Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 15 (2004) 2727–2728
Tetrahedron: *Asymmetry*

Preface

Integrating biocatalysis into organic synthesis

The 45 contributions in this special issue of Tetrahedron: *Asymmetry* on 'Integrating Biocatalysis into Organic Synthesis' show the increasing impact of biocatalysis on organic synthesis and especially on the synthesis of enantiopure compounds. Major themes in this issue include the continuing importance of hydrolases, increasing interest in redox, especially oxidation reactions, and in carbon–carbon bond forming reactions, strategies to convert both substrate enantiomers into a single product enantiomer, and protein engineering and process design.

Hydrolases

Esterases and lipases, the workhorses of biocatalysis, continue to serve as enantioselective catalysts for synthesis. A maturing understanding of these enzymes allows researchers to use them predictably on more complex structures and to attempt more difficult-to-resolve substrates. Examples in this issue include resolutions or desymmetrizations of primary alcohols (precursors for synthesis of analogs of diglycerides and phospholipids), bulky substrates, and synthetic intermediates containing multiple stereocenters or more distant stereocenters. Penicillin G acylase can add and remove protecting groups. As modern molecular biology methods discover new esterases and lipases in unusual microorganisms such as thermophiles and extremophiles, the substrate mapping of these enzymes can identify new synthetic applications.

The discovery and substrate mapping of other hydrolases—nitrile hydratases, nitrilases, amidases, epoxide hydrolases, hydantoinases, and glycosidases—promises a new wave of applications in asymmetric synthesis. For example, α-mannosidases remove sugar moieties from complex glycopeptide antibiotics.

Oxidations

A number of contributions focus on redox enzymes, especially oxidation reactions. These include NAD^+ oxidases for regeneration of NAD^+, laccases to replace a Swern oxidation in a complex synthesis, controlling the chemoselectivity of toluene dioxygenase, p450 enzymes, and fatty acid desaturases. Even poly(leucine) or nonredox enzymes such chymotrypsin can act as chiral templates to impart enantioselectivity on chemical oxidation and reduction reagents such hydrogen peroxide or sodium borohydride.

Among enzymes for reduction, new enzymes include a C–C bond reductase to make 2-chloropropionic acid, a new dehydrogenase to make *N*-methylphenylalanine, and enantiocomplementary yeast reductases discovered in the yeast genome sequence. Most applications are to make key intermediates for further synthesis, but one application is to screen ligands for an organometallic-catalyzed reaction. Enzyme-catalyzed oxidation of the product gives a color change and shows which ligands give the fastest reactions.

Carbon–carbon bond forming reactions

Other contributions explore carbon–carbon bond formation using Michael additions catalyzed by tryptophan synthase, aldol additions catalyzed by fructose-1,6-diphosphate aldolase using nitro group containing substrates, acyloin condensation catalyzed by benzaldehyde lyase to form 2-hydroxy ketones, or cyanide additions catalyzed by hydroxynitrile lyase using an ionic liquid as an organic phase.

Converting both substrate enantiomers into a single product enantiomer

Resolutions, which separate enantiomers, normally yield a maximum of 50% of one enantiomer. Strategies to increase the yield beyond 50% are increasingly important. For example, a Mitsunobu inversion of the unwanted secondary alcohol enantiomer coverts it to the desired enantiomer. An important class of new reactions is desymmetrizations, where one enantiomer converts to the other during the resolutions. This inversion of configuration may occur via a racemization reaction

0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2004.08.001

or by an enantioconvergent reaction—stereoselective inversion of one enantiomer. For these reactions, the discovery of new racemases is important, as is the discovery of enantiocomplementary enzymes. Since these transformations yield only one enantiomer, to get the other enantiomer, one needs an enzyme with the opposite enantiopreference.

Protein engineering and process design

Getting the enantioselective enzyme-catalyzed reactions into manufacturing faces a number of different hurdles—from discovering reactions fast enough for the rapid pharmaceutical drug development to optimizing enantioselectivity and reaction rates to compete with alternative methods such as chemical catalysis. Contributions in this area describe assays for rapid screening of enzymes, statistical methods to view screening data and enzyme similarity, use of absorbent resins to reduce substrate and product inhibitions, lower temperatures to increase enantioselectivity, immobilization to increase rate and reuse enzymes, directed evolution to expand the substrate range of $p450_{cam}$, faster reactions of hydroxynitrile lyase in ionic liquids, comparing chemical and enzymatic methods. Interestingly, the ability to screen enzymes more quickly than traditional chemical catalysts is an advantage in some cases.

Most important, I thank all the contributors for submitting excellent work to this special issue and for sticking to the short deadline. I also thank Kevin Burgess for the invitation to organize this issue.

Romas Kazlauskas
McGill University, Montréal, Québec, Canada

Photographer: Tim Rummelhoff

Available online 11 September 2004