

## Contents

### **List of Contributors XIII**

### **Preface XVII**

|       |  |
|-------|--|
| 1     | <b>Introduction 1</b>  |
|       | <i>Wei Zhang and Shu-Li You</i>  |
| 1.1   | Why Asymmetric Dearomatization Reactions? 1                              |
| 1.2   | Discovery of Aromatic Compounds and Dearomatization Reactions 1          |
| 1.3   | Development of Dearomatization Reactions 3                               |
| 1.4   | Asymmetric Dearomatization Reactions 7                                   |
|       | References 8   |
| 2     | <b>Asymmetric Dearomatization with Chiral Auxiliaries and Reagents 9</b> |
|       | <i>E. Peter Kündig</i>   |
| 2.1   | Introduction 9   |
| 2.2   | Chiral $\sigma$ -Bound Auxiliaries 9                                     |
| 2.2.1 | Oxazolines 9   |
| 2.2.2 | Imines, Oxazolidines, and Hydrazones 15                                  |
| 2.2.3 | Chiral Ethers and Amines 16  |
| 2.3   | Diastereospecific Anionic Cyclizations 20                                |
| 2.4   | Use of Chiral Reagents 21  |
| 2.4.1 | Chiral Bases in Dearomatizing Cyclizations 21                            |
| 2.4.2 | Chiral Nucleophiles 23   |
| 2.4.3 | Chiral Ligands in Enantioselective Nucleophilic Additions 23             |
| 2.5   | Chiral $\pi$ -Complexes 26   |
| 2.5.1 | Planar Chiral $\eta^6$ -Arene Complexes 26                               |
| 2.5.2 | $\eta^6$ -Arene Complexes with a Chiral Ligand 28                        |
| 2.5.3 | Complexes with Stereogenic Metal Centers 29                              |
| 2.6   | Conclusion 30  |
|       | References 30  |

|         |  |    |
|---------|--|----|
| 3       | <b>Organocatalytic Asymmetric Transfer Hydrogenation of (Hetero)Arenes</b>           | 33 |
|         | <i>Gaëlle Mingat and Magnus Rueping</i>  |    |
| 3.1     | Introduction   | 33 |
| 3.2     | Organocatalytic Asymmetric Transfer Hydrogenation of Heteroaromatics                 | 34 |
| 3.2.1   | Quinolines   | 34 |
| 3.2.1.1 | Proof-of-Concept   | 34 |
| 3.2.1.2 | 2-Substituted Quinolines   | 35 |
| 3.2.1.3 | 4-Substituted Quinolines   | 40 |
| 3.2.1.4 | 3-Substituted Quinolines   | 41 |
| 3.2.1.5 | 2,3-Disubstituted Quinolines   | 42 |
| 3.2.1.6 | <i>Spiro</i> -Tetrahydroquinolines   | 45 |
| 3.2.2   | Benzoxazines, Benzothiazines, and Benzoxazinones                                     | 47 |
| 3.2.3   | Benzodiazepines and Benzodiazepinones  | 49 |
| 3.2.4   | Pyridines  | 51 |
| 3.2.5   | 3 <i>H</i> -Indoles  | 51 |
| 3.2.6   | Quinoxalines and Quinoxalinones  | 52 |
| 3.3     | Organocatalytic Asymmetric Transfer Hydrogenation in Aqueous Solution                | 53 |
| 3.4     | Cascade Reactions  | 54 |
| 3.4.1   | Introduction   | 54 |
| 3.4.2   | <i>In situ</i> Generation of the Heteroarene   | 54 |
| 3.4.3   | Dearomatization of Pyridine/Asymmetric <i>aza</i> -Friedel–Crafts Alkylation Cascade | 56 |
| 3.4.4   | Combining Photochemistry and Brønsted Acid Catalysis                                 | 57 |
| 3.4.4.1 | Quinolines   | 57 |
| 3.4.4.2 | Pyrylium ions  | 58 |
| 3.5     | Cooperative and Relay Catalysis: Combining Brønsted Acid- and Metal-Catalysis        | 59 |
| 3.5.1   | Introduction   | 59 |
| 3.5.2   | Improvements in Transfer Hydrogenation   | 60 |
| 3.5.2.1 | Regenerable Hydrogen Sources   | 60 |
| 3.5.2.2 | Asymmetric Relay Catalysis (ARC)   | 62 |
| 3.5.3   | Cooperative Metal–Brønsted Acid Catalysis  | 63 |
| 3.6     | Summary and Conclusion   | 65 |
|         | References   | 66 |
| 4       | <b>Transition-Metal-Catalyzed Asymmetric Hydrogenation of Aromatics</b>              | 69 |
|         | <i>Ryoichi Kuwano</i>  |    |
| 4.1     | Introduction   | 69 |
| 4.2     | Catalytic Asymmetric Hydrogenation of Five-Membered Heteroarenes                     | 71 |
| 4.2.1   | Catalytic Asymmetric Hydrogenation of Azoles and Indoles                             | 71 |

|         |   |     |
|---------|---|-----|
| 4.2.1.1 | Rhodium-Catalyzed Asymmetric Hydrogenation of Indoles                                       | 71  |
| 4.2.1.2 | Ruthenium-Catalyzed Asymmetric Hydrogenation of Azoles                                      | 73  |
| 4.2.1.3 | Palladium-Catalyzed Asymmetric Hydrogenation of Azoles                                      | 75  |
| 4.2.1.4 | Iridium-Catalyzed Asymmetric Hydrogenation of Indoles                                       | 77  |
| 4.2.2   | Catalytic Asymmetric Hydrogenation of Oxygen-Containing Heteroarenes                        | 77  |
| 4.2.3   | Catalytic Asymmetric Hydrogenation of Sulfur-Containing Heteroarenes                        | 79  |
| 4.3     | Catalytic Asymmetric Hydrogenation of Six-Membered Heteroarenes                             | 79  |
| 4.3.1   | Catalytic Asymmetric Hydrogenation of Azines  | 80  |
| 4.3.1.1 | Iridium-Catalyzed Asymmetric Hydrogenation of Pyridines                                     | 80  |
| 4.3.1.2 | Iridium-Catalyzed Asymmetric Hydrogenation of Pyrimidines                                   | 81  |
| 4.3.2   | Catalytic Asymmetric Hydrogenation of Benzo-Fused Azines                                    | 82  |
| 4.3.2.1 | Iridium-Catalyzed Asymmetric Hydrogenation of Quinolines                                    | 82  |
| 4.3.2.2 | Ruthenium-Catalyzed Asymmetric Hydrogenation of Quinolines                                  | 85  |
| 4.3.2.3 | Iridium-Catalyzed Asymmetric Hydrogenation of Isoquinolines                                 | 87  |
| 4.3.2.4 | Iridium-Catalyzed Asymmetric Hydrogenation of Quinoxalines                                  | 89  |
| 4.3.2.5 | Ruthenium-Catalyzed Asymmetric Hydrogenation of Quinoxalines                                | 90  |
| 4.3.2.6 | Iron-Catalyzed Asymmetric Hydrogenation of Quinoxalines                                     | 92  |
| 4.3.2.7 | Catalytic Asymmetric Hydrogenation of Miscellaneous Six-Membered Heteroarenes               | 92  |
| 4.3.3   | Catalytic Asymmetric Reduction of Quinolines with Reducing Agents Other Than H <sub>2</sub> | 94  |
| 4.4     | Catalytic Asymmetric Hydrogenation of Carbocyclic Arenes                                    | 95  |
| 4.4.1   | Ruthenium-Catalyzed Asymmetric Hydrogenation of Carbocycles in Benzo-Fused Heteroarenes     | 96  |
| 4.4.2   | Ruthenium-Catalyzed Asymmetric Hydrogenation of Naphthalenes                                | 97  |
| 4.5     | Summary and Conclusion  | 97  |
|         | References  | 98  |
| <br>    |   |     |
| 5       | <b>Stepwise Asymmetric Dearomatization of Phenols</b>                                       | 103 |
|         | <i>Qing Gu</i>  |     |
| 5.1     | Introduction  | 103 |
| 5.2     | Stepwise Asymmetric Dearomatization of Phenols  | 103 |
| 5.2.1   | Asymmetric [4+2] Reaction   | 103 |
| 5.2.2   | Asymmetric Heck Reaction  | 106 |
| 5.2.3   | Asymmetric (Hetero) Michael Reaction  | 108 |
| 5.2.4   | Asymmetric Stetter Reaction   | 119 |
| 5.2.5   | Asymmetric Rauhut–Currier Reaction  | 120 |
| 5.2.6   | Asymmetric 1,6-Diene Cyclized Reaction  | 122 |

|          |   |     |
|----------|---|-----|
| 5.3      | Conclusion and Perspective  | 126 |
|          | References  | 127 |
| <b>6</b> | <b>Asymmetric Oxidative Dearomatization Reaction</b>  | 129 |
|          | <i>Muhammet Uyanik and Kazuaki Ishihara</i>   |     |
| 6.1      | Introduction  | 129 |
| 6.2      | Diastereoselective Oxidative Dearomatization using Chiral Auxiliaries                                 | 129 |
| 6.3      | Enantioselective Oxidative Dearomatization using Chiral Reagents or Catalysts                         | 132 |
| 6.3.1    | Chiral Transition Metal Complexes   | 132 |
| 6.3.2    | Chiral Hypervalent Iodines(III, V) and Hypoiodites(I)   | 139 |
| 6.4      | Conclusions and Perspectives  | 148 |
|          | References  | 149 |
| <b>7</b> | <b>Asymmetric Dearomatization via Cycloaddition Reaction</b>  | 153 |
|          | <i>Sarah E. Reisman, Madeleine E. Kieffer, and Haoxuan Wang</i>                                       |     |
| 7.1      | Introduction  | 153 |
| 7.2      | [2 + 1] Cycloaddition   | 153 |
| 7.2.1    | Asymmetric Büchner Reaction   | 153 |
| 7.2.2    | Cyclopropanation of Heterocyclic Compounds  | 155 |
| 7.3      | [3 + 2] Cycloaddition   | 156 |
| 7.4      | [3 + 3] Cycloaddition   | 161 |
| 7.5      | [4 + 2] Cycloaddition   | 163 |
| 7.6      | [4 + 3] Cycloaddition   | 170 |
| 7.7      | Conclusion  | 173 |
|          | References  | 173 |
| <b>8</b> | <b>Organocatalytic Asymmetric Dearomatization Reactions</b>   | 175 |
|          | <i>Susana S. Lopez, Sri K. Nimmagadda, and Jon C. Antilla</i>   |     |
| 8.1      | Introduction  | 175 |
| 8.2      | Diels–Alder   | 175 |
| 8.3      | Oxidative Dearomatization   | 179 |
| 8.4      | Cascade Reactions   | 186 |
| 8.5      | Stepwise  | 193 |
| 8.6      | Nucleophilic Dearomatization  | 200 |
| 8.7      | Summary and Conclusion  | 204 |
|          | References  | 205 |
| <b>9</b> | <b>Dearomatization via Transition-Metal-Catalyzed Allylic Substitution Reactions</b>                  | 207 |
|          | <i>Tetsuhiro Nemoto and Yasumasa Hamada</i>   |     |
| 9.1      | Introduction  | 207 |
| 9.2      | Dearomatization of Indoles and Pyrroles via Transition-Metal-Catalyzed Allylic Substitution Reactions | 208 |

|           |  |            |
|-----------|--|------------|
| 9.3       | Dearomatization of Phenols via Transition-Metal-Catalyzed Allylic Substitution Reactions       | 216        |
| 9.4       | Dearomatization of Phenols and Indoles via Activation of Propargyl Carbonates with Pd Catalyst | 221        |
| 9.5       | Conclusion   | 226        |
|           | References   | 226        |
| <b>10</b> | <b>Dearomatization via Transition-Metal-Catalyzed Cross-Coupling Reactions</b>                 | <b>229</b> |
|           | <i>Robin B. Bedford</i>  |            |
| 10.1      | Introduction: From Cross-Coupling to Catalytic Dearomatization                                 | 229        |
| 10.2      | Dearomatization of Phenolic Substrates   | 231        |
| 10.3      | Dearomatization of Nitrogen-Containing Substrates  | 240        |
| 10.4      | Conclusion and Outlook   | 244        |
|           | References   | 245        |
| <b>11</b> | <b>Dearomatization Reactions of Electron-Deficient Aromatic Rings</b>                          | <b>247</b> |
|           | <i>Chihiro Tsukano and Yoshiji Takemoto</i>  |            |
| 11.1      | Introduction   | 247        |
| 11.2      | Dearomatization of Activated Pyridines and Other Electron-Deficient Heterocycles               | 248        |
| 11.2.1    | Dearomatization via Alkyl Pyridinium Salts   | 248        |
| 11.2.1.1  | Reduction with Borohydrides  | 248        |
| 11.2.1.2  | Reduction with $\text{Na}_2\text{S}_2\text{O}_4$   | 249        |
| 11.2.1.3  | Reduction with Other Reducing Agents   | 250        |
| 11.2.1.4  | Nucleophilic Addition of Grignard Reagents   | 251        |
| 11.2.1.5  | Nucleophilic Addition of Cyanide   | 252        |
| 11.2.1.6  | Addition of Other Carbon Nucleophiles  | 252        |
| 11.2.2    | Dearomatization via Alkoxy carbonylpyridinium Salts  | 253        |
| 11.2.2.1  | Reduction with Hydride Nucleophiles  | 254        |
| 11.2.2.2  | Addition of Metal Nucleophiles, Including Grignard Reagents                                    | 255        |
| 11.2.2.3  | Addition of Enolates and Related Carbon Nucleophiles   | 261        |
| 11.2.2.4  | Nucleophilic Addition of Cyanide   | 264        |
| 11.2.2.5  | Addition of Other Nucleophiles   | 265        |
| 11.2.3    | Dearomatization via Acyl Pyridinium Salts  | 266        |
| 11.2.3.1  | Reduction with Hydride Reducing Agents   | 266        |
| 11.2.3.2  | Addition of Metal Nucleophiles Including Grignard Reagents                                     | 269        |
| 11.2.3.3  | Addition of Enolates and Related Carbon Nucleophiles   | 270        |
| 11.2.4    | Dearomatization through Other Pyridinium Cations   | 270        |
| 11.3      | Summary and Conclusion   | 274        |
|           | References   | 274        |

|          |  |     |
|----------|--|-----|
| 12       | <b>Asymmetric Dearomatization Under Enzymatic Conditions</b>               | 279 |
|          | <i>Simon E. Lewis</i>  |     |
| 12.1     | Introduction   | 279 |
| 12.2     | Dearomatizing Arene <i>cis</i> -Dihydroxylation                            | 280 |
| 12.2.1   | Early Development  | 280 |
| 12.2.2   | Types of Arene Dioxygenase   | 281 |
| 12.2.3   | Substrate Scope and Regioselectivity                                       | 283 |
| 12.2.3.1 | Monocyclic Substituted Benzene Substrates (Excluding Biaryls)              | 299 |
| 12.2.3.2 | Biaryl Substrates  | 299 |
| 12.2.3.3 | Naphthalene Substrates   | 299 |
| 12.2.3.4 | Benzoic Acid Substrates  | 299 |
| 12.2.3.5 | Heterocyclic Substrates (Mono- and Bicyclic)                               | 300 |
| 12.2.3.6 | Bicyclic Carbocyclic Substrates (Other than Naphthalenes)                  | 300 |
| 12.2.3.7 | Tricyclic Substrates (Carbo- and Heterocyclic)                             | 300 |
| 12.2.4   | Availability of Arene <i>cis</i> -Diols                                    | 300 |
| 12.2.5   | Uses in Synthesis  | 302 |
| 12.2.5.1 | Total Synthesis  | 302 |
| 12.2.5.2 | Pharmaceuticals and Agrochemicals  | 315 |
| 12.2.5.3 | Polymers   | 317 |
| 12.2.5.4 | Flavors and Fragrances   | 320 |
| 12.2.5.5 | Dyes   | 321 |
| 12.2.5.6 | Ligands and MOFs   | 321 |
| 12.2.6   | Increasing the Substrate Scope   | 324 |
| 12.2.7   | Accessing Both Enantiomeric Series   | 326 |
| 12.2.8   | Improvements to the Production Process                                     | 328 |
| 12.3     | Dearomatizing Arene Epoxidation  | 328 |
| 12.4     | Dearomatizing Arene Reduction  | 330 |
| 12.5     | Summary and Conclusion   | 330 |
|          | List of Abbreviations  | 331 |
|          | References   | 332 |
| 13       | <b>Total Synthesis of Complex Natural Products via Dearomatization</b>     | 347 |
|          | <i>Weiqing Xie and Dawei Ma</i>  |     |
| 13.1     | Introduction   | 347 |
| 13.2     | Natural Products Synthesis via Oxidative Dearomatization                   | 348 |
| 13.2.1   | Enzymatic Dihydroxylative Dearomatization of Arene                         | 348 |
| 13.2.2   | Oxidative Dearomatization of Phenol  | 349 |
| 13.2.3   | Oxidative Cycloisomerization Reaction of Phenol                            | 355 |
| 13.2.4   | Oxidative Dearomatization of Indole in Synthesis of Natural Products       | 357 |
| 13.3     | Dearomatization via Cycloaddition in Synthesis of Natural Products         | 360 |
| 13.4     | Dearomatization via Nucleophilic Addition in Synthesis of Natural Products | 367 |

|           |   |            |
|-----------|---|------------|
| 13.5      | Reductive Dearomatization in Synthesis of Natural Products                  | 367        |
| 13.6      | Dearomatization via Electrophilic Addition in Synthesis of Natural Products | 369        |
| 13.7      | Dearomatization via Intramolecular Arylation in Natural Products Synthesis  | 371        |
| 13.8      | Summary and Perspective   | 373        |
|           | References  | 374        |
| <b>14</b> | <b>Miscellaneous Asymmetric Dearomatization Reactions</b>                   | <b>379</b> |
|           | <i>Wei Zhang and Shu-Li You</i>   |            |
| 14.1      | Introduction  | 379        |
| 14.2      | Miscellaneous Asymmetric Dearomatization Reactions                          | 379        |
| 14.3      | Conclusions and Perspectives  | 388        |
|           | References  | 388        |
|           | <b>Index</b>  | <b>391</b> |