

## Contents

<b>Foreword</b>	XXVII
<b>Preface</b>	XXIX
<b>List of Contributors</b>	XXXI
<b>Abbreviations</b>	XLI

### Volume 1: Privileged Catalysts

#### Part I Amino Acid-Derived Catalysts 1

<b>1</b>	<b>Proline-Related Secondary Amine Catalysts and Applications</b>	<b>3</b>
	<i>Hiyoshizo Kotsuki and Niiha Sasakura</i>	
1.1	Introduction	3
1.2	Prolinamide and Related Catalysts	3
1.3	Prolinamine and Related Catalysts	8
1.4	Proline Tetrazole and Related Catalysts	10
1.5	Prolinamine Sulfonamide and Related Catalysts	13
1.6	Prolinamine Thiourea and Related Catalysts	15
1.7	Miscellaneous	16
1.8	Conclusions	21
	Acknowledgments	21
	References	21
<b>2</b>	<b>TMS-Prolinol Catalyst in Organocatalysis</b>	<b>33</b>
	<i>Hao Jiang, Łukasz Albrecht, Gustav Dickmeiss, Kim L. Jensen, and Karl Anker Jørgensen</i>	
2.1	Introduction	33
2.2	Enamine Activation	34
2.3	Iminium-Ion Activation	37
2.4	Cascade Reactions	41
2.5	Dienamine Activation	42
2.6	Trienamine Activation	46
2.7	Summary and Conclusions	48
	References	48

<b>3</b>	<b>Non-Proline Amino Acid Catalysts</b>	<b>51</b>
	<i>Li-Wen Xu and Yixin Lu</i>	
3.1	Introduction	51
3.2	Primary Amino Acids in Amino Catalysis	52
3.3	Primary Amino Acid-Derived Organic Catalysts	53
3.3.1	Unmodified Amino Acids	55
3.3.2	Protected Primary Amino Acids	55
3.3.3	Primary Amino Acid-Derived Diamine Catalysts	55
3.3.4	Other Primary Amino Acid Catalysts	55
3.4	Applications of Non-Proline Primary Amino Acid Catalysts	56
3.4.1	Aldol Reaction	56
3.4.2	Mannich Reaction	60
3.4.3	Michael Addition	62
3.4.4	Other Reactions	64
3.5	Conclusions	65
	Acknowledgments	66
	References	66
<b>4</b>	<b>Chiral Imidazolidinone (MacMillan's) Catalyst</b>	<b>69</b>
	<i>Rainer Mahrwald</i>	
4.1	Introduction	69
4.2	Enamine Catalysis	69
4.3	Iminium Catalysis	81
4.4	Cascade Reaction – Merging Iminium and Enamine Catalysis	86
	References	91
<b>5</b>	<b>Oligopeptides as Modular Organocatalytic Scaffolds</b>	<b>97</b>
	<i>Roberto Fanelli and Umberto Piarulli</i>	
5.1	Introduction	97
5.2	C–C Bond Forming Reactions	98
5.2.1	Aldol Reactions	98
5.2.2	Michael Reactions	101
5.2.3	Morita–Baylis–Hillman Reactions	105
5.2.4	Hydrocyanation of Aldehydes	107
5.3	Asymmetric Acylations	108
5.4	Asymmetric Phosphorylations	110
5.5	Enantioselective Oxidations	111
5.6	Hydrolytic Reactions	114
5.7	Summary and Conclusions	114
	References	114

**Part II Non-Amino Acid-Derived Catalysts 117**

- 6 Cinchonas and Cupreidines 119**  
*Steen Ingemann and Henk Hiemstra*
- 6.1 Introduction 119
  - 6.2 Cinchona Alkaloid Derivatives 120
  - 6.3 Natural Cinchona Alkaloids, Cupreine, and Cupreidine 121
    - 6.3.1 Structural Properties 121
    - 6.3.2 Catalysis with Natural Cinchona Alkaloids 122
    - 6.3.3 Catalysis with Cupreine and Cupreidine 125
  - 6.4 Cinchona Alkaloids with an Ether or Ester Group at C9 127
    - 6.4.1 Structural Properties 127
    - 6.4.2 Catalysis with C9 Ethers of Natural Cinchona Alkaloids 127
    - 6.4.3 Catalysis with C9 Ethers of Cupreine and Cupreidine 129
    - 6.4.4 Catalysis with C9 Esters 133
  - 6.5 Cinchona Alkaloid Derivatives with a Sulfonamide, Urea, Thiourea, Squaramide, or Guanidine Function 134
    - 6.5.1 Structural Properties 134
    - 6.5.2 Catalysis with C9 and C6' Thiourea Derivatives 136
    - 6.5.3 Catalysis with C9 Sulfonamide, Squaramide, and Guanidine Derivatives 141
  - 6.6 Cinchona Alkaloids with a Primary Amine Group at C9 145
    - 6.6.1 Structural Properties 145
    - 6.6.2 Catalysis with C9 Amino Derivatives 146
  - 6.7 Cinchona Alkaloids in Phase-Transfer Catalysis 149
  - 6.8 Ether Bridged Dimers 151
  - 6.9 Some Novel Cinchona Alkaloid Derivatives 153
  - 6.10 Prospects 154
  - References 155
- 7 Chiral C<sub>2</sub> Catalysts 161**  
*Daisuke Uraguchi, Kohsuke Ohmatsu, and Takashi Ooi*
- 7.1 Introduction 161
  - 7.2 Chiral Lewis Base Catalysts 161
    - 7.2.1 Phosphoramides 162
    - 7.2.2 Bipyridine *N,N'*-Dioxides 167
    - 7.2.3 Bisphosphine Dioxides 169
  - 7.3 Phosphines 172
  - 7.4 Chiral C<sub>2</sub>-Symmetric Secondary and Primary Amines 174
  - 7.5 Chiral C<sub>2</sub>-Symmetric Brønsted Bases: Guanidines 177
  - 7.6 Chiral C<sub>2</sub>-Symmetric Brønsted Acids 181
    - 7.6.1 Binaphthol and Biphenol Derivatives 181
    - 7.6.2 Pyridinium Disulfonates 182
    - 7.6.3 Dicarboxylic Acids 183
    - 7.6.4 Chiral Disulfonimides 186

- 7.7 Chiral  $C_2$ -Symmetric Bis-Thioureas 188  
7.8 Chiral  $C_2$ -Symmetric Aminophosphonium Ions 189  
7.9 Summary and Conclusions 190  
References 190
- 8 Planar Chiral Catalysts 195**  
*Olivier R.P. David*
- 8.1 Introduction 195  
8.2 Lewis/Brønsted Bases 198  
8.2.1 Nitrogen Bases 198  
8.2.1.1 Azaferrocenes 199  
8.2.1.2 Pyridinoferrrocenes 200  
8.2.1.3 Imidazoles 204  
8.2.1.4 PIP: Paracyclophane-2,3-dihydroimidazolo[1,2-*a*]pyridine Bases 204  
8.2.1.5 Imine 205  
8.2.2 Oxygen Lewis Bases 206  
8.2.3 Phosphine 207  
8.2.4 N-Heterocyclic Carbenes 209  
8.2.5 Sulfides 210  
8.3 Lewis/Brønsted Acids 211  
8.3.1 Boronic Acids 211  
8.3.2 Phenols 212  
8.3.3 Thioureas 212  
8.4 Redox Reactions 213  
8.4.1 Flavin Derivatives 213  
8.4.2 Hantzsch Esters 214  
8.5 Summary and Conclusions 214  
References 215
- 9 Dynamic Approaches towards Catalyst Discovery 221**  
*Patrizia Galzerano, Giulio Gasparini, Marta Dal Molin, and Leonard J. Prins*
- 9.1 Introduction 221  
9.2 Self-Assembly 222  
9.2.1 Self-Assembled Organocatalysts 223  
9.2.2 Catalysis in Confined Self-Assembled Space 227  
9.3 Self-Selected Catalysts 232  
9.3.1 Dynamic Combinatorial Chemistry 232  
9.4 Conclusions 236  
Acknowledgments 236  
References 236

**Appendix A1**

**Volume 2: Activations****Part I Asymmetric Catalysis with Non-Covalent Interactions 239**

- 10 Brønsted Acids 241**  
*Yunus E. Türkmen, Ye Zhu, and Viresh H. Rawal*
- 10.1 Introduction 241
- 10.2 Chiral Alcohol Catalysts 245
- 10.3 Chiral Squaramides as Hydrogen-Bond Donor Catalysts 252
- 10.3.1 Introduction 252
- 10.3.1.1 Michael Addition Reaction Involving Nitroalkenes 253
- 10.3.1.2 Michael Addition Reaction Involving *trans*-Chalcones 257
- 10.3.1.3 Michael Addition Reaction Involving Other C=C Michael Acceptors 259
- 10.3.1.4 Reactions Involving a C=N Bond 261
- 10.3.1.5 Reactions Involving a C=O Bond 261
- 10.3.1.6 Reactions Involving a N=N Bond 263
- 10.3.1.7 Dynamic Kinetic Resolution and Desymmetrization 263
- 10.3.1.8 Cascade Reactions 266
- 10.3.2 Summary and Outlook 268
- 10.4 Guanidines/Guanidiniums 269
- 10.5 Miscellaneous Brønsted Acids 275
- 10.5.1 Aminopyridiniums 275
- 10.5.2 Tetraaminophosphoniums 278
- 10.5.3 Axially Chiral Dicarboxylic Acids 280
- 10.5.4 Stronger Brønsted Acids 282
- 10.6 Addendum 282
- References 282
- 
- 11 Brønsted Acids: Chiral Phosphoric Acid Catalysts in Asymmetric Synthesis 289**  
*Keiji Mori and Takahiko Akiyama*
- 11.1 Introduction 289
- 11.1.1 Design of Chiral Phosphoric Acids 289
- 11.2 Reaction with Imines 291
- 11.2.1 Mannich Reaction 291
- 11.2.2 Hydrophosphonylation 293
- 11.2.3 Cycloaddition Reaction 295
- 11.2.4 Transfer Hydrogenation 297
- 11.3 Friedel–Crafts Reaction 304
- 11.4 Intramolecular Aldol Reaction 309
- 11.5 Ring Opening of *meso*-Aziridines 311
- 11.6 Future Prospects 312
- References 312

<b>12</b>	<b>Brønsted Acids: Chiral (Thio)urea Derivatives</b>	<b>315</b>
	<i>Gergely Jakab and Peter R. Schreiner</i>	
12.1	Introduction	315
12.1.1	Explicit Double Hydrogen-Bonding Interactions	315
12.1.2	The Beginnings of (Thio)urea Catalysis	316
12.2	Important Chiral (Thio)urea Organocatalysts	318
12.2.1	Takemoto's Catalyst	318
12.2.2	Cinchona Alkaloids in (Thio)urea Organocatalysis	322
12.2.3	Pyrrrolidine-(thio)urea Catalysis	325
12.2.4	Nagasawa's Catalyst	326
12.2.5	Ricci's Thiourea Catalyst	328
12.2.6	Binaphthylamine Scaffolds in (Thio)urea Catalysis	329
12.2.7	Jacobsen's Catalyst Family	330
12.2.8	<i>N</i> -Sulfinyl (Thio)urea Catalysts	335
12.3	Summary	336
	References	336
<b>13</b>	<b>Brønsted Bases</b>	<b>343</b>
	<i>Amal Ting and Scott E. Schaus</i>	
13.1	Introduction	343
13.2	Cinchona Alkaloids	344
13.2.1	Cinchona Alkaloids in Asymmetric Transformations	345
13.2.2	Asymmetric Activation of Conjugate Addition to Enones	346
13.2.3	Asymmetric Activation of Conjugate Addition to Imines	347
13.2.4	Asymmetric Aminations	349
13.2.5	Asymmetric Activation of Isocyanoacetates	350
13.2.6	Asymmetric Diels–Alder Reaction	351
13.3	Brønsted Base-Derived Thiourea Catalysts	352
13.3.1	Asymmetric Conjugate Addition with Carbonyls and Imines	353
13.3.2	Asymmetric Conjugate Additions with Non-Traditional Substrates	354
13.3.2.1	Asymmetric Cascade Reactions	356
13.4	Chiral Guanidine Catalysts	356
13.4.1	Asymmetric Conjugate Addition to Enones and Imines	357
13.4.2	Asymmetric Diels–Alder Reactions	360
13.5	Conclusion	361
	References	361
<b>14</b>	<b>Chiral Onium Salts (Phase-Transfer Reactions)</b>	<b>365</b>
	<i>Seiji Shirakawa and Keiji Maruoka</i>	
14.1	Introduction	365
14.2	Phase-Transfer Catalysis	366
14.2.1	Phase-Transfer Reaction of Active Methylene or Methine Compounds with Inorganic Base	366
14.2.1.1	Generation of Onium Carbanion	366
14.2.1.2	Nucleophilic Substitution	367

- 14.2.1.3 Nucleophilic Addition 368
- 14.2.2 Phase-Transfer Catalyzed Addition of Anion Supplied as Metal Salt 370
- 14.2.3 Base-Free Neutral Phase-Transfer Reaction 371
- 14.3 Onium Fluorides 372
- 14.4 Onium Phenoxides and Related Compounds 374
- 14.4.1 Onium Phenoxides as Lewis Base Catalysts 375
- 14.4.2 Onium Phenoxides and Related Compounds as Brønsted Base Catalysts 375
- 14.5 Conclusions 377
- References 377

## 15 Lewis Bases 381

*Pavel Kočovský and Andrei V. Malkov*

- 15.1 Introduction 381
- 15.2 Allylation Reactions 382
- 15.2.1 Catalytic Allylation of Aldehydes 382
- 15.2.2 Stoichiometric Allylation of Aldehydes and Ketones 393
- 15.3 Propargylation, Allenylation, and Addition of Acetylenes 395
- 15.3.1 Addition to Aldehydes 395
- 15.3.2 Addition to Imines 395
- 15.4 Aldol-Type Reactions 396
- 15.5 Cyanation and Isonitrile Addition 404
- 15.5.1 Cyanation of Aldehydes 404
- 15.5.2 Cyanation of Imines (Strecker Reaction) 407
- 15.6 Reduction Reactions 408
- 15.7 Epoxide Opening 417
- 15.8 Conclusion and Outlook 421
- References 421

## 16 Lewis Acids 431

*Tatjana Heckel and René Wilhelm*

- 16.1 Introduction 431
- 16.2 Silyl Cation Based Catalysts 433
- 16.3 Hypervalent Silicon Based Catalysts 438
- 16.4 Phosphonium Cation Based Catalysts 444
- 16.5 Carbocation Based Catalysts 448
- 16.6 Ionic Liquids 455
- 16.7 Miscellaneous Catalysts 458
- 16.8 Conclusion 459
- References 459

**Part II Asymmetric Catalysis with Covalent Interactions 463**

- 17 Rationalizing Reactivity and Selectivity in Aminocatalytic Reactions 465**  
*Raghavan B. Sunoj*
- 17.1 Introduction 465
  - 17.2 Secondary Amine Catalysis 466
    - 17.2.1 Mechanism of Secondary Amine Catalysis 466
      - 17.2.1.1 Important Intermediates in Amino Catalysis 467
      - 17.2.1.2 Experimental Identification of Enamines in Organocatalysis 469
      - 17.2.1.3 Enamine Radical Cation: The Concept of SOMO Activation 471
    - 17.3 Stereoselectivity in Proline-Catalyzed Reactions 472
      - 17.3.1 Transition State Models for Proline-Catalyzed Reactions 473
      - 17.3.2 Limitations of Hydrogen-Bonding Guided Transition State Models 475
    - 17.4 Mechanism and Stereoselectivity in Organocatalytic Cascade Reactions 482
      - 17.4.1 Stereoselectivity in Other Amino Acid Catalyzed Reactions 485
  - 17.5 Rational Design of Catalysts 486
  - 17.6 Summary and Conclusions 491
    - Acknowledgments 492
    - References 492
- 18 Carbene Catalysts 495**  
*Karen Thai, Eduardo Sánchez-Larios, and Michel Gravel*
- 18.1 Introduction 495
  - 18.2 Reactions of Acyl Anion Equivalents 497
    - 18.2.1 Benzoin Reaction 497
      - 18.2.1.1 Homo-Benzoin Reaction 497
      - 18.2.1.2 Cross-Benzoin Reaction 498
      - 18.2.1.3 Aza-Benzoin Reaction 501
    - 18.2.2 Stetter Reaction 501
      - 18.2.2.1 Intramolecular Stetter Reactions 501
      - 18.2.2.2 Intermolecular Stetter Reactions 503
      - 18.2.2.3 Application of Stetter Reactions to Natural Product Synthesis 505
    - 18.2.3 Hydroacylation Reactions 505
  - 18.3 Extended Umpolung 506
    - 18.3.1 Reactions of  $\alpha$ -Reducible Aldehydes 506
    - 18.3.2 Reactions of Enals and Ynals 508
      - 18.3.2.1 C–C Bond Forming Reactions at the  $\beta$  Position 508
      - 18.3.2.2  $\beta$ -Protonation of Homo-enolates 511
      - 18.3.2.3 Oxidation of Enals 513
  - 18.4 Umpolung of Activated Olefins 514
  - 18.5 Nucleophilic Catalysis 515
  - 18.6 Conclusion 518
    - References 518

- 19 Oxides and Epoxides 523**  
*Harry J. Milner and Alan Armstrong*
- 19.1 Alkene Epoxidation 523
    - 19.1.1 Ketone-Mediated Epoxidation 524
    - 19.1.2 Iminium Salt-Catalyzed Epoxidation 532
    - 19.1.3 Aspartate-Derived Peracid Catalysis 536
  - 19.2 Hypervalent Iodine-Catalyzed Oxidations 537
    - 19.2.1 Asymmetrical Naphthol Dearomatization 537
    - 19.2.2 Enantioselective  $\alpha$ -Oxysulfonylation of Ketones 538
  - 19.3 Oxidation of Thioethers and Disulfides 539
  - 19.4 Resolution of Alcohols by Oxidation 540
  - References 542
- 20 Ylides 547**  
*Saihu Liao, Peng Wang, and Yong Tang*
- 20.1 Introduction 547
  - 20.2 Enantioselective Sulfur Ylide Catalysis 548
    - 20.2.1 Epoxidation 549
      - 20.2.1.1 Catalysis via Sulfide Alkylation/Deprotonation 549
      - 20.2.1.2 Catalysis via Transition Metal-Mediated Carbene Transfer to Sulfides 556
    - 20.2.2 Aziridination 560
    - 20.2.3 Cyclopropanation 562
  - 20.3 Enantioselective Phosphorus and Arsenic Ylide Catalysis 566
  - 20.4 Enantioselective Nitrogen Ylide Catalysis 570
  - 20.5 Enantioselective Selenium and Tellurium Ylide Catalysis 573
  - 20.6 Summary and Conclusions 574
  - References 575
- Part III Tuning Catalyst Activity and Selectivity by the Reaction Medium and Conditions 579**
- 21 “Non-Classical” Activation of Organocatalytic Reactions (Pressure, Microwave Irradiation.) 581**  
*Piotr Kwiatkowski, Krzysztof Dudziński, and Dawid Łyżwa*
- 21.1 Introduction 581
  - 21.2 Asymmetric Organocatalysis under High-Pressure Conditions 581
  - 21.3 Asymmetric Organocatalysis under Microwave Irradiation—Thermal Effect 593
  - 21.4 Asymmetric Organocatalysis under Ultrasound Irradiation 601
  - 21.5 Asymmetric Organocatalysis under Ball Milling Conditions 605
  - 21.6 Summary and Conclusions 612
  - References 613

- 22 Ionic Liquid Organocatalysts 617**  
*Dmitry E. Silyutkin, Alexander S. Kucherenko, and Sergei G. Zlotin*
- 22.1 Introduction 617
  - 22.2 Ionic Liquids as Recyclable Solvents for Asymmetric Organocatalytic Reactions 618
    - 22.2.1  $\alpha$ -Amino Acid-Promoted Reactions in IL Media 618
    - 22.2.2 Reactions in the Presence of Other Chiral Organocatalysts in IL Media 623
  - 22.3 “Non-Solvent” Applications of Ionic Liquids and Their Congeners in Asymmetric Organocatalysis 625
    - 22.3.1 Immobilization of Organocatalysts through Electrostatic Interaction with Ionic Fragments 626
      - 22.3.1.1 Biphasic Non-Covalent Immobilization on Ionic Liquids and Ionic Polymers 626
      - 22.3.1.2 Ion-Pair Immobilization on Ionic Liquids 628
    - 22.3.2 Modification of Organocatalysts by Ionic Groups through Covalent Bonding 630
      - 22.3.2.1 Ionic Organocatalysts Incorporating  $\alpha$ -Amino Acid Units 631
      - 22.3.2.2 Ionic Organocatalysts Incorporating  $\alpha$ -Amino Amide Units 636
      - 22.3.2.3 Pyrrolidine-Sourced Ionic Organocatalysts 638
      - 22.3.2.4 Other Organocatalysts Bearing Ionic Groups 644
  - 22.4 Conclusion 646
  - References 647
- 23 Polymer and Mesoporous Material Supported Organocatalysts 651**  
*Tor Erik Kristensen and Tore Hansen*
- 23.1 Introduction 651
  - 23.2 Polymer-Supported Organocatalysts 652
    - 23.2.1 Polymer Resins for Immobilization of Chiral Organocatalysts 652
    - 23.2.2 Polymer-Supported Cinchona Derivatives 653
    - 23.2.3 Polymer-Supported Enamine–Iminium Organocatalysts 656
    - 23.2.4 Miscellaneous Polymer-Supported Chiral Organocatalysts 662
  - 23.3 Mesoporous-Supported Organocatalysts 663
    - 23.3.1 Mesoporous Materials for Immobilization of Chiral Organocatalysts 663
    - 23.3.2 Inorganic and Inorganic–Organic Hybrid Material Supported Chiral Organocatalysts 664
  - 23.4 Conclusions and Outlook 668
  - References 668
- 24 Water in Organocatalytic Reactions 673**  
*Francesco Giacalone and Michelangelo Gruttadauria*
- 24.1 Introduction 673
  - 24.2 Aldol Reactions 678
    - 24.2.1 Primary Amines 678

- 24.2.2 Secondary Amines 682
- 24.2.3 Prolines Substituted at the 4-Position 683
- 24.2.4 Prolinamides 687
- 24.2.5 Supported Proline and Proline Derivatives 694
- 24.3 Michael Reactions 696
- 24.4 Mannich Reaction 705
- 24.5 Diels–Alder Reaction 707
- 24.6 Miscellaneous Examples 710
- References 713

### Volume 3: Reactions and Applications

#### Part I Alpha-Alkylation and Heteroatom Functionalization 719

- 25 S<sub>N</sub>2-Type Alpha-Alkylation and Allylation Reactions 721**  
*Christine Tran and Peter I. Dalko*
- 25.1 S<sub>N</sub>2-Type Alkylation under Homogenous Conditions 721
- 25.2 Domino Reactions Including S<sub>N</sub>2-Type Alkylations 722
- 25.2.1 Michael/S<sub>N</sub>2 Reactions with the Halide on the Donor 723
- 25.2.2 Michael/S<sub>N</sub>2 Reactions with the Halide on the Acceptor 724
- 25.3 Intermolecular S<sub>N</sub>2' Alkylations under Homogenous Conditions 726
- 25.4 Summary 727
- References 727
  
- 26 Alpha-Alkylation by S<sub>N</sub>1-Type Reactions 729**  
*Andrea Gualandi, Diego Petruzzello, Enrico Emer, and Pier Giorgio Cozzi*
- 26.1 Introduction 729
- 26.2 S<sub>N</sub>1-Type Nucleophilic Reaction by Generation of Carbocations 730
- 26.3 Organocatalytic Stereoselective S<sub>N</sub>1-Type Reactions with Enamine Catalysis 733
- 26.4 Asymmetric S<sub>N</sub>1-Type  $\alpha$ -Alkylation of Ketones 737
- 26.5 Combination of Enamine Catalysis and Lewis Acids in S<sub>N</sub>1-Type Reactions 738
- 26.6 Organocatalytic S<sub>N</sub>1-Type Reactions with Brønsted Acids 741
- 26.6.1 Organocatalytic S<sub>N</sub>1-Type Reactions with Brønsted Acids and Metals 746
- 26.7 S<sub>N</sub>1-Type Reaction Promoted by Chiral Thioureas 747
- 26.8 S<sub>N</sub>1-Type Organocatalytic Reaction of Iminium, Oxonium, and Aziridinium Intermediates 749
- 26.9 Conclusions and Perspectives 751
- References 751

<b>27</b>	<b>Alpha-Heteroatom Functionalization of Carbonyl Compounds</b>	<b>757</b>
	<i>Gabriela Guillena</i>	
27.1	Introduction	757
27.2	Enantioselective $\alpha$ -Pnictogenation of Carbonyl Compounds	758
27.2.1	Amination of Carbonyl Compounds	758
27.2.1.1	Aziridination of $\alpha,\beta$ -Unsaturated Carbonyl Compounds	758
27.2.1.2	Direct $\alpha$ -Amination	761
27.2.2	Phosphination of Carbonyl Compounds	769
27.3	Enantioselective $\alpha$ -Chalcogenation	770
27.3.1	C–O Formation	770
27.3.1.1	Darzens Reaction	770
27.3.1.2	Epoxidation of $\alpha,\beta$ -Unsaturated Carbonyl Compounds	771
27.3.1.3	Aminoxylation of Carbonyl Compounds	774
27.3.1.4	Miscellaneous Oxidation Processes	777
27.3.2	Sulfenylation and Selenenylation Processes	778
27.4	Enantioselective $\alpha$ -Halogenation of Carbonyl Compounds	779
27.5	Summary and Conclusions	783
	References	783
	<b>Part II Nucleophile Addition to C=X Bonds</b>	<b>791</b>
<b>28</b>	<b>Aldol and Mannich-Type Reactions</b>	<b>793</b>
	<i>Nobuyuki Mase and Carlos F. Barbas III</i>	
28.1	Introduction	793
28.2	Enamine Catalysis	795
28.2.1	Aldol Reactions in Enamine Catalysis	796
28.2.1.1	Intermolecular Aldol Reactions in Enamine Catalysis	796
28.2.1.2	Intramolecular Aldol Reactions Using Enamine Catalysis	799
28.2.1.3	Aldol Reactions in Water, on Water, and by Water	801
28.2.1.4	Metal-Catalyzed and Organocatalytic Reaction Sequences	805
28.2.1.5	Organocatalytic and Biocatalytic Reaction Sequences	805
28.2.2	Mannich Reactions in Enamine Catalysis	806
28.2.2.1	<i>Anti</i> -Selective Mannich Reactions	806
28.2.2.2	Mannich Reactions of Acetaldehyde Donors	809
28.3	Brønsted Acid Catalysis Including Hydrogen-Bond Catalysis	810
28.3.1	Aldol Reactions in Brønsted Acid and Hydrogen-Bond Catalysis	811
28.3.1.1	Intermolecular Aldol Reactions in Brønsted Acid and Hydrogen-Bond Catalysis	811
28.3.1.2	Intramolecular Aldol Reactions in Brønsted Acid Catalysis	814
28.3.2	Mannich Reactions with Brønsted Acid and Hydrogen-Bond Catalysis	815
28.3.2.1	Vinylogous Mukaiyama Mannich Reactions with Brønsted Acid Catalysis	815
28.3.2.2	Mannich-Type Reactions of Encarbamates with Brønsted Acid Catalysis	816

28.3.2.3	Mannich Reactions Catalyzed by Chiral Calcium Phosphate	817
28.4	Brønsted Base Catalysis Including Bifunctional Catalysis	817
28.4.1	Aldol Reactions in Brønsted Base Catalysis Including Bifunctional Catalysis	818
28.4.1.1	Vinylogous Aldol Reactions in Brønsted Base Catalysis	818
28.4.1.2	Nitroaldol (Henry) Reactions with Brønsted Base Catalysis	818
28.4.1.3	Brønsted Base Catalyzed Aldol Reactions of Isatins	819
28.4.1.4	Brønsted Base Catalyzed Aldol Reaction of 5 <i>H</i> -Oxazol-4-ones	821
28.4.2	Mannich Reactions in Brønsted Base Catalysis Including Bifunctional Catalysis	822
28.4.2.1	Solvent-Dependent Guanidine Base Catalyzed Mannich Reactions	822
28.4.2.2	Chiral Ammonium Betaine-Catalyzed Mannich Reactions	822
28.4.2.3	Quaternary Phosphonium Salt-Catalyzed Mannich Reactions	823
28.5	Phase-Transfer Catalysis	824
28.5.1	Aldol Reactions in Phase-Transfer Catalysis	824
28.5.1.1	Axially Chiral Quaternary Ammonium Salt-Catalyzed Aldol Reactions	824
28.5.1.2	Guanidinium-Thiourea-Catalyzed Nitroaldol Reactions	825
28.5.2	Mannich Reactions in Phase-Transfer Catalysis	826
28.5.2.1	Quaternary Ammonium Salt-Catalyzed Mannich Reactions	826
28.5.2.2	Guanidinium-Thiourea-Catalyzed Mannich Reactions	827
28.5.2.3	Quaternary Phosphonium Salt-Catalyzed Mannich Reactions	828
28.5.3	Quaternary Ammonium Salt-Catalyzed 6π Electrocyclization	829
28.6	<i>N</i> -Heterocyclic Carbene (NHC) Catalysis	829
28.6.1	NHC-Catalyzed Mannich-Type Reactions	829
28.7	Supported Organocatalysis	831
28.7.1	Covalently Supported Organocatalysts	831
28.7.1.1	Magnetically Supported Organocatalysts	831
28.7.2	Non-Covalently Supported Organocatalysts	832
28.7.2.1	Polyoxometalate-Supported Organocatalysts	832
28.7.2.2	Clay-Supported Organocatalysts	832
28.7.3	Supported Organocatalysts in Multiphasic Systems	834
28.7.3.1	Tagged Organocatalysts	834
28.7.3.2	Supported Ionic Liquid Phase Catalysis	834
28.8	Summary and Conclusions	835
	References	835
<b>29</b>	<b>Additions of Nitroalkyls and Sulfones to C=X</b>	<b>841</b>
	<i>Aitor Landa, Rosa López, Mikel Oiarbide, and Claudio Palomo</i>	
29.1	Organocatalytic Addition of Nitroalkanes to C=O (The Henry Reaction)	841
29.1.1	Organocatalytic Addition of Nitroalkanes to Aldehydes	841
29.1.2	Organocatalytic Addition of Nitroalkanes to Ketones	846
29.2	Addition of Nitroalkanes to C=NR (The Aza-Henry or Nitro-Mannich Reaction)	851

29.2.1	Brønsted Base Catalyzed Aza-Henry Reactions	852
29.2.2	Hydrogen Bond Catalyzed Aza-Henry Reactions	857
29.2.3	Phase-Transfer Conditions (PTC)	862
29.2.4	Miscellaneous	864
29.3	Organocatalytic Addition of Sulfones to C=X	864
29.3.1	Introduction	864
29.3.2	Organocatalytic Addition of Sulfones to C=O	864
29.3.3	Organocatalytic Addition of Sulfones to C=N	865
29.4	Summary and Outlook	868
	References	868
<b>30</b>	<b>Hydrocyanation and Strecker Reactions</b>	<b>873</b>
	<i>Carsten Kramer and Stefan Bräse</i>	
30.1	Introduction	873
30.1.1	Overview	873
30.2	Amino-Acid Containing Catalysts for Carbonyl Hydrocyanation	873
30.3	Thiourea Catalysts for Carbonyl Hydrocyanation	875
30.4	C <sub>2</sub> -Symmetrical Guanidines and N,N'-Dioxides	876
30.5	Diketopiperazines as Catalysts for the Strecker Reaction	877
30.6	(Thio)urea Catalysts for the Strecker Reaction	878
30.7	Guanidines as Catalysts for the Strecker Reaction	886
30.8	N,N'-Dioxides and Bis-Formamides as Catalysts for the Strecker Reaction	886
30.9	Chiral Quaternary Ammonium Salts as Catalysts for the Strecker Reaction	890
30.10	BINOL-Phosphates as Catalysts for the Strecker Reaction	893
30.11	Other Catalysts for the Strecker Reaction	895
	References	896
<b>31</b>	<b>The Morita–Baylis–Hillman (MBH) and Hetero-MBH Reactions</b>	<b>899</b>
	<i>Yin Wei and Min Shi</i>	
31.1	Introduction	899
31.2	Recent Mechanistic Insights into the MBH/aza-MBH Reaction and Its Asymmetric Version	900
31.2.1	Amine Catalyzed Mechanism	900
31.2.2	Phosphine Catalyzed Mechanism	905
31.2.3	Mechanistic Insights into the MBH/aza-MBH Reaction Using Co-catalytic Systems or Multi-/Bifunctional Catalysts	906
31.2.4	Stereoselectivity of the MBH/aza-MBH Reaction	908
31.3	Recent Developments of Essential Components	910
31.4	Recent Developments of Asymmetric MBH/aza-MBH Reactions	914
31.4.1	Asymmetric Induction with Substrates	914
31.4.2	Catalytic Asymmetric Induction with Chiral Lewis Bases	916
31.4.2.1	Chiral Tertiary Amine Catalysts	916

- 31.4.2.2 Chiral Tertiary Phosphine Catalysts 922
- 31.4.3 Catalytic Asymmetric Induction with Chiral Lewis Acids 929
- 31.4.4 Catalytic Asymmetric Induction with Chiral Brønsted Acids 930
  - 31.4.4.1 Catalytic Asymmetric Induction with Chiral Thioureas 930
  - 31.4.4.2 Catalytic Asymmetric Induction with Proline Derivatives 933
  - 31.4.4.3 Catalytic Asymmetric Induction with Chiral Thiols 936
- 31.5 Conclusions 937
- References 938
  
- 32 Reduction of C=O and C=N 941**  
*Guilong Li and Jon C. Antilla*
  - 32.1 Introduction 941
  - 32.2 Hantzsch Ester as the Hydride Source 941
    - 32.2.1 Reduction of C=N Bonds in Acyclic Systems 942
    - 32.2.2 Reduction of C=N Bonds in Cyclic Substrates 947
      - 32.2.2.1 Reduction of C=N Bonds in Heteroarenes 947
      - 32.2.2.2 Reduction of Cyclic Imines 948
    - 32.2.3 Transfer Hydrogenation Combined with Other Transformations 951
    - 32.2.4 Immobilized Chiral Catalysts for C=N Bond Reduction 953
    - 32.2.5 Mechanistic Consideration 954
  - 32.3 Trichlorosilane as the Reducing Reagent 955
    - 32.3.1 Asymmetric Reduction of Ketimines 955
    - 32.3.2 Reduction of Enamines 960
    - 32.3.3 Reduction of C=N Bonds Catalyzed by Recoverable Lewis Base Catalysts 962
    - 32.3.4 Asymmetric Reduction of C=O Bonds 963
  - 32.4 Other Hydrogen Sources 964
    - 32.4.1 Benzothiazolines 964
    - 32.4.2 Boranes 966
    - 32.4.3 Hydrogen as the Source<sup>3</sup> 967
      - 32.4.3.1 Chiral Frustrated Lewis Pairs as Catalysts 967
      - 32.4.3.2 H<sub>2</sub> as a Terminal Hydrogen Source: Combined Hydrogenation by Organocatalysis and Metal Catalysis 969
  - 32.5 Summary and Conclusions 971
  - References 971

### Part III Nucleophile Addition to C=C Bonds 975

- 33 Addition to  $\alpha,\beta$ -Unsaturated Aldehydes and Ketones 977**  
*Ramon Rios and Xavier Companyó*
  - 33.1 Introduction 977
    - 33.1.1 Iminium Activation 978
      - 33.1.1.1 Historical Overview 978
    - 33.2 Nucleophilic Addition to Enals and Ketones 979
      - 33.2.1 Iminium Activation 979

33.2.1.1	Catalyzed by Secondary Amines	980
33.2.1.2	Primary Amine Catalysis	982
33.2.1.3	ACDC Catalysts	982
33.2.2	Scope of the Nucleophilic Addition to Enals	983
33.2.2.1	C–C Bond Formation	983
33.2.2.2	C–N Bond Formation	989
33.2.2.3	C–O Bond Formation	993
33.2.2.4	C–S Bond Formation	994
33.2.2.5	C–P Bond Formation	994
33.2.2.6	C–H Bond Formation	996
33.2.3	Scope of the Nucleophilic Addition to $\alpha,\beta$ -Unsaturated Ketones	997
33.2.3.1	C–C Bond Formation	997
33.2.3.2	C–N Bond Formation	1003
33.2.3.3	C–O Bond Formation	1004
33.2.3.4	C–S Bond Formation	1005
33.2.3.5	Other Michael Reactions	1006
33.3	Conclusion	1008
	References	1008
<b>34</b>	<b>Addition to Nitroolefins and Vinyl Sulfones</b>	<b>1013</b>
	<i>Christèle Roux and Cyril Bressy</i>	
34.1	Introduction	1013
34.2	Addition to Nitroolefins	1013
34.2.1	Enamine Activation	1013
34.2.1.1	Secondary Amines	1013
34.2.1.2	Primary Amines – <i>Anti</i> -Selectivity	1015
34.2.1.3	Applications in Total Synthesis	1018
34.2.2	Hydrogen Bonding Activation	1019
34.2.2.1	Carbon-Centered Nucleophiles	1019
34.2.2.2	Oxa-Michael Addition	1021
34.2.2.3	Sulfa-Michael Addition	1023
34.2.2.4	Aza-Michael Addition	1023
34.2.2.5	Applications in Total Synthesis	1025
34.2.3	Acidic Activation	1026
34.2.4	Basic Activation	1026
34.2.5	Challenging Substrates	1027
34.2.5.1	$\alpha,\beta$ -Disubstituted Nitroolefins	1027
34.2.5.2	Terminally Unsubstituted Nitroolefins	1030
34.2.5.3	Acetaldehyde	1031
34.2.6	Miscellaneous	1031
34.3	Addition to Vinyl Sulfones	1032
34.3.1	Enamine Activation of Aldehydes and Ketones	1032
34.3.2	Non-Covalent Activation	1037
34.4	Addition to Vinyl Selenones	1037

34.5	Summary and Conclusions	1040
	Acknowledgments	1040
	References	1040
<b>35</b>	<b>Organocatalyzed Asymmetric Arylation and Heteroarylation Reactions</b>	<b>1043</b>
	<i>Renata Marcia de Figueiredo and Jean-Marc Campagne</i>	
35.1	Introduction	1043
35.2	Representative Classes of Electrophiles	1046
35.2.1	$\alpha,\beta$ -Unsaturated Aldehydes	1046
35.2.2	$\alpha,\beta$ -Unsaturated Enones	1047
35.2.3	Nitroolefins	1048
35.2.4	Carbonyl Compounds	1049
35.2.5	Imines (Aza-Friedel–Crafts Reaction)	1050
35.2.6	Other Electrophiles	1051
35.3	Friedel–Crafts in Organocascade Transformations	1053
35.4	Application in Biologically Interesting and Natural Product Syntheses	1057
35.5	Miscellaneous	1061
35.6	Conclusion	1062
	References	1063
	<b>Part IV Ring-Forming Reactions</b>	<b>1067</b>
<b>36</b>	<b>Intramolecular Reactions</b>	<b>1069</b>
	<i>You-Cai Xiao and Ying-Chun Chen</i>	
36.1	Introduction	1069
36.2	Intramolecular Ring-Forming Reactions via Covalent Catalysis	1070
36.2.1	Enamine Catalysis	1070
36.2.2	Iminium Catalysis	1073
36.2.3	SOMO Catalysis	1075
36.2.4	Carbene Catalysis	1077
36.2.5	Lewis Base Catalysis of Tertiary Amines or Phosphines	1079
36.3	Intramolecular Ring-Forming Reactions by Non-Covalent Catalysis	1081
36.3.1	Brønsted Acid Catalysis	1081
36.3.2	Bifunctional Catalysis	1085
36.4	Conclusion	1087
	References	1087
<b>37</b>	<b>Formation of 3-, 4- and 5-Membered Cycles by Intermolecular Reactions</b>	<b>1091</b>
	<i>Hélène Pellissier</i>	
37.1	Introduction	1091
37.2	Organocatalytic Asymmetric Synthesis of Five-Membered Cycles	1092

37.2.1	Synthesis of Five-Membered Cycles via [3+2] Cycloadditions	1092
37.2.1.1	[3+2] Cycloadditions of Nitrones	1092
37.2.1.2	[3+2] Cycloadditions of Azomethine Ylides	1096
37.2.1.3	Miscellaneous [3+2] Cycloadditions	1098
37.2.2	Five-Membered Cycles via Domino Reactions	1101
37.2.2.1	Domino Reactions Initiated by the Michael Reaction	1101
37.2.2.2	Miscellaneous Domino Reactions	1110
37.3	Organocatalytic Asymmetric Synthesis of Four-Membered Cycles	1112
37.4	Organocatalytic Asymmetric Synthesis of Three-Membered Cycles	1115
37.4.1	Synthesis of Cyclopropanes	1115
37.4.2	Synthesis of Aziridines	1120
37.5	Conclusion	1123
	References	1124
<b>38</b>	<b>Diels-Alder and Hetero-Diels–Alder Reactions</b>	<b>1131</b>
	<i>Haifeng Du and Kuiling Ding</i>	
38.1	Introduction	1131
38.2	Organocatalytic Diels–Alder Reaction	1132
38.2.1	Chiral Secondary or Primary Amines as Catalysts	1132
38.2.1.1	Chiral Secondary Amine	1132
38.2.1.2	Chiral Primary Amine	1140
38.2.2	Chiral Brønsted Acids Catalysts (Hydrogen-Bonding or Brønsted Acid Activation)	1142
38.2.3	Chiral Bifunctional Catalysts	1144
38.3	Organocatalysis of Oxa-Hetero-Diels–Alder Reaction	1147
38.3.1	Chiral Bases as Catalysts	1148
38.3.2	Chiral Brønsted Acids as Catalysts	1150
38.3.3	Chiral <i>N</i> -Heterocyclic Carbenes as Catalysts	1152
38.4	Organocatalysis of Aza-Hetero-Diels–Alder Reaction	1154
38.4.1	Chiral Carbenes as Catalysts	1154
38.4.2	Chiral Amines as Catalysts	1155
38.4.3	Chiral Brønsted Acids as Catalysts	1157
38.5	Conclusion	1159
	References	1160
	<b>Part V Increasing Complexity</b>	<b>1163</b>
<b>39</b>	<b>Organocatalytic Radical and Electron Transfer Reactions</b>	<b>1165</b>
	<i>Thibault Gallavardin and Peter I. Dalko</i>	
39.1	Introduction	1165
39.2	Chemically Induced Oxidative Electron-Transfer Reactions	1166
39.2.1	Oxamination Reactions	1169
39.2.2	Additions to Olefins and Alkynes	1169

39.2.3	Asymmetric Intermolecular Allylation of Aldehydes	1170
39.2.4	Asymmetric Allylation of Ketones	1172
39.2.5	Intramolecular Asymmetric Allylations	1172
39.2.6	$\alpha$ -Enolation	1173
39.2.7	$\alpha$ -Vinylolation	1174
39.2.8	Carbo-Oxidation of Styrenes	1175
39.2.9	Polyene Cyclizations	1175
39.2.10	Intramolecular $\alpha$ -Arylation	1176
39.2.11	Cascade Cycloadditions	1177
39.2.12	Asymmetric Nitroalkylation of Aldehydes	1180
39.3	Photoredox Catalysis	1180
39.3.1	$\alpha$ -Alkylation of Aldehydes	1182
39.3.2	$\alpha$ -Benzylation of Aldehydes	1184
39.3.3	$\alpha$ -Trifluoromethylation of Aldehydes	1185
39.4	Photochemical Asymmetric Synthesis	1186
39.5	Conclusion	1188
	References	1189
<b>40</b>	<b>Organocatalytic Sigmatropic Reactions</b>	<b>1191</b>
	<i>Guillem Valero and Albert Moyano</i>	
40.1	Introduction	1191
40.2	Steglich and Related Rearrangements	1192
40.3	1,3-Sigmatropic Rearrangements	1203
40.4	1,4-Sigmatropic Rearrangements	1207
40.5	2,3-Sigmatropic Rearrangements	1208
40.6	3,3-Sigmatropic Rearrangements	1209
40.7	Aza-Petasis–Ferrier Rearrangement	1215
40.8	Pinacol and Related Rearrangements	1216
	Acknowledgments	1220
	References	1220
<b>41</b>	<b>Regio- and Position Selective Reactions and Desymmetrizations</b>	<b>1225</b>
	<i>Alan C. Spivey and Stelios Arseniyadis</i>	
41.1	Introduction	1225
41.2	Kinetic Resolution of Alcohols	1225
41.2.1	Acylation-Based Processes	1225
41.2.1.1	Mechanistic Studies	1226
41.2.1.2	Synthetic Studies	1229
41.2.2	Phosphorylation-Based Process	1251
41.2.3	Sulfonylation- and Sulfinylation-Based Process	1256
41.2.4	Silylation-Based Process	1258
41.3	Kinetic Resolution of Amines	1263
41.3.1	Acylation-Based Process	1263
41.4	Concluding Remarks	1278
	References	1279

<b>42</b>	<b>Three or More Components Reactions (Single Catalyst Systems)</b>	<b>1285</b>
	<i>René Tannert, Antonio Moran, and Paolo Melchiorre</i>	
42.1	General Introduction	1285
42.2	Covalent Modes of Catalysis—Developing MCRs by Asymmetric Aminocatalysis	1287
42.2.1	Asymmetric MCRs Based on a Single Aminocatalytic Step	1288
42.2.2	Asymmetric MCRs Based on Two Aminocatalytic Steps	1294
42.2.3	Asymmetric MCRs Based on Three or More Aminocatalytic Steps	1300
42.2.4	One-Pot Asymmetric MCRs for the Preparation of Active Pharmaceutical Ingredients	1307
42.3	Non-Covalent Modes of Catalysis	1309
42.3.1	Introduction	1309
42.3.2	Mannich Reactions	1310
42.3.3	Strecker Reactions	1314
42.3.4	Kabachnik–Fields Reaction	1314
42.3.5	Petasis Reaction	1315
42.3.6	Ugi-Type Reaction	1317
42.3.7	Reductive Amination	1317
42.3.8	Hantzsch Dihydropyridine and Related Reactions	1319
42.3.9	Biginelli Reactions	1321
42.3.10	1,3-Dipolar (Huisgen) Cycloaddition Reactions	1322
42.3.11	Diels–Alder Reactions	1324
42.3.12	Other Reactions	1325
42.4	Merging Covalent and Non-Covalent Activation Modes	1325
42.5	Summary and Outlook	1326
	Acknowledgments	1327
	References	1327
<b>43</b>	<b>Multi-Catalyst Systems</b>	<b>1333</b>
	<i>Liwen Xu, Huameng Yang, and Zhihui Shao</i>	
43.1	Introduction	1333
43.2	Combinational Use of Dual Brønsted Acids	1334
43.3	Combinational Use of Chiral Brønsted Acid and Chiral or Achiral Lewis Base	1335
43.4	Carbene-Based Dual Organocatalysis	1338
43.5	Amino Catalyst-Based Cooperative Catalysis with Multifarious Co-Catalysts	1343
43.6	Conclusions	1354
	Acknowledgments	1355
	References	1355

<b>44</b>	<b>Organocatalysis in Total Synthesis</b>	<b>1359</b>
	<i>Eugenia Marqués-López and Raquel P. Herrera</i>	
44.1	Introduction	1359
44.2	Aminocatalysis in Natural Product Synthesis	1359
44.2.1	Enamine Catalysis	1360
44.2.2	Dienamine Catalysis	1363
44.2.3	Iminium Catalysis	1363
44.2.4	Organocascade Catalysis: Combinations of Enamine and Iminium Catalysis	1365
44.3	Hydrogen Bond Catalysis in Total Synthesis	1365
44.3.1	Phosphoric Acids	1366
44.3.2	(Thio)urea Organocatalyzed Processes	1368
44.4	Cinchona Alkaloids in Total Synthesis	1370
44.5	Phase-Transfer Catalysis in Target Molecule Synthesis	1371
44.6	Industrial Applications of Organocatalysis	1373
44.6.1	Aminocatalysis in the Industrial Sector	1373
44.6.2	Thiourea Catalysis at the Industrial Scale	1374
44.6.3	Cinchona Alkaloids at the Industrial Level	1375
44.6.4	Phase-Transfer Catalysis in Industry	1376
44.7	Conclusions	1376
	References	1377
	<b>Index</b>	<b>1385</b>

