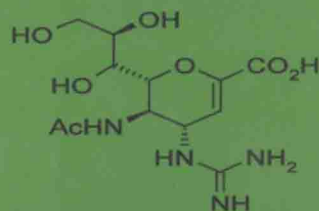


PRACTICAL METHODS FOR BIOCATALYSIS AND BIOTRANSFORMATIONS

Editors JOHN WHITTALL | PETER W. SUTTON

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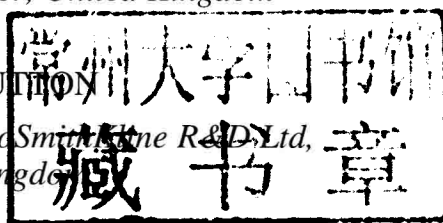
Editors

JOHN WHITTALL

*Manchester Interdisciplinary Biocentre,
University of Manchester, United Kingdom*

PETER SUTTON

*Synthetic Chemistry, GlaxoSmithKline R&D Ltd,
United Kingdom*



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Practical Methods for Biocatalysis and Biotransformations

Preface

During the early to mid 1990s Professor Stan Roberts was chief editor of a series of loose-leaf laboratory protocols detailing the use of biotransformations in synthetic organic chemistry that were collected together and published in book form (*Preparative Biotransformations*, Wiley, Chichester, 1999). This led to the publication of the series of books *Catalysts for Fine Chemical Synthesis*, volumes 1–5, by the same publisher which covered the application of chemo- and bio-catalytic procedures for the synthesis of fine chemicals; for this series, Dr John Whittall became co-editor on the homogeneous catalysis volumes. Following the format of this series, *Practical Methods in Biocatalysis and Biotransformations* has been prepared. In keeping with these earlier formats, we aim to provide the readership with enough information to understand when a biocatalytic or biotransformation method would be a suitable practical method to carry out their synthetic transformation.

In recent times, the employment of enzymes and whole cells to perform a range of organic reactions has become much more commonplace, and biotransformation has become accepted as a powerful method for application in synthetic organic chemistry. However, for chemists developing synthetic methods for a particular target molecule, the understanding of the advantages and limitations of biocatalysis and biotransformation is not always clear. Therefore, this book intends to review the industrial background to when biotransformations are used and introduce the nonmicrobiologist to the background of how biocatalysts are discovered and developed and then give detailed experimental procedures for a comprehensive range of useful biotransformation methods.

In order to place the later chapters in proper context, Chapter 1 offers a comprehensive review of biotransformation from the perspective of a large pharmaceutical company (GSK) and Chapter 2 gives an introduction that allows an appreciation of molecular biology for scientists with no formal training in this area.

In the remaining chapters, key biotransformations have been identified from the recent primary literature (learned journals) and the respective authors have amplified the disclosure of their methodologies in this volume. These disclosures often contain additional equipment and experimental details to those found in the experimental section of most journals, allowing the reader to decide whether these methods are suitable for addressing their needs.

Chapter 3 describes the application of lipases, proteases and sulfatases for the kinetic resolution of a range of interesting molecules. A selection of dynamic kinetic resolution (DKR) procedures is disclosed in Chapter 4. DKRs are attracting a significant amount of

interest as they allow access to >50 % yields of single enantiopure products from racemates. Other useful synthetic applications of hydrolase enzymes are covered in Chapter 5, including desymmetrization and regio- and chemo-selective transformations.

Chapters 6 and 7 cover sugar-type chemistry, focusing on aldol and glycosylation methods which can offer substantial advantages over traditional chemical approaches.

Chapter 8 describes the application of hydroxyl nitrile lyases to the synthesis of new chiral cyanohydrins and α -hydroxy acids and includes new approaches to the transformation of 'difficult' aldehyde and ketone substrates using substrate engineering and immobilization techniques.

The latter part of the book is dedicated to redox biotransformation application, with Chapter 9 disclosing several methods for the synthesis of chiral secondary alcohols using a range of commercially available ketoreductases (alcohol dehydrogenases) which are now being applied regularly on a large scale.

Chapter 10 covers reductive enzymes with an emphasis on transaminase enzymes, which are enjoying widespread application in the synthesis of nonnatural amino acids which are key building blocks for several products of industrial importance.

The use of a range of oxidative enzymes in synthesis is covered in Chapter 11, whilst the very powerful technique of regio- and stereo-specific biohydroxylation of even complex molecules by fermenting whole-cell methods is covered in Chapter 12.

The Editors are most grateful to the authors who have submitted details of their procedures in the prescribed format for inclusion in this book. We hope that this book will increase the exposure of these methods to the chemical community and contribute to the expanded employment of biocatalysis in organic synthesis.

John Whittall, Manchester
Peter Sutton, Stevenage
2009

Abbreviations

A	adenine
ABTS	2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid
7-ACA	7-aminocephalosporanic acid
ACN	acetonitrile
AcOH	acetic acid
ACS GCI	American Chemical Society Green Chemistry Institute
7-ADCA	7-aminodesacetoxycephalosporanic acid
ADH	alcohol dehydrogenase (alternative name for a ketoreductases or KREDs)
ADH-RE	alcohol dehydrogenase from <i>Rhodococcus erythropolis</i>
AIBN	2,2'-azobis(2-methylpropionitrile)
6-APA	6-aminopenicillanic acid
API	active pharmaceutical ingredient
Ara-G	9- β -D-arabinofuranosylguanidine
Ara-U	9- β -D-arabinofuranosyluridine
AspAT	aspartate aminotransferase
AT	aminotransferases
AZT	3'-azido-2',3'-dideoxythymidine (zidovudine)
BEHP	bis(2-ethylhexyl)phthalate
BES	<i>N,N</i> -bis(2-hydroxyethyl)-2-aminoethanesulfonic acid
BLAST	basic local alignment search tool
BREP	butanol-rinsed enzyme preparation
BSA	bovine serum albumin
BSA	<i>N</i> -bromosuccinimide
BVMO	Baeyer–Villiger monooxygenase
C	cytosine
CAL-A	lipase A from <i>Candida antarctica</i>
CAL-B	lipase B from <i>Candida antarctica</i>
Car	carboxylic acid reductase
CASTing	combinatorial active site saturation test
Cbz	Benzyloxycarbonyl
CCL	lipase from <i>Candida cylindracea</i> (now known as lipase from <i>Candida rugosa</i> or CRL)

CDI	1,1'-carbonyldiimidazole
CDW	cell dry weight
cGMP	current good manufacturing practice
CHMO	cyclohexanone monooxygenase
CINV	chemotherapy-induced nausea
CLEA	cross-linked enzyme aggregate
CLEC	cross-linked enzyme crystal
CNS	Central nervous system
CPDMO	cyclopentadecanone monooxygenase
CPO	chloroperoxidase
CRL	lipase from <i>Candida rugosa</i>
CSA	cysteine sulfinic acid
CYP	cytochrome P450
DBDMH	<i>N,N'</i> -dibromodimethylhydantoin
DBE	di- <i>n</i> -butylether
DCM	dichloromethane
DCW	dry cell weight
DDI	drug–drug interaction
DERA	2-deoxyribose-5-phosphate aldolase
dGTP	deoxyguanosine triphosphate
DHA	dihydroxyacetone
DHAP	dihydroxyacetone phosphate
DHF	dihydrofolate
DIPE	diisopropylether
DKR	dynamic kinetic resolution
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
dNTP	deoxyribonucleotide triphosphate
DoE	design of experiment
DOT	dissolved oxygen tension
DSMZ	Deutsche Sammlung von Mikroorganismen und Zellkulturen
dsDNA	double-stranded DNA
D4T	dideoxydidehydrothymidine
DTT	dithiothreitol
dUDP	2'-deoxyuridine-5'-diphosphate
dUMP	2'-deoxyuridine-5'-monophosphate
<i>E</i>	enantiomeric ratio
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid

EHS	environmental health and safety
epPCR	error-prone PCR
EtOAc	Ethyl acetate
FACS	fluorescence-activated cell sorting
FAD	flavin adenine dinucleotide
FADH ₂	flavin adenine dinucleotide, reduced form
FASTA	FAST ALL (a programme for fast protein comparison or fast nucleotide sequence comparison)
FDA	Food and Drug Administration (United States)
FDH	formate dehydrogenase
FMN	flavin mononucleotide (riboflavin-5'-phosphate)
FPLC	fast protein liquid chromatography
<i>FruA</i>	fructose-1,6-bisphosphate aldolase
FSA	D-fructose-6-phosphate aldolase
FTIR	Fourier-transform infrared spectroscopy
GABA	γ-aminobutyric acid
G	guanine
GC	gas chromatography
GDH	glucose dehydrogenase
GlcI	glucose isomerase
GMO	genetically modified organism
GMM	genetically modified microorganism
G6P	glucose-6-phosphate
G6PDH	glucose-6-phosphate dehydrogenase
GPC	gel permeation chromatography
GPO	L-glycerol-3-phosphate oxidase
GR	glucocorticoid receptor
GRAS	generally recognized as safe
GSK	GlaxoSmithKline
HBV	hepatitis B virus
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HIV	human immunodeficiency virus
HMQC	heteronuclear multiple quantum coherence
HNL	hydroxynitrile lyase
HOBt	1-hydroxybenzotriazole
HOPhPr	hydroxyphenylpropanol
HOTYR	hydroxytyrosol
HPA	hydroxypyruvate
HPI	N-hydroxyphthalimide
HPLC	high-performance liquid chromatography
HTS	high-throughput screening
HVAIc	Homovanillic alcohol

IMI	imidacloprid
Indels	insertions and deletions
IP	intellectual property
IPTG	isopropyl- β -D-thiogalactopyranoside
ISPR	<i>in situ</i> product removal
KPB	potassium phosphate buffer
KR	kinetic resolution
KRED	ketoreductase (alternative name for an alcohol dehydrogenase or ADH)
LAS	lovastatin ammonium salt
LB	Luria–Bertani
LCA	life cycle analysis
LovD	acyltransferase from the lovastatin biosynthetic pathway
Mab	monoclonal antibody
MAO-N	monoamine oxidase
MEA	malt extract agar
MES	2-morpholino ethansulfonic acid monohydrate
MGF	minimum genome factories
MML	lipase from <i>Mucor</i> sp.
MOPS	3-morpholino propane sulfonic acid
m.p.	melting point
MPA	mycophenolic acid
MPLC	medium-pressure chromatography
mRNA	messenger RNA
MS	molecular sieves
MTBE	<i>tert</i> -butylmethylether
MTQ	methyl-tetrahydroisoquinoline
MYB	malt yeast broth
NAD ⁺	β -nicotinamide adenine dinucleotide
NADH	β -nicotinamide adenine dinucleotide, reduced form
NADPH	β -nicotinamide adenine dinucleotide 2'-phosphate, reduced form
NADP ⁺	β -nicotinamide adenine dinucleotide 2'-phosphate
NAG	<i>N</i> -acetyl-D-glucosamine
NAM	<i>N</i> -acetyl-D-mannosamine
NANA	<i>N</i> -acetyl-D-neuraminic acid
NCE	new chemical entity
NK-1	neurokinin-1
NME	new molecular entity
NMR	nuclear magnetic resonance
NP	nucleoside phosphorylase
OCH	6-oxo camphor hydrolase
ORI	origin of replication
P450	cytochrome P450

P450 BM-3	cytochrome P450 BM-3 from <i>Bacillus megaterium</i>
PAMO	phenylacetone monooxygenase
Pase	acid phosphatase
PAT	process analytical technology
PCL	lipase from <i>Pseudomonas cepacia</i> (now renamed to <i>Burkholderia cepacia</i>)
PCR	polymerase chain reaction
PDCB	potato–dextrose–carrot broth
PEP	phosphoenolpyruvic acid
PFL	lipase from <i>Pseudomonas fluorescens</i>
PGA	penicillin G acylase
Pip2C	Δ^1 -piperidine-2-carboxylate reductase
PLE	pig liver esterase
<i>p</i> NPG	<i>p</i> -nitrophenyl- β -D-glucopyranoside
PNP	purine nucleoside phosphorylase
PPL	porcine pancreatic lipase
ProSAR	protein sequence–activity relationship
QbD	quality by design
QSAR	quantitative structure–activity relationship
RAMA	rabbit muscle aldolase (fructose-1,6-bis-phosphate aldolase)
R&D	research and development
rDNA	recombinant DNA
rRNA	ribosomal RNA
R_f	retention factor
RhaD	rhamnulose-1-phosphate aldolase
RNA	ribonucleic acid
ROH	generic alcohol
R_t	retention time
SAS	simvastatin ammonium salt
SCR	<i>Saccharomyces cerevisiae</i> carbonyl reductase
SIGEX	substrate-induced gene-expression screening
SMB	simulated moving bed chromatography
SOT	Spirulina–Ogawa–Terui
ssDNA	single-stranded DNA
T	thymine
Taq	a thermostable DNA polymerase from <i>Thermus aquaticus</i>
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TBME	<i>tert</i> -butylmethylether
TCA	trichloroacetic acid
TDP	thymidine 5'-phosphate
TdR	thymidine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THFo	tetrahydrofolate
ThDP	thiamine pyrophosphate
TK	transketolase
TLC	thin-layer chromatography
TMP	thymidine 5'-monophosphate
TMS	tetramethyl silane
TMOS	tetramethyl orthosilicate
TMSOTf	trimethylsilyl triflate
TP	thymidine-5'-phosphorylase
tris-HCl	tris(hydroxymethyl)aminomethane HCl
TTN	total turnover number
TYR	tyrosol
U	unit of enzyme activity ($\mu\text{mol min}^{-1}$)
U	uracil
UdR	2'-deoxyuridine
UDP	uridine-5'-diphosphate
UTP	uridine-5'-triphosphate
UDPGA	uridine-5'-diphosphoglucuronic acid
UDPGT	uridine-5'-diphosphoglucuronyl transferase
URDP	uridine-5'-phosphorylase
UV	ultraviolet
VVM	gas volume flow per unit of liquid volume per minute
WFCC	World Federation for Culture Collections
YPG	yeast extract–peptone–glucose

List of Contributors

Joseph P. Adams, GlaxoSmithKline, Synthetic Chemistry, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

Reiner Aichholz, Metabolism and Pharmacokinetics, NIBR, Novartis Pharma AG, CH-4002 Basel, Switzerland

Yasuhisa Asano, Biotechnology Research Center and Department of Biotechnology, Toyama Prefectural University, 5180 Kurokawa, Imizu, Toyama 939-0398, Japan

Manuela Avi, Institute of Organic Chemistry, Graz University of Technology, Stremayrgasse 16, 8010 Graz, Austria

Michèle P. Bertrand, Laboratoire de Chimie Moléculaire Organique, LCP UMR 6264, Boite 562, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Tek Chand Bhalla, Department of Biotechnology, Himachal Pradesh University, Shimla 171005, India

John Blacker, NPIL Pharma Ltd, Leeds Road, Huddersfield, HD1 9GA, UK

Lahssen El Blidi, Laboratoire SEESIB, UMR 6504 CNRS, Université Blaise Pascal, 24 avenue des Landais 63177 Aubière cedex, France

Pavla Bojarová, Institute of Microbiology, Center of Biocatalysis and Biotransformations, Academy of Sciences of the Czech Republic, Vídeňská 1083, CZ-142 20 Prague 4, Czech Republic

Jean Bolte, Department of Chemistry, Université Blaise Pascal, Clermont-Ferrand, France

Uwe T. Bornscheuer, Department of Biotechnology and Enzyme Catalysis, Institute of Biochemistry, Greifswald University, Felix-Hausdorff-Str. 4, 17487 Greifswald, Germany

Gary Breen, GlaxoSmithKline, Synthetic Chemistry, Leigh, Tonbridge, Kent, TN11 9AN, UK

Katja Buehler, Laboratory of Chemical Biotechnology, Faculty of Biochemical and Chemical Engineering, TU Dortmund, Emil-Figge-Strasse 66, 44221 Dortmund, Germany

J. van Buijtenen, Eindhoven University of Technology, Laboratory of Macromolecular and Organic Chemistry, PO Box 513, 5600 MB Eindhoven, The Netherlands

Andrew J. Carnell, Department of Chemistry, Robert Robinson Laboratories, University of Liverpool, Liverpool, L69 7ZD, UK

José A. Castillo, Biotransformation and Bioactive Molecules Group, Instituto de Química Avanzada de Cataluña, Consejo Superior de Investigaciones Científicas, Jordi Girona 18-26, 08034 Barcelona, Spain

Franck Charmantray, Laboratoire SEESIB, UMR 6504 CNRS, Université Blaise Pascal, 24 avenue des Landais, 63177 Aubière, France

Cinzia Chiappe, Dipartimento di Chimica e Chimica Industriale, Università di Pisa, 56126 Pisa, Italy

Cosimo Chirivì, Istituto di Chimica del Riconoscimento Molecolare, C.N.R., Via Mario Bianco 9, 20131 Milano, Italy

Gaik Khuan Chuah, Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 119260, Republic of Singapore

Pere Clapés, Biotransformation and Bioactive Molecules Group, Instituto de Química Avanzada de Cataluña, Consejo Superior de Investigaciones Científicas, Jordi Girona 18-26, 08034 Barcelona, Spain

Andrew J. Collis, GlaxoSmithKline, Biotechnology and Environmental Shared Service, North Lonsdale Road, Ulverston, Cumbria LA12 9DR, UK

Stefano Colonna, Dipartimento di Scienze Molecolari Applicate ai Biosistemi (DISMAB), Facoltà di Farmacia, Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy

Philip Conway, School of Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin 4, Ireland

Maria Serrano Correia, Rua Maria Auxiliadora, n°147, 6°andar porta 3, Bairro do Rosário, P-2750-616 Cascais, Portugal

María-Isabel Covas, Research Unit on Lipids and Cardiovascular Epidemiology, Institut Municipal d'Investigació Mèdica (IMIM). Universitat Pompeu Fabra (CEXS-UPF), Barcelona, Spain

Yi-jun Dai, Nanjing Engineering Research Center for microbiology, Jiangsu Key Laboratory for Biodiversity and Biotechnology, College of Life Science, Nanjing Normal University, 1, Wenyuan Rd, Nanjing 210046, PR China

Philippe Dellis, Synkem, 47 rue de Longvic, 21300 Chênôve, France

Paul Devine, Process Research, Merck Research Laboratories, Merck & Co. Inc. Rahway, NJ, USA

Andrew J. Ellis, School of Chemistry, Manchester Interdisciplinary Biocentre, University of Manchester, 131 Princess Street, Manchester, M1 7DN, UK

Tadashi Ema, Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan

Paul Engel, School of Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin 4, Ireland

Nobuyoshi Esaki, Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

Kurt Faber, Department of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Heinrichstrasse 28, 8010 Graz, Austria

Susana Fernández, Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, 33006-Oviedo (Asturias), Spain

Miguel Ferrero, Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, 33006-Oviedo (Asturias), Spain

Fred Fleitz, Process Research, Merck Research Laboratories, Merck & Co. Inc. Rahway, NJ, USA

Kam Loon Fow, Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 119260, Republic of Singapore

Aya Fujino, Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Petra Gadler, Department of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Heinrichstrasse 28, 8010 Graz, Austria

Nicoletta Gaggero, Dipartimento di Scienze Molecolari Applicate ai Biosistemi (DISMAB), Facoltà di Farmacia, Università degli Studi di Milano, via Venezian 21, 20133 Milano, Italy

Stéphane Gastaldi, Laboratoire de Chimie Moléculaire Organique, LCP UMR 6264, Boite 562, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Thierry Gefflaut, Department of Chemistry, Université Blaise Pascal, Clermont-Ferrand, France

Oreste Ghisalba, Ghisalba Life Sciences GmbH, Habshagstrasse 8c, CH-4153 Reinach, Switzerland

Gérard Gil, Laboratoire de Stéréochimie Dynamique et Chiralité, ISM2, UMR 6263, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Vicente Gotor, Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Biotecnología de Asturias, Universidad de Oviedo, 33006-Oviedo (Asturias), Spain

William A. Greenberg, Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Rd., La Jolla, CA 92037, USA

Herfried Griengl, Research Centre Applied Biocatalysis, Petersgasse 14, 8010 Graz, Austria

Gideon Grogan, York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York, YO10 5YW, UK

F. Hamzah, School of Chemical Engineering, Engineering Campus, Universiti Sains Malaysia, Seri Ampangan, 14300, Nibong Tebal, Penang, Malaysia

Bernhard Hauer, Institute of Technical Biochemistry, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany

Laurence Hecquet, Laboratoire SEESIB, UMR 6504 CNRS, Université Blaise Pascal, 24 avenue des Landais, 63177 Aubière, France

Virgil Hélaine, Laboratoire SEESIB, UMR 6504 CNRS, Université Blaise Pascal, 24 avenue des Landais, 63177 Aubière, France

Richard K. Henderson, GlaxoSmithKline, Centre of Excellence for Sustainability and Environment, Park Road, Ware, Hertfordshire SG12 0DP, UK

Cheryl Hill, York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York, YO10 5YW, UK

Frank Hollmann, Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany

C. Akira Horiuchi, Department of Chemistry, Rikkyo (St.Paul's) University, Nishi-Ikebukuro, Toshima-Ku, Tokyo 171-8501, Japan

Rui-Zhen Hou, Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, Jilin University, Changchun, 130021, PR China

Yi-Bing Huang, Key Laboratory for Molecular Enzymology and Engineering of Ministry of Education, Jilin University, Changchun, 130021, PR China

L.A. Hulshof, Eindhoven University of Technology, Laboratory of Macromolecular and Organic Chemistry, PO Box 513, 5600 MB Eindhoven, The Netherlands

Sayaka Ide, Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan

Masaya Ikunaka, Fine Chemicals Department, Nagase & Co., Ltd., 5-1, Nihonbashi-Kobunacho, Chuo-ku, Tokyo 103-8355, Japan

Tomoyuki Inoue, Institute of Microbiology, University of Stuttgart, Allmandring 31, 70569 Stuttgart, Germany

Stephan Jaenicke, Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 119260, Republic of Singapore

Dick B. Janssen, Biochemical Laboratory, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Nijenborgh 4, 9747 AG, Groningen, The Netherlands

Jesús Joglar, Biotransformation and Bioactive Molecules Group, Instituto de Química Avanzada de Cataluña, Consejo Superior de Investigaciones Científicas, Jordi Girona 18-26, 08034 Barcelona, Spain

Dimitris Kalaitzakis, Department of Chemistry, University of Crete, Iraklion-Voutes, 71003 Crete, Greece

Azlina Kamaruddin, School of Chemical Engineering, Engineering Campus, Universiti Sains Malaysia, Seri Ampangan, 14300, Nibong Tebal, Penang, Malaysia

Bjoern-Arne Kaup, DECHEMA e.V., Karl-Winnacker-Institut, Biochemical Engineering Group, Theodor-Heuss-Allee 25, 60486 Frankfurt, Germany

Romas J. Kazlauskas, Department of Biochemistry, Molecular Biology & Biophysics and The Biotechnology Institute, University of Minnesota, 1479 Gortner Avenue, Saint Paul, MN 55108, USA

Arshdeep Khare, Center for Biocatalysis and Bioprocessing, 2501 Crosspark Road, Suite C100 MTF, University of Iowa, Iowa City, Iowa, IA 52242-5000, USA

Olha Khymenets, Pharmacology Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain

Piotr Kielbasiński, Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, NL-6525 ED Nijmegen, The Netherlands

Mahn-Joo Kim, Department of Chemistry, Pohang University of Science and Technology (POSTECH), San-31, Hyojadong, Pohang 790-784, Korea

Anett Kirschner, Department of Biotechnology and Enzyme Catalysis, Institute of Biochemistry, Greifswald University, Felix-Hausdorff-Str. 4, 17487 Greifswald, Germany

Matthias Kittelmann, GDC/PSB/Bioreactions, Novartis Institutes of Biomedical Research (NIBR), Novartis Pharma AG, CH-4002 Basel, Switzerland

Soo-Byung Ko, Department of Chemistry, Pohang University of Science and Technology (POSTECH), San-31, Hyojadong, Pohang 790-784, Korea

Yoshinori Kondo, Department of Biomolecular Science, Gifu University, Yanagido 1-1, Gifu 501-1193, Japan

Birgit Kosjek, Process Research, Merck Research Laboratories, Merck & Co. Inc. Rahway, NJ, USA

Udo Kragl, Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany