

Contents

List of Contributors IX

1	Introduction: A Survey of How and Why to Separate Enantiomers	1
	<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
2	Stoichiometric Kinetic Resolution Reactions	13
	<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 <i>s</i> Factors Higher than 10 for Some Reactions	70
	References	71
3	Catalytic Kinetic Resolution	75
	<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
4	Application of Enzymes in Kinetic Resolutions, Dynamic Kinetic Resolutions and Deracemization Reactions	123
	<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
5	Dynamic Kinetic Resolution (DKR)	161
	<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
6	Enantiodivergent Reactions: Divergent Reactions on a Racemic Mixture and Parallel Kinetic Resolution	217
	<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
7	Rare, Neglected and Potential Synthetic Methods for the Separation of Enantiomers	267
	<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