

Contents

Foreword *xi*

Preface *xiii*

1	The Historical Development of Asymmetric Hydrogenation	1
	<i>John M. Brown</i>	
1.1	Introduction	1
1.2	Early Work on the Recognition of Molecular Asymmetry	1
1.3	Origins and Early Development of Asymmetric Synthesis	4
1.4	Early Developments in the Asymmetric Heterogeneous Hydrogenation of Alkenes	8
1.5	The Development of Rhodium Asymmetric Homogeneous Hydrogenation of Alkenes	10
1.6	The Development of Ruthenium Asymmetric Homogeneous Hydrogenation of Alkenes	16
1.7	Conclusions	18
	References	19
2	Asymmetric (Transfer) Hydrogenation of Functionalized Alkenes During the Past Decade	25
	<i>Christian Bruneau</i>	
2.1	Introduction	25
2.2	Asymmetric Hydrogenation with Rhodium Catalysts	25
2.2.1	Chiral Bisphosphine Ligands	25
2.2.2	Chiral Ferrocenyl Bisphosphine Ligands	27
2.2.3	Chiral Phosphine–Phosphoramidite and Phosphine–Phosphite Ligands	31
2.2.4	Self-assembled Diphosphine Ligands	33
2.2.5	Monodentate Phosphorus Ligands	33
2.2.6	Asymmetric Transfer Hydrogenation with Rhodium Catalysts	34
2.3	Asymmetric Hydrogenation with Iridium Catalysts	36
2.3.1	Chiral Bidentate Ferrocenyl Ligands	36
2.3.2	Other Chiral Bidentate P,N-ligands	37
2.3.3	Asymmetric Transfer Hydrogenation with Iridium Catalysts	42

2.4	Asymmetric Hydrogenation with Other Transition Metal Catalysts	43
2.4.1	Asymmetric Hydrogenation with Ruthenium Catalysts	43
2.4.2	Asymmetric Hydrogenation with Palladium Catalysts	46
2.5	Asymmetric (Transfer) Hydrogenation with First-row Transition Metal Catalysts	48
2.6	Conclusion	48
	References	49

3 Asymmetric (Transfer) Hydrogenation of Functionalized Ketones 55

Noriyoshi Arai and Takeshi Ohkuma

3.1	Introduction	55
3.2	Asymmetric (Transfer) Hydrogenation of Alkyl Ketones	57
3.3	Asymmetric Hydrogenation of α,β -Unsaturated Ketones	66
3.3.1	Alkenyl Alkyl Ketones	66
3.3.2	Alkynyl Alkyl Ketones	71
3.4	Asymmetric Hydrogenation of α -Aminoketones	73
3.5	Asymmetric Hydrogenation of α -hydroxyketones	77
3.6	Asymmetric Hydrogenation of α -Oxophosphonates	80
3.7	Summary and Conclusions	83
	References	83

4 Asymmetric (Transfer) Hydrogenation of Aryl and Heteroaryl Ketones 87

Jian-Hua Xie and Qi-Lin Zhou

4.1	Introduction	87
4.2	Asymmetric Hydrogenation of Aryl and Heteroaryl Ketones	88
4.2.1	Chiral Ruthenium Catalysts	90
4.2.1.1	Chiral Ruthenium-Diphosphine/Diamine Catalysts	90
4.2.1.2	Chiral Arene-Ruthenium-Diamine Catalysts	95
4.2.1.3	Chiral Ruthenium-Phosphine-Oxazoline Catalysts	96
4.2.1.4	Chiral Ruthenium Catalysts Containing Tridentate Pincer Ligands	97
4.2.1.5	Chiral Ruthenium Catalysts Containing Tetradentate Ligands	98
4.2.2	Chiral Iridium Catalysts	98
4.2.3	Other Chiral Metal Catalysts	100
4.3	Asymmetric Transfer Hydrogenation of Aryl and Heteroaryl Ketones	103
4.3.1	Chiral Ruthenium Catalysts	104
4.3.1.1	Chiral Arene Ruthenium-N-Sulfonylated 1,2-Diamine Complexes	104
4.3.1.2	Chiral Ruthenium Catalysts with Other Bidentate Ligands	107
4.3.1.3	Chiral Ruthenium Catalysts Containing Tridentate and Tetradentate Ligands	111
4.3.2	Chiral Rhodium and Iridium Catalysts	112
4.3.2.1	Chiral Rhodium and Iridium Complexes Containing Diamine and Related Ligands	113

4.3.2.2	Chiral Rhodium and Iridium Catalysts Containing Other Ligands	116
4.3.3	Other Chiral Metal Catalysts	117
4.3.3.1	Chiral Iron Catalysts	118
4.3.3.2	Chiral Osmium Catalysts	119
4.3.3.3	Other Chiral Metal Catalysts	119
4.4	Summary	120
	References	121
5	Asymmetric (Transfer) Hydrogenation of Substituted Ketones Through Dynamic Kinetic Resolution	129
	<i>Pierre-Georges Echeverria, Tahar Ayad, Phannarath Phansavath and Virginie Ratovelomanana-Vidal</i>	
5.1	Introduction	129
5.2	α -Substituted Ketones	130
5.3	α -Substituted Cyclic Ketones	135
5.4	α, α' -Disubstituted Cyclic Ketones	142
5.5	α, β -Disubstituted Cyclic Ketones	143
5.6	α -Substituted β -Keto Esters	144
5.6.1	α -Amino β -Keto Esters	144
5.6.2	Other α -Substituted β -Keto Esters	151
5.7	α -Substituted β -Keto Amides	156
5.8	α -Substituted β -Keto Sulfones, Sulfonamides, and Phosphonates	160
5.9	β -Substituted α -Keto Esters and Phosphonates	163
5.10	β -Alkoxy Ketones	166
5.11	1,2-Diketones	167
5.12	β -Substituted Ketones	167
5.13	α -Substituted Aldehydes	168
5.14	Summary and Conclusions	169
	References	169
6	Industrial Applications of Asymmetric (Transfer) Hydrogenation	175
	<i>Xumu Zhang and Pan-Lin Shao</i>	
6.1	Introduction	175
6.2	Industrial Applications of Asymmetric Hydrogenation	177
6.2.1	Asymmetric Hydrogenation of Enamide	177
6.2.1.1	L-DOPA	177
6.2.1.2	Ramipril	178
6.2.1.3	Sitagliptin	179
6.2.1.4	(R)-3-Amino-1-butanol	181
6.2.1.5	(S)-2,6-Dimethyltyrosine	182
6.2.1.6	Apremilast	184
6.2.2	Asymmetric Hydrogenation of Ketone	185
6.2.2.1	Duloxetine	185
6.2.2.2	Dorzolamide	186

6.2.2.3	(<i>R</i>)-1-(3,5-Bis(trifluoromethyl)-phenyl)ethanol	187
6.2.2.4	4-AA (Key Intermediate to Carbapenem Antibiotics)	189
6.2.2.5	Rivastigmine	190
6.2.2.6	Montelukast	191
6.2.2.7	Crizotinib	192
6.2.2.8	(<i>R</i>)-Phenylephrine	194
6.2.2.9	Atorvastatin Calcium Salt	197
6.2.2.10	Orlistat	198
6.2.2.11	Ezetimibe	199
6.2.3	Asymmetric Hydrogenation of Olefin	201
6.2.3.1	L-Menthol	201
6.2.3.2	Sacubitril	202
6.2.3.3	Naproxen, Ibuprofen, and Flurbiprofen	204
6.2.3.4	Ramelteon	205
6.2.3.5	Aliskiren	205
6.2.3.6	(+)- <i>cis</i> -Methyl Dihydrojasmonate	207
6.2.4	Asymmetric Hydrogenation of Imine	209
6.2.4.1	Solifenacin	209
6.2.4.2	(<i>S</i>)-Metolachlor	210
6.2.5	Asymmetric Transfer Hydrogenation	211
6.3	Summary and Conclusions	212
	References	212
7	Tethered Ruthenium(II) Catalysts in Asymmetric Transfer Hydrogenation	221
	<i>Vijyesh K. Vyas, Richard C. Knighton and Martin Wills</i>	
7.1	Introduction: The Rationale Behind Tethered Catalysts Design	221
7.2	Tethered Ru(II) Catalysts and Their Syntheses	222
7.2.1	Synthetic Approaches to Tethered Catalysts	224
7.3	Applications to Asymmetric Reductions of Ketones and Imines	226
7.3.1	Reductions of Acetophenone Derivatives	226
7.3.1.1	Asymmetric Transfer Hydrogenation Using Formic Acid	228
7.3.1.2	Reduction Under Aqueous Conditions	231
7.3.1.3	Hydrogenation with Hydrogen Gas	232
7.3.1.4	Racemic Catalysts for Reductions	232
7.3.1.5	Specific Applications to Complex Acetophenone Derivatives	232
7.3.2	Reductions of Acetylenic Ketones	235
7.3.3	Reductions of Benzophenone Ketones	235
7.3.4	Reductions of Diverse Ketones	237
7.3.5	Dynamic Kinetic Resolutions	242
7.3.6	Reductions of Imines	247
7.4	Conclusions and Outlook	248
	References	249

8 Homogeneous Asymmetric Hydrogenation of Heteroaromatic Compounds Catalyzed by Transition Metal Complexes 255

Qing-Hua Fan, Yan-Mei He and Fa-Ju Li

- 8.1 Introduction 255
- 8.2 Asymmetric Hydrogenation of Quinolines 257
- 8.3 Asymmetric Hydrogenation of Quinoxalines 260
- 8.4 Asymmetric Hydrogenation of Isoquinolines 262
- 8.5 Asymmetric Hydrogenation of Pyridines and Pyrazines 263
- 8.6 Asymmetric Hydrogenation of Indoles and Pyrroles 265
- 8.7 Asymmetric Hydrogenation of Heteroarenes with Multi-*N*-Heterocycles 268
- 8.8 Asymmetric Hydrogenation of Other *N*-Heteroarenes 270
- 8.9 Asymmetric Hydrogenation of *O*- and *S*-Heteroarenes 273
- 8.10 Summary and Conclusions 275
- Acknowledgments 276
- References 276

9 Asymmetric (Transfer) Hydrogenation of Imines 281

Itziar Peñafiel, Juan Mangas-Sánchez and Carmen Claver

- 9.1 Asymmetric Hydrogenation of Imines 281
 - 9.1.1 Iridium Catalysts 281
 - 9.1.1.1 (P,P) Ligands 281
 - 9.1.1.2 (P,N) Ligands 282
 - 9.1.1.3 P-Monodentate Ligands 286
 - 9.1.2 Rhodium and Palladium Catalysts 287
- 9.2 Asymmetric Transfer Hydrogenation of Imines 288
 - 9.2.1 Ruthenium Catalysts 289
 - 9.2.2 Iridium and Rhodium Catalysts 290
 - 9.2.3 Iron Catalysts 290
- 9.3 New Approaches 292
 - 9.3.1 Metal Free 292
 - 9.3.2 Biocatalytic Imine Reduction 293
 - 9.3.2.1 Artificial Metalloenzymes 294
 - 9.3.2.2 Imine Reductases (IREDs) 297
- 9.4 Summary and Conclusions 301
- References 301

10 Asymmetric Hydrogenation in Continuous-Flow Conditions 307

Gergely Farkas, József Madarász and József Bakos

- 10.1 Introduction 307
- 10.2 Chirally Modified Metal Surfaces 308
- 10.3 Well-defined Transition-metal Complexes 314

10.3.1	Immobilized Systems	315
10.3.1.1	Covalently Anchored Ligands	315
10.3.1.2	Immobilization by the Augustine Method	316
10.3.1.3	Ionic Liquids as Matrices for Transition-metal Complex Catalysts	321
10.3.2	Homogeneous Systems	325
10.3.3	Self-supported Systems	328
10.4	Organocatalysts	329
10.5	Chiral Auxiliary-controlled Asymmetric Hydrogenation in Flow	332
10.6	Summary and Outlook	333
	References	333

11 Organocatalytic Asymmetric Transfer Hydrogenation Reactions 339

Sayantani Das, Vijay N. Wakchaure and Benjamin List

11.1	Introduction	339
11.2	Reduction of C=C Double Bonds	341
11.3	Reduction of C=N Double Bonds	347
11.4	Cascade Reactions	359
11.5	Dearomatization	365
11.6	Conclusions	369
	References	369

Index 375