# Contents

Preface xi Abbreviations xiii

- 1 Fundamentals of the Stereochemistry of Organophosphorus Compounds 1
- 1.1 Historical Background 1
- 1.2 Some Common Definitions in Stereochemistry 4
- 1.3 Determination of Enantiomer Composition 7
- 1.3.1 Method of Nuclear Magnetic Resonance 8
- 1.3.1.1 Chiral Solvating Agents 8
- 1.3.1.2 Complexes of Metals (Shift Reagents) 10
- 1.3.1.3 Chiral Derivatizing Agents for NMR 11
- 1.3.2 Chromatographic Methods of Analysis 14
- 1.3.2.1 Gas Chromatography 15
- 1.3.2.2 Liquid Chromatography 16
- 1.4 Determination of the Absolute Configuration *17*
- 1.4.1 X-ray Crystal Analysis 17
- 1.4.2 Method of Chemical Correlation 19
- 1.4.3 The Assignment of Absolute Configuration by NMR 19
- 1.5 Asymmetric Induction and Stereochemistry 24
- 1.5.1 Asymmetric Induction 24
- 1.5.2 Asymmetric Synthesis 25
- 1.5.3 Asymmetric Transformation 25
- 1.5.4 An Enantioselective Reaction 25
- 1.5.5 Enantioselective Synthesis 25
- 1.6 Summary 26 References 26

### 2 Asymmetric Synthesis of P-Chirogenic Phosphorus Compounds 35

- 2.1 Introduction 35
- 2.2 Low-Coordinated Phosphorus Compounds 36
- 2.3 Trivalent Tricoordinated Phosphorus Compounds 41
- 2.3.1 Configuration Stability of P(III)-Compounds 41
- 2.3.2 Asymmetric Nucleophilic Substitution at P (III) 43
- 2.3.2.1 Secondary Alcohols as Chiral Auxiliaries 45
- 2.3.2.2 Optically Active Amines as Chiral Auxiliaries 54

- viii Contents
  - 2.3.2.3 Ephedrine as Inductor of Chirality at P(III) 58
  - 2.3.3 Asymmetric Oxidation of P(III) Compounds 67
  - 2.3.4 Asymmetric Electrophilic Substitution at P(III) 68
  - 2.3.4.1 Asymmetric Michaelis Arbuzov Reaction 70
  - 2.4 Pentavalent P(IV)-Phosphorus Compounds 71
  - 2.4.1 Introduction 71
  - 2.4.2 Nucleophilic Substitution Reactions 72
  - 2.4.2.1 Nucleophilic Substitution at P(IV) with Chiral Alcohol 74
  - 2.4.2.2 Nucleophilic Substitution at P(IV) with Chiral Amines 78
  - 2.5 Chiral P(V) and P(VI) Phosphorus Compounds 802.6 Summary 86

References 87

### 3 Phosphorus Compounds with Chiral Side-Chain Centers 101

- 3.1 Introduction 101
- 3.2 Asymmetric Induction in Side Chains 102
- 3.2.1 Transfer of Chirality from Phosphorus to Other Centers 103
- 3.2.1.1 Chiral Phosphorus-Stabilized Anions 103
- 3.2.1.2 1,2-Asymmetric Induction 105
- 3.2.1.3 1,4-Asymmetric Induction 107
- 3.3 Enantioselective Olefination *113*
- 3.4 Stereoselective Addition of Phosphorous Nucleophiles to C=X Bonds 117
- 3.4.1 Phospha-Aldol Reaction 119
- 3.4.2 Phospha-Mannich Reaction 130
- 3.4.3 Phospha-Michael Reaction 142
- 3.5 Asymmetric Reduction 147
- 3.6 Asymmetric Oxidation 152
- 3.7 C-Modification 156
- 3.8 Asymmetric Cycloaddition 157
- 3.9 Multiple Stereoselectivity 159
- 3.10 Summary 169 References 170

## 4 Asymmetric Catalysis with Metal Complexes 187

- 4.1 Introduction 187
- 4.2 Asymmetric Catalytic Hydrogenation and Other Reactions of Reduction *188*
- 4.2.1 Hydrogenation of C=C Phosphorus Compounds 188
- 4.2.2 Hydrogenation of C=O Phosphorus Compounds 200
- 4.3 Asymmetric Reduction and Oxidation 203
- 4.3.1 Reduction of C=O, C=N, and C=C bonds 204
- 4.3.2 Asymmetric Oxidation 210
- 4.4 Electrophilic Asymmetric Catalysis 211
- 4.4.1 Catalytic Electrophilic Substitution at the Phosphorus Atom 212
- 4.4.1.1 Alkylation and Arylation of P(III) Compounds 213
- 4.4.2 Catalytic Electrophilic Substitution in a Side Chain 217
- 4.4.2.1 Alkylation 217
- 4.4.2.2 Halogenation 219

- 4.4.2.3 Amination 221
- 4.5 Nucleophilic Asymmetric Catalysis 223
- 4.5.1 Asymmetric Addition of Phosphorus Nucleophiles to Multiple Bonds 223
- 4.5.1.1 Phospha-Aldol Reaction 224
- 4.5.1.2 Phospha-Mannich Reaction 229
- 4.5.1.3 Phospha-Michael Reaction 232
- 4.6 Cycloaddition Reactions 237
- 4.7 Summary 240 References 241

#### 5 Asymmetric Organocatalysis 253

- 5.1 Introduction 253
- 5.2 Modes for Catalytic Activation of Substrates in Asymmetric Organocatalysis 254
- 5.3 Phospha-Aldol Reaction 258
- 5.3.1 Catalysis with Cinchona Alkaloids 258
- 5.3.2 Catalysis with Cinchona-Thiourea 259
- 5.3.3 Catalysis by Other Organocatalysts 260
- 5.4 Phospha-Mannich Reactions 262
- 5.4.1 Organocatalysis by Cinchona Alkaloids 262
- 5.4.2 Organocatalysis by Imines 263
- 5.4.3 Organocatalysis by Iminium salts 265
- 5.4.4 Organocatalysis by Chiral Brønsted acids 265
- 5.5 Phospha-Michael Reaction 269
- 5.5.1 Organocatalysis by Cinchona Alkaloids 269
- 5.5.2 Organocatalysis by Thiourea 270
- 5.5.3 Organocatalysis by Iminium salts 272
- 5.5.4 Organocatalysis by N-Heterocyclic Carbenes 274
- 5.5.5 Organocatalysis Using Proline Derivatives 274
- 5.6 Organocatalytic Addition to Ketophosphonates 282
- 5.6.1 Proline, Amino Acids, and Their Derivatives 282
- 5.6.2 Organocatalysis by Thiourea 288
- 5.7 Phospha-Henry Reaction 288
- 5.8 Organocatalytic Modification of *P*-ylids 290
- 5.9 Asymmetric Catalysis with Chiral Diamines 292
- 5.10 Miscellaneous 303 References 305

#### 6 Asymmetric Biocatalysis 315

- 6.1 Introduction 315
- 6.2 Enzymatic Synthesis of Organophosphorus Compounds 315
- 6.2.1 Kinetic Resolution of Hydroxyphosphonates 316
- 6.2.2 Resolution of α-Hydroxyphosphonates by Biocatalytic Transesterification *317*
- 6.2.3 Resolution of α-Hydroxyphosphonates by Biocatalytic Hydrolysis 319
- 6.2.4 Dynamic Kinetic Resolution of α-Hydroxyphosphonates 323
- 6.2.5 Resolution of  $\beta$  and  $\omega$ -Hydroxyphosphonates 323
- 6.2.6 Dynamic Kinetic Resolution of β-Hydroxyphosphonates 331

**x** Contents

- 6.2.7 Resolution of Aminophosphonates 332
- 6.3 Biosynthesis of Compounds with C–P Bond 335
- 6.4 Resolution of *P*-Chiral Phosphorus Compounds 337
- 6.5 Microbiological Synthesis of Chiral Organophosphorus Compounds 349
- 6.5.1 Yeast-Catalyzed Synthesis 349
- 6.5.2 Synthesis Using Unicellular Fungi 354
- 6.5.3 Synthesis Using Bacteria 356
- 6.6 Summary 358

References 358

**Index** 369