Editorial Commentary

Mark J. Burk

Mark J. Burk

The commercial potential of biological catalysts was realized more than two millennia ago when yeast and the enzyme rennet were found to provide such gastronomical delicacies as leavened breads, fine wines, and savory cheeses. Despite these and other early examples, many years passed before biological catalysis was considered as a general means for industrial production. Today, biological catalysis encompasses fermentations and whole-cell biotransformations, as well as biocatalysis using isolated enzymes, cell lysates, or crude extracts. However, notwithstanding scores of successful applications, biological catalysts remain under-utilized for manufacture in the chemical and pharmaceutical industries. The reasons for this situation are manifold. Historically, this may be related to the fact that the products of these industries are *de facto* chemicals, the synthesis of which has largely relied upon the use of chemical techniques. Chemistry alone, however, does not always provide the most effective solution to a synthetic challenge. Indeed, biological catalysis can be far superior in many cases and, when applied in combination with chemical synthesis or chemical catalysis, can provide facile access to molecules not easily prepared by conventional methods.

The literature is replete with articles expounding the virtues of biological catalysts as synthetic tools. Biological catalysts offer many attractive traits such as high selectivity, mild reaction conditions, high catalytic efficiency, and ready mutability. Biocatalytic processes are environmentally responsible methods for manufacturing since they often afford few by-products and may involve use of an immobilized catalyst that can be easily recovered and recycled. Moreover, biological catalysis often obviates the need for numerous protecting group manipulations, and may be performed in aqueous solution rather than dangerous organic solvents. Interestingly, while chemical catalysts can offer only some of these benefits, relative to biological catalysts, chemical catalysts have been much more widely adopted by the chemical industry. The barriers to employing biological catalysts certainly should be no greater than those associated with chemical catalysts.

The question then arises, why has the use of biological catalysis in production remained limited? Biological catalysts have long suffered from: 1) high enzyme costs, 2) limited number of commercially available or "off-the-shelf" enzymes, 3) unreliable enzyme supply sources, 4) limited range of industrially useful transformations, 5) limited reaction generality or substrate scope, 6) ready access to only one product enantiomer, 7) enzyme instability under industrial reaction conditions, 8) unreliable or unpredictable biological processes, 9) long development times, and 10) low substrate concentrations and/or volumetric productivity (space-time yield). However, significant progress has been made over the past ten years in the areas of microbiology, molecular biology, and bioengineering that have vanquished many of these obstacles. Modern cloning and host engineering techniques allow rapid, cost-effective methods for overexpression of enzymes. Many more enzymes are becoming readily available in larger quantities as a result. Directed evolution procedures provide a facile means to optimize enzyme properties. Attributes such as temperature and pH stability, substrate scope, selectivity, product inhibition, and catalyst activity and productivity now are easily addressable through protein engineering strategies. High throughput screening methods have been developed to allow rapid selection of ideal enzymes and conditions, thus greatly reducing development times. An ever-expanding array of new enzymes with unprecedented activity and selectivity profiles is becoming available through discovery efforts that focus upon accessing biodiversity from unique environments.

Biological catalysis can provide methods that facilitate the synthesis of molecules in situations where viable alternative chemical technologies are limited or unavailable. But, perhaps, their greatest potential is only begin-

  1615-4150/01/34306–7-499–500 $ 17.50-.50/0

ning to be realized! The techniques of chemistry, chemical catalysis, and biological catalysis should not be considered as independent entities competing for the same reaction vessel. Biological catalysis and chemical catalysis are often complementary methods of synthesis. Far more can be gained through successful integration of chemical and biological methodologies for application in multi-step processes. Capturing the synergies of these two techniques can provide synthetic advantages that can open innumerable opportunities.

For example, integration of fermentation processes with either biocatalysis or chemical methods can provide direct access to a range of very complex molecules. Fermentation processes are particularly useful for the synthesis of intricate natural products where a chemical route would be intractable and/or economically unattractive. The importance of fermentation for drug manufacture was galvanized by development of the antibiotic penicillin in the early 1940's. Subsequently, fermentation has become a mainstay for production of many valuable natural product therapeutics. But an incessant desire for improved properties inspired the semi-synthetic approach to drug production, which entails the use of fermentation to provide the central scaffold, followed by chemical or biocatalytic elaboration. This successful combination of biology and chemistry has led to a multitude of processes for the manufacture of drugs including second generation penicillin, cephalosporin, and tetracycline antibiotics, steroid derivatives such as cortisone, and more recently the blockbuster cholesterol-lowering drugs simvastatin and pravastatin. The latter two drugs had worldwide sales of ca. US$ 5.3 billion and US$ 3.5 billion, respectively, in year 2000. In both cases, development of an economically viable route to these compounds involving purely chemical methods would have been difficult, if not impossible.

Tremendous benefits also may be gained through integration of enzymatic and chemical catalysis. For instance, Wong and Sharpless teamed up to develop an elegant approach to carbohydrates by combining the strengths of asymmetric osmium-catalyzed dihydroxylation and aldolase-catalyzed addition reactions. Scientists at Chirotech Technologies showed that a broad array of novel D- and L-α-amino acids could be produced with very high chemical and enantiomeric purity through asymmetric rhodium-catalyzed hydrogenation of *N*-acetylenamides followed by aminoacylase-catalyzed deprotection. Finally, enzymes and metal catalysts recently have been asked to perform in the same reactor. One manifestation of this involves dynamic kinetic resolution of chiral alcohols through lipase-catalyzed acylation with concomitant ruthenium-catalyzed racemization of the starting alcohols to allow high yields of enantiomerically pure *O*-acylated products. These and other examples amply demonstrate the important concept of catalysis technology integration, which is certain to find wider application in the future.

The number of readily available, robust enzymes is rapidly increasing and methods for optimizing biological catalysts through directed evolution have overcome many debilitating limitations. Although progress is being made, the chemical industry has yet to fully recognize or exploit the power of biotechnology. A major factor contributing to this situation seems to be a general unfamiliarity with the availing features that biological catalysis can bestow upon the chemical industry. Selection and development of the most appropriate enzyme for a given industrial transformation can be demanding. Information and expertise that can facilitate this process is becoming much more accessible. But, in the end, chemists themselves must elevate their comfort level and gain confidence in biological catalysis to the extent that these methods are considered as practical alternatives during early stages of synthesis route selection. It is our hope that the current Special Issue of *Advanced Synthesis & Catalysis* featuring Biocatalysis will help to broaden the scope of techniques that the chemist employs when first faced with a synthetic challenge.

Mark J. Burk
Diversa Corporation
4955 Directors Place
San Diego, CA 92121, USA
Tel: (+1) 858-526-5343
Fax: (+1) 858-526-5843
e-mail: mburk@diversa.com
web: http://www.diversa.com/