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Preface

Biocatalysts in synthetic organic chemistry

The employment of enzymes and whole cells has been important in many industries for centuries. The most obvious usages have been in the food and drink businesses where the production of wine, beer, cheese etc. is dependent on the effects of microorganisms. For years fermentation technology provides a variety of amino acids, citric acid and other feed additives. Nowadays, the enzyme transglutaminase is widely used to give meat a fresh appearance, while an isomerase is used to produce fructose on a very large scale.

Other outlets for enzyme-controlled reactions are in the tanning industry, the household/cosmetic industries (for example biological washing powders), bioremediation and the production of natural flavours such as vanillin.

However, it is only in the last 30 years that the use of enzymes for the synthesis of high-value fine chemicals has enjoyed increasing popularity. Personally, in the 1970s I found lectures by first Bryan Jones then George Whitesides and papers by Charles Sih, highly influential and like many other organic chemists, I was attracted to the field by these brilliant pioneers and their peers.[1] Many breakthroughs have been recorded since these early days; high on the list must be the popularisation of the use of hydrolases in organic solvents for acylation and esterification processes. More recently, the application of error-prone polymerase chain reactions for the construction of 'designer' enzymes and the alteration of metabolic pathways to produce 'cell factories' are two techniques which have only just begun to be exploited for fine chemical manufacture.

For three years (1996–8) I reviewed the field of biotransformations for *J.C.S. Perkin Transactions*; for these reviews I summarised the biotransformations that appeared in the 'Top Twenty' Organic Chemistry Journals: the various sub-divisions of the topic attracted different volumes of work (Table 1). The use of esterases and lipases for the catalysis of hydrolysis and esterification reactions was most popular, not least because many of the enzymes were (and are) available commercially. The potential of epoxide hydrolases, nitrilases and nitrile hydratases was beginning to be explored. Reduction of carbonyl compounds, usually involving readily available microorganisms, such as bakers' yeast, represented about 10% of the activity, on average.

Not surprisingly, various oxidation reactions involving enzymes (e.g., monooxygenases, dioxygenases and oxidoreductases) tended to be undertaken in more specialist laboratories since the transformations often utilised microorganisms which needed to be grown and harvested before use.

The field of carbohydrate chemistry had warmly embraced this aspect of biotechnology, not least because the regioselectivity of the enzyme-controlled processes often circumvented long-winded protection/deprotection sequences. Moreover the mild conditions that could be employed kept the carbohydrate core structure intact.

Interestingly, virtually the same proportions of work in the different areas are seen in this Symposium-in-Print (Table 1).

Esterases and lipases are used almost routinely these days to provide optically active building blocks for the construction of imaginative new routes to chiral target molecules. The increased interest in epoxide hydrolases and the hydrolysis of nitriles is reflected in the submitted papers. While somewhat surprisingly enzyme-catalysed amide formation is not featured to a large extent in this Symposium-in-Print, readers will find an excellent review on enzymic acylation of chiral amines, in the next pages of this issue.[2]

Reduction reactions feature prominently, not only asymmetric reductions of carbonyl compounds but also of imines (for dynamic compound-library formation). Oxidation reactions that are featured herein include the exploitation

Table 1. Popularity of enzyme-catalysed transformations 1996–1998 and topics featured in this issue

Transformation type	Percentage of total biotransformations in the years 1996–1998 and in this Symposium-in-Print			
	1996	1997	1998	S-i-P
Hydrolysis	20	25	22	42
Esterification	18	23	23	
Amide formation	3	5	6	3
Reduction	9	13	9	14
Oxidation	21	12	18	19
C–C Bond formation	8	5	6	3
Carbohydrate modfn.	10	10	6	10
Others	11	6	11	9
	100	100	100	100

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of dioxygenases for the preparation of chiral cyclohexadienediol derivatives and the stereoselective oxidation of sulfides.

Carbon–carbon bond forming reactions are represented by the enzyme-controlled formation of cyanohydrins and the modern-day construction of compound libraries using aldolases. There is a splendid survey of some of the modern work involving carbohydrate modification, while in the 'other' category (equally important, in my view, to all the other areas) the employment of laccases and the impact of novel catalytic antibodies are featured.

It is stating the obvious to say that biocatalysis is not a panacea for synthetic organic chemistry. However, advances over the past thirty years mean that it would be a serious mistake not to consider the employment of a biocatalyst, in, perhaps, the key step in a sequence of transformations that turn a cheap starting material into an expensive fine chemical. If pressed to be more quantitative, I reckon that, if one totally ignores the opportunities offered by biocatalysts, the best route to a target fine chemical may be overlooked in about 10% of cases. Fortunately excellent, recently published textbooks[3] and a comprehensive database[4] are available fully to apprise chemists and other scientists of the possibilities for using Nature's catalysts in present-day organic synthesis.

It has been a pleasure for me to compile this Symposium-in-Print. Papers were forthcoming (on schedule!) from academic and industrial laboratories situated in 10 different countries. I thank all the authors for their hard work. Particularly, I thank Professor Jenny Littlechild (University of Exeter) for providing the picture for the cover. The shot shows a γ-lactamase forming a tetrahedral intermediate in a reaction involving the hydrolysis of a γ-lactam.[5] (This biotransformation formed a key step in the preparation of an optically active intermediate *en route* to the anti-HIV drug Abacavir.[6]) Finally, I have taken advantage of much positive advice from the *Tetrahedron* Editors, Professor Richard Taylor and Professor Harry Wasserman. The professional help of Dr Peter O'Brien and the *Tetrahedron* Staff in the York Office has also proved to be invaluable.

References and notes

1. For a review of the early work see: *Applications of biochemical systems in organic chemistry; Parts 1 and 2*; Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976.
2. van Rantwijkt, F.; Sheldon, R. A. Enantioselective Acylation of Chiral Amines Catalysed by Serine Hydrolases, *Tetrahedron* **2004**, *60*, 501–519.
3. Zwanenburg, B.; Mikolajczyk, M.; Kielbasinski, P. *Enzymes in action*; Kluwer Academic: Dordrecht, 2000. Fessner, W. D. *Biocatalysis from discovery to application*; Springer: Berlin, 2000. Faber, K. *Biotransformations*. Springer: Berlin, 2000. *Enzyme catalysis in organic synthesis*; Drauz, K., Waldmann, H., Eds.; Wiley–VCH: New York, 2002.
4. BioCatalysis (Accelrys). Contact Professor Bryan Jones for further information (jbjones@chem.utoronto.ca).
5. PDB code 1HL7.
6. Taylor, S. J. C.; Brown, R. C.; Keene, P. A.; Taylor, I. N. *Bioorg. Med. Chem.* **1999**, *7*, 2163.

S. M. Roberts
Department of Chemistry,
University of Liverpool,
The Robert Robinson Laboratories,
Liverpool L69 7ZD, UK
E-mail address: smrsm@liverpool.ac.uk