# *Enantiomeric excess in the cyanosulfidic chemistry*

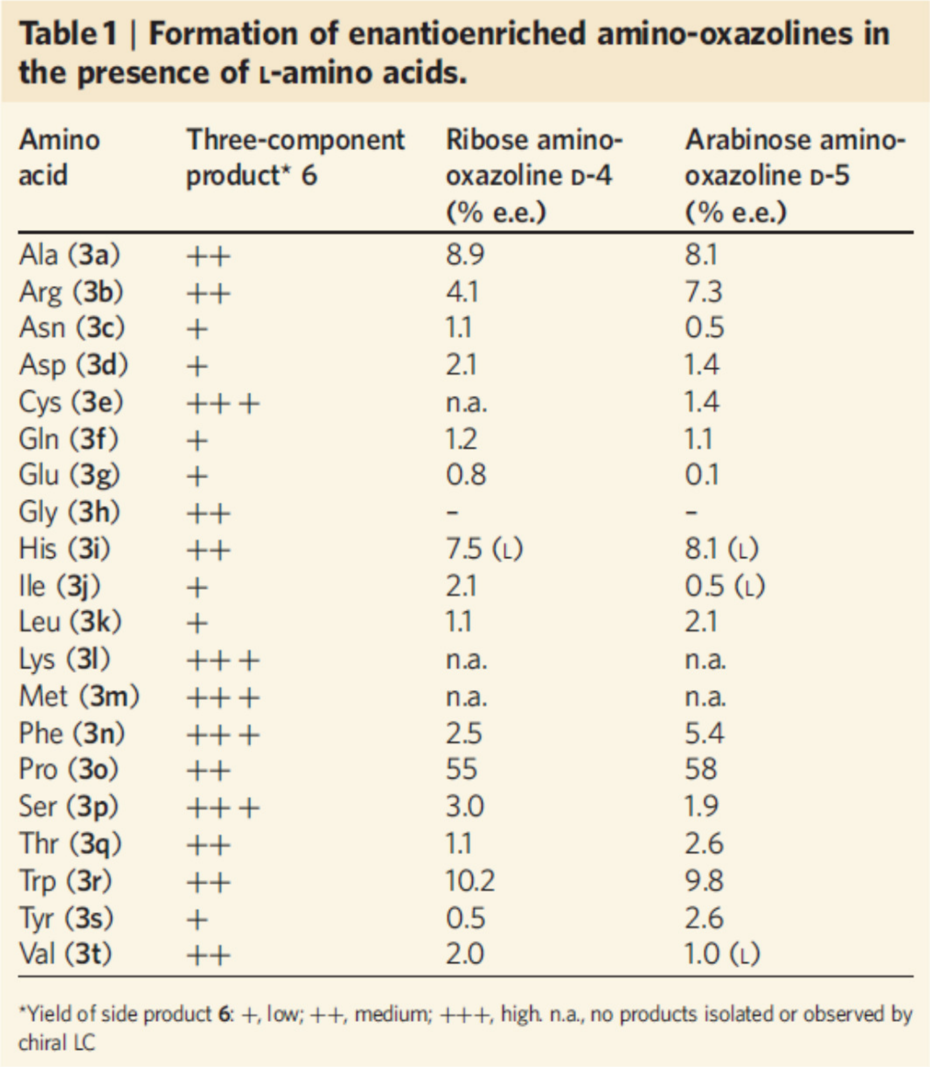
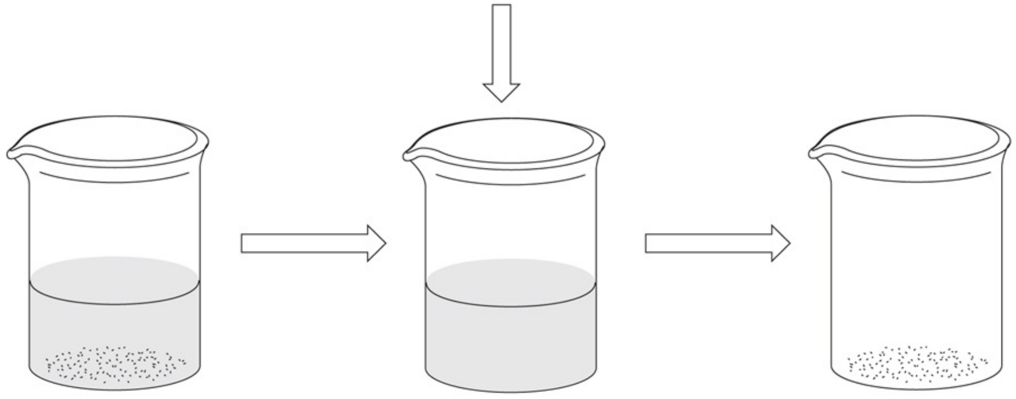


**Table 1 | Formation of enantioenriched amino-oxazolines in the presence of L-amino acids.**

| Amino acid | Three-component product* 6 | Ribose amino-oxazoline D-4 (% e.e.) | Arabinose amino-oxazoline D-5 (% e.e.) |
|---|---|---|---|
| Ala (**3a**) | ++ | 8.9 | 8.1 |
| Arg (**3b**) | ++ | 4.1 | 7.3 |
| Asn (**3c**) | + | 1.1 | 0.5 |
| Asp (**3d**) | + | 2.1 | 1.4 |
| Cys (**3e**) | +++ | n.a. | 1.4 |
| Gln (**3f**) | + | 1.2 | 1.1 |
| Glu (**3g**) | + | 0.8 | 0.1 |
| Gly (**3h**) | ++ | - | - |
| His (**3i**) | ++ | 7.5 (L) | 8.1 (L) |
| Ile (**3j**) | + | 2.1 | 0.5 (L) |
| Leu (**3k**) | + | 1.1 | 2.1 |
| Lys (**3l**) | +++ | n.a. | n.a. |
| Met (**3m**) | +++ | n.a. | n.a. |
| Phe (**3n**) | +++ | 2.5 | 5.4 |
| Pro (**3o**) | ++ | 55 | 58 |
| Ser (**3p**) | +++ | 3.0 | 1.9 |
| Thr (**3q**) | ++ | 1.1 | 2.6 |
| Trp (**3r**) | ++ | 10.2 | 9.8 |
| Tyr (**3s**) | + | 0.5 | 2.6 |
| Val (**3t**) | ++ | 2.0 | 1.0 (L) |

*Yield of side product **6**: +, low; ++, medium; +++, high. n.a., no products isolated or observed by chiral LC



Racemic glyceraldehyde
2-amino-oxazole

1% e.e. proline

Enantioenriched
amino-oxazolines

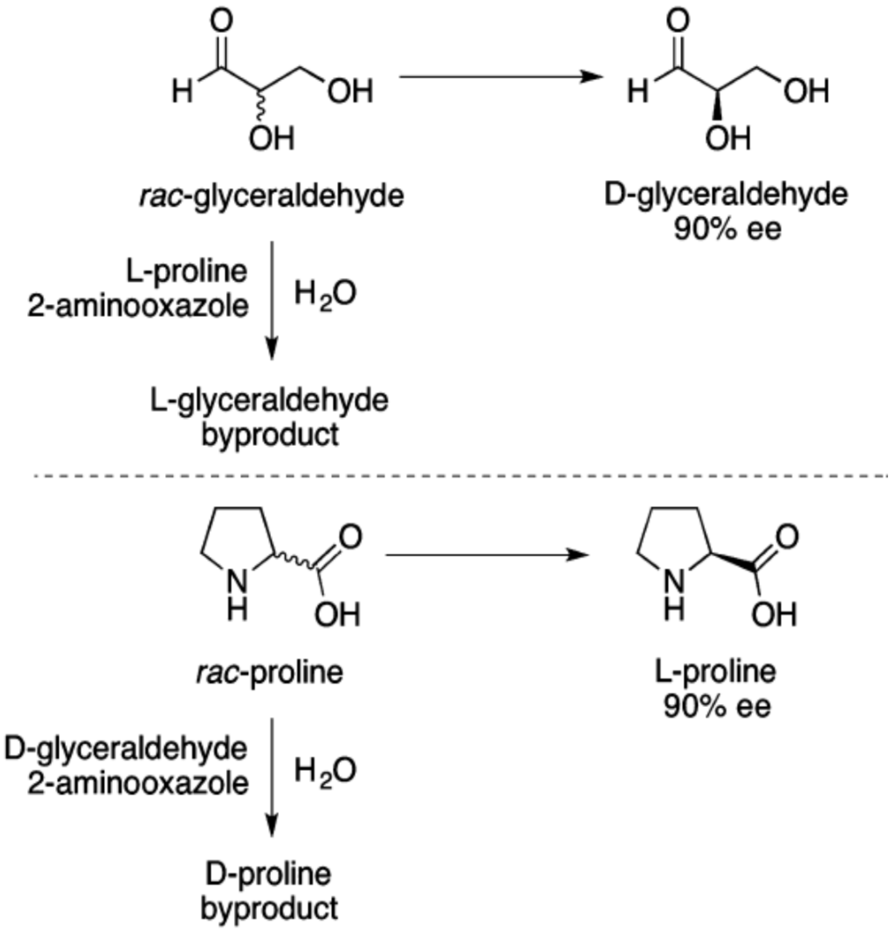
Enantiopure
ribo-amino-oxazoline
crystals

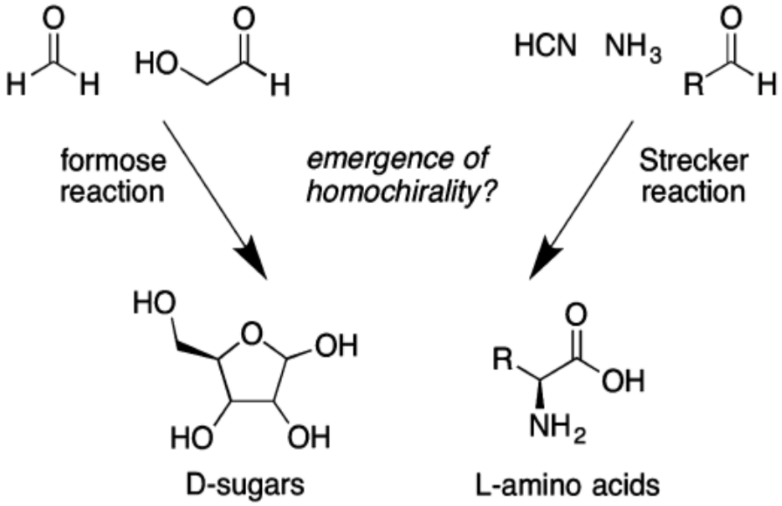
Physical enrichment → Chemical enrichment → Physical enrichment

1% e.e. L-proline (3o) is suspended in solvent (either $CHCl_3$ or EtOH). After equilibration, the remaining solid is removed and the solvent is evaporated from the supernatant. Racemic glyceraldehyde DL-**1** and amino-oxazole **2b** are then added and the mixture is dissolved in water. The ensuing reaction produces amino-oxazolines **4** and **5** in 20–80% e.e. Cooling the mixture to 4 °C induces crystallization of enantiopure ribo-amino-oxazoline crystals.

J. E. Hein, E. Tse, D. G. Blackmond, *Nature Chem.*, **2011**, *3*, 704-706

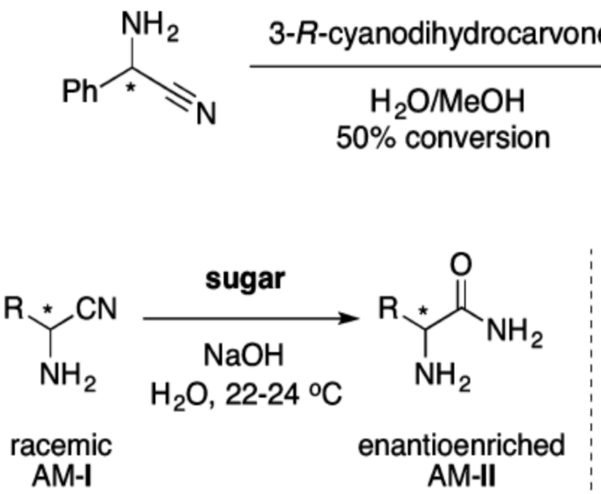
# *Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis*





D. G. Blackmond *et al.*, *ACS Cent. Sci.*, **2017**, *3*, 322-328

# *Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis*



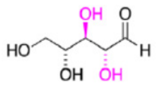
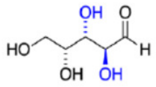
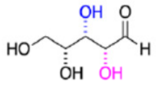
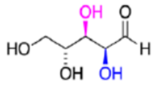
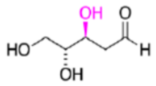
AM = Ala R = $CH_3$
AM = Phe R = $CH_2$-Ph
AM = Trp R = $CH_2$-indole

**Table 2. Opposite Sense of Enantioenrichment of Phe-II for L-Sugars**[a]

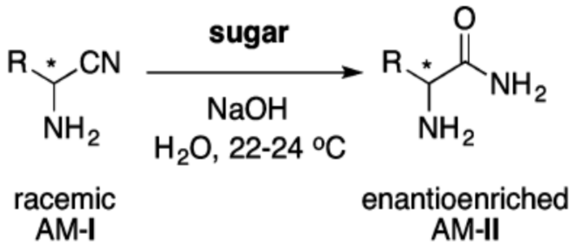
| Sugar | Phe-**II** e.e. (%) |
|---|---|
| L-ribose | 69 (L) |
| L-lyxose | 81 (D) |
| L-xylose | 31 (L) |
| L-arabinose | 43 (D) |

D. G. Blackmond *et al.*, *ACS Cent. Sci.*, **2017**, *3*, 322-328

**Table 1. Enantioenrichment of Amino Acid Precursors Driven by D-Sugars (Scheme 3)**[a]

| Sugar | | Ala-**II** e.e.(%) | Phe-**II** e.e.(%) | Trp-**II** e.e.(%) |
|---|---|---|---|---|
| D-ribose |  | 65 (D) | 70 (D) | 33 (D) |
| D-lyxose |  | 83 (L) | 83 (L) | 59 (L) |
| D-xylose |  | 45 (D) | 35 (D) | 11 (D) |
| D-arabinose |  | 58 (L) | 48 (L) | 38 (L) |
| D-deoxyribose |  | 29 (D) | 32 (D) | 33 (D) |
| D-ribose + D-lyxose | | 45 (L) | 14 (L) | 18 (L) |
| D-ribose + D-lyxose + D-xylose + D-arabinose | | 47 (L) | 18 (L) | 20 (L) |

# *Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis*



AM = Ala  R = $CH_3$
AM = Phe  R = $CH_2$-Ph
AM = Trp  R = $CH_2$-indole

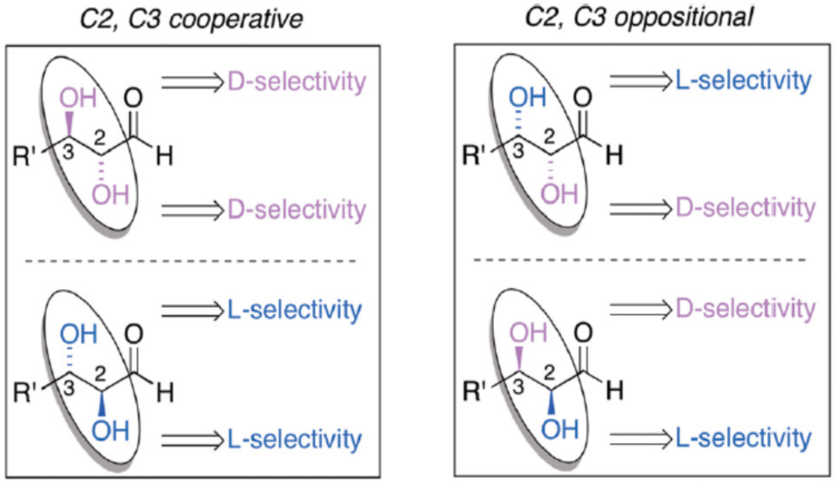
Table 3. Effect of Sugar Concentration on Phe-II ee (%) for Reaction Mediated by D-Ribose[a]

| [D-ribose] (M) | D-ribose (equiv) | Phe-**II** e.e. (%) |
|---|---|---|
| 0.025 | 0.1 | 9 (D) |
| 0.050 | 0.2 | 14 (D) |
| 0.10 | 0.4 | 23 (D) |
| 0.25 | 1 | 43 (D) |
| 0.5 | 2 | 43 (D) |
| 1.0 | 4 | 41 (D) |
| 2.0 | 8 | 42 (D) |

Table 4. Effect of Solution pH on Phe-II ee (%) for Reaction Mediated by D-Ribose[a]

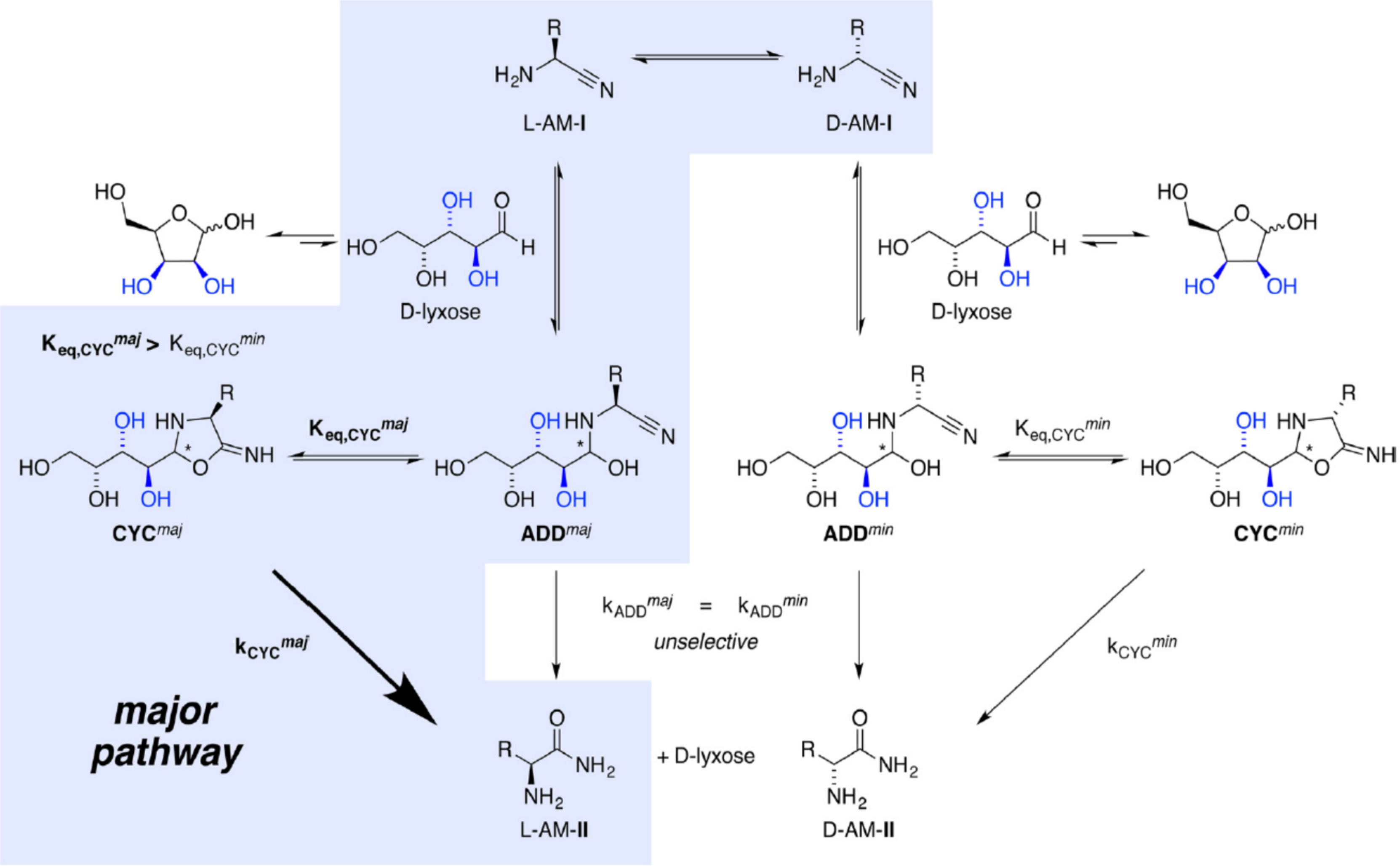
| NaOH (M) | Effective pH | Temperature (ºC) | Phe-**II** e.e. (%) |
|---|---|---|---|
| -[b] | 7 | 22-24 | 35 (D) |
| -[b] | 7 | 37 | 46 (D) |
| 0.00010 | 10 | 22-24 | 36 (D) |
| 0.00010 | 10 | 37 | 36 (D) |

Scheme 4. Stereochemical Rationalization of Enantioenrichment by Chiral Sugars



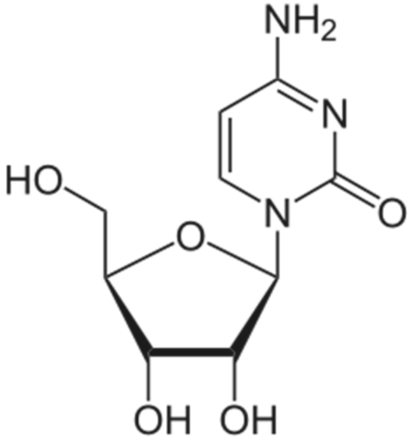
D. G. Blackmond *et al.*, *ACS Cent. Sci.*, **2017**, *3*, 322-328

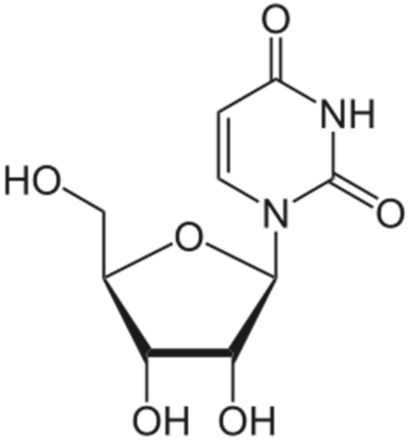
# *Chiral sugars drive enantioenrichment in prebiotic aminoacid synthesis*

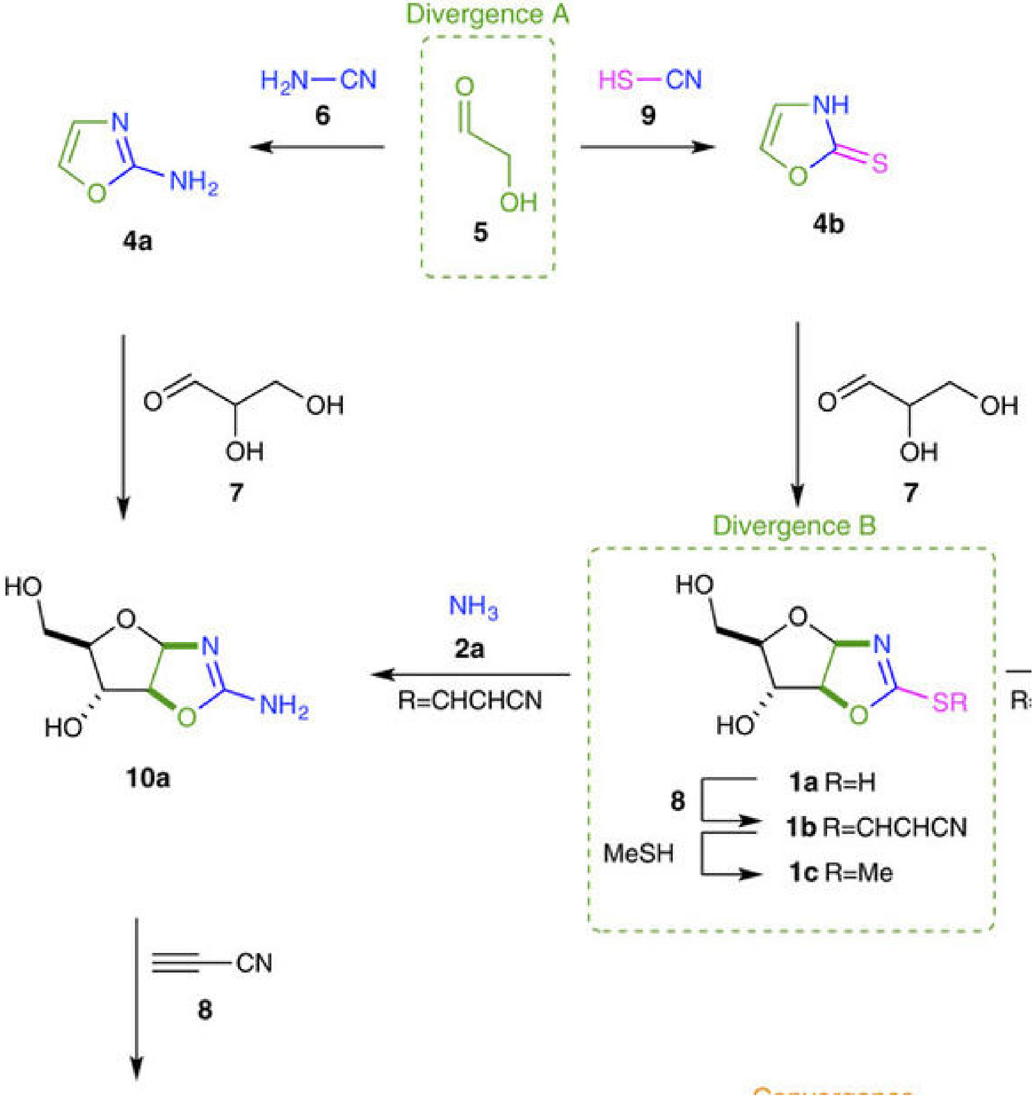


D. G. Blackmond *et al.*, *ACS Cent. Sci.*, **2017**, *3*, 322-328

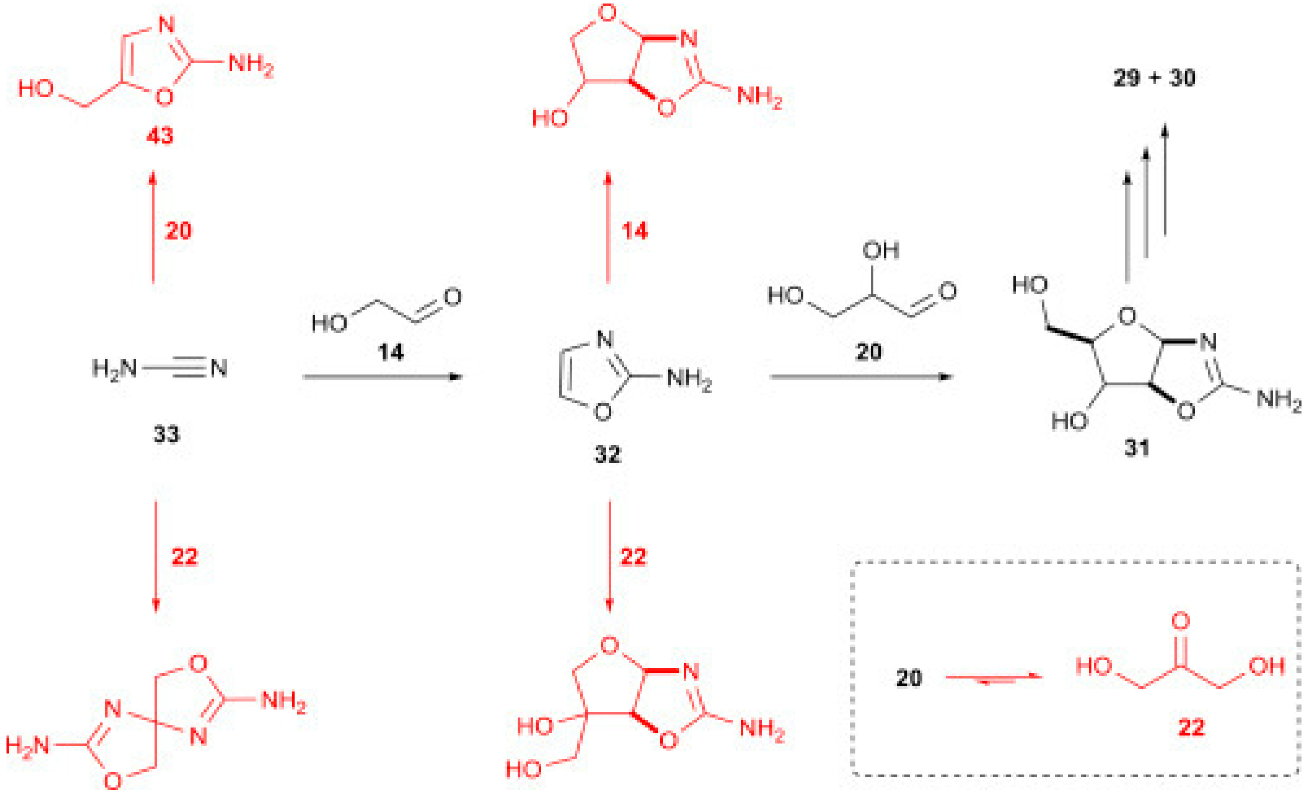
# *Nucleoside synthesis – further development*







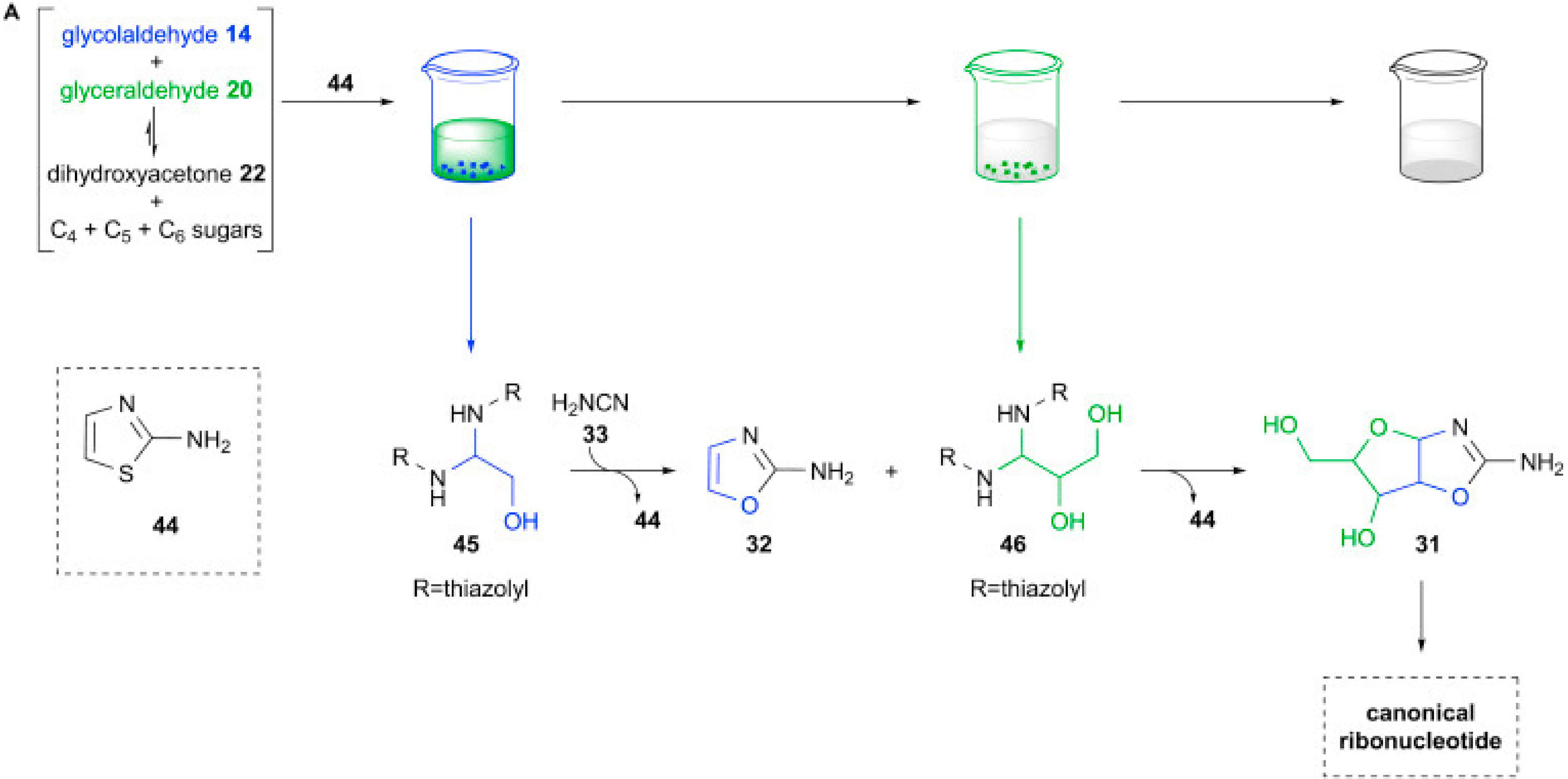
# *Overcome of the Formation of Prebiotic Clutter.*



The synthesis of activated pyrimidine ribonucleotides **29** and **30** is dependent on the controlled formation of pentose aminooxazolines **31** (black), but the synthesis of **31** is wholly reliant on the ordered introduction of pure glycolaldehyde **14** (to cyanamide 33) and glyceraldehyde **20** (to 2-aminooxazole **32**) to prevent the formation of numerous deleterious by-products (red). Ribonucleotide synthesis fails without the adherence to this order of synthetic steps. Glyceraldehyde **20** is highly susceptible to equilibration with dihydroxyacetone **22**, especially in phosphate buffer, which results in diminishing amounts of pentose aminooxazolines **31** being formed (inset).

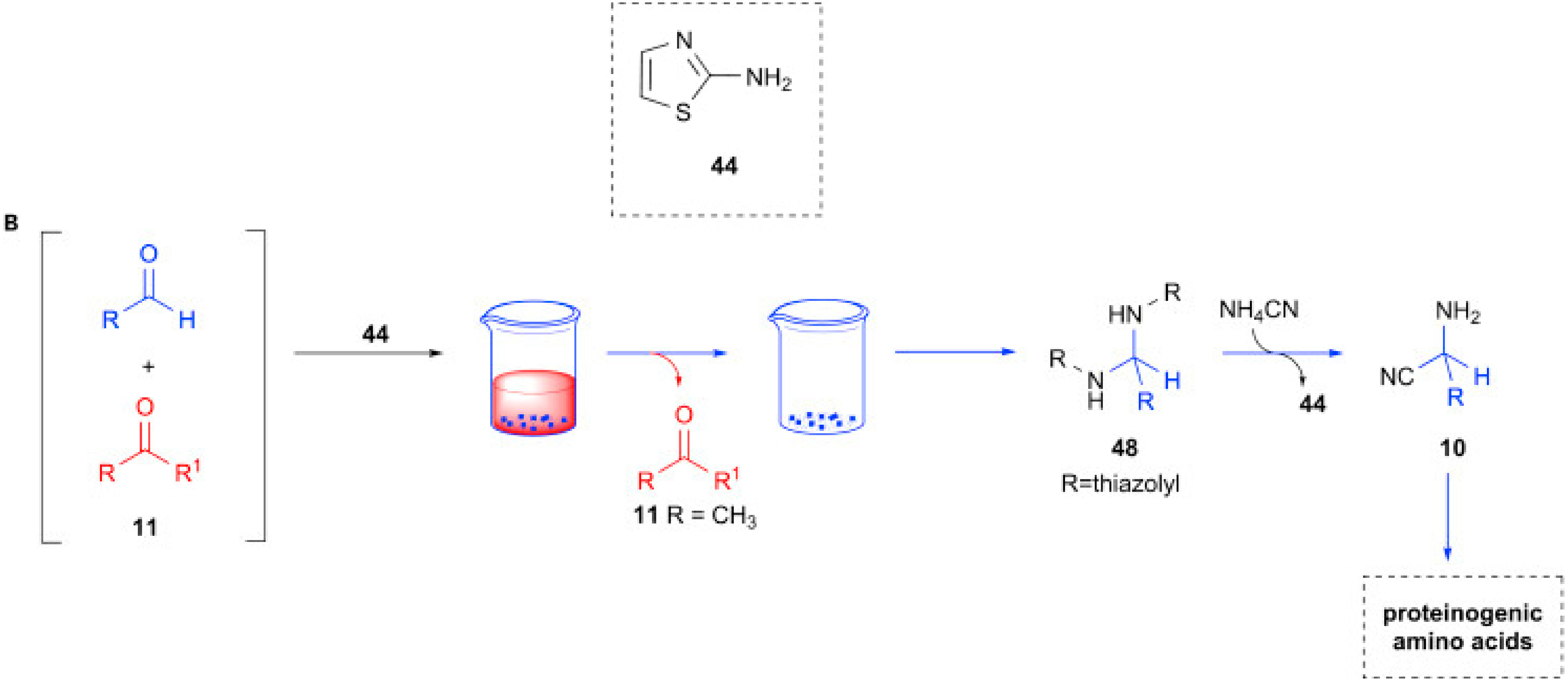
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

# *2-Aminothiazole-Controlled Aldehyde Sequestration*



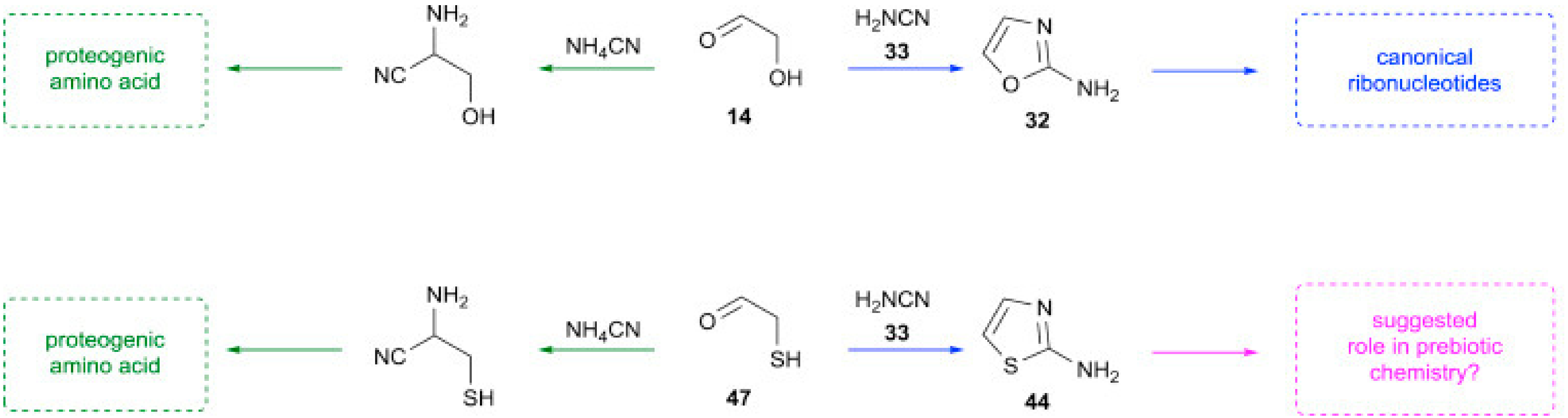
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

# *2-Aminothiazole-Controlled Aldehyde Sequestration*



S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

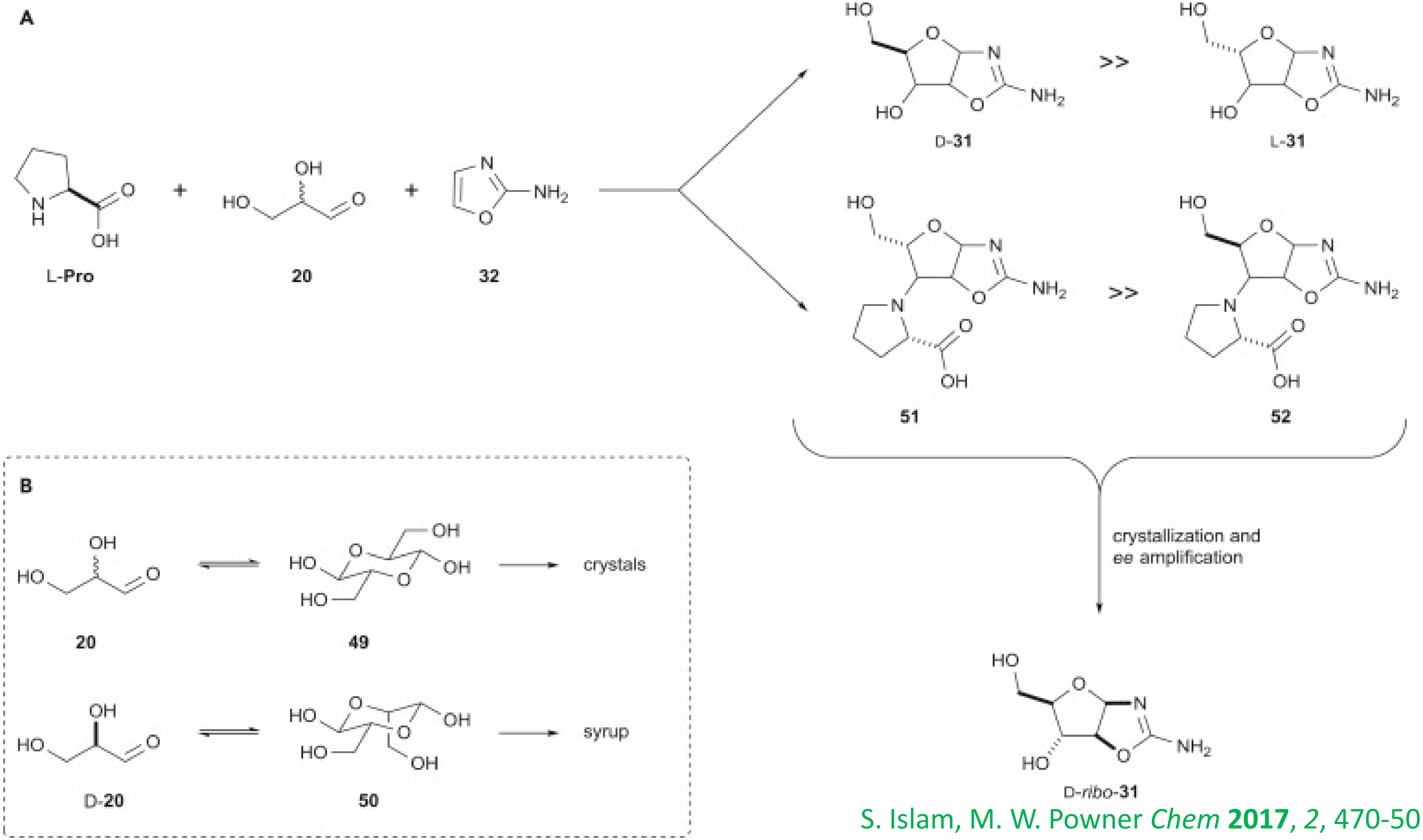
# *Systems Chemical Analysis of Amino Acid and Nucleotide Syntheses*



Analysis of the prebiotic amino acid and nucleotide syntheses reveal that glycolaldehyde **14—**a serine and ribonucleotide precursor—lies at a generational node between these two metabolite classes. The same analysis applied to cysteine suggested that b-mercaptoacetaldehyde **47** would be as important as glycolaldehyde **14** and that the reactivity of 2-aminothiazole **44** might have key implications for the concomitant prebiotic synthesis of amino acid and nucleotides

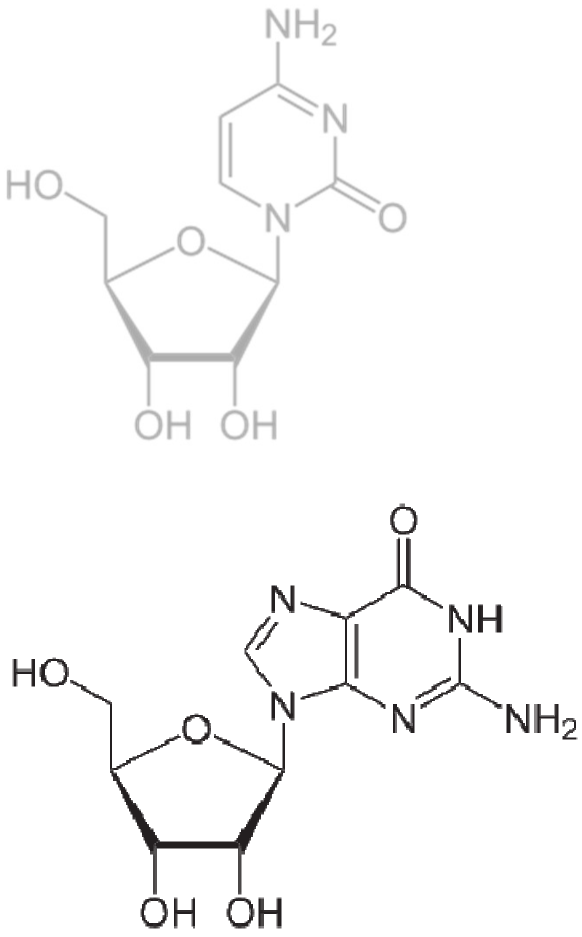
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

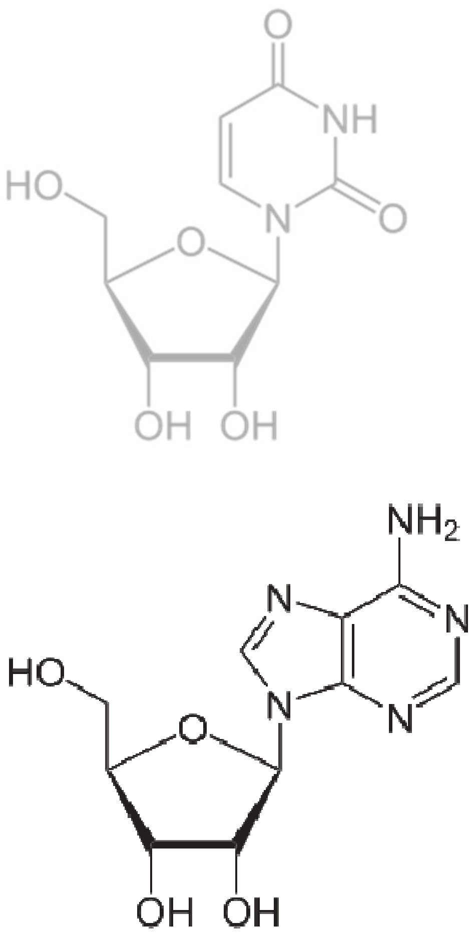
# *Strategies toward Enantio-enriched Glyceraldehyde and Ribonucleotide Precursors*



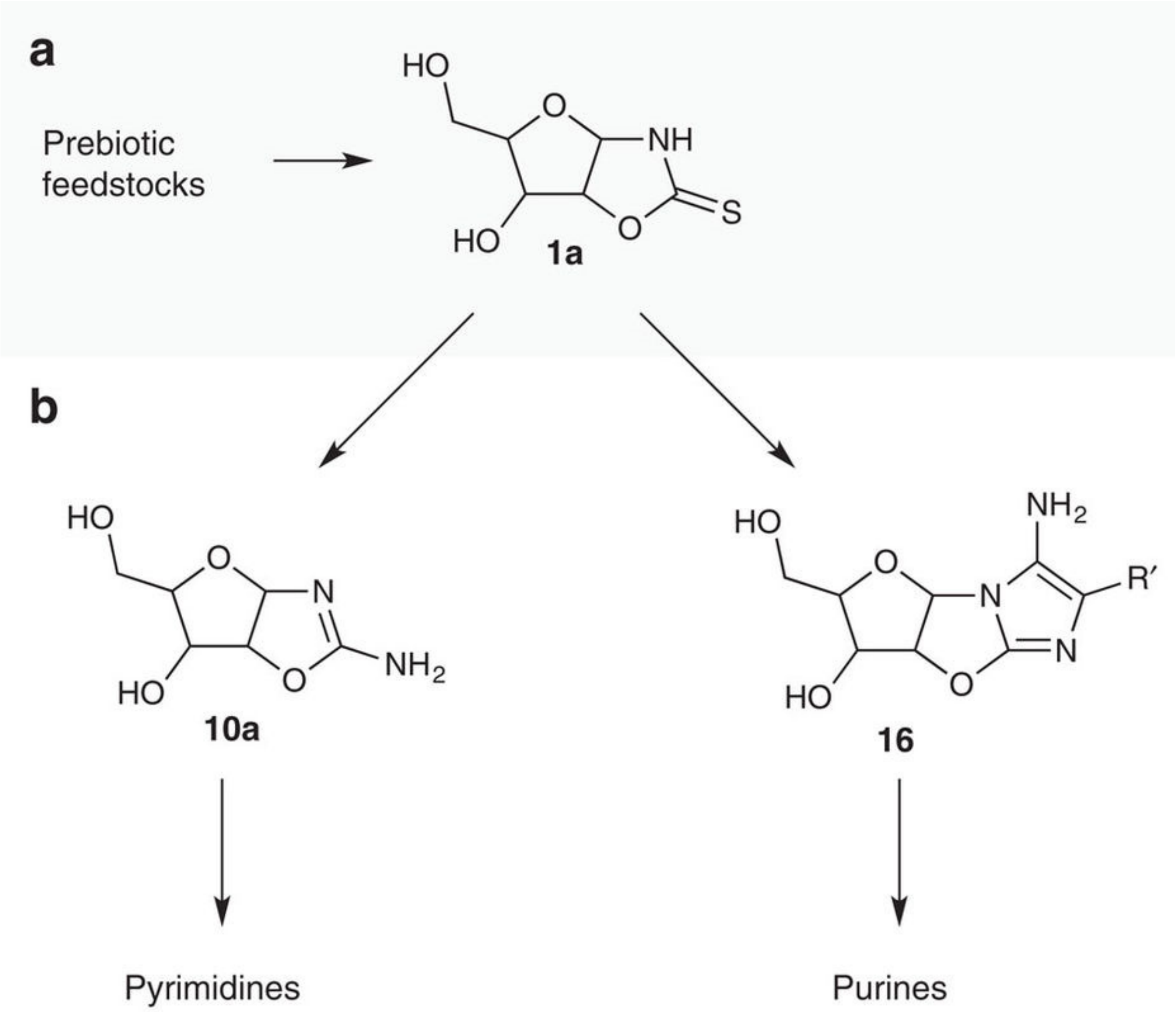
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

# *Purine nucleoside synthesis via cyanosulfidic chemistry*

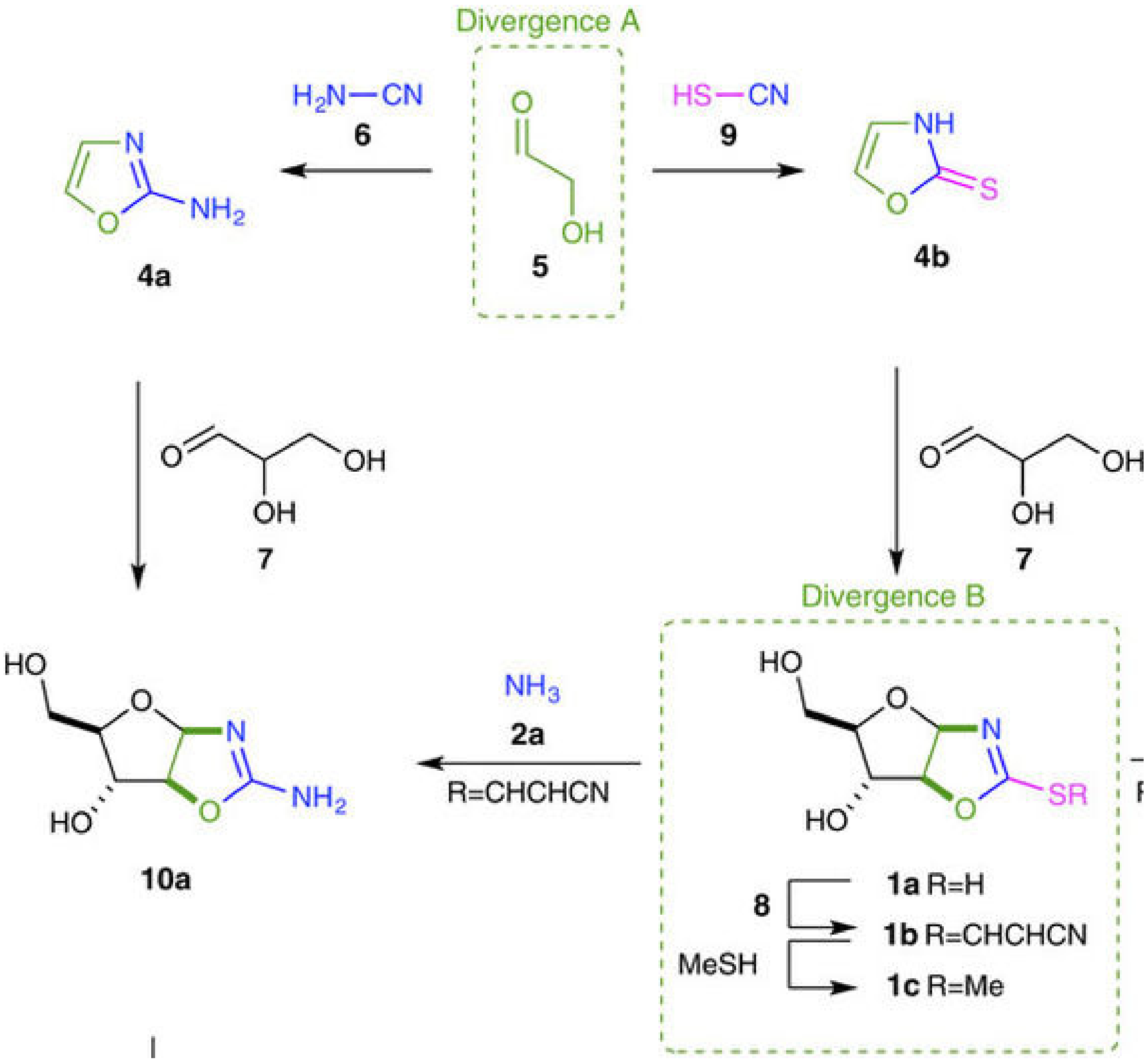




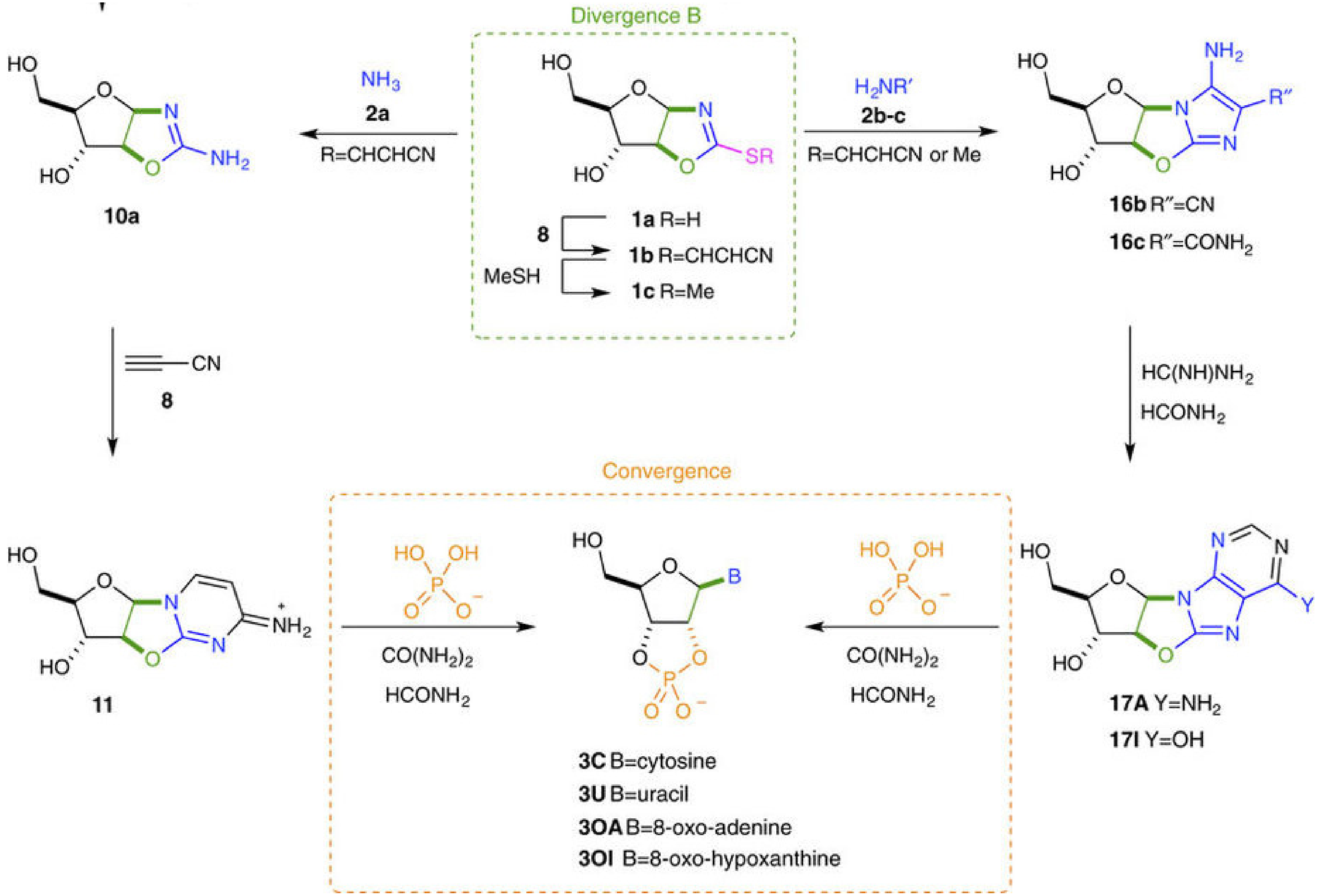
# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*



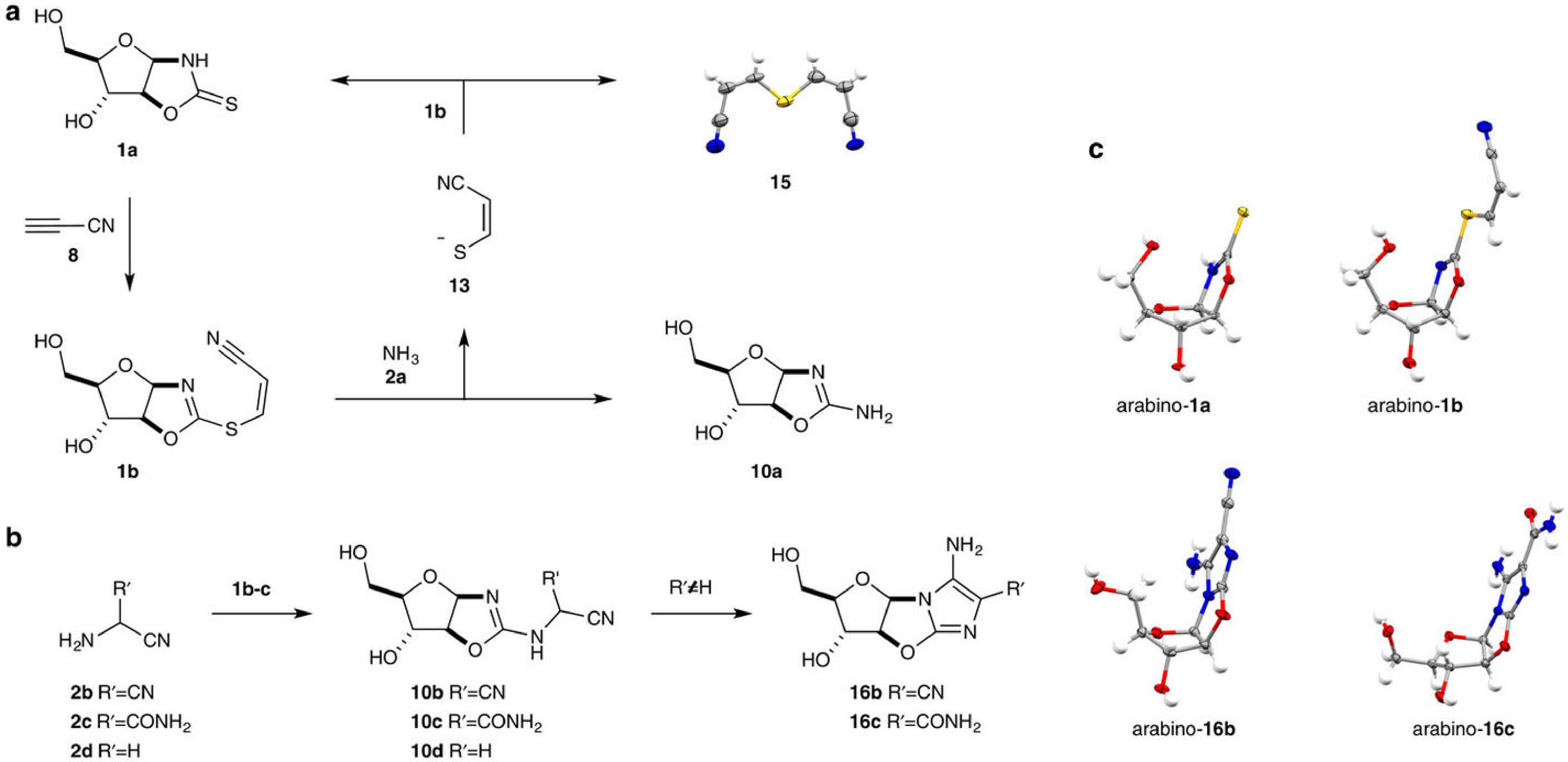
# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*



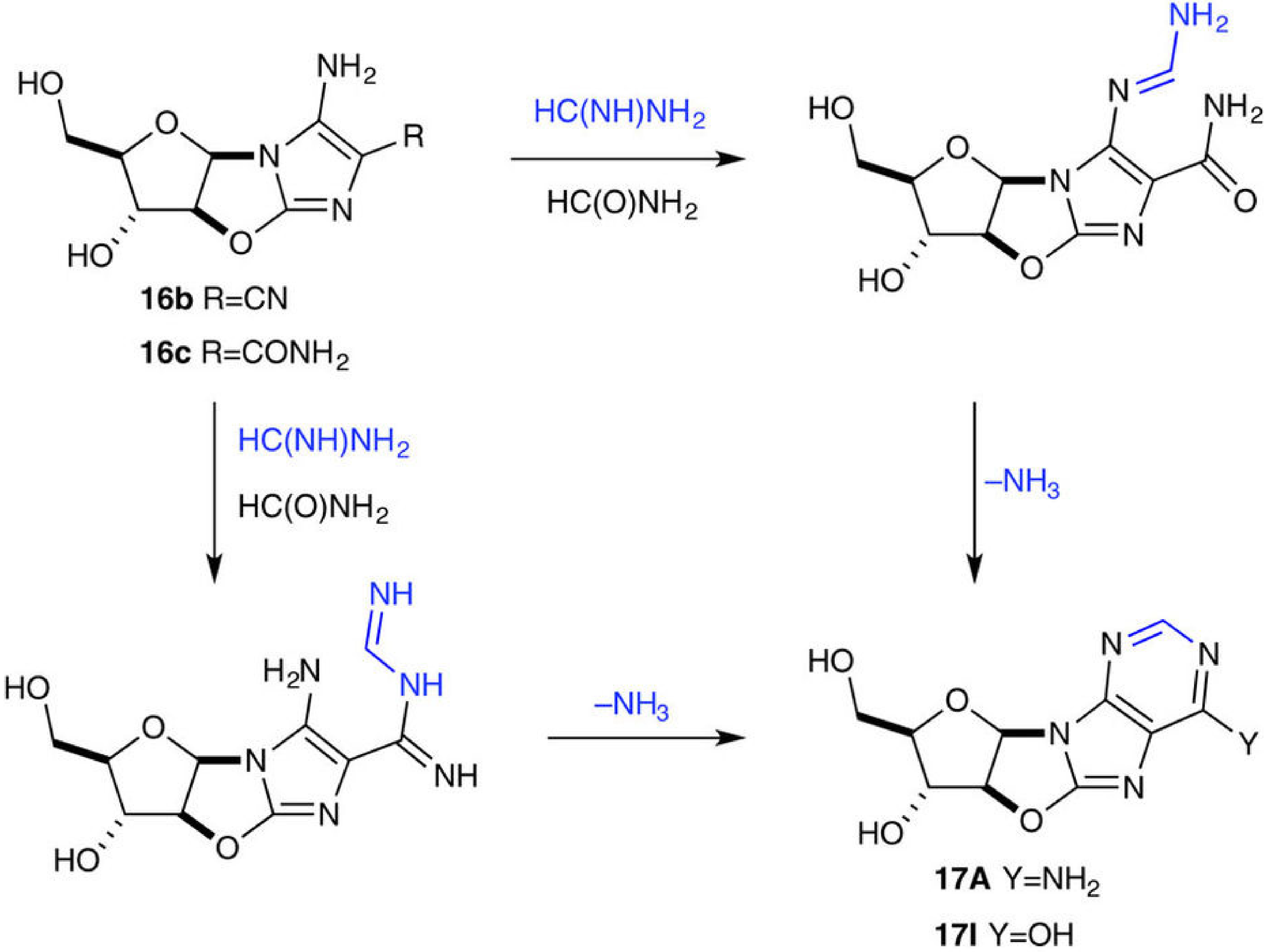
# 8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry



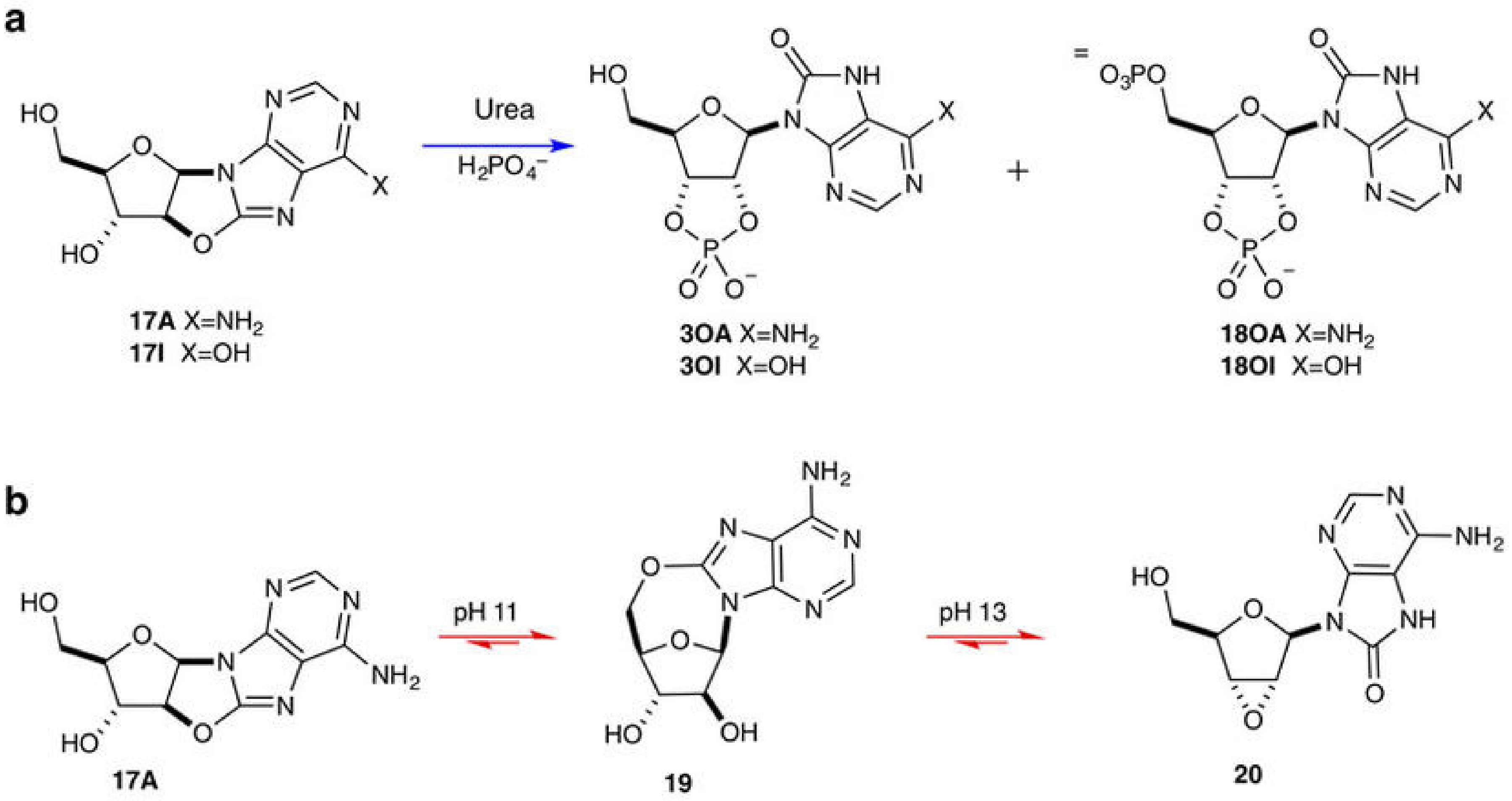
# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*



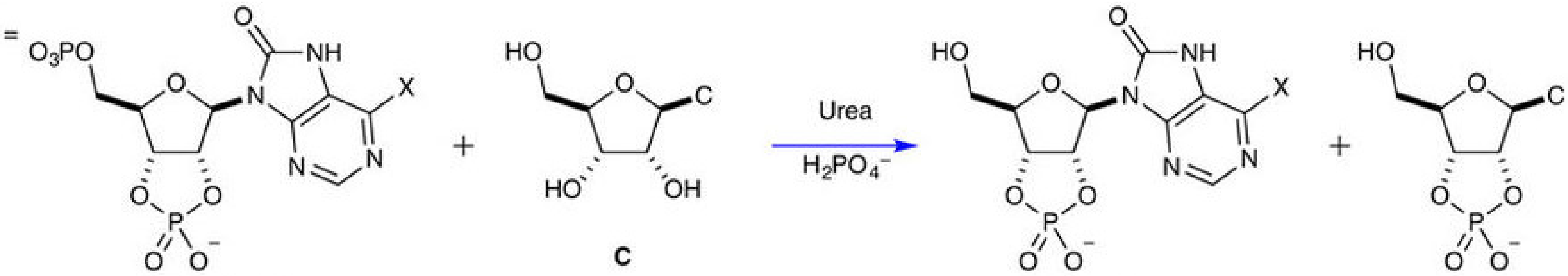
# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*



# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*



# *8-Oxo-purine nucleoside synthesis via cyanosulfidic chemistry*

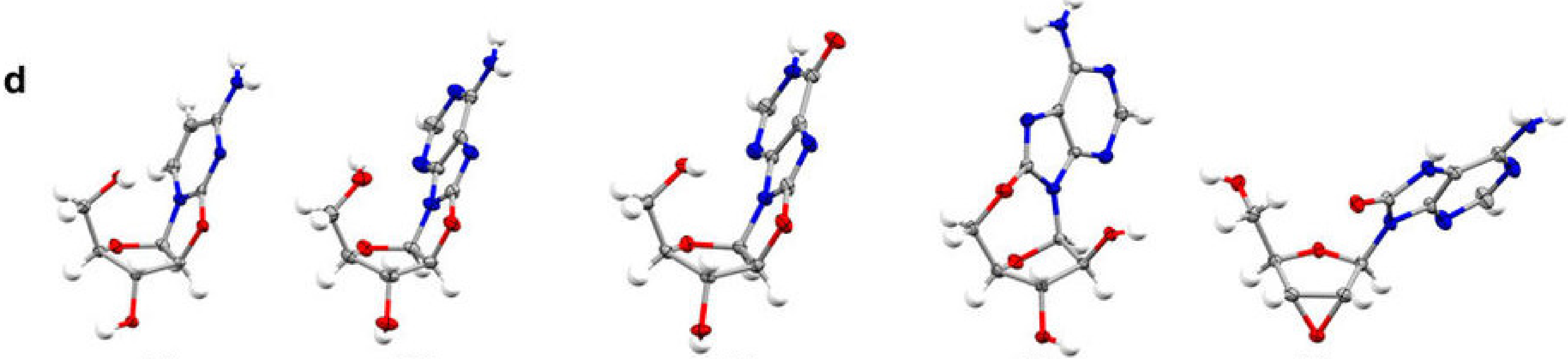


**18OA** X=NH$_2$
**18OI** X=OH

**C**

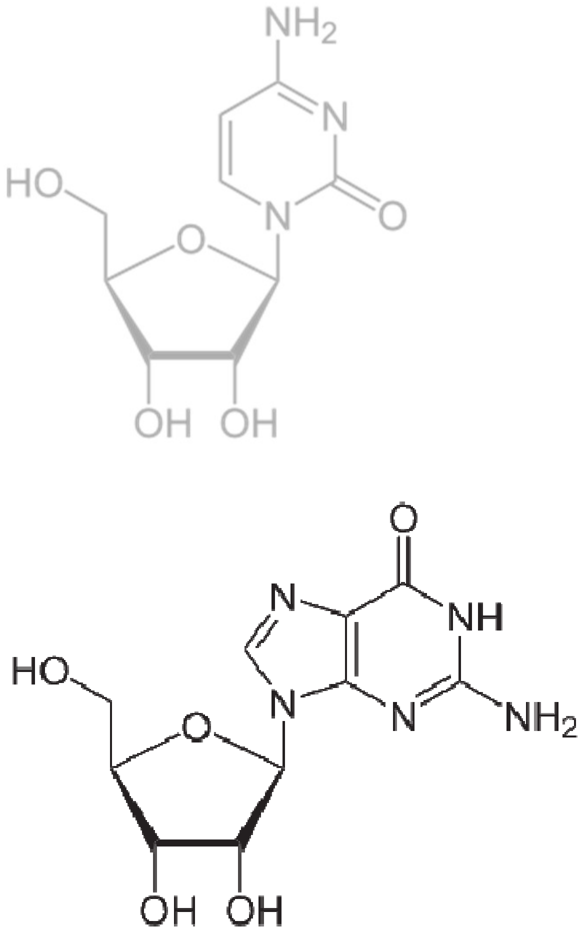
**3OA** X=NH$_2$
**3OI** X=OH

**3C**



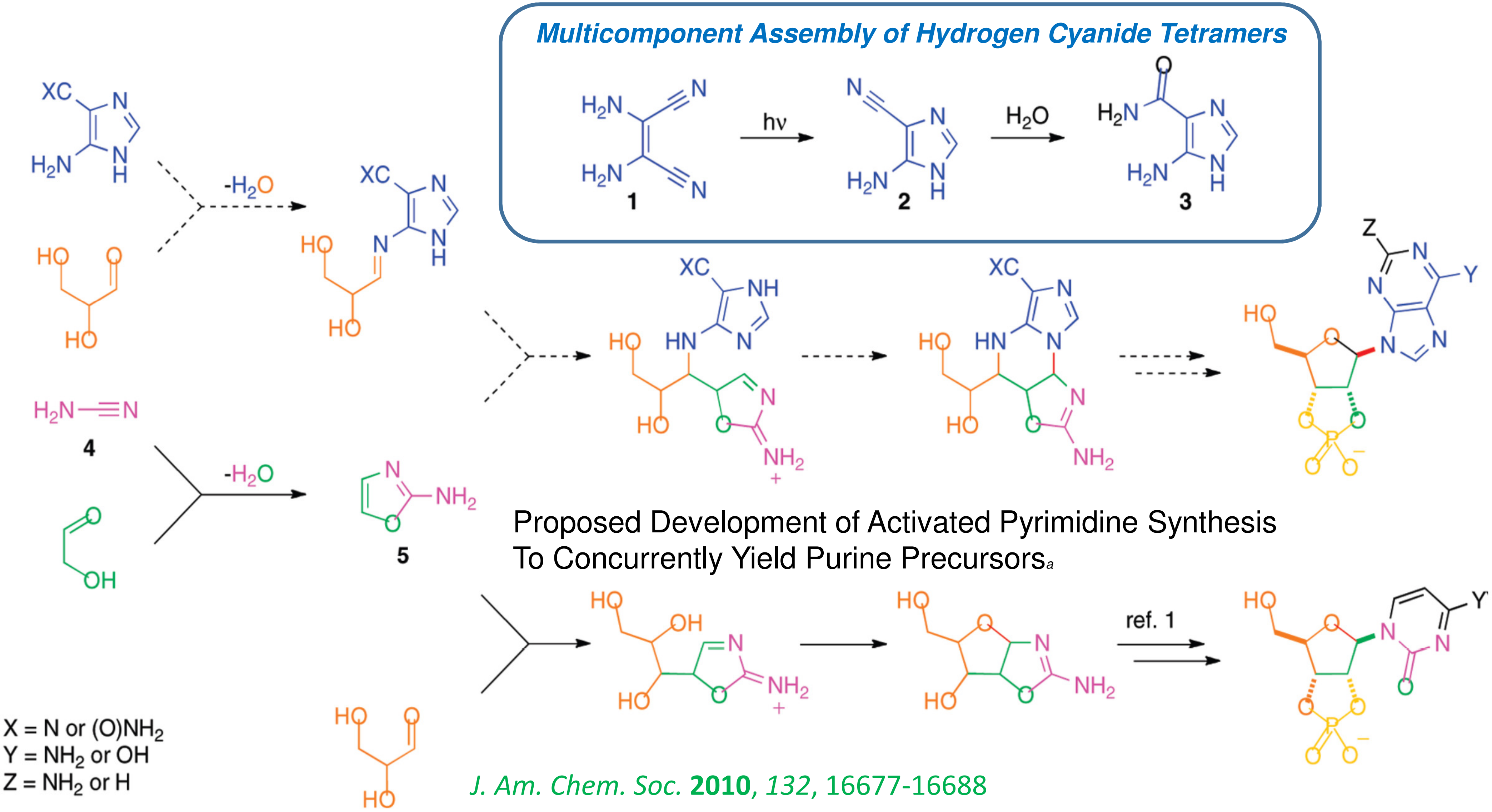
**11** **17A** **17I** **19** **20**

# *Canonical purine nucleoside synthesis via cyanosulfidic chemistry*



# *Cyanosulfidic chemistry*

### *Multicomponent Assembly of Hydrogen Cyanide Tetramers*



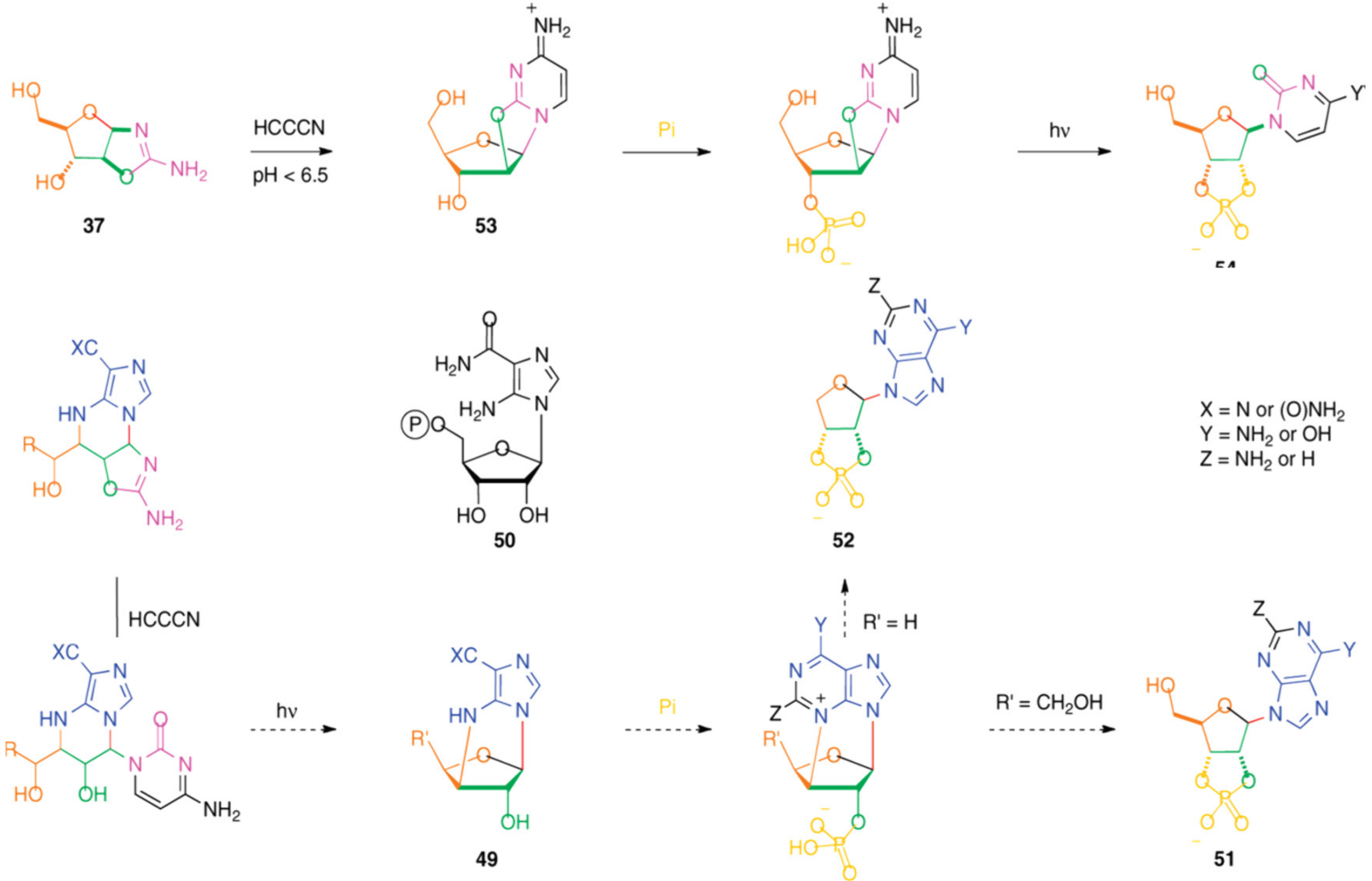
Proposed Development of Activated Pyrimidine Synthesis To Concurrently Yield Purine Precursors[a]

X = N or (O)$NH_2$
Y = $NH_2$ or OH
Z = $NH_2$ or H

*J. Am. Chem. Soc.* **2010**, *132*, 16677-16688

# *Cyanosulfidic chemistry*

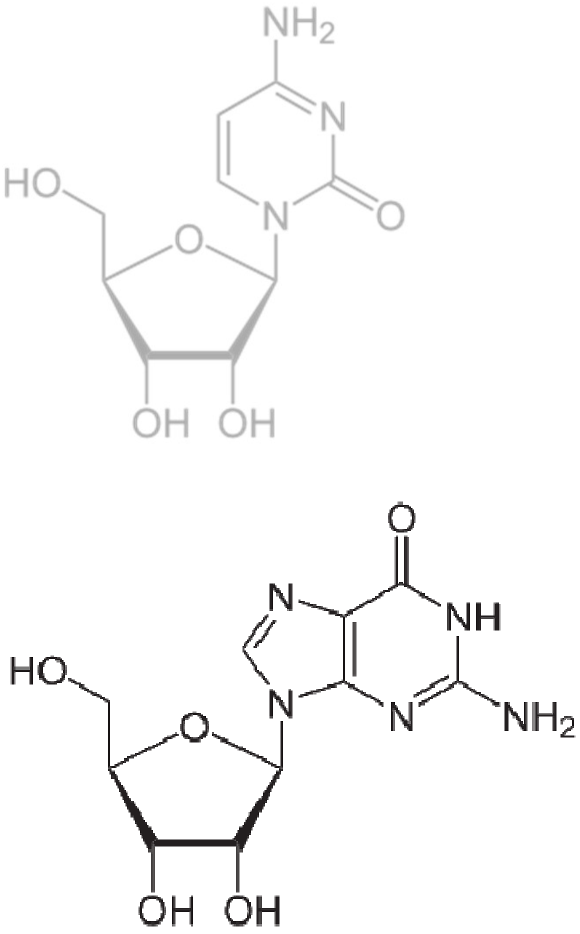
beta-Ribofuranosyl-pyrimidine nucleotide assembly and potential stepwise, regioselective beta-ribofuranosyl-purine assembly
Pathway via the intermediacy of tetrahydroimidazo[1′,3′]-2′′-aminooxazolo[1′,2′]-pyrimidinesa



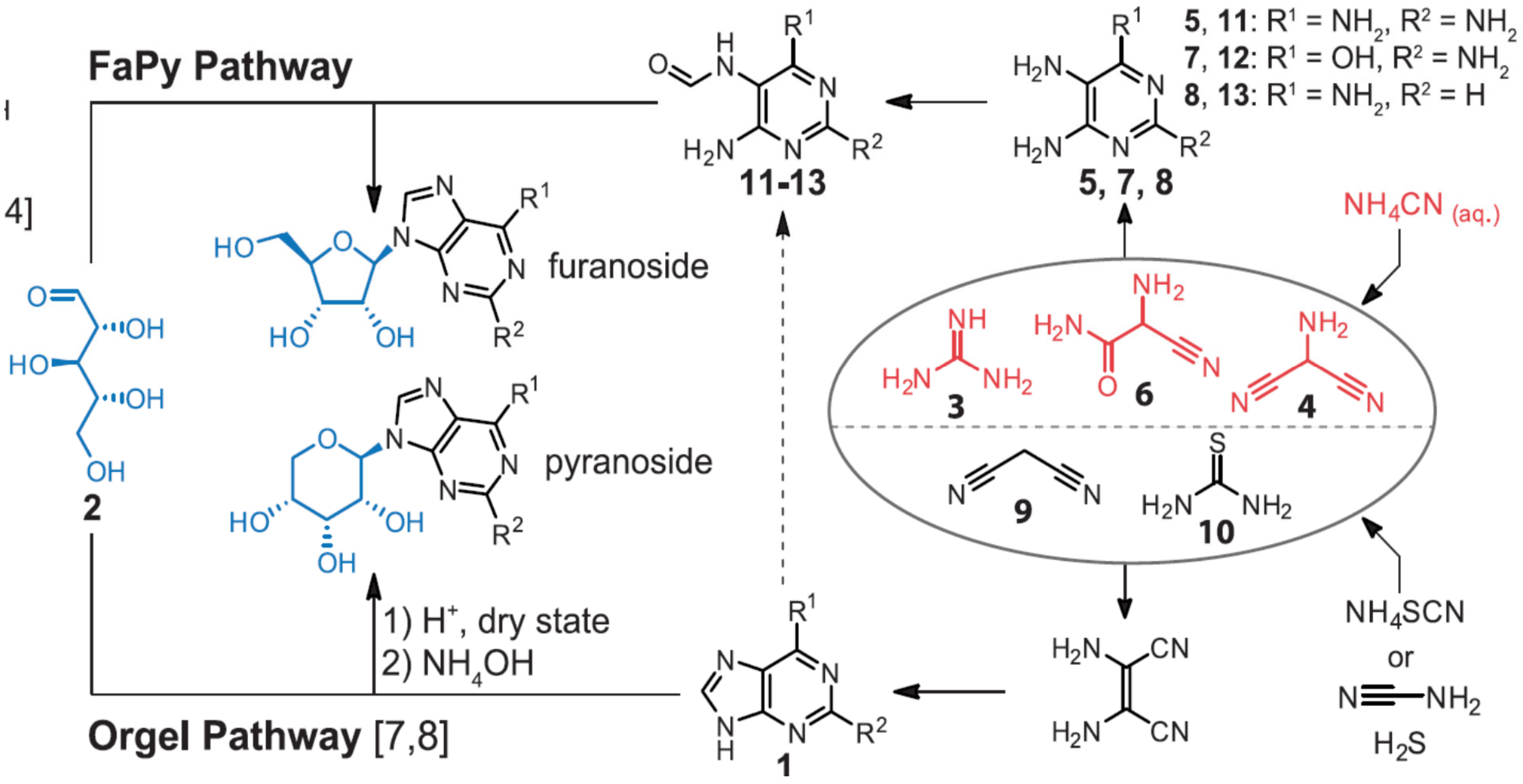
X = N or (O)NH$_2$
Y = NH$_2$ or OH
Z = NH$_2$ or H

M. W. Powner, J. D. Sutherland, J. W. Szostak *J. Am. Chem. Soc.* **2010**, *132*, 16677-16688

# *Purine nucleoside synthesis - alternatives*

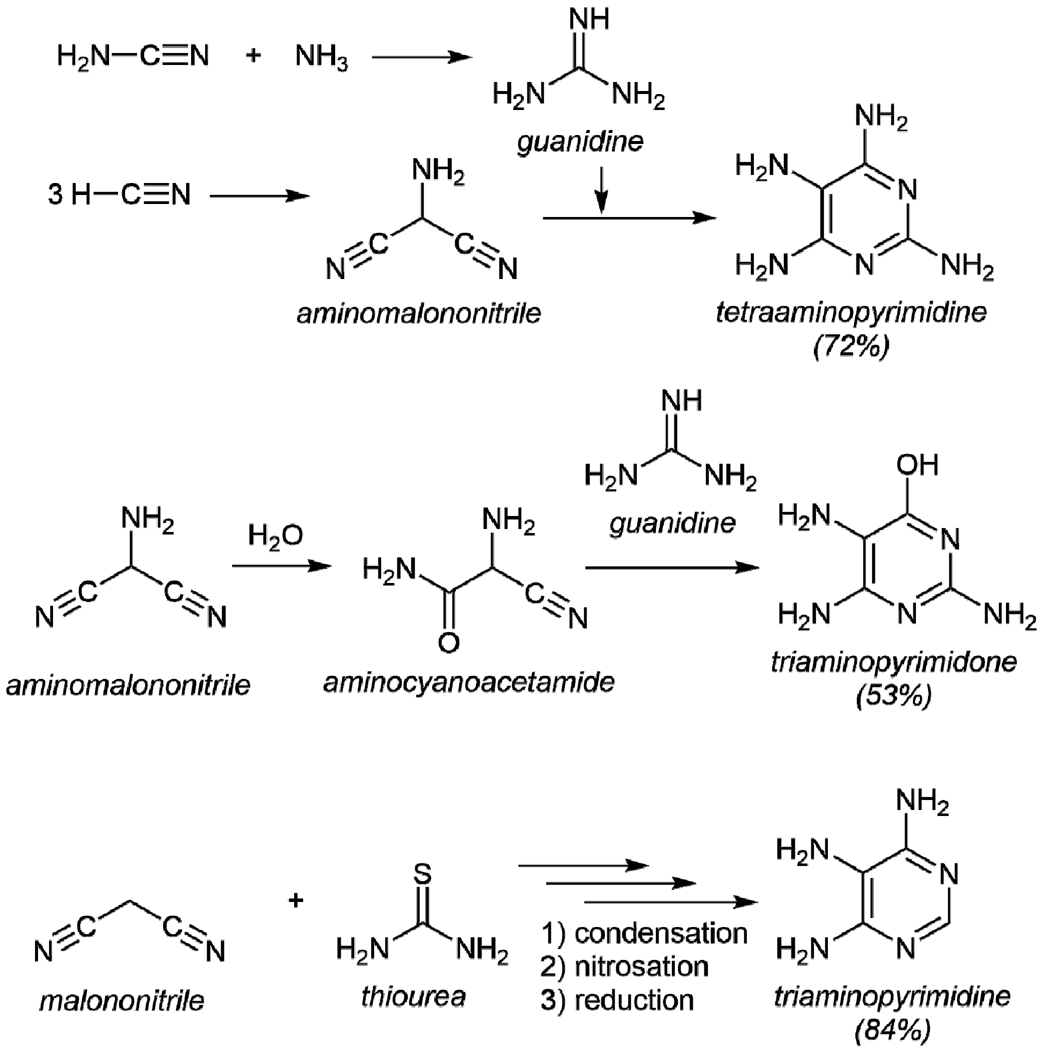


# *Prebiotic synthesis of purine nucleosides –FaPY pathway*



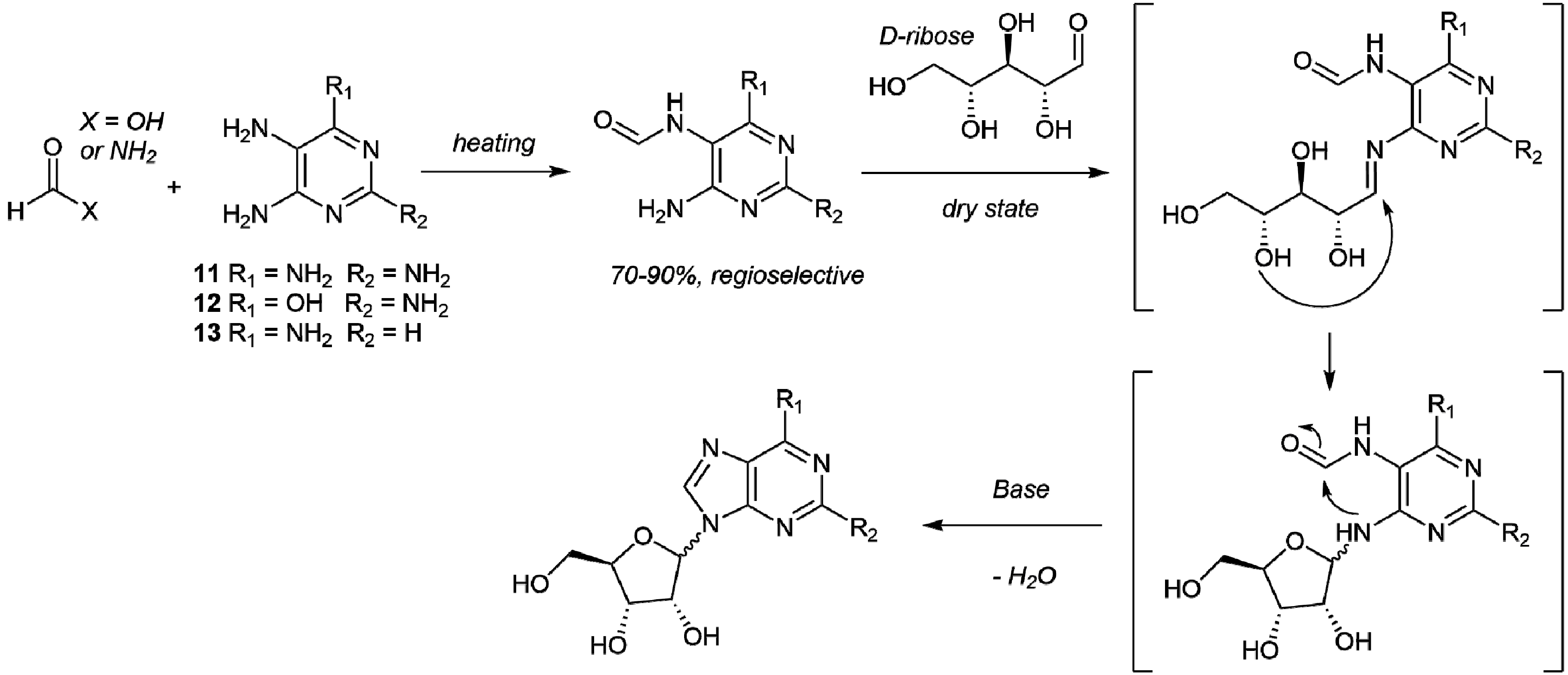
T. Carell, *Nature* **2016**, *352(6287)*, 833-836

# *Prebiotic syntheses of aminopyrimidines*

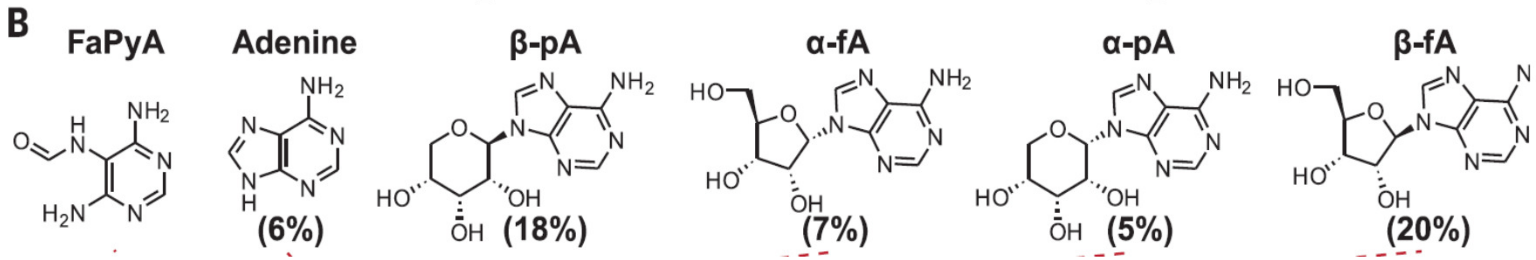


T. Carell, *Nature* **2016**, *352(6287)*, 833-836

# *Prebiotic synthesis of purine nucleosides –FaPY pathway*

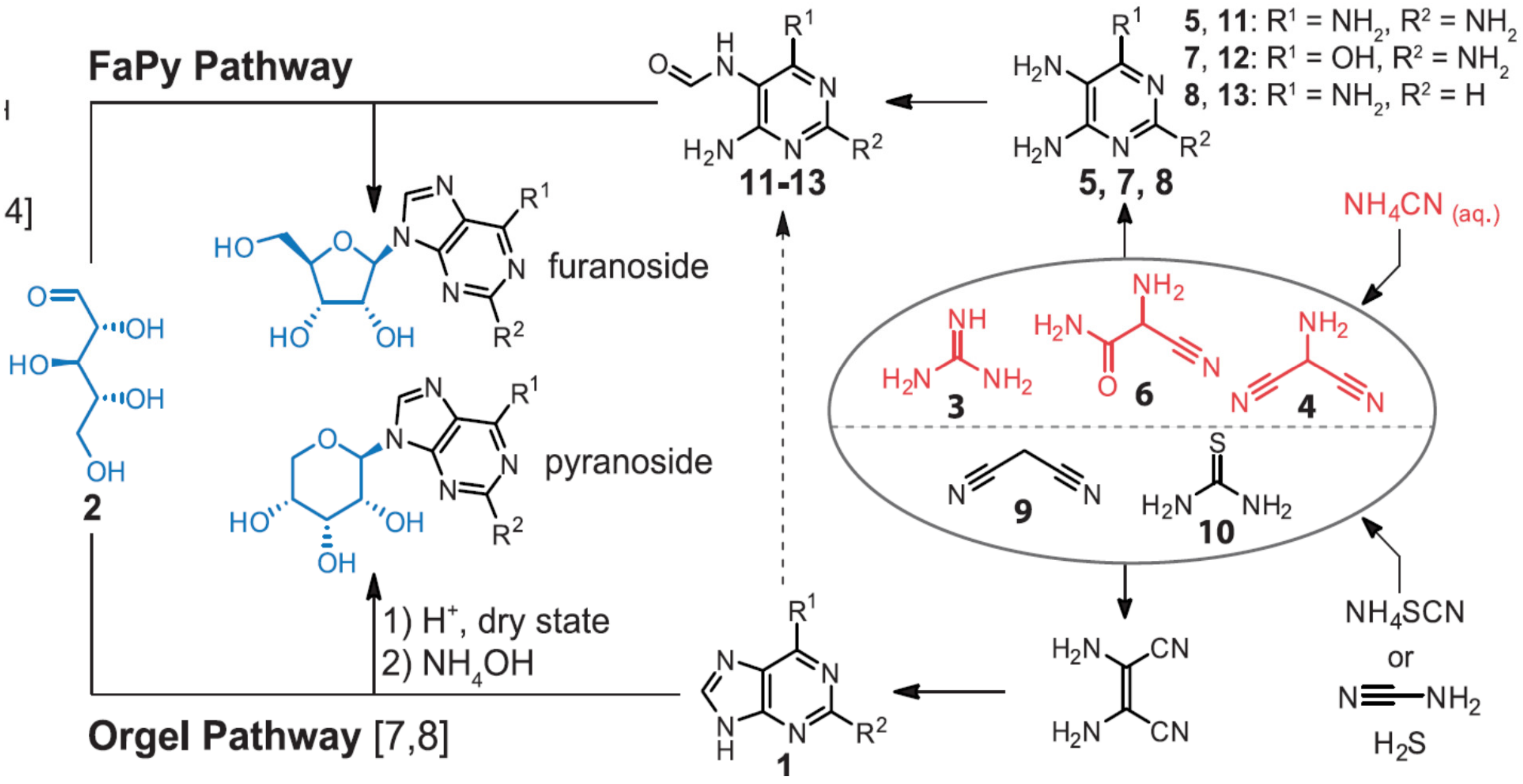


**11** $R_1 = NH_2$ $R_2 = NH_2$
**12** $R_1 = OH$ $R_2 = NH_2$
**13** $R_1 = NH_2$ $R_2 = H$



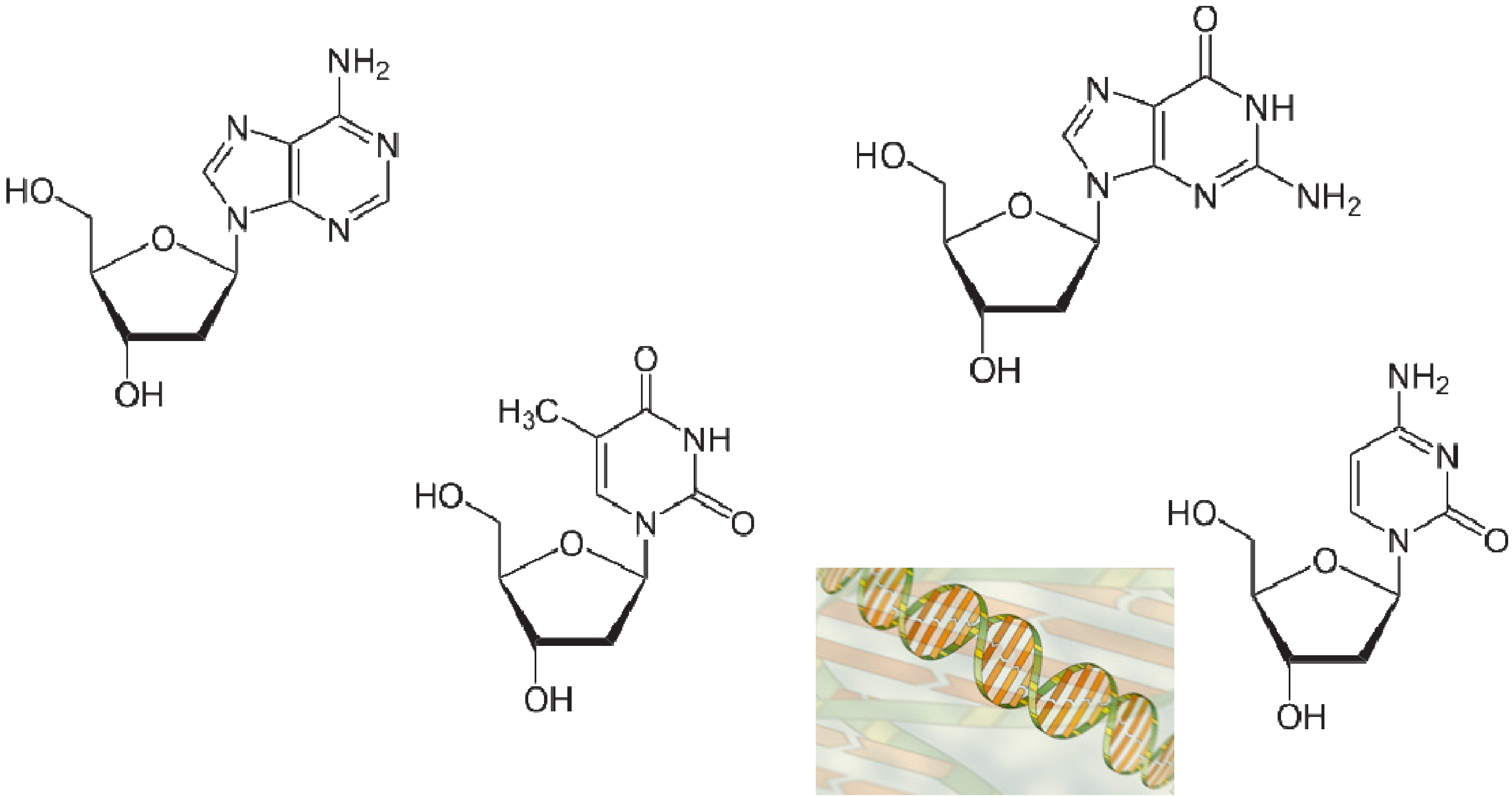
T. Carell, *Nature* **2016**, *352(6287)*, 833-836

# *Prebiotic synthesis of purine nucleosides –FaPY pathway*

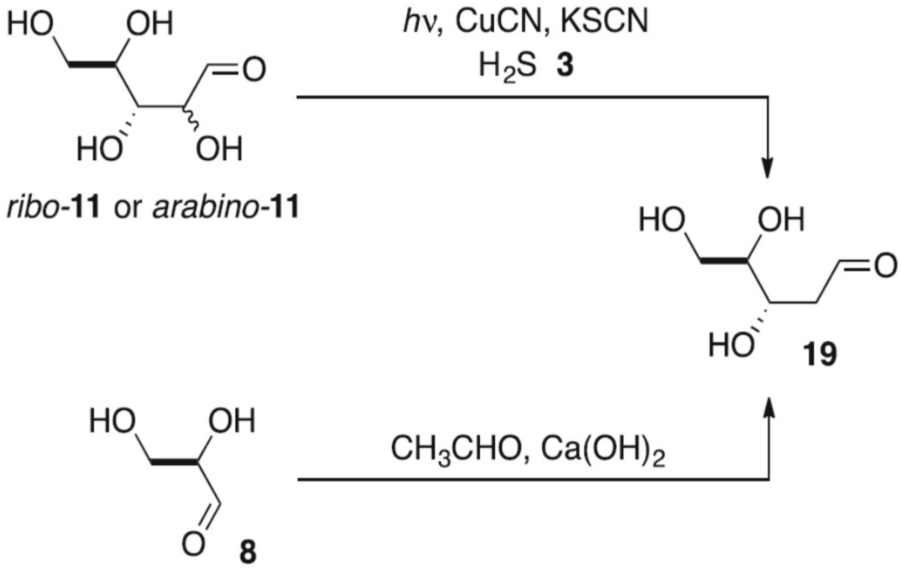


T. Carell, *Nature* **2016**, *352(6287)*, 833-836

# *Prebiotic synthesis of deoxyribonucleosides*

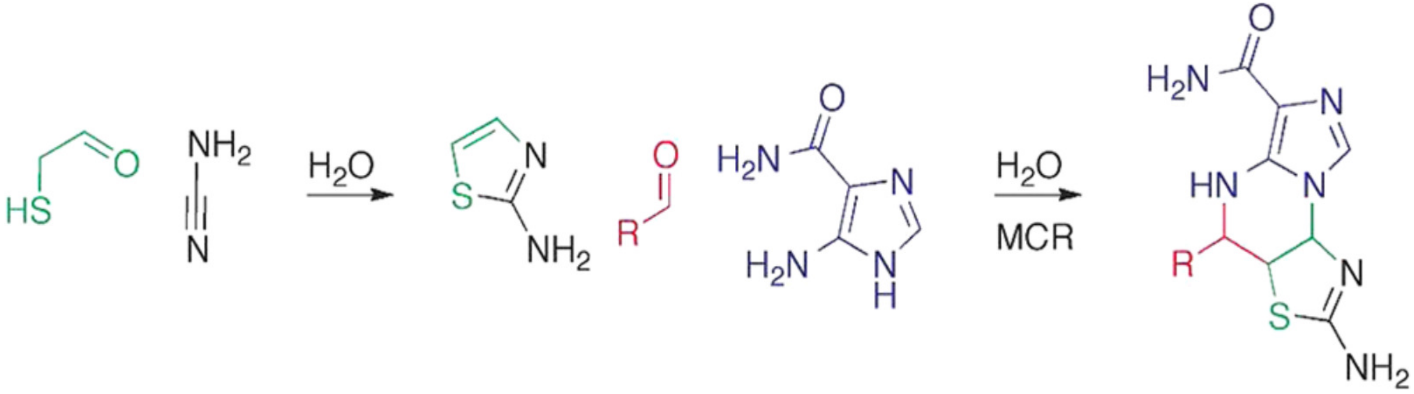


# *Prebiotic synthesis of deoxyribonucleosides*



D. J. Ritson, J. D. Sutherland *J. Mol. Evol.* **2014**, *38*, 245-250

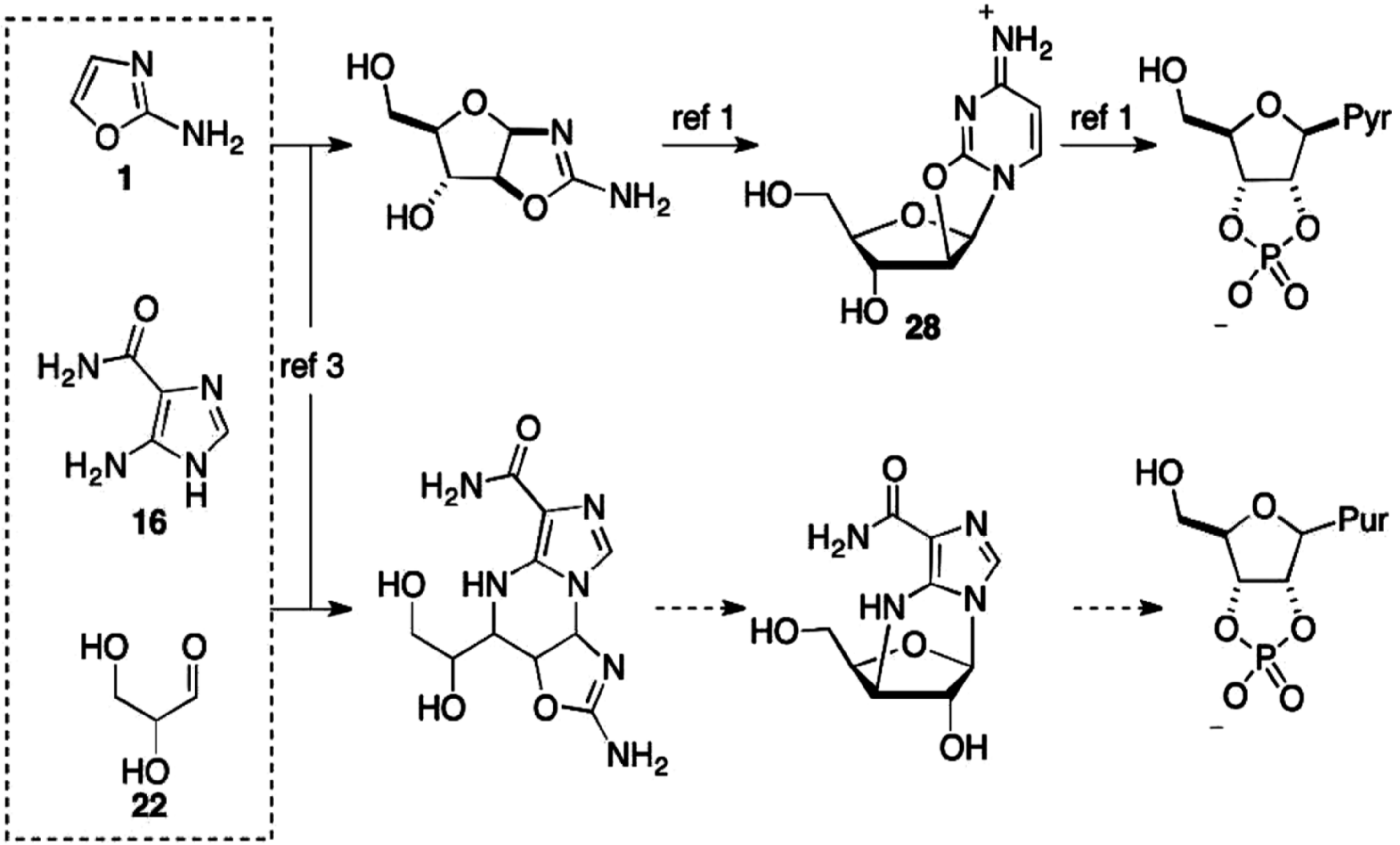
# *Prebiotic synthesis of deoxyribonucleosides*



M. W. Powner, S.-L. Zheng,  J. W. Szostak *J. Am. Chem. Soc.* **2012**, *134*, 13889-13895

# *Prebiotic synthesis of deoxyribonucleosides*

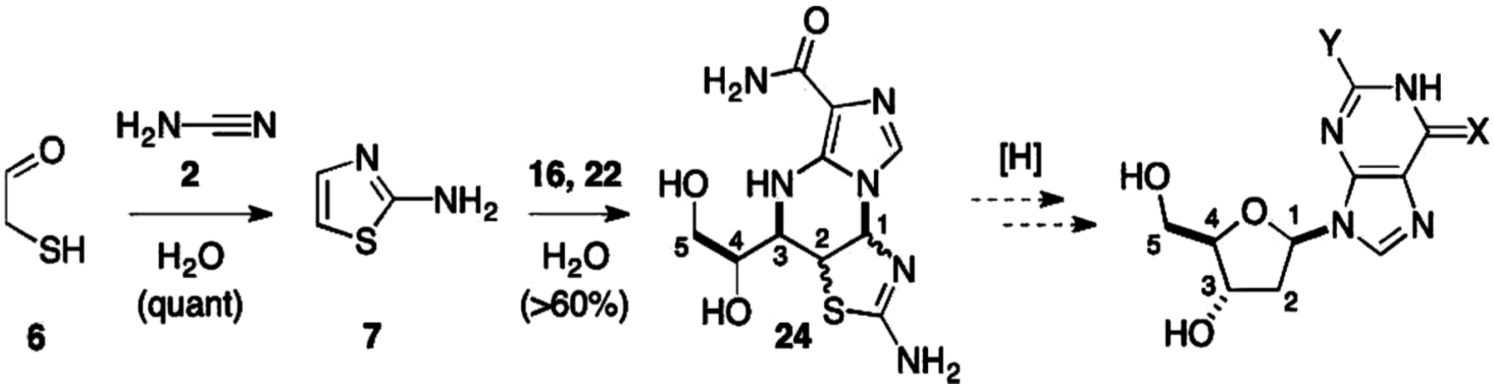
proposed multicomponent ribonucleotide syntheses



M. W. Powner, S.-L. Zheng,  J. W. Szostak *J. Am. Chem. Soc.* **2012**, *134*, 13889-13895

# *Prebiotic synthesis of deoxyribonucleosides*

proposed multicomponent deoxyribonucleotide syntheses

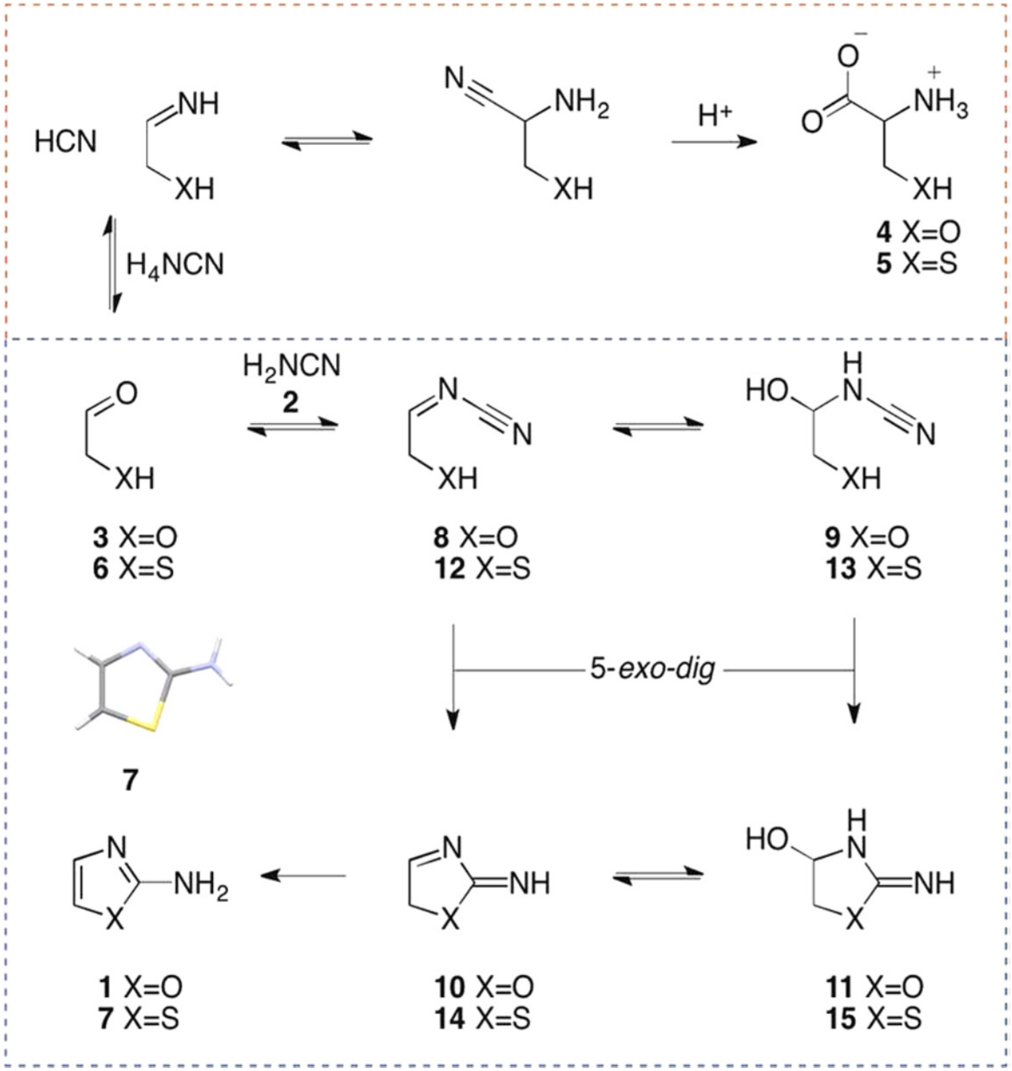


M. W. Powner, S.-L. Zheng, J. W. Szostak *J. Am. Chem. Soc.* **2012**, *134*, 13889-13895

# *Prebiotic synthesis of deoxyribonucleosides*

Strecker-Type Synthesis of Amino Acids

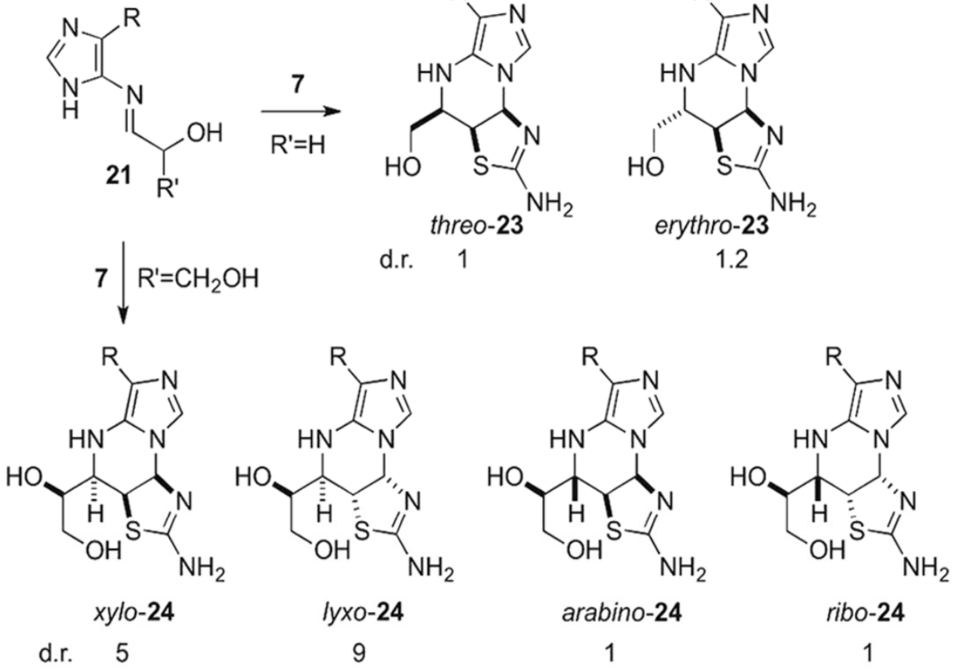
Azole Synthesis in Water

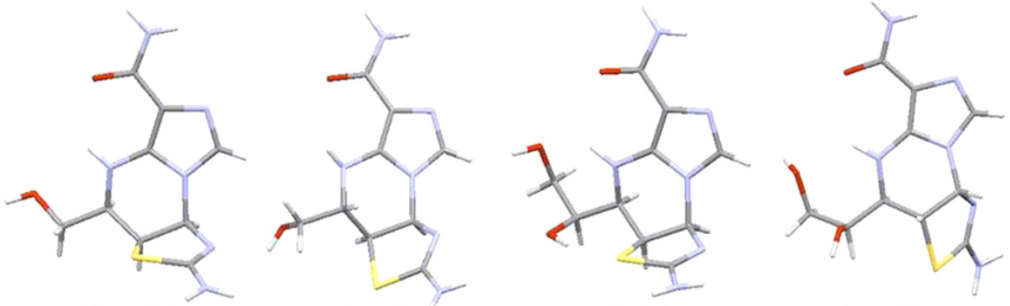


M. W. Powner, S.-L. Zheng, J. W. Szostak *J. Am. Chem. Soc.* **2012**, *134*, 13889-13895

# ***Prebiotic synthesis of deoxyribonucleosides***

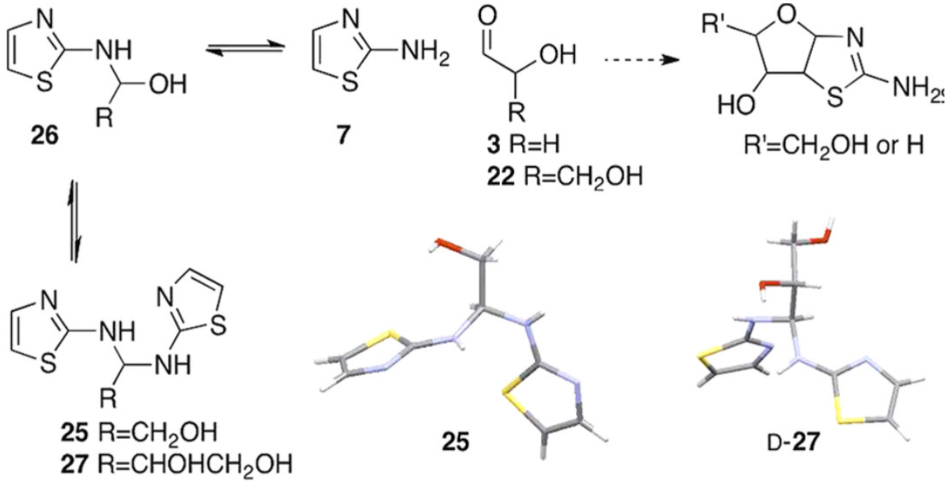
## Three-Component Reaction of 2-Aminothiazole **7**, 4-Aminoimidazole-5-carboxamide **16**, and Glyceraldehyde **22**





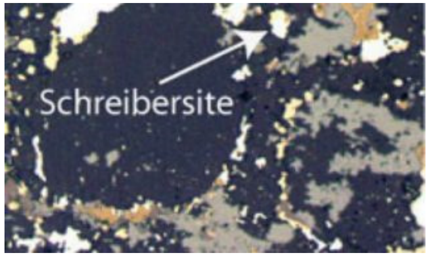
# *Prebiotic synthesis of deoxyribonucleosides*

Crystallization of Bis-(2-aminothiazole)-aminals of Glycolaldehyde **3** and D-Glyceraldehyde **22** from Water at pH 7



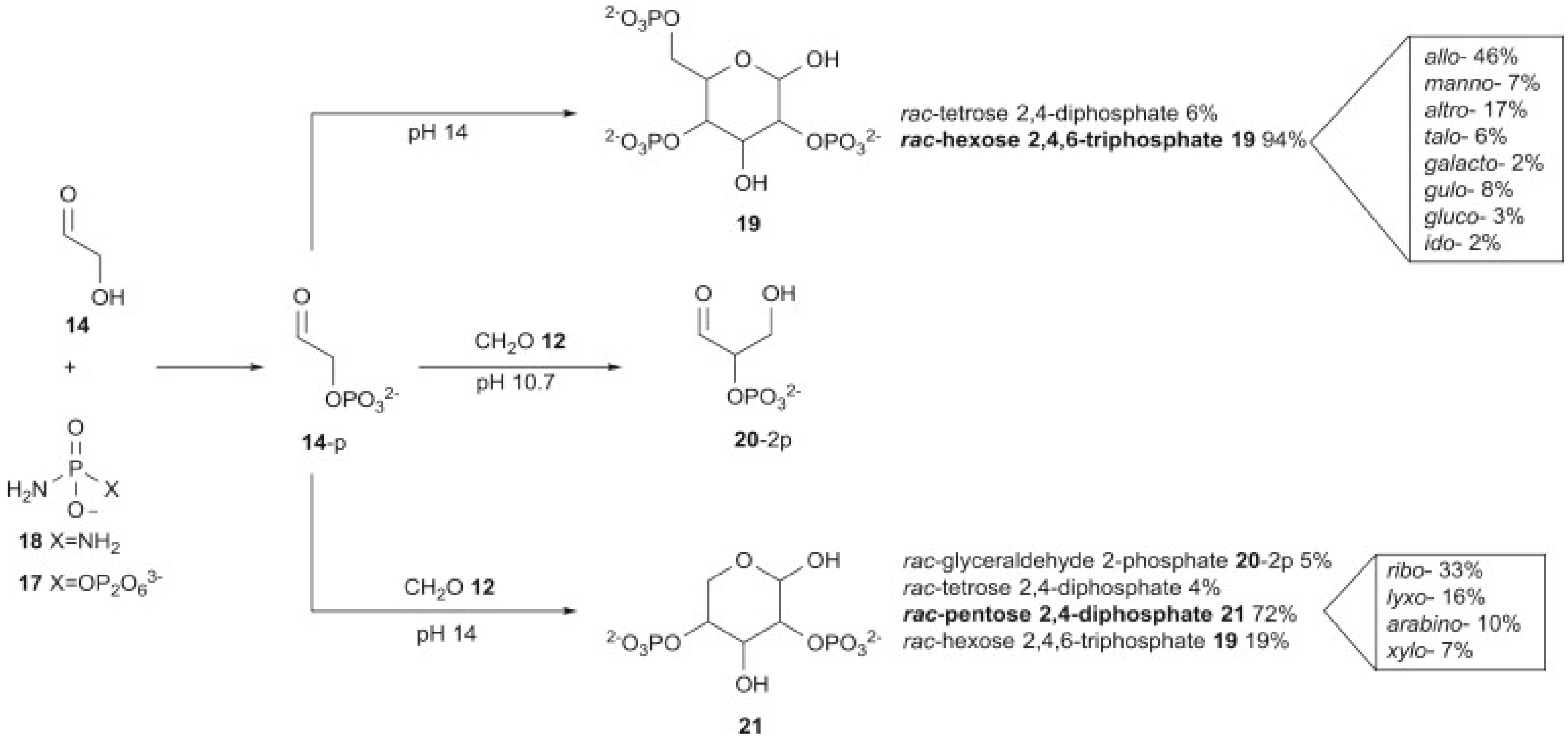
M. W. Powner, S.-L. Zheng, J. W. Szostak *J. Am. Chem. Soc.* **2012**, *134*, 13889-13895

# *Prebiotic phosphorylations*



***vivianite***

# *Selective Phosphorylation of Glycolaldehyde and Aldol Reactions of Glycolaldehyde Phosphate*



*rac*-tetrose 2,4-diphosphate 6%
***rac*-hexose 2,4,6-triphosphate 19** 94%

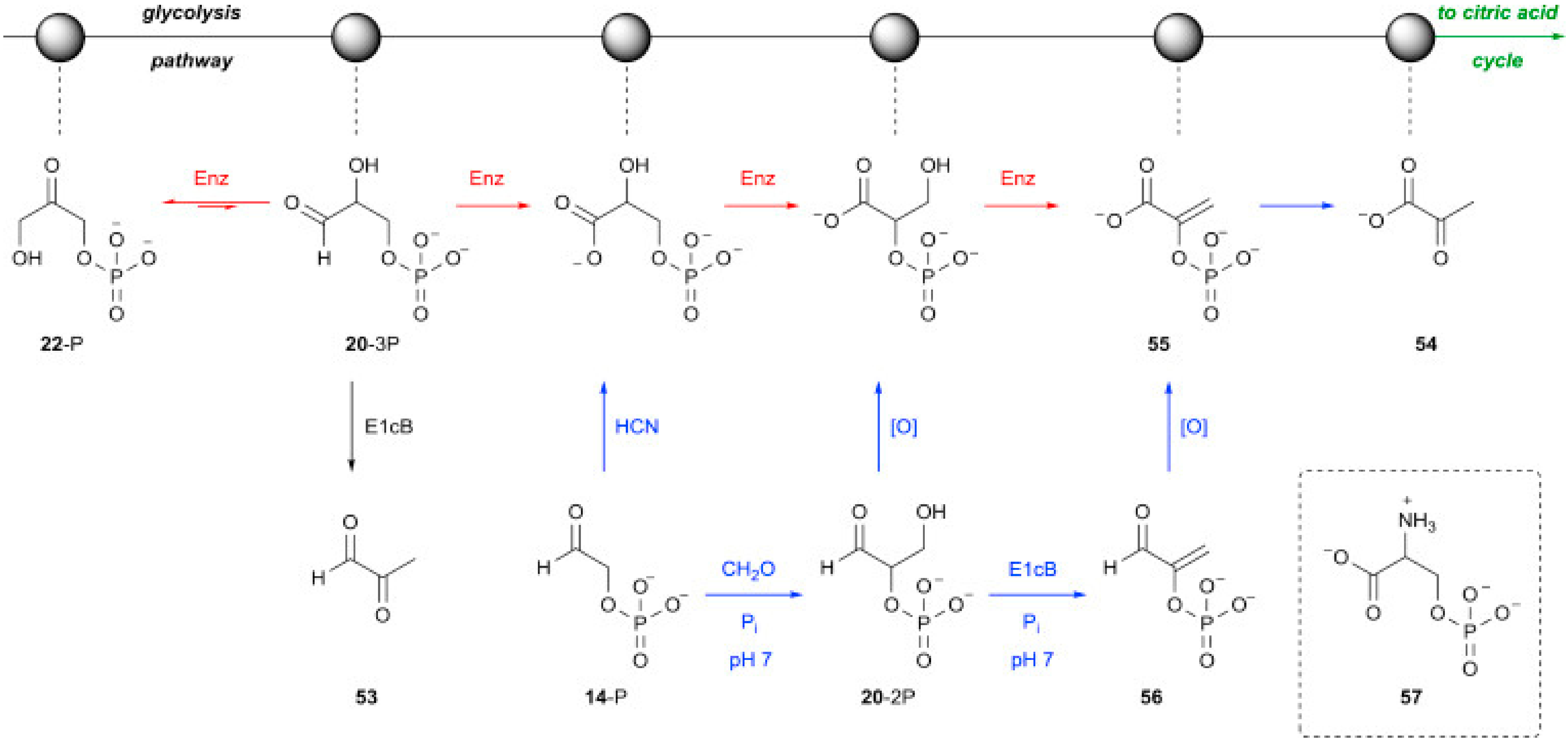
*allo*- 46%
*manno*- 7%
*altro*- 17%
*talo*- 6%
*galacto*- 2%
*gulo*- 8%
*gluco*- 3%
*ido*- 2%

*rac*-glyceraldehyde 2-phosphate **20**-2p 5%
*rac*-tetrose 2,4-diphosphate 4%
***rac*-pentose 2,4-diphosphate 21** 72%
*rac*-hexose 2,4,6-triphosphate **19** 19%

*ribo*- 33%
*lyxo*- 16%
*arabino*- 10%
*xylo*- 7%

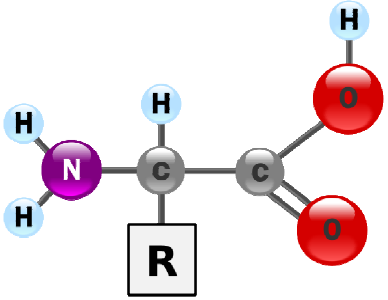
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

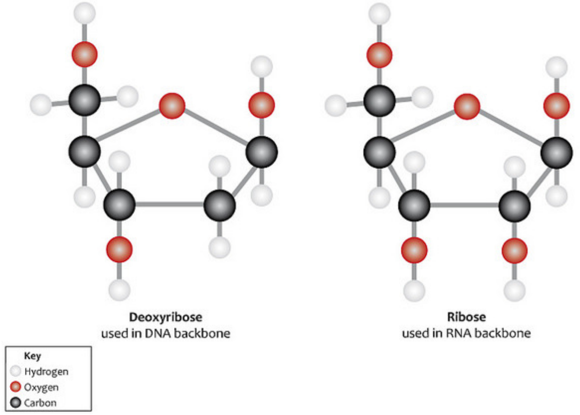
# Prebiotic Reconstruction of the Triose Glycolysis Pathway by Selective a-Phosphorylation of Sugars



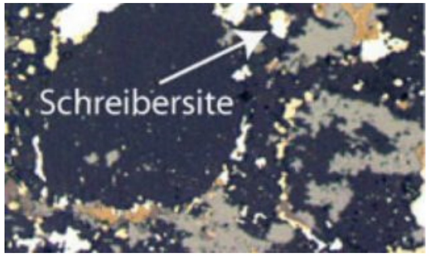
S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

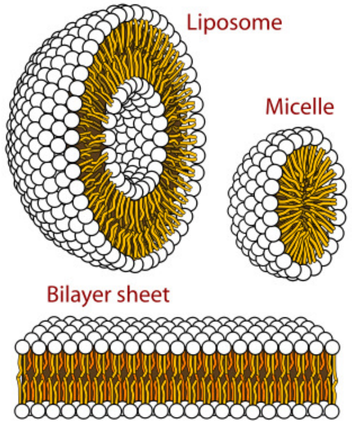
# *Prebiotic soup - summary*

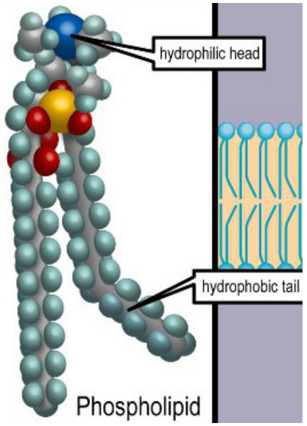


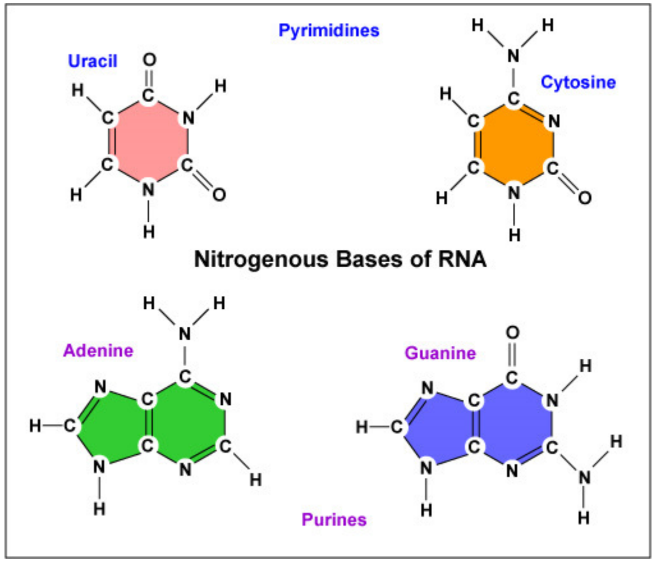


***vivianite***



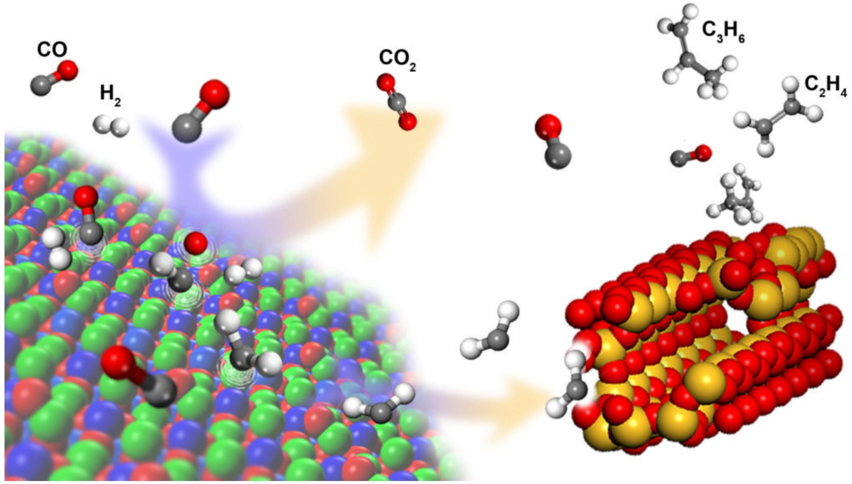




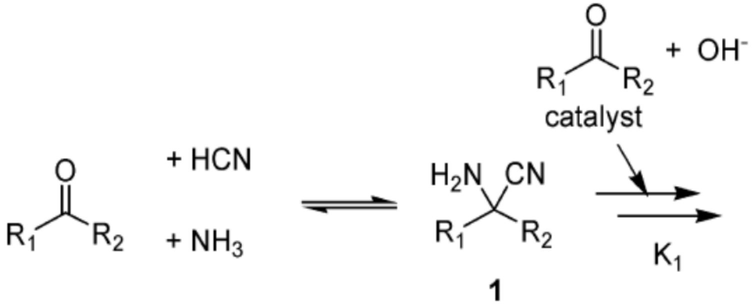


# *Prebiotic soup - summary*

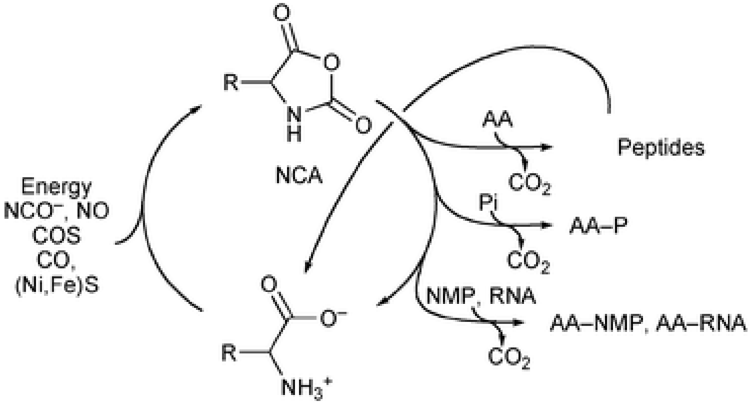
## Fischer-Tropsch chemistry - lipids



## Strecker chemistry - aminoacids

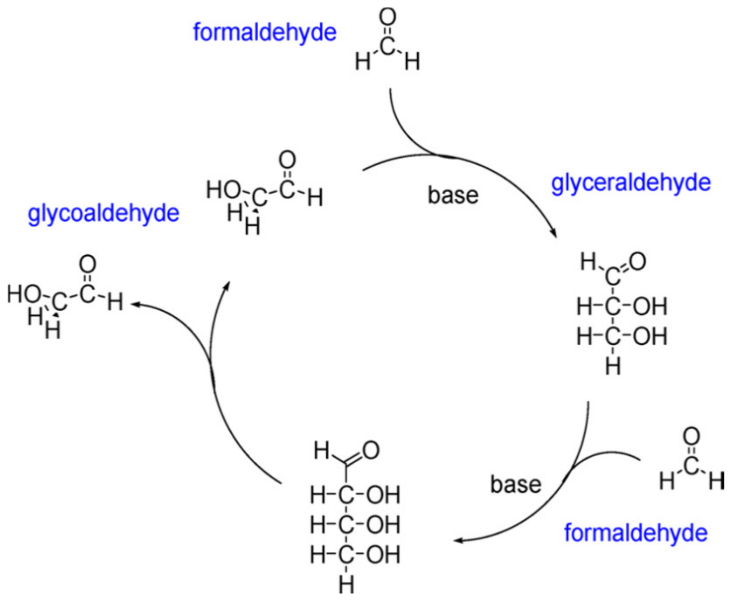


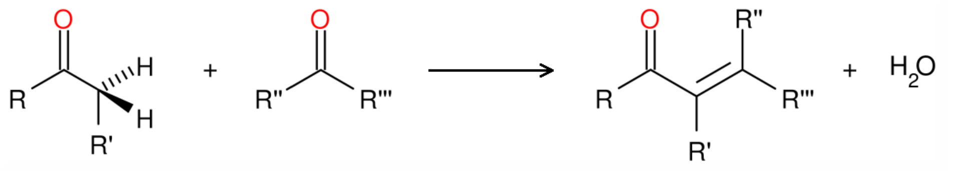
## Dehydrating agents (COS, NO) – condensation of AAs to peptides

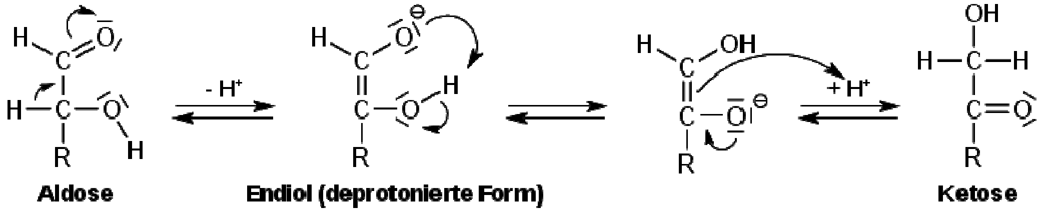


# *Prebiotic soup - summary*

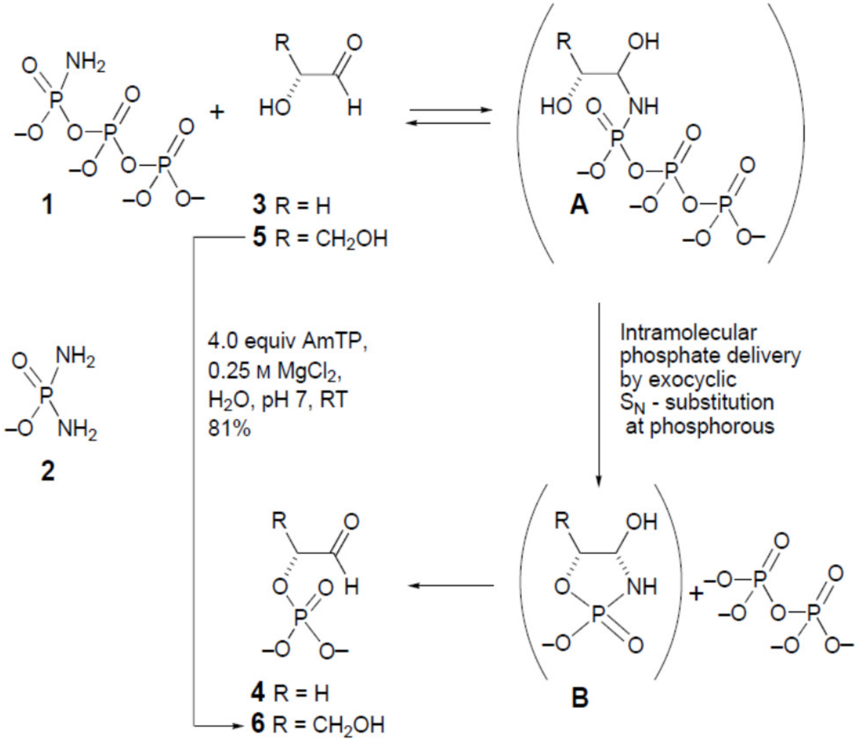
## Formose chemistry - carbohydrates





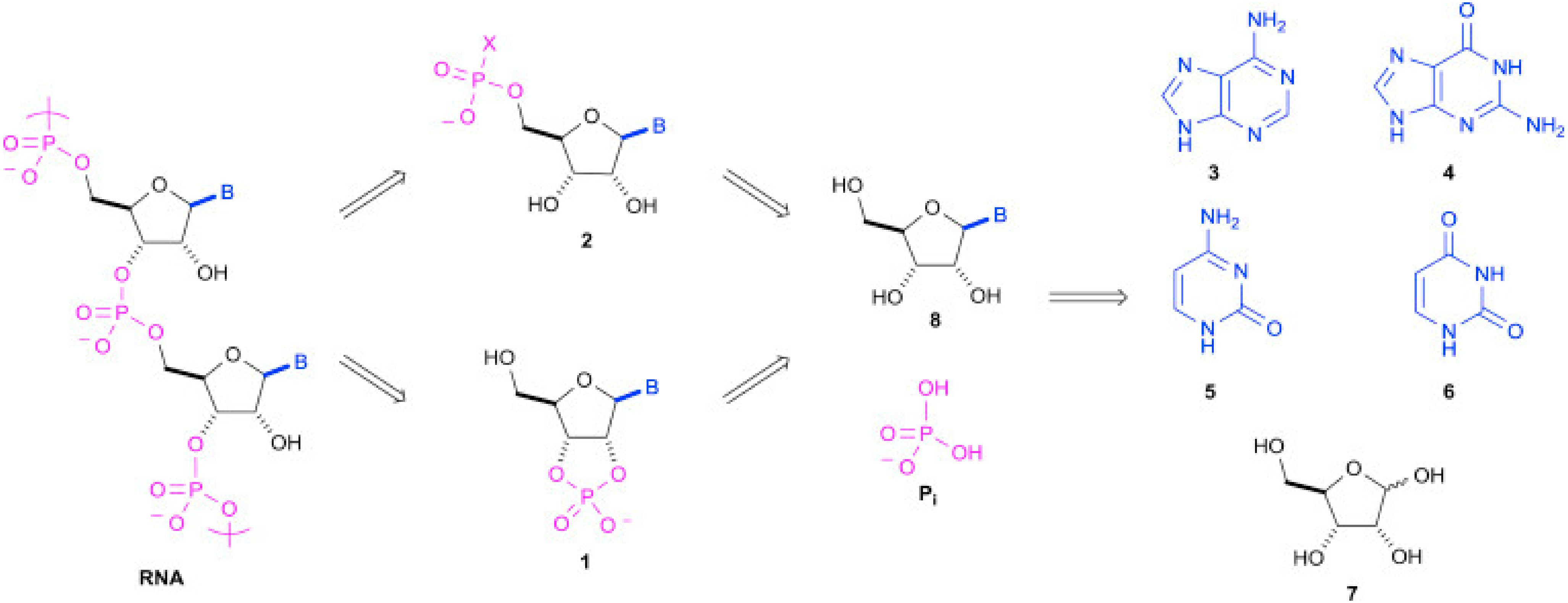


## Phosphorus reactivity - phosphates



# *Prebiotic soup - summary*

*The Traditional Modular Retrosynthetic Analyses Disconnect RNA to Ribofuranosyl Sugar, Inorganic Phosphate, and Canonical RNA Nucleobases.*

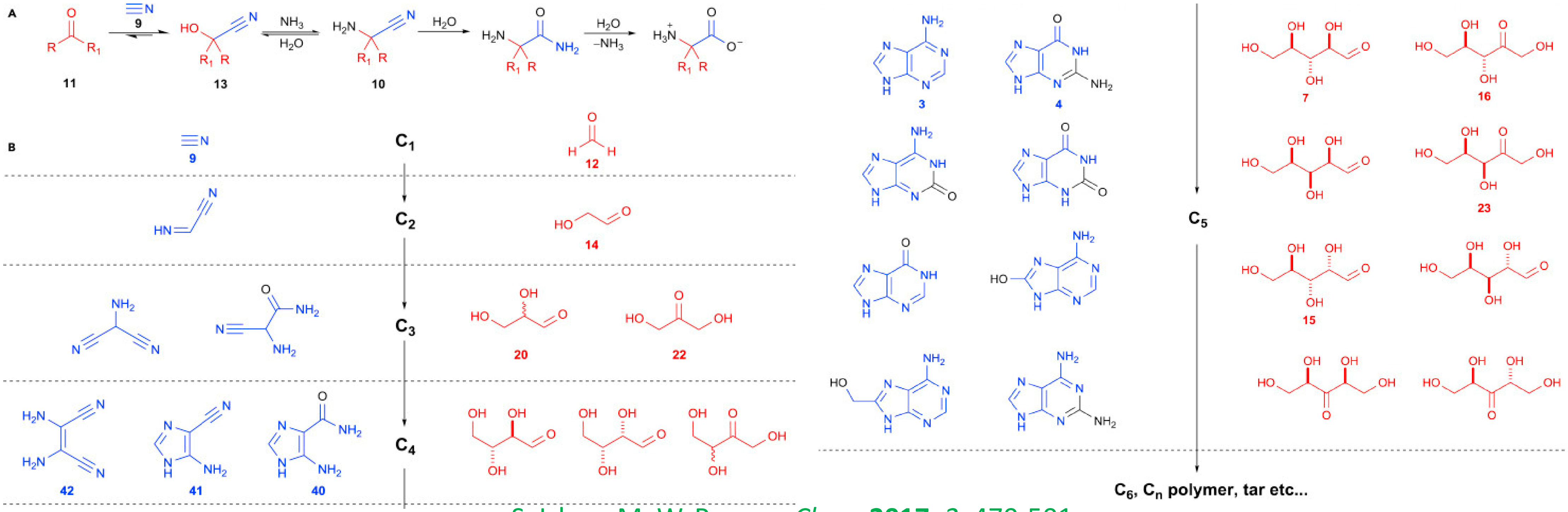


S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

# *Prebiotic soup - summary*

*The Three Pillars of Prebiotic Chemistry*

*(A) The spark discharge aminonitrile synthesis (The Miller-Urey experiment.),*
*(B) Nucleobase synthesis by HCN oligomerization, and*
*(C) Sugar synthesis by the formose reaction.*



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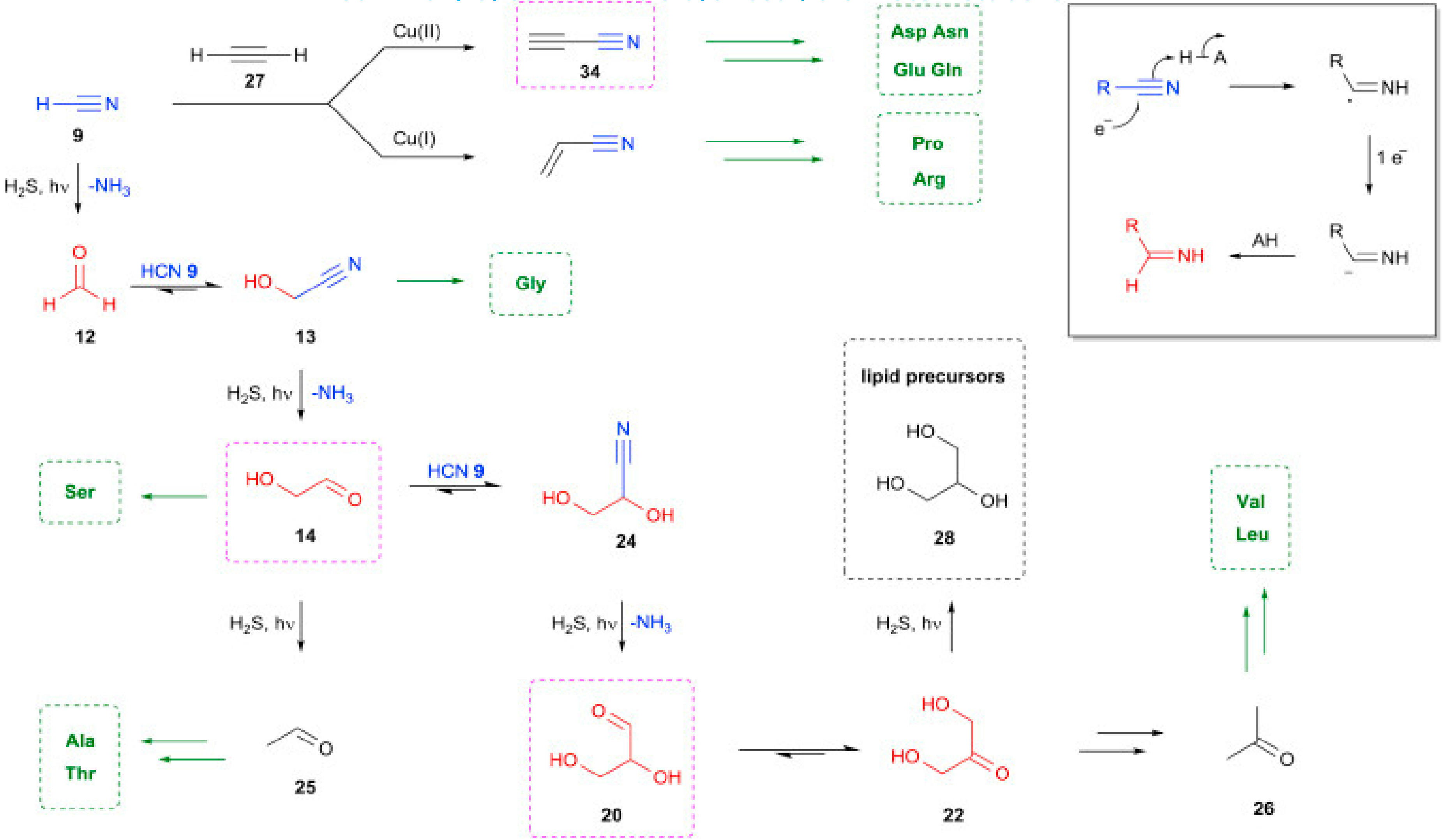
# *Prebiotic soup - summary*

*Summary of Sutherland's Cyanosulfidic Protometabolism*



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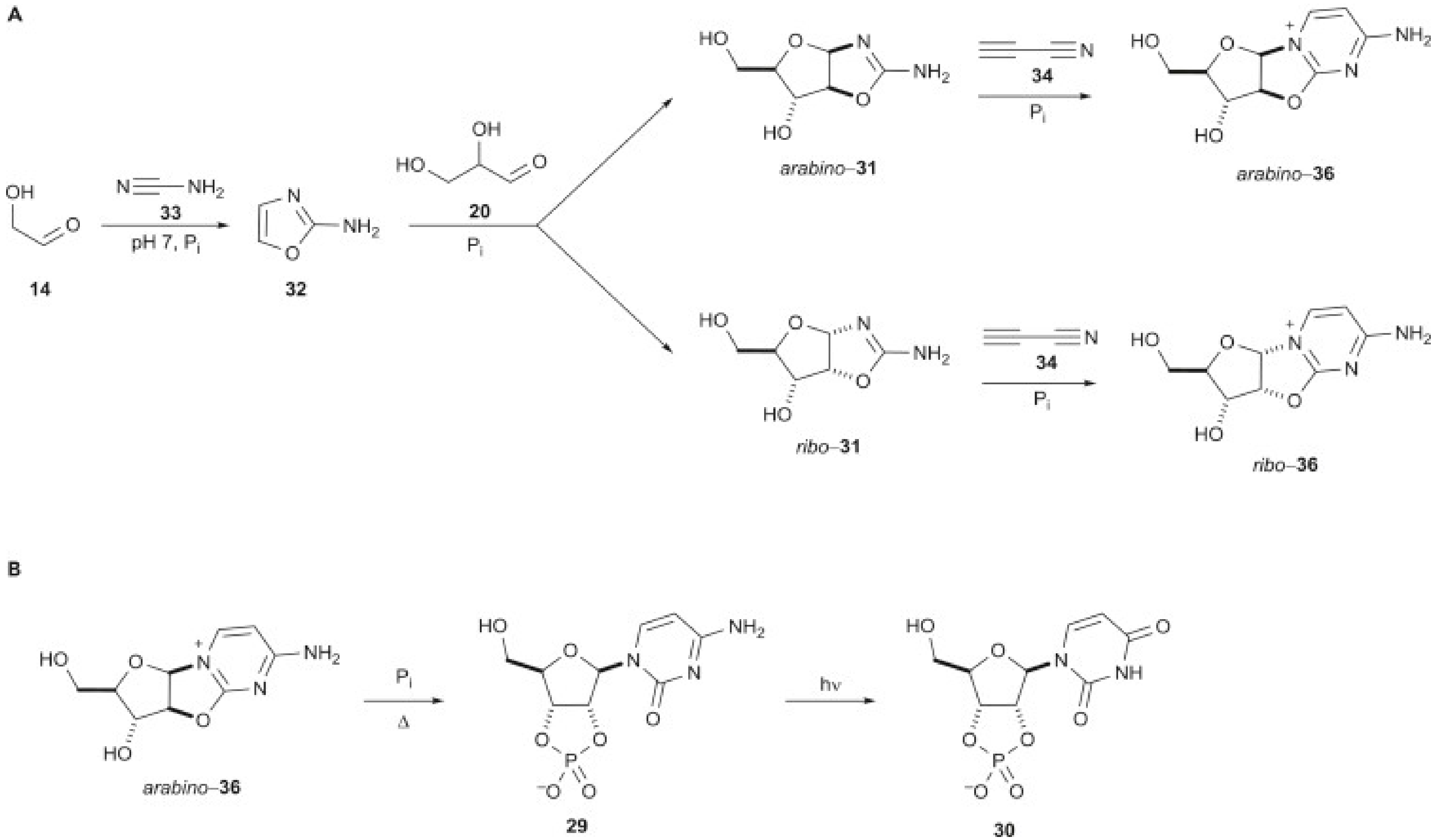
# ***Prebiotic soup - summary***

*Summary of the Prebiotic Syntheses of the Activated Pyrimidine Ribonucleotides*



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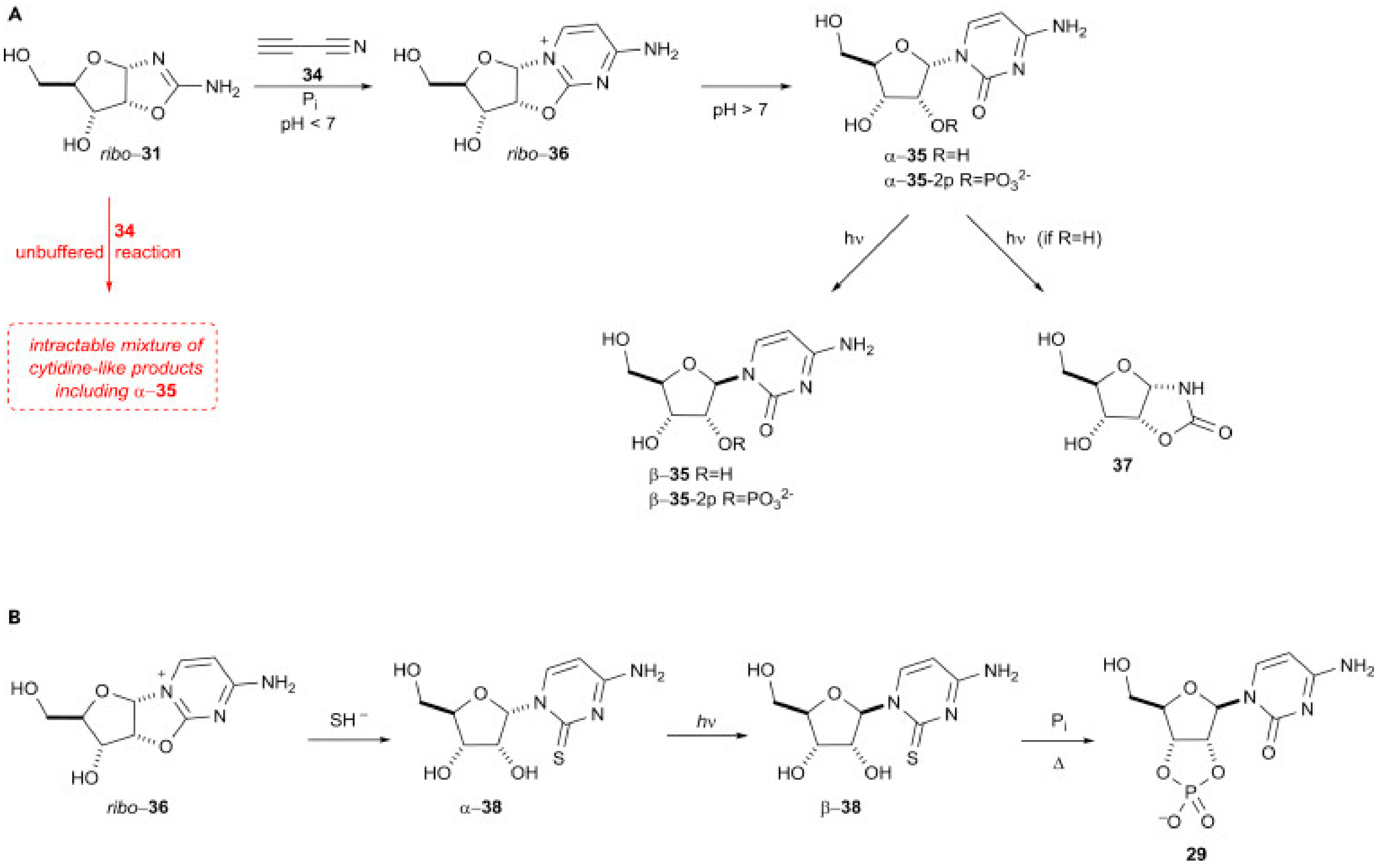
# *Prebiotic soup - summary*

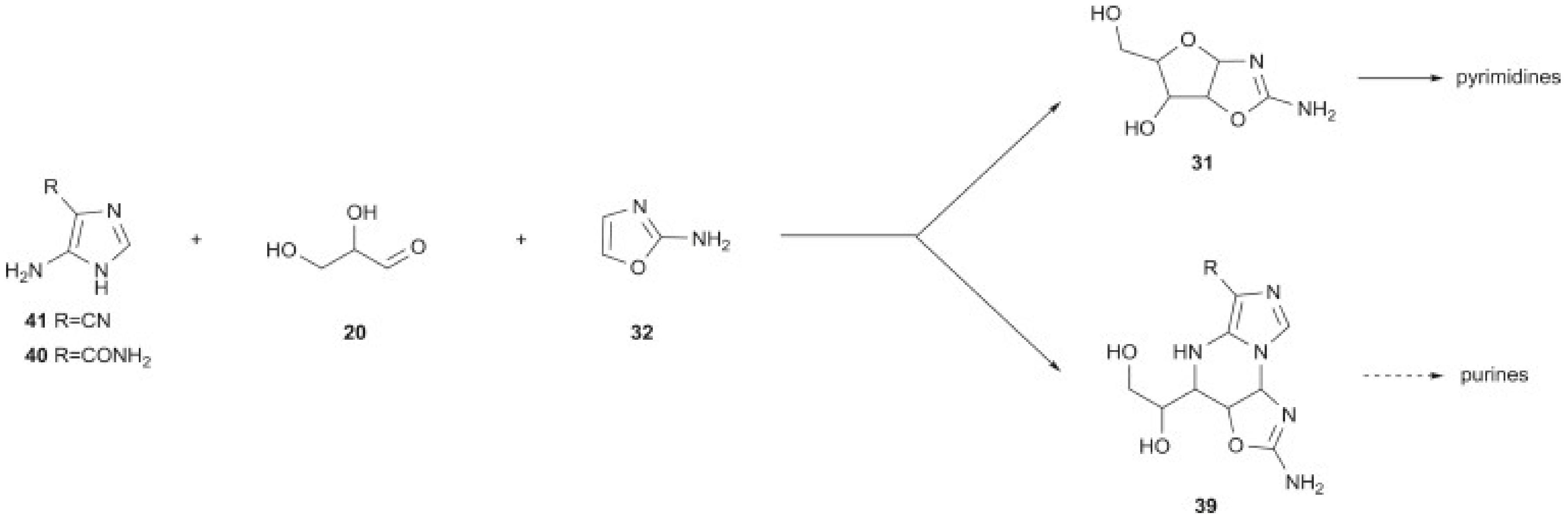
## *Conversion of Ribose Aminooxazoline to Activated Pyrimidine Ribonucleotides*



S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

# Prebiotic soup - summary

## *Simultaneous pH-Controlled Multicomponent Assembly of Purine and Pyrimidine Nucleotide Precursors*



HCN tetramers AICA **40** and AICN **41** participate in a high-yielding pH-dependent three-component reaction with glyceraldehyde **20** and 2-aminooxazole **32**. This produces potential purine ribonucleotide precursors **39**. The Mannich-type reactivity results in N9-purination with absolute regiospecificity. At pH 6–6.5, both purine **39** and pyrimidine **31** ribonucleotide precursors are observed, suggesting that a divergent synthesis of purine and pyrimidine ribonucleotides from within one pool of reagents is an enticing prospect.

S. Islam, M. W. Powner *Chem* **2017**, *2*, 470-501

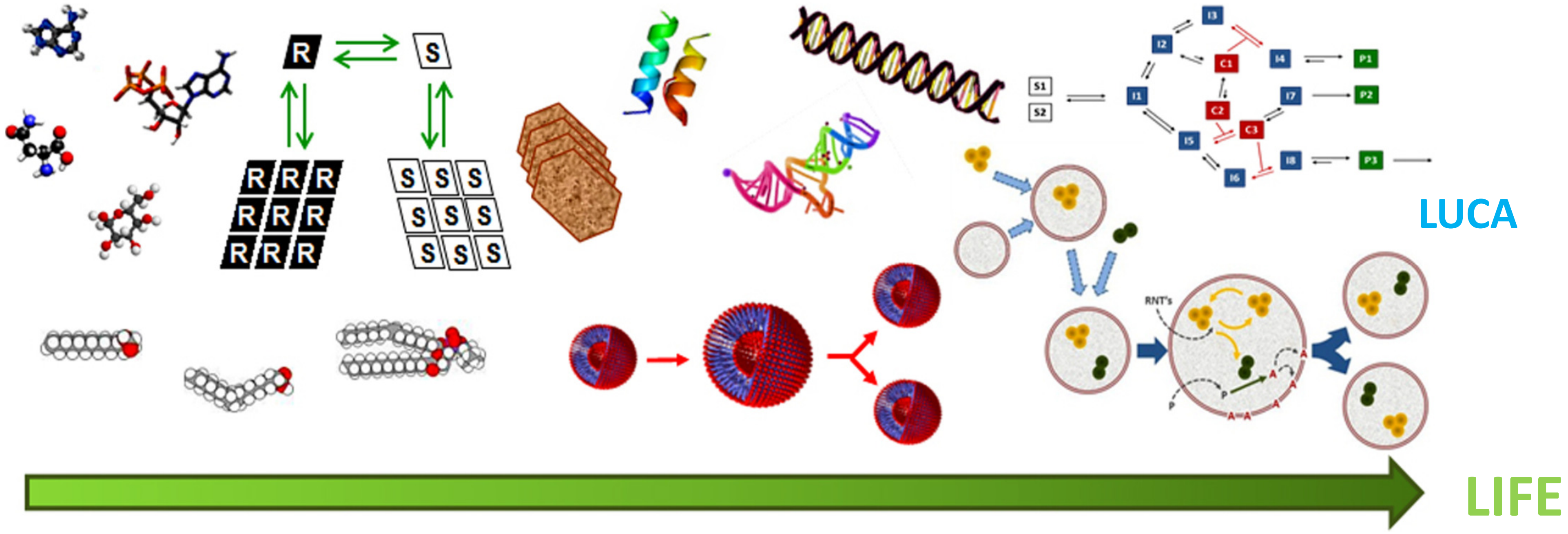
*Origin of the Universe – stars, planets, elements*

*Origin of biorelevant monomers – primordial soup*

***Complex chemical processes on the way to living systems***

*Protocells and LUCA*

# *Self-organization of molecules and chemical reactions*



Increasing complexity from molecules to systems