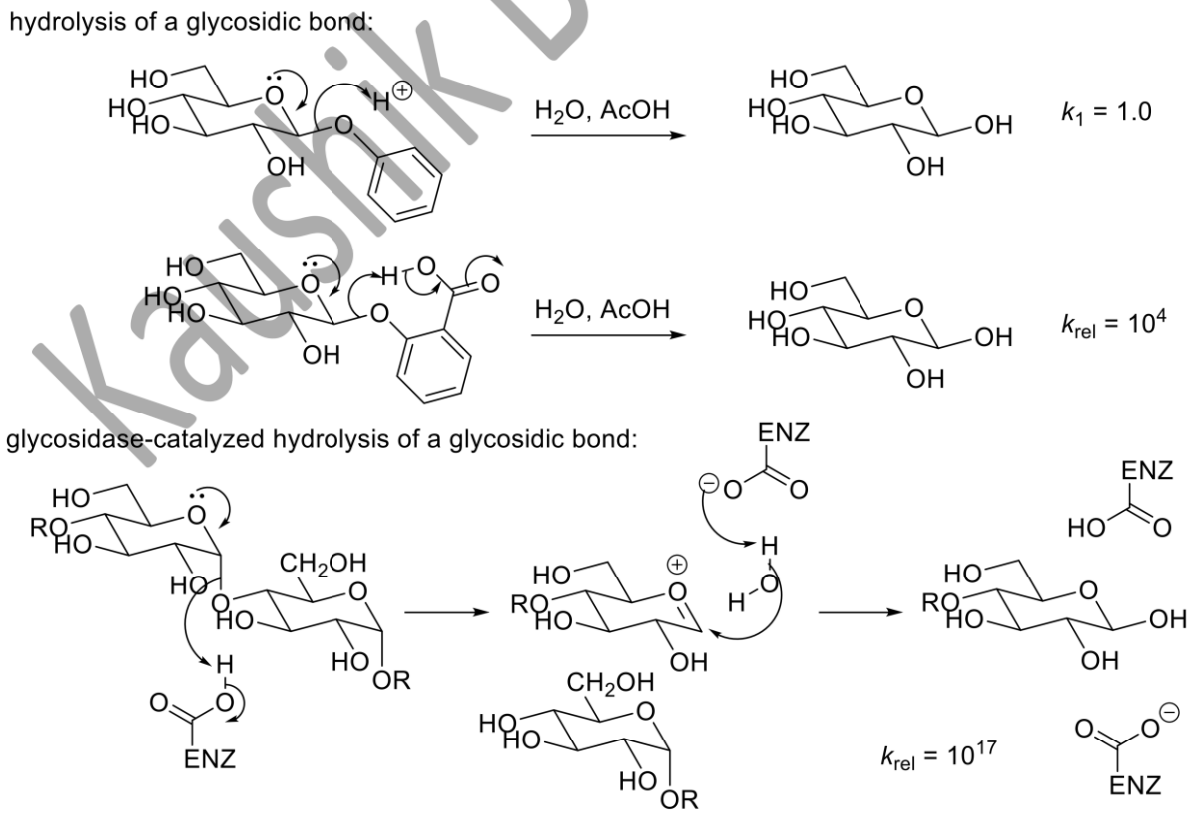
B] Biomimetic chemistry and multifunctional reagents

Biomimetic chemistry is the field which attempts to design either a laboratory procedure that imitates the characteristic of natural reactions or a chemical compound that mimics biological materials such as enzymes, in terms of improving the rate and selectivities of the transformation concerned.

The term biomimetic chemistry was popularized by Ronald Breslow. To quote him, "On the border between chemistry and biology, information can flow in both directions. Information from chemistry into biology helps us understand how biological systems work and also furnishes many of the tools needed to explore and understand biology generally. However, there is another aspect in which information from biology flows into chemistry. This inspires new chemistry based on the principles used by Nature, a field that I have named "biomimetic chemistry". It mirrors an activity that humans have pursued for a long time: inventing new things inspired by what Nature does.

For example, when humans were trying to decide how to fly, they examined the flying organisms, birds and insects, and realized that wings were a major and fundamental idea. However, when early inventors tried to make the wings flap the way they do in birds and insects, they discovered that there were better ways to furnish the power. People took the principle of flight using wings, but not the details of how biology actually used them. As Philip Ball has stated, a jumbo jet is not just a scaled-up pigeon. In biomimetic chemistry, we also take inspiration, but not blueprints, from natural chemistry."

Exploring and drawing inspiration from nature's optimized (over billion years) processes – enhancing the rate of hydrolysis of a glycosidic bond:



Kaushik Basu, SPCMC

Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay

Examples of different products synthesized using biocatalysis.

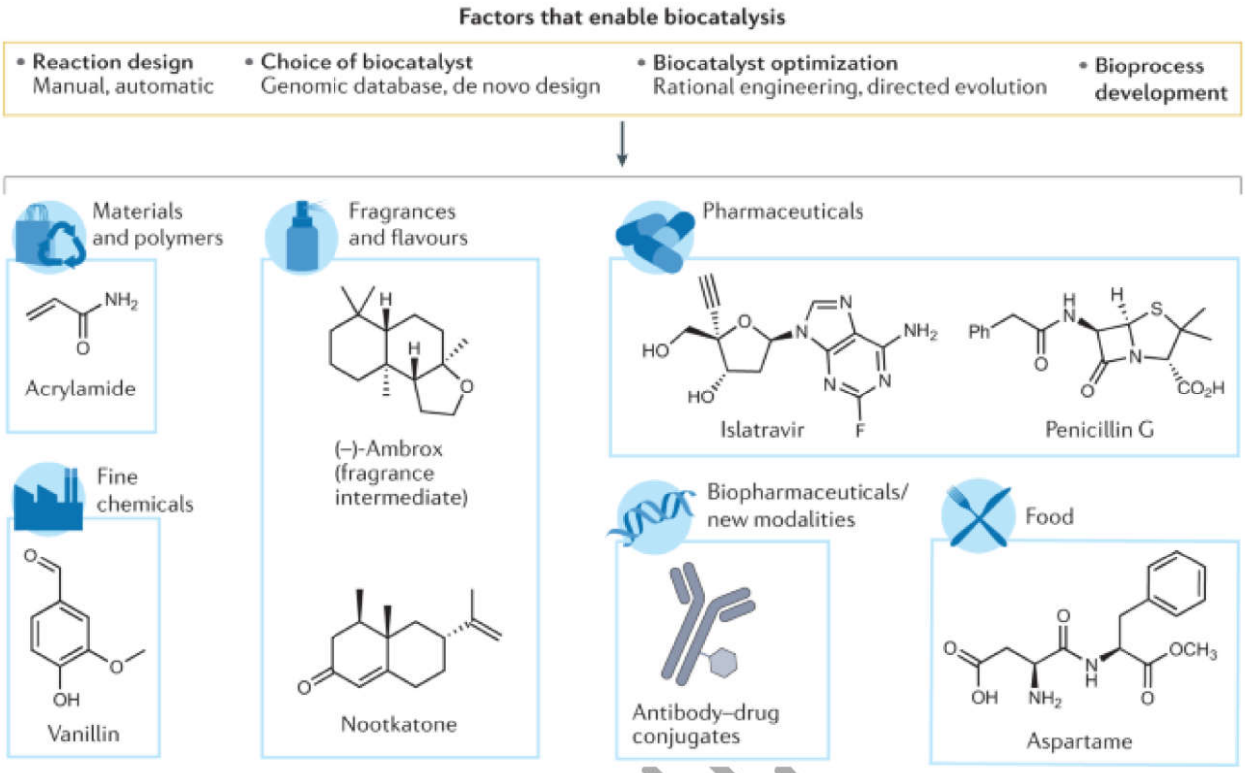


Image collected from: https://www.nature.com/articles/s43586-021-00044-z

Advantages of biocatalysis:

1. Biggest advantage of enzyme-catalysed reactions is selectivity, particularly, enantioselectivity where e.e. > 99% is achieved routinely. Not easy to replicate in the conventional organic synthesis.

2. Reactions occur in aqueous medium, near room temp., close to neutral pH. Milder reaction conditions are at per with the principles of Green Chemistry and sustainability.

3. Air is often not a problem for enzymes, while many homogenous and heterogeneous catalysts will be oxidized and deactivated by air, even at room temperature.

4. Reactions are highly accelerated; much higher rate than conventional procedures – thus, energy and resource efficient.

5. Enzymes obviate the need of protection-deprotection strategy as they are highly selective for the functional group they target and do not disturb other moieties present in the substrate; this leads to better overall yield, in comparison to multistep procedures.

6. Side reactions are minimum; less wastage.

7. Many enzyme-catalysed processes are already optimized to perform at a large industrial scale, such as antibiotic productions.

8. Further improvement of biotransformation can be achieved through alteration of enzyme structure by genetically modifying the organism that produces the enzyme.

Kaushik Basu

Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay

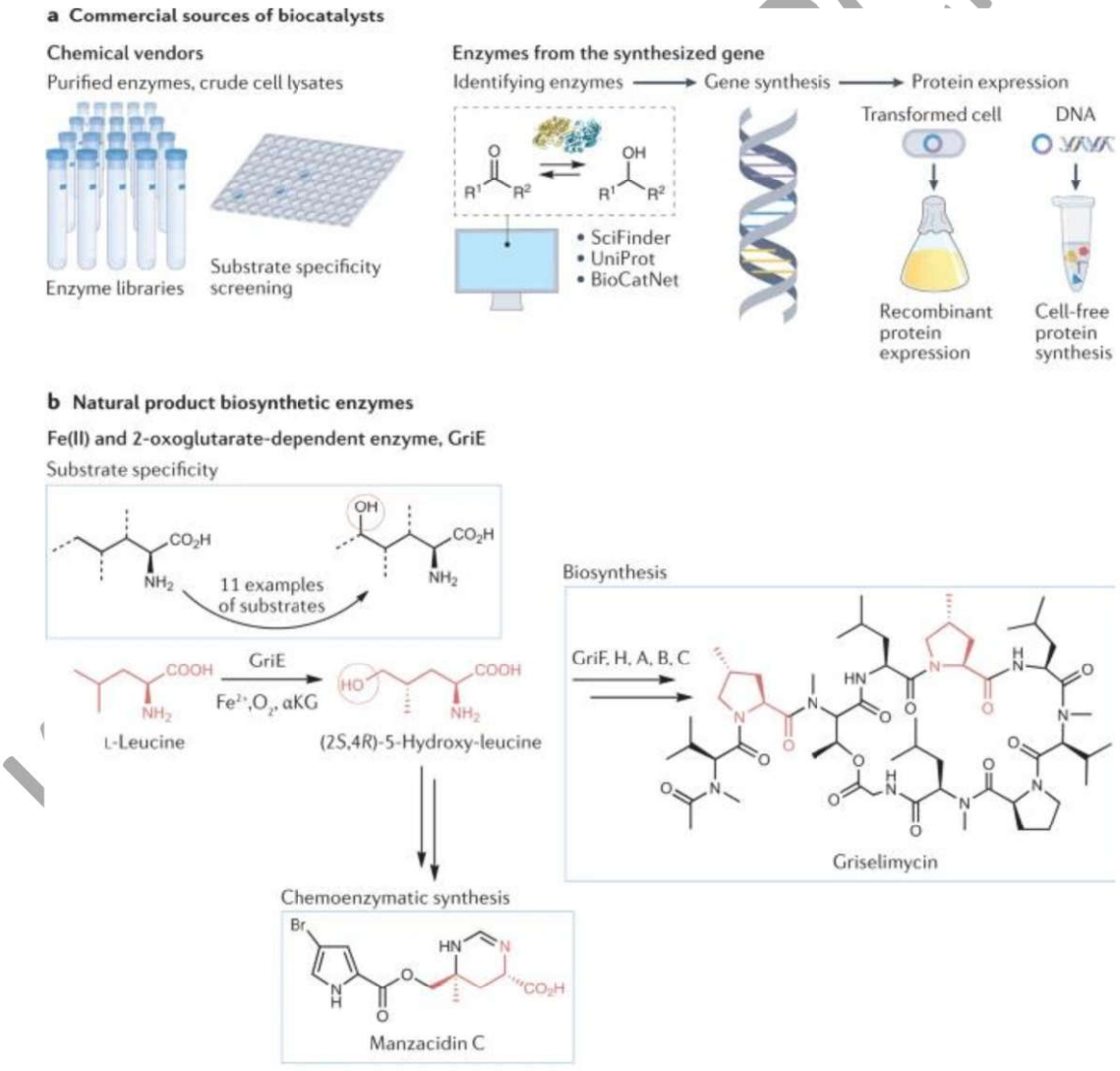
Drawbacks:

1. Often, the biocatalyst is not stable in the desired medium. A deviation as little as 1 Å in the conformation of the protein (enzyme) may result in severe loss of activity. This highlights the most stringent requirement to preserve structural integrity of the enzyme in the reaction media.

2. Too few biocatalysts exist for a desired reaction from available substrates to targeted products, i.e., even though there are biocatalysts capable of performing almost every reaction, often these are either uncharacterized, proprietary, or at least not commercially available. The situation is, however, rapidly improving.

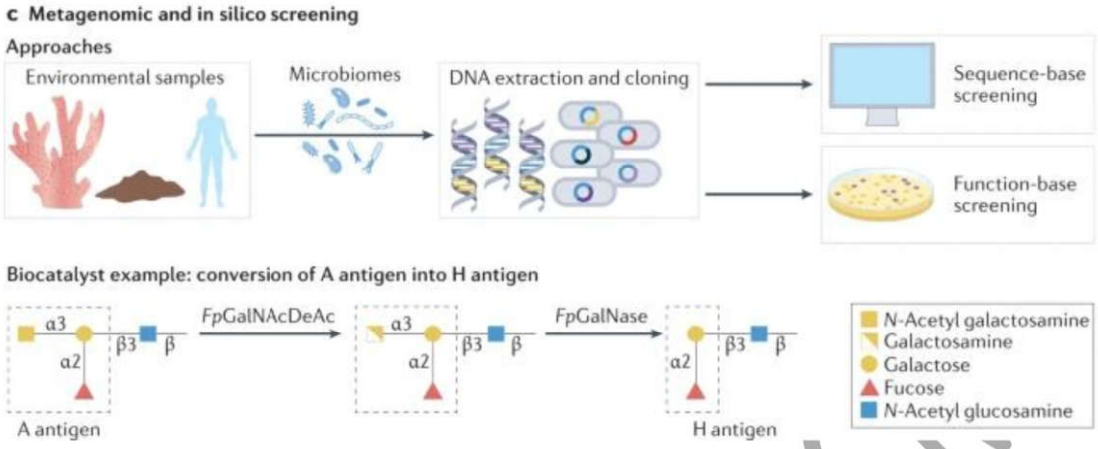
3. Development cycles are too long for new and developed biocatalysts which typically require 10-20 years to become ready for large scale applications. But, with improved knowledge of biotechnology, the time period is also decreasing.

Sources of Biocatalysts:



a) Types of biocatalyst useful in chemoenzymatic synthesis and biochemical applications. b) Natural product biosynthetic enzymes. In the biosynthetic pathway of griselimycin, the Fe(II) and 2-oxoglutarate-

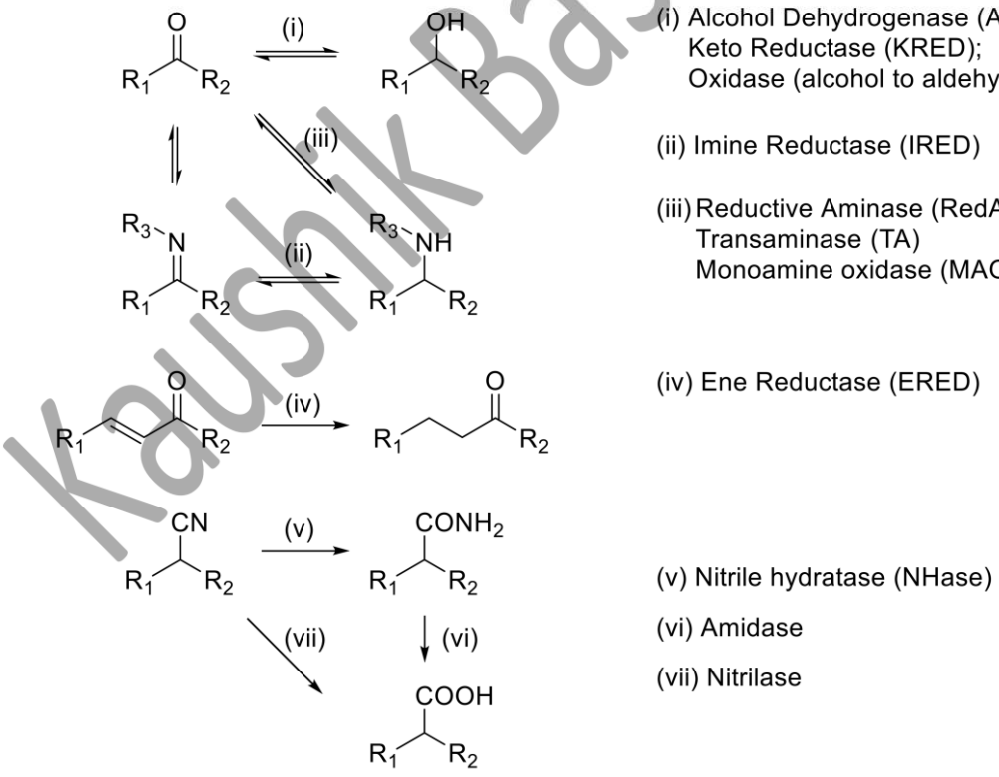
dependent enzyme, GriE, reacts with L-leucine to give (2*S*,4*R*)-5-hydroxyleucine. This regioselective and stereoselective hydroxylation enables a chemoenzymatic synthesis of manzacidin C.



c) Metagenomic screening approaches. Top: first step of metagenomics screening is extraction of total DNA from environmental samples such as marine sponges or soil microorganism communities. This DNA is constructed into a metagenomic library and is commonly screened using sequence-based or function-based approaches. Bottom: enzymatic conversion of A/B antigens into H antigen. All blood group antigens depicted are type I.

Image collected from: https://www.nature.com/articles/s43586-021-00044-z

Common biocatalysis enzymes and their associated chemical transformations:



(i) Alcohol Dehydrogenase (ADH);
Keto Reductase (KRED);
Oxidase (alcohol to aldehyde/ketone)

(ii) Imine Reductase (IRED)

(iii) Reductive Aminase (RedAm);
Transaminase (TA)
Monoamine oxidase (MAO)

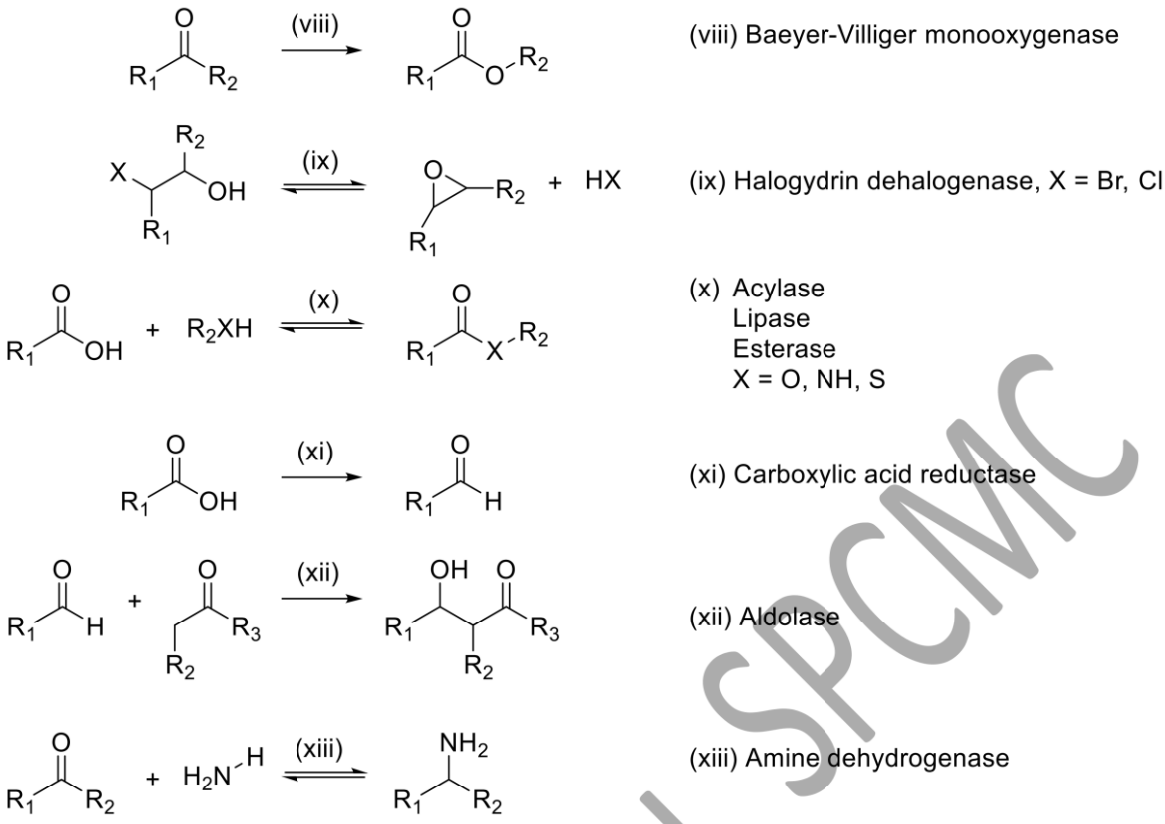
(iv) Ene Reductase (ERED)

(v) Nitrile hydratase (NHase)

(vi) Amidase

(vii) Nitrilase

Kaushik Basu, SPC



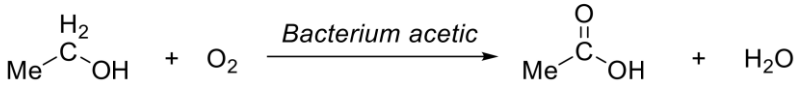
The interconversion between alcohols and aldehydes or ketones is catalysed by alcohol dehydrogenases, ketoreductases (KREDs) and alcohol oxidases (reaction i). Imine reductases catalyse the reduction of imines to amines (reaction ii). Reductive aminases and transaminases transfer amino groups to prochiral ketones or aldehydes, giving rise to chiral amine products. Monoamine oxidases catalyse the oxidation of compounds containing one amino group and the resulting imine spontaneously forms a ketone in water (reaction iii). Ene reductases reduce C–C double bonds (reaction iv). Nitrile hydratases catalyse the addition of water across nitriles producing amides (reactions v, vi). The hydrolysis of nitriles to carboxylic acids and ammonia is catalysed by nitrilases (reaction vii). Baeyer–Villiger monooxygenases oxidize ketones to esters (reaction viii). Halohydrin dehalogenases produce enantiopure epoxides and corresponding ring-opening products (reaction ix). Acylases hydrolyse amide bonds, whereas lipases and esterases do so for ester bonds (reaction x). Part of the esterase group, thioesterases catalyse the hydrolysis of the thioester bonds. Carboxylic acid reductases reduce aromatic or aliphatic acids to aldehydes (reaction xi). Aldolases catalyse Aldol reactions (reaction xii). Amine dehydrogenases catalyse the reductive amination of carbonyl compounds (reaction xiii).

Collected from: https://www.nature.com/articles/s43586-021-00044-z

Different types of biocatalytic transformations:

a) Microbial oxidations:

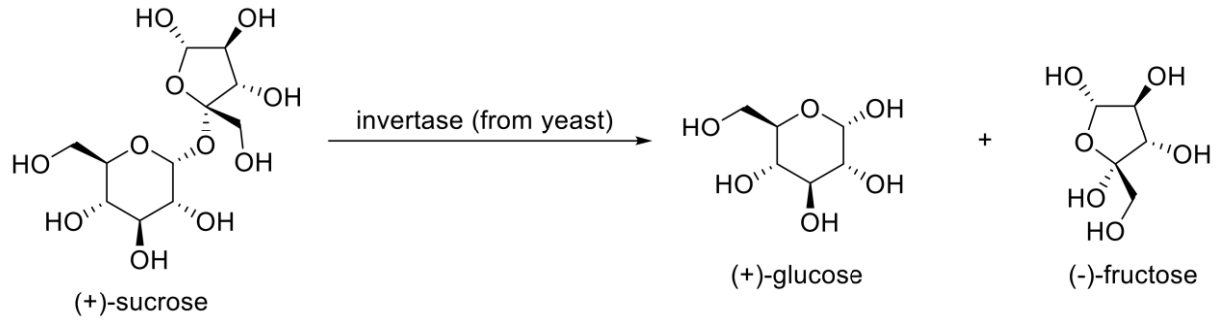
i) Quick vinegar process; Oxidation of ethanol to acetic acid by *Bacterium acetic*.



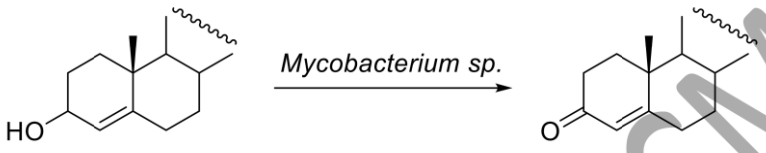
ii) Conversion of the disaccharide sucrose ($C_{12}H_{22}O_{11}$) into monosaccharides glucose and fructose by the enzyme invertase.

Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay

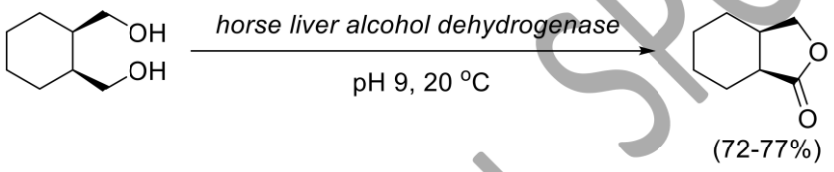
Kaushik Basu, SPCMC



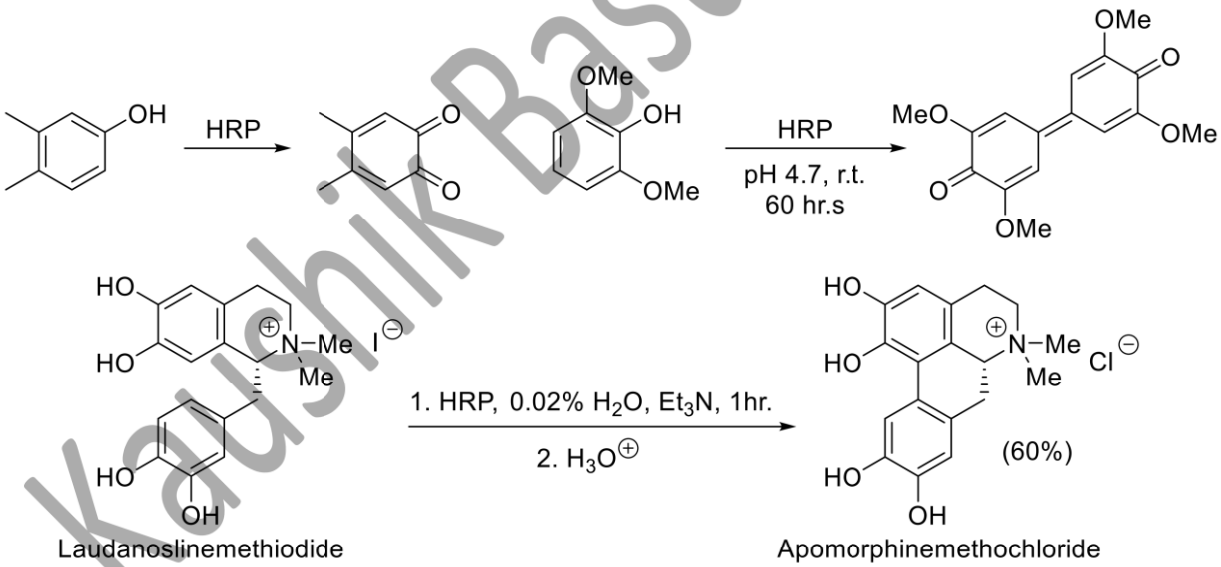
iii) Conversion of the cholesterol into cholest-4-en-3-one by enzymes from *Mycobacterium sp*.



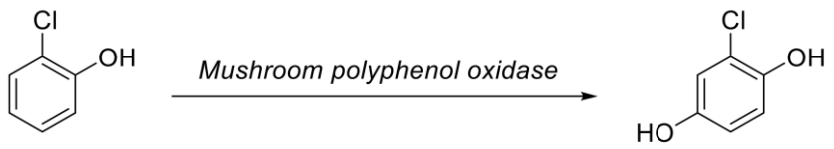
iv) Conversion of *cis*-diol into the corresponding cyclic ester by *horse liver alcohol dehydrogenase*.



v) Quite a few oxidations can be done with the enzyme *horseradish peroxidase* (HRP).



vi) Hydroxylation of phenols by *mushroom polyphenol oxidase*.

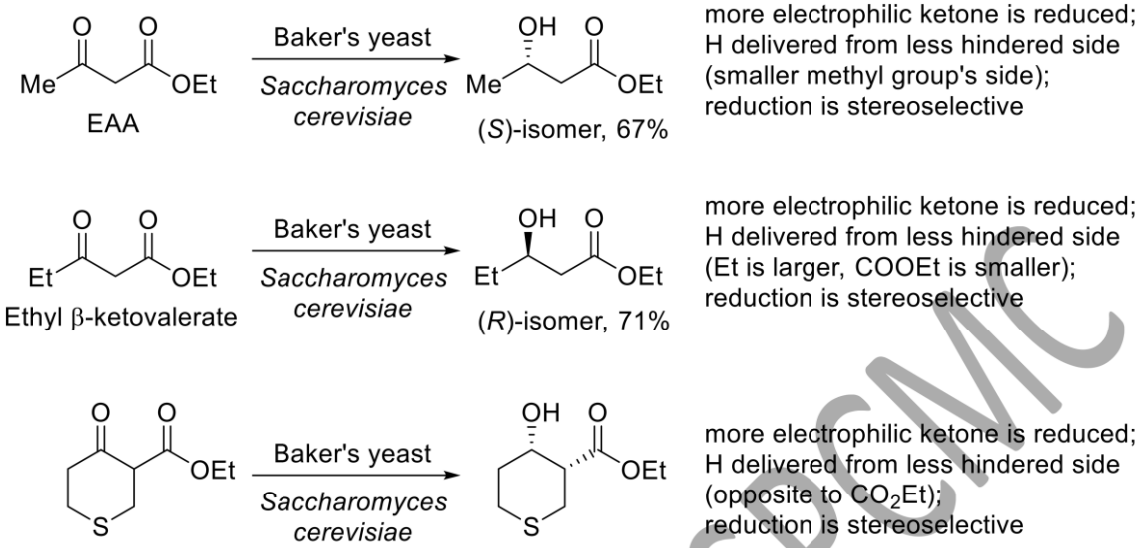


Kaushik Basu, SPCMC

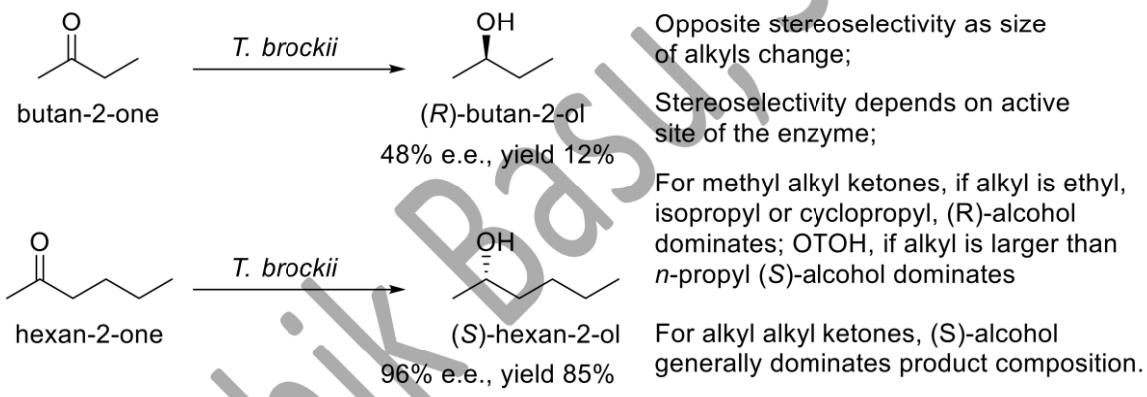
Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay

b) Microbial reductions:

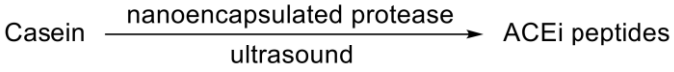
i) Reduction of β-ketoesters by Baker's yeast:



ii) Reduction of ketones by a thermostable ADH from Thermoanaerobium brockii:



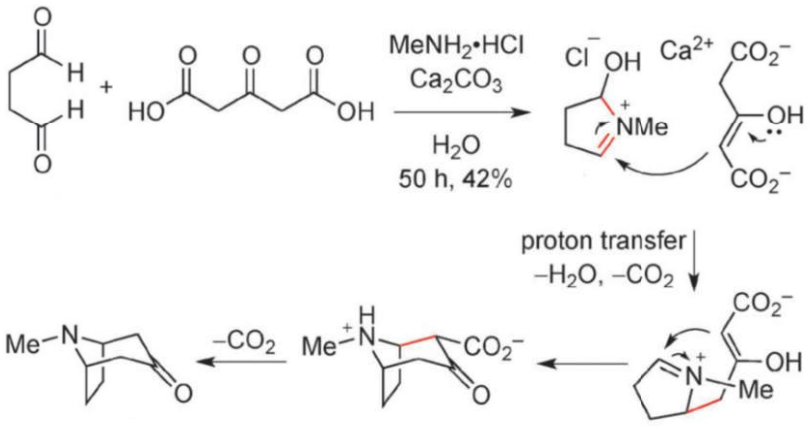
c) ACE inhibitor from casein: Angiotensin I-Converting Enzyme is a key component in regulating blood pressure. ACE inhibition lowers the blood pressure and is a key clinical target for blood pressure control. For this, many synthetic ACE inhibitors (ACEi), such as captopril, enalapril, fosinopril, lisinopril, and ramipril were identified and used for the treatment of hypertension. However, these synthetic inhibitors have side effects including coughing, taste disturbance and skin rash. Thus, one of the major challenges to today's world healthcare sectors is to identify ACE inhibitors from natural resources. Milk bioactive peptides constitute alternatives for this, serving directly as ACE inhibitors, or providing a scaffold for the engineering of novel molecules with clinical potential. For example, nanoencapsulated protease enzyme is used for ultrasound-assisted hydrolysis of milk protein casein to produce ACEi peptides:



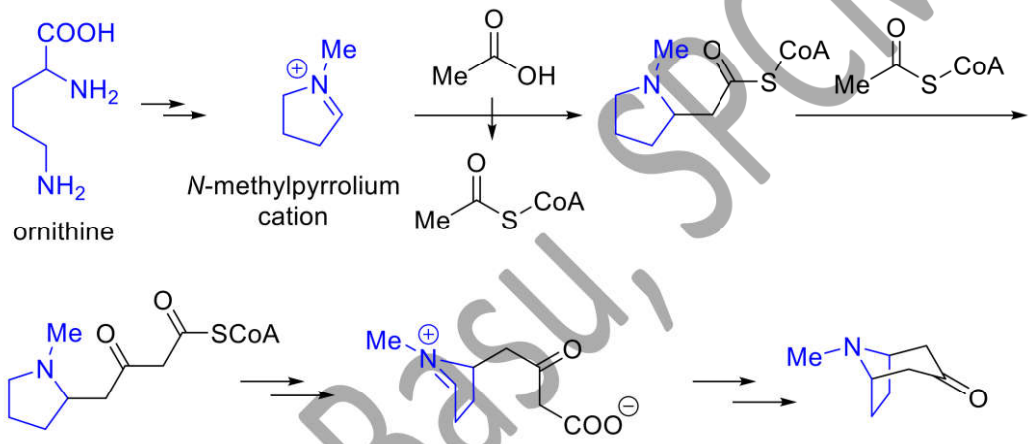
d) Biomimetic synthesis of alkaloid tropionone by Sir Robert Robinson: Tropinone is a bicyclic molecule, but the reactants used in its preparation are simple: succinaldehyde, methylamine, and acetonedicarboxylic acid (or even acetone). The synthesis is a good example of a biomimetic reaction or biogenetic-type synthesis because biosynthesis makes use of the same building blocks.

Kaushik Basu, SPCMC

Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay



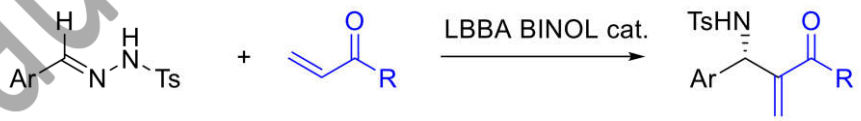
Biosynthetic path:



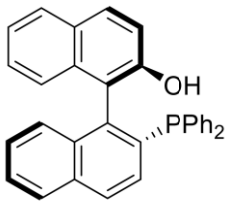
Multifunctional reagents

These are small or macromolecules that have diverse reactivity, i.e., can react at more than one sites. Following the concepts of biomimetic chemistry, multifunctional catalysts can be designed for transforming organic molecules with high precision. A few examples:

i) Phosphine and phenolic hydroxyl group-type of multifunctional chiral phosphine-catalyzed asymmetric aza-Morita Baylis Hillman Reaction:

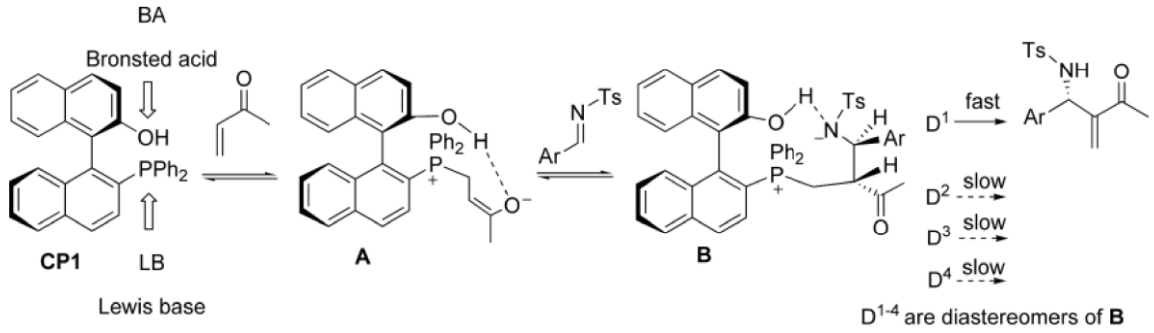


1,1'-bi-2,2'-naphthol (BINOL)-derived chiral LBBA bifunctional phosphine (LB = PPh_3, BA = Ph-OH)



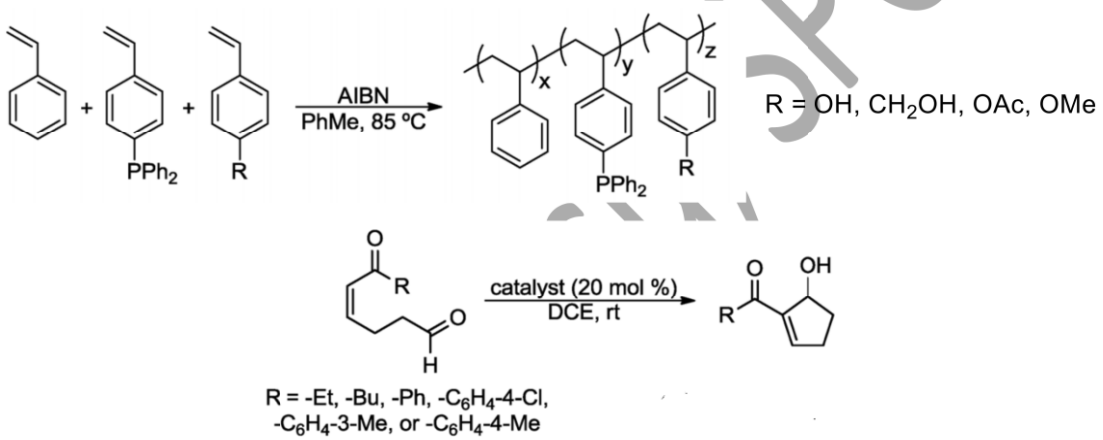
Kaushik Basu, SPCMC

A plausible mechanism for the enantioselective transformation is:

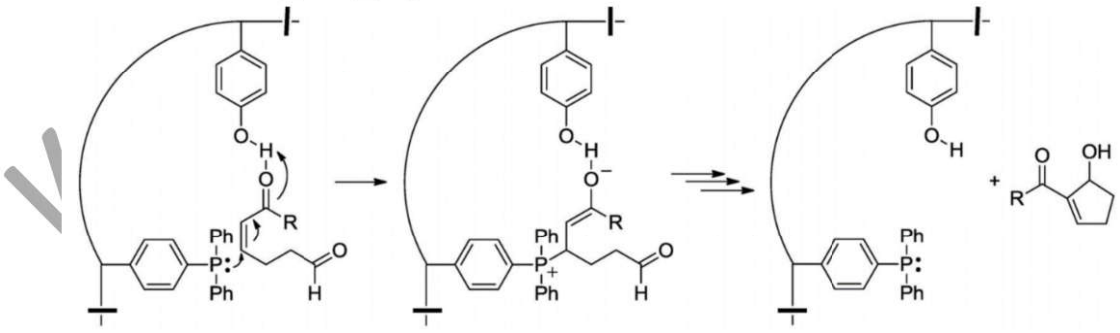


Source: 10.1021/ar900271g

A series of soluble non-cross-linked polystyrenes functionalized with both phosphine groups and either hydrogen bond donating or accepting groups has been prepared for use as catalysts in intramolecular MBH reactions by polymerizing appropriate mixtures of monomers under free radical conditions



A plausible mechanism for the enantioselective transformation is:

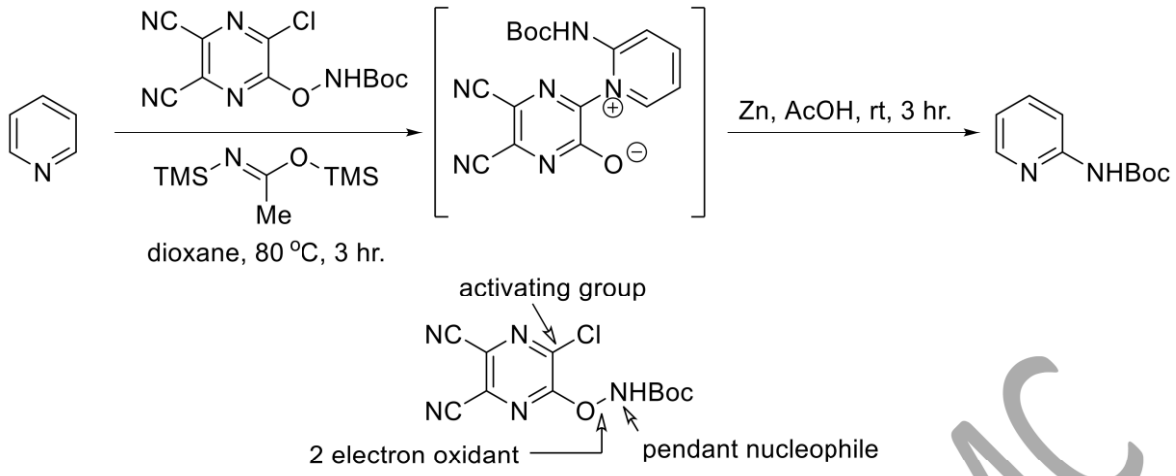


Source: 10.1351/PAC-CON-12-04-13

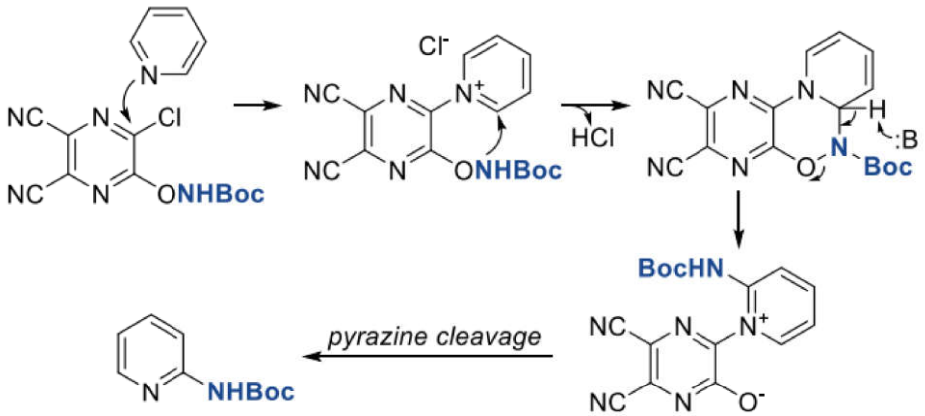
ii) Site-selective amination of pyridines using a multifunctional reagent:

Fier et al. have developed a multifunctional reagent for the direct conversion of pyridines to Boc-protected 2-aminopyridines with exquisite site selectivity and chemoselectivity. The novel reagent was prepared on 200-g scale in a single step, reacts under mild conditions without precautions toward air or moisture, and is tolerant of nearly all common functionality.

Book Consulted: An Insight into green Chemistry by Chandrakanta Bandopadhyay; New Trends in GREEN CHEMISTRY by V. K. Ahluwalia and M. Kidwai; A Textbook of Green Chemistry by S.P. Dey and N. Sepay



A plausible mechanism for site-selective amination:



Source: 10.1021/jacs.0c03537

The multifunctional reagent - (i) reacts with pyridine to form a reactive pyridinium salt, (ii) provides intramolecular delivery of a nitrogen nucleophile, and thereby (iii) direct functionalization exclusively to C-2, (iv) prevents ring opening, and ultimately (v) promotes two-electron oxidation/rearomatization through N−O bond cleavage.

Kaushik Bhattacharjee MC