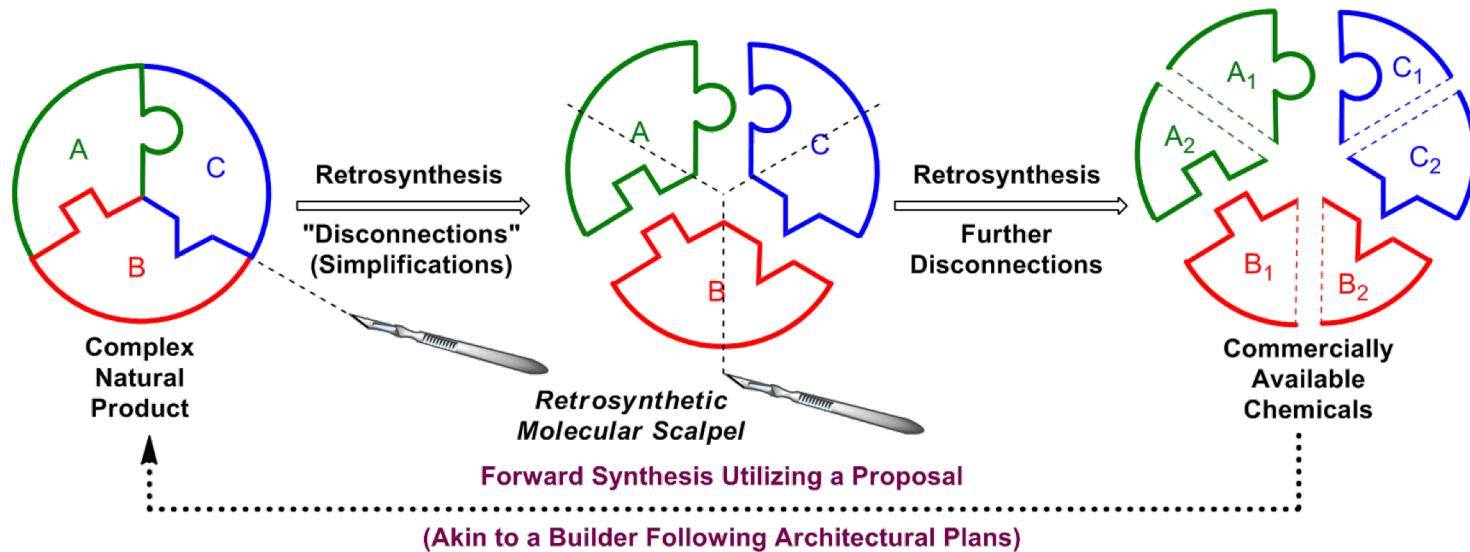


BIOCATALYTIC RETROSYNTHESIS

Andreas Schneider

Institute of Biochemistry & Technical Biochemistry

Retrosynthesis



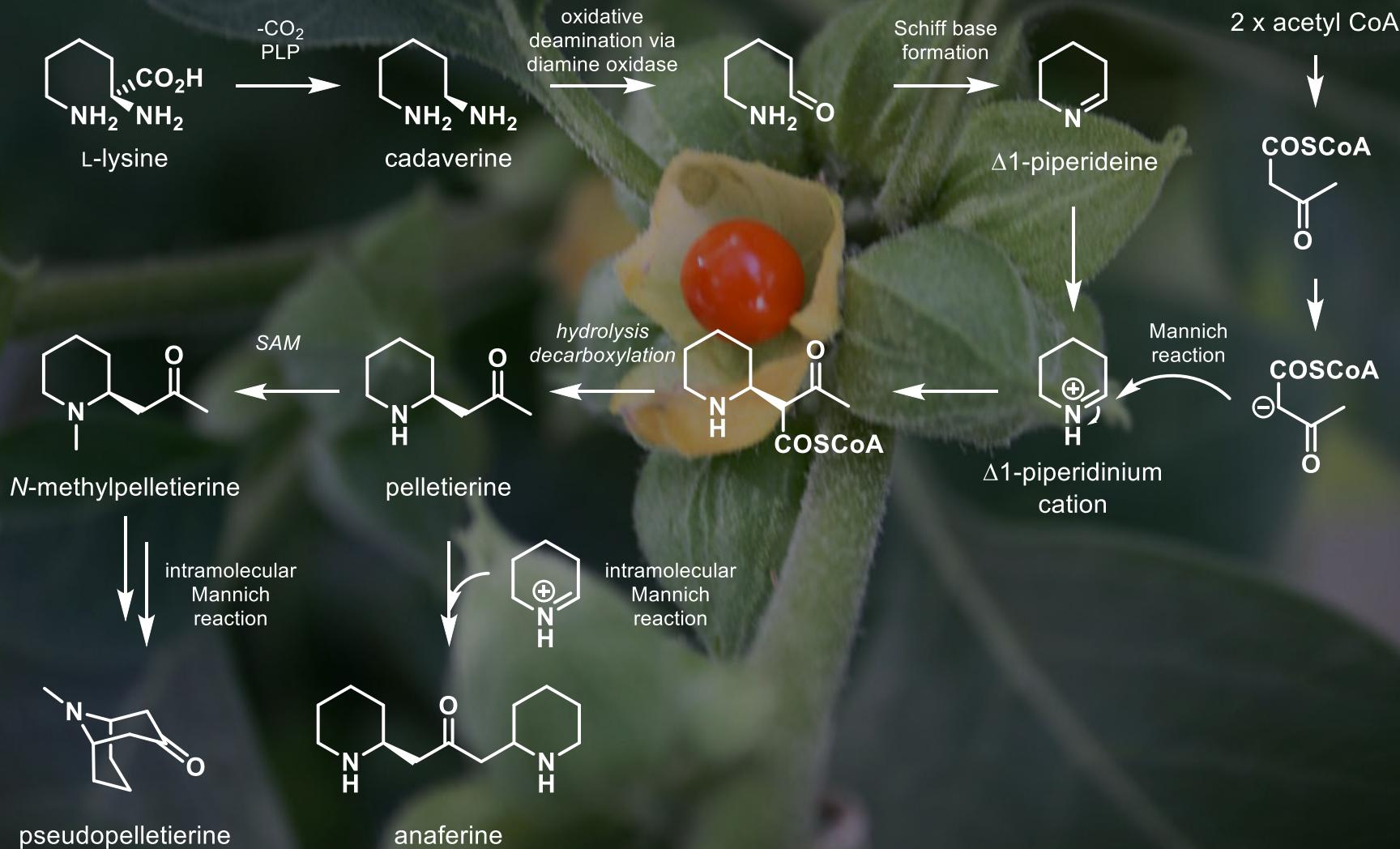
Chemical: dismantling a molecule step by step all the way back to a smaller, simpler precursors using known reactions

Biological: reversed biotransformations to a target product following pathways to substrates that are endogenous to a chassis organism

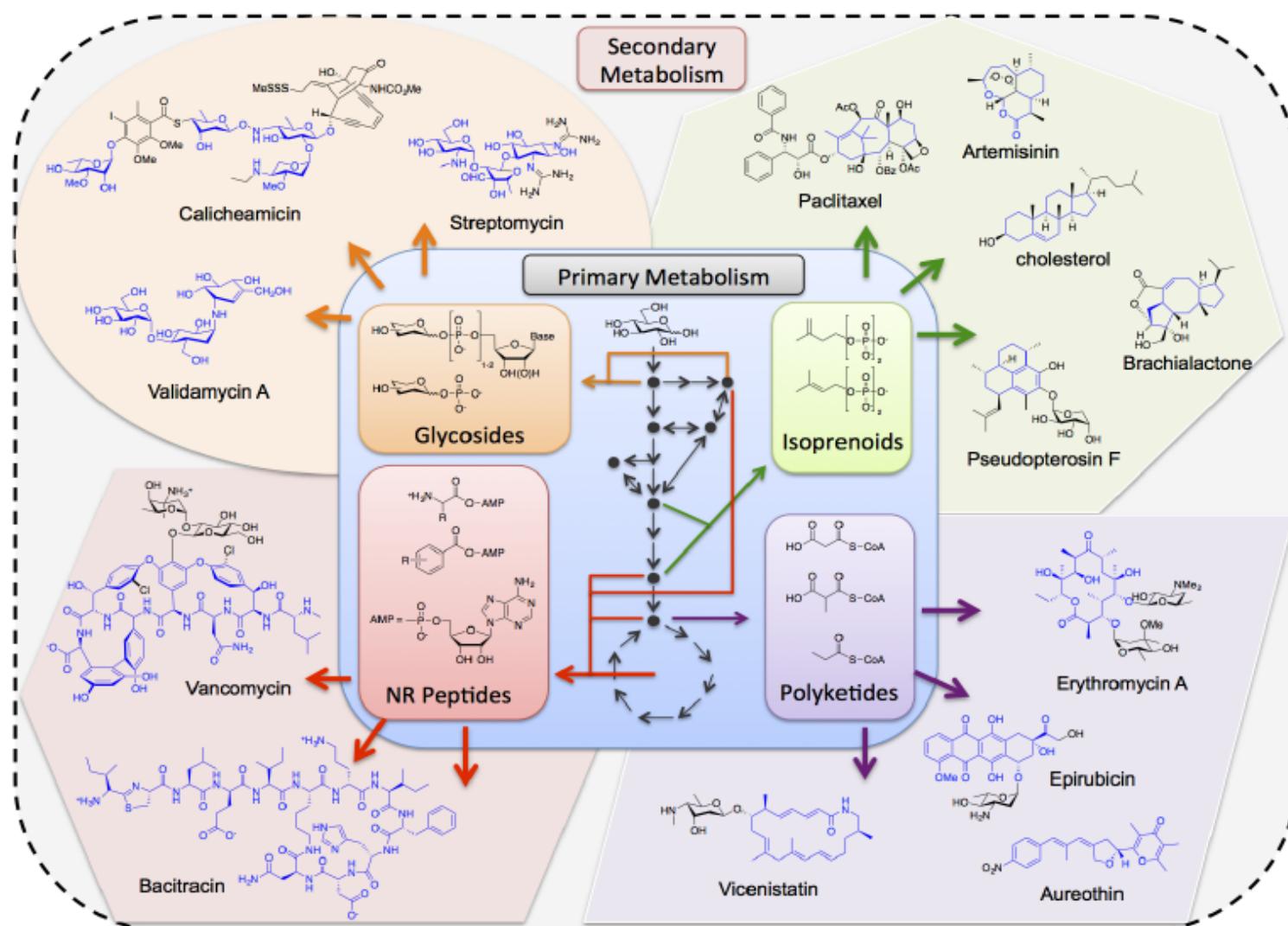
Biocatalytic: disconnecting molecules with considerations of applying biocatalysts (engineered enzymes) as well as chemical reagents

NATURE

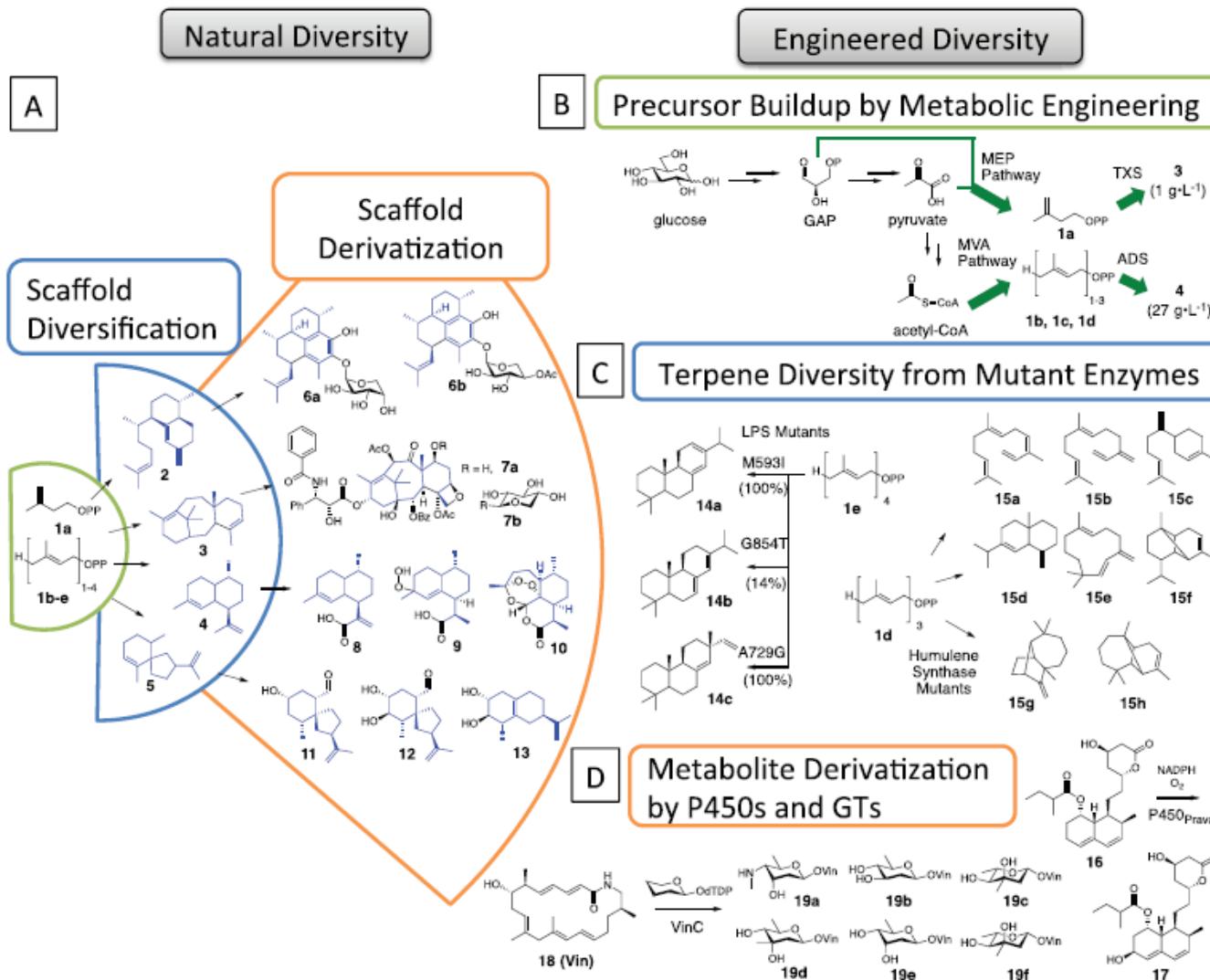
World's Best Synthetic Chemist



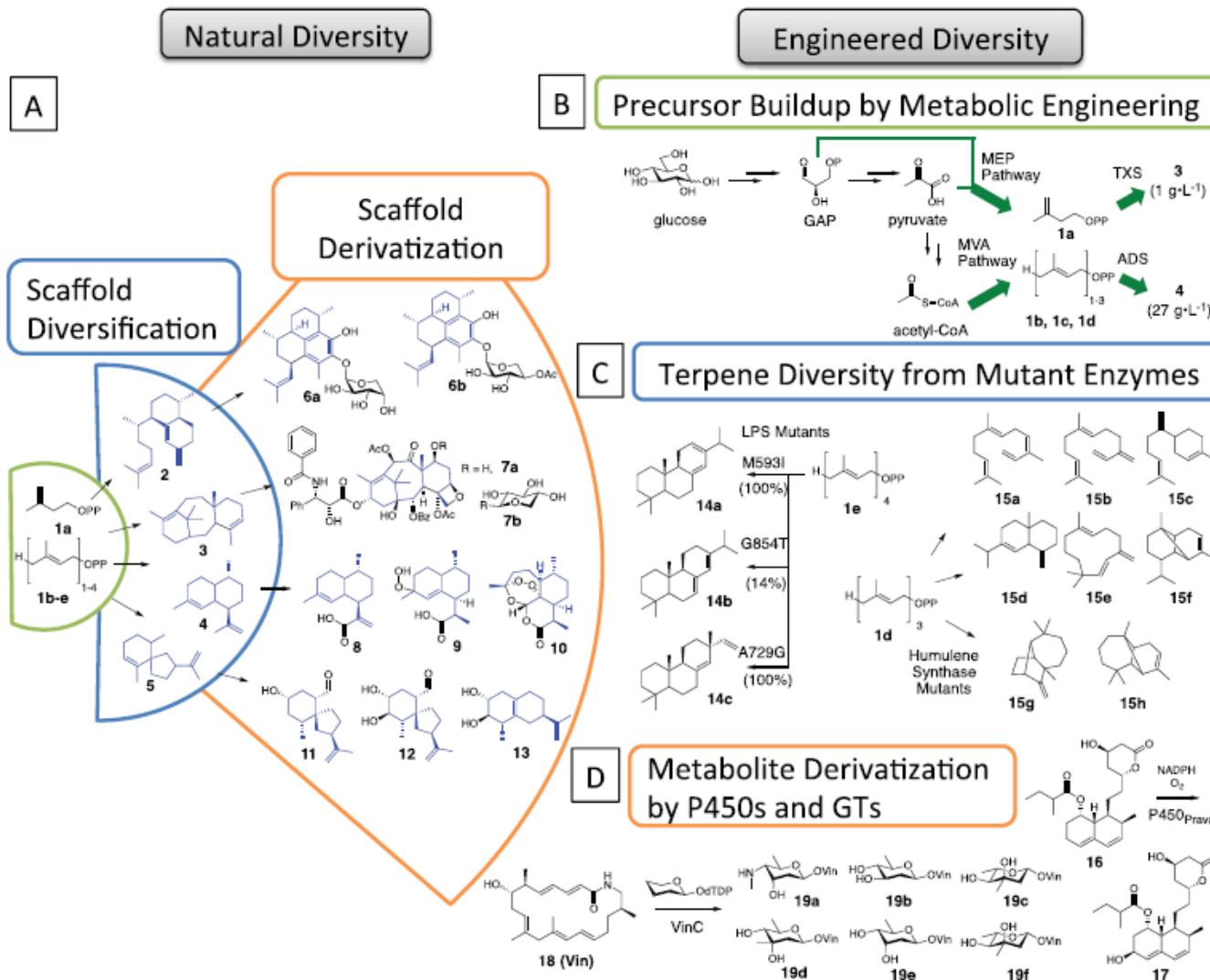
Natural Diversity in Secondary Metabolism



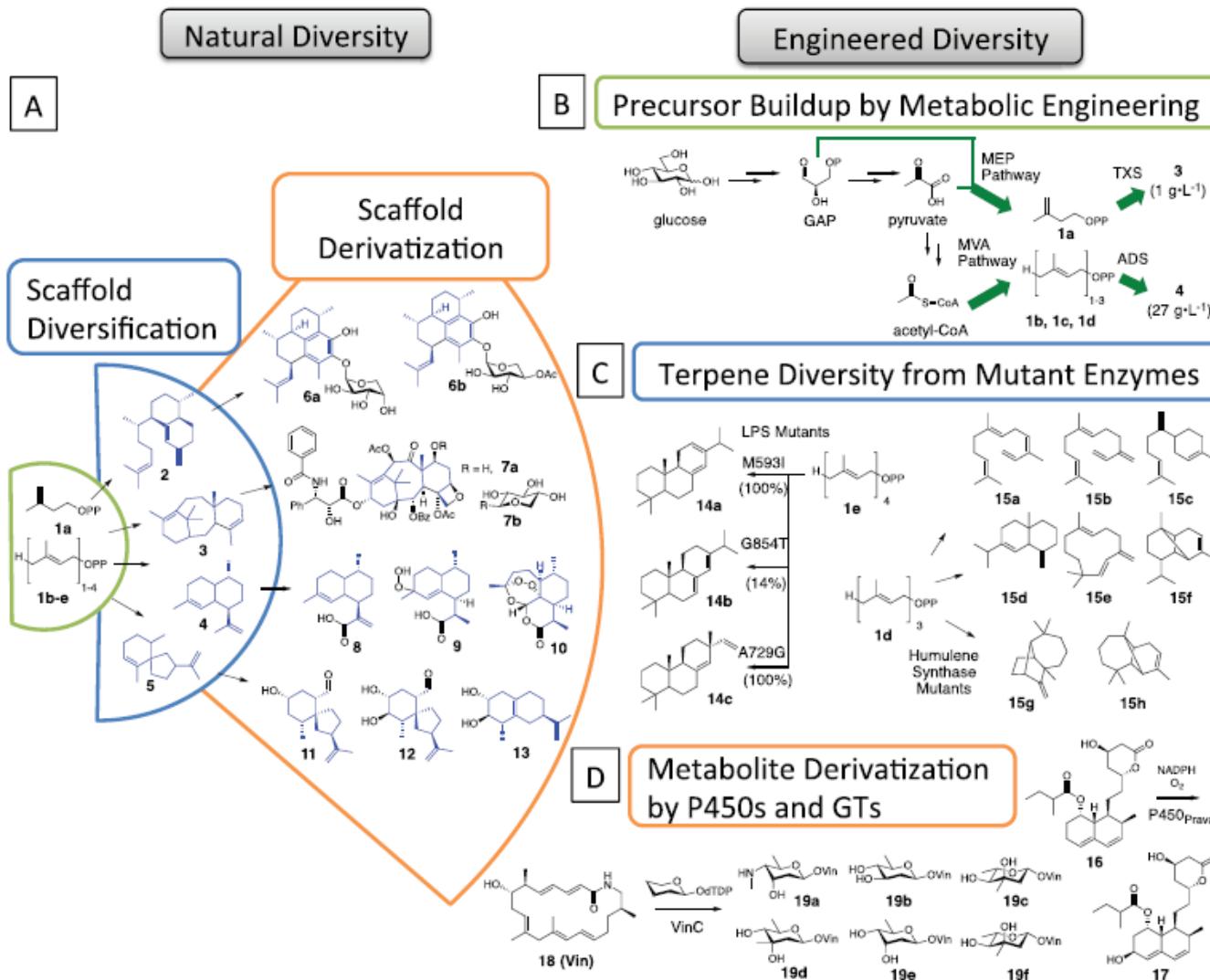
Natural vs. Engineered Diversity



Natural vs. Engineered Diversity



Natural vs. Engineered Diversity



THREE APPROACHES TO SYNTHESIS

- New reagents and catalysts
- Retrosynthesis
- Synthetic strategy

Organic
Synthesis

- Engineered biocatalysts
- Broad specificity
- Synthetic biology

Biosynthesis

Biocatalysis

- Natural products
- Biosynthetic pathways
- Specialised enzymes

TERMINOLOGY

target molecule

retrosynthetic analysis

reverse step

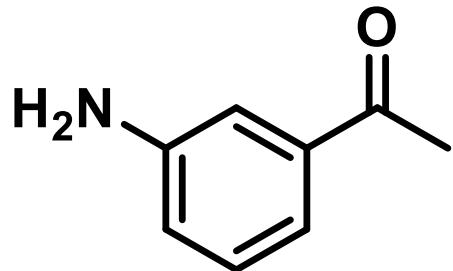
disconnection

synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY



The **target molecule** is the goal, the target, the molecule you are trying to make ...

target molecule

reverse step

synthon

functional group interconversion

retrosynthetic analysis

disconnection

synthetic equivalent

TERMINOLOGY



Retrosynthetic analysis (or retrosynthesis) is the idea of working backward, one step at a time, to **simplify** a molecule. It is the logical approach to planning a synthesis. Each precursor becomes the target for further analysis.

target molecule

retrosynthetic analysis

reverse step

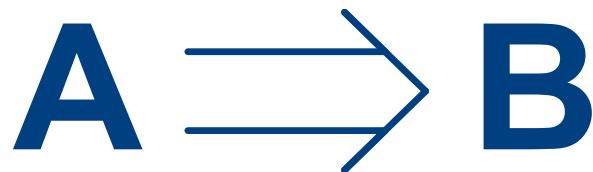
disconnection

synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY



A **logical** backwards step. This arrow effectively means 'can be made from'.

target molecule

retrosynthetic analysis

reverse step

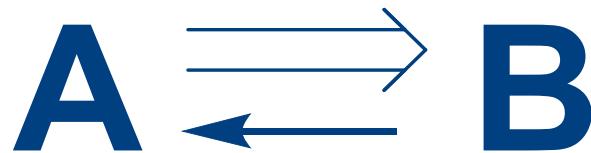
disconnection

synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY



A **logical** backwards step. This arrow effectively means 'can be made from'.

To be of any value, there must be a **real reaction** that corresponds to the forward reaction.

target molecule

retrosynthetic analysis

reverse step

disconnection

synthon

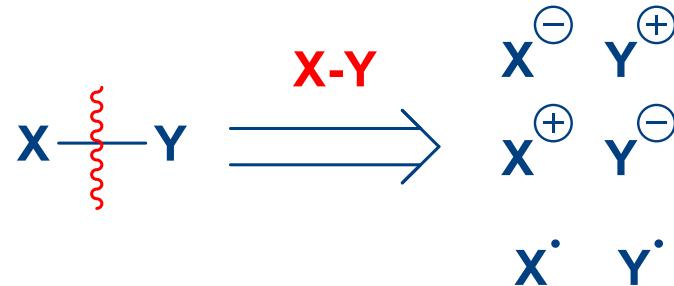
synthetic equivalent

functional group interconversion

TERMINOLOGY

A retrosynthetic (reverse) step involving the breaking of a bond to form two (or more) **synthons**.

The more reactions you know the more possibilities you can invoke.



target molecule

retrosynthetic analysis

reverse step

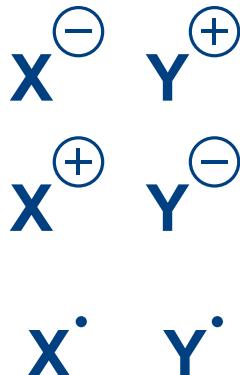
disconnection

synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY



A **synthon** is an idealised fragment.

It **does not** have to exist. It aids thought/ retrosynthesis. It should have a **synthetic equivalent** to be any use.

target molecule

retrosynthetic analysis

reverse step

disconnection

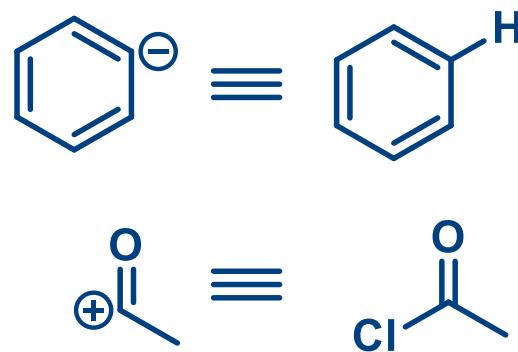
synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY

The **synthetic equivalent** is a real compound that corresponds to the synthon. Ideally, a commercially available reagent (or the next target in your retrosynthesis).



target molecule

retrosynthetic analysis

reverse step

disconnection

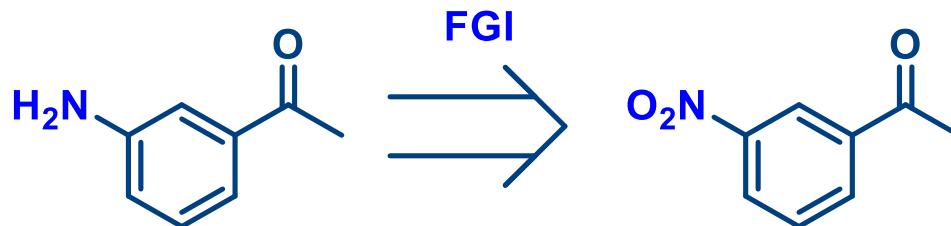
synthon

synthetic equivalent

functional group interconversion

TERMINOLOGY

FGI = functional group interconversion



The imaginary conversion of one functional group into another in order to aid simplification, help planning or uncover a disconnection. There must be a good 'forward' (real) reaction.

target molecule

retrosynthetic analysis

reverse step

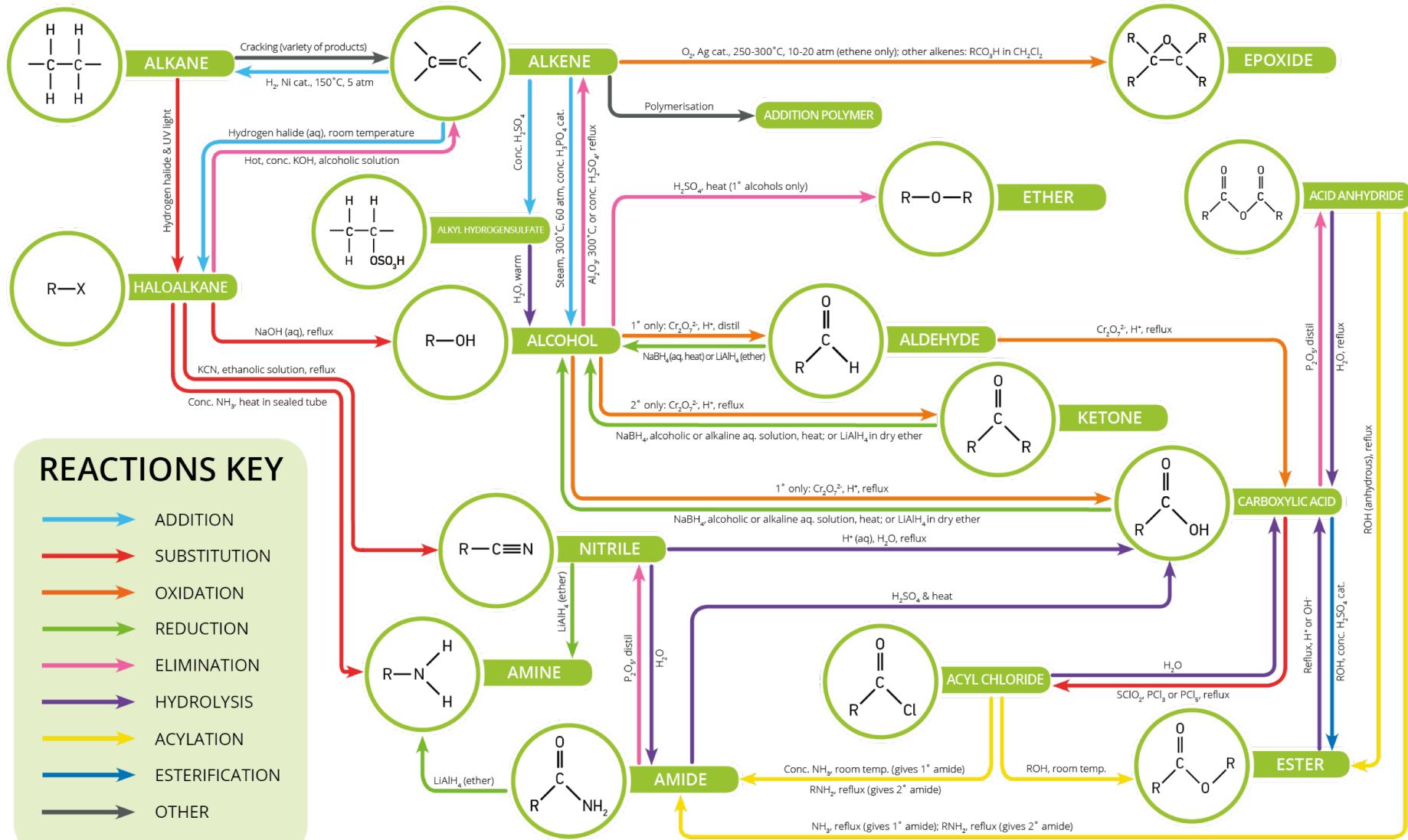
disconnection

synthon

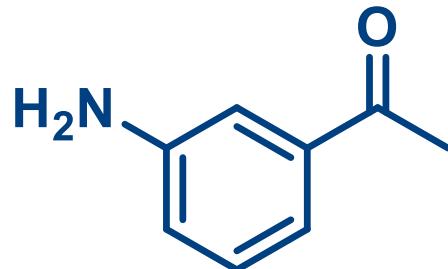
synthetic equivalent

functional group interconversion

ORGANIC REACTIONS MAP



GUIDElines



Where do we start when we plan a synthesis?

Below are a set of guidelines to help you logically approach retrosynthesis or the planning stage. They are not rules, the only rule is that you want to simplify the problem whilst using chemically allowable transformations.

1. identify functional groups

2. identify patterns

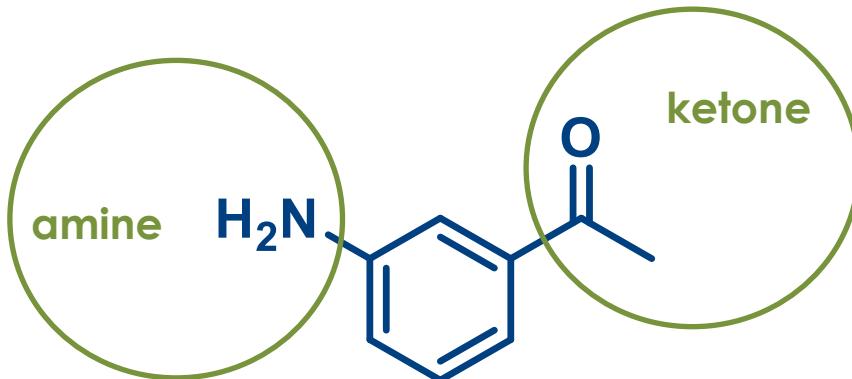
3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

GUIDElines



Functional groups are the signposts to retrosynthesis. Without functionality, we have a very limited range of reactions at our disposal. Frequently, they control where we can apply disconnections.

1. identify functional groups

2. identify patterns

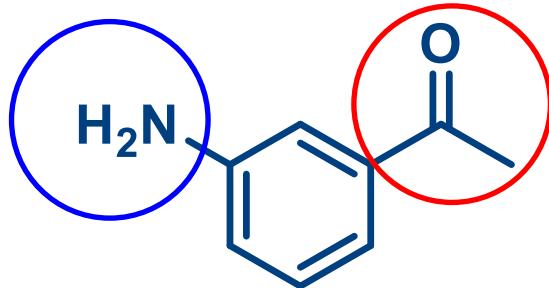
3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

GUIDElines



The pattern or connections between **functional groups** often reveal which reactions you can employ. Learning to recognise patterns of functional groups is very important for retrosynthesis. The pattern of functional groups frequently indicates the order reactions should be approached.

1. identify functional groups

2. identify patterns

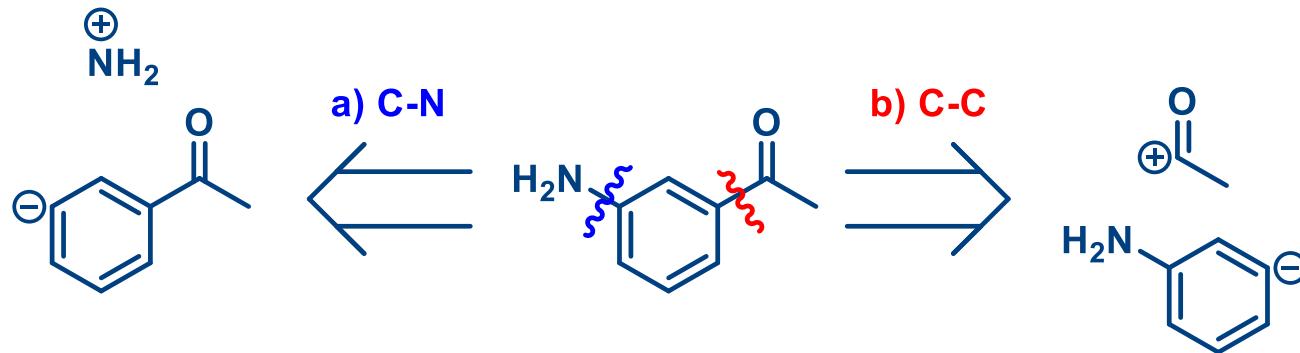
3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

GUIDElines



To begin with, you need to examine all possible disconnections. With practice you will learn that some can readily be ignored. You must also remember not to look at backwards just one step but to go further back. Short-sightedness has ruined many a retrosynthesis.

1. identify functional groups

2. identify patterns

3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

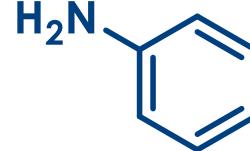
GUIDElines

route a



no synthetic equivalent

route b



Are all the disconnections chemically allowable? Will the reaction proceed with the correct regio-, stereo- or chemoselectivity? Does the disconnection simplify the problem?

1. identify functional groups

2. identify patterns

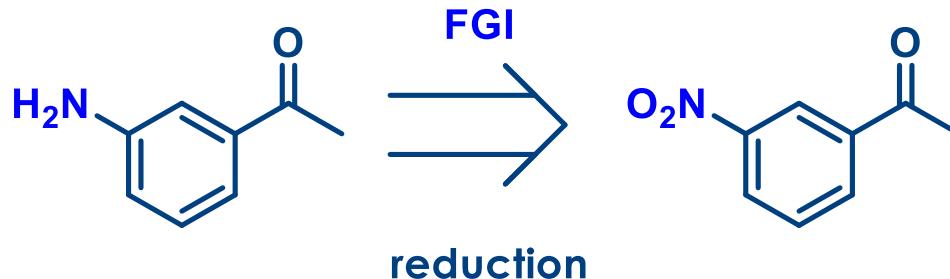
3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

GUIDElines



Functional group interconversions do not simplify a structure, but they do overcome problems and/or allow disconnections that will simplify the target.

1. identify functional groups

2. identify patterns

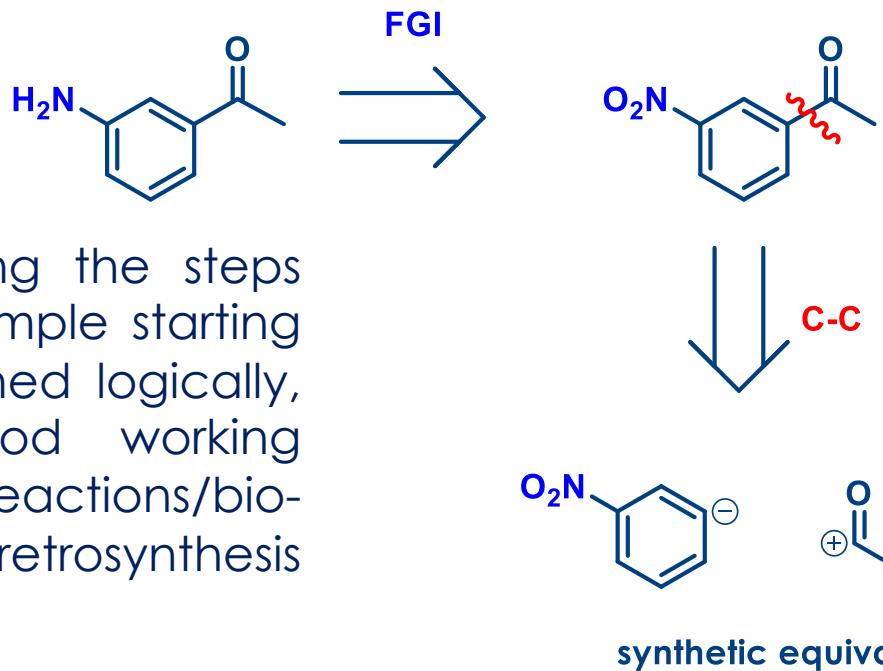
3. examine disconnections

4. identify problems

5. consider FGI

6. repeat

GUIDElines



1. identify functional groups

2. identify patterns

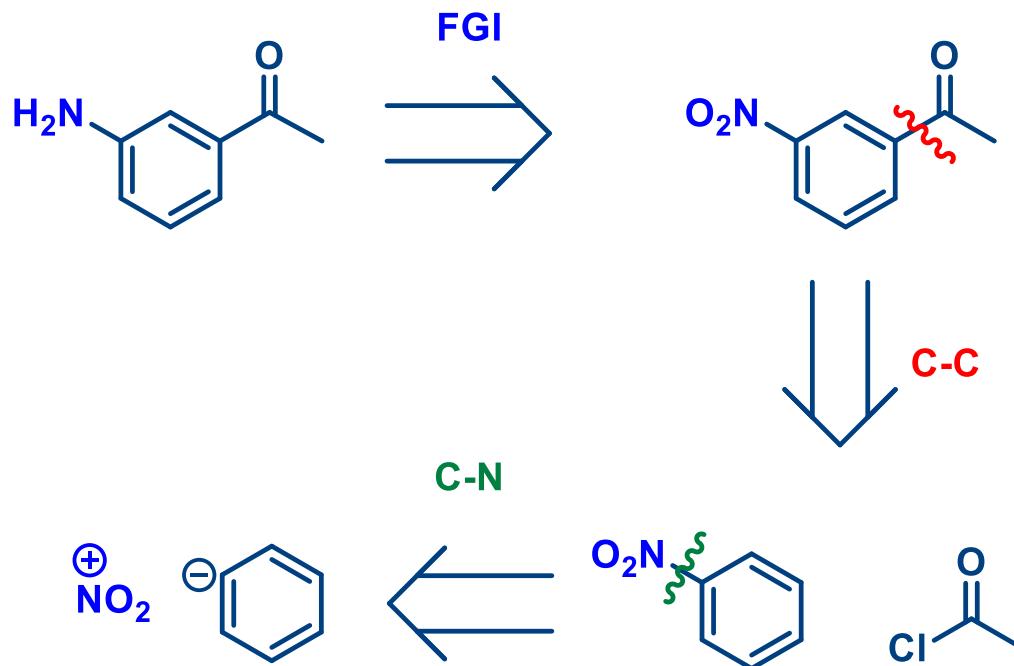
3. examine disconnections

4. identify problems

5. consider FIG

6. repeat

GUIDElines



1. identify functional groups

2. identify patterns

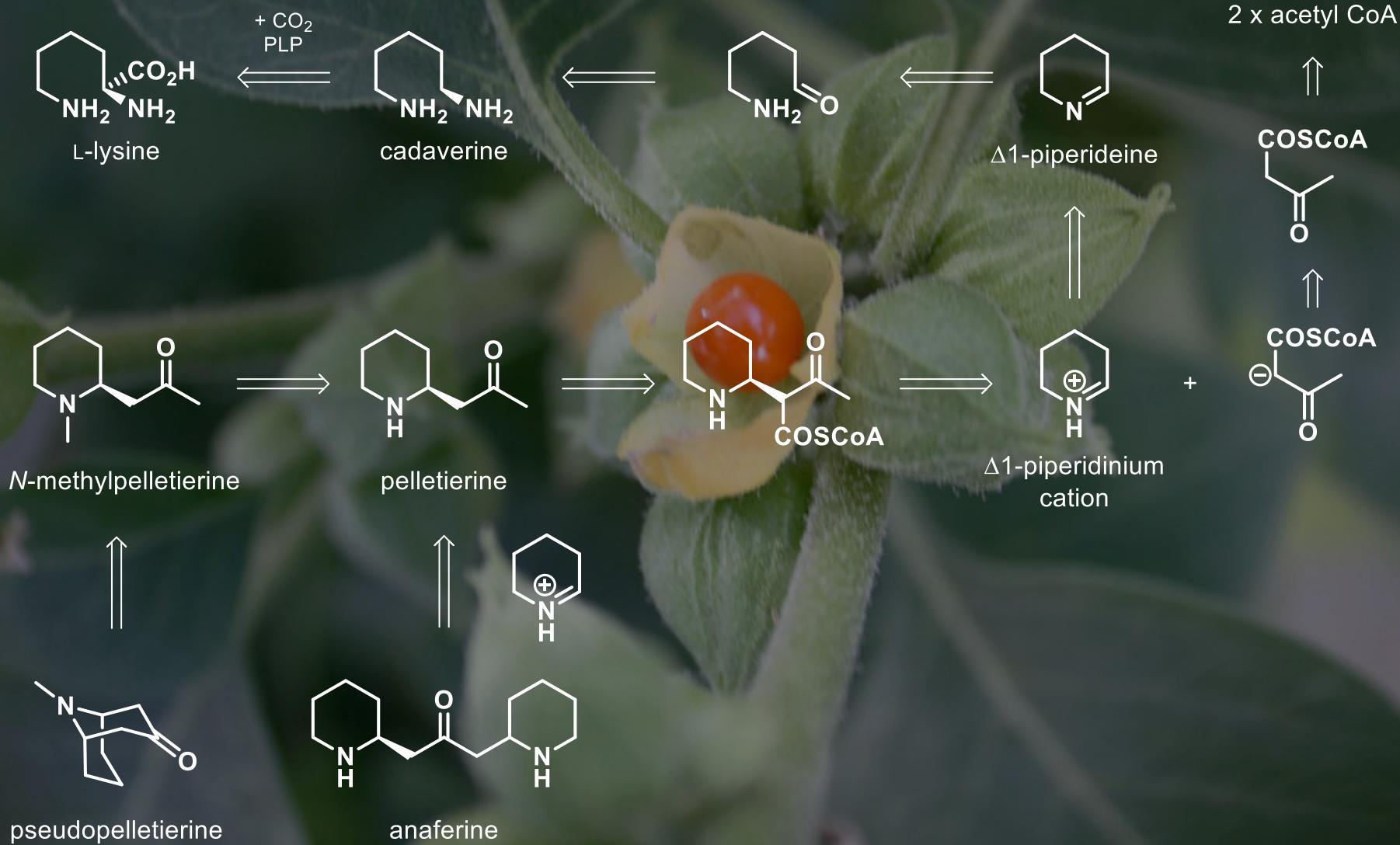
3. examine disconnections

4. identify problems

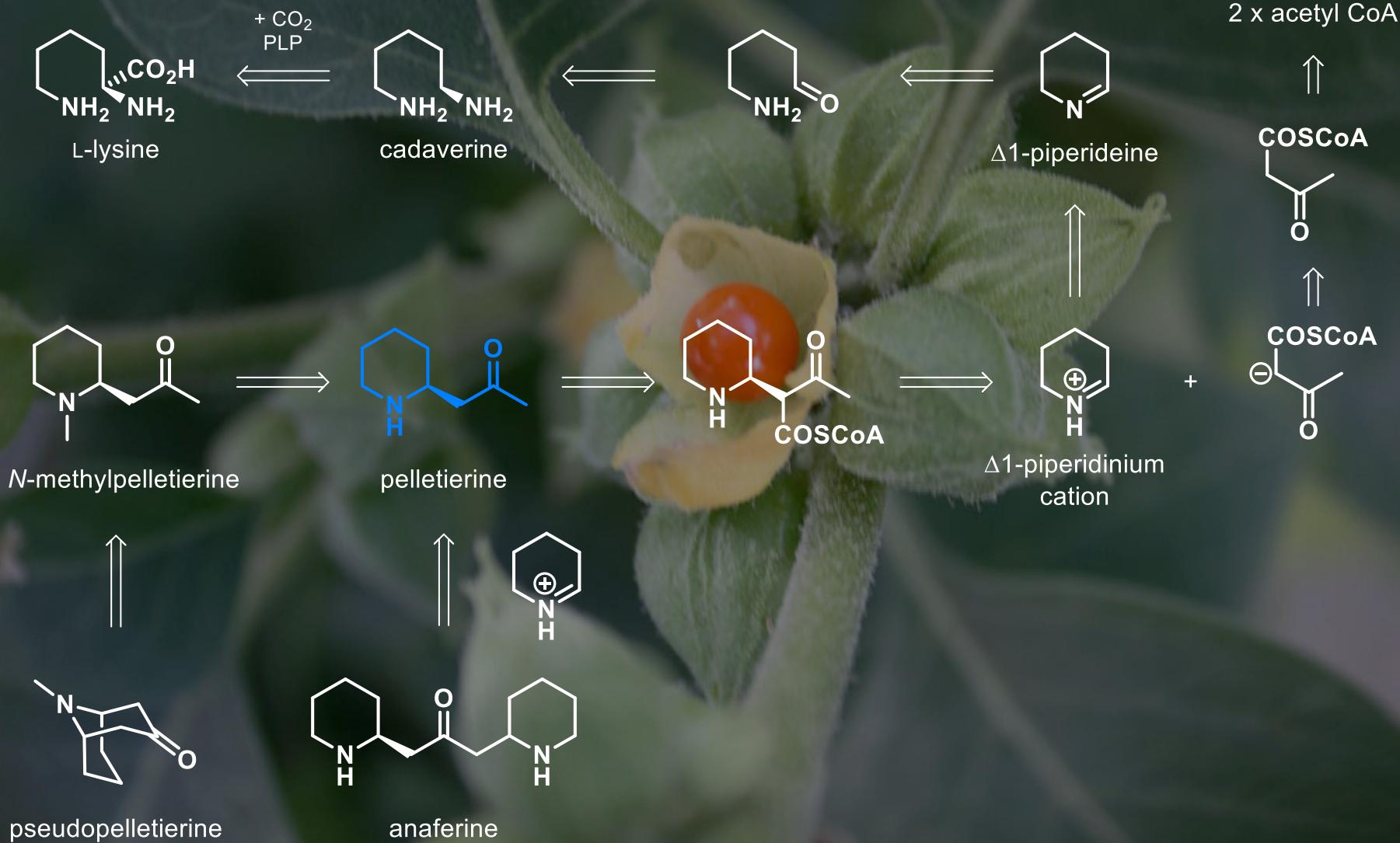
5. consider FIG

6. repeat

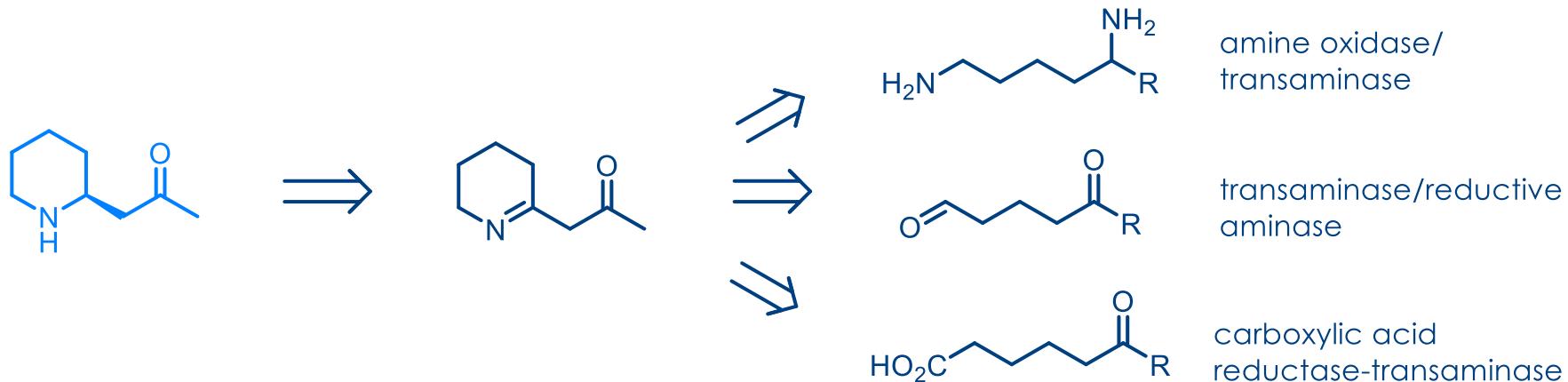
RETROSYNTHESIS ALKALOIDS



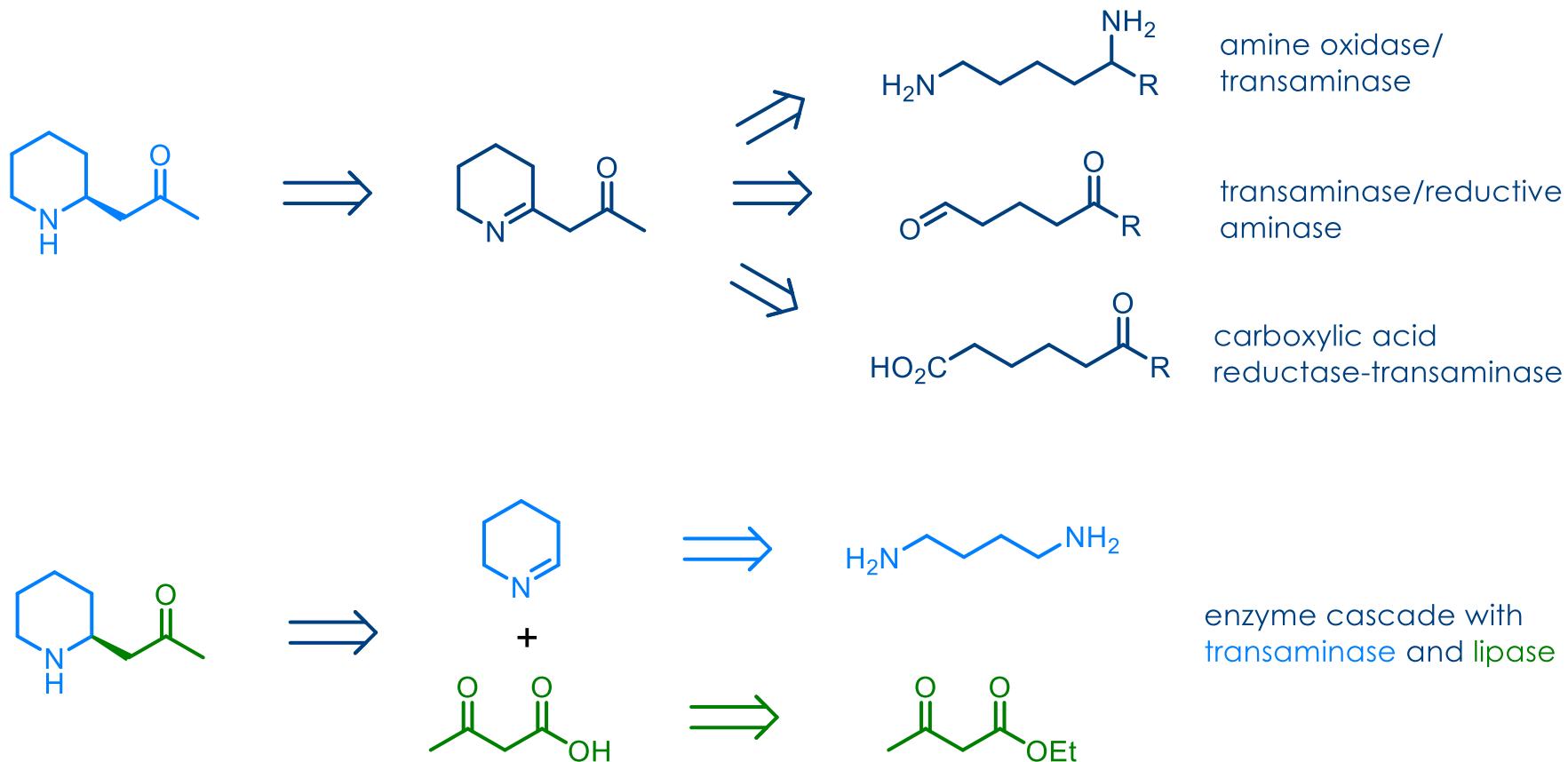
RETROSYNTHESIS ALKALOIDS



BIOCATALYTIC RETROSYNTHESIS



BIOCATALYTIC RETROSYNTHESIS

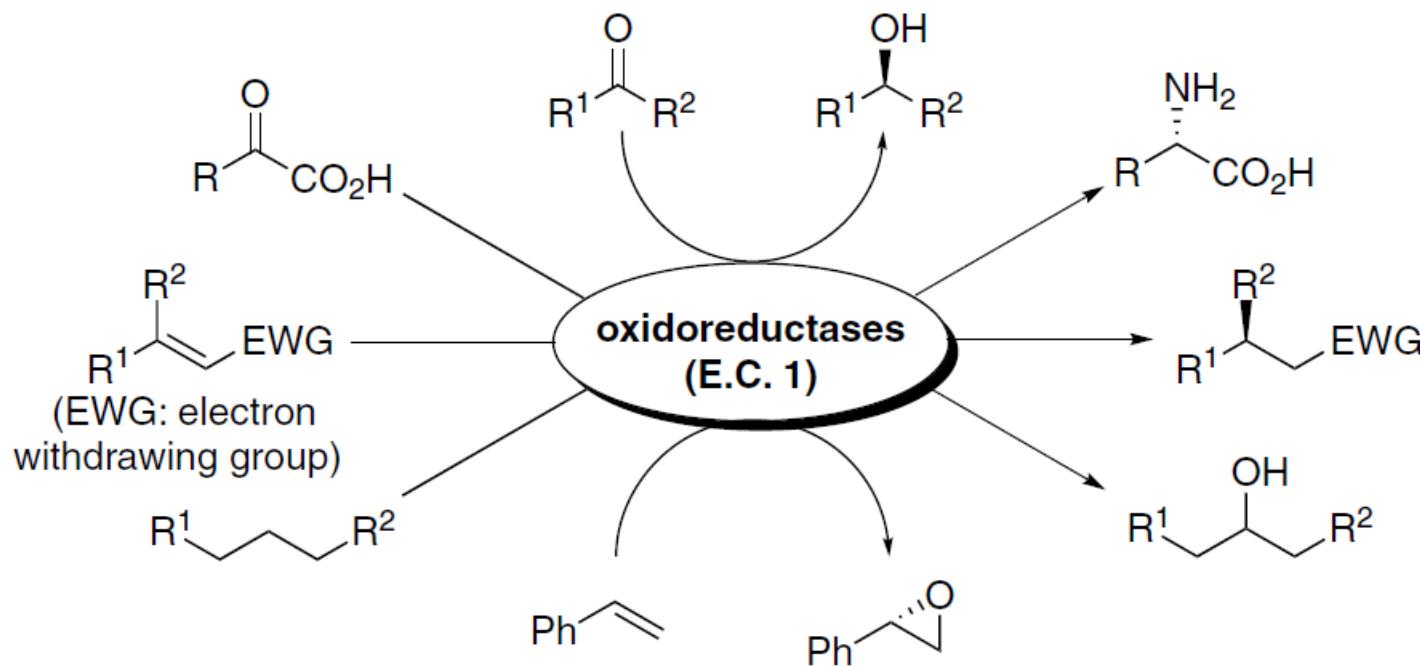


CATEGORIZATION OF ENZYMES

ENZYME CLASS	EC NUMBER	SELECTED REACTIONS
Oxidoreductases	1	Reduction of C=O, C=N, and C=C; reductive amination of C=O; oxidation of C-H, C=C, C-N, and C-O, cofactor reduction/oxidation
Transferases	2	Transfer of functional groups such as amino, acyl, phosphoryl, methyl, glycosyl, nitro and sulfur-containing groups
Hydrolases	3	Hydrolysis of esters, amides, lactones, lactams, epoxides, nitriles; reverse reactions to form such functionalities
Lyases	4	Addition of small molecules to double bonds such as C=C, C=N, and C=O
Isomerases	5	Interconversion of isomers (isomerisations) such as racemisations, epimerisations, and rearrangement reactions
Ligases	6	Formation of complex compounds (in analogy to lyases), enzymatically active only when combined with ATP cleavage

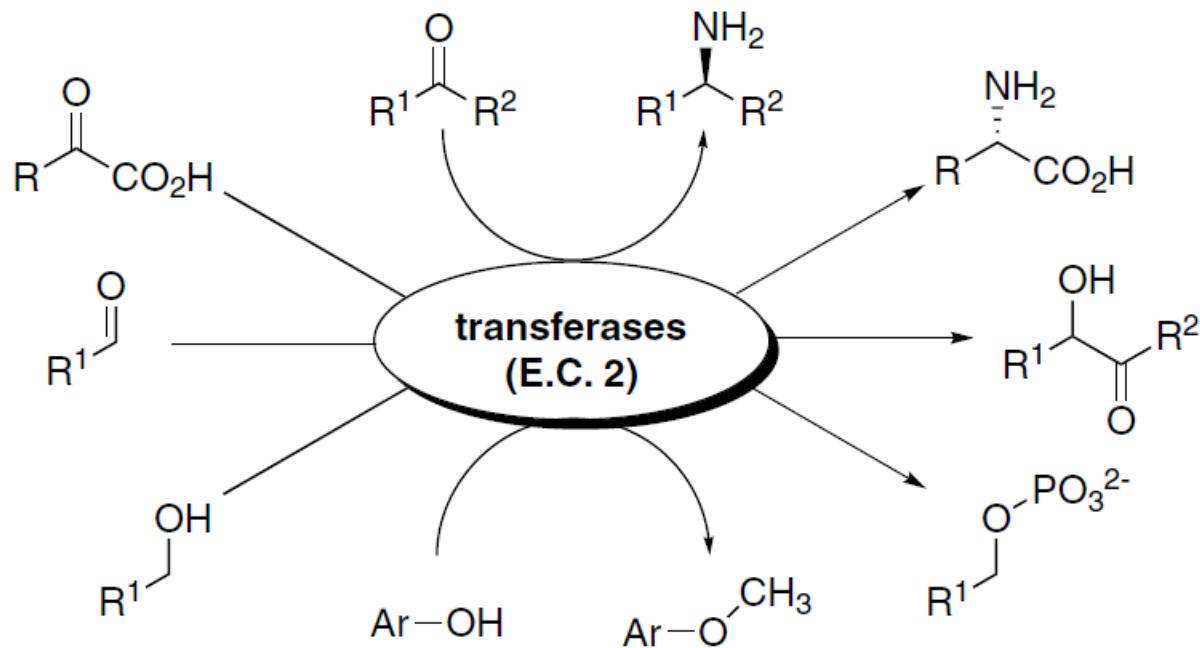
OXIDOREDUCTASES

Overview of selected reactions



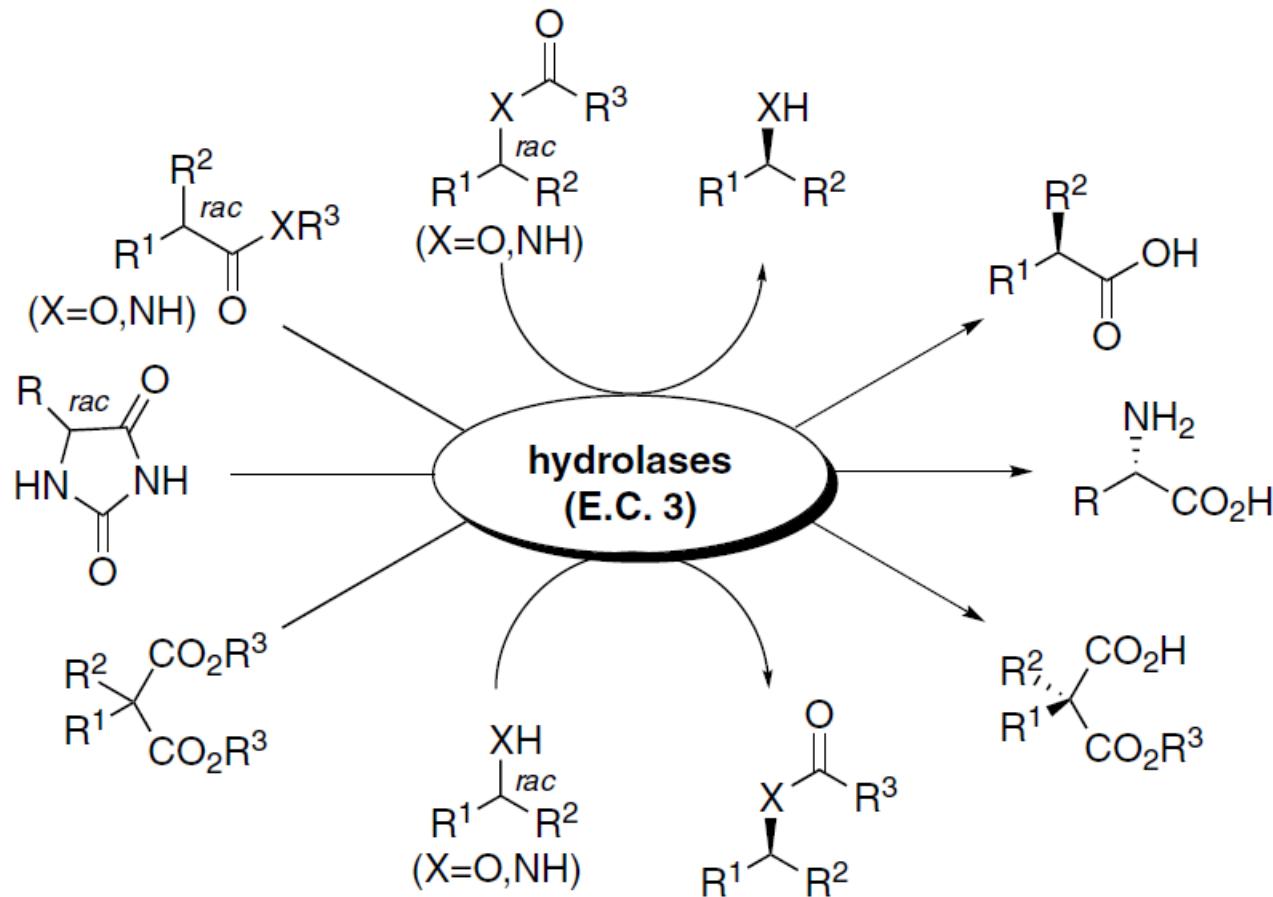
TRANSFERASES

Overview of selected reactions



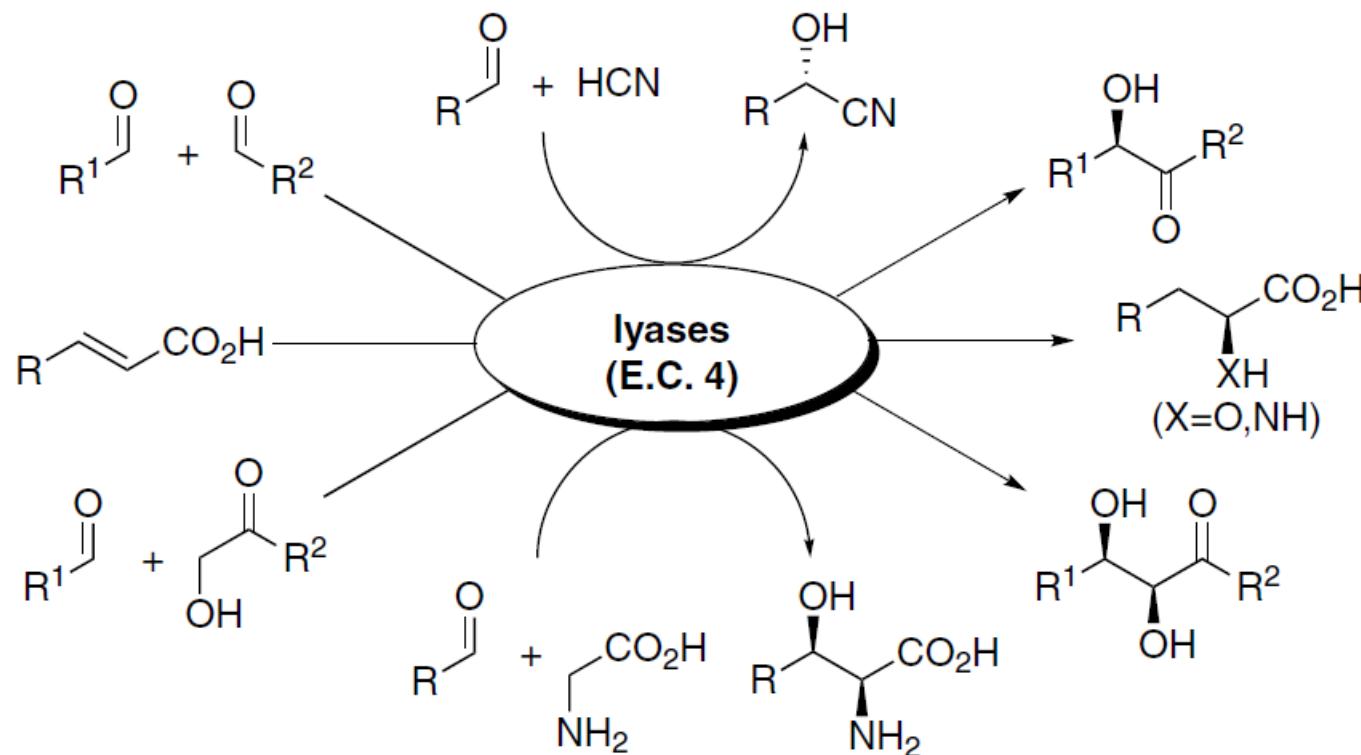
HYDROLASES

Overview of selected reactions



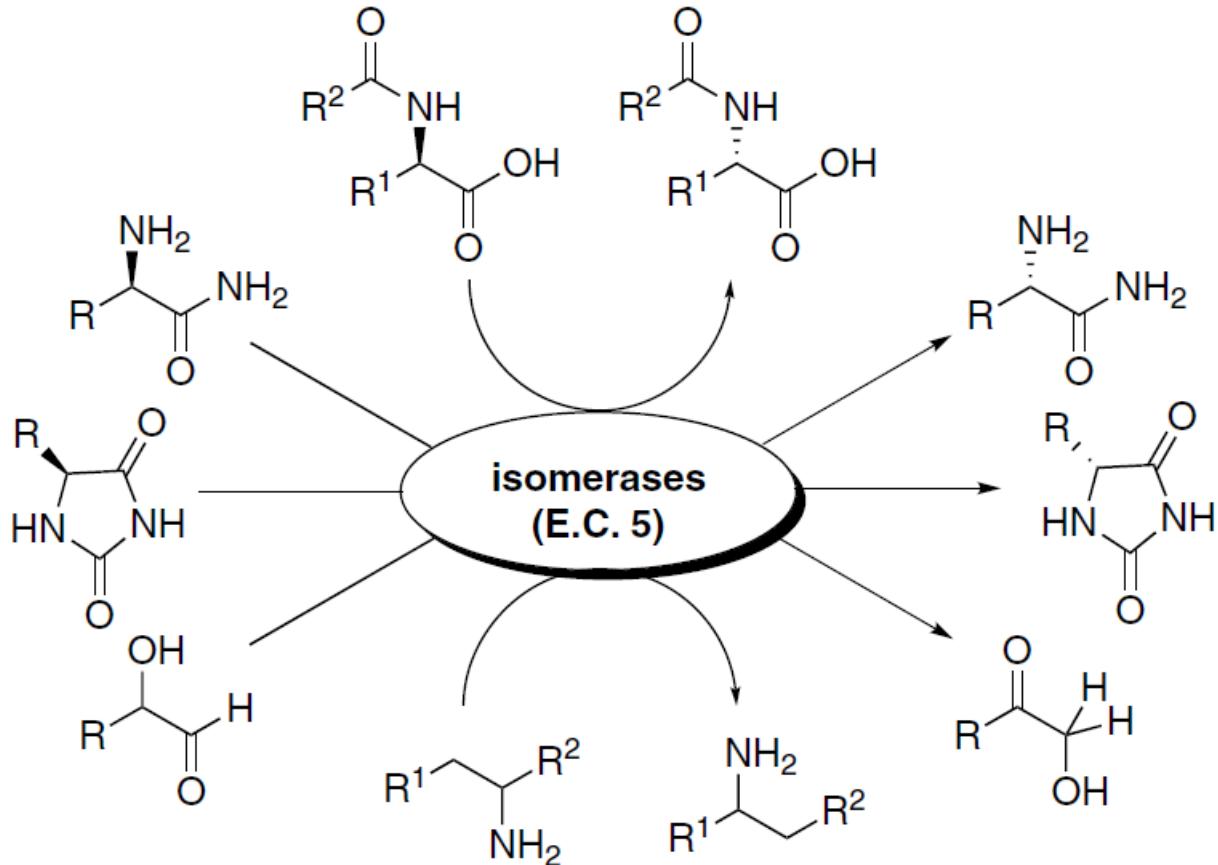
LYASES

Overview of selected reactions



ISOMERASES

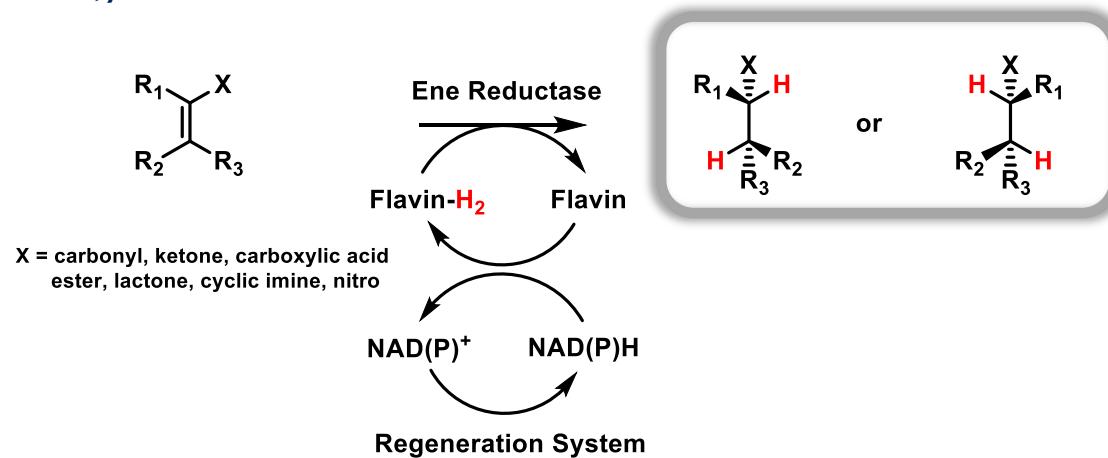
Overview of selected reactions



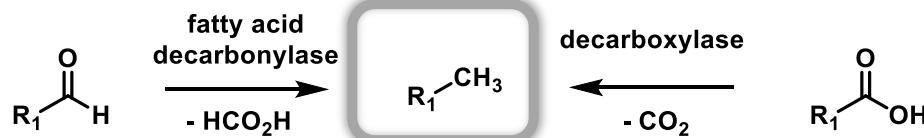
ENZYMES FROM A RETROSYNTHETIC PERSPECTIVE

ALKANES

- Reduction of α,β -unsaturated C=C bonds

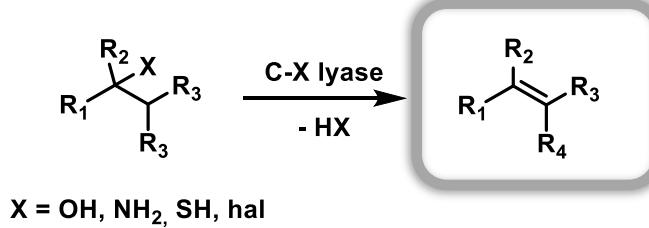


- Decarbonylase and decarboxylase

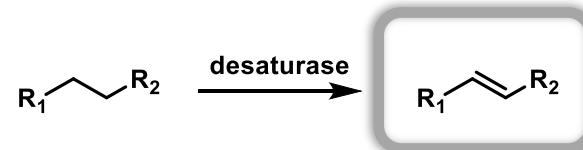


ALKENES

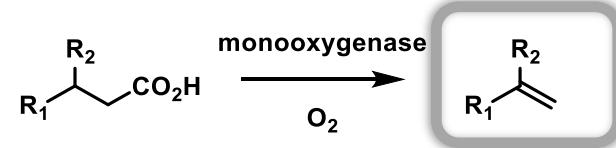
- *Elimination of nucleophile using a C-X lyase*



- *Dehydrogenation of non-activated methylene groups*

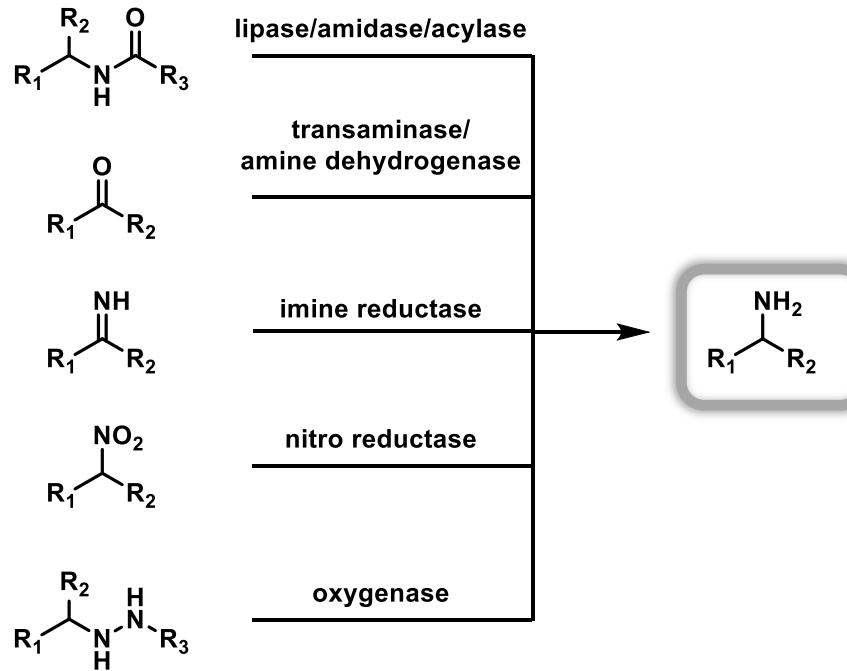


- *Oxidative decarboxylation*

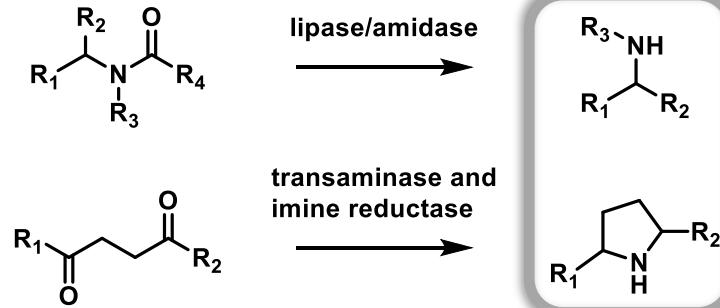


AMINES

- Primary amines via hydrolysis, amino transfer and reductions

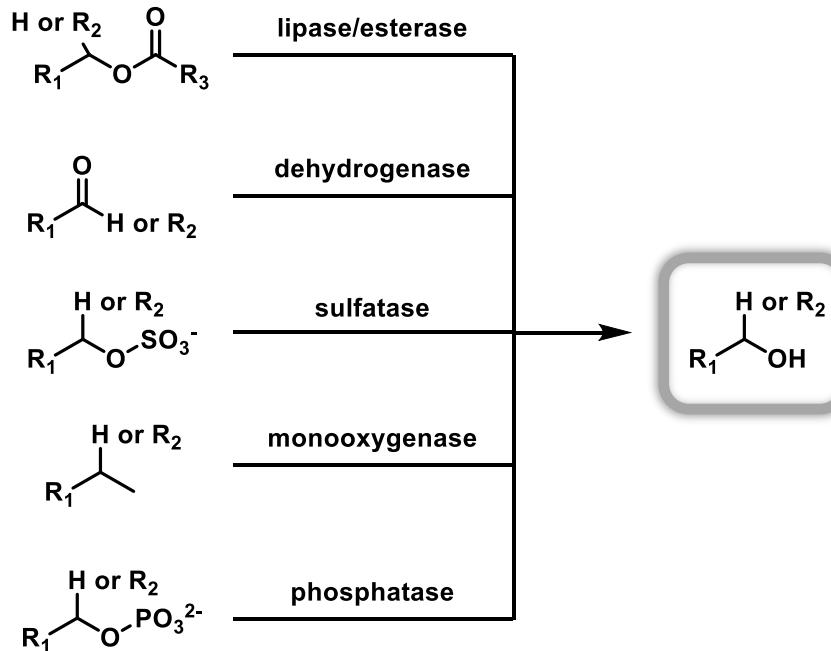


- Secondary amines via hydrolysis and monoamination/reduction

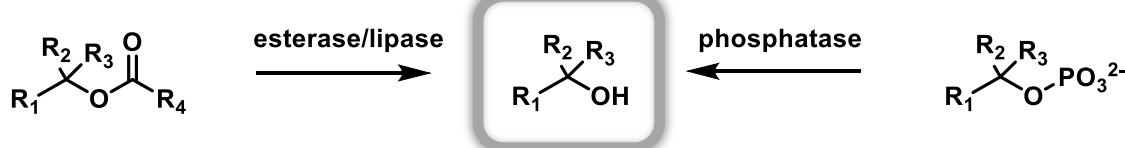


ALCOHOLS

- Primary and secondary alcohols via hydrolysis, reduction and oxidation

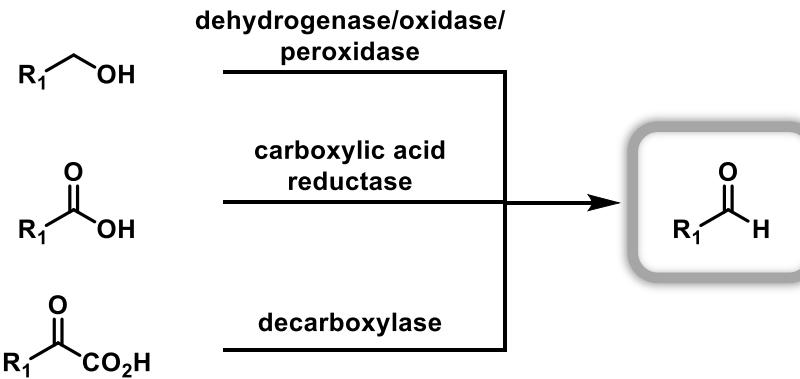


- Tertiary alcohols via hydrolysis

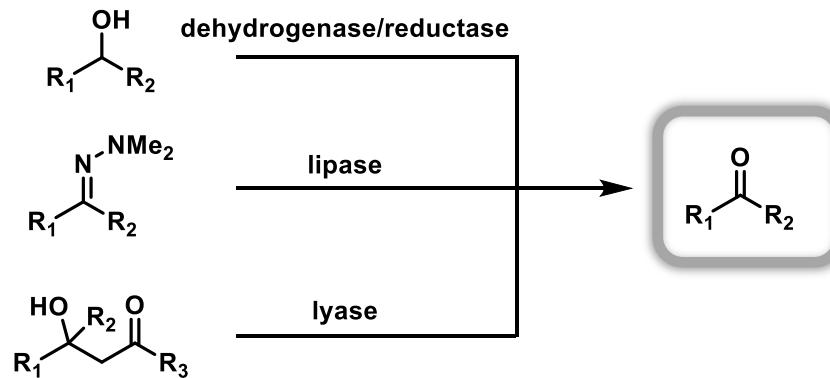


ALDEHYDES and KETONES

- Oxidation, reduction and decarboxylation

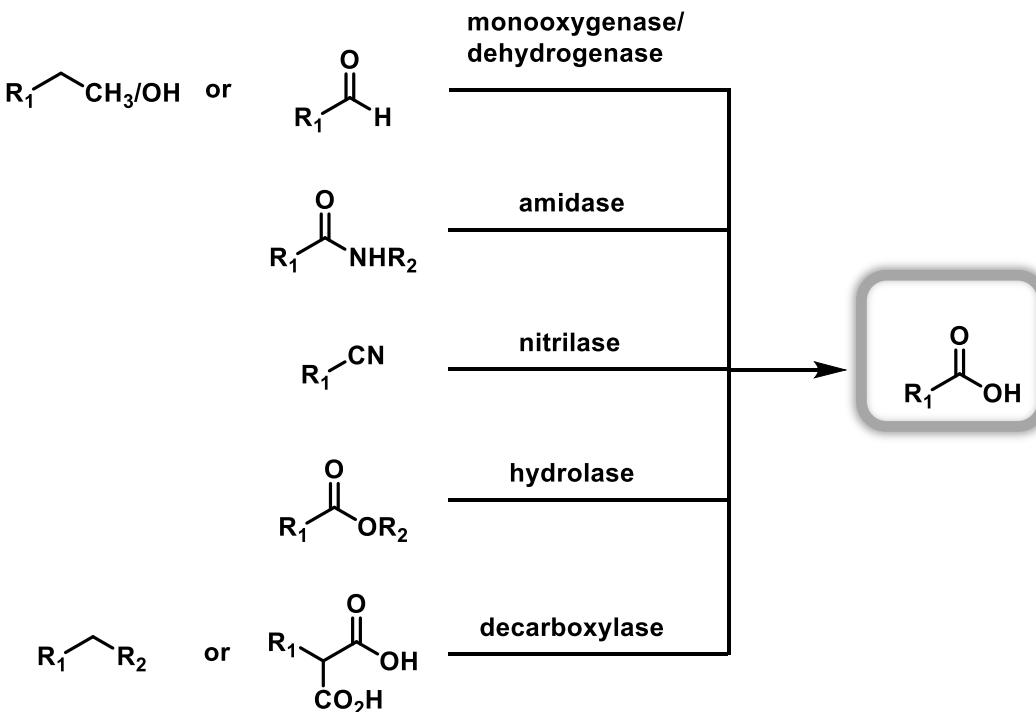


- Oxidation and cleavage of hydroxyketones



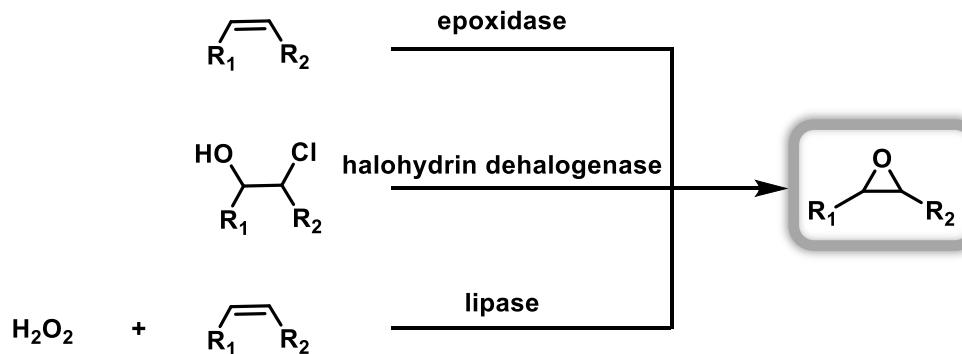
CARBOXYLIC ACIDS

- Oxidation, hydrolysis, cleavage and addition of carboxy group



EPOXIDES, ESTERS and AMIDES

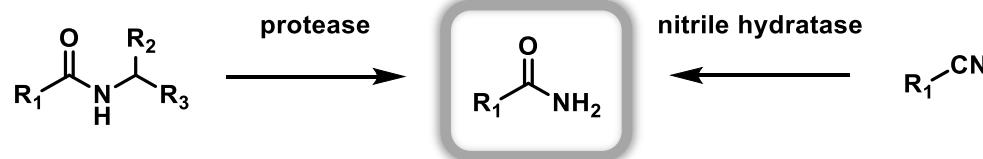
- *Epoxides*



- *Esters*

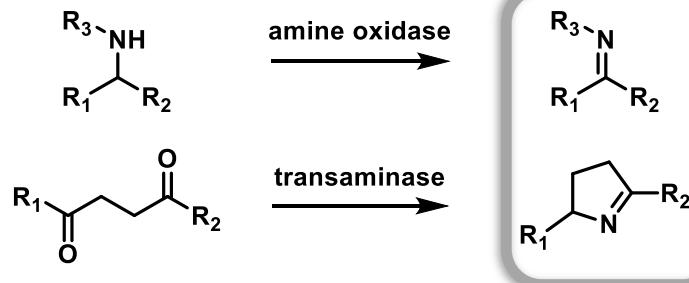


- *Amides*

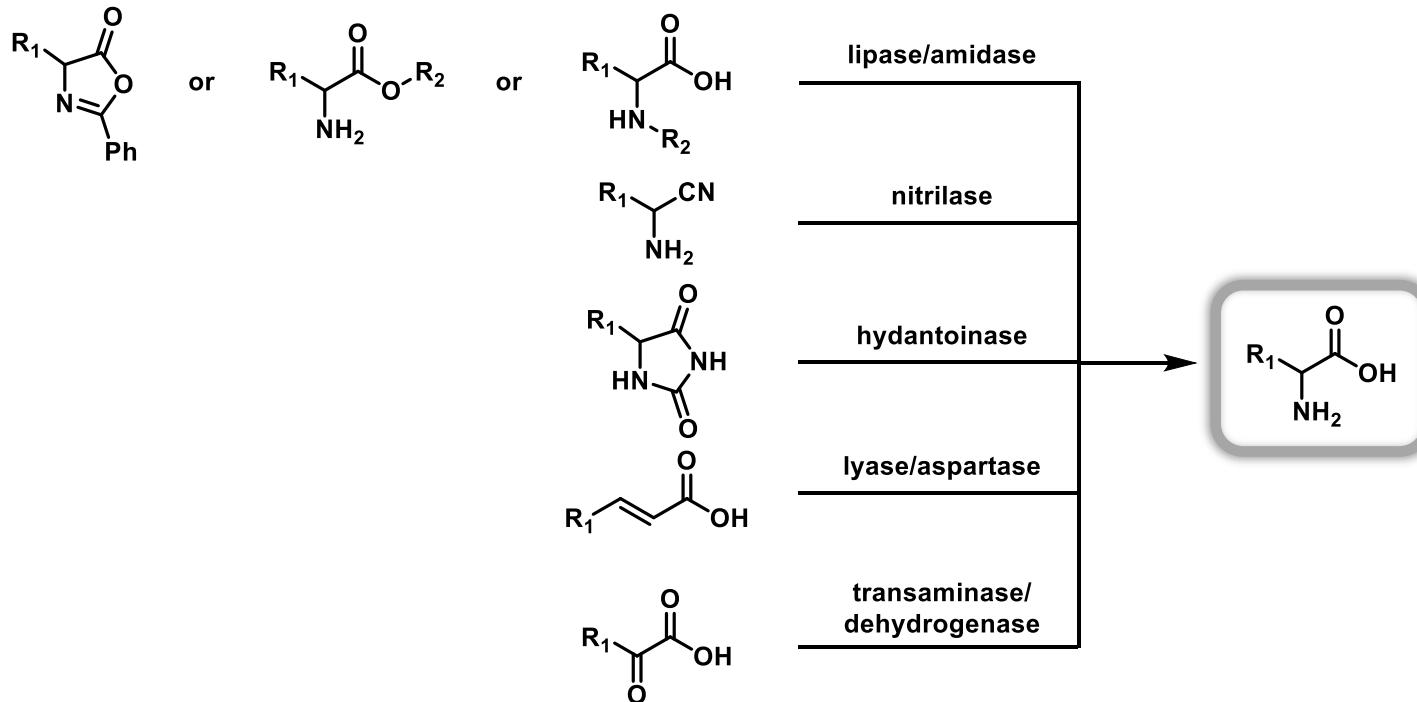


IMINES and AMINO ACIDS

- *Imines*

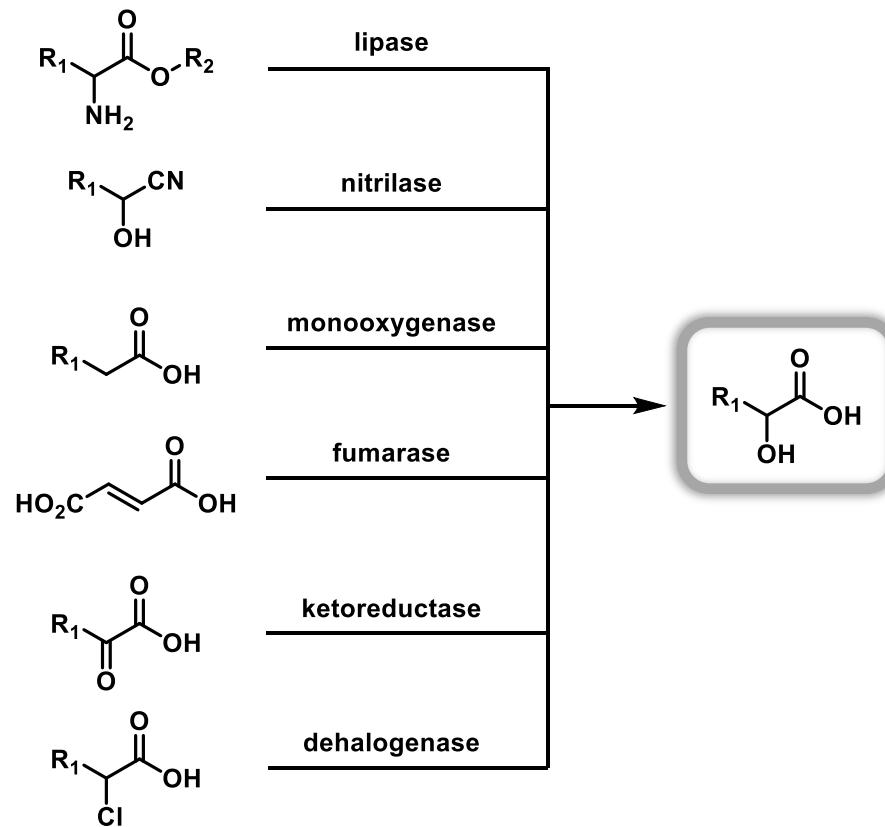


- *Amino acids*



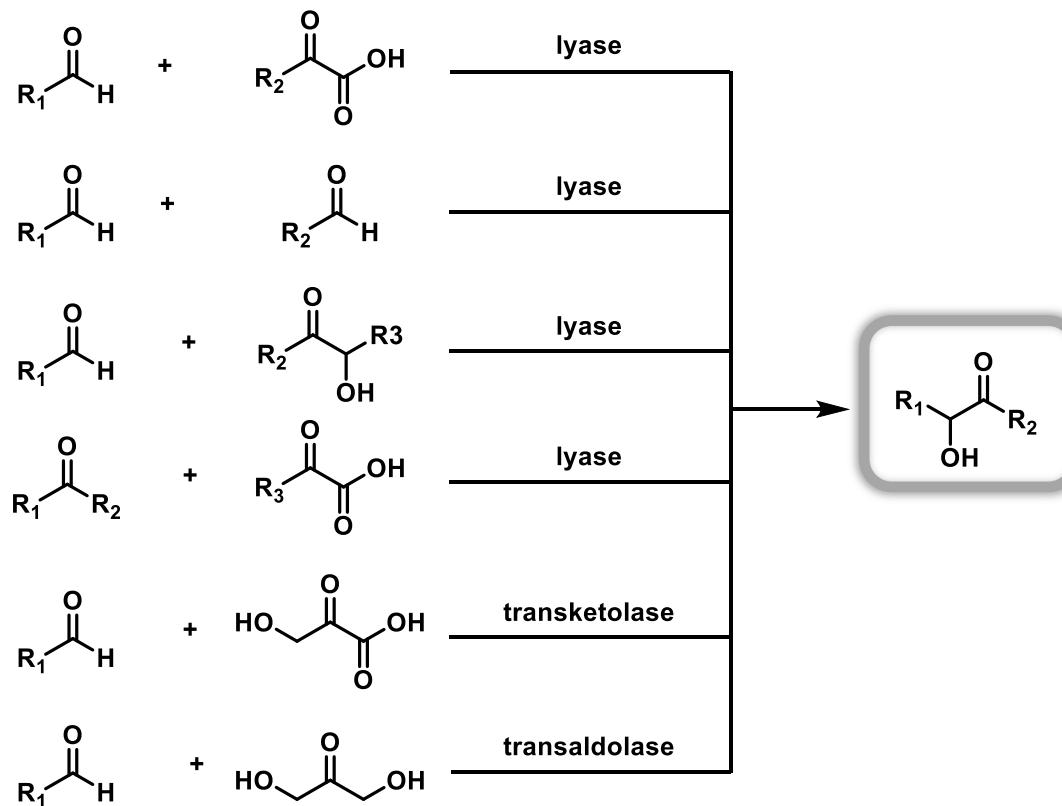
α -HYDROXY ACIDS

- Hydrolysis, reduction, α -carbon oxidation and addition of water



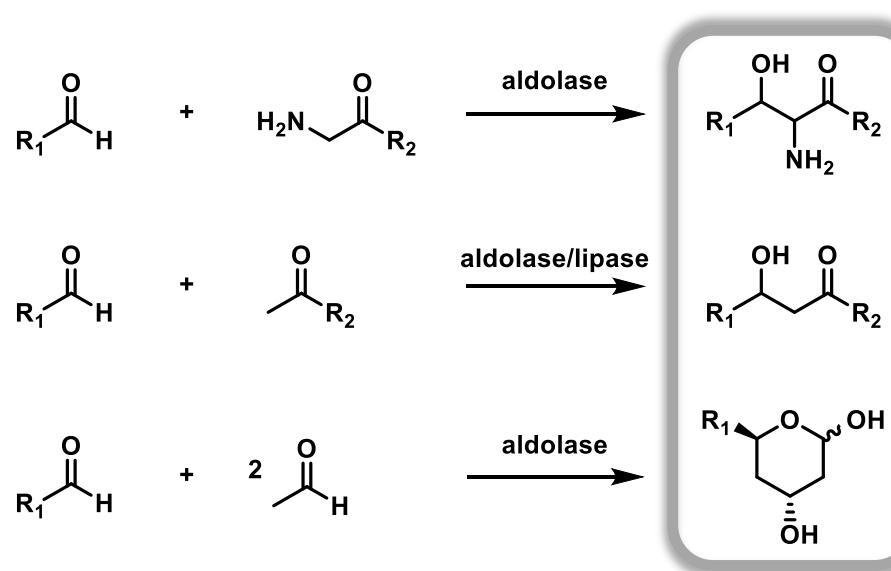
α -HYDROXY KETONES

- Acyloin condensations and carboliogations



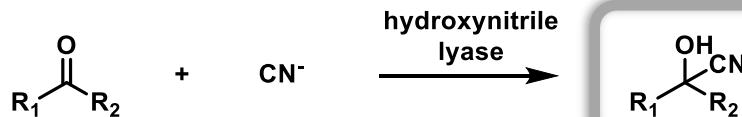
α -HYDROXY ALDEHYDES, KETONES and CARBOXYLIC ACIDS

- *Aldol condensations*

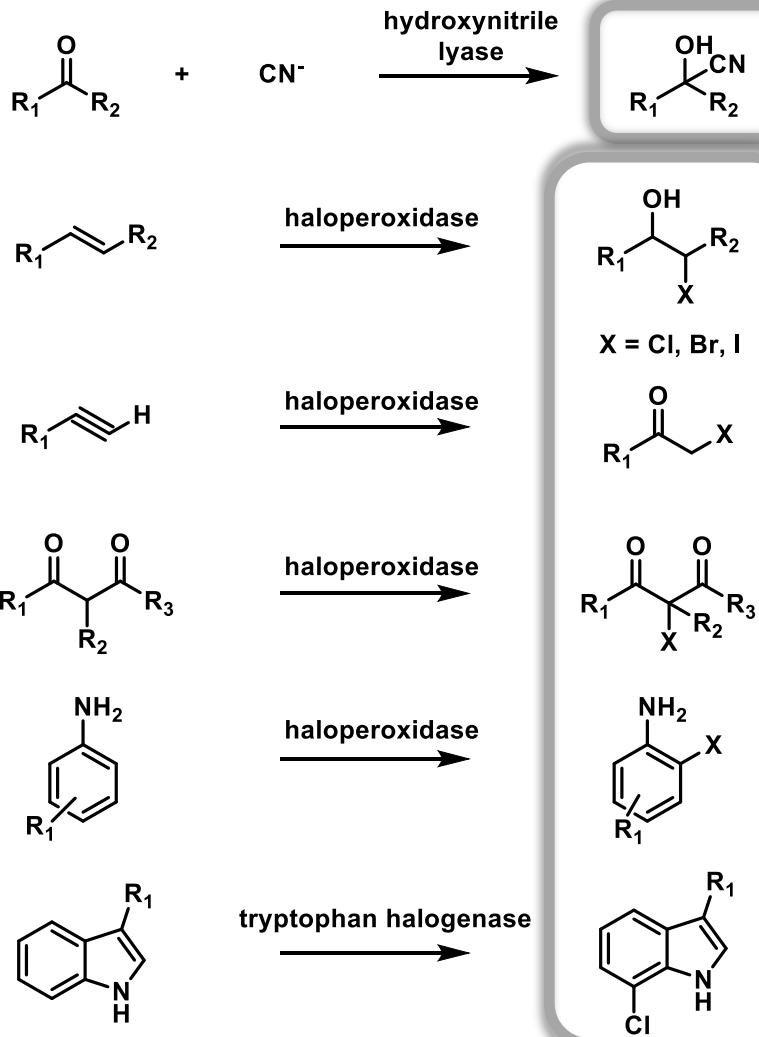


CYANOHYDRINES and HALIDES

- Cyanohydrines

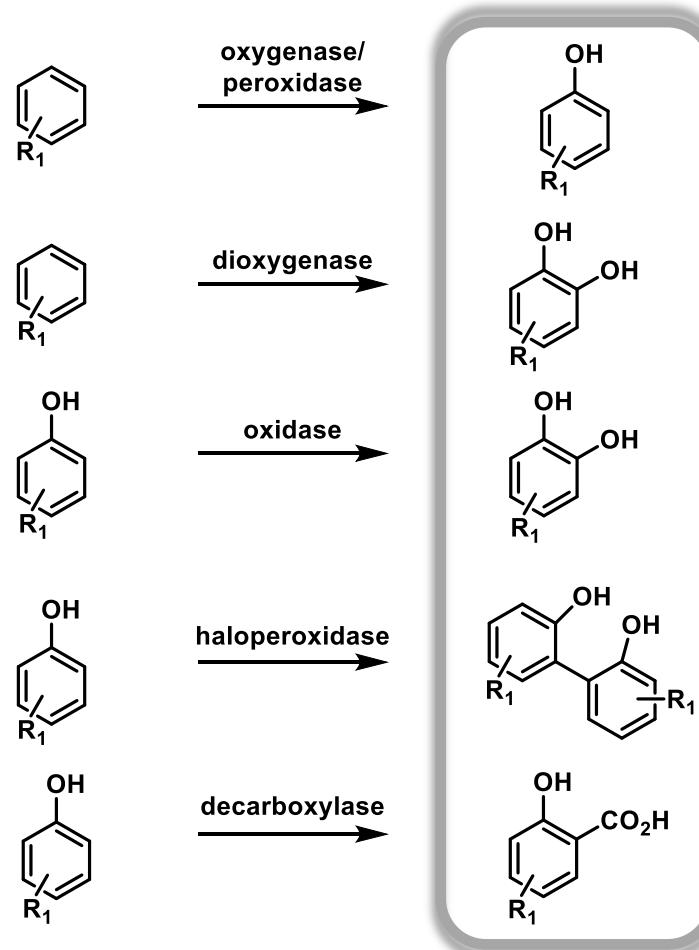


- Halides



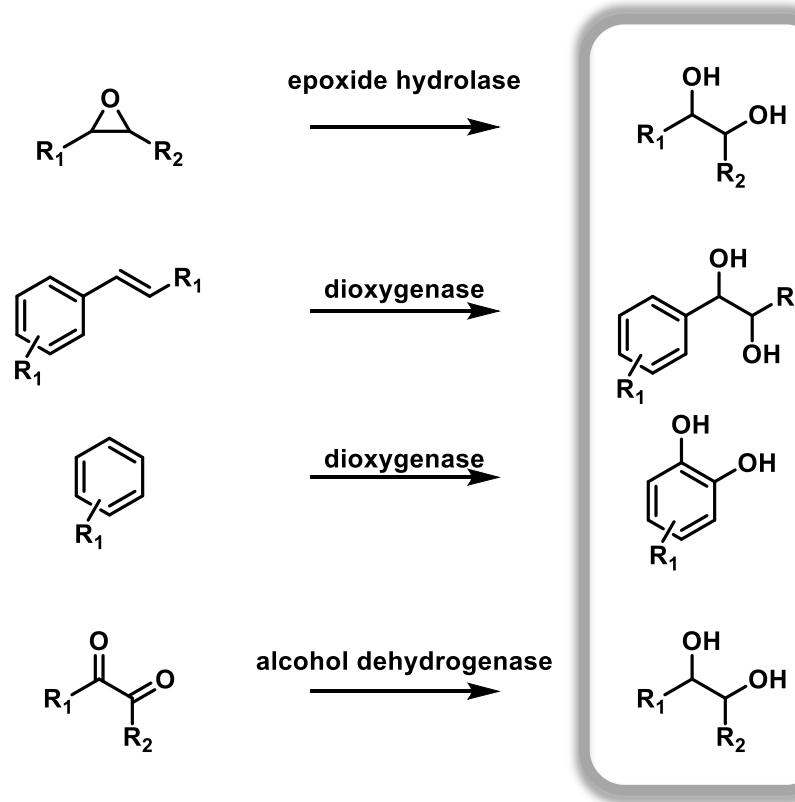
FUNCTIONALIZATION OF ARENES

- Hydroxylation, general oxidation, oxidative dimerisation and carboxylation



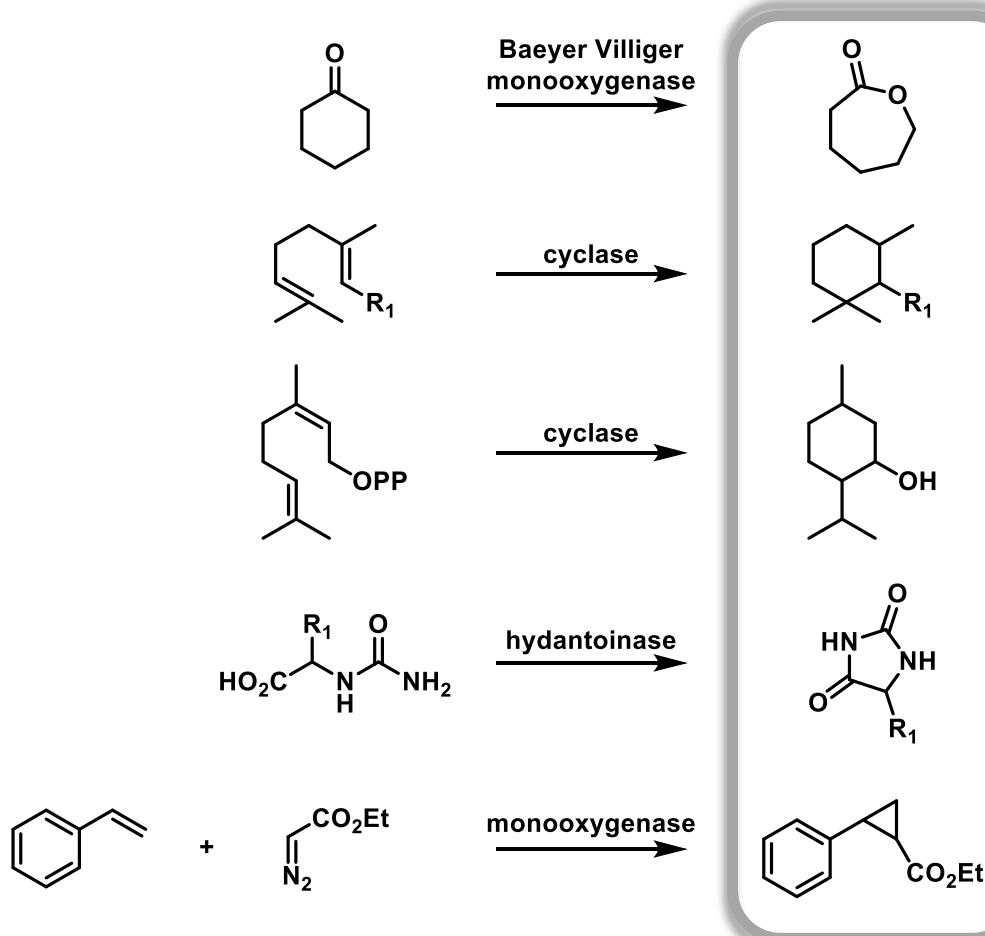
VICINAL DIOLS

- Hydroxylation, general oxidation, oxidative dimerisation and carboxylation



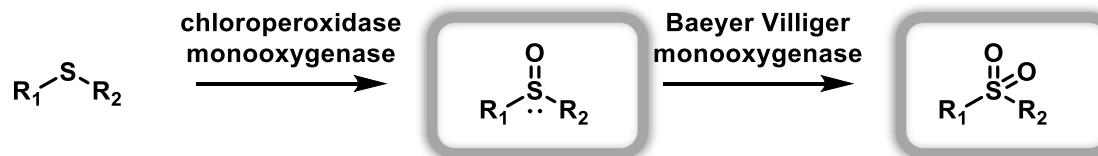
CYCLIC COMPOUNDS

- Oxidation, macrocyclisation and reversible hydrolysis

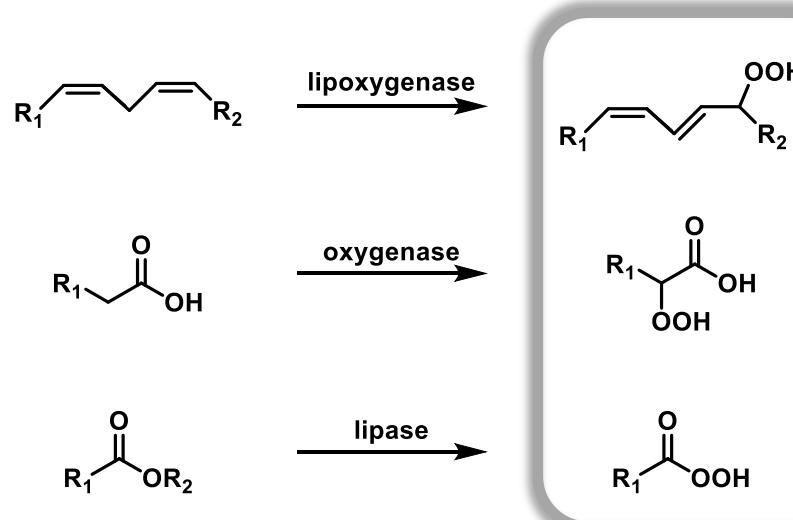


SULFOXIDES, SULFONES and PEROXIDES

- Oxidation of organic sulfides

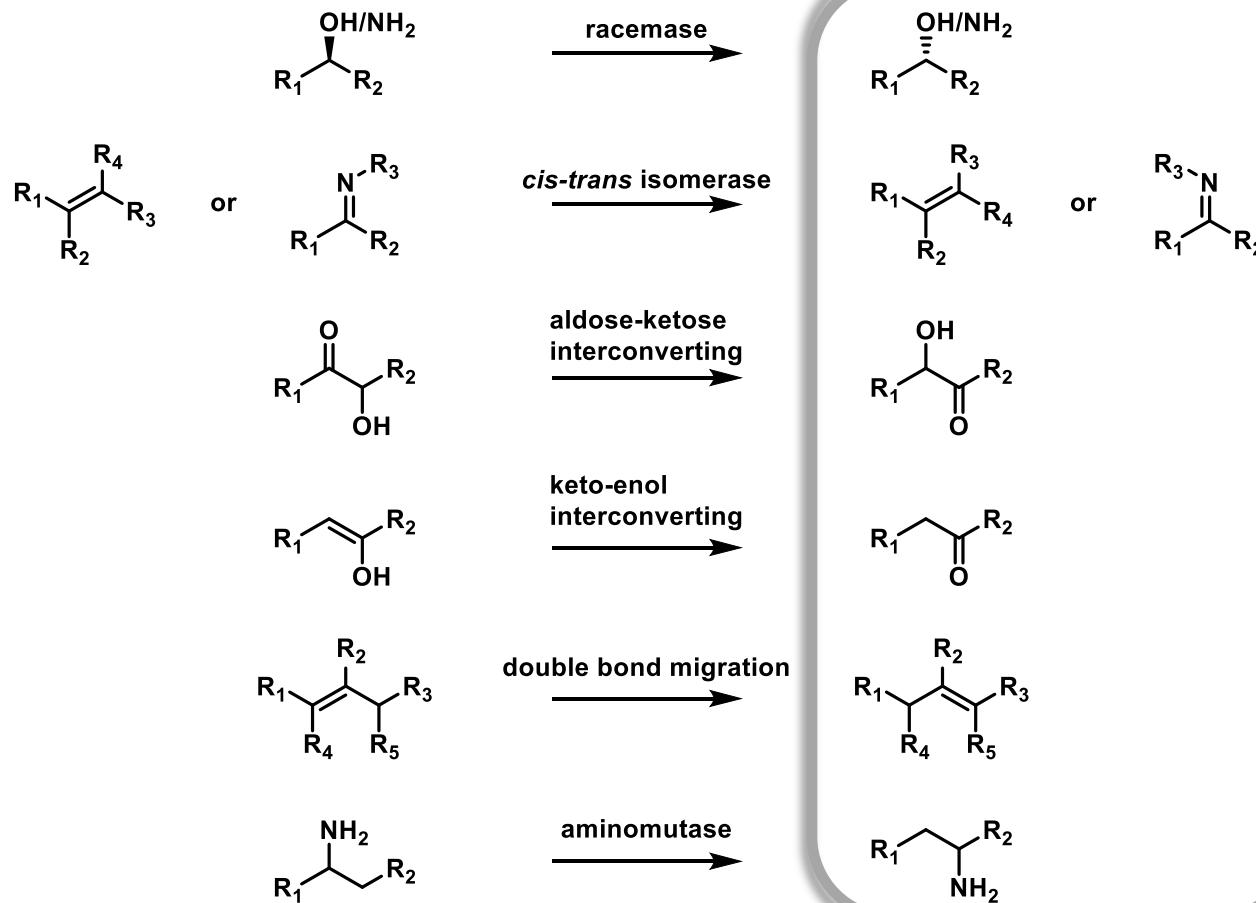


- Diene functionalisation and oxidation



ISOMERISATION

- Hydroxylation, general oxidation, oxidative dimerisation and carboxylation



RETROSYNTHESE - ÜBUNGEN

Präsentationsdauer: 10 min

Fragestellung:

- Warum könnte diese Verbindung **interessant** sein? (Spezielle Wirkung, Baustein)
- Wie wird diese Verbindung **hergestellt**? (chemisch, fermentativ)
- Wie könnte eine **neue**, effiziente biosynthetische **Route** aussehen?
- Was wäre der **Startpunkt** für diese neue Synthese?
- Was wären die **Vorteile** dieser Syntheseroute?
- Kann diese Verbindung rein enzymatisch hergestellt werden oder müssten Enzyme mit chemischen Katalysatoren in **Kaskaden** kombiniert werden?
- Welche **Herausforderungen** sehen Sie in der Etablierung der Route?
- Sehen Sie eine Möglichkeit **Derivate** davon herzustellen?