Abstracts

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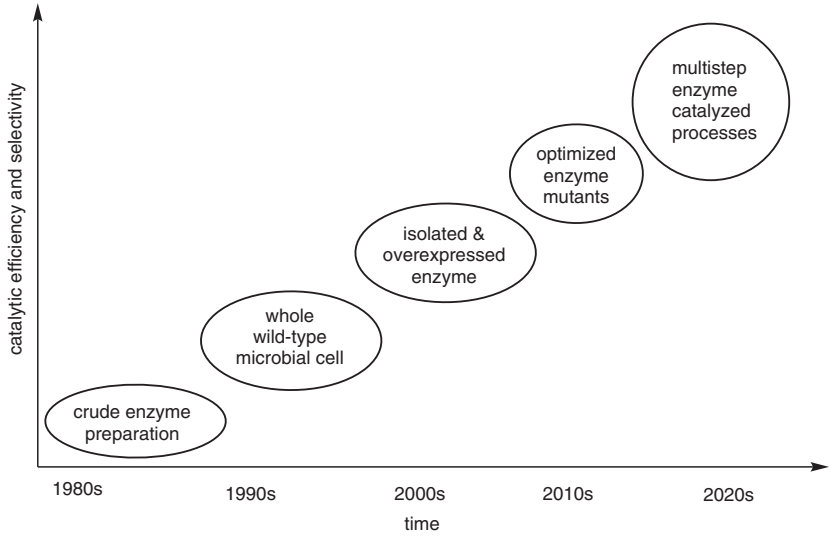
1.1.1 Historical Perspectives: Paving the Way for the Future

S. Servi, D. Tessaro, and F. Hollmann

This chapter describes the evolution of modern biocatalysis, focusing on the application of both whole-cell biocatalysts and isolated enzymes in organic synthesis. Milestones in this process are the application to β-lactam and amino acid chemistry, the preparation of chiral synthons as single enantiomers for the synthesis of pharmaceutical intermediates, the modification of carbohydrates and the synthesis of value-added products from lipids. The application of hydrolytic enzymes (lipases, proteases, esterases, and nitrile hydratases) has evolved in time toward more complex enzymatic systems such as oxidoreductases involving cofactor recycling or aminotransferases (transaminases) leading to the formation of chiral amines. The recently developed techniques of molecular biology and directed evolution toward the preparation of better enzymatic catalysts are dramatically improving the availability and efficiency of the enzymes and thus significantly increasing the role of biocatalysis in organic synthesis.



Keywords: chiral synthons · whole-cell biocatalysis · hydrolytic enzymes · oxidoreductases · cofactor recycling · directed evolution · cascade biocatalysis

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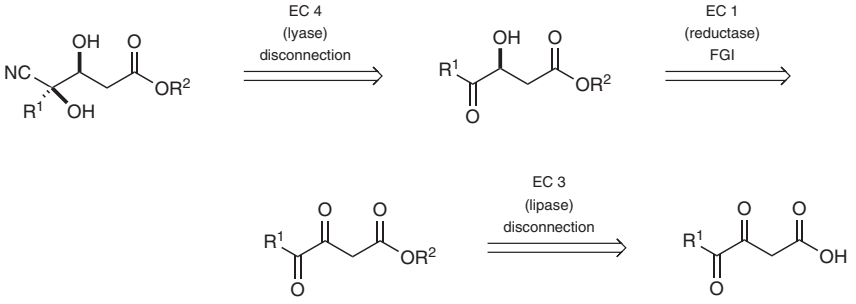
1.1.2 Enzyme Classification and Nomenclature and Biocatalytic Retrosynthesis

A. Liese and L. Pesci

The enzyme nomenclature system is based on six different enzyme classes, defined by the type of chemical reaction catalyzed; hence, for a given synthetic step, it is possible to plan an enzymatic transformation (even thinking in a retrosynthetic manner) for the synthesis and/or modification of a certain compound. With this premise, the possibility of combining the methods of traditional chemical retrosynthesis with biocatalytic transformations provides an enormous potential benefit for organic chemists, including the use of mod-

ern feedstocks and "sustainable chemistry" criteria. In this chapter, enzyme nomenclature is discussed, and the related information is used as a basis for applying biocatalytic retrosynthetic analysis to several classes of organic molecules. Some key examples are provided in order to appreciate the real potential of biocatalytic retrosynthesis, especially when used in combination with more traditional chemical strategies.



Keywords: enzyme nomenclature · reaction types · organic synthesis · retrosynthesis · green chemistry

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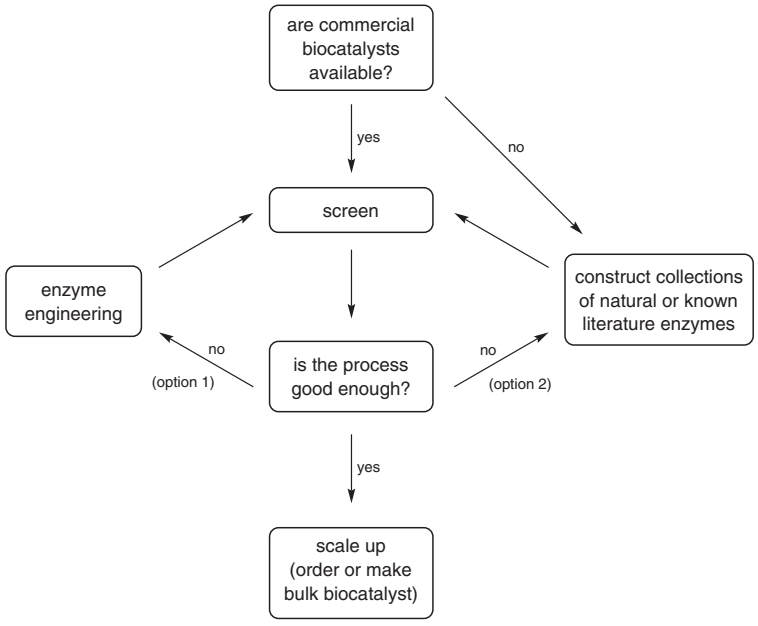
1.1.3 Enzyme Sources and Selection of Biocatalysts

R. Lauchli and D. Rozzell

Biocatalysts can be obtained from commercial suppliers, natural organisms, or from enzyme engineering efforts. This chapter discusses the sources from which one can obtain biocatalysts, and presents strategies for efficiently obtaining enzymes that meet the demands of medium- to large-scale chemical processes.



Keywords: enzyme catalysis · catalysts · genomics · green chemistry

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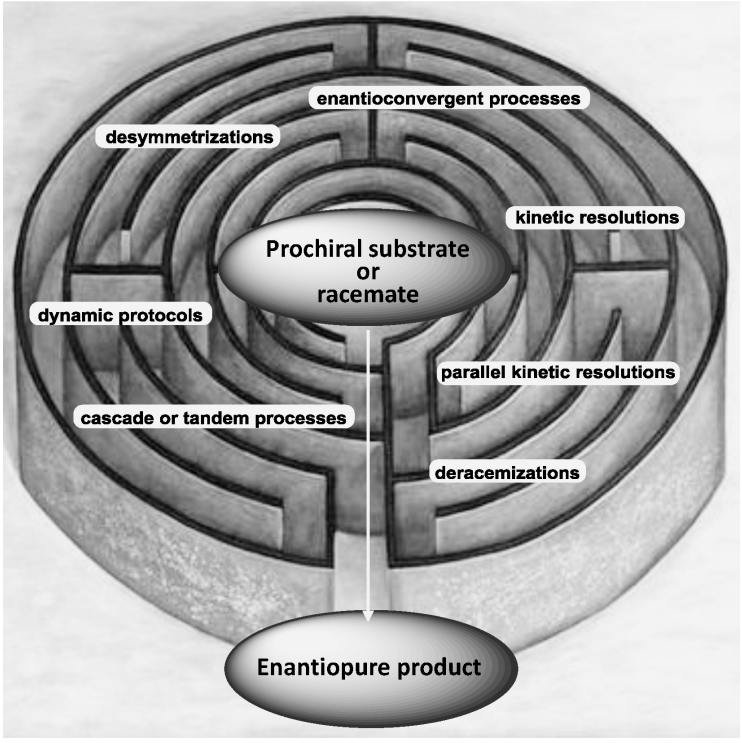
1.2 Strategies and Methods in Biocatalysis

A. Díaz-Rodríguez and I. Lavandera

The use of biocatalysts in organic synthesis and, particularly, in the preparation of optically pure chemicals offers major advantages in terms of selectivity, efficiency, safety, and sustainability. Thus, research groups are becoming more interested in biocatalysis as a tool for challenging synthetic routes. Herein we focus on the different strategies and methods that chemists have designed in order to obtain enantioenriched compounds starting from prochiral or racemic derivatives using enzymes or whole cells as catalysts. In the first part of the chapter, enzymatic desymmetrizations are presented, followed by other established systems dealing with racemates to attain a single or two enantiopure derivatives in the same reaction vessel. Then, the preparation of optically pure compounds in excellent yields and enantiomeric excesses by means of deracemization techniques is discussed. Finally, some recent examples where the combination of enzymes with other (bio)catalysts has provided high-added-value targets are shown.



Keywords: desymmetrizations · kinetic resolutions · parallel kinetic resolutions · (cyclic) deracemizations · enantioconvergent processes · dynamic kinetic resolutions · dynamic kinetic asymmetric transformations · concurrent catalysis · cascade reactions · tandem reactions · one-pot reactions · multistep catalysis

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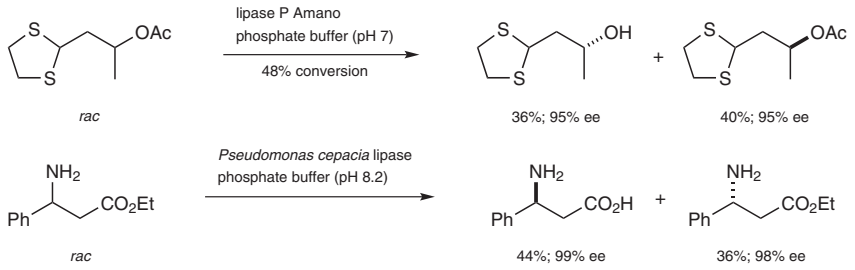
1.3.1 Resolution of Alcohols, Acids, and Esters by Hydrolysis

M. Bertau and G. E. Jeromin

This chapter reviews the use of enzymes, principally esterases and lipases, as catalysts for the resolution of racemic carboxylic acid derivatives via hydrolysis. The resolution of esters of chiral primary, secondary, and tertiary alcohols, as well as diols, are examined. Bio-

catalytic hydrolytic methods for the desymmetrization of prochiral substrates and *meso*-compounds are also considered.



Keywords: carboxylic acids · carboxylic esters · alcohols · diols · resolution · esterase · lipase · hydrolysis · *meso*-trick · desymmetrization · dynamic kinetic resolution · substrate engineering · substrate design

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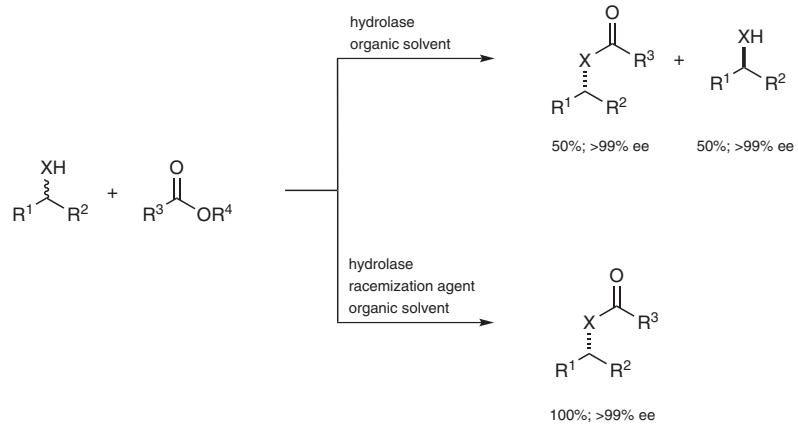
1.3.2 Resolution of Alcohols, Amines, Acids, and Esters by Nonhydrolytic Processes

M. Rodríguez-Mata and V. Gotor-Fernández

The use of hydrolases has become a conventional process in organic synthesis, not only for the preparation of optically pure compounds, but also for regio- and chemoselective processes. Their utility for selective transformations under mild reaction conditions make hydrolases attractive catalysts for performing certain transformations that are difficult to achieve by nonenzymatic strategies. Nowadays, many companies use lipases for the preparation of high-added-value compounds and pharmaceuticals because of the advantages of hydrolase-catalyzed processes, which include cost and environmental benefits. Their commercial availability, lack of cofactor dependency, and activity in both aqueous and organic media has allowed the development of asymmetric transformations which are summarized in this chapter. After a brief general introduction discussing the potential of hydrolases in organic synthesis, asymmetric reverse hydrolytic processes are analyzed, substituting the conventional hydrolase nucleophile, water, for other species such as alcohols, amines, esters, or ammonia. The kinetic resolution and dynamic kinetic resolution reactions of alcohols and amines are presented, using esters or carbonates for the production of esters, amides, and carbamates in optically active form. Finally, the resolution of carboxylic acids or esters is described via less-employed interesterification, aminolysis, and ammonolysis processes.



Keywords: acylation · alcohols · alkoxycarbonylation · amines · aminolysis · ammonolysis · asymmetric synthesis · carbonates · esters · hydrolases · interesterification · kinetic resolution · lipases · transesterification

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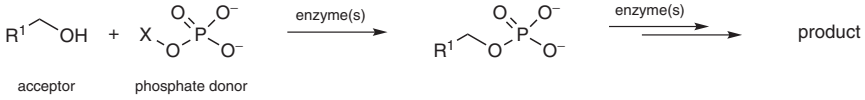
1.3.3 Transphosphorylation

R. Wever, L. Babich, and A. F. Hartog

The transfer of phosphoryl groups from one compound to another is one of the most important mechanisms by which cell function is controlled and orchestrated. Phosphorylated compounds find several applications such as in prodrugs or drugs, flavor enhancers, and key intermediates in the synthesis of pharmaceuticals. Regiospecific introduction of a phosphate group into a biomolecule via chemical methods is a challenge, particularly when the molecule has several potential phosphorylation sites or is labile. Protection and deprotection steps have to be introduced in the synthetic procedure, leading to waste and poor yields. Enzymes are able to catalyze reactions in a regio- or stereoselective manner and to date many synthetic methods and routes using enzymes have been developed. In particular, enzymatic cascade reactions in one pot are being used either in one step or multiple steps. These cascades make use of (parts of) naturally occurring biochemical pathways in which high-energy phosphorylated compounds drive the reaction to the desired product. This chapter describes the more classical enzymatic methods as well as the more recently developed cascade reactions to synthesize (phosphorylated) compounds.



Keywords: transphosphorylation · kinases · adenosine triphosphate · phosphoenol pyruvate · acetyl phosphate · glucose 6-phosphate · fructose 1,6-bisphosphate · glycerol phosphate · dihydroxyacetone phosphate · pyrophosphate · polyphosphate · glyceraldehyde 3-phosphate · phosphorylated nucleosides · inosine monophosphate · phosphorylated carbohydrates · alkaline phosphatase · aldolases · acid phosphatases · phosphorylases · enzymatic cascade reactions

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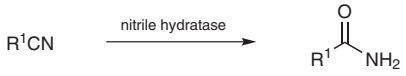
1.4.1 Hydrolysis of Nitriles to Amides

Y. Asano

Nitrile hydratase (NHase; EC 4.2.1.84) catalyzes the hydration of nitriles to form amides. The reaction catalyzed by nitrile hydratase is strikingly fast and versatile and a wide range of nitriles, including aromatic and arylalkyl nitriles, α- and β-substituted nitriles, and aminonitriles can be hydrated to the corresponding amides. Although nitrile hydratase generally has low stereoselectivity, its use in conjunction with highly stereospecific amidases provides a valuable route for the stereoselective synthesis of carboxylic acids. The powerful nature of nitrile hydratase has had a huge impact on the progress of applied microbiology, enzyme engineering, and enzyme-catalyzed organic synthesis. The best-known applications of nitrile hydratase on an industrial scale are the production of acrylamide and nicotinamide from acrylonitrile and pyridine-3-carbonitrile, respectively.

This chapter provides an overview of the current scope of nitrile hydratase mediated reactions and focuses on whole-cell biotransformations.



Keywords: nitriles · amides · nitrile hydratase · hydrolysis · hydration · chemoselectivity · carboxylic acids · kinetic resolution · desymmetrization · whole-cell biotransformations · aldoxime–nitrile pathway

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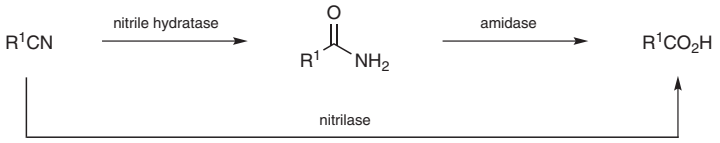
1.4.2 Hydrolysis of Nitriles to Carboxylic Acids

L. Martínková and A. B. Veselá

The synthesis of carboxylic acids from nitriles utilizes two pathways of nitrile biotransformations: direct hydrolysis by nitrilase and bienzymatic hydrolysis by nitrile hydratase and amidase. General procedures consist of using whole cells or isolated enzymes as catalysts in aqueous media with a small fraction of organic cosolvent. These methods afford a number of products that are often difficult to prepare by chemical means such as 3-oxoamides, cyano carboxamides and cyano carboxylic acids, enantiopure 2- and 3-substituted carboxylic acids and carboxamides, and enantiopure (hetero)cyclic carboxylic acids and carboxamides. Stereochemistry is mainly recognized by amidase, but in some cases also by nitrilase and nitrile hydratase. Nitrile hydrolysis has also been employed in chemoenzymatic and multienzymatic methods such as the synthesis of aromatic and heterocyclic amides from aldehydes, the synthesis of enantiopure 2-hydroxy acids from aldehydes, the synthesis of enantiopure 3-hydroxy acids from 3-oxonitriles, and the synthesis of cyclophellitols from benzo-1,4-quinone.



Keywords: nitriles · carboxylic acids · carboxamides · aldehydes · nitrilase · nitrile hydratase · amidase · stereochemistry · chemoenzymatic methods · multienzymatic methods

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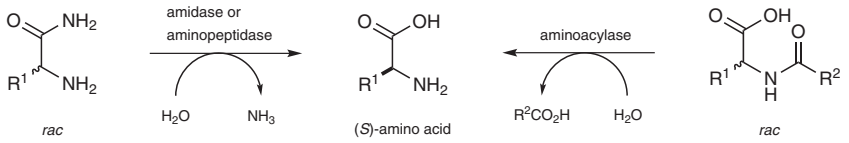
1.4.3 Hydrolysis of Amides

M. Hall, K. Faber, and G. Tasnádi

This chapter describes the enzymatic hydrolysis of amide substrates. The main target compounds are amino acids, obtained via the kinetic resolution of amino acid amides and N-acylated amino acids using aminopeptidases, amidases, and aminoacylases. In addition, methods leading to enantiopure carboxylic acids and amines as well as lactamase-catalyzed processes are presented.



Keywords: amide hydrolysis · amino acids · amines · carboxamides · lactams · Vince lactam · amidases · aminopeptidases · aminoacylases · lactamases

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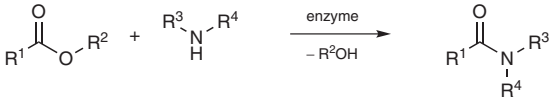
1.4.4 Enzymatic Synthesis of Amides

J. W. Schmidberger, L. J. Hepworth, A. P. Green, and S. L. Flitsch

The synthesis of amides is one of the most common reactions performed in organic chemistry. Biocatalysis is an attractive alternative to chemical methodologies because of the mild reaction conditions and excellent atom economy, combined with the potential for stereoselectivity. Here, we provide an overview of the literature on enzyme-catalyzed amide-bond formation on a preparative scale, with a focus on nonnatural substrates.



Keywords: amines · amides · esters · aminolysis · enzymes · regioselectivity · chemoselectivity · stereoselectivity · kinetic resolution · lipases · esterases · penicillin acylases · proteases · nitrile hydratases

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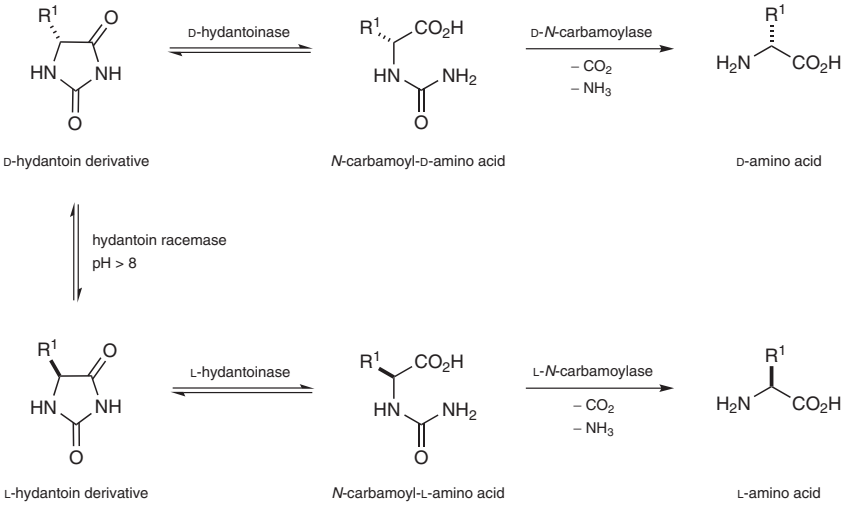
1.4.5 Hydrolysis of Hydantoins, Dihydropyrimidines, and Related Compounds

C. Slomka, U. Engel, C. Syldatk, and J. Rudat

Providing advantages including high chemo-, regio-, and enantioselectivity as well as mild reaction conditions, biocatalytic reaction systems are becoming increasingly important for the synthesis of chiral fine chemicals. This chapter focuses on hydantoins and related compounds as promising substrates for the synthesis of optically pure amino acids and on the enzymes involved in these processes. In particular, the production of D-amino acids, such as D-4-hydroxyphenylglycine, via the so-called "hydantoinase process" is now well established. Many investigations regarding the synthesis of L-amino acids with the help of this process have also been carried out. A further interesting application is the synthesis of β-amino acids, which are gaining importance in the pharmaceutical industry due to their special structure. Different possibilities for the application of modified hydantoinase processes are discussed, in which dihydropyrimidines serve as substrates for β-amino acid synthesis. Moreover, various methods to improve the synthesis of amino acids are described.



Keywords: hydantoins · dihydropyrimidines · hydrolysis · racemization · enantioselectivity · *N*-carbamoylamino acids · hydantoinase process · amino acids · D-4-hydroxyphenylglycine · β-amino acids · directed evolution · whole-cell biocatalysis · immobilization · recombinant expression

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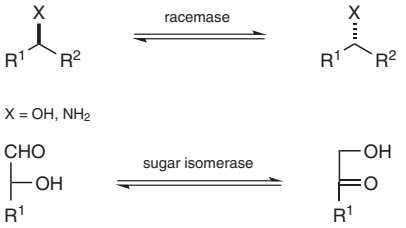
1.5 Isomerizations: Racemization, Epimerization, and *E*/*Z*-Isomerization

K. Faber and S. M. Glueck

Biocatalytic racemization represents the reversible interconversion of an enantiomer to its mirror image and is catalyzed by racemases. In the context of organic synthesis, it represents the key step to turn a kinetic resolution into a dynamic process. In contrast, sugar isomerases, acting as intramolecular oxidoreductases, are a subclass of isomerases and catalyze the interconversion of aldoses into ketoses, which finds application in the biotechnological production of (unnatural) rare sugars. The field of enzymatic isomerization is complemented by (carbohydrate) epimerization, alkene *E*/*Z*-isomerization, and mutase-catalyzed rearrangement reactions.



Keywords: isomerization · racemization · epimerization · *E*/*Z*-isomerization · mutase · aldose · ketose

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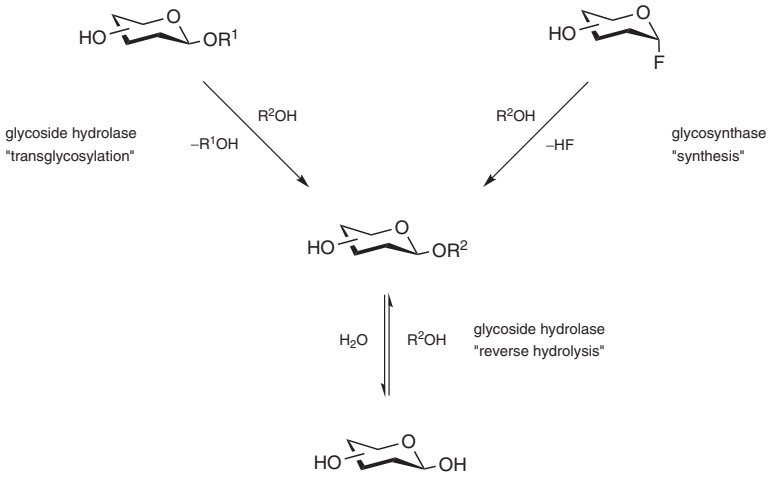
1.6.1 Glycosidases and Glycosynthases

B. Cobucci-Ponzano and M. Moracci

Enzymatic synthesis of glycans, as an alternative to classical chemical synthesis, is of great interest due to the exquisite stereospecificity and improved processivity and regioselectivity of the biological catalysts, and for the possibility of using reagents less toxic to the environment. Nonetheless, the limitations intrinsic to the natural enzymes promoting sugar synthesis, namely glycoside hydrolases and glycosyltransferases, have prompted efforts to engineer the former catalysts, obtaining glycosynthases that promote the synthesis of oligosaccharides, polysaccharides, and glycoconjugates in quantitative yields from inexpensive substrates. In this chapter we survey methods that exploit glycosidases and glycosynthases to allow the efficient and reliable preparation of glycans of synthetic relevance.



R^1 = leaving group; R^2 = glycoside/sugar

Keywords: carbohydrate active enzymes · carbohydrate synthesis · enzyme engineering · glycobiology · glycochemistry · glycoconjugates · glycosidase reaction mechanism · glycosyltransferase · oligosaccharides · polysaccharides · protein glycosylation

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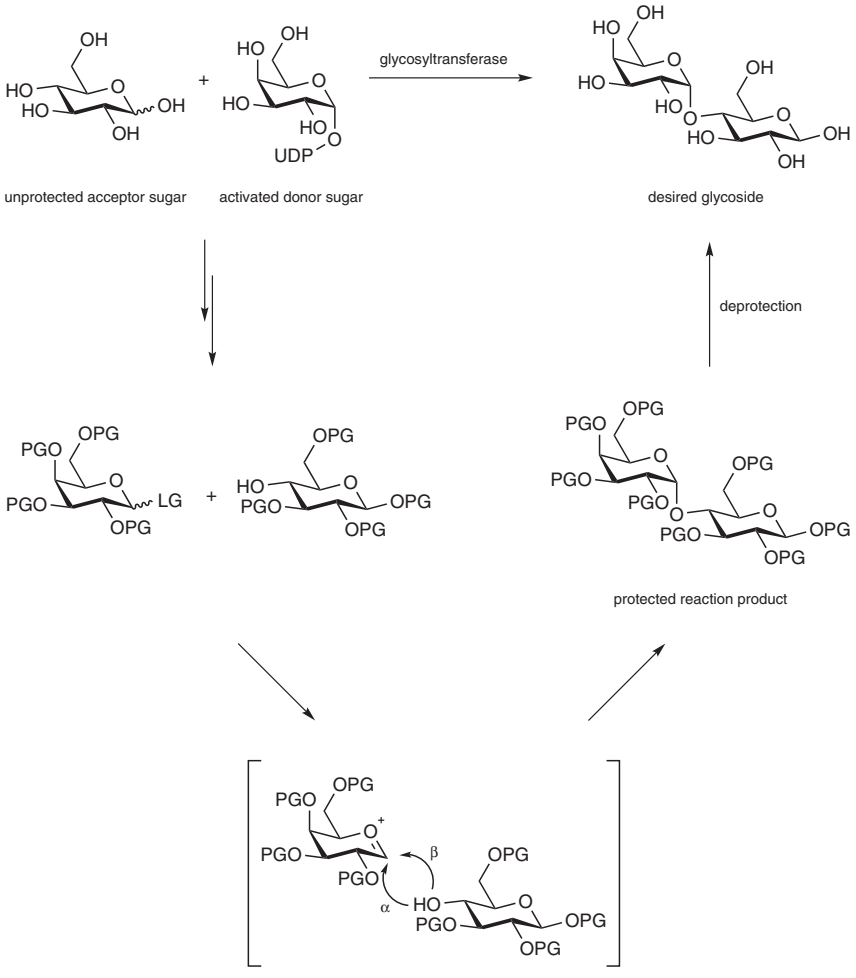
1.6.2 Glycosyltransferases

J. Voglmeir and S. L. Flitsch

The stereo- and regioselective properties and the high selectivity of glycosyltransferases toward donor and acceptor substrates make these enzymes highly attractive for synthetic applications. Various examples of recombinantly expressed glycosyltransferases demonstrate the versatility of both in vivo and in vitro syntheses of oligosaccharides from milligram to kilogram scale. However, due to the enormous variety of carbohydrate structures in living organisms, to date only a small proportion of carbohydrate epitopes have been synthesized in a routine manner. This chapter summarizes recent approaches to the application of glycosyltransferases in both preparative sugar synthesis and biotransformation.



Keywords: glycosyltransferases · enzymatic synthesis · nucleotide sugars · glycoconjugates · green chemistry