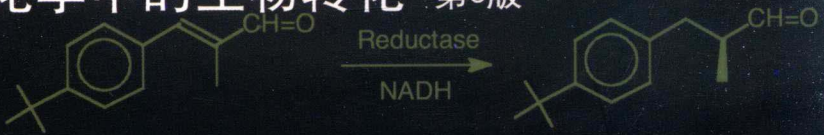
Kurt Faber

Biotransformations in Organic Chemistry

A Textbook

6th Edition

有机化学中的生物转化 第6版



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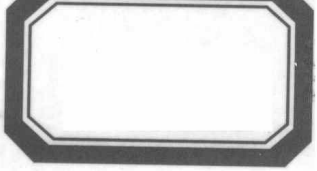

Biotransformations in Organic Chemistry

A Textbook

Sixth revised
and corrected edition

Springer

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Biotransformations in Organic Chemistry

Preface

The use of natural catalysts – enzymes – for the transformation of nonnatural man-made organic compounds is not at all new: they have been used for more than 100 years, employed either as whole cells, cell organelles or isolated enzymes [1]. Certainly, the object of most of the early research was totally different from that of the present day. Thus the elucidation of biochemical pathways and enzyme mechanisms was the main reason for research several decades ago. It was mainly in the steep rise of asymmetric synthesis during the 1980s, that the enormous potential of applying natural catalysts to transform nonnatural organic compounds was recognized. What started as an academic curiosity in the late 1970s became a hot topic in synthetic organic chemistry in the 1990s. Although the early euphoria during the 'gold rush' in this field seems to have eased somewhat, there is still no limit to be seen for the future development of such methods, as indicated by the wave-like appearance of novel types of biocatalytic principles. As a result of this extensive research, there have been an estimated 15,000 papers published on the subject. To collate these data as a kind of 'super-review' would clearly be an impossible task and, furthermore, such a hypothetical book would be unpalatable for the non-expert [2–6].

The point of this textbook is to provide a *condensed* introduction to this field. It is written from an organic chemist's viewpoint in order to encourage more 'pure' organic chemists of any level to take a deep breath and leap over the gap between the 'biochemical' sciences and 'synthetic organic chemistry' by persuading them to consider biocatalytic methods as an equivalent tool when they are planning the synthesis of an important target molecule. At several academic institutions this book has served as a guide for updating a dusty organic chemistry curriculum into which biochemical methods had to be incorporated. The wide repertoire of classic synthetic methods has not changed but it has been significantly widened and enriched due to the appearance of biochemical methods. This is illustrated by the fact that the proportion of papers on the asymmetric synthesis of enantiopure compounds employing biocatalytic methods has constantly risen from zero in 1970 to about 8% in 1989 [7] and it was estimated that this value is now approaching a

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steady share of 15%. Certainly, biochemical methods are not superior in a general sense – they are no panacea – but they definitely represent a powerful synthetic tool to complement other methodology in modern synthetic organic chemistry.

In this book, the main stream of novel developments in biotransformations, which already had significant impact on organic chemistry, are put to the fore. Other cases, possessing great potential but still having to show their reliability, are mentioned more briefly. The literature covered by the sixth edition of this textbook extends to the end of 2010. Special credit, however, is given to some 'very old' papers as well as acknowledging the appearance of novel concepts. References are selected according to the philosophy that 'more is not always better'. Generally, I have attempted to sort out the most useful references from the pack, in order to avoid writing a book with the charm of a telephone directory! Thus, special emphasis is placed on reviews and books, which are often mentioned during the early paragraphs of each chapter to facilitate rapid access to a specific field if desired.

The first edition of this book appeared in September 1992 and was predominantly composed as a monograph. It was not only well received by researchers in the field but also served as a basis for courses in biotransformations worldwide. In the second, completely revised edition, emphasis was laid on didactic aspects in order to provide the first textbook on this topic in 1995. Its great success has led to the demand for updated versions with emphasis on new trends and developments. In this context, novel techniques – dynamic resolution, stereoinversion, and enantioconvergent processes – were incorporated, in addition to the basic rules for the handling of biocatalysts.

My growing experience of teaching the use of biotransformations at several universities and research institutions around the world has enabled me to modify the text of this sixth edition so as to facilitate a deeper understanding of the principles, not to mention the correction of errors, which escaped my attention during previous editions. I am grateful to numerous unnamed students for pointing them out and for raising questions and to my old Macintosh IIci, which reliably served for 14 years without crashing.

I wish to express my deep gratitude to Stanley M. Roberts (UK) for undergoing the laborious task of correcting the manuscripts of the early editions of this book, for raising numerous questions and for helpful comments. Special thanks also go to M. Müller, U. Bornscheuer, W.-D. Fessner, A. Liese (Germany), N.J. Turner (UK), J.-E. Bäckvall (Sweden), R. Kazlauskas (USA), B. Nidetzky, and W. Kroutil (Graz) for their helpful hints and discussions. This revised edition would not have been possible without the great assistance of A. Preisz and B. Mautner.

I shall certainly be pleased to receive comments, suggestions, and criticism from readers for incorporation in future editions.

Graz, Austria
Spring 2011

Kurt Faber

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Contents

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Chapter 1
Introduction and Background Information

1.1 Introduction

Any exponents of classical organic chemistry might probably hesitate to consider a biochemical solution for one of their synthetic problems. This would be due to the fact, that biological systems would have to be handled. Where the growth and maintenance of whole microorganisms is concerned, such hesitation is probably justified. In order to save endless frustrations, close collaboration with a microbiologist or a biochemist is highly recommended to set up and use fermentation systems [1, 2]. On the other hand, isolated enzymes (which may be obtained increasingly easily from commercial sources either in a crude or partially purified form) can be handled like any other chemical catalyst.[1] Due to the enormous complexity of biochemical reactions compared to the repertoire of classical organic reactions, it follows that most of the methods described will have a strong empirical aspect. This 'black box' approach may not entirely satisfy the scientific purists, but as organic chemists are rather prone to be pragmatists, they may accept that the understanding of a biochemical reaction mechanism is not a conditio sine qua non for the success of a biotransformation.[2] In other words, a lack of detailed understanding of a biochemical reaction should never deter us from using it, if its usefulness has been established. Notwithstanding, it is undoubtedly an advantage to have an acquaintance with basic biochemistry and enzymology and with molecular biology, in particular.

Worldwide, about 80% of all chemical processes are performed catalytic leading to an annual product value of around 400 billion €. In this context, biocatalytic methods represent the main pillar of applied biotechnology, which has been coined

[1]The majority of commonly used enzyme preparations are available through chemical suppliers. Nevertheless, for economic reasons, it may be worth contacting an enzyme producer directly, in particular if bulk quantities are required. For a list of enzyme suppliers see the appendix (Chap. 5).

[2]After all, the exact structure of a Grignard-reagent is still unknown.

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as *White Biotechnology* by EuropaBio 2003, and which stands for the application of Nature's toolset to sustainable industrial production.[3]

1.2 Common Prejudices Against Enzymes

If one uses enzymes for the transformation of nonnatural organic compounds, the following prejudices are frequently encountered:

- *'Enzymes are sensitive'*.
  This is certainly true for most enzymes if one thinks of boiling them in water, but that also holds for most organic reagents, e.g., butyl lithium. When certain precautions are met, enzymes can be remarkably stable. Some candidates can even tolerate hostile environments such as temperatures greater than 100°C and pressures beyond several hundred bars (100 bar = 10 MPa) [3–5].
- *'Enzymes are expensive'*.
  Some are, but others can be very cheap if they are produced on a reasonable scale. Considering the higher catalytic power of enzymes compared to chemical catalysts, the overall efficiency of an enzymatic process may be better even if a rather expensive enzyme is required. Moreover, enzymes can be reused if they are immobilized. It should be emphasized that for most chemical reactions relatively crude and thus reasonably priced enzyme preparations are adequate. Due to the rapid advances in molecular biology, costs for enzyme production are constantly dropping.
- *'Enzymes are only active on their natural substrates'*.
  This statement is certainly true for some enzymes, but it is definitely false for the majority of them. Much of the early research on biotransformations was impeded by a tacitly accepted dogma of traditional biochemistry which stated that 'enzymes are nature's own catalysts developed during evolution for the regulation of metabolic pathways'. This narrow definition implied that man-made organic compounds cannot be regarded as substrates. Once this scholastic problem was surmounted [6], it turned out that the fact that nature has developed its own peculiar catalysts over 3×10^9 years does not necessarily imply that they are designed to work only on their natural target molecules. Research during the past two decades has shown that the substrate tolerance of many enzymes is much wider than previously believed and that numerous biocatalysts are capable of accepting nonnatural substrates of an unrelated structural type by often exhibiting

[3]Other sectors of biotechnology have been defined as 'Red' (biotechnology in medicine), 'Green' (biotechnology for agriculture and plant biotech) and 'Blue' (marine biotechnology), http://www.EuropaBio.org, http://www.bio.org

the same high specificities as for the natural counterparts. It seems to be a general trend, that, the more complex the enzyme's mechanism, the narrower the limit for the acceptability of 'foreign' substrates. It is a remarkable paradox that many enzymes display high specificities for a specific type of reaction while accepting a wide variety of substrate structures. After all, there are many enzymes whose natural substrates – if there are any – are unknown.

- *'Enzymes work only in their natural environment'.*
  It is generally true that an enzyme displays its highest catalytic power in water, which in turn represents something of a nightmare for the organic chemist if it is the solvent of choice. However, biocatalysts *can* function in nonaqueous media, such as organic solvents, ionic liquids, and supercritical fluids, as long as certain guidelines are followed. Only a decade ago, some key rules for conducting biotransformations in organic media were delineated. Although the catalytic activity is usually lower in nonaqueous environments, many other advantages can be accrued by enabling to catalyze reactions which are impossible in water and making many processes more effective (Sect. 3.1) [7–11].

1.3 Advantages and Disadvantages of Biocatalysts

1.3.1 Advantages of Biocatalysts

- *Enzymes are very efficient catalysts.*
  Typically the rates of enzyme-mediated processes are faster by a factor of 10^8–10^{10} than those of the corresponding noncatalyzed reactions, – in some cases even exceeding a factor of 10^{17}, and are thus far above the values that chemical catalysts are capable of achieving [12–14]. As a consequence, chemical catalysts are generally employed in concentrations of a mole percentage of 0.1–1%, whereas most enzymatic reactions can be performed at reasonable rates with a mole percentage of 10^{-3}–10^{-4}% of catalyst, which clearly makes them more effective by some orders of magnitude (Table 1.1).

Table 1.1 Catalytic efficiency of representative enzymes

Enzyme	Reaction catalyzed	TON
Carbonic anhydrase	Hydration of CO_2	600,000
Acetylcholine esterase	Ester hydrolysis	25,000
Penicillin acylase	Amide hydrolysis	2,000
Lactate dehydrogenase	Carbonyl reduction	1,000
Mandelate racemase	Racemisation	1,000
α-Chymotrypsin	Amide hydrolysis	100

TON = turnover number

- *Enzymes are environmentally acceptable.*
  Unlike heavy metals, for instance, biocatalysts are environmentally benign reagents since they are completely biodegradable.

- *Enzymes act under mild conditions.*
  Enzymes act within a range of about pH 5–8 (typically around pH 7) and in a temperature range of 20–40°C (preferably at around 30°C). This minimizes problems of undesired side-reactions such as decomposition, isomerization, racemization, and rearrangement, which often plague traditional methodology.

- *Enzymes are compatible with each other.*[4]
  Since enzymes generally function under the same or similar conditions, several biocatalytic reactions can be carried out in a reaction cascade in a single flask. Thus, sequential reactions are feasible by using multienzyme systems in order to simplify reaction processes, in particular if the isolation of an unstable intermediate can be omitted. Furthermore, an unfavorable equilibrium can be shifted towards the desired product by linking consecutive enzymatic steps. This unique potential of enzymes is increasingly being recognized as documented by the development of multienzyme systems, also denoted as 'artificial metabolism' [15].

- *Enzymes are not restricted to their natural role.*
  They exhibit a high substrate tolerance by accepting a large variety of man-made nonnatural substances and often they are not required to work in water. If advantageous for a process, the aqueous medium can often be replaced by an organic solvent (Sect. 3.1).

- *Enzymes can catalyze a broad spectrum of reactions.*
  Like catalysts in general, enzymes can only *accelerate* reactions but have no impact on the position of the thermodynamic equilibrium of the reaction. Thus, in principle, enzyme-catalyzed reactions can be run in both directions.

There is an enzyme-catalyzed process equivalent to almost every type of organic reaction [16], for example:

- Hydrolysis-synthesis of esters [17], amides [18], lactones [19], lactams [20], ethers [21], acid anhydrides [22], epoxides [23], and nitriles [24].
- Oxidation of alkanes [25], alcohols [26], aldehydes, sulfides, sulfoxides [27], epoxidation of alkenes [28], hydroxylation and dihydroxylation aromatics [29], and the Baeyer-Villiger oxidation of ketones [30, 31].
- Reduction of aldehydes/ketones, alkenes, and reductive amination [32].
- Addition-elimination of water [33], ammonia [34], hydrogen cyanide [35].
- Halogenation and dehalogenation [36], Friedel-Crafts-type alkylation [37], *O*-and *N*-dealkylation [38], carboxylation [39], and decarboxylation [40], isomerization [41], acyloin [42], and aldol reactions [43]. Even Michael

[4]Only proteases are exceptions to this rule for obvious reasons.

additions [44], Stetter reactions [45], Nef reactions [46], and Diels-Alder reactions [47–49] have been reported.

Some major exceptions, for which equivalent reaction types cannot be found in nature, is the Cope rearrangement – although [3,3]-sigmatropic rearrangements such as the Claisen rearrangement are known [50, 51]. On the other hand, some biocatalysts can accomplish reactions impossible to emulate in organic chemistry, e.g., the selective functionalization of ostensibly nonactivated positions in organic molecules, such as the hydroxylation of aliphatics.

This catalytic flexibility of enzymes is generally denoted as 'catalytic promiscuity' [52–58], which is divided into 'substrate promiscuity' (conversion of a nonnatural substrate), 'catalytic promiscuity' (a nonnatural reaction is catalyzed), and 'condition promiscuity' (catalysis occurring in a nonnatural environment).

Enzymes display three major types of selectivities:

- *Chemoselectivity*
  The purpose of an enzyme is to act on a single type of functional group, other sensitive functionalities, which would normally react to a certain extent under chemical catalysis, do survive unchanged. As a result, reactions generally tend to be 'cleaner' so that laborious removal of impurities, associated to side reactions, can largely be omitted.

- *Regioselectivity and Diastereoselectivity*
  Due to their complex three-dimensional structure, enzymes may distinguish between functional groups which are chemically identical but situated in different positions within the same substrate molecule [59, 60].

- *Enantioselectivity*
  Last but not least, all enzymes are made from L-amino acids and thus are chiral catalysts.[5] As a consequence, any type of chirality present in the substrate molecule is 'recognized' upon formation of the enzyme-substrate complex. Thus, a prochiral substrate may be transformed into an optically active product through a desymmetrization process and both enantiomers of a racemic substrate usually react at different rates, affording a kinetic resolution.

These latter properties collectively constitute the 'stereoselectivity' (in desymmetrizations) or 'enantioselectivity' (in kinetic resolutions) of an enzyme and represent its most important feature for asymmetric exploitation [62]. It is remarkable that this key feature was already recognized by E. Fischer back in 1898 [63].

All the major biochemical events taking place within an organism are governed by enzymes. Since the majority of them are highly selective with respect to the chirality of a substrate, it is obvious that the enantiomers of a given bioactive

[5]For exceptional D-chiral proteins see [61].

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