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APPLICATIONS OF BIOCATALYSTS IN REDUCTION REACTION: A REVIEW

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What is green chemistry

Green chemistry is the design of chemical products and processes that reduce or eliminate the use of generation of hazardous substances. *The green chemistry also called as sustainable chemistry* is an area of chemistry and chemical engineering focused on the design of product and processess that minimize the use the *Paul Anastas* and *John warner*. Green chemistry emerged from a various existing ideas and research efforts (such as atom economy and catalysis) in the period leading up to the 1990' s in content of attention to problem of chemical pollution and resource depletion.[4,5]

Biocatalysis and The "12" Principles of Green Chemistry[5]

Figure 1: Principle of green chemistry.

Table no. 1

Sr. No.	Green chemistry principles	Biocatalysis
1	Waste prevention	Significantly reduced waste
2	Atom Economy	More atom and step economical
3	Less Hazardous Syn.	Generally Low Toxicity
4	Design for safer products	Not Relevant(product not process)
5	Safer solvents and auxiliaries	Usually performed in water
6	Energy efficient	Mild condition
7	Renewable feedstocks	Enzyme are renewable
8	Reduce Derivatization	Biocatalysis Obviates The need for protection /Deprotection enzyme are catalyst.
9	Catalysis	Enzyme are catalysts
10	Design for degradation	Not relevant but enzymes themselves
11	Real –time analysis for pollution prevention	Can be ap applicable in biocatalytic processes
12	Inherently safer processes	Performed under mild and safe conditions.

ABSTRACT

Reduction play a crusial role in organic synthesis producing chiral product with new modern functionalities. Enzymes can catalyse such reactions with stereoselectivity, regioselectivity and chemoselectivity, enzymes the natural catalysts offer virtually endless possibilities. In this review we describe the chemical synthesis biocatalyst reduction reactions.[7,9,12]

KEYWORDS: Bioreductions, Biocatalytic, Dehydrogenases, Reductases, Imine reductase.

INTRODUCTION

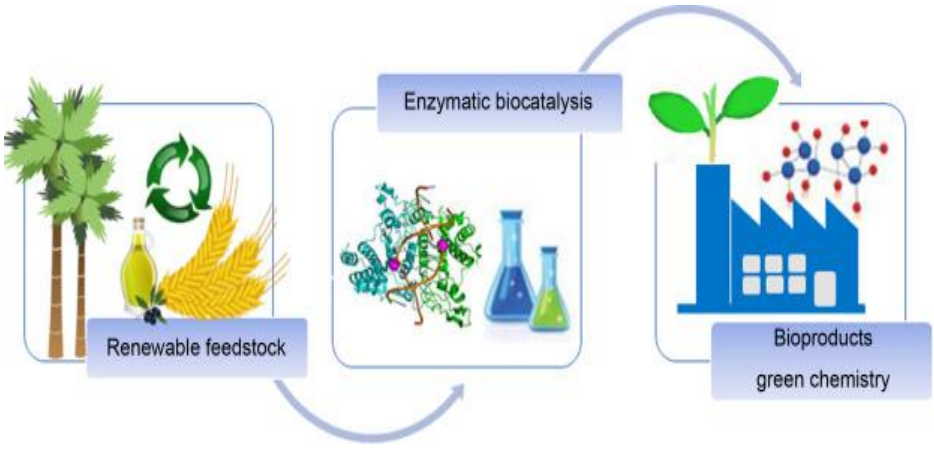
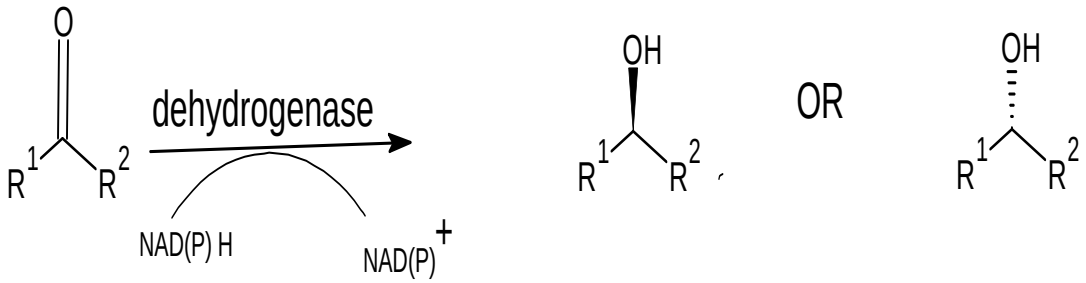


Figure no. 2

Enzyme which are catalysts found in nature. offer virtually endless opportunities to access a range of chemical reaction. Reduction in particular can result in the production of several

chiral centres novel functional groups in addition items in the pharmaceuticals and fine chemical industries currently, biocatalytic reduction are able to access molecules like chiral carbonyls with an alpha and beta substitution, secondary amines lactones and alcohols. We provide a critical evaluation of the use of in this review oxidoreductases for the production of chemicals. In order to synthesise a variety of chemicals compounds, biocatalysts, making it a suitable tool for green chemistry. It must be emphasised that using enzyme is nothing new, Ancient sumerians and babylonians used a variety of based on the action of uncultivated microorganisms biochemical enzyme processes. Biocatalysts which uses enzyme as biocatalysis to create products like bread, wine, vinegar, beer and dough rising is an excellent green chemical technique cheese and other dairy product manufacture as well as the fermentation of cabbage are conducted in an aqueous medium, at a neutral PH, at ambient temperature and under typical have a high catalytic activity under pressure. one of the biggest benefits of using high natural selectivity biocatalysts for enzymatic reaction (chemoselectivity), (regioselectivity) and (stereoselectivity) that facilitates the elimination of unnecessary reaction steps compared to chemical catalysts used in traditional processes. Prochiral ketone biocatalytic reduction is one of the important industrial processes.

Reaction



Reaction no. 1

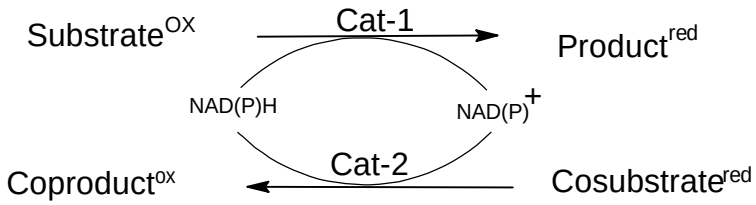
Use of dehydrogenases in various types of bioreduction reaction with cofactor recycling a variety of well -known chemical technique are employed. The use of entire cells from microbes or plant tissue has received more and more intrest in recent years. they have the required cofactors and enzymes.[10]

The catalysts

Historically, carbonyl reduction have dominated the field of biocatalytic reduction chemistry for many years the most common transformation has been the stereoselective reduction of prochiral ketones. The (RE) – Discovery of ene reductases for the reduction of conjugated

C=C bond the reductive amination of aldehyde and ketone by trasaminases. imine reductases, amine dehydrogenases etc. More recently the reduction of carboxylic acids by carboxylic acid reductases and aldehyde oxidoreduction have all significantly altered this situation since the early 2000's. The preferred catalysts for converting aldehyde and ketone into their corresponding alcohol are alcohol dehydrogenases (ADHS). The reduced form of nicotinamide use NAD(P) H an adenine dinucleotide cofactors as a stoichiometric reductant that transfer a hydride in a reversible manner to carbonyl C- atom.

Source of reducing equivalent



Regeneration reaction

Table no. 2

Cosubstrate	**Cat-2**	**Co-product(gmol $^{-1)}$**
H_2	Hase	-(o)
HCO2H	FDH	$CO_{2(44)}$
Glucose	GDH	Gluconic acid
Isopropanol	ADH	Acetone(58)
MeoH	ADH	Co_2 (15)
	AldDH	
	FDH	
Diols	Lactones	Variable but irreversible

Biocatalytic reductions require reducing chemicals to drive the process, much like any other non-enzymatic reduction reaction the reduce nicotinamide adenine is used by the majority of oxidoreductases. cofactors for dinucleotides (NADH Or NADPH) oxidation converts NAD(P)H to NAD(P) due to economy and to prevent any potential inhibiting effects of building for the puroose of reduction of carbonyl groups approach to substrate regeneration utilising isopropanol as a stoichiometric reductant is mostly used. exploiting the reversibility of the ADH reaction, the production enzyme is also used for regeneration of the nicotinamide cofactor or Table 2(Cat=1, Cat-2) Amongst the coupled enzyme regeneration approaches formate and glucose are the cosubstrate when formate dehydrogenase (FDH) OR glucose dehydrogenase (GDH) are used as regeneration enzymes, respectively both regeneration system are irreversible but differ significantly with respect to the by pruduct while the FDH

reaction yields volatile CO2 as a by product ,which does not accumulate in reaction mixture GDH eventually yields gluconic acid which remains in the reaction medium and lower the Ph significantly Hydrogen represents an attractive stioichiometric reductant as a principle it yields no by products. now a days robustness issues of the hydrogenases available, however applied for next improvement. *Algae can also be used for selective reduction process.*[13]

Catalytic reduction

Catalytic hydrogenation perfectly embodies the concept of precision in organic synthesis. Molecular hydrogen is a clean and abundant raw material and catalytic hydrogenations are generally 100% atom efficient, with the exception of a few examples, e.g. nitro group reduction, in which water is formed as a coproduct. They have a tremendously broad scope and exhibit high degrees of che moregio, diastereo and enantioselectivity. ***"Catalytic hydrogenation is one of the most useful and versatile tools available to the organic chemist. The scope of the reaction is very broad; most functional groups can be made to undergo reduction, frequently in high yield, to any of several products. Multifunctional molecules can often be reduced selectively at any of several functions. A high degree of stereochemical control is possible with considerable predictability, and products free of contaminating reagents are obtained easily. Scale up of laboratory experiments to industrial processes presents little difficulty." Paul Rylander (1979*)** Catalytic hydrogenation is unquestionably the workhorse of catalytic organic synthesis, with a long tradition dating back to the days of Sabatier. who received the 1912 Nobel Prize in Chemistry for his pioneering work in this area. It is widely used in the manufacture of fine and specialty chemicals and a special issue of the journal Advanced Synthesis and Catalysis was recently devoted to this important topic. According to Roessler, 10–20% of all the reac_tion steps in the synthesis of vitamins (even 30% for vitamin E) at Hoffmann_La Roche (in 1996) are catalytic hydrogenations. Most of the above comments apply to heterogeneous catalytic hydrogenations over supported Group VIII metals (Ni, Pd, Pt, etc.). They are equally true, however, for homogeneous catalysts where spectacular progress has been made in the last three decades, culminating in the award of the 2001 Nobel Prize in Chemistry to W.S. Knowles and R. Noyori for their development of catalytic asymmetric hydrogenation (and to K.B. Sharpless for asymmetric oxidation catalysis). Recent trends in the application of catalytic hydrogenation in fine chemicals production, with emphasis on chemo-, regio- and stereoselectivity using both heterogeneous and homogeneous catalysts, is the subject of an excel_lent review by Blaser and coworkers.

Biocatalysis

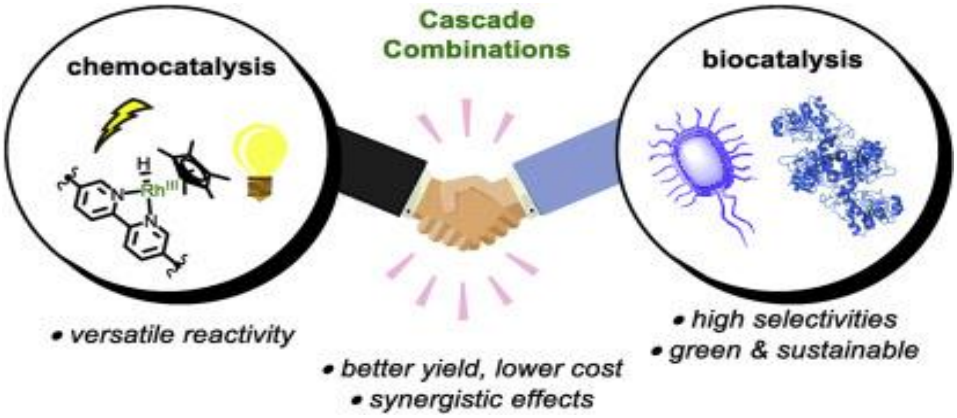


Figure no. 3: Comparision between Chemocatalysis and Biocatalysis.

Proteins (enzymes) or in a few instances nucleic acid may serve as biocatalysts (Ribozymes; some RNA molecules can catalyse the hydrolysis of RNA). These ribozymes were discovered in the 1980s. In order to catalyse all reactions in living system, scientists now understand that enzymes are fast, selective, chemical processes are needed for their survival and reproduction and successfully. These processes can also be catalysed by isolated enzymes.

1. Biocatalysis avoids the use of, and contamination of products by, scarce precious metals such as palladium, platinum, and rhodium. The long-term commercial viability of many "endangered" elements, such as various noble metals, is questionable. Moreover, the costs of removing traces of noble metals, to an acceptable level, from end products can be substantial.
2. Reactions are performed in an environmentally compatible solvent (water) under mild conditions (physiological pH and ambient temperature and pressure)
3. Reactions of multifunctional molecules proceed with high activities and chemo-, regio-, and stereoselectivities and generally without the need for functional group activation, protection, and deprotection steps required in traditional organic syntheses. This affords processes that are more step eco_nomic and more efficient in energy and raw material consumption, generate less waste, and are, therefore, both environmentally and economically more attractive than conventional routes.
4. As a direct result of the higher selectivities and milder reaction conditions, biocatalytic processes often afford products in higher purity than traditional chemical or chemo-catalytic processes. 6. Enzymatic processes (but not fermentations) can be conducted in standard multipurpose batch reactors and, hence, do not require any extra

investment, for example, for high-pressure equipment.

5. Biocatalytic reactions are conducted under roughly the same conditions of temperature and pressure, and, hence, it is relatively easy to integrate multiple reactions into eco-efficient catalytic cascade processes.[11]

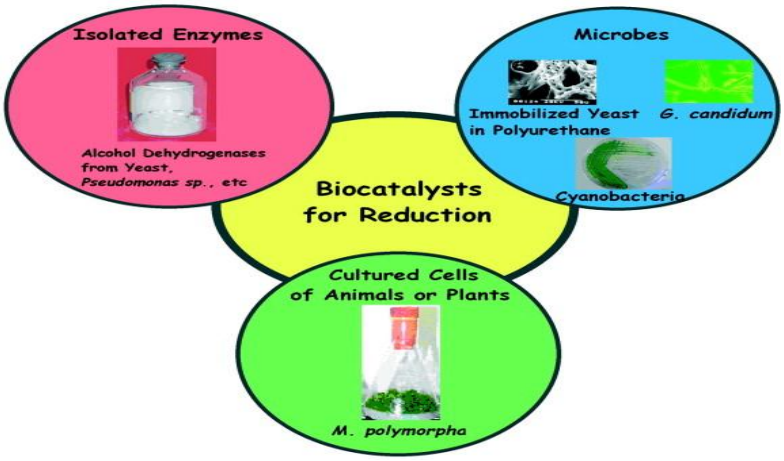


Figure no. 4: Biocatalysts for reduction.

Table no. 3: Advantages and Disadvantages of cells and enzymes as biocatalysts in comparison with chemical catalysts.

Advantages
Stereo-and regioselective.
Low temperature(0-110 degree celcius)
Low energy consumption.
Active at pH 2-12.
Nontoxic when correctly used.
Can be degraded biologically
Disadvantages: Cells and enzymes are
Unstable at high temperatures.
Unstable at extreme PH values.
Inhibited by some metal ions.

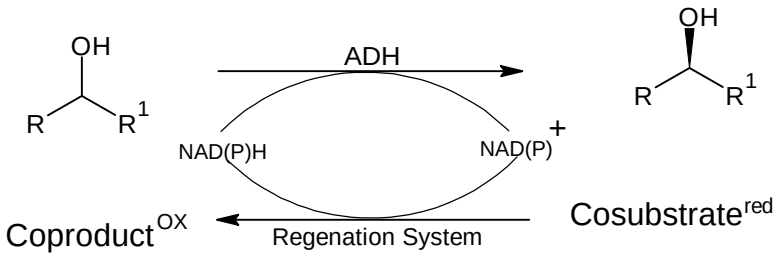
A) Reduction of C=O Bonds

1. Reduction of ketone to alcohols

1. ADHs are the catalysts of choice for the stereoselective reduction of ketones to alcohols. Systems utilising other enzyme classes such as ene reductases or Baeyer–Villiger monooxygenases are still at an early stage. ADHs, how_ever, have been investigated for more than four decades now and a vast variety of enzymes (and variants) are available. Hence, also the industrial interest in ADH catalysis is steadily growing. A selection of ADH-derived alcohols. Pleasingly, ADH-catalysed ketor_eduction reactions are

increasingly performed at significant substrate loadings, resulting in preparatively relevant product concentrations in the molar range.

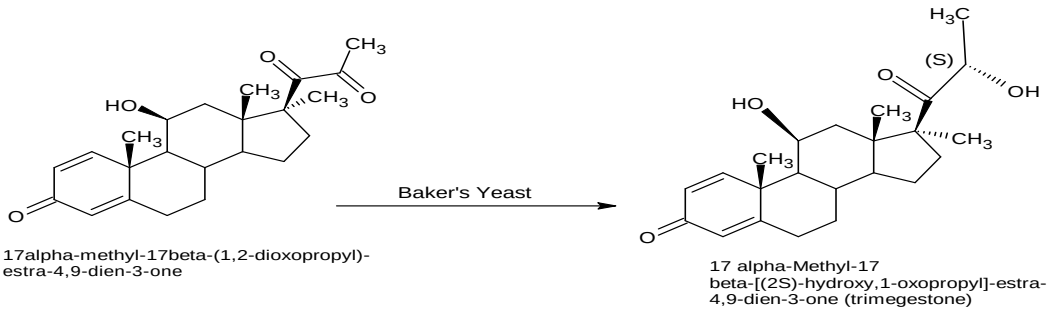
Selection Of ADH-Catalysed Stereoselective Ketone Reductions :-



Reaction 2

The biocatalytic asymmetric reduction of ketones to alcohols has been of great interest to organic chemists over many decades. A large range of reactions with an even larger number of ketone substrates carrying a variety of substituent functional groups has been developed. Microbial reduction of phenylglyoxylic acid to mandelic acid by yeast has been found more than a century ago. The investigation of the absolute stereochemical course of hydride transfer to carbonyl groups of decalin derivatives in reductions by microorganisms like Curvularia falcata has led Vladimir Prelog to rationalize these numerous experimental facts by a simple scheme connecting the substrate orientation in the plane of the carbonyl group with the spatial hydride transfer relative to this plane, later called Prelog's rule for the absolute configuration of the obtained chiral alcohols. Prelog's rule states that the alcohols that were formed by the microbial reductions studied had all the (S)- configuration and explains this fact by the pro-R hydride transfer from the cofactor to the Re-face of the carbonyl group, a property not only of the microbial reducing agents used but also of the oxidoreductase enzymes. The later discoveries of microorganisms and alcohol dehydrogenases, for example, from Mucor javanicus, Pseudomonas sp., and Lactobacillus kefir, with the pro-R hydride transfer from the cofactor to the opposite Si-face of the carbonyl group leading to alcohols with the (R)-configuration are described to have anti-Prelog enantioselectivity. The catalytic asymmetric reduction of prochiral cyclohexanones to their corresponding axially chiral (R)- and (S)-alcohols is a reduction where chiral transition metal catalysts fail, but where excellent enantioselectivity has been achieved with alcohol dehydrogen_ases and the reversal of enantioselectivity by directed evolution. The form of the biocatalysts used has varied widely from whole cells like baker's yeast, Geotrichum candidum or isolated enzymes thereof to the isolated animal-derived enzymes like horse liver

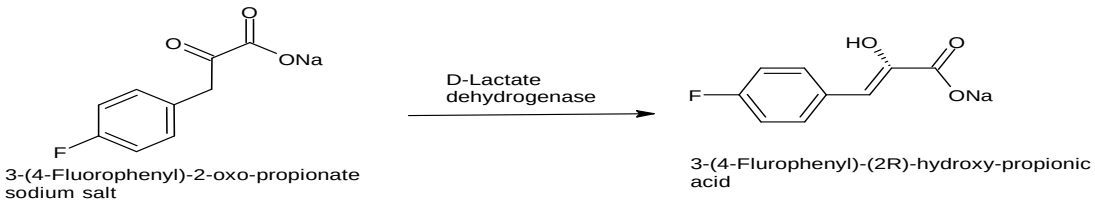
alcohol dehydrogenase (HLADH) and isolated enzymes from microorganisms like Saccharomyces cerevisiae,[44] Thermoanaerobium brockii, and L. kefir. The progress in the development and production of recombinant and engineered alcohol dehydrogenases or ketoreductases. has accelerated its use in laboratory and industrial-scale processes. A recombinant short-chain alcohol dehydrogenase RasADH from Ralstonia sp. overexpressed in Escherichia. Biocatalytic Reductions of C¼O Double Bonds j 3 coli has been shown to reduce ketones with two bulky substituents to the corresponding optically highly enriched alcohols with very high stereoselectivity according to Prelog's rule.



17alpha-methyl-17beta-(1,2-dioxopropyl)-estra-4,9-dien-3-one

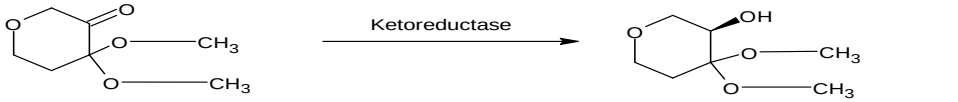
17 alpha-Methyl-17 beta-[(2S)-hydroxy,1-oxopropyl]-estra-4,9-dien-3-one (trimegestone)

Reaction 3



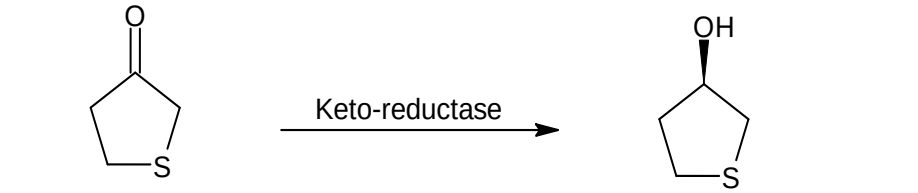
3-(4-Fluorophenyl)-2-oxo-propionate sodium salt

3-(4-Flurophenyl)-(2R)-hydroxy-propionic acid



(R)-4,4-Dimethoxytetrahydro-2H-pyran-3-ol

Reaction 3

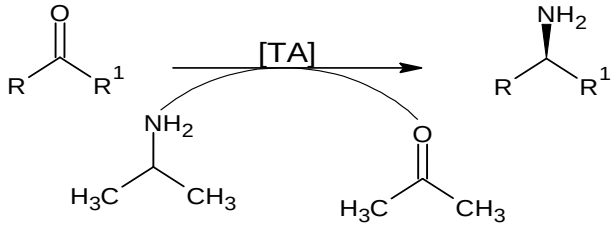


Tetrahydrothiopene-3-one

(R)-Ttetrahydrothiopene-3-ol

Reaction 4

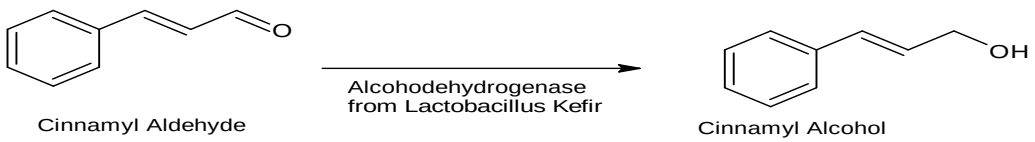
To amines



Reaction 5

2. Reduction of aldehyde to alcohol[11,12]

Biocatalytic reductions of furfural to furfuryl alcohol by yeast have been first described more than a century ago and continue to attract interest even today despite the efficient industrial chemo –catalytic reduction processes one area where biocatalytic reduction are of particular interest in the flavor and fragrance industry and efficient biocatalytic process for the reduction of cinnamyl aldehyde to the aroma chemical cinnamyl alcohol has been developed using recombinant whole cells overexpressing an alcohol dehydrogenase from L.Kefir and a glucose dehydrogenase from Thermoplasma acidophilum.



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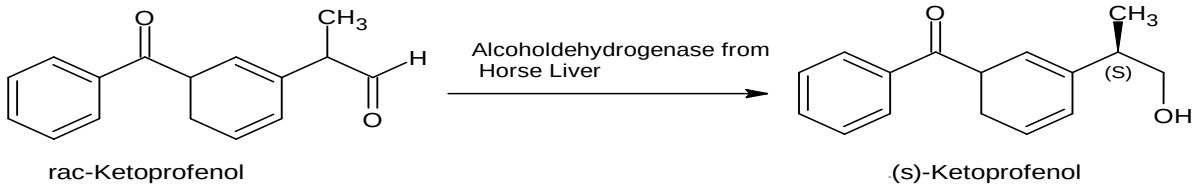

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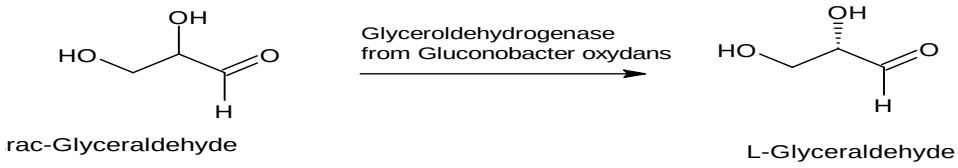
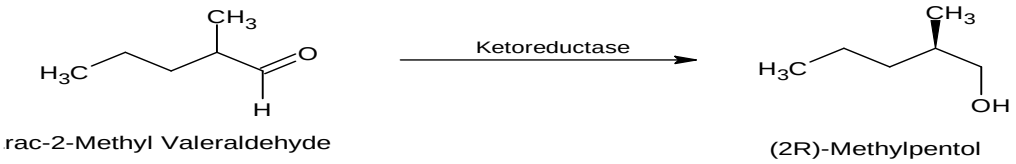


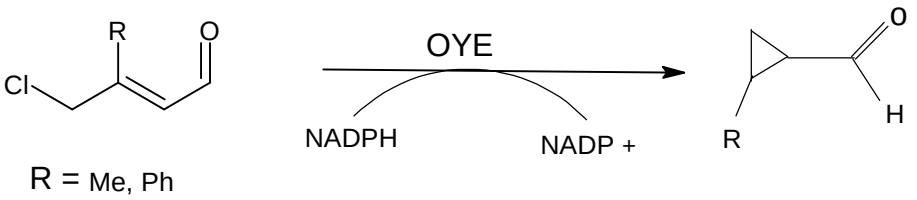


Reaction 8

B) Reduction of C-C multiple bonds[11,12]

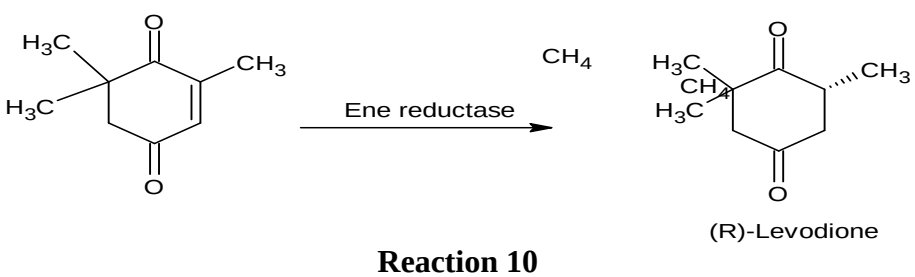
1. Biocatalytic reduction of C=C Double bonds

OYEs are flavin mononucleotide (FMN)-dependent oxidoreductases that catalyse the reduction of a,b-unsaturated compounds with an electron-withdrawing group (EWG) comprising either an aldehyde, ketone, acid, ester, nitro or nitrile group. The appeal of OYEs in synthetic chemistry is their ability for asymmetric hydrogenation, providing routes to chiral a-substituted and/or b-substituted compounds, often with exquisite enantioselectivity. As the hydrogenation occurs in a trans fashion, the products are complementary to the well-established non-enzymatic cis hydrogenation .Moreover, directed evolution studies have been successful in producing enzymes with opposite facial selection of the flavin ("flipped" binding mode), yielding the opposite enantiomers



Reaction 9

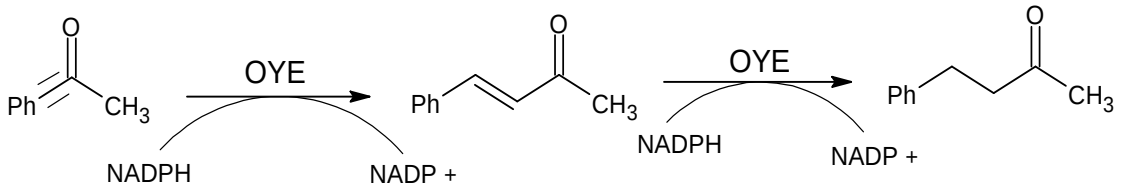
Catalytic asymmetric reductions of carbon–carbon double bonds can be done in a cis_or trans-fashion and generate up to two new chiral centers. The biocatalytic asymmetric reduction of carbon–carbon double bonds occurs with exclusive trans-stereospecificity except for some rare cases of cis-stereoselectivity. Biocatalytic reductions are therefore complementary to the high standard of transition 1 Development of Sustainable Biocatalytic Reduction Processes for Organic Chemists metal-catalyzed cis-hydrogenation and an increasing number of successful syntheses have been achieve over the last few years using cloned enoate reductases making this an established methodology with many benefits selected C¼C double The oxygen-stable enoate reductases 12-oxophytodienoate reductase isoenzymes OPR1 and OPR3 from tomato and the "old yellow enzyme" homolog YqjM from B.



Reaction 10

2. Biocatalytic reduction of c triple bond[11,12]

Now a days the only biocatalysis reduction alkyne was that of 4-phenyl – 3 –butyn-2-one by ERS from the OYE family to form only corresponding trans alkene isomer. as these OYEs also reducef c=c double bonds , the alkene intermediate was simultaneously reduced to 4-phenyl – 2-butanone.



Reaction 11

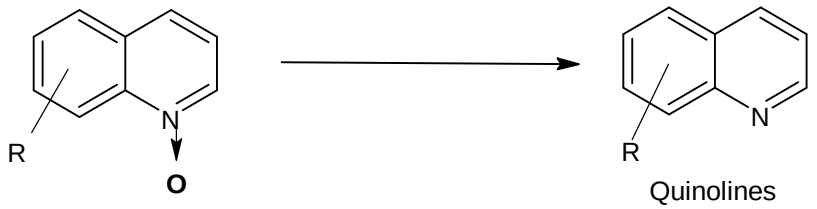
C) Biocatalytic reduction of C-X[10,11,12]

Nature offers enzymes capable of reductive deoxygena_tion of C_-OH groups.In reactions catalysed by ribonucle_otide reductase, cobalamin-generated thiyl radicals perform H-atom abstraction and overall reduction of the diol thioredoxin serves as reductant. This appealing reaction, however, has so far not received much interest in the context of preparative biocatalysis. This is also true for further cobalamin (vitamin B12)-dependent enzymes such as a range of dehalogenases catalysing the selective reductive dehalogenation of a broad range of compounds. While the latter are rather well-known in the context of environmental biotechnology, they are practically unknown in the biocatalysis community. Reductive dehalogenation has been reported with a highly reduced, thermophilic CYP119 from Sulfolobus solfataricus and by using reductive dehalogenases (cobala_min-dependent) from some dehalogenating microbes such as Dehalobacter or Dehalococcus. Hence, enzymatic reductive deoxygenations and dehalogenations remain a highly prom_ising, yet to be explored new frontier of biocatalysis! More straightforward are indirect, cascade reactions, which overall entail a reductive deamination or deoxygenation. A cascade comprising amino acid ammonium lyases and ene reductases for example, results in an overall reductive deamination of amino acids.

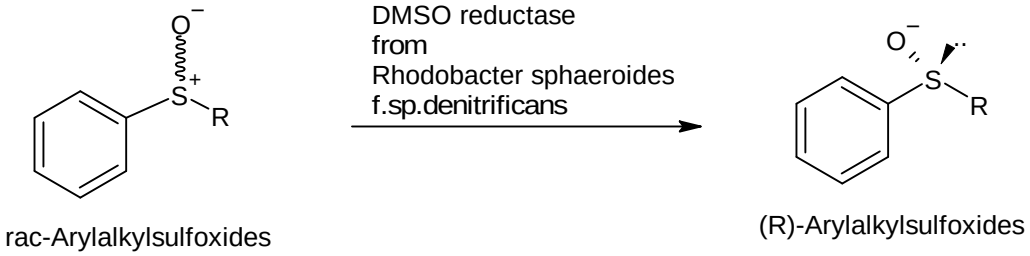
D) Biocatalytic deoxygenation reaction[7,8,10]

A selection of biocatalytic deoxygenation reactions The reducing power of baker's yeast in an ethanol–water mixture and sodium hydroxide at 60_C has been found effective for the rapid and selective reduction of a series of N-oxides like aromatic and heteroaromatic N-oxide compounds DMSO reductase from Rhodobacter sphaeroides f. sp. denitrificans

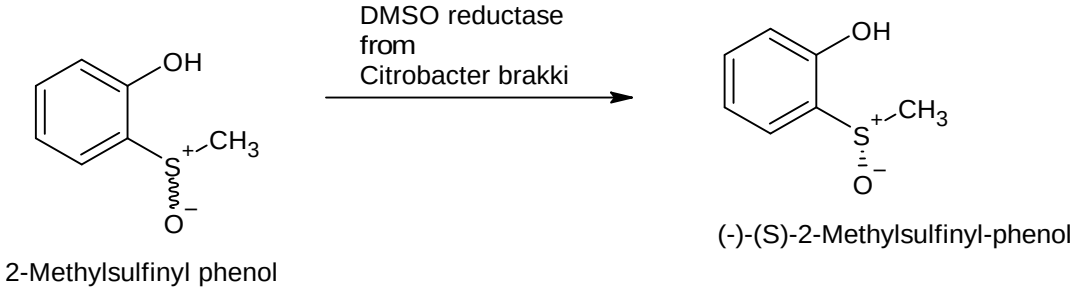
catalyzed the (S)-enantioselective reduction of various sulfoxides and enabled the resolution of racemic sulfoxides for the synthesis of (R)-sulfoxides with >97%. Purified dimethyl sulfoxide reductase from Rhodobacter capsulatus resolved a racemic mixture of methyl p-tolyl sulfoxide by catalyzing the reduction of (S)-methyl p-tolyl sulfoxide and gave enantio_merically pure (R)-methyl p-tolyl sulfoxide in 88% yield, while whole cells of E. coli, 1Development of Sustainable Biocatalytic Reduction Processes for Organic Chemists Proteus mirabilis and Proteus vulgaris reduced the same sulfoxide with opposite enantioselectivity. The resolution of racemic alkylaryl sulfoxides and thiosulfi_nates by dimethyl sulfoxide reductase from the anaerobic bacterium Citrobacter braakii gave the corresponding enantiopure alkylaryl sulfoxides and thiosulfinates. Recombinant ribonucleoside triphosphate reductase from Lactobacillus leichman.nii has been used for the 20 -deoxygenation of ATP to prepare 20 -deoxyadenosin_triphosphate with a high degree of conversion and high yield using 1,4-dithio-DL_threitol as artificial reducing agent for the ribonucleoside triphosphate reductase.



Reaction 12



Reaction 13



Reaction 14

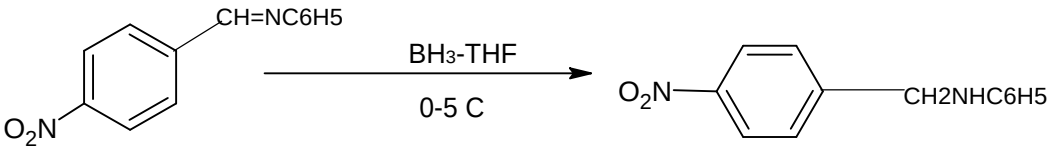
Reduction of organic compounds

A) Reduction of organic nitrogen compounds

A variety of organic functional groups containing a multiple bonded nitrogen are reduced with boran reagents most of the efforts has been directed towards the reduction of imines, oximes, nitro derivatives and nitriles.

1. Imines

The reduction of Schiff bases with BH3-THF proceeds under very mild conditions giving excellent yields of the corresponding amines. This reduction and similar reduction of Schiff bases can also be carried out the milder reducing agent, sodium borohydride. Consequently the boran reagents would appear to be of limited utility for imine reductions.

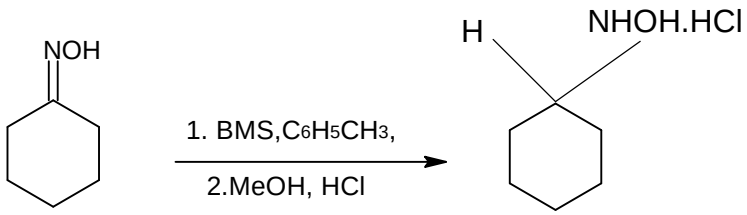


Reaction 15

2. **Oximes**

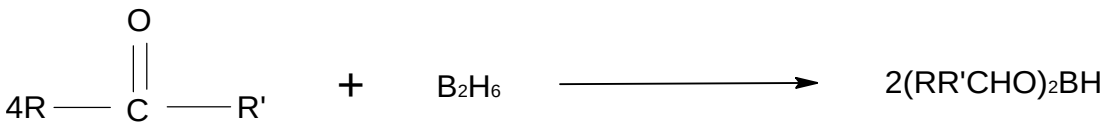
The reduction of the readily available aldoximes and ketoximes with BH3-THF provides a facile and convenient synthesis of N-monosubstituted hydroxylamines.

BMS can also as the reducing agent and offers as an advantage,a much simpler isolation procedure for example.



Reaction 16: Reduction of organic oxygen compounds.

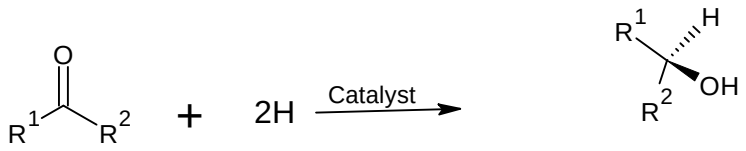
1) Aldehyde and Ketones



Reaction 17

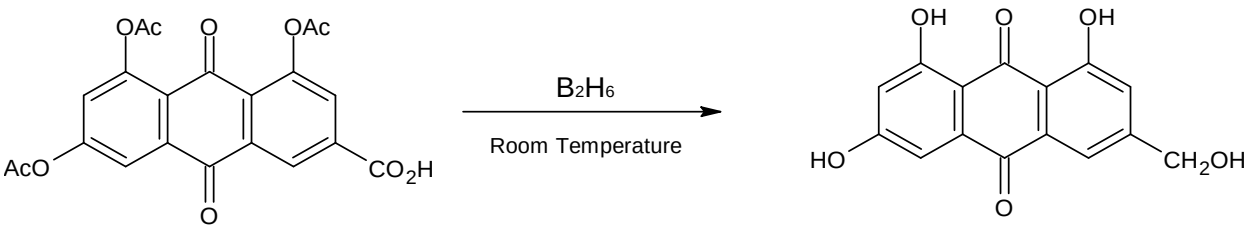
Excess diborane reacts readily at room temperature with aldehydes and ketones to yields the corresponding dialkoxy derivatives of borane.

2) Asymmetric ketone reduction



Reaction 18

A) Quinones



A reaction **B reaction**

Reaction 19

The slow reaction of diborane with the anthra-quinone structure has been utilized to achieve the selective reduction of a and b in 60% yield by avoding the presence of excess reagent.

DISCUSSION

1. Are biocatalytic reduction economically fessible

Yes. To assess the economic feasibility, many factors have to be taken into account. Amongst them the cost contribution of the (bio) catalyst to the product as well as the reaction costs are discussed briefly. To assess the cost contribution of the biocatalyst to a final product, the production costs and the performance of the catalyst need to be taken into account. Tufvesson and Woodley have pointed out the dependency of the production costs of whole cells and enzymes on the scale of the fermentation. The production costs for industrial (non_purified) enzymes range between 250 and 1000 Ek**).** As a rule of thumb, to achieve economic feasibility, an enzyme should perform at least 25 000 catalytic cycles for the production of pharmaceuticals and more than 5 000 000 catalytic cycles for the production of bulk chemicals, respectively. Similar (but lower) numbers can also be calculated for whole-cell biotransformations. Next to the biocatalyst of course other factors contribute to the production costs, such as space–time yield and the effort needed for product isolation.

2. Are biocatalytic reactions green?

Possibly. Today, the statement "biocatalysis is intrinsically green" has become a mantra for many researches. arguments such as the mild reaction conditions, the renewable and biodegradable character of the catalysts and the generally aqueous reaction conditions are brought forward to substan_tiate the "greenness" of biocatalytic reactions. These argu_ments, however, are rather superficial and generally lack any quantitative substantiation. First of all, researchers should be aware that no chemical transformation (including biocatalytic reactions) is green, as in all cases resources are consumed and waste is generated, thereby putting a burden on the environment. We believe that a given reaction of methodology can be greener than another reaction. Such a comparison, however, should be based on quantitative data rather than on general statements. Com_parative full life cycle assessments (LCA) represent the "gold standard" for such comparisons, but are usually time-inten_sive due to the large data basis required for a meaningful comparison. Sheldon_E-factorand possibly its derivative, the E+-factor, taking energy-related CO2 emissions into account,represent an acceptable alternative for the preparative chemist.

CONCLUSION

When preparing the chemical experiment, we werw inspired by the available literature describing the preparations of the chiral alcohols from to prochiral ketones catalyzed, aldehyde to ketones, C-X bonds, etc.

And other chemicals, we carefully focused on the choice of appropriate ketone and organic solvents. which are financially available and in terms of safety. The widely accepted and complementary a more informative knowedge. Biocatalysis offers bnumerous benefits in the context. Reactions are conducted under mild conditions employing a catalyst that biocompatible and biodegradable and derived from renewable resources, thus avoiding the scarcity and associated with uses of noble metal catalysis.

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