Contents

List of Contributors *xi*
Foreword *xv*

1 Flow Photochemistry – a Green Technology with a Bright Future *1*
Michael Oelgemöller, Tyler Goodine, and Padmakana Malakar
1.1 Introduction to Synthetic Organic Photochemistry *1*
1.2 Conventional Batch Photochemistry *3*
1.2.1 Batch Photochemical Technology *3*
1.2.2 Photochemistry and Green Chemistry *4*
1.3 Continuous-Flow Chemistry *5*
1.3.1 Introduction to Continuous-Flow Chemistry *5*
1.3.2 Continuous-Flow Photochemistry *6*
1.3.3 Continuous-Flow Photochemical Technology *6*
1.4 Selected Examples of Photochemical Reactions under Flow Conditions *8*
1.4.1 Homogeneous Photoreactions *8*
1.4.2 Heterogeneous Photoreactions *14*
1.5 Summary, Conclusion, and Outlook *16*
Acknowledgments *17*
References *17*

2 Continuous Flow Synthesis Using Recyclable Reaction Media *25*
Takahide Fukuyama, Akihiro Furuta, and Ilhyong Ryu
2.1 Introduction *25*
2.2 Continuous Flow Reactions Using an Ionic Liquid *26*
2.3 Continuous Flow Reactions Using a Fluorous Solvent *32*
2.4 Conclusions *39*
References *39*

3 Synthesis and Application of H_2O_2 in Flow Reactors *43*
Minjing Shang and Volker Hessel
3.1 Introduction *43*
3.2 The Synthesis of Hydrogen Peroxide from Hydrogen and Oxygen in Flow Process with Microtechnology *45*

3.2.1 The Synthesis of Hydrogen Peroxide in Trickle-Bed or Packed-Bed Reactor *45*
3.2.2 The Synthesis of Hydrogen Peroxide in Coated Microreactors *47*
3.2.3 The Synthesis of Hydrogen Peroxide on Pilot Scale *52*
3.3 Application of Hydrogen Peroxide in Microreactors *52*
3.3.1 The Synthesis of Epoxides with H_2O_2 *52*
3.3.2 The Production and Application of Organic Peroxides *56*
3.3.3 The Synthesis of Sulfoxides and Sulfones from Sulfides and H_2O_2 *58*
3.3.4 The Synthesis of Adipic Acid from Cyclohexene and Hydrogen Peroxide *59*
3.3.5 Other Oxidation Reactions with H_2O_2 *60*
3.4 Conclusions *66*
Acknowledgments *67*
References *67*

4 Scale-Up of Flow Processes in the Pharmaceutical Industry *73*
Peter Poechlauer and Wolfgang Skranc
4.1 Introduction *73*
4.2 Stages of Pharmaceutical Development *75*
4.2.1 Preclinical Development *75*
4.2.2 Clinical Development *76*
4.2.3 Process for Launch *76*
4.2.4 Second-Generation Process *76*
4.2.5 Continuous Improvement *77*
4.3 Sustainability of Supply – The Role of Continuous Processing *77*
4.3.1 Sustainability *77*
4.3.2 Requirements for a Profitable Process *77*
4.3.3 Requirements for a Socially Sustainable Process *79*
4.3.4 Requirements for an Environmentally Sustainable Process *80*
4.3.4.1 Chemical Efficiency: Atom Economy, E-Factor, and PMI *80*
4.3.4.2 Global Warming Potential: GWP *81*
4.3.4.3 Materials Input per Service: MIPS *81*
4.3.4.4 Missing Metrics *81*
4.4 Comparison of Batch to Continuous Large-Scale Processing *83*
4.4.1 Process Knowledge of Batch versus Continuous Manufacturing *83*
4.4.2 Process Intensity – Decisive for Sustainability *84*
4.4.3 Environmental Sustainability and Process Intensity *84*
4.4.4 Economic Sustainability and Process Intensity *85*
4.5 Scale-Up of a Flow Process *86*
4.5.1 Current Status of Industry *86*
4.5.2 Implementing Continuous Processes Requires a Different Approach *88*
4.5.3 The New Approach Needs Better Collaboration of Disciplines *89*
4.5.4 Changing Plant Configurations and Continuous Improvement. *90*
4.5.5 Numbering Up *91*
4.6 Flow Processes in the Manufacture of Pharmaceuticals: Examples of Scale-Up *94*

4.6.1 Reactions Which Are Difficult to Scale Up *94*
4.6.1.1 Thermal Overman Rearrangement *94*
4.6.1.2 Vilsmeier Reaction *95*
4.6.2 Large-Volume Products *96*
4.6.2.1 CETP Inhibitors *96*
4.6.2.2 SGLT2 Inhibitors *98*
4.7 Summary and Outlook on Future Scale-Up *99*
References *100*

5 Organic Synthesis in Flow: Toward Higher Levels of Sustainability *103*
Danny C. Lenstra and Floris P. J. T. Rutjes
5.1 Introduction *103*
5.2 Semi-automated Optimization *105*
5.2.1 Semi-automated High-Throughput Screening *105*
5.2.2 Experimental Designs for Optimization in Continuous Flow *106*
5.2.2.1 Example: Swern–Moffat Oxidation at Elevated Temperatures *107*
5.2.2.2 Controlled Optimization and Synthesis of Potentially Explosive Azides *108*
5.2.3 Response Surface Modeling (RSM) Using Box–Behnken Design *110*
5.2.3.1 Biodiesel Production in Continuous Flow *111*
5.2.3.2 Processing Biodiesel Waste-Streams *113*
5.2.4 Optimization Using Design of Experiment in Conclusion *115*
5.3 Self-Optimizing Microreactor Systems *116*
5.3.1 Self-Optimization for the Controlled Synthesis of CdSe Quantum Dots *116*
5.3.2 Sustainable Etherification in Green Supercritical CO_2 *117*
5.3.3 Highly Efficient Self-Optimizing Heck Reaction *121*
5.3.4 Self-Optimization of a Paal–Knorr Reaction *123*
5.3.5 Algorithms for Self-Optimization in Comparison *124*
5.3.5.1 Knoevenagel Condensation of *p*-Anisaldehyde *125*
5.3.5.2 Benzyl Alcohol Oxidation by CrO_3 *126*
5.4 Sustainability in Microreactor Technology *127*
5.4.1 Ecological Advantages *128*
5.4.2 Economical Advantages *128*
5.5 Conclusion *129*
References *131*

6 Sustainable Flow Chemistry in Drug Discovery *135*
Jesús Alcázar
6.1 Introduction *135*
6.2 Laboratory Equipment *136*
6.3 Advantages of Improved Sustainability *138*
6.3.1 Cleaner Chemistry *138*
6.3.2 Enhanced Synthesis *140*
6.3.3 New Reactivity Patterns *142*
6.3.4 Improved Safety *144*

6.4 Sustainable Drug Discovery *145*
6.4.1 Library Synthesis *146*
6.4.2 Integrated Platforms *149*
6.4.3 Lead Optimization *154*
6.4.4 Other Technologies Applicable to Drug Discovery *157*
6.5 Conclusions and Outlook *159*
References *160*

7 Flow Tools to Define Waste/Time/Energy-Minimized Protocols *165*
Luigi Vaccaro, Chiara Petrucci, Vadym Kozell, and Eleonora Ballerini
7.1 Introduction *165*
7.2 Minimization of Solvents and Reuse of Catalytic Systems *166*
7.2.1 Flow Approaches to Minimize Waste in Cross-Coupling Reactions *167*
7.2.2 Exploiting Polystyrene-Supported Phosphazene Base in Flow *169*
7.2.3 Activation of Silylated-Nucleophile to Access Target Molecules in Flow *172*
7.2.4 Heterogeneous Acidic Catalyst in Flow for Waste Minimized Processes *178*
7.3 Time/Cost/Energy Saving Examples Using Flow Approach *180*
7.3.1 Process Intensification and Easy Scale-Up *181*
7.3.2 Energy and Cost Efficiency *183*
7.3.3 Minimization of Reaction Time *185*
7.4 Conclusions *187*
Acknowledgments *187*
References *188*

8 The Application of Flow Chemistry in the Use of Highly Reactive Intermediates and Reagents *193*
Paul Watts
8.1 Introduction *193*
8.2 Hydrogenation Reactions in Flow *195*
8.3 Carbonylation in Flow *200*
8.4 Organometallic Reagents in Flow *202*
8.5 Synthesis of Azides and Diazoacetates in Flow *205*
8.6 The Use of Flow Reactors to Prepare Unstable Intermediates Using Photochemistry *207*
8.7 The Use of Flow Reactors to Prepare Unstable Intermediates Using Electrochemistry *210*
8.8 Fluorination and Trifluoromethylation in Flow *212*
8.9 Conclusions *215*
Acknowledgments *215*
References *215*

9 Nonconventional Techniques in Sustainable Flow Chemistry *219*
Antonio de la Hoz and Angel Díaz-Ortiz
9.1 Introduction *219*
9.2 Microwave-Assisted Flow Chemistry *220*
9.2.1 Commercial and Industrial Microwave Reactors *221*
9.2.2 Micro- and Home-Made Flow Reactors *224*
9.3 Inductive Heating in Flow Chemistry *230*
9.4 Sonochemistry in Flow Chemistry *233*
9.5 Organic Electrochemistry in Flow Chemistry *234*
9.6 Conclusions *244*
References *245*

10 Life Cycle Assessment of Flow Chemistry Processes *249*
Alexei A. Lapkin and Polina Yaseneva
10.1 Introduction *249*
10.2 Environmental Sustainability Assessment *250*
10.2.1 Brief Introduction into a Generic LCA Methodology for Chemical Industries *252*
10.2.2 LCA for Process Improvement; Simplified LCA *257*
10.2.3 LCA as Stage-Gating of Research Projects *258*
10.3 Flow Processes LCA Case Studies *261*
10.3.1 LCA of Buchwald–Hartwig Amination in Flow: LCA of Organometallic Catalysts *261*
10.3.2 LCA of Two-Step Flow Process: Continuous Synthesis of Artemisinin *266*
10.3.3 LCA of Microreactors *270*
10.4 Conclusions *271*
References *271*

11 Solids in Continuous Flow Reactors for Specialty and Pharmaceutical Syntheses *277*
Alexei A. Lapkin, Konstantin Loponov, Giovanna Tomaiuolo, and Stefano Guido
11.1 Introduction *277*
11.2 Mechanisms of Solids Formation in Flow Reactors *278*
11.2.1 Nucleation *278*
11.2.2 Surface Fouling *280*
11.2.3 Colloidal Fouling *283*
11.3 Manufacture of Solids in Flow: Soft Particles and APIs *286*
11.3.1 Soft Particles *286*
11.3.2 Manufacture of Solid Actives in Pharmaceutical Industry in Flow *288*
11.4 Use of Solids Suspension Catalysts in Flow *291*
11.4.1 Suspended Micro-particles in Flow *291*
11.4.2 Suspended Nanoparticles in Flow *292*

11.5 Avoiding Blockage of Flow Reactors by Insoluble By-Products: Flow Focusing *294*
11.6 Green Engineering Aspects *300*
Acknowledgments *301*
References *301*

Index *309*