Contents

List of Contributors  IX

1 Introduction: A Survey of How and Why to Separate Enantiomers  1
Matthew Todd
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

2 Stoichiometric Kinetic Resolution Reactions  13
Mahagundappa R. Maddani, Jean-Claude Fiaud, and Henri B. Kagan
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

3 Catalytic Kinetic Resolution 75
Hélène Pellissier
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

4 Application of Enzymes in Kinetic Resolutions, Dynamic Kinetic Resolutions and Deracemization Reactions 123
Cara E. Humphrey, Marwa Ahmed, Ashraf Ghanem, and Nicholas J. Turner
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
Contents

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

6 Enantiodivergent Reactions: Divergent Reactions on a Racemic Mixture and Parallel Kinetic Resolution 217
Trisha A. Russell and Edwin Vedejs
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

7 Rare, Neglected and Potential Synthetic Methods for the Separation of Enantiomers 267
Matthew Todd
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

Index 291