## Contents

Foreword *xiii* Preface *xvii* 

- 1 Industrial Milestones in Organometallic Chemistry 1 Ben M. Gardner, Carin C.C. Johansson Seechurn, and Thomas J. Colacot
- 1.1 Definition of Organometallic and Metal–Organic Compounds 1

|v

- 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

- vi Contents
  - 2 Design, Development, and Execution of a Continuous-flow-Enabled API Manufacturing Route 23 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 2.1 Continuous-flow-Enabled Synthetic Strategy 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 2.2.5Continuous Scale-up and Manufacturing 38 2.3 Design and Scale-up of a Buchwald–Hartwig Cross-coupling 42 2.3.1Initial Screening 43 Synthesis and Isolation of Pd(dba)DPEPhos Precatalyst 45 2.3.2 2.3.3 Workup Procedure, Metal Removal, and Crystallization 46 2.3.4 Scale-up and Manufacturing 48 2.4 Impurity Control 48 Solubility and Impurity Spiking Studies 50 2.4.12.5 Conclusions 54 Biography 54 References 58 3 Continuous Manufacturing as an Enabling Technology for Low-Temperature Organometallic Chemistry 61 Andreas Hafner and Joerg Sedelmeier 3.1 Introduction 61 3.2 Organo-Li and Mg Processes in Flow Mode 62 3.2.1Technological 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 Development of a Flow Process 73 3.4 3.4.1Screening Phase: Feasibility Study 74 3.4.2Process Development Phase: Extended Evaluations Including Technical Feasibility 75 Literature Examples: Flow Processes on Multi 100 g Scale 3.5 76 3.5.1 Manufacture of Verubecestat (MK-8931) 77 3.5.2 Manufacture of Edivoxetine 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 91
	Jean-Nicolas Desrosiers and Chris H. Senanayake
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
4.0.1	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 Deferences 115
	References 115
-	Development of them Cotalized Kurseds Crease security of faith a
5	Development of Iron-Catalyzed Kumada Cross-coupling for the

- Large-Scale Production of Aliskiren Intermediate 121 Srinivas Achanta, Debjit Basu, Uday K. Neelam, Rajeev R. Budhdev, Apurba Bhattacharya, and Rakeshwar Bandichhor
- 5.1 Introduction 121
- 5.2 Optimization of Grade and Equivalents of Mg Metal *123*

viii	Contents

- 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)<sub>3</sub> 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 137

Collin Chan, Albert J. DelMonte, Chao Hang, Yi Hsiao, and Eric M. Simmons

- 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 171 Anita Mehta, Naresh Kumar, and Biswajit Saha
- 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
7.4.2	Synthesis in Organic Solvents <i>187</i> C–H Activation Followed by C—O and C—N Bond Formation:
7.4.2	Heterocycle Synthesis in Green Solvents 189
7.5	Conclusion 196
1.0	Biography 197
	References 198
8	Cross-couplings in Water – A Better Way to Assemble New
	Bonds 203
	Tharique N. Ansari, Fabrice Gallou, and Sachin Handa
8.1	Introduction 203
8.2	Transition Metal Catalysis in Organic Solvents vs Micellar
	Catalysis 204
8.2.1	
8.2.2	8 1 8
	Enhance Reaction Rate 206
8.2.3	1
8.2.4	
8.2.5	
8.2.6	Increasing the Efficiency in Micellar Catalysis 209
8.2.7	Order of Addition 210
8.2.8	
8.2.9	
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	
8.3.5	Aminations 225
8.3.6	
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
	Stephen Roseblade
9.1	Homogeneous Hydrogenation: A Brief Introduction 239
9.2	Catalyst Selection by Effective Screening Approaches 240

9.2 Catalyst Selection by Effective Screening Approaches 2409.3 Considerations for Reaction Scale-up 244

**x** Contents

- 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
- John H. Phillips
- 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 Alex John

- 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<sub>2</sub>/XantPhos/(<sup>t</sup>Bu)<sub>4</sub>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