Contents

Foreword VII Preface XVII List of Contributors XXIII

 I
 Stereoselective Synthesis of α-Branched Amines by Nucleophilic

 Addition of Unstabilized Carbanions to Imines
 1

André B. Charette

- 1.1 Introduction 1
- 1.2 Overview of the Methods for the Preparation of Imines 3
- 1.2.1 N-Aryl and N-Alkyl Imines and Hydrazones 3
- 1.2.2 N-Sulfinyl Imines 3
- 1.2.3 *N*-Sulfonyl Imines 4
- 1.2.4 *N*-Phosphinoyl Imines 5
- 1.2.5 N-Acyl and N-Carbamoyl Imines 6
- 1.3 Chiral Auxiliary-Based Approaches 6
- 1.3.1 Imines Derived from Chiral Aldehydes 7
- 1.3.2 Imines Bearing a Chiral Protecting/Activating Group 9
- 1.4 Catalytic Asymmetric Nucleophilic Addition to Achiral Imines 15
- 1.4.1 Catalytic Asymmetric Addition of sp³ Hybridized Carbanions 16
- 1.4.1.1 Copper-Catalyzed Dialkylzinc Additions 16
- 1.4.1.2 Zinc Alkoxide-Catalyzed Dialkylzinc Additions 20
- 1.4.1.3 Early Transition Metal (Zr, Hf)-Catalyzed Dialkylzinc Additions 20
- 1.4.1.4 Rhodium-Catalyzed Dialkylzinc Addition Reactions 23
- 1.4.2 Catalytic Asymmetric Allylation of Imines 24
- 1.4.3 Catalytic Asymmetric Addition of sp² Hybridized Carbanions 29
- 1.4.3.1 Catalytic Asymmetric Vinylation 31
- 1.4.3.2 Catalytic Asymmetric Arylation 32
- 1.4.3.2.1 Amino Alcohol-Catalyzed Addition of Organozinc Reagents 32
- 1.4.3.2.2 Rhodium Phosphine-Catalyzed Arylation of Imines 34
- 1.4.3.2.3 Rhodium Diene-Catalyzed Arylation of Imines 38
- 1.4.4 Catalytic Asymmetric Addition of sp Hybridized Carbanions 39

X Contents

1.5	Conclusion 42
	References 44
2	Asymmetric Methods for Radical Addition
	to Imino Compounds 51
	Gregory K. Friestad
2.1	Background and Introduction 51
2.2	Intermolecular Radical Addition Chiral N-Acylhydrazones 52
2.2.1	Design of Chiral N-Acylhydrazones 52
2.2.2	Preparation of Chiral N-Acylhydrazones 54
2.2.3	Tin-Mediated Addition of Secondary and Tertiary Radicals 55
2.2.4	In-Free Radical Addition 58
2.2.5	Manganese-Mediated Radical Addition 59
2.2.6	Manganese-Mediated Coupling with Multifunctional Precursors 60
2.2.0.1	Hydrid Radical–Ionic Annulation 60
2.2.0.2	Freeursors Containing Hydroxyl or Protected Hydroxyl Groups 62
2.2.0.3	Additions to Ketone Hudrosenes 64
2.2.0.4	Additions to Retorie Hydrazones 65
2.5	Closing Domerka 68
2.4	Pafarancac 60
	References 09
3	Enantioselective Synthesis of Amines by Chiral Brønsted
-	Acid Catalysts 75
	Masahiro Terada and Norie Momiyama
3.1	Introduction 75
3.2	Carbon–Carbon Bond Forming Reactions 76
3.2.1	Mannich and Related Reactions 76
3.2.1.1	Mannich Reaction 76
3.2.1.2	Nucleophilic Addition of Diazoacetates to Aldimine 81
3.2.1.3	Vinylogous Mannich Reaction 83
3.2.1.4	Aza-Petasis-Ferrier Rearrangement 84
3.2.2	One-Carbon Homologation Reactions 85
3.2.2.1	Strecker Reaction 85
3.2.2.2	Aza-Henry Reaction 86
3.2.2.3	Imino-Azaenamine Reaction 87
3.2.3	Friedel–Crafts and Related Reactions 87
3.2.3.1	Friedel–Crafts Reaction via Activation of Aldimines 87
3.2.3.2	Friedel–Crafts Reaction via Activation of Electron-Rich Alkenes 91
3.2.3.3	Pictet–Spengler Reaction 93
3.2.4	Cycloaddition Reactions 94
3.2.4.1	Hetero-Diels–Alder Reaction of Aldimines with Siloxydienes 94
3.2.4.2	Direct Cycloaddition Reaction of Aldimines with Cyclohexenone 95
3.2.4.3	Inverse Electron-Demand Aza-Diels-Alder Reaction
	(Povarov Reaction) 96

Contents XI

- 3.2.4.4 1,3-Dipolar Cycloaddition Reaction 97
- 3.2.5 Aza–Ene-Type Reactions 99
- 3.2.5.1 Aza–Ene-Type Reaction of Aldimines with Enecarbamates 99
- 3.2.5.2 Cascade Transformations Based on Tandem Aza–Ene-Type Reaction 99
- 3.2.5.3 Two-Carbon Homologation of Hemiaminal Ethers 100
- 3.2.5.4 Homocoupling Reaction of Enecarbamates 102
- 3.2.6 Miscellaneous Reactions 104
- 3.2.6.1 Aza-Cope Rearrangement 104
- 3.2.6.2 Aldol-Type Reaction of Azlactones with Vinyl Ethers 104
- 3.2.6.3 Cooperative Catalysis by Metal Complexes and Chiral Phosphoric Acids 106
- 3.3 Carbon–Hydrogen Bond Forming Reactions 108
- 3.3.1 Transfer Hydrogenation of Acyclic and Cyclic Imines 109
- 3.3.2 Cascade Transfer Hydrogenation of Quinoline and Pyridine Derivatives *113*
- 3.3.3 Application of Transfer Hydrogenation to Cascade Reaction 116
- 3.4 Carbon–Heteroatom Bond Forming Reactions 117
- 3.4.1 Hydrophosphonylation (Kabachnik–Fields Reaction) 117
- 3.4.2 Formation of (Hemi)Aminals 119
- 3.4.3 Nucleophilic Ring Opening of Aziridines and Related Reactions 121
- 3.5 Conclusion 123
 - References 125
- 4 Reduction of Imines with Trichlorosilane Catalyzed by Chiral Lewis Bases 131
 - Pavel Kočovský and Sigitas Stončius
- 4.1 Introduction 131
- 4.2 Formamides as Lewis-Basic Organocatalysts in Hydrosilylation of Imines 132
- 4.3 Other Amides as Organocatalysts in Hydrosilylation of Imines 141
- 4.4 Sulfinamides as Organocatalysts in Hydrosilylation of Imines 143
- 4.5 Supported Organocatalysts in Hydrosilylation of Imines 144
- 4.6 Mechanistic Considerations 147
- 4.7 Synthetic Applications 149
- 4.8 Conclusions 151
- 4.9 Typical Procedures for the Catalytic Hydrosilylation of Imines 152
- 4.9.1 Catalytic Hydrosilylation of Simple Imines *152*
- 4.9.2 Catalytic Hydrosilylation of Enamines 153 References 154
- 5 Catalytic, Enantioselective, Vinylogous Mannich Reactions 157 Christoph Schneider and Marcel Sickert
- 5.1 Introduction 157
- 5.2 Vinylogous Mukaiyama–Mannich Reactions of Silyl Dienolates 159
- 5.3 Direct Vinylogous Mannich Reactions of Unmodified Substrates 170

XII Contents

5.4	Miscellaneous 174
5.5	Conclusion 175
	References 176
6	Chiral Amines from Transition-Metal-Mediated Hydrogenation and Transfer Hydrogenation 179
	Tamara L. Church and Pher G. Andersson
6.1	Scope and Related Publications 179
6.2	Chiral Amines with a Disubstituted Nitrogen Atom, HNR*R ¹ 179
6.2.1	Direct Asymmetric Hydrogenation of Alkyl- and Aryl-Substituted Imines 179
6.2.1.1	Development 180
6.2.1.1.1	A Representative Synthesis 183
6.2.1.2	Pressure in the Asymmetric Hydrogenation of Alkyl- and Aryl-Substituted Imines 183
6.2.1.3	Reducing the Environmental Impact of the Reaction 185
6.2.2	Direct Asymmetric Hydrogenation of Heteroaromatics 190
6.2.2.1	Quinolines and Isoquinolines 190
6.2.2.1.1	Quinolines – A Representative Synthesis 195
6.2.2.1.2	Isoquinolines – A Representative Synthesis 196
6.2.2.2	Quinoxalines 197
6.2.2.3	Pyridines 198
6.2.3	Direct Asymmetric Hydrogenation of "Activated" Imines 202
6.2.4	Asymmetric Transfer Hydrogenation of Imines 204
6.2.4.1	Reducing the Environmental Impact of the Reaction 207
6.2.4.2	Syntheses Using the Asymmetric Transfer Hydrogenation of Imines as a Key Step 211
6.3	Chiral Amines with Trisubstituted Nitrogen, NR*R ¹ R ² 211
6.3.1	Hydrogenation and Transfer Hydrogenation of <i>N</i> , <i>N</i> -Disubstituted Iminiums 211
6.3.2	Hydrogenation and Transfer Hydrogenation of Enamines 213
6.4	Conclusion 216
	References 218
7	Asymmetric Reductive Amination 225 Thomas C. Nugent
7.1	Introduction 225
7.2	Transition Metal-Mediated Homogeneous Reductive Amination 226
7.3	Enantioselective Organocatalytic Reductive Amination 231
7.4	Diastereoselective Reductive Amination 234
7.4.1	Stereoselective Reductive Amination with Chiral Ketones 234
7.4.2	The Phenylethylamine Auxiliary and Stereoselective Reductive Amination 237
7.4.3	The <i>tert</i> -Butylsulfinamide Auxiliary and Stereoselective Reductive Amination 240

7.5	Conclusions 243
	References 244
8	Enantioselective Hydrogenation of Enamines with Monodentate
	Phosphorus Ligands 247
	Qin-Lin Zhou and Jian-Hua Xie
8.1	Introduction 247
8.2	Asymmetric Hydrogenation of Enamides 249
8.2.1	Chiral Monodentate Phosphoramidite Ligands 249
8.2.2	Chiral Monodentate Phosphite Ligands 257
8.2.3	Other Chiral Monodentate Phosphorus Ligands 262
8.2.4	Mixed Chiral Monodentate Phosphorus Ligands 263
8.3	Asymmetric Hydrogenation of N, N-Dialkyl Enamines 264
8.4	Conclusion and Outlook 269
	References 270
9	Bidentate Ligands for Enantioselective Enamide Reduction 273
	Xiang-Ping Hu and Zhuo Zheng
9.1	Introduction 273
9.2	Catalytic Enantioselective Hydrogenation of Enamides 274
9.2.1	Synthesis of Enamides 274
9.2.2	Catalytic Asymmetric Hydrogenation of Acyclic Enamides 276
9.2.2.1	Chiral Phospholane Ligands for Rh-Catalyzed Asymmetric
	Hydrogenation 276
9.2.2.2	Chiral 1,4-Diphosphine Ligands for Rh-Catalyzed Asymmetric
	Hydrogenation 278
9.2.2.3	Bisaminophosphine Ligands for Rh-Catalyzed Asymmetric
	Hydrogenation 283
9.2.2.4	Unsymmetrical Hybrid Phosphorus-Containing Ligands for
	Rh-Catalyzed Asymmetric Hydrogenation 284
9.2.3	Catalytic Asymmetric Hydrogenation of Cyclic Enamides 289
9.3	Conclusions 296
	References 297
10	Enantioselective Reduction of Nitrogen-Based Heteroaromatic
	Compounds 299
	Da-Wei Wang, Yong-Gui Zhou, Qing-An Chen, and Duo-Sheng Wang
10.1	Asymmetric Hydrogenation of Quinolines 299
10.1.1	Ir- and Ru-Catalyzed Asymmetric Hydrogenation of Quinolines 299
10.1.2	Organocatalyzed Asymmetric Transfer Hydrogenation
	of Quinolines 318
10.2	Asymmetric Hydrogenation of Isoquinolines 320
10.3	Asymmetric Hydrogenation of Indoles 322
10.4	Asymmetric Hydrogenation of Pyrroles 327
10.5	Asymmetric Hydrogenation of Quinoxalines 329

XIV Contents

10.6	Asymmetric Hydrogenation of Pyridine Derivatives 329
10.7	Summary and Outlook 336
	References 337
11	Asymmetric Hydroamination 341
	Alexander L. Reznichenko and Kai C. Hultzsch
11.1	Introduction: Synthesis of Amines via Hydroamination 341
11.2	Hydroamination of Simple, Nonactivated Alkenes 342
11.2.1	Intermolecular Hydroamination of Simple Alkenes 342
11.2.2	Intramolecular Asymmetric Hydroamination of Simple
	Aminoalkenes 346
11.2.2.1	Rare Earth Metal-Based Catalysts 346
11.2.2.2	Alkali Metal-Based Catalysts 353
11.2.2.3	Group 4 Metal-Based Catalysts 356
11.2.2.4	Organocatalytic Asymmetric Hydroamination 358
11.3	Hydroamination of Dienes, Allenes, and Alkynes 360
11.3.1	Intermolecular Hydroaminations 360
11.3.2	Intramolecular Reactions 361
11.4	Hydroamination with Enantiomerical Pure Amines 363
11.4.1	Hydroaminations Using Achiral Catalysts 363
11.4.2	Kinetic Resolution of Chiral Aminoalkenes 366
11.5	Synthesis of Chiral Amines via Tandem Hydroamination/
	Hydrosilylation 368
11.6	Conclusions 369
11.7	Experimental Section 369
	References 372
12	Enantioselective C–H Amination 377
	Nadège Boudet and Simon B. Blakey
12.1	Nadège Boudet and Simon B. Blakey Introduction 377
12.1 12.2	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378
12.1 12.2 12.3	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379
12.1 12.2 12.3 12.3.1	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379
12.1 12.2 12.3 12.3.1 12.3.2	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C-H Amination 379 Intramolecular C-H Amination 379 Intermolecular C-H Amination 382
12.1 12.2 12.3 12.3.1 12.3.2 12.4	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384 Enantioselective C–H Amination of Achiral Substrates 386
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384 Enantioselective C–H Amination of Achiral Substrates 386 Enantioselective C–H Amination with Rhodium(II) Catalysts 386
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384 Enantioselective C–H Amination of Achiral Substrates 386 Enantioselective C–H Amination with Rhodium(II) Catalysts 386 Enantioselective C–H Amination with Ruthenium(II) Catalysts 390
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384 Enantioselective C–H Amination of Achiral Substrates 386 Enantioselective C–H Amination with Rhodium(II) Catalysts 386 Enantioselective C–H Amination with Ruthenium(II) Catalysts 390 Conclusion 392
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C–H Amination 379 Intramolecular C–H Amination 379 Intermolecular C–H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C–H Amination 384 Enantioselective C–H Amination of Achiral Substrates 386 Enantioselective C–H Amination with Rhodium(II) Catalysts 386 Enantioselective C–H Amination with Ruthenium(II) Catalysts 390 Conclusion 392 References 394
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C-H Amination 379 Intramolecular C-H Amination 379 Intermolecular C-H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C-H Amination 384 Enantioselective C-H Amination of Achiral Substrates 386 Enantioselective C-H Amination with Rhodium(II) Catalysts 386 Enantioselective C-H Amination with Ruthenium(II) Catalysts 390 Conclusion 392 References 394
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6 13	Nadège Boudet and Simon B. BlakeyIntroduction 377Background 378Racemic C-H Amination 379Intramolecular C-H Amination 379Intermolecular C-H Amination 382Substrate-Controlled Chiral Amine Synthesis via C-H Amination 384Enantioselective C-H Amination of Achiral Substrates 386Enantioselective C-H Amination with Rhodium(II) Catalysts 386Enantioselective C-H Amination with Ruthenium(II) Catalysts 390Conclusion 392References 394Chiral Amines Derived from Asymmetric Aza-Morita-Baylis-HillmanBasetian 207
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6 13	Nadège Boudet and Simon B. Blakey Introduction 377 Background 378 Racemic C-H Amination 379 Intramolecular C-H Amination 379 Intermolecular C-H Amination 382 Substrate-Controlled Chiral Amine Synthesis via C-H Amination 384 Enantioselective C-H Amination of Achiral Substrates 386 Enantioselective C-H Amination with Rhodium(II) Catalysts 386 Enantioselective C-H Amination with Ruthenium(II) Catalysts 386 Enantioselective C-H Amination with Ruthenium(II) Catalysts 390 Conclusion 392 References 394 Chiral Amines Derived from Asymmetric Aza-Morita-Baylis-Hillman Reaction 397 Ium 7bi Dai and Min Shi
12.1 12.2 12.3 12.3.1 12.3.2 12.4 12.5 12.5.1 12.5.2 12.6 13	Nadège Boudet and Simon B. BlakeyIntroduction 377Background 378Racemic C-H Amination 379Intramolecular C-H Amination 379Intermolecular C-H Amination 382Substrate-Controlled Chiral Amine Synthesis via C-H Amination 384Enantioselective C-H Amination of Achiral Substrates 386Enantioselective C-H Amination with Rhodium(II) Catalysts 386Enantioselective C-H Amination with Ruthenium(II) Catalysts 390Conclusion 392References 394Chiral Amines Derived from Asymmetric Aza-Morita-Baylis-HillmanReaction 397Lun-Zhi Dai and Min ShiIntroduction 397

Contents XV

- Recent Mechanistic Insights 398 13.2 Asymmetric Aza-MBH Reaction 400 13.3 13.4 Chiral Auxiliary-Induced Diastereoselective Aza-MBH Reaction 400 13.5 Chiral Tertiary Amine Catalysts 401 Cinchona-Derived Bifunctional Catalysts 401 13.5.1 Chiral Binol-Derived Bifunctional Amine Catalysts 408 13.5.2 Chiral Acid/Achiral Amine 410 13.5.3 13.6 Chiral Phosphine Catalysts 411 13.7 Chiral Bifunctional N-Heterocyclic Carbenes 418 Chiral Ionic Liquids as Reaction Medium 419 13.8 Aza-MBH-Type Reaction to Obtain Chiral Amines 419 13.9 Strategies for the Removal of Protecting Groups 422 13.10 Selected Typical Experimental Procedures 423 13.11 13.11.1 Typical Procedures for 1a-Catalyzed Aza-MBH Reaction of Methyl Acrylate with N-Benzylidene-4-Nitrobenzenesulfonamide 423 13.11.2 Typical Procedures for β-ICD-Catalyzed Aza-MBH Reaction of MVK with N-(p-Ethylbenzenesulfonyl)Benzaldimine 423 Typical Procedures for Chiral Phosphine 23-Catalyzed Aza-MBH 13.11.3 Reaction of MVK with N-(Benzylidene)-4-Chlorobenzenesulfonamide 424 General Procedures of Aza-MBH Reactions Involving 13.11.4 Aliphatic Imines 424 13.11.5 Typical Procedures for 25a and Benzoic Acid-Catalyzed Aza-MBH Reaction of N-Sulfonated Imine with MVK 424 13.11.6 Typical Procedures for Trifunctional Phosphine 27-Catalyzed Aza-MBH Reaction of *N*-Tosylimines with MVK 424 General Procedures for the Synthesis of Enantiomerically Enriched 13.11.7 Aza-MBH-Type Adducts Catalyzed by Chiral Sulfide 29 425 General Procedures for the Removal of *N-p*-Toluenesulfinyl 13.11.8 Group 425 General Procedures for the Removal of *N*-Tosyl Group 13.11.9 425 13.11.9.1 Reduction of the Aza-MBH Reaction Product with LiAlH₄ 425 13.11.9.2 Boc-Protection 426 13.11.9.3 Detosylation 426 13.12 Summary and Outlook 426 References 428 14 Biocatalytic Routes to Nonracemic Chiral Amines 431 Nicholas J. Turner and Matthew D. Truppo Introduction 431 14.1 14.2 Kinetic Resolution of Racemic Amines 432 Hydrolytic Enzymes 432 14.2.1 Transaminases 441 14.2.2 14.2.3 Amine Oxidases 443
- DKR and Deracemization of Amines 444 14.3

XVI Contents

- 14.3.1 DKR Using Hydrolytic Enzymes and Racemization Catalysts 444
- 14.3.2 Deracemization Reactions Using Amine Oxidases 448
- 14.4 Asymmetric Synthesis of Amines Using Transaminases 450
- 14.5Conclusions and Future Perspectives455References457

Appendix: Solution 461

Index 479