

Contents

Preface XIII

List of Contributors XV

Part One Asymmetric Synthesis of Nitrogen Heterocycles Containing Only One Heteroatom 1

1	Asymmetric Synthesis of Three- and Four-Membered Ring Heterocycles 3
	<i>Giuliana Cardillo, Luca Gentilucci and Alessandra Tolomelli</i>
1.1	Substituted Aziridines 3
1.1.1	Generalities 3
1.1.2	Asymmetric Aziridination via Cyclization Methods 6
1.1.2.1	Cyclization of a Nucleophilic N on an Electrophilic C (Pathway A) 7
1.1.2.2	Cyclization of a Stabilized Anion on an Electrophilic N (Pathway B) 9
1.1.3	Asymmetric Aziridination via Cycloaddition Methods 12
1.1.3.1	Addition of Nitrenes to Alkenes 12
1.1.3.2	Reaction between Carbenes and Imines 16
1.1.4	Ring Transformation Methods 27
1.1.4.1	Aziridines from Epoxides 27
1.1.4.2	Aziridines from Other Heterocycles 30
1.1.5	Racemate Resolution 31
1.1.6	Asymmetric Synthesis of Azirines 33
1.1.6.1	The Neber Reaction 33
1.1.6.2	Thermal or Photochemical Treatment of Vinyl Azides 34
1.1.6.3	Elimination from Aziridines 34
1.1.6.4	Resolution of Racemic Azirines 35
1.1.6.5	Oxidation of Aziridines 36
1.2	Substituted Monocyclic Azetidines and Carbocyclic-Fused systems 36
1.2.1	Generalities 36
1.2.2	Cyclization Methods: Introduction 38

1.2.2.1	Cyclization methods: Enantiopure Azetidines via Formation of C–N Bond	39
1.2.2.2	Cyclization Methods: Enantiopure Azetidines via Formation of C–C Bond	40
1.2.3	Azetidines by Resolution of Racemates	42
1.2.4	Azetidines by Ring Transformation	44
	References	45
2	Asymmetric Synthesis of Five-Membered Ring Heterocycles	51
	<i>Pei-Qiang Huang</i>	
2.1	Monocyclic Pyrrolidines and Pyrrolidinones	51
2.1.1	Generalities	51
2.1.2	Cyclization Methods	52
2.1.2.1	Cyclization via C ₁ /C ₅ –N Bond Formation	52
2.1.2.2	Cyclization via C ₂ –C ₃ Bond Formation	61
2.1.2.3	Cyclization Involving C ₃ –C ₄ Bond Formation	62
2.1.3	Cycloaddition Methods	64
2.1.3.1	Cycloaddition Approach	64
2.1.3.2	Annulation Approach	66
2.1.4	Ring Transformation Methods	67
2.1.4.1	Ring Expansion Methods	67
2.1.4.2	Ring Contraction Methods	68
2.1.5	Substitution of Already Formed Heterocycle	68
2.1.5.1	By Nucleophilic Reaction of Pyrrolidinium Ions	71
2.1.5.2	By Nucleophilic Reaction of Cyclic Imides	72
2.1.5.3	By Nucleophilic Addition/Cycloaddition of Pyrrolidine Nitrones	74
2.1.5.4	By Functionalization of 2-Pyrrolines	76
2.1.5.5	By Enantioselective Reactions	77
2.1.5.6	By Functionalization at C ₃ /C ₄ Positions of Pyrrolidines	77
2.2	Pyrrolines	79
2.2.1	Synthesis of Pyrrolines by Cyclization and Annulation Reactions	79
2.2.2	Synthesis of Pyrrolines by Substitution of Already Formed Heterocycles	80
2.3	Fused Bicyclic Systems with Bridgehead Nitrogen	82
2.3.1	Pyrrolizidines	82
2.3.1.1	Through Extension of Methods for the Synthesis of Pyrrolidines	82
2.3.1.2	Other Methods for the Synthesis of Pyrrolizidines	83
2.3.1.3	Asymmetric Synthesis of Polyhydroxylated Pyrrolizidines	85
2.4	Acknowledgments	87
	References	87
3	Asymmetric Synthesis of Six-Membered Ring Heterocycles	95
	<i>Naoki Toyooka</i>	
3.1	Introduction	95
3.2	Dihydropyridines	95

3.3	Tetrahydropyridines	98
3.3.1	Ring-Closing Metathesis (RCM)	98
3.3.2	Reduction of Pyridine Derivatives	101
3.3.3	Deracemization Processes	101
3.3.4	Michael Addition Followed by Elimination	102
3.3.5	Enamine Reaction	102
3.3.6	Electrocyclization	105
3.4	Monocyclic Piperidines and Carbocyclic Fused Systems	107
3.4.1	Generalities	107
3.4.2	Cyclization Methods	107
3.4.2.1	Nitrogen as a Nucleophile	108
3.4.2.2	C–C Bond Formation	113
3.4.3	Cycloaddition Methods	117
3.4.3.1	[4 + 2] Azadiene Cycloaddition	117
3.4.3.2	[4 + 2] Acylnitroso Cycloaddition	117
3.4.3.3	[3 + 2] Cycloaddition	119
3.4.4	Ring Transformation Methods	119
3.4.4.1	Ring Enlargement of Pyrrolidines to Substituted Piperidines	120
3.4.4.2	Ring Transformation of Lactones to 2-Piperidones	121
3.4.4.3	Ring Enlargement of γ -Lactam to 2-Piperidones	122
3.4.5	Substitution of Already Formed Heterocycle	123
3.4.5.1	Phenylglycinol-Derived Oxazolidine	123
3.4.5.2	Asymmetric Michael Addition	125
3.4.5.3	Nitrone Cycloaddition	127
3.4.5.4	Iminium Strategies	128
3.4.5.5	Oxidative Methods	131
3.5	Fused Tri- or Bicyclic System with Bridgehead Nitrogen	132
	References	135

4 Asymmetric Synthesis of Seven- and More-Membered Ring

Heterocycles 139

Yves Troin and Marie-Eve Sinibaldi

4.1	Substituted Azepines	139
4.1.1	Generalities	139
4.1.2	Cyclization Methods	142
4.1.2.1	Lactamization: C–N Bond Formation	142
4.1.2.2	Radical Cyclization	146
4.1.2.3	Intramolecular Cyclization	149
4.1.2.4	Oxidative Phenol Coupling Reaction	155
4.1.2.5	The Ring Closure Metathesis	155
4.1.3	Cycloaddition Methods	161
4.1.3.1	[5 + 2] Cycloaddition	162
4.1.3.2	[4 + 3] Cycloaddition	162
4.1.3.3	Nitrone Cycloaddition	162

x | *Contents*

4.1.3.4	Intramolecular Diels–Alder Reactions (IMDA) – [4 + 2] Cycloaddition	163
4.1.4	Ring Transformation Methods	163
4.1.4.1	Classical Methods	164
4.1.4.2	Ring Expansion	166
4.1.4.3	Substitution of Already Formed Heterocycles	169
4.2	Substituted Azocines	171
4.2.1	Azocines from Intramolecular Nucleophilic Substitution	172
4.2.2	Ring Transformations Methods	173
4.2.3	Cycloaddition Approaches to Azocines	174
4.2.4	Ring-Closing Metathesis	175
4.3	Substituted Large Nitrogen-Containing Rings	177
	References	181

Part Two Asymmetric Synthesis of Nitrogen Heterocycles with More Than One Heteroatom 187

5 Asymmetric Synthesis of Three- and Four-Membered Ring Heterocycles with More Than One Heteroatom 189

Steve Lanners and Gilles Hanquet

5.1	Introduction	189
5.2	Three-Membered N-Heterocycles with Two Heteroatoms	189
5.2.1	Diaziridines	190
5.2.1.1	Substrate-Controlled Diastereoselective Diaziridination Using Chiral Enantiomerically Pure Amines	191
5.2.1.2	Substrate-Controlled Diastereoselective Diaziridination Using Chiral Enantiomerically Pure Ketones	192
5.2.2	Diazirines	193
5.2.3	Oxaziridines	194
5.2.3.1	Chiral Peracidic Oxidation of Achiral Imines	195
5.2.3.2	Achiral Peracidic Oxidation of Chiral Nonracemic Imines	196
5.2.3.3	Photocyclization of Nitrones	207
5.3	Four-Membered N-Heterocycles with Two Heteroatoms	208
5.3.1	Diazetidines	208
5.3.2	Oxazetidines	210
5.3.2.1	Thiazetidines	212
5.4	Conclusions	217
	References	217

6 Asymmetric Synthesis of Five-Membered Ring Heterocycles with More Than One Heteroatom 223

Catherine Kadouri-Puchot and Claude Agami

6.1	Five-Membered Heterocycles with N and O Atoms	223
6.1.1	Oxazolidines	223

6.1.1.1	N-Alkyloxazolidines	224
6.1.1.2	N-Tosyl and N-Boc Oxazolidines	228
6.1.2	Oxazolines (4,5-dihydrooxazoles)	230
6.1.3	Oxazolidinones	235
6.1.3.1	Oxazolidin-2-ones	235
6.1.3.2	Oxazolidin-4-ones and 5-ones	242
6.1.4	Isoxazolines and Isoxazolidines	243
6.1.4.1	Isoxazolidines	244
6.1.4.2	Isoxazolines	246
6.2	Five-Membered Heterocycles with Two N Atoms	249
6.2.1	Imidazolidines and Imidazolidinones	249
6.2.1.1	Imidazolidines	249
6.2.1.2	Imidazolidinones	252
6.2.2	Pyrazolidines and Pyrazolines	255
6.2.2.1	Pyrazolidines	255
6.2.2.2	Pyrazolines	257
6.2.3	Pyrazolidinones	260
6.3	Five-Membered Heterocycles with N and S Atoms	263
6.3.1	Thiazolidines	263
6.3.1.1	Iminothiazolidines	267
6.3.1.2	Thiazolidinethiones	268
6.3.1.3	Thiazolidinones	269
6.3.2	Thiazolines	270
6.3.2.1	2-Thiazolines	270
6.3.2.2	3-Thiazolines	275
6.3.3	Sultams	276
	References	281

7	Asymmetric Synthesis of Six-Membered Ring Nitrogen Heterocycles with More Than One Heteroatom	293
	<i>Péter Mátýus and Pál Tapolcsányi</i>	
7.1	Six-Membered Rings with Another Heteroatom in the Same Ring	293
7.1.1	Pyridazines	293
7.1.1.1	Ring Closure of Optically Active Precursors	294
7.1.1.2	Diels–Alder Reactions	299
7.1.2	Pyrimidines	302
7.1.2.1	Formation of the Pyrimidine Ring	302
7.1.2.2	Stereoselective Transformation by the Involvement of the Pyrimidine Ring	307
7.1.3	Piperazines	311
7.1.3.1	Formation of the Piperazine Ring	311
7.1.3.2	Stereoselective Transformation of the Piperazine Ring	327
7.1.4	Oxadiazines	332
7.1.4.1	1,2,5-Oxadiazines	332
7.1.4.2	1,3,4-Oxadiazines	332

7.1.5	Morpholines	335
7.1.5.1	Formation of the Morpholine Ring	335
7.1.5.2	Asymmetric Transformations with the Involvement of the Morpholine Ring	352
	References	359
8	Asymmetric Synthesis of Seven-Membered Rings with More Than One Heteroatom	367
	<i>Jacques Royer</i>	
8.1	Diazepines	367
8.1.1	1,2-Diazepines	367
8.1.2	1,3-Diazepines	368
8.1.3	1,4-Diazepines	371
8.1.3.1	1,4-Benzodiazepines	371
8.1.3.2	Other 1,4-Diazepines	376
8.2	Oxazepines	378
8.2.1	1,2-Oxazepine	378
8.2.1.1	Diels–Alder Cycloaddition	378
8.2.1.2	Intramolecular 3 + 2 Cycloaddition	379
8.2.1.3	Pd-Catalyzed 4 + 3 Cycloaddition	379
8.2.1.4	Rearrangements	379
8.2.2	1,3-Oxazepines	380
8.2.2.1	N,O-Acetals	380
8.2.3	1,4-Oxazepines	383
8.2.3.1	Amino Alcohol Double Condensation	383
8.2.3.2	Other Cyclization Methods	383
8.2.3.3	Pd-Catalyzed Allene Cyclization	384
8.2.3.4	Radical Cyclization	385
8.2.3.5	Ring Enlargement	385
8.2.3.6	Cycloaddition	386
8.3	Thiazepines	386
8.3.1	1,2-Thiazepines	387
8.3.2	1,3-Thiazepines	387
8.3.3	1,4-Thiazepines	388
8.3.3.1	From Mercaptopropionic Acid Derivatives	388
8.3.3.2	From Amino Thiols	390
8.3.3.3	Others	391
	References	392
	Index	399