

Biosynthesis – Inspiration for Drug Discovery

Key Aspects

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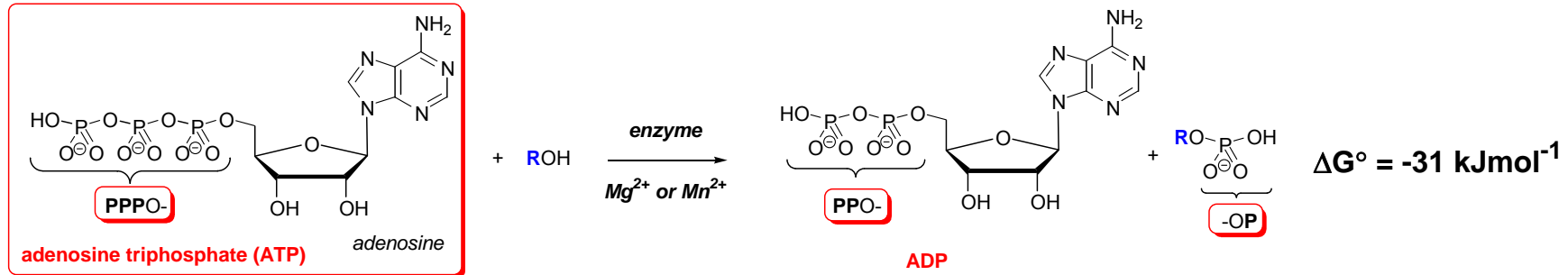
Dec 2008

Format & Scope of Lecture

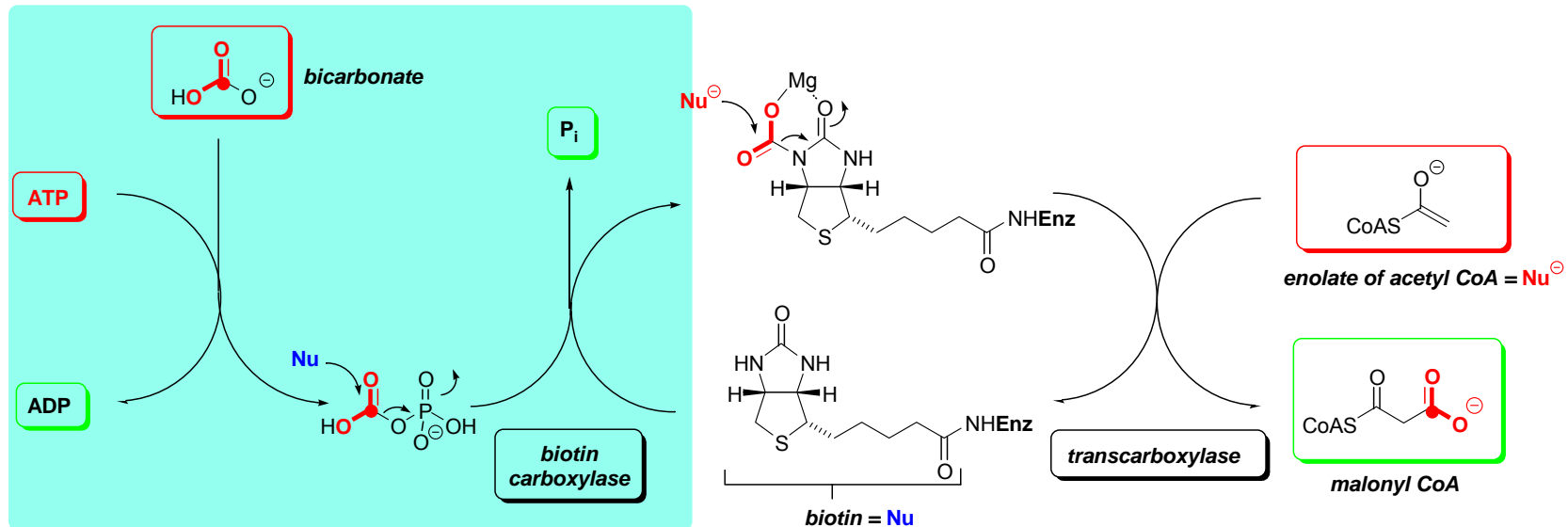
- **Enzyme cofactor chemistry:**
 - ATP, CoASH, SAM, DMAPP, biotin, NAD(P)⁺, NAD(P)H, FAD, FADH₂, peroxy-FADH₂, P₄₅₀ & PLP
- **Shikimate pathway:**
 - PEP + E-4-P → aromatic α-amino acids
- **Alkaloids**
 - Lys & Orn pathways to pyrrolidine & piperidine alkaloids – PLP chemistry
 - Phenolic coupling
- **Fatty acids and polyketides:**
 - The fatty acid synthase (FAS) iterative cycle
 - The polyketide synthase (PKS) iterative cycle(s)
- **Isoprenoids:**
 - The mevalonate pathway: 3× acetyl CoA → IPP & DMAPP
 - Pathways to linear C₁₀, C₁₅ & C₂₀ isoprenoids: geranyl PP, farnesyl PP, geranylgeranyl PP

ATP - Free Energy Releasing Couple

– Key process:

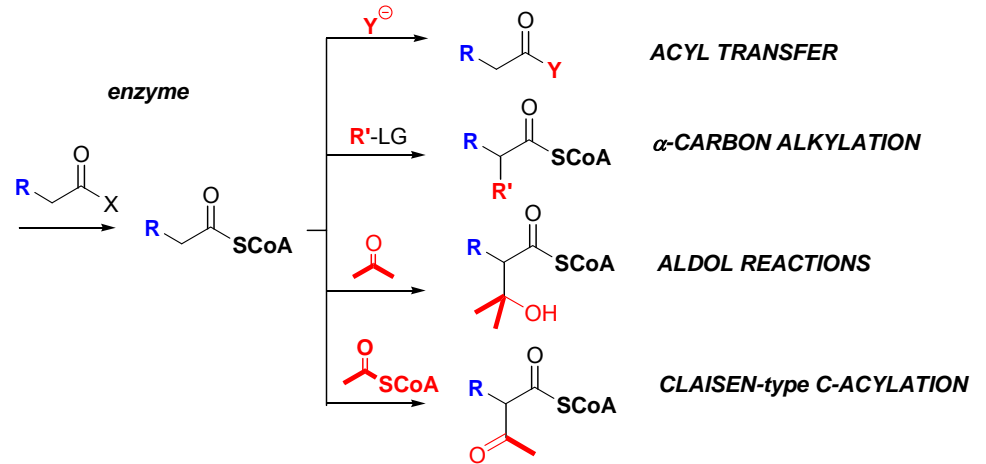
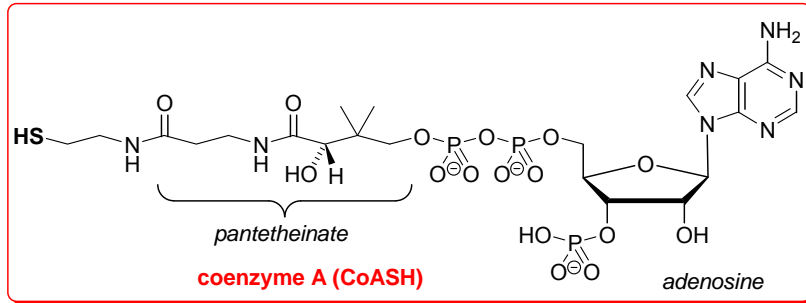


– e.g. activation of bicarbonate in malonyl CoA biosynthesis (FA + PK lecture)

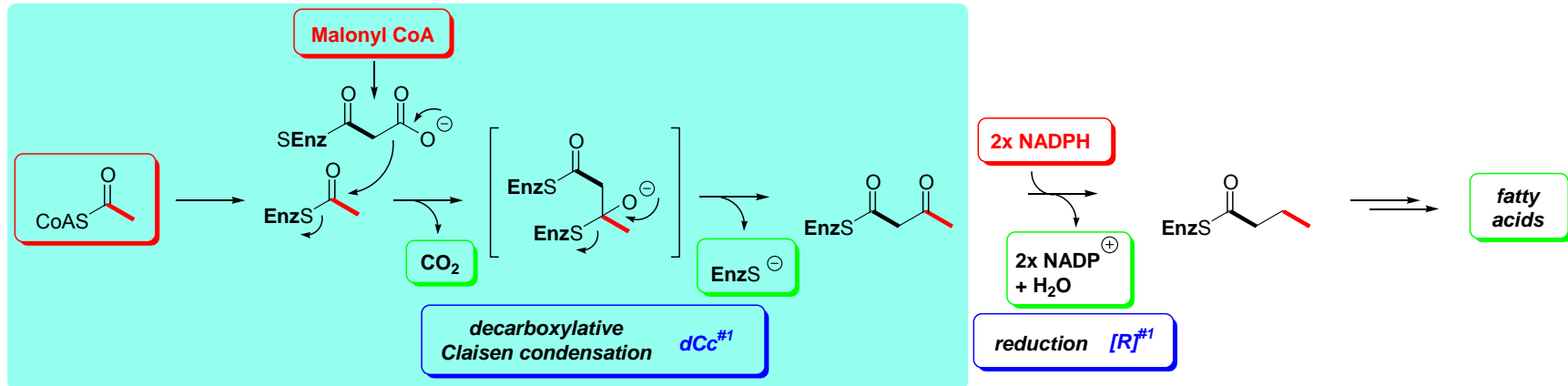


CoASH - C-C Bond Formation

- Key processes:

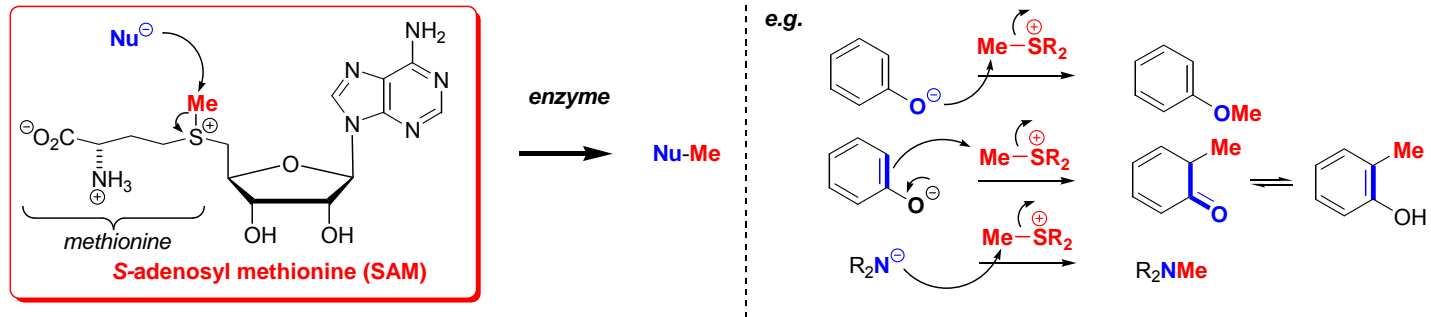


- e.g. iterative decarboxylative Claisen condensations in fatty acid biosynthesis (FA + PK lecture)

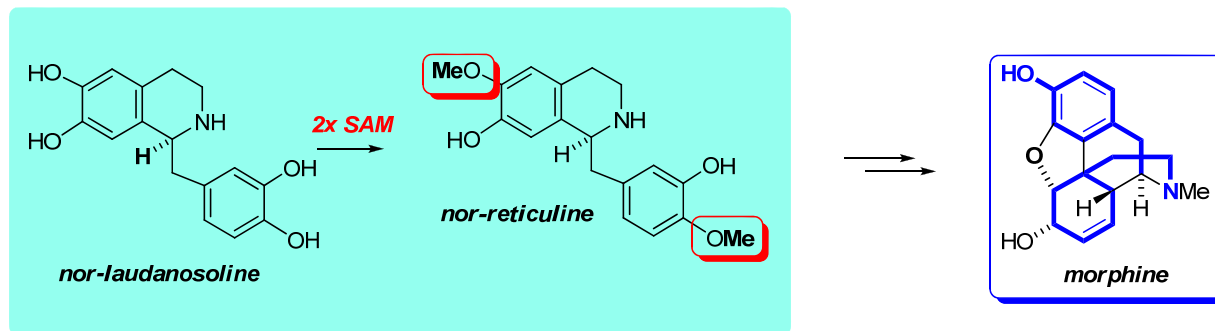


SAM - Methylation

- Key processes:



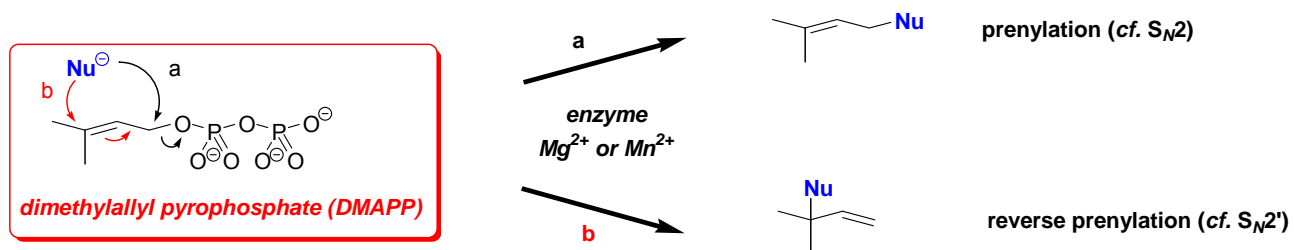
- e.g. phenol O-methylation to control subsequent oxidative phenolic coupling (alkaloid lecture)



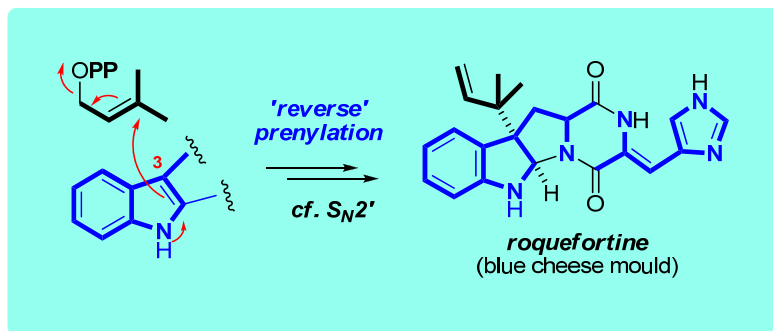
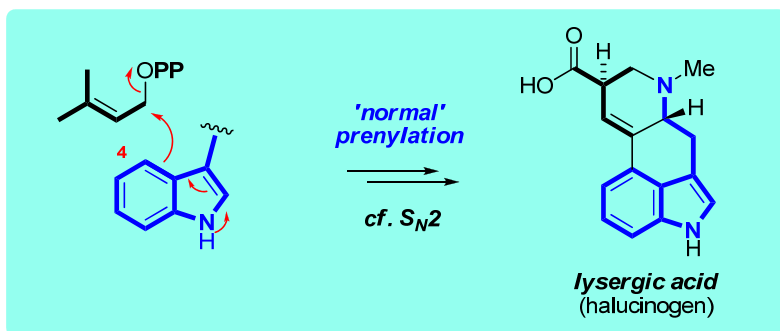
DMAPP - Dimethylallylation

– Key process:

- NB. via allylic carbocation with trapping by nucleophile at either more or least substituted end...

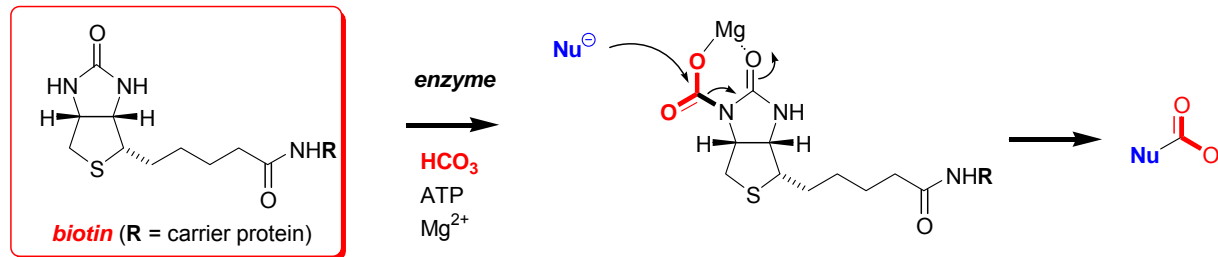


– e.g. prenylation & reverse prenylation of alkaloids (isoprene lecture)

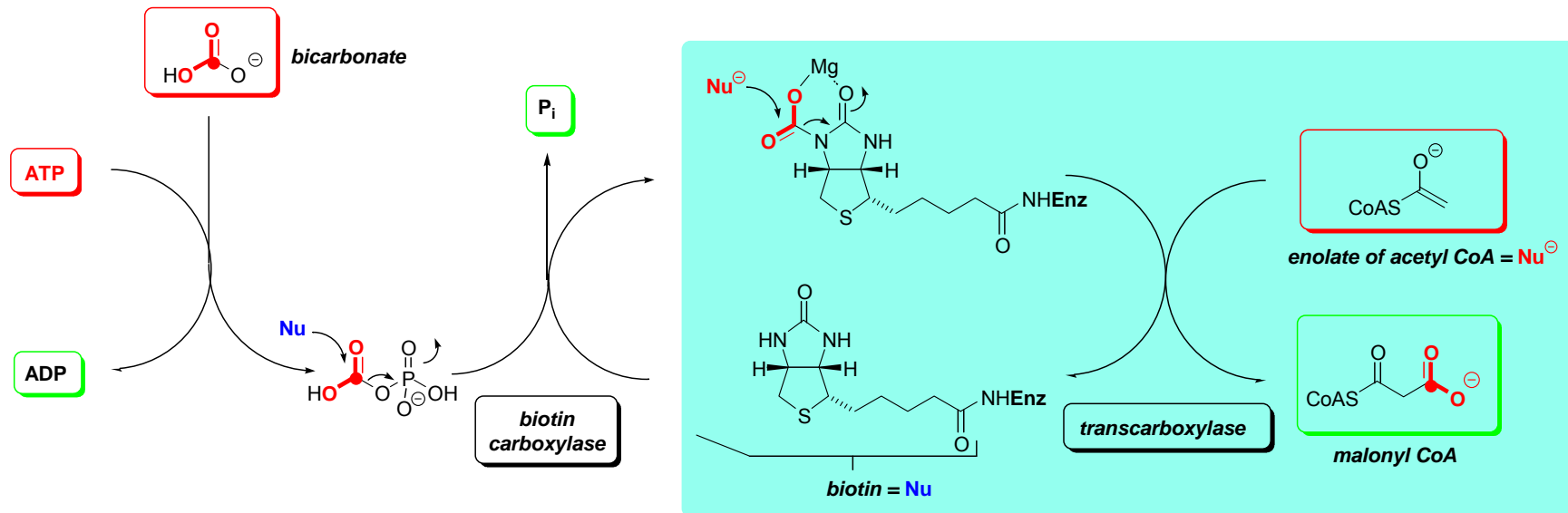


Biotin - Carboxylation

- Key process:

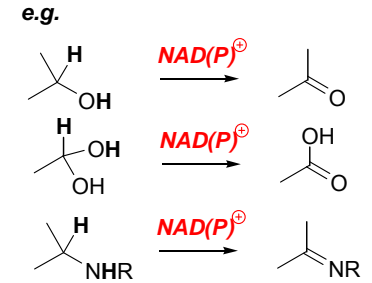
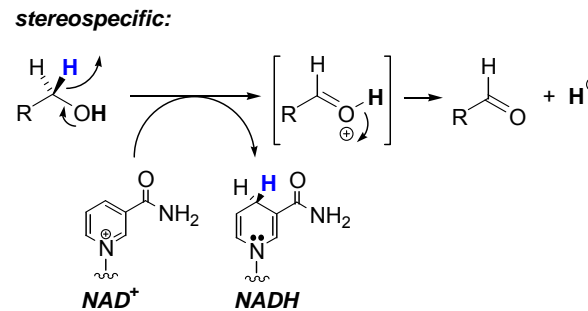
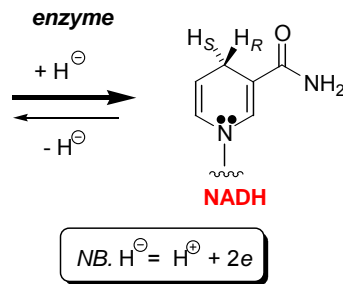
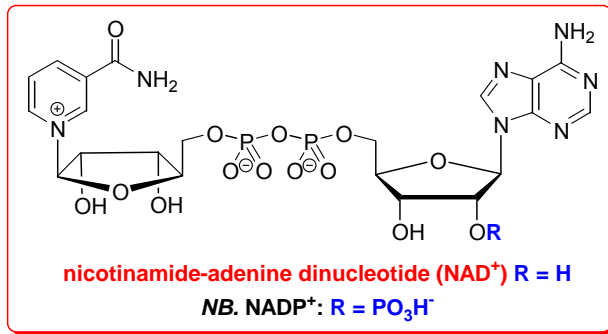


- e.g. carboxylation of acetyl CoA to give malonyl CoA (FA + PK lecture)

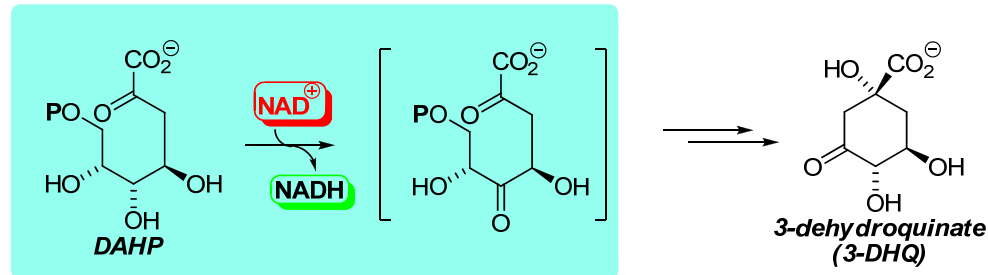


NAD(P)⁺ - Oxidation

- Key process:

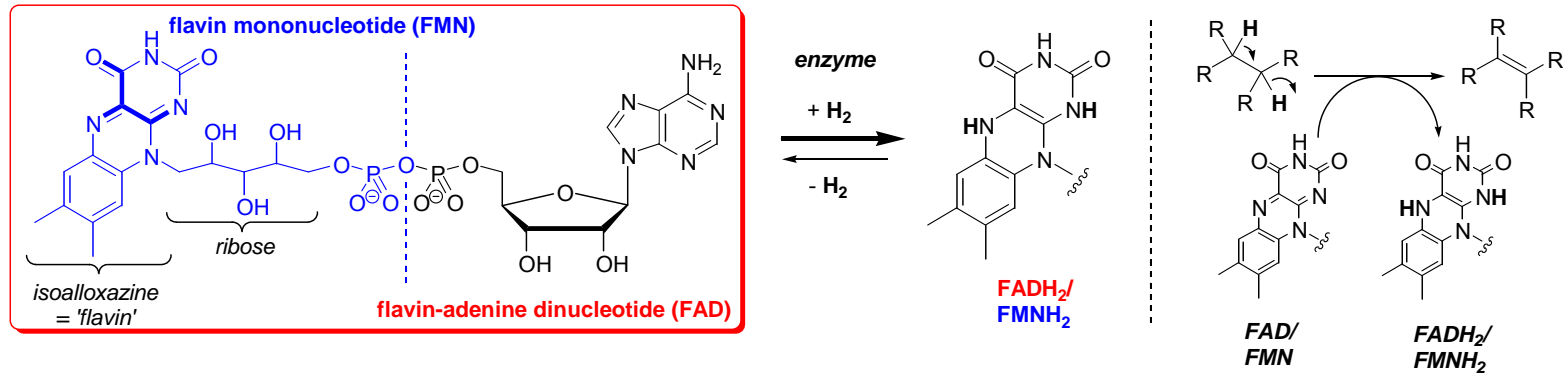


- e.g. 2° alcohol to ketone oxidation catalysed by 3-dehydroquinate synthase (shikimate lecture)

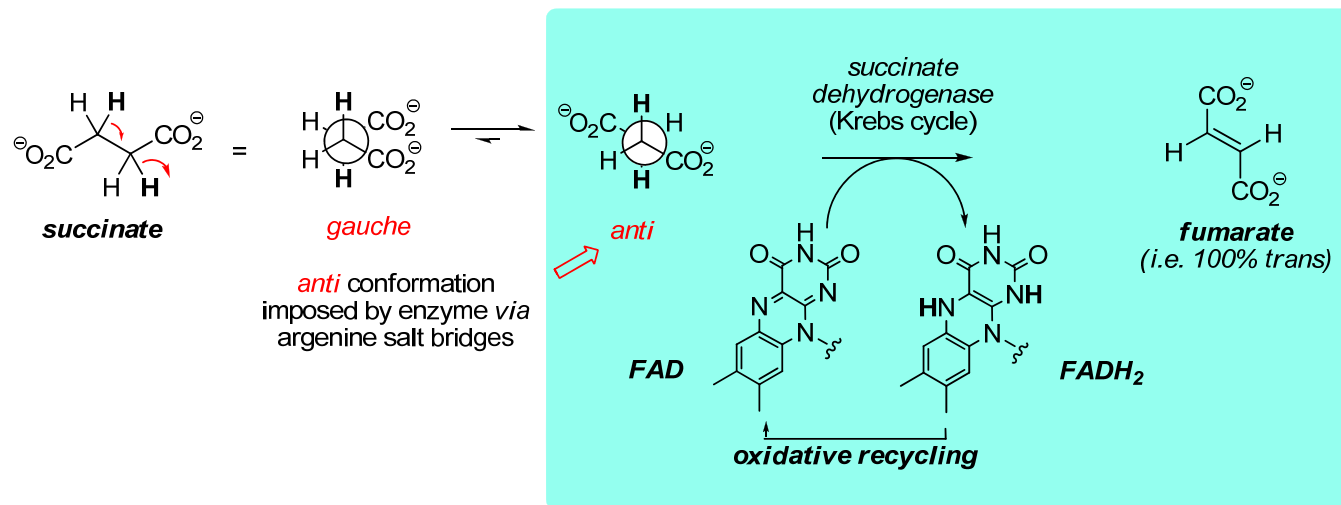


Flavin - Oxidation

- Key process:

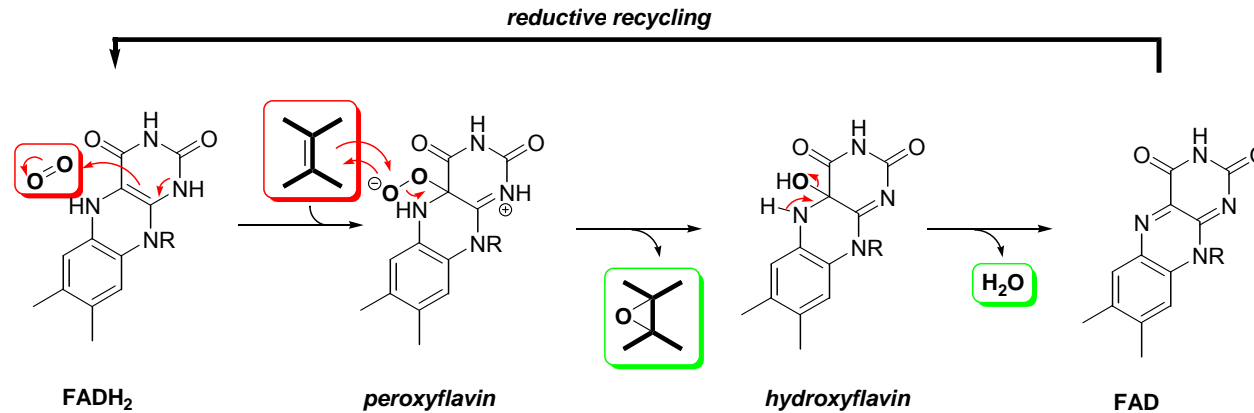


- e.g. dehydrogenation of succinate → fumarate (co-factor lecture)

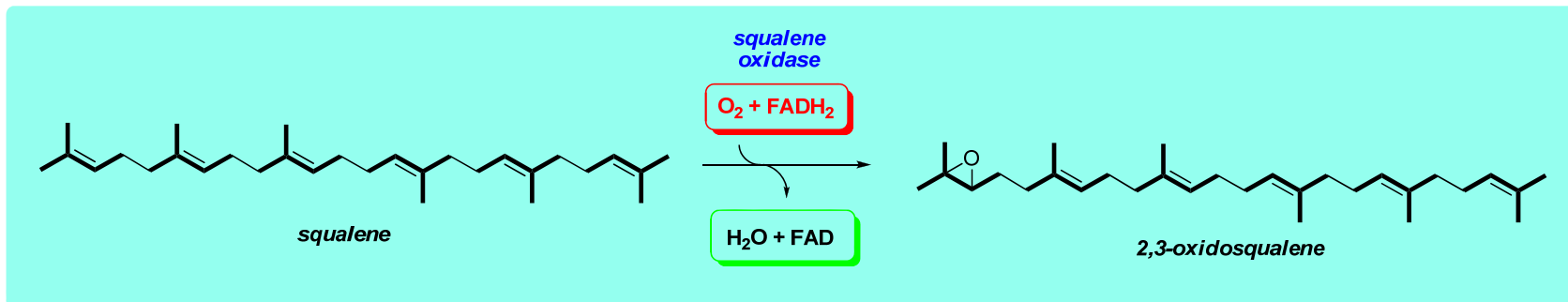


Peroxyflavin - Oxidation

- Key process:

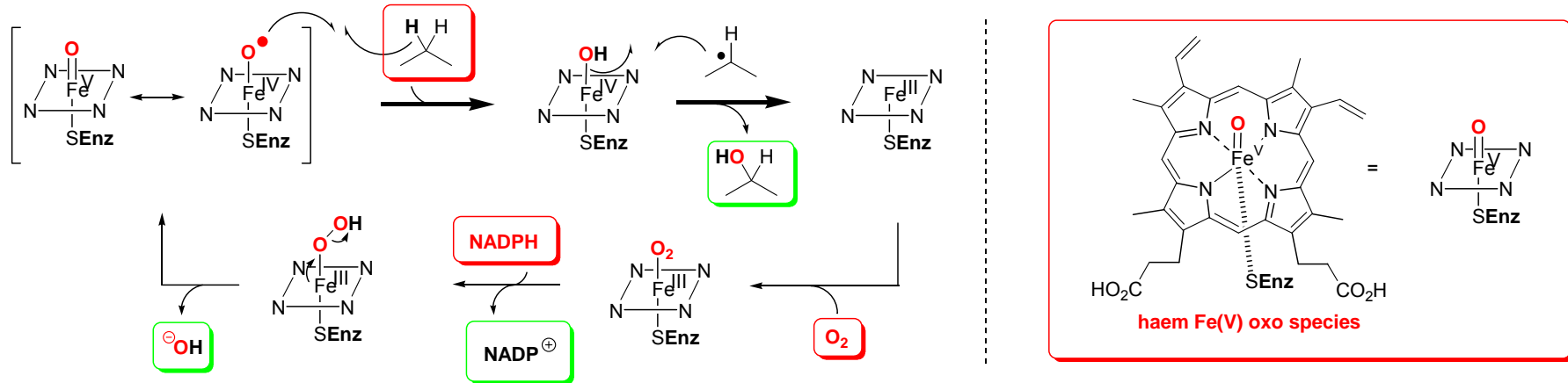


- e.g. squalene → 2,3-oxidosqualene (isoprene lecture)

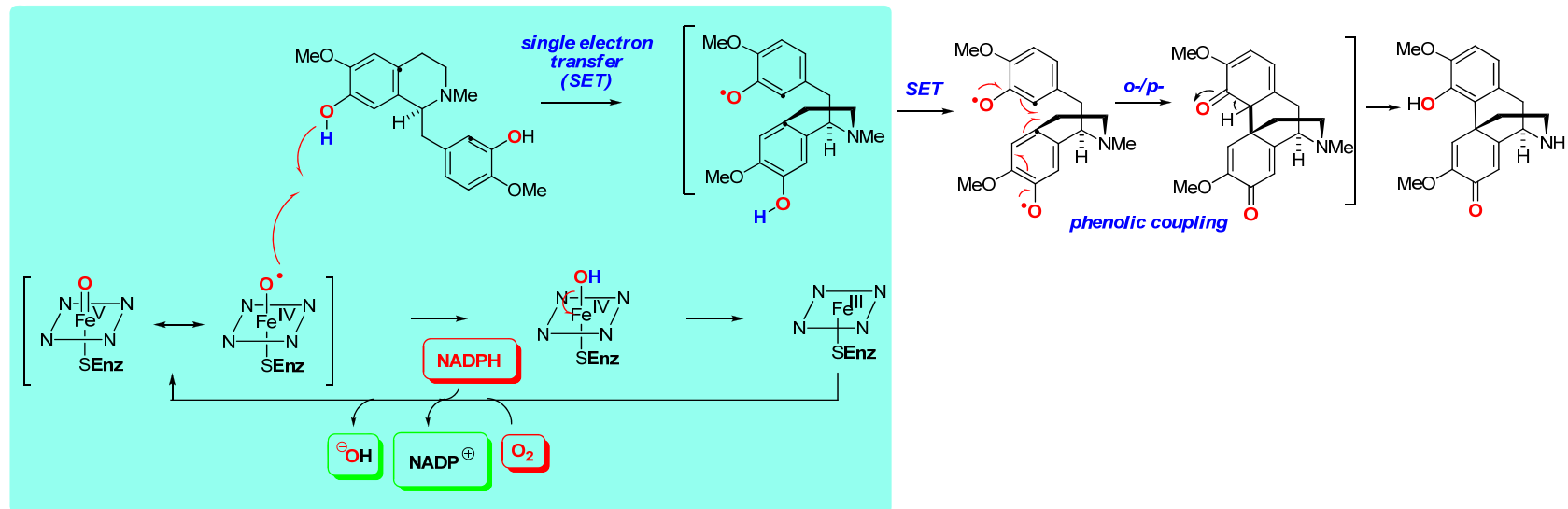


P_{450} Iron oxo - Oxidation

- Key process:

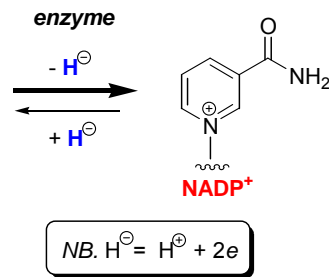
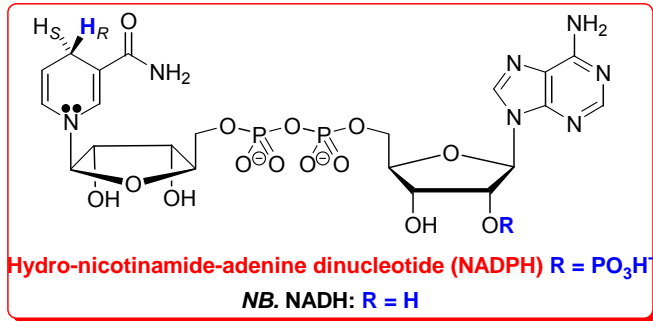


- e.g. Sequential di-phenolic radical formation \rightarrow morphine (alkaloid lecture)

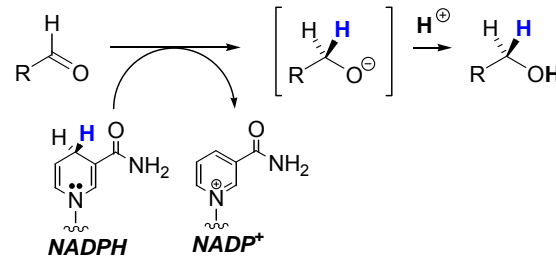


NAD(P)H - Reduction

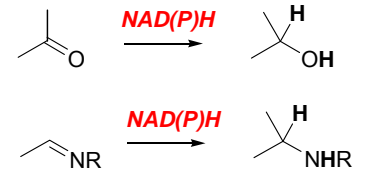
– Key process:



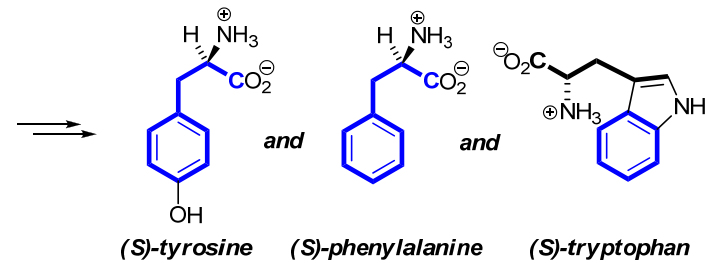
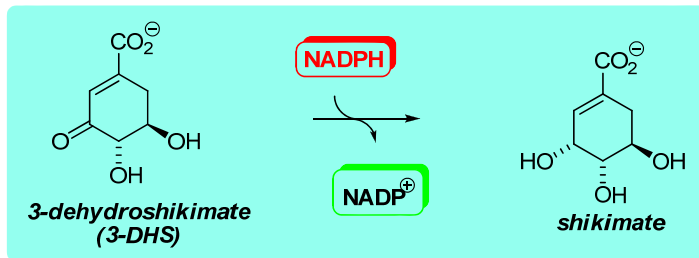
stereospecific:



e.g.

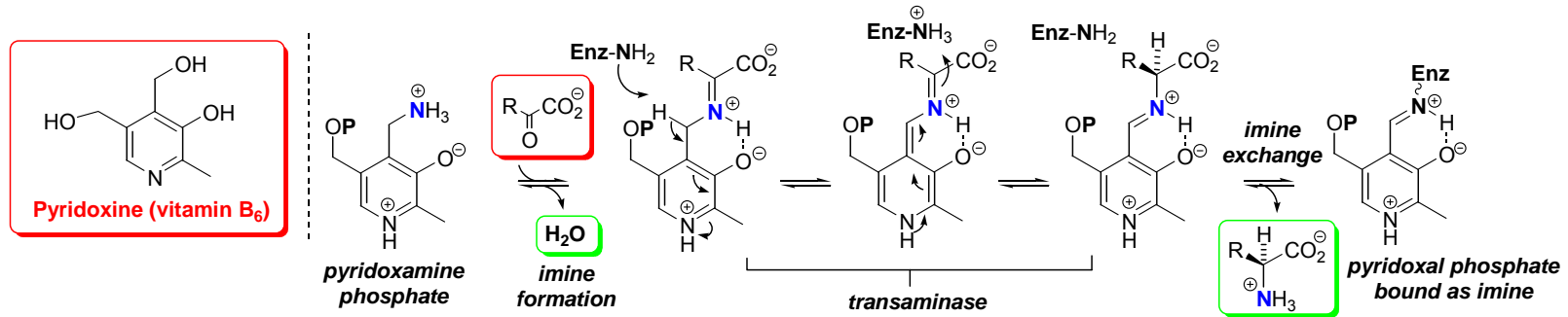


– e.g. stereospecific ketone to alcohol reduction in aromatic α -amino acid synthesis (shikimate lecture)

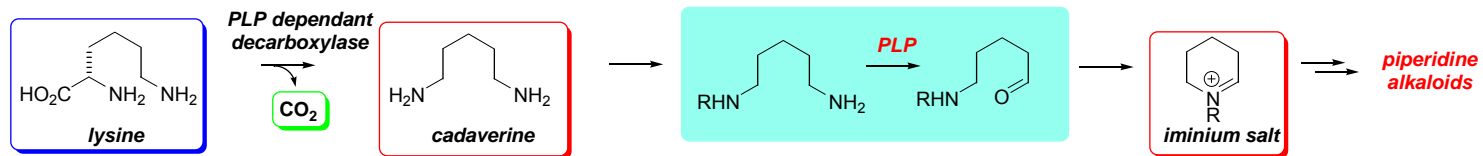


PLP - Transamination

- Key process:

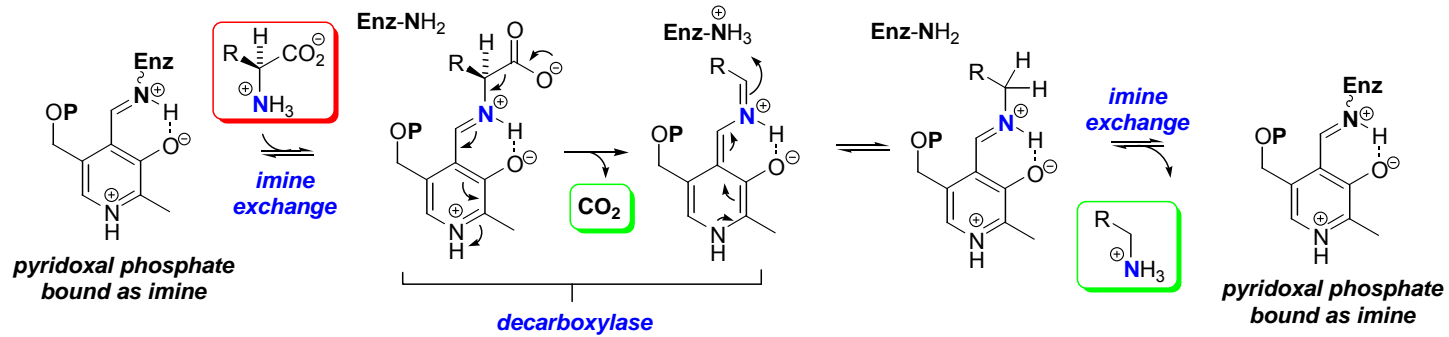


- e.g. oxidative deamination of cadaverine *en route* to piperidine alkaloids (alkaloid lecture)

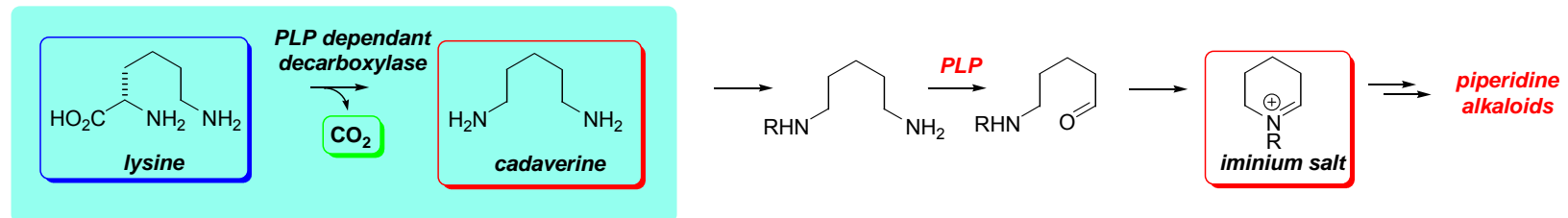


PLP - Decarboxylation

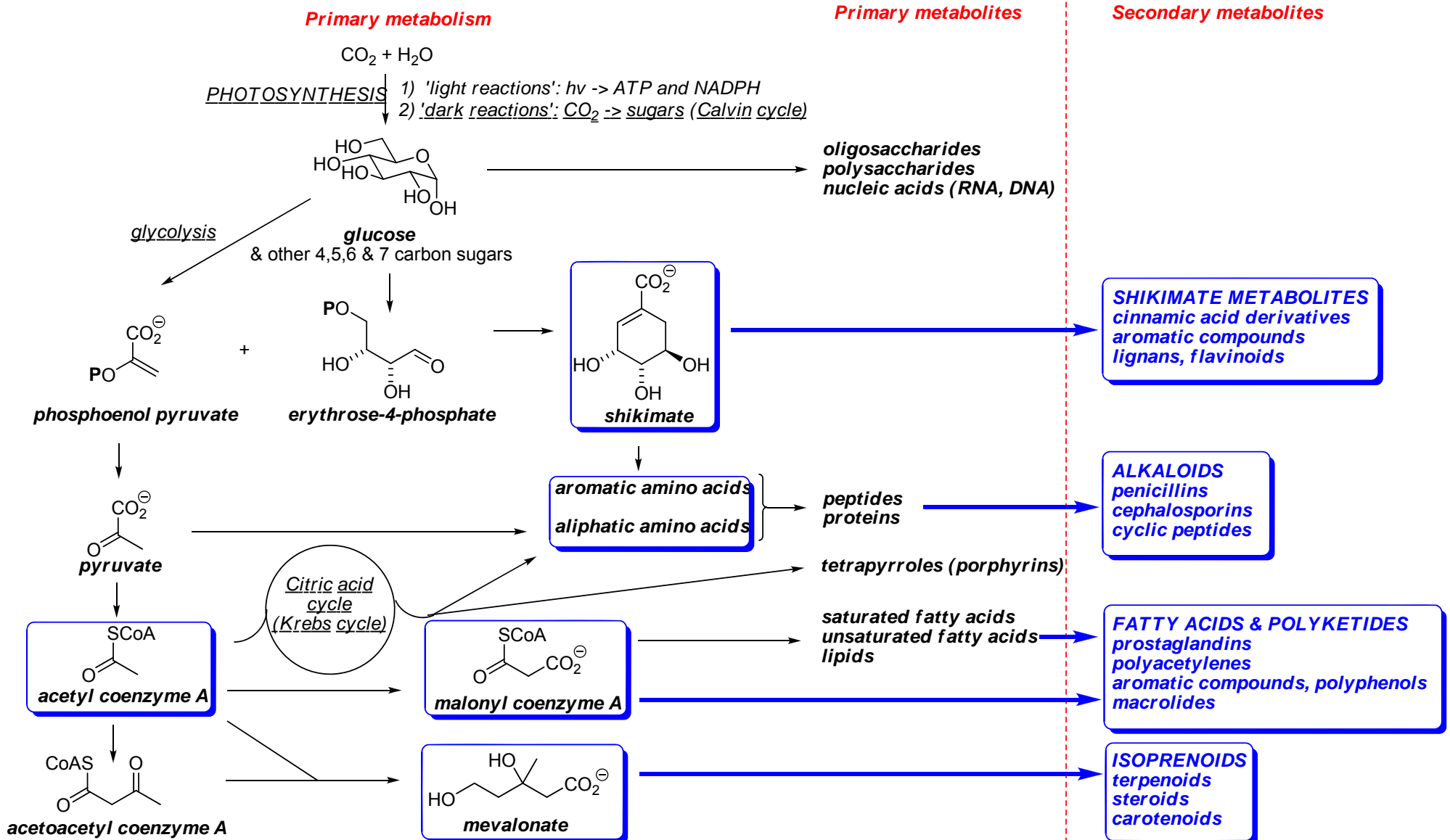
- Key process:



- e.g. lysine decarboxylation to cadaverine (alkaloid lecture)

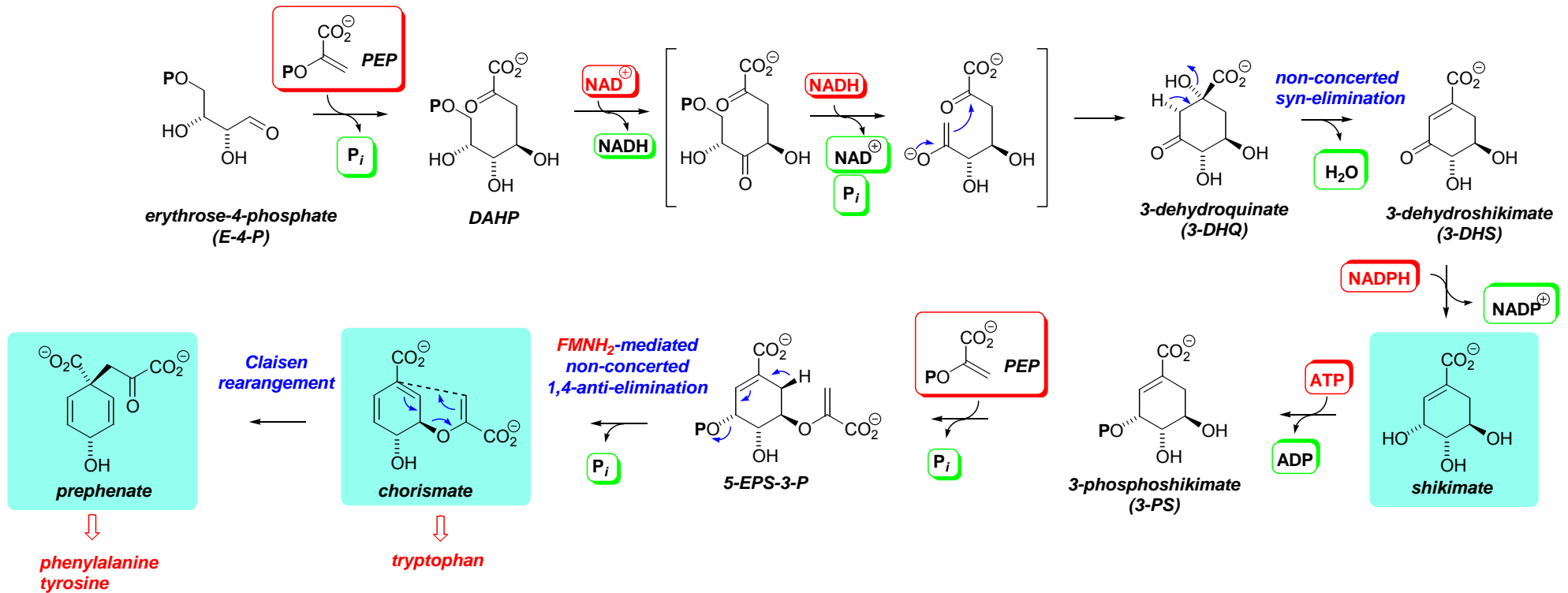


Primary Metabolism - Overview



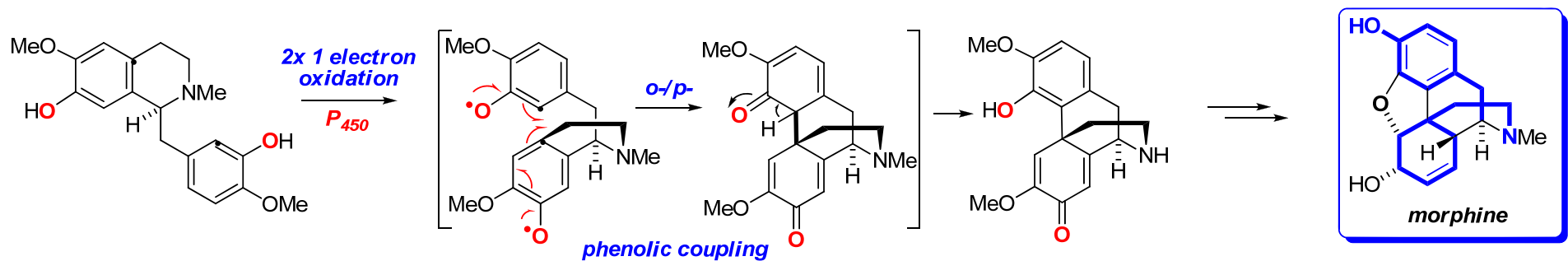
The Shikimate Biosynthetic Pathway

- Phosphoenol pyruvate & erythrose-4-phosphate → shikimate → chorismate → prephenate:**



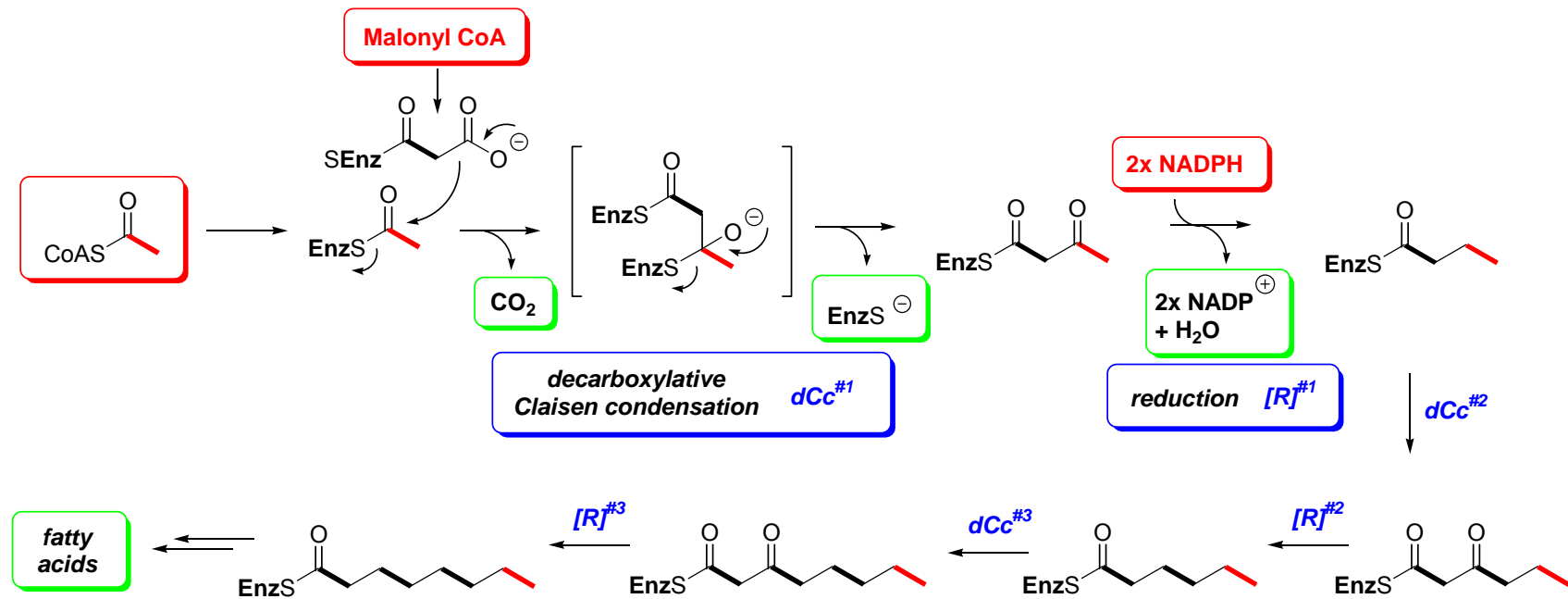
Oxidative Phenolic Coupling

- *e.g. Morphine biosynthesis: o-/p- oxidative phenolic coupling:*



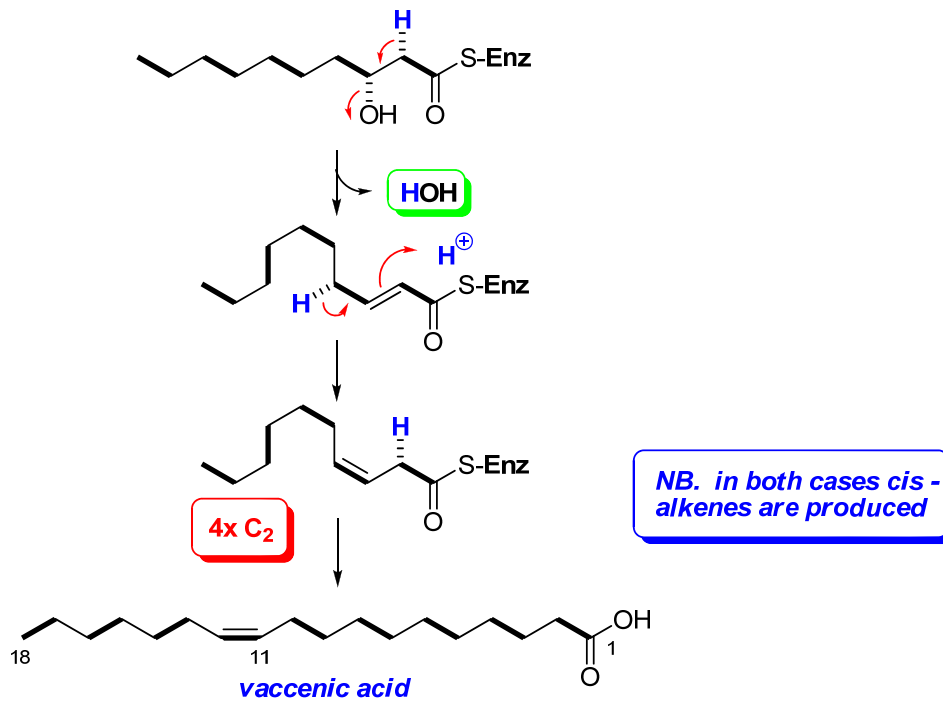
Biosynthesis of Fatty Acids

- Iterative oligomerisation via:
 - Decarboxylative Claisen condensation
 - 3-step ketone reduction

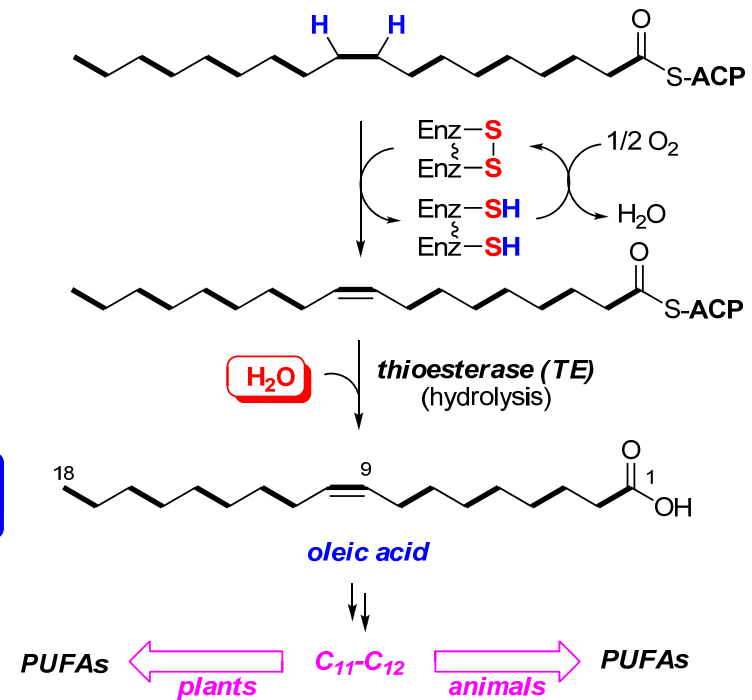


Introduction of Unsaturation

ANAEROBIC ROUTE (bacteria)
 (dehydrogenation occurs during chain elongation)
 mainly MUFAs but some PUFAs



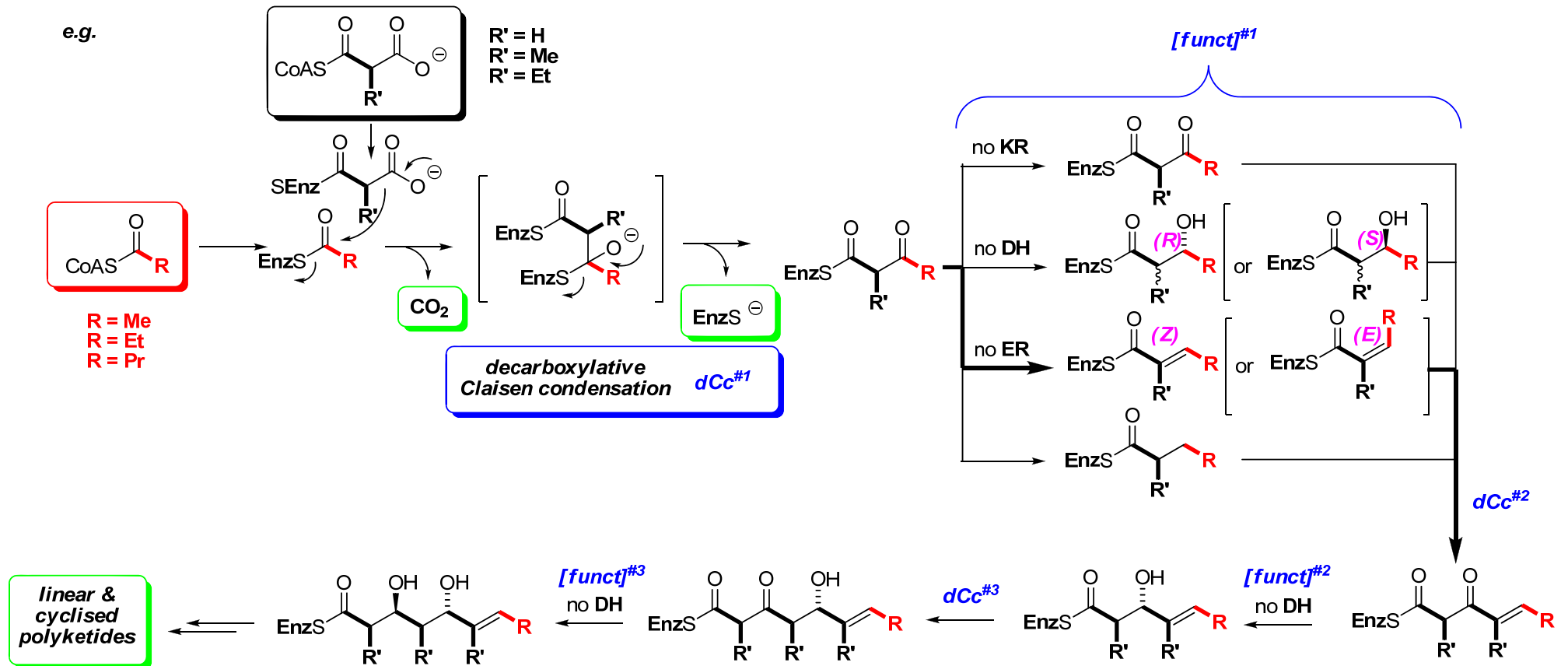
AEROBIC ROUTE (mammals, insects & plants)
 (dehydrogenation occurs after chain elongation)
 MUFAs & PUFAs



Biosynthesis of Polyketides

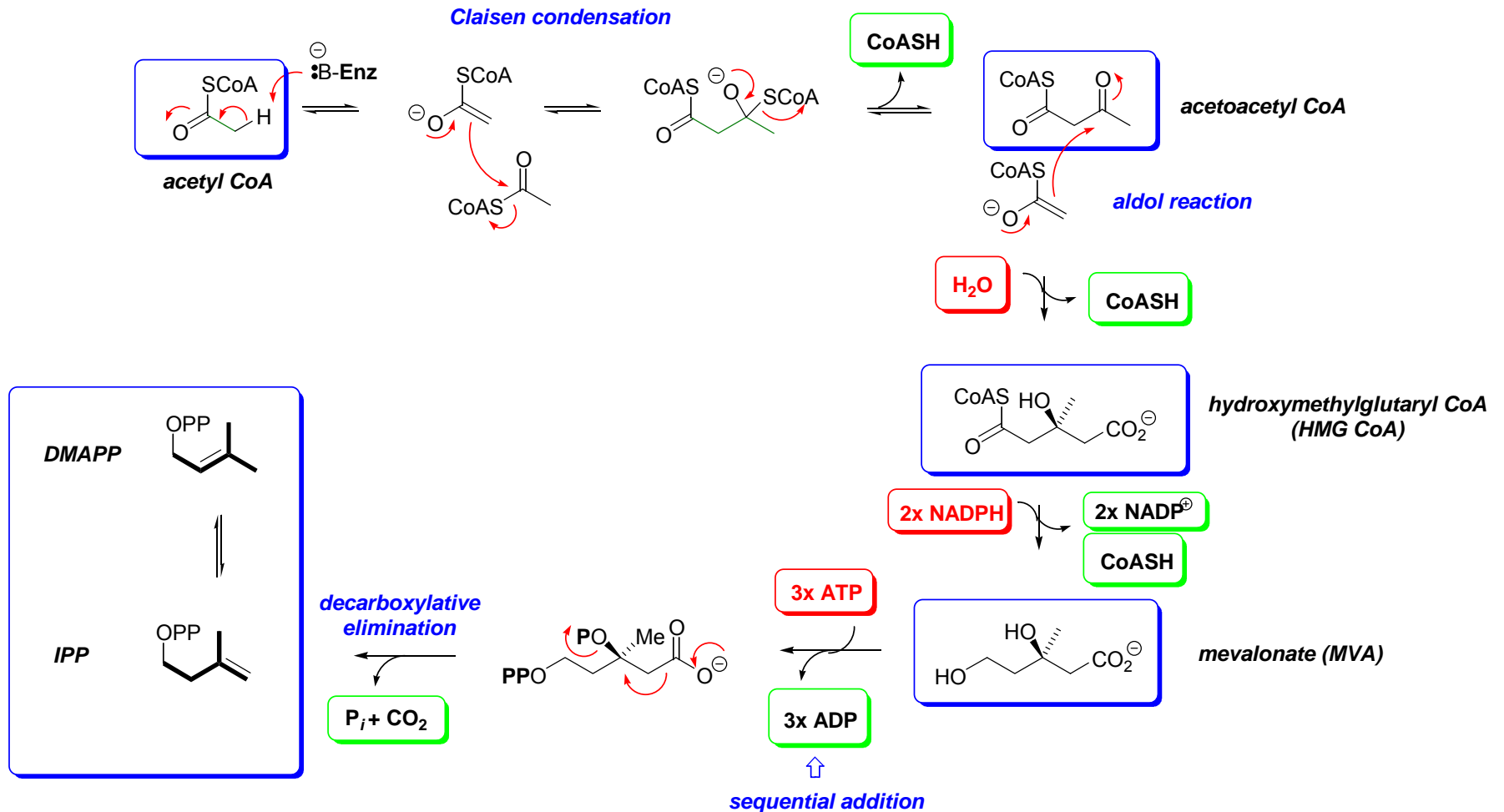
– Iterative oligomerisation via:

- Decarboxylative Claisen condensation
- Variable levels of reductive ketone processing in each iteration

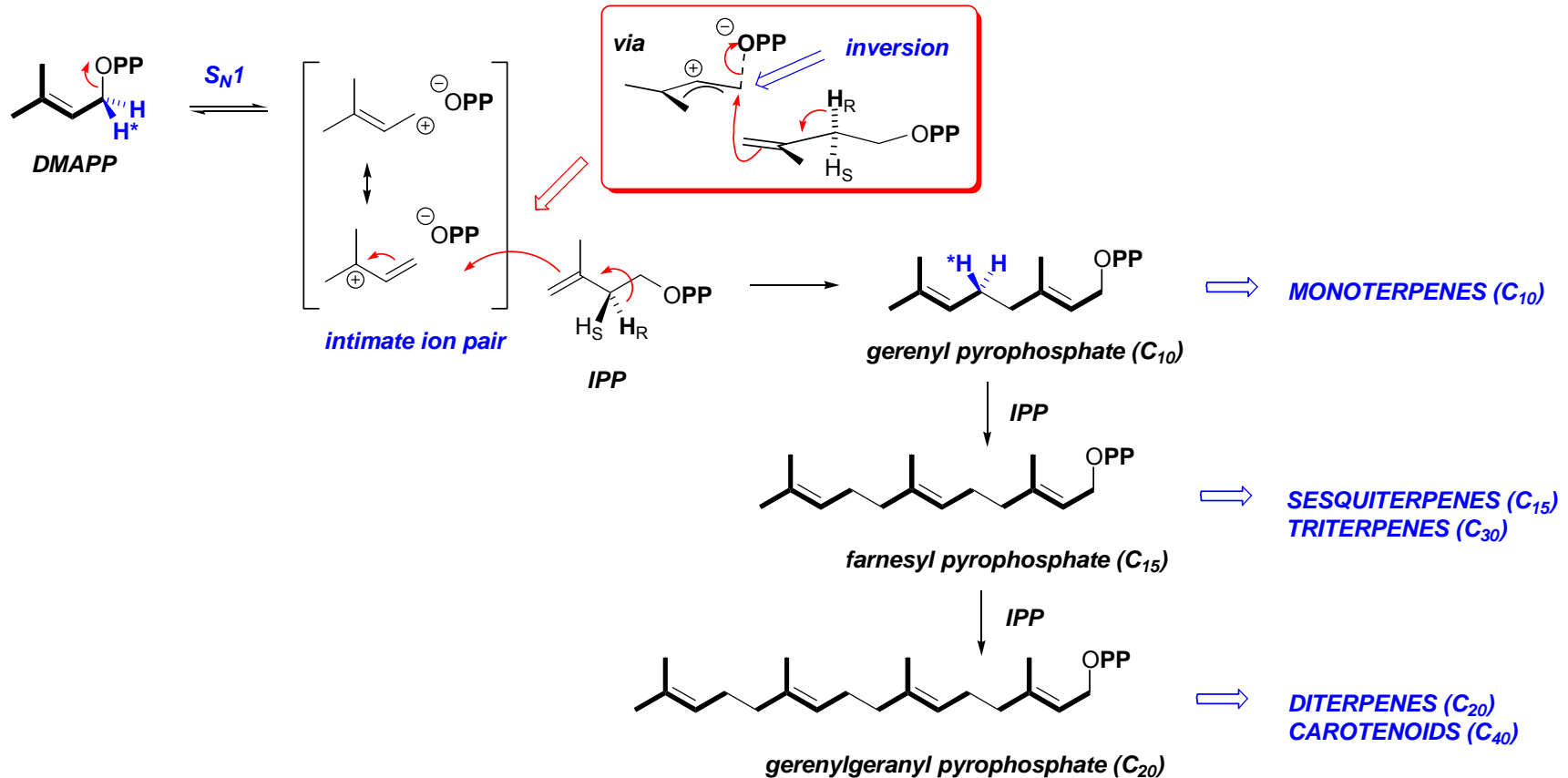


Biosynthesis of IPP & DMAPP

- $acetyl\ CoA \rightarrow acetoacetyl\ CoA \rightarrow HMG\ CoA \rightarrow mevalonate \rightarrow IPP \rightarrow DMAPP$:



'Head-to-tail' Oligomerisation → Isoprenoids



Primary Metabolism - Overview

