

Contents

Foreword *xiii*

Preface *xvii*

| | | |
|----------|--|----------|
| 1 | Industrial Milestones in Organometallic Chemistry | 1 |
| | <i>Ben M. Gardner, Carin C.C. Johansson Seechurn, and Thomas J. Colacot</i> | |
| 1.1 | Definition of Organometallic and Metal–Organic Compounds | 1 |
| 1.1.1 | Applications and Key Reactivity | 1 |
| 1.1.1.1 | Electronic Applications | 1 |
| 1.1.1.2 | Polymers | 2 |
| 1.1.1.3 | Organic Synthesis | 2 |
| 1.2 | Industrial Process Considerations | 7 |
| 1.3 | Brief Notes on the Historical Development of Organometallic Chemistry for Organic Synthesis Applications Pertaining to the Contents of this Book | 8 |
| 1.3.1 | Synthesis of Stoichiometric Organometallic Reagents | 9 |
| 1.3.1.1 | Conventional Batch Synthesis | 9 |
| 1.3.1.2 | Organometallics in Flow | 10 |
| 1.3.2 | Cross-coupling Reactions | 10 |
| 1.3.2.1 | C–H Bond Activation | 12 |
| 1.3.2.2 | Carbonylation | 13 |
| 1.3.2.3 | Catalysis in Water – Micellar Catalysis | 13 |
| 1.3.3 | Hydrogenation Reactions | 14 |
| 1.3.4 | Olefin Formation Reactions | 15 |
| 1.3.4.1 | Wittig Reaction | 15 |
| 1.3.4.2 | Metathesis Reactions | 15 |
| 1.3.4.3 | Dehydrative Decarbonylation | 16 |
| 1.3.4.4 | Olefins as Starting Materials | 16 |
| 1.3.5 | Poly- or Oligomerization Processes | 17 |
| 1.3.6 | Photoredox Catalysis for Organic Synthesis | 17 |
| 1.4 | Conclusion and Outlook | 17 |
| | Biography | 18 |
| | References | 19 |

| | | |
|----------|---|-----------|
| 2 | Design, Development, and Execution of a Continuous-flow-Enabled API Manufacturing Route | 23 |
| | <i>Alison C. Brewer, Philip C. Hoffman, Timothy D. White, Yu Lu, Laura McKee, Moussa Boukerche, Michael E. Kobierski, Nessa Mullane, Mark Pietz, Charles A. Alt, Jim R. Stout, Paul K. Milenbaugh, and Joseph R. Martinelli</i> | |
| 2.1 | Continuous-flow-Enabled Synthetic Strategy | 25 |
| 2.2 | Design and Scale-up of Chan–Lam Coupling | 28 |
| 2.2.1 | Development of Homogeneous Conditions | 31 |
| 2.2.2 | Application of a Platform Technology to Aerobic Oxidation | 32 |
| 2.2.3 | Optimization of Reaction and Workup Parameters | 35 |
| 2.2.4 | Safety Considerations for Aerobic Oxidation on Scale | 37 |
| 2.2.5 | Continuous Scale-up and Manufacturing | 38 |
| 2.3 | Design and Scale-up of a Buchwald–Hartwig Cross-coupling | 42 |
| 2.3.1 | Initial Screening | 43 |
| 2.3.2 | Synthesis and Isolation of Pd(dba)DPEPhos Precatalyst | 45 |
| 2.3.3 | Workup Procedure, Metal Removal, and Crystallization | 46 |
| 2.3.4 | Scale-up and Manufacturing | 48 |
| 2.4 | Impurity Control | 48 |
| 2.4.1 | Solubility and Impurity Spiking Studies | 50 |
| 2.5 | Conclusions | 54 |
| | Biography | 54 |
| | References | 58 |
| 3 | Continuous Manufacturing as an Enabling Technology for Low-Temperature Organometallic Chemistry | 61 |
| | <i>Andreas Hafner and Joerg Sedelmeier</i> | |
| 3.1 | Introduction | 61 |
| 3.2 | Organo-Li and Mg Processes in Flow Mode | 62 |
| 3.2.1 | Technological Advantages of Flow Technology Compared to Traditional Batch Operation | 62 |
| 3.2.2 | Temperature Profile of Continuous Flow Reactions | 64 |
| 3.2.3 | Flash Chemistry: Functional Group Tolerance | 65 |
| 3.2.4 | Flash Chemistry: Selectivity | 66 |
| 3.2.5 | Flash Chemistry: Stoichiometry and Chemoselectivity | 67 |
| 3.3 | Continuous Flow Technology | 69 |
| 3.3.1 | Clogging as a Major Hurdle in Flow Chemistry | 71 |
| 3.3.2 | Start-up and Shutdown Operation | 72 |
| 3.3.3 | Material of Construction | 72 |
| 3.3.4 | Safety Concept and Emergency Strategies | 73 |
| 3.4 | Development of a Flow Process | 73 |
| 3.4.1 | Screening Phase: Feasibility Study | 74 |
| 3.4.2 | Process Development Phase: Extended Evaluations Including Technical Feasibility | 75 |
| 3.5 | Literature Examples: Flow Processes on Multi 100 g Scale | 76 |
| 3.5.1 | Manufacture of Verubecestat (MK-8931) | 77 |
| 3.5.2 | Manufacture of Edovoxetine | 77 |
| 3.5.3 | Scale-up of Highly Reactive Aryl Lithium Chemistry | 80 |

| | | |
|----------|--|------------|
| 3.5.4 | Synthesis of Bromomethyltrifluoroborates in Continuous Flow Mode | 81 |
| 3.5.5 | Two-Step Synthesis Toward Boronic Acids | 82 |
| 3.5.6 | Reaction Sequence Toward a Highly Substituted Benzoxazole Building Block | 84 |
| 3.6 | Conclusion and Future Prospects | 86 |
| | Biography | 86 |
| | References | 87 |
| 4 | Development of a Nickel-Catalyzed Enantioselective Mizoroki–Heck Coupling | <i>91</i> |
| | <i>Jean-Nicolas Desrosiers and Chris H. Senanayake</i> | |
| 4.1 | Introduction | 91 |
| 4.1.1 | Nonprecious Metal Catalysis Advantages for Industry | 91 |
| 4.1.2 | Mizoroki–Heck Couplings in Industry with Palladium | 92 |
| 4.1.3 | Emergence of Nickel-Catalyzed Mizoroki–Heck Couplings | 93 |
| 4.1.4 | Enantioselective Nickel-Catalyzed Couplings | 94 |
| 4.1.5 | Synthesis of Oxindoles via Mizoroki–Heck Cyclizations | 96 |
| 4.2 | Development of a Nickel-Catalyzed Heck Cyclization to Generate Oxindoles with Quaternary Stereogenic Centers | 97 |
| 4.2.1 | Precedents and Challenges | 97 |
| 4.2.2 | Optimization of Reducing Agent and Base | 97 |
| 4.2.3 | Ligand Screening | 98 |
| 4.2.4 | Impact of Aryl Electrophile and of Stereochemistry of Alkene Moiety | 100 |
| 4.2.5 | Exploration of the Substrate Scope | 102 |
| 4.2.6 | Limitations of the Methodology | 104 |
| 4.2.7 | Mechanistic Considerations | 104 |
| 4.3 | Development of First Enantioselective Nickel-Catalyzed Heck Coupling | 107 |
| 4.3.1 | Ligand Screening | 107 |
| 4.3.2 | Impact of Alkene Stereochemistry | 107 |
| 4.3.3 | Neutral vs Cationic Pathways | 108 |
| 4.3.4 | Nickel Precatalyst Complex Synthesis | 109 |
| 4.3.5 | Exploration of the Substrate Scope | 110 |
| 4.3.6 | Mechanistic Studies | 110 |
| 4.4 | Conclusions | 113 |
| | Biography | 114 |
| | References | 115 |
| 5 | Development of Iron-Catalyzed Kumada Cross-coupling for the Large-Scale Production of Aliskiren Intermediate | <i>121</i> |
| | <i>Srinivas Achanta, Debjit Basu, Uday K. Neelam, Rajeev R. Budhdev, Apurba Bhattacharya, and Rakeshwar Bandichhor</i> | |
| 5.1 | Introduction | 121 |
| 5.2 | Optimization of Grade and Equivalents of Mg Metal | 123 |

| | | |
|----------|---|------------|
| 5.3 | Optimization of Equivalents of 1,2-Dibromoethane | 123 |
| 5.4 | Effect of Solvent Concentration on Preparation of Grignard Reagent and Kumada–Corriu Coupling | 124 |
| 5.5 | Effect of Alkyl Chloride 3 Addition Time on the Grignard Reagent Preparation | 125 |
| 5.6 | Stability of Grignard Reagent at 0–5 °C | 125 |
| 5.7 | Iron-Catalyzed Cross-coupling Reaction | 127 |
| 5.8 | Optimization of Equivalents of NMP and Fe(acac) ₃ | 129 |
| 5.9 | Optimization of Equivalents of Substrate 4 and Its Rate of Addition | 129 |
| 5.10 | Execution at Pilot Scale and Scale-up Issues | 129 |
| 5.11 | Agitated Thin Film Evaporator (ATFE) for Purification of 2 | 131 |
| 5.12 | Conclusion | 132 |
| | Acknowledgments | 133 |
| | Biography | 133 |
| | References | 135 |
| 6 | Development and Scale-Up of a Palladium-Catalyzed Intramolecular Direct Arylation in the Commercial Synthesis of Beclabuvir | <i>137</i> |
| | <i>Collin Chan, Albert J. DelMonte, Chao Hang, Yi Hsiao, and Eric M. Simmons</i> | |
| 6.1 | Introduction | 137 |
| 6.2 | KOAc/DMAc Process | 141 |
| 6.3 | TMAOAc/DMF Process | 141 |
| 6.4 | TMAOAc/DMAc Process | 149 |
| 6.4.1 | Cyclization Reaction | 151 |
| 6.4.2 | Mechanistic Understanding of the Cyclization Reaction and Impurity Formation | 159 |
| 6.4.3 | Hydrolysis and Workup | 162 |
| 6.4.4 | Crystallization and Drying | 164 |
| 6.5 | Conclusion | 167 |
| | Biography | 168 |
| | References | 169 |
| 7 | Ruthenium-Catalyzed C—H Activated C—C/N/O Bond Formation Reactions for the Practical Synthesis of Heterocycles and Pharmaceutical Agents | <i>171</i> |
| | <i>Anita Mehta, Naresh Kumar, and Biswajit Saha</i> | |
| 7.1 | Introduction | 171 |
| 7.2 | C—H Activation Followed by C—C Bond Formation | 172 |
| 7.2.1 | C—H Activation Followed by C—C Bond Formation: Biaryl/Heterobiaryl Synthesis in Organic Solvents | 172 |
| 7.2.2 | C—H Activation Followed by C—C Bond Formation: Biaryl/Heterobiaryl Synthesis in Green Solvents | 181 |
| 7.3 | Alkyl/Acyl/Alkenyl Substitution on Heterocycles | 185 |

| | | |
|----------|--|------------|
| 7.4 | C—H Activation Followed by C—O/N Bond Formation: Heterocycle Synthesis | 187 |
| 7.4.1 | C—H Activation Followed by C—O/N Bond Formation: Heterocycle Synthesis in Organic Solvents | 187 |
| 7.4.2 | C—H Activation Followed by C—O and C—N Bond Formation: Heterocycle Synthesis in Green Solvents | 189 |
| 7.5 | Conclusion | 196 |
| | Biography | 197 |
| | References | 198 |
| 8 | Cross-couplings in Water – A Better Way to Assemble New Bonds | 203 |
| | <i>Tharique N. Ansari, Fabrice Gallou, and Sachin Handa</i> | |
| 8.1 | Introduction | 203 |
| 8.2 | Transition Metal Catalysis in Organic Solvents vs Micellar Catalysis | 204 |
| 8.2.1 | Micellization | 205 |
| 8.2.2 | Surfactant Solution – A Highly Organized Reaction Medium to Enhance Reaction Rate | 206 |
| 8.2.3 | Reaction Temperature | 207 |
| 8.2.4 | Size of Micelles | 207 |
| 8.2.5 | Nature of Catalyst | 208 |
| 8.2.6 | Increasing the Efficiency in Micellar Catalysis | 209 |
| 8.2.7 | Order of Addition | 210 |
| 8.2.8 | Product Precipitation or Extraction | 211 |
| 8.2.9 | Trace Metal in the Product | 211 |
| 8.3 | Highly Valuable Reactions in Water | 212 |
| 8.3.1 | Suzuki–Miyaura Couplings | 212 |
| 8.3.2 | Heck Couplings | 217 |
| 8.3.3 | Negishi Couplings | 219 |
| 8.3.4 | C—H Arylations | 221 |
| 8.3.5 | Aminations | 225 |
| 8.3.6 | Borylation | 228 |
| 8.3.7 | Arylation of Nitro Compounds | 228 |
| 8.3.8 | Adoption of Micellar Technology by Pharmaceutical Industry | 229 |
| 8.4 | Conclusions | 234 |
| | Biography | 234 |
| | References | 235 |
| 9 | Aspects of Homogeneous Hydrogenation from Industrial Research | 239 |
| | <i>Stephen Roseblade</i> | |
| 9.1 | Homogeneous Hydrogenation: A Brief Introduction | 239 |
| 9.2 | Catalyst Selection by Effective Screening Approaches | 240 |
| 9.3 | Considerations for Reaction Scale-up | 244 |

| | | |
|-----------|---|------------|
| 9.4 | Notes on Additive Effects | 247 |
| 9.5 | A Novel Approach to Aliskiren Using Asymmetric Hydrogenation as a Key Step | 249 |
| 9.6 | Efficient Chemoselective Aldehyde Hydrogenation | 252 |
| 9.7 | Closing Remarks/Summary | 253 |
| | Biography | 255 |
| | References | 255 |
| 10 | Latest Industrial Uses of Olefin Metathesis | 259 |
| | <i>John H. Phillips</i> | |
| 10.1 | Introduction | 259 |
| 10.2 | General Information | 260 |
| 10.2.1 | Non-ruthenium Catalysts | 260 |
| 10.2.2 | Ruthenium Catalysts | 261 |
| 10.3 | Industrial Uses | 262 |
| 10.3.1 | Ring-closing Metathesis (RCM) | 262 |
| 10.3.2 | Cross-metathesis (CM) | 264 |
| 10.3.3 | Ring-Opening Metathesis Polymerization (ROMP) | 268 |
| 10.4 | Reaction Considerations | 270 |
| 10.4.1 | Catalyst Choice | 271 |
| 10.4.2 | Catalyst Loading | 273 |
| 10.4.3 | Solvent | 273 |
| 10.4.4 | Reaction Concentration | 273 |
| 10.4.5 | Overall Handling | 274 |
| 10.4.6 | Application Guide and Availability | 274 |
| 10.5 | Troubleshooting | 275 |
| 10.5.1 | Catalyst Removal | 275 |
| 10.5.2 | Functional Group Tolerance | 276 |
| 10.5.3 | Substrate Purity | 276 |
| 10.5.4 | Catalyst Decomposition – Isomerization | 277 |
| 10.6 | Conclusion | 277 |
| | Biography | 277 |
| | References | 278 |
| 11 | Dehydrative Decarbonylation | 283 |
| | <i>Alex John</i> | |
| 11.1 | Introduction | 283 |
| 11.2 | Use of Sacrificial Anhydride and Catalytic Mechanism | 285 |
| 11.3 | Rh-, Pd-, and Ir-Catalysis | 286 |
| 11.3.1 | Early Studies | 286 |
| 11.3.2 | Recent Studies | 289 |
| 11.4 | Milder Temperatures | 291 |
| 11.4.1 | PdCl ₂ /XantPhos/(^t Bu) ₄ biphenol System | 291 |
| 11.4.2 | Well-Defined Pd-bis(phosphine) Precatalysts | 294 |
| 11.5 | Nickel and Iron Catalysis | 295 |
| 11.6 | Ester Decarbonylation | 297 |
| 11.7 | Synthetic Utility: α -Vinyl Carbonyl Compounds | 299 |

11.8 Conclusions and Future Prospects 300
 Biography 300
 References 301

Index 305