

## Contents

### List of Contributors IX

|          |                                                                       |           |
|----------|-----------------------------------------------------------------------|-----------|
| <b>1</b> | <b>Introduction: A Survey of How and Why to Separate Enantiomers</b>  | <b>1</b>  |
|          | <i>Matthew Todd</i>                                                   |           |
| 1.1      | Classical Methods                                                     | 2         |
| 1.2      | Kinetic Resolution ('KR')                                             | 3         |
| 1.3      | Dynamic Kinetic Resolution ('DKR')                                    | 5         |
| 1.4      | Divergent Reactions of a Racemic Mixture ('DRRM')                     | 7         |
| 1.5      | Other Methods                                                         | 8         |
|          | Acknowledgments                                                       | 9         |
|          | References                                                            | 9         |
| <b>2</b> | <b>Stoichiometric Kinetic Resolution Reactions</b>                    | <b>13</b> |
|          | <i>Mahagundappa R. Maddani, Jean-Claude Fiaud, and Henri B. Kagan</i> |           |
| 2.1      | Introduction                                                          | 13        |
| 2.2      | Kinetic Treatment                                                     | 14        |
| 2.2.1    | Reactions First-Order in Substrate                                    | 14        |
| 2.2.1.1  | Scope and Validity of Equation 2.6                                    | 18        |
| 2.2.1.2  | Equivalent Formulations of the Basic Equation 2.6                     | 19        |
| 2.2.2    | Reactions Zero- or Second-Order in Substrate                          | 19        |
| 2.2.3    | Improvement of Kinetic Resolution Processes                           | 20        |
| 2.2.4    | Use of Enantio-Impure Auxiliaries                                     | 21        |
| 2.3      | Chiral Reagents and Racemic Substrates                                | 22        |
| 2.3.1    | Esterification                                                        | 22        |
| 2.3.2    | Amide and Peptide Formation                                           | 30        |
| 2.3.3    | Cycloaddition Reactions                                               | 35        |
| 2.3.4    | Conjugate Additions                                                   | 39        |
| 2.3.5    | Borane-Involving Reactions                                            | 41        |
| 2.3.6    | Kinetic Resolution of Allenes                                         | 43        |
| 2.3.7    | Olefination Reactions                                                 | 45        |
| 2.3.8    | Deprotonation Reactions                                               | 48        |
| 2.3.9    | Miscellaneous                                                         | 49        |
| 2.4      | Enantiodivergent Formation of Chiral Product                          | 51        |

|          |                                                                                                                |            |
|----------|----------------------------------------------------------------------------------------------------------------|------------|
| 2.4.1    | Introduction                                                                                                   | 51         |
| 2.4.2    | Creation of a Stereogenic Unit                                                                                 | 52         |
| 2.4.3    | Formation of Regioisomers                                                                                      | 54         |
| 2.5      | Enantioconvergent Reactions                                                                                    | 55         |
| 2.6      | Diastereomer Kinetic Resolution                                                                                | 56         |
| 2.7      | Some Applications of Kinetic Resolution                                                                        | 58         |
| 2.7.1    | Organometallics and Analogues                                                                                  | 58         |
| 2.7.2    | Racemic Catalysts                                                                                              | 61         |
| 2.7.3    | Enantiomeric excess's and Stereoselectivity Factor Measurements by Mass Spectrometry                           | 63         |
| 2.7.4    | Mechanistic Studies. The Hoffmann Test                                                                         | 66         |
| 2.7.5    | Miscellaneous                                                                                                  | 69         |
| 2.8      | Conclusion                                                                                                     | 70         |
| 2.A      | Table of $s$ Factors Higher than 10 for Some Reactions                                                         | 70         |
|          | References                                                                                                     | 71         |
| <b>3</b> | <b>Catalytic Kinetic Resolution</b>                                                                            | <b>75</b>  |
|          | <i>Hélène Pellissier</i>                                                                                       |            |
| 3.1      | Introduction                                                                                                   | 75         |
| 3.2      | Kinetic Resolution of Alcohols                                                                                 | 76         |
| 3.2.1    | KR of Alcohols Using Chiral Acylation Catalysts                                                                | 76         |
| 3.2.2    | Oxidative KR of Alcohols                                                                                       | 81         |
| 3.2.3    | Miscellaneous Kinetic Resolutions                                                                              | 87         |
| 3.3      | Kinetic Resolution of Epoxides                                                                                 | 88         |
| 3.3.1    | Hydrolytic Kinetic Resolution                                                                                  | 88         |
| 3.3.2    | Ring Opening of Epoxides by Nucleophiles Other than Water                                                      | 92         |
| 3.4      | Kinetic Resolution of Amines                                                                                   | 93         |
| 3.5      | Kinetic Resolution of Alkenes                                                                                  | 97         |
| 3.6      | Kinetic Resolution of Carbonyl Derivatives                                                                     | 101        |
| 3.7      | Kinetic Resolution of Sulfur Compounds                                                                         | 102        |
| 3.8      | Kinetic Resolution of Ferrocenes                                                                               | 103        |
| 3.9      | Conclusions                                                                                                    | 105        |
|          | Abbreviations                                                                                                  | 105        |
|          | References                                                                                                     | 107        |
| <b>4</b> | <b>Application of Enzymes in Kinetic Resolutions, Dynamic Kinetic Resolutions and Deracemization Reactions</b> | <b>123</b> |
|          | <i>Cara E. Humphrey, Marwa Ahmed, Ashraf Ghanem, and Nicholas J. Turner</i>                                    |            |
| 4.1      | Introduction                                                                                                   | 123        |
| 4.2      | Kinetic Resolutions Using Hydrolytic Enzymes                                                                   | 123        |
| 4.2.1    | Lipases in Organic Synthesis                                                                                   | 123        |
| 4.2.2    | Structural Features of Lipases                                                                                 | 124        |
| 4.2.3    | Typical Substrates for Lipases and Esterases                                                                   | 125        |
| 4.2.4    | Monitoring the Progress of Lipase-Catalysed Resolutions                                                        | 126        |

|          |                                                                                               |            |
|----------|-----------------------------------------------------------------------------------------------|------------|
| 4.2.5    | Kazlauskas' Rule                                                                              | 127        |
| 4.2.6    | Activated Acyl Donors                                                                         | 128        |
| 4.2.7    | Examples of Lipase-, Lipolase- and Hydrolase-Catalysed Reactions in Synthesis                 | 129        |
| 4.2.7.1  | Resolution of Secondary Alcohols                                                              | 129        |
| 4.2.7.2  | Resolution of Amines                                                                          | 131        |
| 4.2.7.3  | Hydrolysis of Lactams and Nitriles                                                            | 132        |
| 4.2.7.4  | Epoxide Hydrolases                                                                            | 133        |
| 4.2.8    | Strategies for Controlling and Enhancing the Enantioselectivity of Enzyme-Catalysed Reactions | 134        |
| 4.2.8.1  | Substrate Engineering                                                                         | 134        |
| 4.2.8.2  | Solvent Engineering                                                                           | 135        |
| 4.2.8.3  | Immobilization and Chemical Modification                                                      | 136        |
| 4.2.8.4  | Directed Evolution and Enzyme Libraries                                                       | 137        |
| 4.3      | Dynamic Kinetic Resolution                                                                    | 138        |
| 4.3.1    | Non-Enzyme-Catalysed Racemization                                                             | 139        |
| 4.3.1.1  | <i>In Situ</i> Racemization via Protonation/Deprotonation                                     | 139        |
| 4.3.1.2  | <i>In Situ</i> Racemization via Addition/Elimination                                          | 140        |
| 4.3.1.3  | <i>In Situ</i> Racemization via Oxidation/Reduction                                           | 140        |
| 4.3.1.4  | <i>In Situ</i> Racemization via Nucleophilic Substitution                                     | 141        |
| 4.3.1.5  | <i>In Situ</i> Racemization via Free Radical Mechanism                                        | 141        |
| 4.3.2    | Metal-Catalysed Racemization                                                                  | 141        |
| 4.3.2.1  | Ruthenium-Based Catalysts                                                                     | 142        |
| 4.3.2.2  | Non-Ruthenium Catalysts                                                                       | 145        |
| 4.3.3    | Enzyme-Catalysed Racemization                                                                 | 147        |
| 4.4      | Deracemization                                                                                | 148        |
| 4.4.1    | Deracemization of Secondary Alcohols                                                          | 148        |
| 4.4.2    | Deracemization of Carboxylic Acids                                                            | 150        |
| 4.4.3    | Deracemization of Amino Acids and Amines                                                      | 151        |
| 4.4.4    | Deracemization of Enol Actates                                                                | 152        |
| 4.5      | Enantioconvergent Reactions                                                                   | 153        |
| 4.6      | Conclusions                                                                                   | 153        |
|          | References                                                                                    | 154        |
| <b>5</b> | <b>Dynamic Kinetic Resolution (DKR)</b>                                                       | <b>161</b> |
|          | <i>Keiji Nakano and Masato Kitamura</i>                                                       |            |
| 5.1      | Introduction                                                                                  | 161        |
| 5.2      | Definition and Classification                                                                 | 162        |
| 5.3      | Dynamic Kinetic Resolution (DKR)                                                              | 164        |
| 5.3.1    | Tautomerization                                                                               | 164        |
| 5.3.2    | Pyramidal Inversion, Deformation and Rotation                                                 | 181        |
| 5.3.3    | Elimination–Addition and Addition–Elimination                                                 | 184        |
| 5.3.4    | Nucleophilic Substitution                                                                     | 193        |
| 5.3.5    | Others                                                                                        | 198        |
| 5.4      | Mathematical Expression                                                                       | 201        |

|          |                                                                                                             |            |
|----------|-------------------------------------------------------------------------------------------------------------|------------|
| 5.5      | DKR-Related Methods                                                                                         | 204        |
| 5.5.1    | DYKAT through a Single Enantiomeric Intermediate                                                            | 205        |
| 5.5.2    | DTR of Two Diastereomeric Intermediates                                                                     | 206        |
| 5.5.3    | Stereoinversion                                                                                             | 206        |
| 5.5.4    | Cyclic Deracemization                                                                                       | 207        |
| 5.5.5    | Enantio-Convergent Transformation                                                                           | 207        |
| 5.6      | Concluding Remarks                                                                                          | 208        |
|          | References                                                                                                  | 209        |
| <b>6</b> | <b>Enantiodivergent Reactions: Divergent Reactions on a Racemic Mixture and Parallel Kinetic Resolution</b> | <b>217</b> |
|          | <i>Trisha A. Russell and Edwin Vedejs</i>                                                                   |            |
| 6.1      | Introduction: The Conceptual Basis for Kinetic Resolution and Enantiodivergent Reactions                    | 217        |
| 6.2      | Divergent RRM Using a Single Chiral Reagent: Ketone Reduction                                               | 222        |
| 6.2.1    | Racemic Ketones and Chiral Non-Enzymatic Hydride Donors                                                     | 227        |
| 6.3      | Divergent RRM under Oxidative Conditions                                                                    | 229        |
| 6.4      | Organometallic Reagents and Regiodivergent RRM                                                              | 237        |
| 6.5      | Regiodivergent RRM in Selective Reactions of Difunctional Substrates                                        | 248        |
| 6.6      | Divergent RRM Using Two Chiral Reagents: Parallel Kinetic Resolution (PKR)                                  | 252        |
| 6.7      | Conclusion                                                                                                  | 262        |
|          | Acknowledgement                                                                                             | 262        |
|          | References                                                                                                  | 262        |
| <b>7</b> | <b>Rare, Neglected and Potential Synthetic Methods for the Separation of Enantiomers</b>                    | <b>267</b> |
|          | <i>Matthew Todd</i>                                                                                         |            |
| 7.1      | Resolution through the Selfish Growth of Polymers: Stereoselective Polymerization                           | 267        |
| 7.2      | Resolution through Photochemical Methods                                                                    | 271        |
| 7.3      | Combinations of Crystallization and Racemization                                                            | 274        |
| 7.3.1    | Crystallization-Induced Dynamic Resolution (CIDR)                                                           | 275        |
| 7.3.2    | Ripening                                                                                                    | 277        |
| 7.4      | Destruction Then Recreation of Stereocentres: Enantioselective Protonations                                 | 278        |
| 7.5      | Dynamic Combinatorial Chemistry                                                                             | 280        |
| 7.6      | Asymmetric Autocatalysis                                                                                    | 282        |
| 7.7      | Miscellaneous                                                                                               | 283        |
| 7.8      | Concluding Remarks                                                                                          | 283        |
|          | Acknowledgements                                                                                            | 284        |
|          | References                                                                                                  | 284        |
|          | <b>Index</b>                                                                                                | <b>291</b> |