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Review article

Using algae cells to drive cofactor regeneration and asymmetric reduction for the synthesis of chiral chemicals

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ABSTRACT

Asymmetric reduction of prochiral ketones via biocatalysis is the most effective method for the synthesis of chiral alcohols. The industrial biocatalytic reduction process requires additional co-substrates and enzymes, e.g., glucose and glucose dehydrogenase, to regenerate reductive cofactors, such as nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH), for efficient substrate conversion and product yield. Thus, increasing the cost in reaction and downstream treatment. Recently, algae cells, due to a combination of microorganism-like properties (rapid growth and high density culture) and plant-like properties (highly active photosynthesis), have attracted much attention as novel host cells in industrial biocatalysis. Particularly, autotrophic photosynthesis in algae is capable of regenerating NADH and NADPH rapidly, eliminating the requirement of additional enzymes and co-substrates for cofactor regeneration in normal biocatalytic processes. Recently, a variety of algae species, such as cyanobacteria, green algae, diatoms, chrysophytes, and red algae, have been applied in asymmetric biocatalysis. Herein, various asymmetric reduction reactions performed by different type of algae cells have been reviewed, and methods for improving the reaction efficiency have been discussed. We aim to attract algae microbiologists and chemists to push forward the study of algae as biocatalytic cell factories for value-added industrial chemical production in the future.

1. Introduction

The most efficient method for synthesizing chiral alcohol is to catalyze the asymmetric reduction of prochiral ketones. However, chemical catalysis is hindered by some disadvantages, such as harsh reaction conditions, low stereo-selectivity, toxic and complex process of chiral catalysts, high cost, and so on [1]. Therefore, an efficient, economic, and environmentally friendly catalyst is urgently needed. Asymmetric biocatalysis is an environmentally friendly preparation method that has become one of the most promising methods for preparing chiral compounds [2,3].

Microorganisms are the most commonly used organisms in biocatalytic asymmetric reduction, in which carbonyl reductases or alcohol dehydrogenases heterologous expressed in microbial cells are used to perform biocatalysis [4,5]. The asymmetric reduction of carbonyl groups usually requires reductive cofactors. At present, bacteria [6], yeast [7], mold [8], and other microorganisms are typical host cells used to catalyze asymmetric reduction reactions in the industrial production of chiral alcohols. Cofactors in active cells can regenerate and recycle through cell metabolism. Given its high cost, cofactors, such as NADH and NADPH, must be converted from its oxidation form for recycling [9].

To date, various strategies for cofactor recycling have been developed in biocatalysis. The most common method involves the addition of a second enzyme and a sacrificial substrate. For example, formate dehydrogenase (FDH), glucose dehydrogenase (GDH) and alcohol dehydrogenase (ADH) (Fig. 1) are frequently used in industrial bioconversion [10]. Alternatively, a second substrate can be used alone in regeneration and production reactions that are performed by the same enzyme. Isopropanol and acetone are common co-substrates for reactions that are catalyzed by alcohol dehydrogenases. In addition, internal regeneration of the cofactor can be achieved using cascade enzymatic reactions. All enzymes that have been shown to be active with these simple biomimetics, so far, have a second cofactor, tightly bound to the enzyme, flavin adenine mononucleotide (FAD) or flavin mononucleotide (FMN), which reportedly facilitate hydride transfer [10]. There are four main types of cofactor regeneration: chemical method, enzymatic chemical method, electrochemical method and

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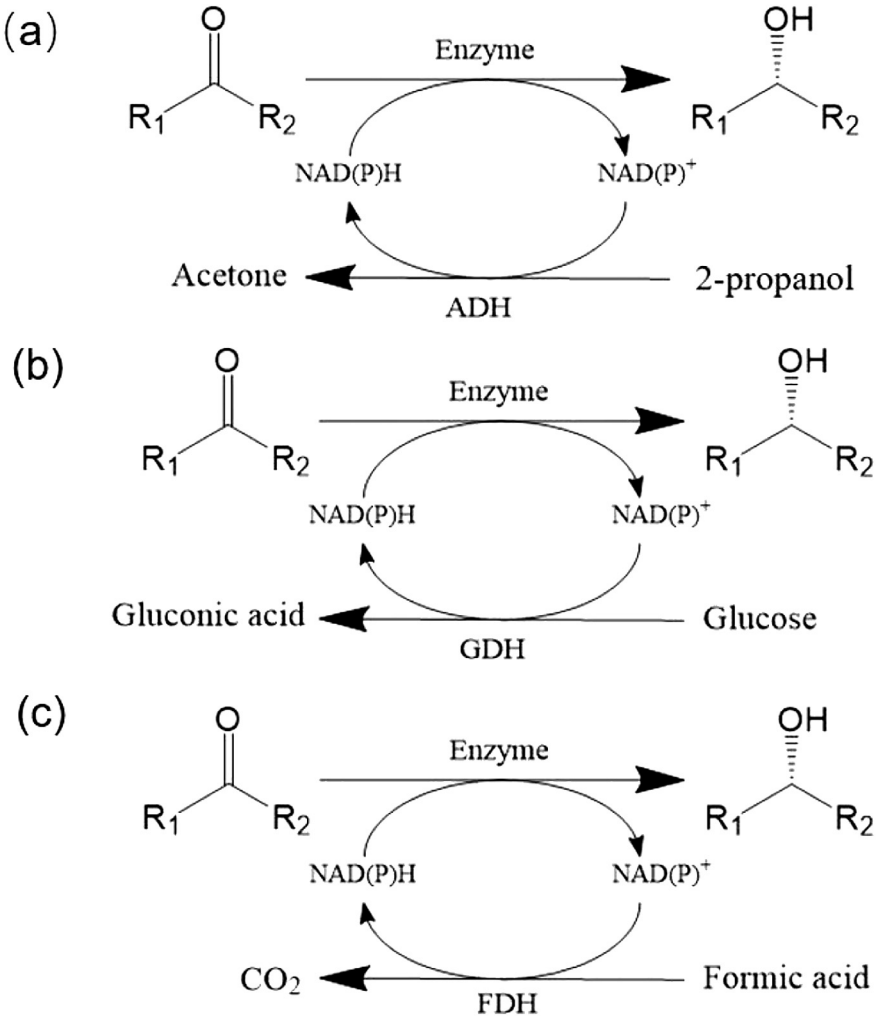

Fig. 1. Regeneration of NAD (P) H by enzyme methods developed in living cells. (a) Alcohol dehydrogenase (ADH); (b) glucose dehydrogenase (GDH); (c) formate dehydrogenase (FDH).

Table 1
Advantages and disadvantages of four strategies for cofactor regeneration.

Method	Advantages	Disadvantages
Enzymatic	Environmentally friendly and high selectivity	Enzyme instability, high enzyme cost, complexity of product isolation
Chemical	Use of H_2, cofactor analogues as reducing	Low selectivity, pollution emissions, low atom cofactor
Electrochemical	Use of clean, renewable electrical energy broad	Low selectivity, electrode fouling, mediator dependent
Photochemical	Use of clean, abundant, cheap solar energy broad applications	Low efficiency, photosensitizer and mediator dependent

photochemical method. All of these cofactor regeneration methods were applied in catalyzing the asymmetric reduction of chiral carbonyls [11]. The advantages and disadvantages are summarized in Table 1.

One method is to use light to regenerate the cofactor, add the auxiliary substrate, add the cofactor regeneration system, and so on [11]. Researchers have highlighted the advantages of plants with abundant source, low cost, high enantiomer selectivity, and the environmental friendliness of the reaction process [12,13]. However, studies on biological catalysts using plant cells have mostly been conducted on isolated cells and tissues. These isolated tissues and cells have short survival time, and their enzymes are vulnerable to inactivation, which is unconducive for industrial applications. The longer growth cycle of plants has further hindered the possibility of large-scale applications.

Although the use of whole-cell microorganisms as the biocatalysts has been widely reported in literature, green strategies with efficient co-factor regeneration for chiral compound production have yet to be developed. NADPH is an important reductive cofactor involved in cell energy and carbon metabolism. Its production is particularly related with the light reaction of plants and algae through photosynthesis, which is the most natural and efficient biocatalytic system on Earth. In the light reaction of plants and algae, two light system response center pigments (P700 and P680) absorb light and produce high-energy electrons (photochemical reaction), which launches a cascade electron transfer and eventually passes electrons to $NADP^+$ for regenerating NADPH through the photosynthetic chain [14].

Algae can use CO_2 and light for photosynthesis to synthesize the metabolites needed for growth. This photosynthesis system can be used to drive cofactor regeneration without additional enzymes and co-substrates, making it a promising green strategy for asymmetric biocatalysis (Fig. 2). Many algae species can catalyze asymmetric reduction reactions, displaying high stereo-selectivity and reaction rate, low