

**Asymmetric Catalysis
on Industrial Scale**

*Edited by
Hans-Ulrich Blaser and
Hans-Jürgen Federsel*

Related Titles

Dai, L.-X., Hou, X.-L. (eds.)

Chiral Ferrocenes in Asymmetric Catalysis

Synthesis and Applications

2010

ISBN: 978-3-527-32280-0

Ma, S. (ed.)

Handbook of Cyclization Reactions

2010

ISBN: 978-3-527-32088-2

Royer, J. (ed.)

Asymmetric Synthesis of Nitrogen Heterocycles

2009

ISBN: 978-3-527-32036-3

Tao, J., Lin, G.-Q., Liese, A.

Biocatalysis for the Pharmaceutical Industry

Discovery, Development, and Manufacturing

2009

ISBN: 978-0-470-82314-9

Swiegers, G.

Mechanical Catalysis

Methods of Enzymatic, Homogeneous, and Heterogeneous Catalysis

2009

ISBN: 978-0-470-26202-3

Ding, K., Uozumi, Y. (eds.)

Handbook of Asymmetric Heterogeneous Catalysis

2008

ISBN: 978-3-527-31913-8

Gotor, V., Alfonso, I., García-Urdiales, E. (eds.)

Asymmetric Organic Synthesis with Enzymes

2008

ISBN: 978-3-527-31825-4

Chorkendorff, I., Niemantsverdriet, J. W.

Concepts of Modern Catalysis and Kinetics

2007

ISBN: 978-3-527-31672-4

Niemantsverdriet, J. W.

Spectroscopy in Catalysis

An Introduction

2007

ISBN: 978-3-527-31651-9

Cornils, B., Herrmann, W. A., Muhler, M., Wong, C.-H. (eds.)

Catalysis from A to Z

A Concise Encyclopedia

2007

ISBN: 978-3-527-31438-6

Asymmetric Catalysis on Industrial Scale

Challenges, Approaches, and Solutions

2nd edition

Edited by

Hans-Ulrich Blaser and Hans-Jürgen Federsel



WILEY-VCH Verlag GmbH & Co. KGaA

The Editors

Dr. Hans-Ulrich Blaser

Solvias AG
P.O. Box
Ch-4002
Basel
Switzerland

Dr. Hans-Jürgen Federsel

Director of Science Pharmaceutical
Development
AstraZeneca
151 85 Södertälje
Sweden

Cover

Production of chiral amines with isopropylamine as NH_2 -donor, catalyzed by an omega-transaminase. The figure inserted in the glass flask shows a homology model of the enzyme. Prepared by Maria Svedendahl and Professor Per Berglund, Royal Institute of Technology, School of Biotechnology, Stockholm, Sweden.

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

Composition Laserwords Private Ltd., Chennai, India

Printing and Binding Strauss GmbH, Mörlenbach

Cover Design Formgeber, Eppelheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32489-7

Contents

List of Contributors XIX

Introduction XXIX

Hans-Ulrich Blaser and Hans-Jürgen Federsel

Part I New processes for Existing Active Compounds (APIs) 1

1 Some Recent Examples in Developing Biocatalytic Pharmaceutical Processes 3

Junhua Tao, J. Liu, and Z. Chen

- 1.1 Introduction 3
- 1.2 Levetiracetam (Keppra®) 3
- 1.3 Atorvastatin (Lipitor®) 6
- 1.4 Pregabalin (Lyrica®) 8
- 1.5 Conclusion 11
- Acknowledgments 11
- References 11

2 Enantioselective Hydrogenation: Applications in Process R&D of Pharmaceuticals 13

Kurt Püntener and Michelangelo Scalone

- 2.1 Introduction 13
- 2.2 Carbonyl Hydrogenations 13
 - 2.2.1 Asymmetric Hydrogenation with Dynamic Kinetic Resolution of Racemic 1,4-Dibenzylpiperidin-3-one 13
 - 2.2.2 Asymmetric Hydrogenation of Methyl 3-Oxotetradecanoate 16
 - 2.2.3 Asymmetric Hydrogenation of 1,1,1-Trifluoroacetone 17
 - 2.2.4 Asymmetric Transfer Hydrogenation of Levodione 19
- 2.3 Imine Hydrogenation 21
 - 2.3.1 Asymmetric Hydrogenation of Hexabase Hydrogensulfate 21
- 2.4 Conclusion 23
- References 24

3	Chiral Lactones by Asymmetric Hydrogenation – a Step Forward in (+)-Biotin Production	27
	<i>Werner Bonrath, Reinhard Karge, Thomas Netscher, Felix Roessler, and Felix Spindler</i>	
3.1	Introduction: (+)-Biotin as an Example for the Industrial Production of Vitamins	27
3.2	Commercial Syntheses and Other Routes to (+)-Biotin by Total Synthesis	28
3.3	Catalytic Asymmetric Reduction of Cyclic Anhydride to D-Lactone	31
3.4	Conclusion	37
	Acknowledgments	38
	References	38
4	Biocatalytic Asymmetric Oxidation for the Production of Bicyclic Proline Peptidomimetics	41
	<i>James J. Lalonde and Jack Liang</i>	
4.1	Introduction	41
4.2	Development of Routes to 1 and 2	43
4.2.1	Early Routes to 1	43
4.2.1.1	Synthesis of Cyclic Amino Acids via Cyanation of Imines	45
4.2.2	Early Routes to 2	46
4.3	Asymmetric Biocatalytic Amine Oxidation	48
4.4	Enzyme Evolution – Current State of the Art	50
4.5	Amine Oxidase Evolution	53
4.6	Chemical Development	55
4.7	Optimization of Cyanation	56
4.8	Conclusion	57
	Acknowledgments	58
	References	59
5	The Asymmetric Reduction of Heterocyclic Ketones – a Key Step in the Synthesis of Potassium-Competitive Acid Blockers (P-CABs)	61
	<i>Andreas Marc Palmer and Antonio Zanotti-Gerosa</i>	
5.1	Potassium-Competitive Acid Blockers – a New Option for the Treatment of Acid-Related Diseases	61
5.2	Discovery and Development of 7H-8,9-Dihydropyrano[2,3-c]imidazo[1,2-a]pyridines as Potassium-Competitive Acid Blockers	62
5.3	Noyori-Type Catalysts for the Asymmetric Reduction of Prochiral Ketones	63
5.4	Research Overview	64
5.5	Asymmetric Reduction of Ketones Bearing the Imidazo[1,2-a]pyridine Skeleton	66

5.6	Asymmetric Reduction of Ketones Bearing the 3,6,7,8-Tetrahydrochromeno[7,8- <i>d</i>]imidazole Skeleton	70
5.7	Large-Scale Asymmetric Synthesis of the 3,6,7,8-Tetrahydrochromeno[7,8- <i>d</i>]imidazole BYK 405879	71
5.8	Conclusions	75
	Acknowledgments	76
	References	76
 Part II Processes for Important Buildings Blocks 79		
6	Application of a Multiple-Enzyme System for Chiral Alcohol Production	81
	<i>Junzo Hasegawa, Hirokazu Nanba, and Yoshihiko Yasohara</i>	
6.1	Introduction	81
6.2	Construction of an Enzymatic Reduction System	82
6.2.1	Searching the Carbonyl Reductases for Making the Library	83
6.2.1.1	Reductases for Chiral Hydroxycarboxylic Acid Ester Production	83
6.2.1.2	Cooperation of Reductase S1 and Glucose Dehydrogenase	84
6.2.1.3	Reductase for Chiral Halohydrin Production	88
6.2.1.4	Reductases for Chiral 3-Pyrrolidinol Production	89
6.2.1.5	Reductase for Chiral Pyridylethanol Derivative Production	92
6.2.2	Searching for a Tough FDH against Halo Ketones	95
6.2.3	Modification of Coenzyme Specificity in Carbonyl Reductase S1	97
6.3	Enzymatic Stereo inversion System	98
6.3.1	First Findings of Microbial Stereo inversion of 1,2-Diols	98
6.3.2	Construction of an Enzymatic Stereo inversion System for Chiral Alcohol Production	105
6.3.2.1	Enzymatic Stereo inversion System for (<i>R</i>)-CPD Production	106
6.3.2.2	Enzymatic Stereo inversion System for (<i>S</i>)-CPD Production	106
	References	108
 7	 Chemoenzymatic Route to the Side-Chain of Rosuvastatin	 111
	<i>Robert A. Holt and Christopher D. Reeve</i>	
7.1	Introduction	111
7.2	Route Selection	113
7.2.1	Deoxyribose-5-phosphate Aldolase-Based Route	113
7.2.2	Lipase-Catalyzed Tetrol Desymmetrization Route	114
7.2.3	Monooxygenase-Catalyzed Baeyer–Villiger Oxygenation	115
7.2.4	Claisen Condensation/Bioreduction Route	116
7.3	Process Development	118
7.3.1	Claisen Condensation	118
7.3.2	Asymmetric Bioreduction	120
7.3.3	Lipase-Catalyzed Transesterification	123
7.3.4	Acetonide Formation	124
7.3.5	Acetyl Deprotection	125

7.4	Conclusion	125
	Acknowledgments	125
	References	126
8	Asymmetric Hydrogenation of a 2-Isopropylcinnamic Acid Derivative <i>en Route</i> to the Blood Pressure-Lowering Agent Aliskiren	127
	<i>Jeroen A. F. Boogers, Dirk Sartor, Ulfried Felfer, Martina Kotthaus, Gerhard Steinbauer, Bert Dielemans, Laurent Lefort, André H. M. de Vries, and Johannes G. de Vries</i>	
8.1	Introduction	127
8.2	Development of Monodentate Phosphoramidites as Ligands for Asymmetric Hydrogenation	127
8.3	Instant Ligand Libraries of Monodentate BINOL-Based Phosphoramidites	130
8.4	Aliskiren TM	132
8.5	High-Throughput Screening in Search of a Cheap Phosphoramidite Ligand	134
8.6	Mixtures of Ligands	135
8.7	Further Screening of Conditions	138
8.8	Validation and Pilot Plant Run	138
8.9	Instant Ligand Library Screening to Further Optimize Rate and <i>ee</i>	141
8.10	Validations	143
8.11	Recent Developments in the Asymmetric Hydrogenation of 3	144
8.12	Conclusion	147
	References	148
9	Asymmetric Phase-Transfer Catalysis for the Production of Non-Proteinogenic α-Amino Acids	151
	<i>Masaya Ikunaka and Keiji Maruoka</i>	
9.1	Background	151
9.1.1	Non-Proteinogenic α -Amino Acids	151
9.1.2	Phase-Transfer-Catalyzed Asymmetric Alkylation to Produce NPAAAs	152
9.2	Designer's Chiral Phase-Transfer Catalysts	153
9.2.1	<i>N</i> -Spiro- <i>C</i> ₂ -Symmetric Chiral Catalyst of Bis-1,1'-binaphthyl Structure	154
9.2.2	<i>C</i> ₂ -Symmetric Chiral Catalyst of Mono-1,1'-binaphthyl Structure	156
9.2.3	Other Features Common to both <i>C</i> ₂ -Symmetric Chiral 1,1'-Binaphthyl-Derived Catalysts	157
9.3	Synthesis of the <i>C</i> ₂ -Symmetric Chiral Mono-1,1'-Binaphthyl-Derived Catalyst	159
9.4	Application of Enantiomers of 21 to the Industrial Production of NPAAAs	160

9.4.1	Ethyl (<i>S</i>)-Allylglycinate <i>p</i> -Toluenesulfonic Acid Salt	160
9.4.2	(<i>R</i>)- α -Methyl-4-fluorophenylalanine	163
9.4.3	<i>anti</i> -(2 <i>R</i> ,3 <i>R</i>)- β -methyl-4-fluorophenylalanine	164
9.5	Conclusion	167
	References	167
10	Development of Efficient Technical Processes for the Production of Enantiopure Amino Alcohols in the Pharmaceutical Industry	171
	<i>Franz Dietrich Klingler</i>	
10.1	Introduction	171
10.2	Phenylephrine	171
10.2.1	In Retrospect: Historic Developments and the Classical Technical Synthesis	171
10.2.2	Development of a New Asymmetric Synthesis for Phenylephrine	172
10.2.2.1	Ligand and Metal Screening	175
10.2.2.2	Optimization of the Ligand	176
10.2.2.3	Mechanistic Considerations	176
10.2.2.4	Optimization of the Reaction Conditions	177
10.2.2.5	Workup and Final Step to Phenylephrine Hydrochloride	178
10.3	Adrenaline (Epinephrine)	178
10.3.1	History and Classical Synthetic Route	178
10.3.2	Development of a New Technical Synthesis Based on Asymmetric Hydrogenation	180
10.4	Lobeline	180
10.4.1	History and Description of the Classical Synthesis	180
10.4.2	Development of an Efficient Two-Step Synthesis of Lobeline	182
10.5	Availability of the Catalyst	183
10.6	General Remarks on the Development of Industrial Processes for Asymmetric Hydrogenation	183
	References	184
11	The Asymmetric Hydrogenation of Enones – Access to a New L-Menthol Synthesis	187
	<i>Christoph Jäkel and Rocco Paciello</i>	
11.1	Introduction	187
11.1.1	Industrial Background	187
11.1.2	Scientific Background	190
11.2	Screening of Metal Complexes, Conditions, and Ligands	192
11.3	Scale-Up and Mechanistic Work	194
11.4	Catalyst Recycling and Continuous Processing	199
11.5	Conclusion	204

	Acknowledgments	204
	References	204
12	Eliminating Barriers in Large-Scale Asymmetric Synthesis	207
	<i>Hideo Shimizu, Noboru Sayo, and Takao Saito</i>	
12.1	Introduction	207
12.2	Improvement of the Synthetic Route to Biaryl Ligands	208
12.3	Development of an Efficient Process <i>En Route</i> to Unprotected β -Amino Acids	214
12.4	Conclusion	217
	References	217
13	Catalytic Asymmetric Ring Opening: A Transfer from Academia to Industry	219
	<i>Dirk Spielvogel</i>	
13.1	Introduction	219
13.2	Catalyst Preparation and Initial Optimization	221
13.3	Further Optimization	222
13.4	Process Adaptation	224
13.5	Protecting Group Adaptation	225
13.6	Use of Benzoate as O-nucleophile	226
13.7	Chemical Elaboration	227
13.8	Conclusion	227
	Acknowledgments	228
	References	229
14	Asymmetric Baeyer–Villiger Reactions Using Whole-Cell Biocatalysts	231
	<i>Roland Wohlgemuth and John M. Woodley</i>	
14.1	Introduction	231
14.2	Chemistry	232
14.3	Biocatalysts	234
14.4	Process Screening and Design	236
14.4.1	Cell Format	236
14.4.2	Sequence of Catalysis	237
14.4.3	Substrate Supply and Product Removal	237
14.4.4	Reactor Type	238
14.4.5	Type of Medium	239
14.5	Downstream Processing	240
14.6	Future Process Developments	240
14.7	Perspective	242
	References	244

15	Large-Scale Applications of Hydrolases in Biocatalytic Asymmetric Synthesis	249
	<i>Roland Wohlgemuth</i>	
15.1	Introduction	249
15.2	Chemistry	251
15.3	Biocatalyst	253
15.4	Process Screening and Design	255
15.5	Downstream Processing and Purification	257
15.6	Future Process Developments	259
15.7	Perspectives	259
	References	260
16	Scale-Up Studies in Asymmetric Transfer Hydrogenation	265
	<i>A. John Blacker and Peter Thompson</i>	
16.1	Background	265
16.2	Reaction Components	267
16.2.1	The Catalyst	267
16.2.2	The Hydrogen Donor	272
16.2.3	The Solvent	274
16.2.4	The Substrate	274
16.2.5	The Process	277
16.3	Case Studies	278
16.3.1	Diltiazem	278
16.3.2	(<i>R</i>)- <i>N</i> -Methyl- α -methyl-3',5'-bis(trifluoromethyl)benzylamine	280
16.3.3	Duloxetine	282
16.3.4	(<i>R</i>)-Styrene Oxide	284
16.3.5	(<i>S</i>)-2-(3-Nitrophenyl)ethylamine Hydrochloride	285
16.3.6	(<i>S</i>)-4-Fluorophenylethanol	285
16.3.7	(<i>R</i>)-1-Tetralol	287
16.4	Conclusions	288
	Acknowledgment	289
	References	289
17	2,2',5,5'-Tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene: A Very Efficient Chiral Ligand for Ru-Catalyzed Asymmetric Hydrogenations on the Multi-Kilograms Scale	291
	<i>Oreste Piccolo</i>	
17.1	Introduction	291
17.2	Case Histories	295
17.2.1	(<i>S</i> -) and (<i>R</i>)-Ethyl 4-Chloro-3-hydroxybutyrate	295
17.2.2	"ZD 3523"	296
17.3	Conclusion	298

Acknowledgments 298

References 298

18	The Power of Whole-Cell Reaction: Efficient Production of Hydroxyproline, Sugar Nucleotides, Oligosaccharides, and Dipeptides	301
	<i>Shin-ichi Hashimoto, Satoshi Koizumi, and Akio Ozaki</i>	
18.1	Introduction	301
18.2	Production of Hydroxyproline by Asymmetric Hydroxylation of L-Proline	302
18.2.1	Screening of Regio- and Stereospecific L-Proline Hydroxylases	303
18.2.2	Cloning and Characterization of Proline Hydroxylases	304
18.2.3	Enzymatic Production of Hydroxyproline from L-Proline	304
18.2.4	Production of Hydroxyproline from Glucose	305
18.2.5	Commercial Production of Hydroxyproline	306
18.3	Oligosaccharide Production by Bacterial Coupling	307
18.3.1	Bacterial Glycosyltransferases	307
18.3.2	Oligosaccharide Synthesis with Purified Enzyme Preparations	307
18.3.3	Production of Sugar Nucleotides by Bacterial Coupling	308
18.3.4	Production of Oligosaccharides by Bacterial Coupling	309
18.3.5	Large-Scale Production of Sugar Nucleotides and Oligosaccharides	311
18.4	Dipeptide Production Systems	311
18.4.1	Screening of a Novel Enzyme, L-Amino Acid α -Ligase	311
18.4.2	Dipeptide Production by a Resting Cell System	312
18.4.3	Dipeptide Production by Fermentation	313
18.4.4	Industrial Production of Dipeptides	314
18.5	Conclusion and Perspective	315
	References	316
19	Enantioselective Ketone Hydrogenation: from Research to Pilot Scale with Industrially Viable Ru–(Phosphine–Oxazoline) Complexes	321
	<i>Frédéric Naud, Felix Spindler, Carsten Rueggeberg, Andreas T. Schmidt, and Hans-Ulrich Blaser</i>	
19.1	Introduction	321
19.2	Ligand Screening and Optimization of the Reaction Conditions	322
19.2.1	Ligand Structure	322
19.2.2	Optimization of Reaction Conditions	323
19.3	Quality Risks	324
19.4	Health and Safety	325
19.5	Catalyst Removal	326
19.6	Final Process	327
	Acknowledgments	329
	References	329

Part III Processes for New Chemical Entities (NCEs) 331

20	Enabling Asymmetric Hydrogenation for the Design of Efficient Synthesis of Drug Substances 333
	<i>Yongkui Sun, Shane Krska, Scott Shultz, and David M. Tellers</i>
20.1	Introduction 333
20.2	Laropiprant 339
20.2.1	Reaction Discovery 339
20.2.2	Reaction Optimization and Demonstration 341
20.2.2.1	Catalyst Identification 341
20.2.2.2	Substrate Solubility 342
20.2.2.3	Temperature and Pressure 342
20.2.2.4	Catalyst Loading 343
20.2.2.5	Reaction Stress Testing 343
20.2.3	Kilogram-Scale Demonstration and Pilot Plant Execution 344
20.2.4	Pilot Plant Implementation 344
20.2.5	Final Remarks 345
20.3	Taranabant 345
20.3.1	Development of a Reductive Dynamic Kinetic Resolution Approach Towards Taranabant 347
20.3.2	Development of Long-Term Asymmetric Synthesis of Taranabant Utilizing Asymmetric Enamide Hydrogenation 350
20.4	Sitagliptin 361
20.5	Conclusions and Outlook 373
	Acknowledgments 373
	References 374
21	Scale-up of a Telescoped Enzymatic Hydrolysis Process for an Intermediate in the Synthesis of a Factor Xa Inhibitor 377
	<i>Hans Iding, Beat Wirz, Jean-Michel Adam, Pascal Dott, Wolfgang Haap, Rosa Maria Rodríguez Sarmiento, Thomas Oberhauser, Reinhard Reents, Rolf Fischer, and Stephan Lauper</i>
21.1	Introduction 377
21.2	The Discovery Chemistry Synthesis 379
21.3	Optimization and Multi-Kilogram Supply of Monoacid (<i>R, R</i>)-2 380
21.3.1	Resolution of Diester (<i>R, R</i>)-1 380
21.3.2	Monohydrolysis of Diester (<i>R, R</i>)-1 382
21.4	Process Development of the <i>N</i> -Boc Approach 383
21.4.1	Resolution: Selection of the Enzyme 383
21.4.1.1	Optimization of Lipase D 383
21.4.1.2	Optimization of Lipolase 100 l 383
21.4.2	Robustness of the Resolution of <i>trans-rac</i> -1 385
21.4.2.1	pH Control 385
21.4.2.2	Substrate Quality 386
21.4.2.3	Stirring Speed 386

21.4.2.4	Isolation	387
21.5	Scalable Enzymatic Monohydrolysis of the Diester (<i>R,R</i>)-1	388
21.5.1	Residual Heptane Content	388
21.5.2	Isolation	389
21.6	Production – Experimental Part	389
21.6.1	Equipment	389
21.6.2	Resolution of <i>N</i> -Boc-Diester-1	390
21.6.3	Isolation of Diester (<i>R,R</i>)-1	390
21.6.4	Monohydrolysis of Diester (<i>R,R</i>)-1	391
21.6.5	Isolation of Monoacid (<i>R,R</i>)-2	391
21.6.6	Points to Consider for Future Campaigns	392
21.7	Evaluation of an Enzymatic Alternative – the <i>N</i> -Difluoroethyl Approach	392
21.7.1	Resolution of Diester <i>trans-rac</i> -3	393
21.7.2	Monohydrolysis of Diester (<i>R,R</i>)-3	393
21.8	Discussion	394
	Acknowledgments	395
	References	396
22	An Efficient, Asymmetric Synthesis of Odanacatib, a Selective Inhibitor of Cathepsin K for the Treatment of Osteoporosis, Using an Enzyme-Mediated Dynamic Kinetic Resolution	397
	<i>Matthew D. Truppo</i>	
22.1	Introduction	397
22.2	Fluoroleucine Synthesis Strategy	397
22.2.1	Retro-Synthetic Analysis	398
22.2.2	Enzyme Screen for Azlactone Ring Opening	399
22.3	First-Generation Enzymatic Dynamic Kinetic Resolution: Batch Process	400
22.4	Development of Enzymatic Dynamic Kinetic Resolution: Towards a Manufacturing Process	401
22.4.1	Kinetic Analysis of the Reaction System	401
22.4.1.1	Effect of Temperature on the Rates of Reaction	402
22.4.1.2	Effects of Azlactone, Ethanol, and Water Concentration on the Rates of Reaction	403
22.4.1.3	Enzyme Deactivation Rate	404
22.4.2	Kinetic Model of Enzymatic Dynamic Kinetic Resolution	405
22.4.2.1	Kinetic Equations	405
22.4.2.2	Kinetic Model Fit to Experimental Batch Reaction Data	406
22.4.3	Fed Batch Reaction System	406
22.4.4	Plug Flow Column Reactor System	408
22.5	Pilot Plant Runs	410
22.6	Conclusion	411
	Acknowledgment	413
	References	413

23	Biocatalytic Routes to the GPIIb/IIIa Antagonist Lotrafiban, SB 214857	415
	<i>Andy Wells</i>	
23.1	Introduction	415
23.2	The Medicinal Chemistry Route of Synthesis	416
23.3	The First Biocatalytic Route – a Late-Stage Resolution	417
23.3.1	Synthesis of Racemic 1,4-Benzodiazepines	418
23.3.2	Functionalization at C-7 – Halogenation and Aminocarbonylation	418
23.3.3	Screening for a Suitable Biocatalyst	422
23.3.4	Product Isolation	424
23.3.5	Bioresolution on Scale	425
23.4	Early-Stage Resolution	426
23.4.1	Substrate and Biocatalyst Selection	426
23.4.2	Work-up and “ <i>In Situ</i> ” Iodination	428
23.4.3	Early-Stage Resolution on Scale	429
23.4.4	Racemization of (<i>R</i>)-1,4-Benzodiazepines	429
23.4.5	The 4,4'-Bipiperidine Issue Solved	430
23.4.6	Carbonylation Using 4,4'-Bipiperidine	431
23.4.7	Aminocarbonylation of SB 240093	431
23.5	Catalase for the Removal of Iodide	432
23.5.1	The Final Steps	434
23.6	Other Synthetic Strategies to Chiral Lotrafiban Intermediates	434
23.7	The End Game	435
	Acknowledgment	436
	References	436
24	Discovery and Development of a Catalytic Asymmetric Conjugate Addition of Ketoesters to Nitroalkenes and Its Use in the Large-Scale Preparation of ABT-546	439
	<i>David M. Barnes</i>	
24.1	Introduction	439
24.2	Retrosynthetic Analysis of ABT-546	440
24.3	Early Asymmetric Syntheses	442
24.4	Synthesis of the Reaction Partners	442
24.5	Discovery of the Asymmetric Conjugate Addition Reaction	444
24.6	Completion of the Synthesis of ABT-546	450
24.7	Extension to Other Reaction Partners	453
24.8	Conclusion	454
	References	454
25	The Kagan Oxidation – Industrial-Scale Asymmetric Sulfoxidations in the Synthesis of Two Related NK1/NK2 Antagonists	457
	<i>David R. J. Hose, Bharti Patel, Sharon A. Bowden, and Jonathan D. Moseley</i>	
25.1	Introduction	457

25.2	Background and Introduction to ZD7944	457
25.3	Introduction to the ZD7944 CBz Sulfoxide Stage	459
25.4	Process Development of ZD7944 CBz Sulfoxide	461
25.5	Additional Investigations in the Development of ZD7944 CBz Sulfoxide	463
25.6	The Impact of Other Stages on the ZD7944 CBz Sulfoxide Process	464
25.7	Summary of ZD7944	465
25.8	Background and Introduction to ZD2249	466
25.9	Process Development of ZD2249 CBz Sulfoxide	467
25.10	Summary of ZD2249	469
25.11	Comparisons and Conclusions	469
	Acknowledgments	470
	References	470
26	Large-Scale Application of Asymmetric Phase-Transfer Catalysis for Amino Acid Synthesis	473
	<i>Daniel E. Patterson, Shiping Xie, Lynda Jones, Martin H. Osterhout, Christopher G. Henry, and Thomas D. Roper</i>	
26.1	Introduction	473
26.2	Initial Strategy	474
26.3	Synthesis of 4,4'-Difluorobenzylhydriyl Bromide	475
26.4	Initial Studies and Optimization	476
26.5	Scale-Up of the PTC Alkylation	478
26.6	Conclusion	481
26.7	Experimental	482
26.7.1	General	482
26.7.2	Synthesis of 4-Fluoro- β -(4-fluorophenyl)-L-tert-butylphenylalanine Benzophenone Imine 7	482
26.7.3	Synthesis of 4-Fluoro- β -(4-fluorophenyl)-L-phenylalanine Hydrochloride 11	483
	References	483
27	Application of Phase-Transfer Catalysis in the Organocatalytic Asymmetric Synthesis of an Estrogen Receptor Beta-Selective Agonist	485
	<i>Jeremy P. Scott</i>	
27.1	Introduction	485
27.2	Medicinal Chemistry Synthesis and Revised Synthetic Plan	485
27.3	Preparation of the Phase-Transfer Substrate 11	488
27.4	Asymmetric Phase-Transfer Michael Addition	489
27.4.1	Catalyst Structure Optimization	490
27.4.2	Preparation of the Phase-Transfer Catalyst 20g	491
27.4.3	Agitation Rate	491

27.4.4	Impurity Issues, Robinson Annulation, and <i>ee</i> Upgrade	492
27.4.4.1	Experimental Details for Catalytic Asymmetric Phase-Transfer Addition: Preparation of (9a <i>S</i>)-8-chloro-7-methoxy-9a-(2-phenoxyethyl)-1,2,9,9a-tetrahydro-3 <i>H</i> -fluoren-3-one (9)	493
27.5	Ether Cleavage, Cyclization, and Chlorination	494
27.6	Conclusion	495
	Acknowledgments	496
	References	496
28	Asymmetric Synthesis of HCV and HPV Drug Candidates on Scale: The Choice Between Enantioselective and Diastereoselective Syntheses	499
	<i>Jeremy D. Cobb, Bob E. Cooley, Roy C. Flanagan, Mary M. Jackson, Lynda A. Jones, Richard T. Matsuoka, Alan Millar, Daniel E. Patterson, Matthew J. Sharp, Jennifer F. Toczko, Shiping Xie, and Xiaoming Zhou</i>	
28.1	Introduction	499
28.2	GSK260983A (1) for the HPV	500
28.2.1	Target and Background	500
28.2.2	Synthetic Strategy	500
28.2.3	Racemic Synthesis	501
28.2.4	Enantioselective Synthesis Through Chiral Catalysis	502
28.2.5	Diastereoselective Synthesis Through Chiral Auxiliaries	503
28.2.5.1	Screening for Selectivity	503
28.2.5.2	Scale-Up of the Reductive Amination	504
28.2.5.3	Completion of the Synthesis: Meeting the Challenges in Removal of the Chiral Auxiliaries and Final API Formation	504
28.2.6	Conclusion	506
28.3	GSK873082X (2) for the HCV	506
28.3.1	Target and Background	506
28.3.2	Synthetic Strategy	507
28.3.3	Racemic Synthesis	508
28.3.4	Diastereoselective Synthesis	509
28.3.5	Enantioselective Synthesis	509
28.3.5.1	The Literature Precedents	509
28.3.5.2	The Concept of Using an Alkaloid as a Bidentate Ligand for the [3 + 2] Cycloaddition	510
28.3.5.3	Proof of Concept of the Chiral Catalysis	511
28.3.5.4	Optimization of the Chiral Catalysis	513
28.3.5.5	Scale-Up of Enantioselective Synthesis	514
28.3.6	Completion of the Synthesis of GSK873082X (2)	516
28.3.6.1	<i>N</i> -Acylation of the Pyrrolidine	516
28.3.6.2	Addressing the Chemoselectivity and Safety Issues in Reduction of an Ester	516
28.3.6.3	Final Steps to the Target	520

XVIII | *Contents*

28.4	Conclusion	520
	Acknowledgments	521
	References	521
	Index	523

List of Contributors

Jean-Michel Adam

F. Hoffmann-La Roche Ltd.
Pharma Research Basel
Technical Sciences
Chemical Synthesis
Synthesis and Process Research
Basel
Switzerland

David M. Barnes

Abbott Laboratories
PPD Process Research
1401 Sheridan Road
North Chicago
IL 60064
USA

A. John Blacker

Piramal Healthcare R&D
Leeds Road
Huddersfield
HD1 9GA
UK

and

University of Leeds
Institute of Process Research
Development
School of Chemistry
Leeds, LS2 9JT
UK

Hans-Ulrich Blaser

Solvias AG
P.O. Box
CH-4002
Basel
Switzerland

Werner Bonrath

DSM Nutritional Products
Research and Development
P.O. Box 2676
4002 Basel
Switzerland

Jeroen A. F. Boogers

DSM Innovative Synthesis BV
A unit of DSM Pharma Chemicals
PO Box 18
6160 MD Geleen
The Netherlands

Sharon A. Bowden

AstraZeneca
PR&D
Avlon Works
Severn Road
Hallen
Bristol, BS10 7ZE
UK

Z. Chen

Elevance Renewable Sciences
175 E. Crossroad Parkway
Bolingbrook
IL 60440
USA

Jeremy D. Cobb

GlaxoSmithKline
Chemical Development
5 Moore Drive
PO Box 13398
Research Triangle Park
NC 27709-3398
USA

Bob E. Cooley

GlaxoSmithKline
Chemical Development
5 Moore Drive
PO Box 13398
Research Triangle Park
NC 27709-3398
USA

Johannes G. de Vries

DSM Innovative Synthesis BV
A unit of DSM Pharma Chemicals
PO Box 18
6160 MD Geleen
The Netherlands

André H. M. de Vries

DSM Innovative Synthesis BV
A unit of DSM Pharma Chemicals
PO Box 18
6160 MD Geleen
The Netherlands

Bert Dielemans

DSM Innovative Synthesis BV
A unit of DSM Pharma Chemicals
PO Box 18
6160 MD Geleen
The Netherlands

Pascal Dott

F. Hoffmann-La Roche Ltd.
Pharma Research Basel
Technical Sciences
Chemical Synthesis
Kilolab
Basel
Switzerland

Hans-Jürgen Federsel

Director of Science
Pharmaceutical Development
AstraZeneca
151 85 Södertälje
Sweden

Ulfried Felfer

DSM Fine Chemicals Austria Nfg
GmbH & Co Kg
St.-Peter-Strasse 25
4021 Linz
Austria

Rolf Fischer

F. Hoffmann-La Roche Ltd.
Pharma Technical Development
Basel
Switzerland

Roy C. Flanagan

GlaxoSmithKline
Chemical Development
5 Moore Drive
PO Box 13398
Research Triangle Park
NC 27709-3398
USA

Wolfgang Haap

F. Hoffmann-La Roche Ltd.
Pharma Research Basel
Discovery Chemistry
Basel
Switzerland