CHAPTER 6
ASYMMETRIC CATALYSIS BY BIOCHEMICAL SYSTEMS

INTRODUCTION

Enzymes and microorganisms constitute an important class of organic chiral reagents. Enzyme systems are known to catalyze a wide variety of chemical reactions. Whereas many enzymes have been used, it is those enzyme systems that possess broad substrate specificities and high enantioselectivities that are best suited for asymmetric catalysis. Either isolated enzymes or intact microorganisms can be used. Since both processes are enzymic in the final analysis, the following illustrative summary of enzymes in asymmetric synthesis does not attempt to separate enzymic from fermentative operations. The factors to be considered in choosing between the two techniques will be discussed later.

(i) Classification of Enzyme Reactions

The International Union of Biochemistry recognizes 6 main groups of enzyme types. These are:

1. Oxidoreductases. These enzymes catalyze oxidation-reduction reactions involving oxygenation, such as C-H → C-OH, or overall removal or addition of hydrogen atom equivalents, for example CH(OH)⇌C=O and CH-CH⇌C=C.

2. Transferases. Enzymes of this type mediate the transfer of various groups, such as, the aldehyde, ketone, acyl, sugar and phosphoryl groups, from one molecule to another.

3. Hydrolases. The range of hydrolysable groups is very broad. It includes esters, amides, peptides and other C-N-containing functions, anhydrides, glycosides and several others.

4. Lyases. These enzymes catalyze additions to, or formation of, double bonds, such as C≡C, C=O and C=N.

5. Isomerases. Various types of isomerizations, including racemization, are catalyzed by enzymes.

6. Ligases. Such enzymes are often termed synthetases. They mediate the formation of C-O, C-S, C-N, C-C and O-P bonds.

For asymmetric synthetic applications, it is the enzymes of groups 1, 3 and 4 that are currently the most useful.
Many enzymes require coenzymes in order to be catalytically active. Some coenzymes are themselves catalytic and are automatically regenerated during the catalytic cycle. These include biotin, thiamine pyrophosphate and pyridoxal phosphate. Other coenzymes are in fact co-substrates in that they are required in stoichiometric proportions during the catalytic process and undergo chemical transformation during the reaction. Coenzymes of this type are nicotinamide adenine dinucleotides (NAD/P) and adenosine triphosphate (ATP) which must be continuously regenerated by an auxiliary chemical or biochemical process. This is not a problem with microorganisms because all of the coenzymes required are either present in the cells or are continuously produced during the fermentation process. With purified enzymes, however, maintaining a sufficient concentration of coenzyme presents a challenge. Coenzymes are expensive. They are therefore generally employed in catalytic quantities only and an inexpensive recycling system is employed to regenerate their active form. This is illustrated below for reductions with the nicotinamide coenzyme required by alcohol dehydrogenases. As the horse liver alcohol dehydrogenase (HLADH)–catalyzed reduction of the decalindione proceeds, the NADH is oxidized to NAD. Ethanol is added as a cosolvent in the reaction medium and, being itself a substrate of HLADH, undergoes reaction with NAD to regenerate the NADH required for the decalindione reduction to continue. In its oxidative mode HLADH reactions, flavin mononucleotide (FMN) can be used to effect NAD/H + NAD conversions. This is a chemical,