

Contents

Foreword V

Preface XVII

List of Contributors XIX

1 Stoichiometric Asymmetric Synthesis 1

- 1.1 Development of Novel Enantioselective Synthetic Methods 1
Dieter Enders and Wolfgang Bettray

1.1.1 Introduction 1

1.1.2 α -Silyl Ketone-Controlled Asymmetric Syntheses 1

1.1.2.1 Regio- and Enantioselective α -Fluorination of Ketones 2

1.1.2.2 α -Silyl Controlled Asymmetric Mannich Reactions 3

1.1.3 Asymmetric Hetero-Michael Additions 5

1.1.3.1 Asymmetric Aza-Michael Additions 5

1.1.3.2 Asymmetric Oxa-Michael Additions 10

1.1.3.3 Asymmetric Phospha-Michael-Additions 11

1.1.4 Asymmetric Syntheses with Lithiated α -Aminonitriles 14

1.1.4.1 Asymmetric Nucleophilic α -Aminoacylation 14

1.1.4.2 Asymmetric Nucleophilic Alkenylation of Aldehydes 16

1.1.5 Asymmetric Electrophilic α -Substitution of Lactones and Lactams 18

1.1.6 Asymmetric Synthesis of α -Phosphino Ketones and 2-Phosphino Alcohols 22

1.1.7 Asymmetric Synthesis of 1,3-Diols and *anti*-1,3-Polyols 24

1.1.8 Asymmetric Synthesis of α -Substituted Sulfonamides and Sulfonates 26

- 1.2 Asymmetric Synthesis of Natural Products Employing the SAMP/RAMP Hydrazine Methodology 38
Dieter Enders and Wolfgang Bettray

1.2.1 Introduction 38

1.2.2 Stigmatellin A 38

1.2.3	Callistatin A	41
1.2.4	Dehydroiridodiol(dial) and Neonepetalactone	51
1.2.5	First Enantioselective Synthesis of Dendrobatid Alkaloids Indolizidine 209I and 223J	53
1.2.6	Efficient Synthesis of (2S,12'R)-2-(12'-Aminotridecyl)pyrrolidine, a Defense Alkaloid of the Mexican Bean Beetle	57
1.2.7	2-epi-Deoxoprosopinine	58
1.2.8	Attenol A and B	62
1.2.9	Asymmetric Synthesis of (+)- and (-)-Streptenol A	64
1.2.10	Sordidin	66
1.2.11	Prelactone B and V	69
1.3	Asymmetric Synthesis Based on Sulfonimidoyl-Substituted Allyltitanium Complexes	75 <i>Hans-Joachim Gais</i>
1.3.1	Introduction	75
1.3.2	Hydroxyalkylation of Sulfonimidoyl-Substituted Allyltitanium Complexes	80
1.3.2.1	Sulfonimidoyl-Substituted Bis(allyl)titanium Complexes	80
1.3.2.2	Sulfonimidoyl-Substituted Mono(allyl)tris(diethylamino)titanium Complexes	82
1.3.3	Aminoalkylation of Sulfonimidoyl-Substituted Allyltitanium Complexes	85
1.3.3.1	Sulfonimidoyl-Substituted Bis(allyl)titanium Complexes	85
1.3.3.2	Sulfonimidoyl-Substituted Mono(allyl)tris(diethylamino)titanium Complexes	86
1.3.4	Structure and Reactivity of Sulfonimidoyl-Substituted Allyltitanium Complexes	88
1.3.4.1	Sulfonimidoyl-Substituted Bis(allyl)titanium Complexes	88
1.3.4.2	Sulfonimidoyl-Substituted Mono(allyl)titanium Complexes	91
1.3.5	Asymmetric Synthesis of Homopropargyl Alcohols	95
1.3.6	Asymmetric Synthesis of 2,3-Dihydrofurans	96
1.3.7	Synthesis of Bicyclic Unsaturated Tetrahydrofurans	98
1.3.8	Asymmetric Synthesis of Alkenyloxiranes	100
1.3.9	Asymmetric Synthesis of Unsaturated Mono- and Bicyclic Prolines	102
1.3.10	Asymmetric Synthesis of Bicyclic Amino Acids	105
1.3.11	Asymmetric Synthesis of β -Amino Acids	108
1.3.12	Conclusion	111
1.4	The “Daniphos” Ligands: Synthesis and Catalytic Applications	115 <i>Albrecht Salzer and Wolfgang Braun</i>
1.4.1	Introduction	115
1.4.2	General Synthesis	116

1.4.3	Applications in Stereoselective Catalysis	120
1.4.3.1	Enantioselective Hydrogenations	120
1.4.3.2	Diastereoselective Hydrogenation of Folic Acid Ester	122
1.4.3.3	Enantioselective Isomerization of Geranylamine to Citronellal	124
1.4.3.4	Nucleophilic Asymmetric Ring-Opening of Oxabenzenorbornadiene	124
1.4.3.5	Enantioselective Suzuki Coupling	126
1.4.3.6	Asymmetric Hydrovinylation	126
1.4.3.7	Allylic Sulfonation	128
1.4.4	Conclusion	129
1.5	New Chiral Ligands Based on Substituted Heterometallocenes	130
	<i>Christian Ganter</i>	
1.5.1	Introduction	130
1.5.2	General Properties of Phosphaferrocenes	131
1.5.3	Synthesis of Phosphaferrocenes	132
1.5.4	Preparation of Bidentate P,P and P,N Ligands	133
1.5.5	Modification of the Backbone Structure	136
1.5.6	Cp-Phosphaferrocene Hybrid Systems	139
1.5.7	Catalytic Applications	145
1.5.8	Conclusion	146
2	Catalytic Asymmetric Synthesis	149
2.1	Chemical Methods	149
2.1.1	Sulfoximines as Ligands in Asymmetric Metal Catalysis	149
	<i>Carsten Bolm</i>	
2.1.1.1	Introduction	149
2.1.1.2	Development of Methods for Sulfoximine Modification	150
2.1.1.3	Sulfoximines as Ligands in Asymmetric Metal Catalysis	162
2.1.1.4	Conclusions	170
2.1.2	Catalyzed Asymmetric Aryl Transfer Reactions	176
	<i>Carsten Bolm</i>	
2.1.2.1	Introduction	176
2.1.2.2	Catalyst Design	177
2.1.2.3	Catalyzed Aryl Transfer Reactions	180
2.1.3	Substituted [2.2]Paracyclophane Derivatives as Efficient Ligands for Asymmetric 1,2- and 1,4-Addition Reactions	196
	<i>Stefan Bräse</i>	

- 2.1.3.1 [2.2]Paracyclophanes as Chiral Ligands 196
2.1.3.2 Synthesis of [2.2]Paracyclophane Ligands 199
2.1.3.2.1 Preparation of FHPG-, AHPC-, and BHPC-Based Imines 199
2.1.3.2 Structural Information on AHPC-Based Imines 199
2.1.3.3 Asymmetric 1,2-Addition Reactions to Aryl Aldehydes 200
2.1.3.3.1 Initial Considerations 200
2.1.3.3.2 Asymmetric Addition Reactions to Aromatic Aldehydes: Scope of Substrates 203
2.1.3.4 Asymmetric Addition Reactions to Aliphatic Aldehydes 205
2.1.3.5 Addition of Alkenylzinc Reagents to Aldehydes 206
2.1.3.6 Asymmetric Conjugate Addition Reactions 208
2.1.3.7 Asymmetric Addition Reactions to Imines 208
2.1.3.8 Asymmetric Addition Reactions on Solid Supports 212
2.1.3.8.1 Applications 213
2.1.3.9 Conclusions and Future Perspective 213
- 2.1.4 Palladium-Catalyzed Allylic Alkylation of Sulfur and Oxygen Nucleophiles – Asymmetric Synthesis, Kinetic Resolution and Dynamic Kinetic Resolution 215
Hans-Joachim Gais
- 2.1.4.1 Introduction 215
2.1.4.2 Asymmetric Synthesis of Allylic Sulfones and Allylic Sulfides and Kinetic Resolution of Allylic Esters 216
2.1.4.2.1 Kinetic Resolution 216
2.1.4.2.2 Selectivity 220
2.1.4.2.3 Asymmetric Synthesis 220
2.1.4.2.4 Synthesis of Enantiopure Allylic Alcohols 224
2.1.4.3 Asymmetric Rearrangement and Kinetic Resolution of Allylic Sulfinates 225
2.1.4.3.1 Introduction 225
2.1.4.3.2 Synthesis of Racemic Allylic Sulfinates 225
2.1.4.3.3 Pd-Catalyzed Rearrangement 226
2.1.4.3.4 Kinetic Resolution 227
2.1.4.3.5 Mechanistic Considerations 228
2.1.4.4 Asymmetric Rearrangement of Allylic Thiocarbamates 229
2.1.4.4.1 Introduction 229
2.1.4.4.2 Synthesis of Racemic O-Allylic Thiocarbamates 229
2.1.4.4.3 Acyclic Carbamates 229
2.1.4.4.4 Cyclic Carbamates 231
2.1.4.4.5 Mechanistic Considerations 232
2.1.4.4.6 Synthesis of Allylic Sulfides 232
2.1.4.5 Asymmetric Synthesis of Allylic Thioesters and Kinetic Resolution of Allylic Esters 233
2.1.4.5.1 Introduction 233

- 2.1.4.5.2 Asymmetric Synthesis of Allylic Thioesters 234
2.1.4.5.3 Kinetic Resolution of Allylic Esters 235
2.1.4.5.4 Memory Effect and Dynamic Kinetic Resolution of the Five-Membered Cyclic Acetate 238
2.1.4.5.5 Asymmetric Synthesis of Cyclopentenyl Thioacetate 242
2.1.4.6 Kinetic and Dynamic Kinetic Resolution of Allylic Alcohols 242
 2.1.4.6.1 Introduction 242
 2.1.4.6.2 Asymmetric Synthesis of Symmetrical Allylic Alcohols 242
 2.1.4.6.3 Asymmetric Synthesis of Unsymmetrical Allylic Alcohols 244
 2.1.4.6.4 Asymmetric Synthesis of a Prostaglandin Building Block 245
 2.1.4.6.5 Investigation of an Unsaturated Analogue of BPA 245
 2.1.4.7 Conclusions 246
- 2.1.5 The QUINAPHOS Ligand Family and its Application in Asymmetric Catalysis 250
 Giancarlo Franciò, Felice Faraone, and Walter Leitner
- 2.1.5.1 Introduction 250
 2.1.5.2 Synthetic Strategy 252
 2.1.5.3 Stereochemistry and Coordination Properties 254
 2.1.5.3.1 Free Ligands 254
 2.1.5.3.2 Complexes 256
 2.1.5.4 Catalytic Applications 261
 2.1.5.4.1 Rhodium-Catalyzed Asymmetric Hydroformylation of Styrene 261
 2.1.5.4.2 Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Alkenes 263
 2.1.5.4.3 Ruthenium-Catalyzed Asymmetric Hydrogenation of Aromatic Ketones 265
 2.1.5.4.4 Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Enones 267
 2.1.5.4.5 Nickel-Catalyzed Asymmetric Hydrovinylation 268
 2.1.5.4.6 Nickel-Catalyzed Cycloisomerization of 1,6-Dienes 270
 2.1.5.5 Conclusions 273
- 2.1.6 Immobilization of Transition Metal Complexes and Their Application to Enantioselective Catalysis 277
 Adrian Crozman, Carmen Schuster, Hans-Hermann Wagner, Melinda Batorfi, Jairo Cubillos, and Wolfgang Hölderich
- 2.1.6.1 Introduction 277
 2.1.6.2 Immobilized Rh Diphosphino Complexes as Catalysts for Asymmetric Hydrogenation 278
 2.1.6.2.1 Preparation and Characterization of the Immobilized Rh-Diphosphine Complexes 279

- 2.1.6.2.2 Enantioselective Hydrogenation over Immobilized Rhodium Diphosphine Complexes 282
- 2.1.6.3 Heterogeneous Asymmetric Epoxidation of Olefins over Jacobsen's Catalyst Immobilized in Inorganic Porous Materials 284
- 2.1.6.3.1 Preparation and Characterization of Immobilized Jacobsen's Catalysts 285
- 2.1.6.3.2 Epoxidation of Olefins over Immobilized Jacobsen Catalysts 287
- 2.1.6.4 Novel Heterogenized Catalysts for Asymmetric Ring-Opening Reactions of Epoxides 291
- 2.1.6.4.1 Synthesis and Characterization of the Heterogenized Catalysts 291
- 2.1.6.4.2 Asymmetric Ring Opening of Epoxides over New Heterogenized Catalysts 293
- 2.1.6.5 Conclusions 295
- 2.2 Biological Methods 298
- 2.2.1 Directed Evolution to Increase the Substrate Range of Benzoylformate Decarboxylase from *Pseudomonas putida* 298
Marion Wendorff, Thorsten Eggert, Martina Pohl, Carola Dresen, Michael Müller, and Karl-Erich Jaeger
- 2.2.1.1 Introduction 298
- 2.2.1.2 Materials and Methods 300
- 2.2.1.2.1 Reagents 300
- 2.2.1.2.2 Construction of Strains for Heterologous Expression of BFD and BAL 300
- 2.2.1.2.3 Polymerase Chain Reactions 301
- 2.2.1.2.4 Generation of a BFD Variant Library by Random Mutagenesis 302
- 2.2.1.2.5 High-Throughput Screening for Carboligation Activity with the Substrates Benzaldehyde and Dimethoxyacetaldehyde 303
- 2.2.1.2.6 Expression and Purification of BFD Variants 303
- 2.2.1.2.7 Protein Analysis Methods 304
- 2.2.1.2.8 Enzyme Activity Assays 304
- 2.2.1.3 Results and Discussion 304
- 2.2.1.3.1 Overexpression of BFD in *Escherichia coli* 304
- 2.2.1.3.2 Random Mutagenesis of BFD Variant L476Q 305
- 2.2.1.3.3 Development of a High-Throughput Screening Assay for Carboligase Activity 305
- 2.2.1.3.4 Identification of a BFD Variant with an Optimized Acceptor Aldehyde Spectrum 306
- 2.2.1.3.5 Biochemical Characterization of the BFD Variants 308
- 2.2.1.3.6 Decreased Benzoyl Formate Decarboxylation Activity of Variant 55E4 308

- 2.2.1.3.7 Formation of 2-Hydroxy-3,3-dimethoxypropiophenone and Benzoin 308
- 2.2.1.3.8 Enantioselectivity of the Carboligation Reaction 310
- 2.2.1.4 Conclusions 311
- 2.2.2 C–C-Bonding Microbial Enzymes: Thiamine Diphosphate-Dependent Enzymes and Class I Aldolases 312
Georg A. Sprenger, Melanie Schürmann, Martin Schürmann, Sandra Johnen, Gerda Sprenger, Hermann Sahm, Tomoyuki Inoue, and Ulrich Schörken
- 2.2.2.1 Introduction 312
- 2.2.2.2 Thiamine Diphosphate (ThDP)-Dependent Enzymes 312
- 2.2.2.2.1 Transketolase (TKT) 313
- 2.2.2.2.2 1-Deoxy-D-xylulose 5-Phosphate Synthase (DXS) 317
- 2.2.2.2.3 Phosphonopyruvate Decarboxylase (PPD) from *Streptomyces viridochromogenes* 318
- 2.2.2.3 Class I Aldolases 318
- 2.2.2.3.1 Transaldolase (TAL) 320
- 2.2.2.3.2 Fructose 6-Phosphate Aldolase (FSA) 321
- 2.2.2.4 Summary and Outlook 321
- 2.2.3 Enzymes for Carboligation – 2-Ketoacid Decarboxylases and Hydroxynitrile Lyases 327
Martina Pohl, Holger Breittaup, Bettina Frölich, Petra Heim, Hans Iding, Bettina Juchem, Petra Siegert, and Maria-Regina Kula
- 2.2.3.1 Introduction 327
- 2.2.3.2 2-Ketoacid Decarboxylases 327
- 2.2.3.2.1 Comparative Biochemical Characterization of Wild-Type PDC and BFD 328
- 2.2.3.2.2 Identification of Amino Acid Residues Relevant to Substrate Specificity and Enantioselectivity 330
- 2.2.3.2.3 Optimization of the Substrate Range of BFD by Site-Directed Mutagenesis 330
- 2.2.3.2.4 Optimization of Stability and Substrate Range of BFD by Directed Evolution 330
- 2.2.3.3 Hydroxynitrile Lyases 332
- 2.2.3.3.1 HNL from *Sorghum bicolor* 333
- 2.2.3.3.2 HNL from *Linum usitatissimum* 337
- 2.2.4 Preparative Syntheses of Chiral Alcohols using (R)-Specific Alcohol Dehydrogenases from *Lactobacillus* Strains 341
Andrea Weckbecker, Michael Müller, and Werner Hummel
- 2.2.4.1 Introduction 341
- 2.2.4.2 (R)-Specific Alcohol Dehydrogenase from *Lactobacillus kefir* 341

2.2.4.3 Comparison of (<i>R</i>)-Specific ADHs from <i>L. kefir</i> and <i>L. brevis</i>	342
2.2.4.4 Preparative Applications of ADHs from <i>L. kefir</i> and <i>L. brevis</i>	345
2.2.4.4.1 Synthesis of (<i>R,R</i>)-Diols	346
2.2.4.4.2 Synthesis of Enantiopure 1-Phenylpropane-1,2-diols	346
2.2.4.4.3 Synthesis of Enantiopure Propargylic Alcohols	346
2.2.4.4.4 Regioselective Reduction of <i>t</i> -Butyl 6-chloro-3,5-dioxohexanoate to the Corresponding Enantiopure (<i>S</i>)-5-Hydroxy Compound	346
2.2.4.5 Coenzyme Regeneration and the Construction and Use of “Designer Cells”	347
2.2.4.6 Discussion	349
2.2.5 Biocatalytic C–C Bond Formation in Asymmetric Synthesis	351
<i>Wolf-Dieter Fessner</i>	
2.2.5.1 Introduction	351
2.2.5.2 Enzyme Mechanisms	352
2.2.5.2.1 Class II Aldolases	352
2.2.5.2.2 Class I Fructose 1,6-Bisphosphate Aldolase	355
2.2.5.2.3 Sialic Acid Synthase	355
2.2.5.2.4 Rhamnose Isomerase	356
2.2.5.3 New Synthetic Strategies	357
2.2.5.3.1 Sugar Phosphonates	357
2.2.5.3.2 Xylulose 5-Phosphate	359
2.2.5.3.3 RhuA Stereoselectivity	359
2.2.5.3.4 Aldolase Screening Assay	361
2.2.5.3.5 Aldose Synthesis	361
2.2.5.3.6 Tandem Chain Extension–Isomerization–Chain Extension	362
2.2.5.3.7 Tandem Bidirectional Chain Extensions	363
2.2.5.3.8 Non-Natural Sialoconjugates	369
2.2.5.4 Summary and Outlook	373
2.2.6 Exploring and Broadening the Biocatalytic Properties of Recombinant Sucrose Synthase 1 for the Synthesis of Sucrose Analogues	376
<i>Lothar Elling</i>	
2.2.6.1 Introduction	376
2.2.6.2 Characteristics of Recombinant Sucrose Synthase 1 (SuSy1) Expressed in <i>Saccharomyces cerevisiae</i>	377
2.2.6.2.1 Expression and Purification of SuSy1 from Yeast	377
2.2.6.2.2 The Substrate Spectrum of SuSy1 from Yeast	378
2.2.6.3 Characteristics of Recombinant Sucrose Synthase 1 (SuSy1) Expressed in <i>Escherichia coli</i>	381
2.2.6.3.1 Expression and Purification of SuSy1 from <i>E. coli</i>	381
2.2.6.3.2 The Substrate Spectrum of SuSy1 from <i>E. coli</i>	382
2.2.6.4 Sucrose Synthase 1 Mutants Expressed in <i>S. cerevisiae</i> and <i>E. coli</i>	383
2.2.6.5 Outlook	384

2.2.7	Flexible Asymmetric Redox Reactions and C–C Bond Formation by Bioorganic Synthetic Strategies	386
	<i>Michael Müller, Michael Wolberg, Silke Bode, Ralf Feldmann, Petra Geilenkirchen, Thomas Schubert, Lydia Walter, Werner Hummel, Thomas Dünnewald, Ayan S. Demir, Doris Kolter-Jung, Adam Nitsche, Pascal Dünkelmann, Annabel Cosp, Martina Pohl, Bettina Lingen, and Maria-Regina Kula</i>	
2.2.7.1	Introduction	386
2.2.7.2	Diversity-Oriented Access to 1,3-Diols Through Regio- and Enantioselective Reduction of 3,5-Dioxocarboxylates	386
2.2.7.2.1	Regio- and Enantioselective Enzymatic Reduction	387
2.2.7.2.2	Dynamic Kinetic Resolution	388
2.2.7.2.3	Stereoselective Access to 1,3-Diols by Diastereoselective Reduction	389
2.2.7.2.4	Nucleophilic Substitution of Chlorine	390
2.2.7.2.5	Application in Natural Product Syntheses	391
2.2.7.2.6	Discussion and Outlook	392
2.2.7.3	Chemo- and Enantioselective Reduction of Propargylic Ketones	395
2.2.7.3.1	Enantioselective Reduction of Aryl Alkynones	395
2.2.7.3.2	Synthesis of Enantiopure 3-Butyn-2-ol	396
2.2.7.3.3	Enzymatic Reduction of α -Halogenated Propargylic Ketones	397
2.2.7.3.4	Modification of α -Halogenated Propargylic Alcohols	398
2.2.7.3.5	Olefinic Substrates	399
2.2.7.3.6	Discussion and Outlook	401
2.2.7.4	Thiamine Diphosphate-Dependent Enzymes: Multi-purpose Catalysts in Asymmetric Synthesis	401
2.2.7.4.1	Formation of Chiral 2-Hydroxy Ketones Through BFD-Catalyzed Reactions	402
2.2.7.4.2	BAL as a Versatile Catalyst for C–C Bond Formation and Cleavage Reactions	405
2.2.7.4.3	Asymmetric Cross-Benzoin Condensation	407
2.2.7.4.4	Discussion and Outlook	408
2.2.7.5	Summary	409
3	Reaction Technology in Asymmetric Synthesis	415
3.1	Reaction Engineering in Asymmetric Synthesis	415
	<i>Stephan Lütz, Udo Kragl, Andreas Liese, and Christian Wandrey</i>	
3.1.1	Introduction	415
3.1.2	Membrane Reactors with Chemical Catalysts	418
3.1.3	Membrane Reactors with Biological Catalysts	420
3.1.3.1	Membrane Reactors with Whole Cells	420
3.1.3.2	Membrane Reactors with Isolated Enzymes	421
3.1.4	Two-Phase Systems	422
3.1.5	Conclusions	425

3.2 Biocatalyzed Asymmetric Syntheses Using Gel-Stabilized Aqueous–Organic Two-Phase Systems 427
Marion B. Ansorge-Schumacher

3.2.1 Gel-Stabilized Two-Phase Systems 428
3.2.2 Benzoin Condensation with Entrapped Benzaldehyde Lyase 430
3.2.3 Reduction of Ketones with Entrapped Alcohol Dehydrogenase 432
3.2.4 Conclusion 433

Index 435

Name Index 443