

## Contents

Preface XIII

List of Contributors XIX

### Part I Synthetic Methods

- 1 Electro spray and Cryospray Mass Spectrometry: From Serendipity to Designed Synthesis of Supramolecular Coordination and Polyoxometalate Clusters 3**  
*Haralampos N. Miras and Leroy Cronin*
- 1.1 Introduction 3
- 1.2 Background to ESI-MS 5
- 1.2.1 Background to CSI-MS 5
- 1.3 Application of High-Resolution ESI-MS and CSI-MS to Polyoxometalate Cluster Systems 6
- 1.3.1 Probing Protonation Versus Heteroatom Inclusion with ESI 7
- 1.3.2 Solution Identification of Functionalized POMs 10
- 1.3.3 Solution Identification of New Isopolyoxotungstates and Isopolyoxoniobates 11
- 1.3.4 Solution Identification and Isolation of Mixed-Metal/Valence POMs with CSI-MS 13
- 1.3.5 Mixed-Metal/Valence Hetero-POMs  $V_2 \subset \{M_{17}V_1\}$  14
- 1.3.6 Periodate-Containing POMs 17
- 1.3.7 Probing the Formation of POM-Based Nano-Structures 17
- 1.3.8 Mechanistic Insights into POM Self-Assembly Using ESI- and CSI-MS 19
- 1.4 Species Identification and Probing Structural Transformations in Multi-Metallic Systems 25
- 1.5 Future Challenges and Conclusions 27
- References 29

- 2 Efficient Synthesis of Natural Products Aided by Automated Synthesizers and Microreactors 33**  
*Shinichiro Fuse, Kazuhiro Machida, and Takashi Takahashi*
- 2.1 Efficient Synthesis of Natural Products Aided by Automated Synthesizers 33
- 2.1.1 The Process of Automating the Supply of Synthetic Intermediates 34
- 2.1.2 Efficient Synthesis of a Cyanohydrin Key Intermediate for Taxol Using Automated Synthesizers 40
- 2.1.3 Efficient Synthesis of a Cyclic Ether Key Intermediate for Nine-Membered Masked Eneidyne, Using an Automated Synthesizer 44
- 2.1.4 List of Reactions Successfully Performed in Automated Synthesizers 50
- 2.2 Continuous-Flow Synthesis of Vitamin D<sub>3</sub> 52
- 2.3 Conclusions 55
- Acknowledgments 55
- References 56
- 3 Chemoselective Reduction of Amides and Imides 59**  
*Shoubhik Das*
- 3.1 Introduction 59
- 3.2 Reduction of Tertiary Amides 61
- 3.3 Reduction of Secondary Amides 70
- 3.4 Dehydration of Primary Amides 73
- 3.5 Reduction of Imides 74
- 3.6 Conclusion 76
- Acknowledgment 76
- References 76
- 4 Ionic Ozonides – From Simple Inorganic Salts to Supramolecular Building Blocks 79**  
*Hanne Nuss and Martin Jansen*
- 4.1 The Forgotten Oxygen Anion 79
- 4.2 The Synthesis of Ionic Ozonides 80
- 4.3 The Structural Variety of Ionic Ozonides 83
- 4.3.1 Simple Binary and Pseudo-Binary Ozonides 83
- 4.3.2 Cs<sub>5</sub>([12]crown-4)<sub>2</sub>(O<sub>3</sub>)<sub>5</sub> – from Simple Salts to Supramolecular Building Blocks 87
- 4.4 Magnetic Properties 89
- 4.5 Conclusions and Perspectives 93
- References 94

## 5 **Chemistry and Biological Properties of Amidinoureas: Strategies for the Synthesis of Original Bioactive Hit Compounds** 97

*Daniele Castagnolo*

- 5.1 Amidinoureas: an Introduction 97
- 5.2 Amidinoureas in Chemistry 99
- 5.3 Synthetic Strategies for the Preparation of Amidinoureas 102
  - 5.3.1 Hydrolysis of Biguanides 103
  - 5.3.2 Reaction of Guanidines with Isocyanates 103
  - 5.3.3 Hydrolysis of Cyanoguanidines 105
  - 5.3.4 Reaction of Acyl-S-Methylisothiurea with Amines 106
  - 5.3.5 Reaction of Di-Boc-Guanidines with Amines 107
- 5.4 Macrocylic Amidinoureas 110
  - 5.4.1 Guanylated Polyamines 111
  - 5.4.2 Conversion of Di-Boc-Guanylated Diamines into Amidinoureas 113
  - 5.4.3 Synthesis of Cyclic Amidinoureas 115
  - 5.4.4 Synthesis of Macrocylic Amidinoureas from Di-Boc-Monoguanylated Triamines 118
  - 5.4.5 Biological Properties of Cyclic Amidinoureas 120
- 5.5 Perspectives 123
- Acknowledgments 124
- References 124

### Part II Catalysis

## 6 **DNA Catalysts for Synthetic Applications in Biomolecular Chemistry** 129

*Claudia Höbartner and P.I. Pradeepkumar*

Abbreviations 129

- 6.1 Introduction 129
- 6.2 *In vitro* Selection of Deoxyribozymes 130
- 6.3 Scope of DNA-Catalyzed Reactions 132
- 6.4 Synthetic Applications of RNA-Cleaving Deoxyribozymes 133
- 6.5 DNA-Catalyzed Linear Ligation of RNA 137
- 6.6 DNA-Catalyzed Synthesis of 2',5'-Branched Nucleic Acids 140
  - 6.6.1 2',5'-Branched RNA 143
  - 6.6.2 2',5'-Branched Nucleic Acids Containing RNA as Scaffold and DNA as Adaptor 144
  - 6.6.3 2',5'-Branched DNA 145
  - 6.6.4 2',5'-Branched Nucleic Acids Containing DNA as Scaffold and RNA as "Adaptor" 146
- 6.7 DNA-Catalyzed Synthesis of Nucleopeptide Conjugates 146
- 6.8 Mechanistic Aspects of DNA Catalysis 147
- 6.9 Conclusions and Outlook 150
- References 150

- 7 Iron-Catalyzed Csp<sup>3</sup>-H Oxidation with H<sub>2</sub>O<sub>2</sub>: Converting a Radical Reaction into a Selective and Efficient Synthetic Tool 157**  
*Laura Gómez*
- 7.1 Introduction and Scope 157
- 7.2 Environmentally Benign C-H Oxidation 158
- 7.3 Inspiration from Nature 158
- 7.4 Mechanistic Considerations 159
- 7.5 Bioinspired C-H Oxidation Catalysts 161
- 7.5.1 Porphyrinic Catalysts 161
- 7.5.2 Non-porphyrinic Mononuclear Iron Catalysts 162
- 7.6 Perspectives 171
- References 172
- 8 Hydrogen Bonds as an Alternative Activation 175**  
*Eugenia Marqués-López and Raquel P. Herrera*
- 8.1 Introduction 175
- 8.1.1 Chiral Thiourea/Urea Organocatalysts 175
- 8.2 Thiourea Catalysts 178
- 8.2.1 Friedel-Crafts Alkylation Reaction 178
- 8.2.2 Michael Addition Reactions 183
- 8.2.2.1 Michael Addition Reaction of *N,N*-Dialkylhydrazones to Nitroalkenes 184
- 8.2.2.2 Michael Addition Reaction of Formaldehyde *N,N*-Dialkylhydrazones to  $\beta$ ,  $\gamma$ -Unsaturated  $\alpha$ -Keto Esters 186
- 8.2.2.3 Hydrophosphonylation Reaction of Nitroalkenes 188
- 8.2.3 Aza-Henry Reaction 191
- 8.3 Conclusions 193
- Acknowledgments 194
- References 194
- 9 Electrosynthesized Structured Catalysts for H<sub>2</sub> Production 201**  
*Patricia Benito, Francesco Basile, Giuseppe Fornasari, Marco Monti, Erika Scavetta, Domenica Tonelli, and Angelo Vaccari*
- 9.1 Introduction 201
- 9.2 Preparation of Structured Catalysts 202
- 9.3 Electrosynthesis 203
- 9.4 Electrosynthesis of Hydrotalcite-Type Compounds 204
- 9.4.1 Experimental 204
- 9.4.2 Ni/Al and Rh/Mg/Al HT Compounds on FeCrAlloy Foams 207
- 9.4.3 Catalysts 210
- 9.4.4 Steam Reforming and Catalytic Partial Oxidation of Methane 212
- 9.5 Summary and Outlook 214
- References 215

<b>10</b>	<b>Microkinetic Analysis of Complex Chemical Processes at Surfaces</b>	<b>219</b>
	<i>Matteo Maestri</i>	
	Notation	219
	Greek letters	219
10.1	Introduction	219
10.2	Time and Length Scales in Heterogeneous Catalysis	221
10.3	Hierarchical Multiscale Approach for Microkinetic Model Development	223
10.3.1	Microkinetic Model Development	224
10.3.1.1	Prediction of Activation Energies Using the UBI-QEP Semiempirical Method	226
10.3.1.2	First-Principles Assessment of the UBI-QEP Semiempirical Method	227
10.3.2	Meso-Scale and Macroscale: Reaction and Reactor Engineering	229
10.3.3	Hierarchical Multiscale Refinement of the Microkinetic Model	230
10.4	Show Case: Microkinetic Analysis of CH <sub>4</sub> Partial Oxidation on Rh	231
10.4.1	Microkinetic Model for the Conversion of CH <sub>4</sub> to Syngas	232
10.4.2	Microkinetic Analysis of Isothermal CPOX Data in Annular Reactor	232
10.4.3	Microkinetic Analysis of Autothermal CPOX Data on Foams	239
10.5	Conclusions	241
	Acknowledgments	242
	References	242
<b>11</b>	<b>Synthetic Potential behind Gold-Catalyzed Redox Processes</b>	<b>247</b>
	<i>Cristina Nevado and Teresa de Haro</i>	
11.1	Introduction	247
11.2	Gold-Catalyzed Reactions Involving Oxygen Functionalities	247
11.2.1	Oxidation of Alkanes	247
11.2.2	Oxidation of Alcohols to Carbonyl Compounds	248
11.2.3	Oxidation of Alkenes	250
11.2.4	Oxidation of Sulfides to Sulfoxides	251
11.2.5	Oxidation of Gold-Carbene Intermediates	251
11.2.6	Substrates as Internal Oxidants	253
11.3	Gold-Catalyzed Reactions Involving Nitrogen Functionalities	255
11.4	Gold-Catalyzed Reactions Involving C–C Bond Formation	256
11.4.1	Ethynylation Reactions	256
11.4.2	Homocoupling Reactions	260
11.4.3	Cross-Coupling Involving B and Si Reagents	262
11.5	Gold-Catalyzed Reactions Involving Alkene Difunctionalization	264
11.6	Gold-Catalyzed Reactions Involving Halogen Functionalities	264
11.7	Summary and Outlook	266
	References	266

- 12 Transition-Metal Complexes in Supported Liquid Phase and Supercritical Fluids –A Beneficial Combination for Selective Continuous-Flow Catalysis with Integrated Product Separation** 273  
*Ulrich Hintermair, Tamilselvi Chinnusamy, and Walter Leitner*
- 12.1 Strategies for Catalyst Immobilization Using Permanent Separation Barriers 273
- 12.2 Supported Liquid-Phase Catalysts Based on Organic Solvents (SLP) 274
- 12.3 Supported Aqueous-Phase Catalysts (SAP) 278
- 12.4 Supported Ionic Liquid-Phase Catalysts (SILP) 280
- 12.4.1 Synthetic Methods 280
- 12.4.2 Characteristics 281
- 12.4.3 Gas-Phase Applications 282
- 12.4.4 Liquid-Phase Applications 283
- 12.5 Supported Liquid-Phase Catalysts and Supercritical Fluids 287
- 12.6 Conclusion 290
- References 292
- Part III Combinatorial and Chemical Biology**
- 13 Inhibiting Pathogenic Protein Aggregation: Combinatorial Chemistry in Combating Alpha-1 Antitrypsin Deficiency** 299  
*Yi-Pin Chang*
- 13.1 Introduction 299
- 13.2  $\alpha_1$ -Antitrypsin Deficiency 301
- 13.2.1  $\alpha_1$ -Antitrypsin and Serpin 301
- 13.2.2 The Polymerization Pathways of Serpins 303
- 13.2.3 Emerging Therapeutic Strategies 304
- 13.3 Targeting the s4A Site with the Peptide Annealing Method 305
- 13.3.1 Functional and Structural Studies of RCLs 305
- 13.3.2 Smaller RCL-Derived and Non-RCL Serpin-Binding Peptides 306
- 13.4 Expanding the Molecular Diversity 307
- 13.4.1 Alanine Scanning, Truncation, and D-Amino Acid Scanning Libraries 308
- 13.4.2 The  $\beta$ -Strand-Directed Library 309
- 13.4.3 The Positional Scanning Library 312
- 13.5 Characterization of the Combinatorially Selected Peptide 314
- 13.5.1 Validation of the Binding by SPR 314
- 13.5.2 Cytotoxicity of the Identified Peptide and the Proposed Structure of the Binary Complex 315
- 13.6 Conclusion and Outlook 316
- Acknowledgments 317
- References 317

**14 Synthesis and Application of Macrocycles Using Dynamic Combinatorial Chemistry 325***Vittorio Saggiomo*

- 14.1 Supramolecular Chemistry 325
- 14.2 Dynamic Combinatorial Chemistry 326
  - 14.2.1 The Next Step: Applications 330
- 14.3 Ion Transport across Membranes Mediated by a Dynamic Combinatorial Library 331
- References 341

**15 Toward Tomorrow's Drugs: the Synthesis of Compound Libraries by Solid-Phase Chemistry 343***Dagmar C. Kapeller and Stefan Bräse*

Abbreviations 343

- 15.1 Introduction 344
  - 15.1.1 The History of Drug Discovery 344
  - 15.1.2 Characteristics of Druglike Molecules 345
  - 15.1.3 Drug Targets 345
  - 15.1.4 Privileged Structures 347
- 15.2 Solid-Phase Synthesis of Selected Privileged Structures 347
  - 15.2.1 Introduction to Solid-Phase Synthesis 347
  - 15.2.2 Benzodiazepines 348
  - 15.2.3 Benzopyrans 354
  - 15.2.4 Indoles 360
  - 15.2.5 Pyrazoles 364
- 15.3 Conclusions and Outlook 371
- Acknowledgment 372
- References 372

**Index 377**