

## Contents

**Series Editors Preface** *xi*

**Volume Editor's Preface** *xv*

**1 Flow Chemistry at the Extremes: Turning Complex Reactions into Scalable Processes** *1*

*Andrew R. Bogdan*

- 1.1 Introduction *1*
- 1.2 Temperature Extremes *2*
  - 1.2.1 Cryogenic Flow Chemistry *2*
    - 1.2.1.1 Organolithium Chemistry in Flow *3*
    - 1.2.1.2 Cyanation *10*
  - 1.2.2 High-Temperature Flow Chemistry *10*
- 1.3 *In Situ* Use of Hazardous Reagents *14*
  - 1.3.1 Vilsmeier Reagent *15*
  - 1.3.2 Phosgene *16*
  - 1.3.3 Diazomethane *17*
- 1.4 Photochemistry on Scale *20*
- 1.5 Conclusion and Outlook *25*
- References *26*

**2 Automated Flow Chemistry Platforms** *33*

*Juan A. Rincón, María José Nieves-Remacha, and Carlos Mateos*

- 2.1 Introduction *33*
- 2.2 Analytical Techniques *33*
  - 2.2.1 In-line NMR Monitoring *34*
  - 2.2.2 In-line Infrared Spectroscopy (IR) *35*
  - 2.2.3 Online HPLC and GC Sampling *35*
  - 2.2.4 UV/Vis Spectroscopy *37*
  - 2.2.5 Other Analytical Techniques *37*
    - 2.2.5.1 Online Mass Spectroscopy *37*
    - 2.2.5.2 In-line Raman Spectroscopy *38*
  - 2.2.6 Future Opportunities *38*
- 2.3 Automation *38*
  - 2.3.1 High-Throughput Screening Platforms *38*

2.3.2	Integrated Chemistry and Bioactivity Screening Platforms	39
2.3.3	Flexible and Modular Automated Platforms	43
2.3.3.1	Robotic Platform for Synthesis in Flow Informed by AI Planning	44
2.3.3.2	Reconfigurable System for Automated Optimization of Diverse Chemical Reactions	44
2.3.3.3	OpenFlowChem as a Flexible Software Platform	49
2.3.3.4	Internet-Based Software Platform	50
2.3.3.5	Other Platforms	51
2.3.4	Self-Optimization Algorithms	52
2.4	Summary and Future Perspective	60
	References	60
<b>3</b>	<b>Flow Chemistry Opportunities for Drug Discovery</b>	<b>67</b>
	<i>María Lourdes Linares, Enol López, Eduardo Palao, and Jesús Alcázar</i>	
3.1	Introduction	67
3.1.1	Drug Discovery	67
3.1.2	Flow Chemistry	68
3.1.3	Merging Flow Chemistry and Drug Discovery	69
3.2	Current Drug Discovery Toolkit	70
3.2.1	Reactions for C-Heteroatom Bond Formation	70
3.2.2	Reactions for C—C Bond Formation	75
3.2.3	Heterocyclic Synthesis	76
3.3	Expanding Drug Discovery Toolkit Through Flow Chemistry	80
3.3.1	Handling Hazardous and Unstable Reagents	80
3.3.2	Combining Flow with Emerging Technologies	85
3.3.2.1	Photochemistry	85
3.3.2.2	Electrochemistry	88
3.4	Automated Flow Synthesis	90
3.5	Integrated Platforms	93
3.6	Conclusions and Outlook	95
	References	95
<b>4</b>	<b>Flow Chemistry in Medicinal Chemistry: Applications to Bcr-Abl Kinase Inhibitors</b>	<b>103</b>
	<i>Paul Richardson</i>	
4.1	Introduction	103
4.2	Discovery of Imatinib	105
4.3	Ley Flow Synthesis of Imatinib	106
4.4	Buchwald Flow Synthesis of Imatinib	121
4.5	Jamison Flow Synthesis of Imatinib	128
4.6	“Hybrid Approach” to Imatinib	135
4.7	Closed-Loop Discovery	140
4.8	Identification of Novel Bcr-Abl Kinase Inhibitors Through Closed-Loop Discovery	144
4.9	Conclusion	154
	References	154

- 5 Integrated Systems for Continuous Synthesis and Biological Screenings 159**  
*Antimo Gioiello, Giada Moroni, and Bruno Cerra*
- 5.1 Introduction: Continuous-Flow Technology to Power Medicinal Chemistry 159
- 5.2 Equipment, Automated Systems, and Methods for Flow-Based Medicinal Chemistry 161
- 5.2.1 Continuous-Flow Synthesis Machines 162
- 5.2.2 Process Analytical Technology (PAT) for Effective Integration of Synthesis and Biological Screenings in Continuous Flow 164
- 5.2.3 Bioassays for In-line Compound Screening 164
- 5.2.4 General Concepts for Automation, Remote Control, and Software Application to Integrated Systems 168
- 5.3 Flow Strategies for Building Bioactive Compound Libraries 169
- 5.3.1 Click Chemistry 169
- 5.3.2 Multicomponent Reactions (MCRs) 174
- 5.3.3 Linear and Multistep Synthesis 177
- 5.4 End-to-End Autonomous Discovery Platforms 181
- 5.5 Conclusions and Future Outlook 191  
References 191
- 6 Application of Continuous-Flow Processing in Multistep API and Drug Syntheses 199**  
*Faith M. Akwi and Paul Watts*
- 6.1 Introduction 199
- 6.2 Antibacterial Agents 200
- 6.2.1 Ciprofloxacin 200
- 6.2.2 Linezolid 201
- 6.2.3 Cefotaxime 202
- 6.2.4 Rifampicin 203
- 6.3 Anticancer Agents 205
- 6.3.1 Lomustine 205
- 6.3.2 Imatinib 205
- 6.4 Antifungal Agents 207
- 6.4.1 Fluconazole 207
- 6.4.2 Flucytosine 210
- 6.5 Anti-HIV Agents 210
- 6.5.1 (*R*)-Propylene Carbonate: An Intermediate Toward Anti-HIV Drug, Tenofovir 210
- 6.5.2 Dolutegravir 211
- 6.5.3 Lamivudine 214
- 6.5.4 Efavirenz 215
- 6.6 Serotonin Modulators and Stimulators 216
- 6.6.1 Flibanserin 216
- 6.6.2 Vortioxetine 217

- 6.6.3 Melitracen HCl 218
- 6.7 Cholinesterase Inhibitor 219
- 6.7.1 Donepezil 219
- 6.8 Antimalarial Agent 220
- 6.8.1 Hydroxychloroquine 220
- 6.9 Non-peptide Angiotensin II Receptor Blocker 221
- 6.9.1 Valsartan 221
- 6.10 Cystic Fibrosis Transmembrane Conductance Regulator 223
- 6.10.1 Ivacaftor 223
- 6.11 Non-steroidal Anti-inflammatory Agent 224
- 6.11.1 Ibuprofen 224
- 6.12 Conclusion 226
- References 226

## **7 Continuous-Flow Multistep Synthesis of Active Pharmaceutical Ingredients 233**

*Yuesu Chen and Jean-Christophe M. Monbaliu*

- 7.1 Introduction 233
- 7.2 Generators of Small Molecule Reagents 234
- 7.3 Two-Step Flow Synthesis 237
- 7.3.1 Clausine C Derivatives 240
- 7.3.2 Amino Alcohol APIs from Glycerol 240
- 7.3.3 Oxymorphone 242
- 7.3.4 Hydroxychloroquine 243
- 7.4 Linear Multistep Flow Synthesis 243
- 7.4.1 Valsartan Precursor 246
- 7.4.2 Eflornithine 246
- 7.4.3 Ketamine 249
- 7.4.4 Lesinurad 251
- 7.5 Convergent Multistep Flow Synthesis 252
- 7.5.1 A Histone Deacetylase Inhibitor Precursor 252
- 7.5.2 Linezolid 252
- 7.6 Advanced Technologies for Multistep Flow Synthesis 255
- 7.6.1 Sensors and In-line Analysis 255
- 7.6.2 Process Analytical Technology (PAT) 256
- 7.6.3 Self-optimization 256
- 7.6.4 Modular Flow System 260
- 7.6.5 Toward Full Automation 261
- 7.7 Conclusion 263
- References 263

## **8 Enantioselective (Bio)Catalysis in Continuous-flow as Efficient Tool for the Synthesis of Advanced Intermediates and Active Pharmaceutical Ingredients 269**

*Laura Amenós, Anna M. Sobolewska, Esther Alza, and Miquel A. Pericàs*

- 8.1 Introduction 269
- 8.2 Homogeneous Enantioselective Catalysis in Continuous Flow 270

8.2.1	Homogeneous Enantioselective Organocatalysis	271
8.2.1.1	Enantioselective Michael Addition	271
8.2.1.2	Enantioselective Aldol Reaction	272
8.2.1.3	Enantioselective Photooxygenation	272
8.2.1.4	Enantioselective Imine Reduction	274
8.2.2	Organometallic Enantioselective Catalysis	275
8.2.2.1	Enantioselective Sulfoxidation	275
8.2.2.2	Enantioselective Epoxidation	276
8.2.2.3	Enantioselective Hydrogenation	277
8.2.2.4	Enantioselective Michael Addition	279
8.3	Heterogeneous Enantioselective Catalysis in Flow	280
8.3.1	Supported Organocatalysts	281
8.3.1.1	Enantioselective Allylation of Aldehydes	281
8.3.1.2	Enantioselective $\alpha$ -Amination	282
8.3.1.3	Enantioselective Arylation of Aldehydes	282
8.3.1.4	Enantioselective Cyclopropanation	283
8.3.1.5	Enantioselective Michael Reaction	284
8.3.1.6	Enantioselective Tandem Michael Addition/Cyclization Reactions	286
8.3.1.7	Enantioselective Reduction of Imines	288
8.3.2	Supported Organometallic Catalysts	289
8.3.2.1	Enantioselective Hydrogenation	289
8.3.2.2	Enantioselective Hydroformylation	291
8.3.2.3	Enantioselective 1,4-Addition to Enone	293
8.3.2.4	Enantioselective Nitroaldol Reaction	294
8.4	Enantioselective Biocatalysis in Flow	295
8.5	Asymmetric Total Synthesis in Continuous Flow	298
8.6	Conclusions	304
	References	304

## **9 Innovative Process Development of Pharmaceutical Intermediates Under Continuous-Flow System 311**

*Koji Machida and Hiroaki Yasukouchi*

9.1	Introduction	311
9.2	Plug Flow Reactor System for Phosgenation Reaction	312
9.2.1	Introduction	312
9.2.2	Feasibility Study	313
9.2.3	Establishment and Development of Continuous-Flow Process for API Synthesis	314
9.3	Simple and Practical Packed-Bed Reactor System for Catalytic Reactions	317
9.3.1	Introduction	317
9.3.2	Deacylation Reaction with Anion-Exchange Resin	318
9.3.2.1	Feasibility Study	318
9.3.2.2	Application for Pharmaceutical Intermediates and Scale-up	319
9.3.3	Reductive Amination with Biocatalyst	322

9.4	Flow Reactor Facility for Large-Scale Production	326
9.4.1	Concept of Our Flow Reactor System	326
9.4.2	Commercial Production	328
9.5	Conclusions	328
	References	329

<b>Index</b>	333
--------------	-----