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of Homogeneous
Hydrogenation**

*Edited by
Johannes G. de Vries
and Cornelis J. Elsevier*

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Contents

Foreword XIX

Preface XXIII

List of Contributors XXV

Part I Introduction, Organometallic Aspects and Mechanism of Homogeneous Hydrogenation

1 Rhodium 3

Luis A. Oro and Daniel Carmona

- 1.1 Introduction 3
- 1.1.1 Monohydride Hydrogenation Catalysts 4
- 1.1.2 Dihydride Hydrogenation Catalysts 4
- 1.2 The Early Years (1939–1970) 5
- 1.3 The $[\text{RhH}(\text{CO})(\text{PPh}_3)_3]$ Catalyst 6
- 1.4 The $[\text{RhCl}(\text{PPh}_3)_3]$ Complex and Related Catalysts 8
- 1.5 The Cationic $[\text{Rh}(\text{diene})(\text{PR}_3)_X]^+$ Catalysts 11
- 1.6 Enantioselective Rhodium Catalysts 14
- 1.6.1 Hydrogenation of Alkenes 14
- 1.6.2 Hydrogenation of Ketones 19
- 1.6.3 Hydrogenation of Imines 20
- 1.6.4 Mechanism of Rhodium-Catalyzed Enantioselective Hydrogenation 21
- 1.7 Some Dinuclear Catalyst Precursors 26
- 1.8 Concluding Remark 26
- Abbreviations 26
- References 27

2 Iridium 31

Robert H. Crabtree

- 2.1 Introduction 31
- 2.2 Historical Aspects 31
- 2.3 Organometallic Aspects 36

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2.4	Catalysis	39
2.4.1	Enantioselective Versions of the Iridium Catalyst	39
2.4.2	Mechanism	40
2.4.3	Practical Considerations	42
	Acknowledgments	43
	Abbreviations	43
	References	43
3	Ruthenium and Osmium	45
	<i>Robert H. Morris</i>	
3.1	Introduction	45
3.2	Ruthenium	46
3.2.1	The First Catalysts for Alkene Hydrogenation: Mechanistic Considerations	46
3.2.2	Synthesis of Ruthenium Precatalysts and Catalysts	50
3.2.3	Dihydrogen Complexes and Non-Classical Hydrogen Bonding in Catalysis	52
3.2.4	Toward the Reduction of Simple Ketones, Nitriles, Esters and Aromatics with Monodentate Phosphine Systems	55
3.2.5	Enantiomeric Hydrogenation of Alkenes with Bidentate Ligand Systems	58
3.2.6	Enantiomeric Hydrogenation of Carbonyl Compounds	60
3.3	Osmium	64
	Acknowledgment	66
	Abbreviations	67
	References	67
4	Palladium and Platinum	71
	<i>Paolo Pelagatti</i>	
4.1	Introduction	71
4.2	Palladium	72
4.2.1	Phosphorus-Containing Catalysts	72
4.2.2	Nitrogen-Containing Catalysts	76
4.2.3	Other Catalysts	78
4.2.4	Mechanistic Aspects	79
4.3	Platinum	84
4.3.1	Platinum Complexes Activated with Sn(II) Salts	84
4.3.1.1	Phosphorus-Containing Catalysts	84
4.3.1.2	Other Catalysts	85
4.3.2	Platinum Complexes not Activated with Sn(II) Salts	86
4.3.3	Mechanistic Aspects	87
	Abbreviations	89
	References	89

5	Nickel	93
	<i>Elisabeth Bouwman</i>	
5.1	Introduction	93
5.2	Coordination Chemistry and Organometallic Aspects of Nickel	94
5.2.1	Nickel–Hydride Complexes	94
5.2.2	Nickel–Alkene and Nickel–Alkyl Complexes	96
5.2.3	Mechanistic Aspects of Hydrogen Activation	97
5.3	Hydrogenation Catalysis	98
5.3.1	Ziegler Systems	98
5.3.2	Nickel Complexes of Oxygen- or Nitrogen-Containing Ligands	99
5.3.3	Nickel Complexes of Triphenylphosphane	100
5.3.4	Nickel Complexes of Didentate Phosphane Ligands	101
5.4	Concluding Remarks	107
	Abbreviations	108
	References	108
6	Hydrogenation with Early Transition Metal, Lanthanide and Actinide Complexes	111
	<i>Christophe Copéret</i>	
6.1	Introduction	111
6.2	Mechanistic Considerations	112
6.3	Group IV Metal Hydrogenation Catalysts	113
6.3.1	Hydrogenation of Alkenes	113
6.3.2	Hydrogenation of Alkynes and Dienes	114
6.3.3	Enantioselective Hydrogenation of Alkenes	116
6.3.4	Enantioselective Hydrogenation of Imines and Enamines	118
6.4	Hydrogenation Catalysts Based on Group III, Lanthanide, and Actinide Complexes	126
6.4.1	Hydrogenation of Alkenes with Group III Metal and Lanthanide Complexes	126
6.4.2	Hydrogenation of Dienes and Alkynes with Group III and Lanthanide Complexes	129
6.4.3	Hydrogenation of Imines with Group III and Lanthanide Complexes	131
6.4.4	Hydrogenation of Alkenes with Actinide Complexes	132
6.4.5	Enantiomeric Hydrogenation of Alkenes	134
6.5	Hydrogenation Catalysts Based on Groups V–VII Transition-Metal Complexes	136
6.5.1	Hydrogenation of Alkenes and Dienes with Groups V–VII Transition-Metal Complexes	136
6.5.2	Hydrogenation of Aromatics with Well-Defined Nb and Ta Aryloxide Complexes	138
6.6	Supported Early Transition-Metal Complexes as Heterogeneous Hydrogenation Catalysts	140
6.6.1	Supported Homogeneous Catalysts	140

6.6.2	Heterogeneous Catalysts Prepared via Surface Organometallic Chemistry	142
6.7	Conclusions	145
	Acknowledgments	146
	Abbreviations	146
	References	146
7	Ionic Hydrogenations	153
	<i>R. Morris Bullock</i>	
7.1	Introduction	153
7.2	Stoichiometric Ionic Hydrogenations	154
7.2.1	Stoichiometric Ionic Hydrogenations using $\text{CF}_3\text{CO}_2\text{H}$ and HSiEt_3	154
7.2.2	Stoichiometric Ionic Hydrogenations using Transition-Metal Hydrides	157
7.2.2.1	General Aspects	157
7.2.2.2	Transition-Metal Hydrides as Proton Donors	157
7.2.3	Transition Metal Hydrides as Hydride Donors	159
7.2.4	Stoichiometric Ionic Hydrogenation of Alkenes with Metal Hydrides as the Hydride Donor	164
7.2.5	Stoichiometric Ionic Hydrogenation of Alkynes	166
7.2.6	Stoichiometric Ionic Hydrogenation of Ketones and Aldehydes using Metal Hydrides as Hydride Donors and Added Acids as the Proton Donor	167
7.2.7	Stoichiometric Ionic Hydrogenation of Acyl Chlorides to Aldehydes with HOTf/Metal Hydrides	171
7.2.8	Stoichiometric Ionic Hydrogenation of Ketones with Metal Dihydrides	173
7.3	Catalytic Ionic Hydrogenation	174
7.3.1	Catalytic Ionic Hydrogenation of C=C Bonds	174
7.3.2	Catalytic Ionic Hydrogenation of Ketones by Anionic Cr, Mo, and W Complexes	174
7.3.3	Catalytic Ionic Hydrogenation of Ketones by Molybdenocene Complexes	176
7.3.4	Catalytic Ionic Hydrogenation of Ketones by Cationic Mo and W Complexes	178
7.3.4.1	In Solution	178
7.3.4.2	Solvent-free	181
7.3.4.3	N-Heterocyclic Carbene Complexes	182
7.3.5	Use of a Pd Hydride in Hydrogenation of C=C Bonds	184
7.3.6	Catalytic Hydrogenation of Iminium Cations by Ru Complexes	184
7.4	Ruthenium Complexes Having an OH Proton Donor and a RuH as Hydride Donor	186
7.4.1	The Shvo System	186
7.4.2	Hydrogenation of Imines by Shvo Complexes	189

7.4.3	Dehydrogenation of Imines and Alcohols by Shvo Complexes	191
7.4.4	Catalytic Hydrogenations with Metal–Ligand Bifunctional Catalysis	193
7.5	Catalytic Hydrogenation of Ketones by Strong Bases	193
7.6	Conclusion	194
	Acknowledgments	194
	Abbreviations	195
	References	195
8	Homogeneous Hydrogenation by Defined Metal Clusters	199
	<i>Roberto A. Sánchez-Delgado</i>	
8.1	Introduction	199
8.1.1	Is a Cluster the Real Catalyst? Fragmentation and Aggregation Phenomena	200
8.2	Hydrogenation of C=C Bonds	201
8.3	Hydrogenation of C≡C Bonds	206
8.4	Hydrogenation of Other Substrates	211
8.5	Concluding Remarks	212
	Abbreviations	213
	References	213
9	Homogeneous Hydrogenation: Colloids – Hydrogenation with Noble Metal Nanoparticles	217
	<i>Alain Roucoux and Karine Philippot</i>	
9.1	Introduction	217
9.2	Concepts	217
9.2.1	Electrostatic Stabilization	218
9.2.2	Steric Stabilization	219
9.3	Hydrogenation of Compounds with C=C Bonds	220
9.3.1	Use of Polymers as Stabilizers	220
9.3.2	Use of Non-Usual Polymers as Stabilizers	221
9.3.3	Use of Dendrimers as Stabilizers	225
9.3.4	Use of Surfactants as Stabilizers	226
9.3.5	Use of Polyoxoanions as Stabilizers	227
9.3.6	Use of Ligands as Stabilizers	228
9.3.7	Biomaterial as a Protective Matrix	232
9.3.8	Ionic Liquids used as Templates for the Stabilization of Metal Nanoparticles	233
9.3.9	Supercritical Microemulsions Used as Templates for the Stabilization of Metal Nanoparticles	236
9.3.10	Conclusion	238
9.4	Hydrogenation of Compounds with C≡C Bonds	238
9.5	Arene Hydrogenation	241
9.6	Hydrogenation of Compounds with C=O Bonds	245
9.7	Enantioselective Hydrogenation	249

9.8	Conclusion	252
	Abbreviations	252
	References	253
10	Kinetics of Homogeneous Hydrogenations: Measurement and Interpretation	257
	<i>Hans-Joachim Drexler, Angelika Preetz, Thomas Schmidt, and Detlef Heller</i>	
10.1	Introduction	257
10.2	The Basics of Michaelis-Menten Kinetics	259
10.3	Hydrogenation From a Kinetic Viewpoint	263
10.3.1	Measurement of Concentration–Time Data and Possible Problems	263
10.3.1.1	Monitoring of Hydrogenations via Hydrogen Consumption	264
10.3.1.2	Monitoring of Hydrogenations by NMR and UV/Visible Spectroscopy	272
10.3.2	Gross-Kinetic Measurements	277
10.3.2.1	Derivation of Michaelis-Menten Kinetics with Various Catalyst-Substrate Complexes	277
10.3.2.2	Data from Gross Kinetic Measurements	280
	Abbreviations	288
	References	288
Part II	Spectroscopic Methods in Homogeneous Hydrogenation	
11	Nuclear Magnetic Resonance Spectroscopy in Homogeneous Hydrogenation Research	297
	<i>N. Koen de Vries</i>	
11.1	Introduction	297
11.1.1	Nuclear Magnetic Resonance (NMR)	297
11.1.2	NMR in Homogeneous Hydrogenation Research	298
11.2	NMR Methods	299
11.2.1	General	299
11.2.2	Chemical Shift	300
11.2.2.1	General	300
11.2.2.2	Chemical Shifts in Homogeneous Hydrogenation Research	300
11.2.3	Coupling Constant	301
11.2.4	2D-NMR	302
11.2.4.1	General	302
11.2.4.2	2D-NMR in Homogeneous Hydrogenation Research	302
11.2.5	Variable Temperature and Variable Pressure Studies	307
11.2.5.1	General	307
11.2.5.2	Variable-Temperature Studies in Homogeneous Hydrogenation Research	307
11.2.5.3	Variable-Pressure Studies in Homogeneous Hydrogenation Research	308

11.2.6	PGSE NMR Diffusion Methods	309
11.3	Outlook	309
	Abbreviations	310
	References	310
12	Parahydrogen-Induced Polarization: Applications to Detect Intermediates of Catalytic Hydrogenations	313
	<i>Joachim Bargon</i>	
12.1	<i>In-Situ</i> Spectroscopy	313
12.1.1	<i>In-Situ</i> NMR Spectroscopy	313
12.1.2	<i>In-Situ</i> PHIP-NMR Spectroscopy	314
12.2	Ortho- and Parahydrogen	315
12.2.1	Magnetic Field Dependence of the PHIP-Phenomenon: PASADENA and ALTADENA Conditions	316
12.2.2	PHIP, CIDNP, and Radical Mechanisms	318
12.2.3	Preparation of Parahydrogen	319
12.2.3.1	Parahydrogen Enrichment	319
12.2.3.2	High-Pressure Apparatus for Parahydrogen Enrichment	320
12.2.3.3	Enrichment of Parahydrogen using Closed-Circuit Cryorefrigeration	321
12.2.4	Preparation of Orthohydrogen	322
12.2.5	Thermal Conductivity Cells for Ortho/Para Determination	322
12.2.6	Determination of the Ortho/Para Ratio	323
12.2.7	Enrichment of Ortho- or Paradeuterium	323
12.3	Applications of PHIP-NMR Spectroscopy	324
12.3.1	<i>In-Situ</i> PHIP-NMR Spectroscopy of Homogeneous Hydrogenations	324
12.3.1.1	Activation of Dihydrogen	324
12.3.1.2	Concepts of Reaction Mechanisms	324
12.3.2	<i>In-Situ</i> PHIP-NMR Observation of Mono- and Binuclear Rhodium Dihydride Complexes	325
12.3.2.1	Reactions of $[\text{RhCl}(\text{NBD})]_2$ with Parahydrogen in the Presence of Tertiary Phosphines	325
12.3.2.2	Formation of the Binuclear Complexes $[(\text{H})(\text{Cl})\text{Rh}(\text{PMe}_3)_2(\mu\text{-Cl})(\mu\text{-H})\text{Rh}(\text{PMe}_3)]$ and $[(\text{H})(\text{Cl})\text{Rh}(\text{PMe}_2\text{Ph})_2(\mu\text{-Cl})(\mu\text{-H})\text{Rh}(\text{PMe}_2\text{Ph})]$	328
12.3.2.3	General Procedure for the Generation of the Complexes $[\text{Rh}(\text{H})_2\text{ClL}_3]$ (L=Phosphine)	329
12.3.3.3	Intermediate Dihydrides of Cationic Rh Catalysts	329
12.3.3.4	Obtaining Structural Information using ^{13}C -Labeled Substrates	332
12.4	Catalyst-Attached Products as Observable Intermediates	335
12.4.1	Enantioselective Substrates	336
12.4.2	Chiral Catalysts	336
12.4.3	Determination of Kinetic Constants	338

- 12.4.4 Computer-Assisted Prediction and Analysis of the Polarization Patterns: DYPAS2 341
- 12.5 Colloidal Catalysts 342
- 12.5.1 *In-Situ* PHIP-NMR Investigation of the Hydrogenation of Ethynylbenzene by $\text{Pd}_x[\text{N}(\text{octyl})_4\text{Cl}]_y$ 342
- 12.6 Transfer of Proton Polarization to Heteronuclei 344
 - 12.6.1 General Aspects 344
 - 12.6.2 Polarization Transfer to ^{13}C 346
 - 12.6.3 Polarization Transfer to ^{19}F 352
 - 12.6.4 Parahydrogen-Assisted Signal Enhancement for Magnetic Resonance Imaging 353
- 12.7 Catalysts Containing other Transition Metals 354
- 12.8 Summary and Conclusions 354
 - Acknowledgment 355
 - Abbreviations 355
 - References 356

13 A Tour Guide to Mass Spectrometric Studies of Hydrogenation Mechanisms 359

Corbin K. Ralph, Robin J. Hamilton, and Steven H. Bergens

- 13.1 Introduction 359
- 13.2 A General Description of ESI-MS 360
- 13.3 Mechanistic Hydrogenation Studies 364
- 13.4 Conclusions 369
 - Acknowledgments 370
 - Abbreviations 370
 - References 370

Part III Homogeneous Hydrogenation by Functional Groups

14 Homogeneous Hydrogenation of Alkynes and Dienes 375

Alexander M. Kluwer and Cornelis J. Elsevier

- 14.1 Stereoselective Homogeneous Hydrogenation of Alkynes to Alkenes 375
 - 14.1.1 Introduction 375
 - 14.1.2 Chromium Catalysts 376
 - 14.1.3 Iron Catalysts 377
 - 14.1.4 Ruthenium Catalysts 378
 - 14.1.5 Osmium Catalysts 382
 - 14.1.6 Rhodium Catalysts 384
 - 14.1.7 Iridium Catalysts 386
 - 14.1.8 Palladium Catalysts 388
 - 14.1.9 Conclusions 394
- 14.2 Homogeneous Hydrogenation of Dienes to Monoenes 394
 - 14.2.1 Introduction 394

14.2.2	Zirconium Catalysts	395
14.2.3	Chromium Catalysts	397
14.2.4	Ruthenium Catalysts	400
14.2.5	Cobalt Catalysts	402
14.2.6	Rhodium Catalysts	402
14.2.7	Palladium and Platinum Catalysts	406
14.2.8	Conclusions	408
	Abbreviations	409
	References	409
15	Homogeneous Hydrogenation of Aldehydes, Ketones, Imines and Carboxylic Acid Derivatives: Chemoselectivity and Catalytic Activity	413
	<i>Matthew L. Clarke and Geoffrey J. Roff</i>	
15.1	Introduction	413
15.2	Hydrogenation of Aldehydes	414
15.2.1	Iridium Catalysts	414
15.2.2	Rhodium Catalysts	417
15.2.2.1	Rh-amine Catalysts	417
15.2.2.2	Cationic Rhodium Phosphine Catalysts	418
15.2.2.3	Water-Soluble Rh Catalysts	419
15.2.3	Ruthenium Catalysts	420
15.2.3.1	Ru-PPh ₃ Catalysts	420
15.2.3.2	Polydentate Ru Catalysts	421
15.2.3.3	Diamine-Modified Ru Catalysts	422
15.2.3.4	Ru-TPPMS/TPPTS Catalysts	423
15.2.4	Other Metal Catalysts	425
15.2.4.1	Copper	425
15.2.4.2	Osmium	425
15.3	Hydrogenation of Ketones	426
15.3.1	Iridium Catalysts	426
15.3.2	Rhodium Catalysts	428
15.3.2.1	Rh-Phosphine Catalysts	428
15.3.2.2	Water-Soluble Rh Catalysts	430
15.3.3	Ruthenium Catalysts	431
15.3.3.1	Ruthenium Carbonyl Clusters	431
15.3.3.2	Ru-PPh ₃ Complexes	431
15.3.3.3	Diamine-Modified Ru Catalysts	433
15.3.3.4	Other Ru Catalysts	434
15.3.4	Other Metal Catalysts	435
15.3.4.1	Copper	435
15.3.4.2	Metal Carbonyls	436
15.4	Domino-Hydroformylation-Reduction Reactions	436
15.4.1	Cobalt Catalysts	436
15.4.2	Rhodium Catalysts	437

- 15.5 Reductive Amination of Ketones and Aldehydes 437
- 15.6 Hydroaminomethylation of Alkenes
(Domino Hydroformylation-Reductive Amination) 439
- 15.7 Hydrogenation of Carboxylic Acid Derivatives 441
 - 15.7.1 Hydrogenation of Acids and Anhydrides 442
 - 15.7.2 Hydrogenation of Esters 445
- 15.8 Summary and Outlook 450
 - Abbreviations 451
 - References 452

- 16 Hydrogenation of Arenes and Heteroaromatics 455**
Claudio Bianchini, Andrea Meli, and Francesco Vizza
 - 16.1 Introduction 455
 - 16.2 Hydrogenation of Arenes 456
 - 16.2.1 Molecular Catalysts in Different Phase-Variation Systems 456
 - 16.2.2 Molecular Catalysts Immobilized on Support Materials 466
 - 16.3 Hydrogenation of Heteroaromatics 470
 - 16.3.1 Molecular Catalysts in Different Phase-Variation Systems 470
 - 16.3.1.1 S-Heteroaromatics 470
 - 16.3.1.2 N-Heteroaromatics 474
 - 16.3.1.3 O-Heteroaromatics 479
 - 16.3.2 Molecular Catalysts Immobilized on Support Materials 479
 - 16.4 Stereoselective Hydrogenation of Prochiral Heteroaromatics 481
 - 16.4.1 Molecular Catalysts in Homogeneous Phase 481
 - 16.4.2 Molecular Catalysts Immobilized on Support Materials 484
 - Abbreviations 484
 - References 485

- 17 Homogeneous Hydrogenation of Carbon Dioxide 489**
Philip G. Jessop
 - 17.1 Introduction 489
 - 17.2 Reduction to Formic Acid 490
 - 17.2.1 Insertion Mechanisms 494
 - 17.2.2 Ionic Hydrogenation 497
 - 17.2.3 Concerted Ionic Hydrogenation 498
 - 17.2.4 Bicarbonate Hydrogenation 498
 - 17.2.5 Other Mechanisms 499
 - 17.3 Reduction to Oxalic Acid 499
 - 17.4 Reduction to Formate Esters 500
 - 17.4.1 In the Presence of Alcohols 500
 - 17.4.2 In the Presence of Alkyl Halides 502
 - 17.4.3 In the Presence of Epoxides 503
 - 17.5 Reduction to Formamides 504
 - 17.6 Reduction to Other Products 506
 - 17.7 Concluding Remarks 507

- Acknowledgments 507
Abbreviations 508
References 508
- 18 **Dehalogenation Reactions** 513
Attila Sisak and Ottó Balázs Simon
- 19 **Homogeneous Catalytic Hydrogenation of Polymers** 547
Garry L. Rempel, Qinmin Pan, and Jialong Wu
- 20 **Transfer Hydrogenation Including the Meerwein-Ponndorf-Verley Reduction** 585
Dirk Klomp, Ulf Hanefeld, and Joop A. Peters
- 21 **Diastereoselective Hydrogenation** 631
Takamichi Yamagishi
- 22 **Hydrogen-Mediated Carbon–Carbon Bond Formation Catalyzed by Rhodium** 713
Chang-Woo Cho and Michael J. Krische
- Part IV **Asymmetric Homogeneous Hydrogenation**
- 23 **Enantioselective Alkene Hydrogenation: Introduction and Historic Overview** 745
David J. Ager
- 24 **Enantioselective Hydrogenation: Phospholane Ligands** 773
Christopher J. Cobley and Paul H. Moran
- 25 **Enantioselective Hydrogenation of Alkenes with Ferrocene-Based Ligands** 833
Hans-Ulrich Blaser, Matthias Lotz, and Felix Spindler
- 26 **The other Bisphosphine Ligands for Enantioselective Alkene Hydrogenation** 853
Yongxiang Chi, Wenjun Tang, and Xumu Zhang
- 27 **Bidentate Ligands Containing a Heteroatom–Phosphorus Bond** 883
Stanton H. L. Kok, Terry T.-L. Au-Yeung, Hong Yee Cheung, Wing Sze Lam, Shu Sun Chan, and Albert S. C. Chan
- 28 **Enantioselective Alkene Hydrogenation: Monodentate Ligands** 995
Michel van den Berg, Ben L. Feringa, and Adriaan J. Minnaard

- 29 **P,N and Non-Phosphorus Ligands** 1029
Andreas Pfaltz and Sharon Bell
- 30 **Enantioselective Hydrogenation of Unfunctionalized Alkenes** 1049
Andreas Pfaltz and Sharon Bell
- 31 **Mechanism of Enantioselective Hydrogenation** 1073
John M. Brown
- 32 **Enantioselective Ketone and β -Keto Ester Hydrogenations
(Including Mechanisms)** 1105
Takeshi Ohkuma and Ryoji Noyori
- 33 **Rhodium-Catalyzed Enantioselective Hydrogenation
of Functionalized Ketones** 1165
André Mortreux and Abdallah Karim
- 34 **Enantioselective Hydrogenation of C=N Functions
and Enamines** 1193
Felix Spindler and Hans-Ulrich Blaser
- 35 **Enantioselective Transfer Hydrogenation** 1215
A. John Blacker
- 36 **High-Throughput Experimentation and Ligand Libraries** 1245
Johannes G. de Vries and Laurent Lefort
- 37 **Industrial Applications** 1279
Hans-Ulrich Blaser, Felix Spindler, and Marc Thommen
- Part V **Phase Separation in Homogeneous Hydrogenation**
- 38 **Two-Phase Aqueous Hydrogenations** 1327
Ferenc Joó and Ágnes Kathó
- 39 **Supercritical and Compressed Carbon Dioxide as Reaction Medium
and Mass Separating Agent for Hydrogenation Reactions
using Organometallic Catalysts** 1361
Walter Leitner
- 40 **Fluorous Catalysts and Fluorous Phase Catalyst Separation
for Hydrogenation Catalysis** 1377
Elwin de Wolf and Berth-Jan Deelman

41 **Catalytic Hydrogenation using Ionic Liquids as Catalyst Phase** 1389
Peter Wasserscheid and Peter Schulz

42 **Immobilization Techniques** 1421
Imre Tóth and Paul C. van Geem

Part VI Miscellaneous Topics in Homogeneous Hydrogenation

43 **Transition Metal-Catalyzed Regeneration
of Nicotinamide Cofactors** 1471
Stephan Lütz

44 **Catalyst Inhibition and Deactivation
in Homogeneous Hydrogenation** 1483
Detlef Heller, André H. M. de Vries, and Johannes G. de Vries

45 **Chemical Reaction Engineering Aspects
of Homogeneous Hydrogenations** 1517
Claude de Bellefon and Nathalie Pestre

Subject Index 1547

Contents

- Part I Introduction, Organometallic Aspects and Mechanism of Homogeneous Hydrogenation**
- 1 Rhodium 3**
Luis A. Oro and Daniel Carmona
- 2 Iridium 31**
Robert H. Crabtree
- 3 Ruthenium and Osmium 45**
Robert H. Morris
- 4 Palladium and Platinum 71**
Paolo Pelagatti
- 5 Nickel 93**
Elisabeth Bouwman
- 6 Hydrogenation with Early Transition Metal, Lanthanide and Actinide Complexes 111**
Christophe Copéret
- 7 Ionic Hydrogenations 153**
R. Morris Bullock
- 8 Homogeneous Hydrogenation by Defined Metal Clusters 199**
Roberto A. Sánchez-Delgado
- 9 Homogeneous Hydrogenation: Colloids – Hydrogenation with Noble Metal Nanoparticles 217**
Alain Roucoux and Karine Philippot

- 10 **Kinetics of Homogeneous Hydrogenations:
Measurement and Interpretation** 257
Hans-Joachim Drexler, Angelika Preetz, Thomas Schmidt, and Detlef Heller
- Part II Spectroscopic Methods in Homogeneous Hydrogenation**
- 11 **Nuclear Magnetic Resonance Spectroscopy
in Homogeneous Hydrogenation Research** 297
N. Koen de Vries
- 12 **Parahydrogen-Induced Polarization: Applications
to Detect Intermediates of Catalytic Hydrogenations** 313
Joachim Bargon
- 13 **A Tour Guide to Mass Spectrometric Studies
of Hydrogenation Mechanisms** 359
Corbin K. Ralph, Robin J. Hamilton, and Steven H. Bergens
- Part III Homogeneous Hydrogenation by Functional Groups**
- 14 **Homogeneous Hydrogenation of Alkynes and Dienes** 375
Alexander M. Kluwer and Cornelis J. Elsevier
- 15 **Homogeneous Hydrogenation of Aldehydes, Ketones, Imines
and Carboxylic Acid Derivatives: Chemoselectivity
and Catalytic Activity** 413
Matthew L. Clarke and Geoffrey J. Roff
- 16 **Hydrogenation of Arenes and Heteroaromatics** 455
Claudio Bianchini, Andrea Meli, and Francesco Vizza
- 17 **Homogeneous Hydrogenation of Carbon Dioxide** 489
Philip G. Jessop

18	Dehalogenation Reactions	513
	<i>Attila Sisak and Ottó Balázs Simon</i>	
18.1	Introduction	513
18.2	Catalytic Dehalogenation with Various Reducing Agents	517
18.2.1	Molecular Hydrogen	517
18.2.2	Simple and Complex Metal Hydrides	520
18.2.3	Hydrosilanes and Hydrostannanes	524
18.2.4	Hydrogen Donors other than Hydrides	526
18.2.5	Biomimetic Dehalogenations	528
18.2.6	Electrochemical Reductions	532
18.2.7	Miscellaneous Reducing Methods	533
18.3	Mechanistic Considerations	534
18.3.1	Activation of the C–X Bond	535
18.3.1.1	Oxidative Addition	535
18.3.1.2	σ -Bond Metathesis	537
18.3.1.3	S _N 2 Attack of the Hydride Ligand	538
18.3.1.4	1,2-Insertion	538
18.3.2	Reaction Steps Involving the Reducing Agents	538
18.3.3	Formation of the Product	539
18.4	Concluding Remarks	540
	Acknowledgments	540
	Abbreviations	540
	References	541
19	Homogeneous Catalytic Hydrogenation of Polymers	547
	<i>Garry L. Rempel, Qinmin Pan, and Jialong Wu</i>	
19.1	General Introduction	547
19.1.1	Diene-Based Polymers	547
19.1.2	Hydrogenation of Diene-Based Polymers	548
19.1.2.1	Heterogeneous Catalysts	549
19.1.2.2	Homogeneous Catalysts	550
19.2	Reaction Art	551
19.2.1	Catalyst Techniques	551
19.2.2	Hydrogenation Kinetic Mechanism	565
19.2.2.1	Rhodium-Based Catalysts	565
19.2.2.2	Ruthenium-Based Catalysts	568
19.2.2.3	Osmium-Based Catalysts	571
19.2.2.4	Palladium Complexes	572
19.2.3	Kinetic Mechanism Discrimination	573
19.3	Engineering Art	573
19.3.1	Catalyst Recovery	574
19.3.1.1	Precipitation	575
19.3.1.2	Adsorption	575
19.3.2	Solvent Recycling	576
19.3.3	Reactor Technology and Catalytic Engineering Aspects	577

- 19.4 A Commercial Example: Production of HNBR via a Homogeneous Hydrogenation Route 578
- 19.5 Future Outlook and Perspectives 579
- Abbreviations 579
- References 579
- 20 Transfer Hydrogenation Including the Meerwein-Ponndorf-Verley Reduction 585**
Dirk Klomp, Ulf Hanefeld, and Joop A. Peters
- 20.1 Introduction 585
- 20.2 Reaction Mechanisms 587
- 20.2.1 Hydrogen Transfer Reduction of Carbonyl Compounds 588
- 20.2.1.1 Meerwein-Ponndorf-Verley Reduction and Oppenauer Oxidation 588
- 20.2.1.2 Transition Metal-Catalyzed Reductions 590
- 20.2.2 Transfer Hydrogenation Catalysts for Reduction of C–C Double and Triple Bonds 595
- 20.3 Reaction Conditions 597
- 20.3.1 Hydrogen Donors 597
- 20.3.2 Solvents 600
- 20.3.3 Catalysts and Substrates 601
- 20.3.4 Selectivity 603
- 20.4 Related Reactions and Side-Reactions 609
- 20.4.1 Aldol Reaction 609
- 20.4.2 Tishchenko Reaction 609
- 20.4.3 Cannizzaro Reaction 609
- 20.4.4 Decarbonylation 610
- 20.4.5 Leuckart-Wallach and Eschweiler-Clarke Reactions 610
- 20.4.6 Reductive Acetylation of Ketones 610
- 20.4.7 Other Hydrogen Transfer Reactions 611
- 20.5 Racemizations 612
- Abbreviations 627
- References 627
- 21 Diastereoselective Hydrogenation 631**
Takamichi Yamagishi
- 21.1 Introduction 631
- 21.2 Hydrogenation of Alkenes, Ketones, and Imines 631
- 21.3 Substrate-Directive Diastereoselective Hydrogenation 638
- 21.3.1 Hydrogenation of Cyclic Alcohols with Endo- or Exo-Cyclic Olefinic Bond 638
- 21.3.2 Hydrogenation of Acyclic Allyl and Homoallyl Alcohols 653
- 21.3.3 Ester Unit- or Amide-Directive Hydrogenation 667
- 21.4 Hydrogenation of Dehydrooligopeptides 671
- 21.5 Diastereoselective Hydrogenation of Keto-Compounds 676

21.5.1	Substrate-Directive Hydrogenation of Keto-Compounds	681
21.5.2	Hydrogenation of Diketo Esters and Diketones	684
21.6	Kinetic Resolution to Selectively Afford Diastereomers and Enantiomers	691
21.7	Kinetic Resolution of Keto- and Imino-Compounds	694
21.8	Dynamic Kinetic Resolution	697
21.9	Conclusions	701
	Abbreviations	708
	References	708
22	Hydrogen-Mediated Carbon–Carbon Bond Formation Catalyzed by Rhodium	713
	<i>Chang-Woo Cho and Michael J. Krische</i>	
22.1	Introduction and Mechanistic Considerations	713
22.2	Reductive Coupling of Conjugated Enones and Aldehydes	716
22.2.1	Intramolecular Reductive Aldolization	716
22.2.2	Intermolecular Reductive Aldolization	720
22.3	Reductive Coupling of 1,3-Cyclohexadiene and α -Ketoaldehydes	723
22.4	Reductive Coupling of Conjugated Enynes and Diynes with Activated Aldehydes and Imines	726
22.5	Reductive Cyclization of 1,6-Diynes and 1,6-Enynes	733
22.6	Conclusion	736
	Acknowledgments	737
	Abbreviations	737
	References	737
Part IV	Asymmetric Homogeneous Hydrogenation	
23	Enantioselective Alkene Hydrogenation: Introduction and Historic Overview	745
	<i>David J. Ager</i>	
23.1	Introduction	745
23.2	Development of CAMP and DIPAMP	746
23.3	DIOP	749
23.4	Ferrocene Ligands	753
23.4.1	Ferrocene Hybrids	756
23.5	Atropisomeric Systems	756
23.6	DuPhos	758
23.7	Variations at Phosphorus	760
23.8	Monophosphorus Ligands	762
23.9	A Return to Monodentate Ligands	762
23.10	Summary	763
	References	764

24	Enantioselective Hydrogenation: Phospholane Ligands	773
	<i>Christopher J. Cobley and Paul H. Moran</i>	
24.1	Introduction and Extent of Review	773
24.2	Phospholane Ligands: Synthesis and Scope	774
24.2.1	Early Discoveries and the Breakthrough with DuPhos and BPE	774
24.2.2	Modifications to the Backbone	778
24.2.3	Modifications to the Phospholane Substituents	779
24.2.4	Other Phospholane-Containing Ligands	783
24.2.5	Related Phosphacycle-Based Ligands	786
24.3	Enantioselective Hydrogenation of Alkenes	788
24.3.1	Enantioselective Hydrogenation of α -Dehydroamino Acid Derivatives	788
24.3.2	Enantioselective Hydrogenation of β -Dehydroamino Acid Derivatives	801
24.3.3	Enantioselective Hydrogenation of Enamides	806
24.3.4	Enantioselective Hydrogenation of Unsaturated Acid and Ester Derivatives	810
24.3.5	Enantioselective Hydrogenation of Unsaturated Alcohol Derivatives	816
24.3.6	Enantioselective Hydrogenation of Miscellaneous C=C Bonds	819
24.4	Enantioselective Hydrogenation of C=O and C=N Bonds	820
24.4.1	Enantioselective Hydrogenation of Ketones	820
24.4.2	Enantioselective Hydrogenation of Imines and C=N-X Bonds	822
24.5	Concluding Remarks	823
	Abbreviations	823
	References	824
25	Enantioselective Hydrogenation of Alkenes with Ferrocene-Based Ligands	833
	<i>Hans-Ulrich Blaser, Matthias Lotz, and Felix Spindler</i>	
25.1	Introduction	833
25.2	Ligands with Phosphine Substituents Bound to One Cyclopentadiene Ring	835
25.3	Ligands with Phosphine Substituents Bound to both Cyclopentadiene Rings	835
25.3.1	Bppfa, Ferrophos, and Mandyphos Ligands	836
25.3.2	Miscellaneous Diphosphines	837
25.4	Ligands with Phosphine Substituents Bound to a Cyclopentadiene Ring and to a Side Chain	839
25.4.1	Josiphos	839
25.4.2	Immobilized Josiphos and Josiphos Analogues	841
25.4.3	Taniaphos	842
25.4.3	Various Ligands	843
25.5	Ligands with Phosphine Substituents Bound only to Side Chains	844

25.6	Major Applications of Ferrocene Diphosphine-Based Catalysts	847
25.6.1	Hydrogenation of Substituted Alkenes	848
25.6.2	Hydrogenation of C=O and C=N Functions	848
	Abbreviations	850
	References	850
26	The other Bisphosphine Ligands for Enantioselective Alkene Hydrogenation	853
	<i>Yongxiang Chi, Wenjun Tang, and Xumu Zhang</i>	
26.1	Introduction	853
26.2	Chiral Bisphosphine Ligands	853
26.2.1	Atropisomeric Biaryl Bisphosphine Ligands	853
26.2.2	Chiral Bisphosphine Ligands Based on DIOP Modifications	860
26.2.3	P-Chiral Bisphosphine Ligands	861
26.2.4	Other Bisphosphine Ligands	862
26.3	Applications in Enantioselective Hydrogenation of Alkenes	864
26.3.1	Enantioselective Hydrogenation of α -Dehydroamino Acid Derivatives	864
26.3.2	Enantioselective Hydrogenation of Enamides	866
26.3.3	Enantioselective Hydrogenation of (β -Acylamino) Acrylates	868
26.3.4	Enantioselective Hydrogenation of Enol Esters	870
26.3.5	Enantioselective Hydrogenation of Unsaturated Acids and Esters	872
26.3.5.1	α,β -Unsaturated Carboxylic Acids	872
26.3.5.2	α,β -Unsaturated Esters, Amides, Lactones, and Ketones	874
26.3.5.3	Itaconic Acids and Their Derivatives	874
26.3.6	Enantioselective Hydrogenation of Unsaturated Alcohols	875
26.4	Concluding Remarks	877
	References	877
27	Bidentate Ligands Containing a Heteroatom–Phosphorus Bond	883
	<i>Stanton H. L. Kok, Terry T.-L. Au-Yeung, Hong Yee Cheung, Wing Sze Lam, Shu Sun Chan, and Albert S. C. Chan</i>	
27.1	Introduction	883
27.2	Aminophosphine-Phosphinites (AMPPs)	883
27.3	Bisphosphinamidite Ligands	907
27.4	Mixed Phosphine-Phosphoramidites and Phosphine-Aminophosphine Ligands	918
27.5	Bisphosphinite Ligands (One P–O Bond)	924
27.6	Bisphosphonite Ligands (Two P–O Bonds)	978
27.7	Bisphosphite Ligands (Three P–O Bonds)	980
27.8	Other Mixed-Donor Bidentate Ligands	981
27.9	Ligands Containing Neutral S-Donors	983
	Acknowledgments	988
	Abbreviations	988
	References	988

28	Enantioselective Alkene Hydrogenation: Monodentate Ligands	995
	<i>Michel van den Berg, Ben L. Feringa, and Adriaan J. Minnaard</i>	
28.1	Introduction	995
28.2	Monodentate Phosphines	997
28.3	Monodentate Phosphonites	1000
28.4	Monodentate Phosphites	1000
28.5	Monodentate Phosphoramidites	1005
28.6	Monodentate Phosphinites, Aminophosphinites, Diazaphospholidines and Secondary Phosphine Oxides	1010
28.7	Hydrogenation of N-Acyl- α -Dehydroamino Acids and Esters	1011
28.8	Hydrogenation of Unsaturated Acids and Esters	1014
28.9	Hydrogenation of N-Acyl Enamides, Enol Esters and Enol Carbamates	1016
28.10	Hydrogenation of N-Acyl- β -Dehydroamino Acid Esters	1020
28.11	Hydrogenation of Ketones and Imines	1021
28.12	Conclusions	1023
	Abbreviations	1024
	References	1024
29	P,N and Non-Phosphorus Ligands	1029
	<i>Andreas Pfaltz and Sharon Bell</i>	
29.1	Introduction	1029
29.2	Oxazoline-Derived P,N Ligands	1030
29.2.1	Phosphino-oxazolines	1030
29.2.2	Phosphite and Phosphinite Oxazolines	1033
29.2.3	Oxazoline-Derived Ligands Containing a P–N Bond	1036
29.2.4	Structurally Related Ligands	1038
29.3	Pyridine and Quinoline-Derived P,N Ligands	1040
29.4	Carbenoid Imidazolylidene Ligands	1042
29.5	Metallocenes	1043
29.6	Other Ligands	1044
29.7	Conclusions	1046
	Abbreviations	1046
	References	1047
30	Enantioselective Hydrogenation of Unfunctionalized Alkenes	1049
	<i>Andreas Pfaltz and Sharon Bell</i>	
31	Mechanism of Enantioselective Hydrogenation	1073
	<i>John M. Brown</i>	
32	Enantioselective Ketone and β-Keto Ester Hydrogenations (Including Mechanisms)	1105
	<i>Takeshi Ohkuma and Ryoji Noyori</i>	

- 33 **Rhodium-Catalyzed Enantioselective Hydrogenation of Functionalized Ketones** 1165
André Mortreux and Abdallah Karim
- 34 **Enantioselective Hydrogenation of C=N Functions and Enamines** 1193
Felix Spindler and Hans-Ulrich Blaser
- 35 **Enantioselective Transfer Hydrogenation** 1215
A. John Blacker
- 36 **High-Throughput Experimentation and Ligand Libraries** 1245
Johannes G. de Vries and Laurent Lefort
- 37 **Industrial Applications** 1279
Hans-Ulrich Blaser, Felix Spindler, and Marc Thommen
- Part V Phase Separation in Homogeneous Hydrogenation**
- 38 **Two-Phase Aqueous Hydrogenations** 1327
Ferenc Joó and Ágnes Kathó
- 39 **Supercritical and Compressed Carbon Dioxide as Reaction Medium and Mass Separating Agent for Hydrogenation Reactions using Organometallic Catalysts** 1361
Walter Leitner
- 40 **Fluorous Catalysts and Fluorous Phase Catalyst Separation for Hydrogenation Catalysis** 1377
Elwin de Wolf and Berth-Jan Deelman
- 41 **Catalytic Hydrogenation using Ionic Liquids as Catalyst Phase** 1389
Peter Wasserscheid and Peter Schulz
- 42 **Immobilization Techniques** 1421
Imre Tóth and Paul C. van Geem

Part VI Miscellaneous Topics in Homogeneous Hydrogenation

**43 Transition Metal-Catalyzed Regeneration
of Nicotinamide Cofactors 1471**

Stephan Lütz

**44 Catalyst Inhibition and Deactivation
in Homogeneous Hydrogenation 1483**

Detlef Heller, André H. M. de Vries, and Johannes G. de Vries

**45 Chemical Reaction Engineering Aspects
of Homogeneous Hydrogenations 1517**

Claude de Bellefon and Nathalie Pestre

Subject Index 1547

Contents

- Part I Introduction, Organometallic Aspects and Mechanism of Homogeneous Hydrogenation**
- 1 Rhodium 3**
Luis A. Oro and Daniel Carmona
- 2 Iridium 31**
Robert H. Crabtree
- 3 Ruthenium and Osmium 45**
Robert H. Morris
- 4 Palladium and Platinum 71**
Paolo Pelagatti
- 5 Nickel 93**
Elisabeth Bouwman
- 6 Hydrogenation with Early Transition Metal, Lanthanide and Actinide Complexes 111**
Christophe Copéret
- 7 Ionic Hydrogenations 153**
R. Morris Bullock
- 8 Homogeneous Hydrogenation by Defined Metal Clusters 199**
Roberto A. Sánchez-Delgado
- 9 Homogeneous Hydrogenation: Colloids – Hydrogenation with Noble Metal Nanoparticles 217**
Alain Roucoux and Karine Philippot

- 10 **Kinetics of Homogeneous Hydrogenations:
Measurement and Interpretation** 257
Hans-Joachim Drexler, Angelika Preetz, Thomas Schmidt, and Detlef Heller
- Part II Spectroscopic Methods in Homogeneous Hydrogenation**
- 11 **Nuclear Magnetic Resonance Spectroscopy
in Homogeneous Hydrogenation Research** 297
N. Koen de Vries
- 12 **Parahydrogen-Induced Polarization: Applications
to Detect Intermediates of Catalytic Hydrogenations** 313
Joachim Bargon
- 13 **A Tour Guide to Mass Spectrometric Studies
of Hydrogenation Mechanisms** 359
Corbin K. Ralph, Robin J. Hamilton, and Steven H. Bergens
- Part III Homogeneous Hydrogenation by Functional Groups**
- 14 **Homogeneous Hydrogenation of Alkynes and Dienes** 375
Alexander M. Kluwer and Cornelis J. Elsevier
- 15 **Homogeneous Hydrogenation of Aldehydes, Ketones, Imines
and Carboxylic Acid Derivatives: Chemoselectivity
and Catalytic Activity** 413
Matthew L. Clarke and Geoffrey J. Roff
- 16 **Hydrogenation of Arenes and Heteroaromatics** 455
Claudio Bianchini, Andrea Meli, and Francesco Vizza
- 17 **Homogeneous Hydrogenation of Carbon Dioxide** 489
Philip G. Jessop
- 18 **Dehalogenation Reactions** 513
Attila Sisak and Ottó Balázs Simon
- 19 **Homogeneous Catalytic Hydrogenation of Polymers** 547
Garry L. Rempel, Qinmin Pan, and Jialong Wu
- 20 **Transfer Hydrogenation Including
the Meerwein-Ponndorf-Verley Reduction** 585
Dirk Klomp, Ulf Hanefeld, and Joop A. Peters

- 21 **Diastereoselective Hydrogenation** 631
Takamichi Yamagishi
References 708
- 22 **Hydrogen-Mediated Carbon–Carbon Bond Formation Catalyzed by Rhodium** 713
Chang-Woo Cho and Michael J. Krische
- Part IV Asymmetric Homogeneous Hydrogenation**
- 23 **Enantioselective Alkene Hydrogenation: Introduction and Historic Overview** 745
David J. Ager
- 24 **Enantioselective Hydrogenation: Phospholane Ligands** 773
Christopher J. Cobley and Paul H. Moran
- 25 **Enantioselective Hydrogenation of Alkenes with Ferrocene-Based Ligands** 833
Hans-Ulrich Blaser, Matthias Lotz, and Felix Spindler
- 26 **The other Bisphosphine Ligands for Enantioselective Alkene Hydrogenation** 853
Yongxiang Chi, Wenjun Tang, and Xumu Zhang
- 27 **Bidentate Ligands Containing a Heteroatom–Phosphorus Bond** 883
Stanton H. L. Kok, Terry T.-L. Au-Yeung, Hong Yee Cheung, Wing Sze Lam, Shu Sun Chan, and Albert S. C. Chan
- 28 **Enantioselective Alkene Hydrogenation: Monodentate Ligands** 995
Michel van den Berg, Ben L. Feringa, and Adriaan J. Minnaard
- 29 **P,N and Non-Phosphorus Ligands** 1029
Andreas Pfaltz and Sharon Bell

30	Enantioselective Hydrogenation of Unfunctionalized Alkenes	1049
	<i>Andreas Pfaltz and Sharon Bell</i>	
30.1	Introduction	1049
30.2	Terminal Alkenes	1050
30.2.1	2-Aryl-1-Butenes	1050
30.2.2	Other Terminal Alkenes	1054
30.3	Trisubstituted Alkenes	1056
30.3.1	Introduction	1056
30.3.2	Ir Catalysts	1057
30.3.3	Standard Test Substrates	1057
30.3.4	Other Substrates	1063
30.4	Tetrasubstituted Alkenes	1066
30.4.1	Substrates	1066
30.5	Dienes and Trienes	1067
30.6	Conclusions	1069
	Abbreviations	1070
	References	1070
31	Mechanism of Enantioselective Hydrogenation	1073
	<i>John M. Brown</i>	
31.1	Introduction	1073
31.2	Rhodium-Catalyzed Hydrogenations	1074
31.2.1	Background	1074
31.2.2	More Recent Developments	1076
31.2.3	Transient and Reactive Intermediates in Rhodium Enantioselective Hydrogenation	1078
31.2.4	Mnemonics for the Sense of Enantioselective Hydrogenation	1082
31.2.5	Status of the Computational Study of Rhodium-Complex-Catalyzed Enantioselective Hydrogenation	1082
31.2.6	Monophosphines in Rhodium-Complex-Catalyzed Enantioselective Hydrogenation	1086
31.2.7	Mechanism of Hydrogenation of β -Dehydroamino Acid Precursors	1087
31.2.8	Current Status of Rhodium Hydrogenations	1088
31.3	Ruthenium-Complex-Catalyzed Hydrogenations	1093
31.3.1	Reactive Intermediates in Ruthenium-Complex-Catalyzed Hydrogenations	1093
31.3.2	Kinetic Analysis of Ruthenium-Complex-Catalyzed Hydrogenations	1093
31.4	Iridium-Complex-Catalyzed Hydrogenations	1094
31.4.1	Background	1094
31.4.2	Mechanistic and Computational Studies	1095
31.4.3	Counter-Ion Effects	1097
31.5	Summary and Conclusions	1098
	Acknowledgments	1099

Abbreviations 1099

References 1099

32 Enantioselective Ketone and β -Keto Ester Hydrogenations (Including Mechanisms) 1105

Takeshi Ohkuma and Ryoji Noyori

- 32.1 Chiral Ligands 1105
 - 32.2 β -Keto Esters and Analogues 1107
 - 32.2.1 β -Keto Esters 1107
 - 32.2.2 1,3-Diketones 1122
 - 32.2.3 β -Keto Phosphonates, Sulfonates, and Sulfones 1125
 - 32.2.4 Dynamic Kinetic Resolution 1127
 - 32.3 Simple Ketones 1131
 - 32.3.1 Alkyl Aryl Ketones 1131
 - 32.3.2 Hetero-Substituted Aromatic Ketones 1141
 - 32.3.3 Diaryl Ketones 1144
 - 32.3.4 Heteroaromatic Ketones 1144
 - 32.3.5 Dialkyl Ketones 1147
 - 32.3.6 Unsaturated Ketones 1148
 - 32.3.7 Kinetic Resolution and Dynamic Kinetic Resolution 1150
 - 32.3.8 Enantioselective Activation and Deactivation 1154
- Abbreviations 1156
References 1156

33 Rhodium-Catalyzed Enantioselective Hydrogenation of Functionalized Ketones 1165

André Mortreux and Abdallah Karim

- 33.1 Introduction 1165
 - 33.2 Basic Principles of Ketone Hydrogenation on Rhodium Catalysts 1166
 - 33.3 Enantioselective Hydrogenation of Ketoesters 1166
 - 33.3.1 Enantioselective Hydrogenation of Ketopantoyllactone (KPL) 1166
 - 33.3.2 Hydrogenation of Ketoesters and Ketoamides 1172
 - 33.3.2.1 α -Ketoesters and Ketoamides 1172
 - 33.3.2.2 α,γ -Diketoesters 1176
 - 33.3.3 Hydrogenation of Amino Ketones 1177
 - 33.3.3.1 α -Amino Ketones 1177
 - 33.3.3.2 β - and γ -Amino Ketones 1184
 - 33.4 Enantioselective Hydrogenation of Fluoroketones 1186
 - 33.5 Conclusions 1188
- Abbreviations and Acronyms 1189
References 1189

34	Enantioselective Hydrogenation of C=N Functions and Enamines	1193
	<i>Felix Spindler and Hans-Ulrich Blaser</i>	
34.1	Introduction	1193
34.2	Chiral Ligands	1195
34.3	N-Aryl Imines	1197
34.4	N-Alkyl Imines	1200
34.5	Cyclic Imines and Heteraromatic Substrates	1202
34.6	Miscellaneous C=N–X Systems	1204
34.7	Enamines	1206
34.8	Mechanistic Aspects	1207
34.9	Alternative Reduction Systems	1209
34.10	Assessment of Catalysts and Conclusions	1210
34.10.1	Iridium Complexes	1210
34.10.2	Rhodium Complexes	1211
34.10.3	Ruthenium Complexes	1211
34.10.4	Titanium Complexes	1211
	Abbreviations	1212
	References	1212
35	Enantioselective Transfer Hydrogenation	1215
	<i>A. John Blacker</i>	
35.1	Introduction	1215
35.2	Homogenous Metal Catalysts	1216
35.2.1	Early studies	1216
35.2.2	Group VIII Metal Catalysts	1217
35.2.3	Chiral Ligands	1218
35.2.4	Immobilized Ligands	1220
35.2.5	Water-Soluble Ligands	1221
35.2.6	Catalyst Selection	1221
35.2.7	Catalyst Preparation	1222
35.2.8	The Reaction Mechanism	1223
35.3	Hydrogen Donors	1224
35.3.1	The IPA System	1224
35.3.2	The TEAF System	1225
35.3.3	Other Hydrogen Donors	1229
35.4	Substrates and Products	1229
35.4.1	Aldehydes	1229
35.4.2	Ketones	1229
35.4.3	Aldimines	1231
35.4.4	Ketimines	1232
35.4.5	Alkenes	1235
35.5	Solvents	1235
35.6	Reaction Conditions, Optimization, and Scale-Up	1236
35.6.1	Temperature	1236

35.6.2	Productivity	1237
35.6.3	Reaction Control	1238
35.6.4	Large-Scale Processes	1239
35.7	Discussion	1239
	Abbreviations	1240
	References	1241
36	High-Throughput Experimentation and Ligand Libraries	1245
	<i>Johannes G. de Vries and Laurent Lefort</i>	
36.1	Introduction	1245
36.2	High-Throughput Experimentation	1248
36.2.1	Serial Mode	1248
36.2.2	Parallel Experimentation	1249
36.2.3	Combinatorial Protocols	1249
36.3	Generating and Testing Libraries of Catalysts and Ligands	1250
36.3.1	Libraries of Individually Synthesized Ligands	1250
36.3.2	Automated Synthesis of Ligand Libraries	1258
36.3.3	Mixtures of Chiral Monodentate Ligands	1263
36.3.4	Mixtures of Chiral Monodentate Ligands and Nonchiral Ligands	1267
36.3.5	Supramolecular Approaches to Ligand Libraries	1270
36.4	Methodology for Testing Catalysts	1272
36.5	High-Throughput Analysis	1273
36.6	Conclusions	1274
	Abbreviations	1275
	References	1275
37	Industrial Applications	1279
	<i>Hans-Ulrich Blaser, Felix Spindler, and Marc Thommen</i>	
37.1	Introduction and Scope of the Chapter	1279
37.2	Requirements for Technical-Scale Applications	1280
37.2.1	Catalyst Performance	1281
37.2.2	Availability and Cost of the Catalyst	1281
37.2.3	Development Time	1282
37.3	Process Development and Equipment	1283
37.4	Industrial Processes: General Comments	1284
37.5	Chemo- and Diastereoselective Hydrogenations	1286
37.6	Enantioselective Hydrogenation of C=C Bonds	1287
37.6.1	Dehydro α -Amino Acid Derivatives	1287
37.6.1.1	L-Dopa (Monsanto, VEB Isis-Chemie)	1288
37.6.1.2	Aspartame (Enichem/Anic, Degussa)	1289
37.6.1.3	Various Pilot- and Bench-Scale Processes for α -Amino Acid Derivatives	1289
37.6.2	Dehydro β -Amino Acid Derivatives	1292
37.6.3	Simple Enamides and Enol Acetates	1293

37.6.4	Itaconic Acid Derivatives	1293
37.6.5	Allylic Alcohols and α,β -Unsaturated Acids	1294
37.6.5.1	Allylic Alcohols	1295
37.6.5.2	α,β -Unsaturated Acids	1296
37.6.6	Miscellaneous C=C Systems	1298
37.6.6.1	Hydrogenation of a Biotin Intermediate (Lonza)	1299
37.6.6.2	Synthesis of (+)-Methyl <i>cis</i> -Dihydrojasmonate (Firmenich)	1300
37.6.6.3	Intermediate for Tipranavir (Chirotech)	1300
37.6.6.4	Various C=C Substrates	1302
37.7	Enantioselective Hydrogenation of C=O Bonds	1302
37.7.1	α -Functionalized Ketones	1302
37.7.2	β -Functionalized Ketones	1305
37.7.3	Aromatic Ketones	1307
37.8	Enantioselective Hydrogenation of C=N Bonds	1308
37.9	Ligands and Metal Complexes for Large-Scale Applications	1311
37.9.1	Companies Offering Services, Technology, Ligands and Catalysts	1312
37.9.2	Chiral Ligands with Established Industrial Performance	1313
37.9.3	Metal Complexes and Anions	1313
37.9.4	Intellectual Property Aspects	1317
37.10	Conclusions and Future Developments	1317
	Acknowledgments	1319
	Abbreviations	1319
	References	1319

Part V Phase Separation in Homogeneous Hydrogenation

38	Two-Phase Aqueous Hydrogenations	1327
	<i>Ferenc Joó and Ágnes Kathó</i>	
38.1	Introduction	1327
38.2	Two-Phase Hydrogenation of Alkenes, Alkynes, and Arenes	1334
38.3	Enantioselective Hydrogenation of Alkenes in Two-Phase Aqueous Systems	1338
38.4	Aqueous Two-Phase Hydrogenation of Aldehydes and Ketones	1344
38.5	Aqueous Two-Phase Hydrogenations of Nitro-Compounds, Imines, Nitriles, Oximes, and Heteroaromatics	1352
38.6	Conclusions	1354
	Abbreviations	1355
	References	1355

- 39 Supercritical and Compressed Carbon Dioxide as Reaction Medium
and Mass Separating Agent for Hydrogenation Reactions
using Organometallic Catalysts 1361**
Walter Leitner
- 39.1 Introduction 1361
- 39.2 The Molecular and Reaction Engineering Basis
of Organometallic-Catalyzed Hydrogenations using Compressed
and scCO₂ 1362
- 39.2.1 Control of Hydrogen Availability 1362
- 39.2.2 Catalyst Recycling and Immobilization 1363
- 39.2.2.1 Solubility Control for Separation 1364
- 39.2.2.2 Membrane Separation 1364
- 39.2.2.3 Biphasic Liquid/Supercritical Systems 1364
- 39.2.2.4 Inverted Biphasic Systems 1364
- 39.2.2.5 Solid-Supported Catalysts 1365
- 39.2.3 Catalytic Systems for Hydrogenation using SCFs,
and their Synthetic Applications 1365
- 39.2.4 Mechanistic Aspects 1371
- 39.3 Conclusions and Outlook 1373
- Abbreviations 1374
- References 1374
-
- 40 Fluorous Catalysts and Fluorous Phase Catalyst Separation
for Hydrogenation Catalysis 1377**
Elwin de Wolf and Berth-Jan Deelman
- 40.1 Introduction 1377
- 40.2 Catalysts Based on Fluorous Alkylphosphines, -Phosphinites,
-Phosphonites, and -Phosphites 1378
- 40.3 Catalysts Based on Perfluoroalkyl-Substituted Arylphosphines 1380
- 40.4 Fluorous Anions for the Separation of Cationic Hydrogenation
Catalysts 1384
- 40.5 Catalysts Based on Nonphosphorus Ligands 1386
- 40.6 Enantioselective Hydrogenation Catalysts 1386
- 40.7 Conclusions 1386
- Abbreviations 1387
- References and Notes 1387
-
- 41 Catalytic Hydrogenation using Ionic Liquids
as Catalyst Phase 1389**
Peter Wasserscheid and Peter Schulz
- 41.1 Introduction to Ionic Liquids 1389
- 41.2 Homogeneous Catalyzed Hydrogenation in Biphasic Liquid–Liquid
Systems 1394
- 41.2.1 Hydrogenation of Olefins 1394
- 41.2.2 Hydrogenation of Arenes 1397

41.2.3	Hydrogenation of Polymers	1400
41.2.4	Stereoselective Hydrogenation	1401
41.2.5	Ketone and Imine Hydrogenation in Ionic Liquids	1407
41.2.6	Imine Hydrogenation	1411
41.3	Homogeneous Catalyzed Hydrogenation in Biphasic Ionic Liquid/Supercritical (sc)CO ₂ System	1412
41.4	Supported Ionic Liquid Phase Catalysis	1413
41.5	Conclusion	1416
	Abbreviations	1417
	References	1417

42 Immobilization Techniques 1421

Imre Tóth and Paul C. van Geem

42.1	Introduction	1421
42.2	Engineering and Experimental Aspects	1422
42.3	Immobilization Methods	1424
42.3.1	Physical Methods of Immobilization	1426
42.3.1.1	Physisorption of Metal Complexes	1427
42.3.1.2	Weak Chemisorption: Supported Hydrogen-Bonded (SHB) Catalysts	1427
42.3.2	Encapsulated Homogeneous Catalysts	1430
42.3.2.1	Synthesis of SIB Catalysts	1431
42.3.2.2	Application of SIB Catalysts	1433
42.3.3	Catalysts Entangled in a Polymer	1434
42.3.4	Catalyst Dissolved in a Supported Liquid-Phase	1435
42.3.4.1	Supported Aqueous-Phase Catalysis	1436
42.3.4.2	Hybrid SLP Systems	1437
42.3.5	Covalently Bound Metal Centers	1438
42.3.6	Covalent Attachment of Ligands	1439
42.3.6.1	Grafting to Oxide Supports	1440
42.3.6.2	Sol–Gel Method	1441
42.3.6.3	Anchoring with Organic Phosphonates	1442
42.3.6.4	Attachment to Polymer Supports	1444
42.3.6.4.1	Functionalized Polymers as Supports	1444
42.3.6.4.2	Enzymes as Support	1448
42.3.6.4.3	Functionalized Monomers	1448
42.3.6.4.4	Dendrimers as Supports: Membrane Filtration	1453
42.3.6.4.5	Grafting to Polymers	1454
42.3.7	Ionic Bonding of Metals to Supports	1455
42.3.7.1	Ionically Bound Metal Centers on Inorganic Supports	1455
42.3.7.2	Ionically Bound Metal Centers on Polymer Supports	1456
42.3.8	Attachment of Ligands via Ion Exchange	1457
42.4	Catalyst Deactivation	1461
42.5	Conclusions	1462
42.6	Outlook	1462

Abbreviations 1463

References 1463

Part VI Miscellaneous Topics in Homogeneous Hydrogenation

43 Transition Metal-Catalyzed Regeneration of Nicotinamide Cofactors 1471

Stephan Lütz

43.1 Introduction 1471

43.2 Enzymatic Cofactor Regeneration 1474

43.3 Electrochemical Cofactor Regeneration 1475

43.4 Chemical Cofactor Regeneration 1477

43.5 Other Chemical Cofactor Regeneration Procedures 1479

43.6 Conclusions and Outlook 1479

Acknowledgments 1480

Abbreviations 1480

References 1480

44 Catalyst Inhibition and Deactivation in Homogeneous Hydrogenation 1483

Detlef Heller, André H. M. de Vries, and Johannes G. de Vries

44.1 Introduction 1483

44.2 Mechanisms of Catalyst Inhibition 1484

44.3 Induction Periods 1485

44.3.1 Introduction 1485

44.3.2 Induction Period Caused by Slow Hydrogenation of COD or NBD 1486

44.4 Substrate and Product Inhibition 1494

44.5 Reversible Inhibition Caused by Materials that can Function as Ligand 1499

44.5.1 Catalyst Deactivation Caused by Solvents 1500

44.5.2 Catalyst Inhibition Caused by Compounds Containing Heteroatoms 1503

44.5.3 Inhibition by CO and sources of CO 1504

44.5.4 Inhibition by Acids and Bases 1505

44.6 Irreversible Deactivation 1507

44.6.1 Inhibition by Anions 1507

44.6.2 Inhibition by Oxidation and by Ligand Modification 1507

44.6.3 Formation of Dimers, Trimers, Clusters, Colloids, and Solids 1509

44.7 Conclusions 1512

Abbreviations 1513

References 1513

45	Chemical Reaction Engineering Aspects of Homogeneous Hydrogenations 1517 <i>Claude de Bellefon and Nathalie Pestre</i>
45.1	Introduction 1517
45.2	Fundamentals 1518
45.2.1	Basics of Mass Transfer in Gas–Liquid Systems 1518
45.2.2	Physical and Chemical Data for Hydrogenations 1521
45.2.2.1	Heat of Reaction 1522
45.2.2.2	Solubility 1522
45.2.2.3	Diffusivity 1525
45.2.3	Coupling Between Mass Transfer and a Single Homogeneous Irreversible Reaction 1526
45.2.4	Coupling of Reaction and Mass Transfer in Ideal Reactors 1533
45.2.4.1	Mass Balance for a Batch Reactor 1534
45.2.4.2	Mass Balance for a CSTR Reactor 1535
45.2.4.2.1	Simplified Mass Balances 1535
45.2.4.3	Mass Balance for a Plug Flow Reactor 1536
45.3	Industrial Reactor and Scale-Up Issues 1536
45.4	Future Developments 1541
	Nomenclature 1542
	Abbreviations 1544
	References 1544
	Subject Index 1547

Foreword

Homogeneous hydrogenation of organic compounds catalyzed by metal complexes is undoubtedly the most studied of the entire class of homogeneously catalyzed reactions. Indeed, advances in hydrogenation systems have contributed significantly to progress in homogeneous catalysis more generally, mainly because of the involvement of intermediate metal hydrides in a wider range of catalytic processes. The historical development of homogeneous hydrogenation is documented in my 1973 text on this topic, which was intended to represent an exhaustive treatise on the subject (the process, prior to the computer era, was certainly *exhausting* as over 1900 multi-language references were compiled).

Before outlining the content of *The Handbook of Homogeneous Hydrogenation*, I will briefly note here a few early facts chronologically for the appropriate context. Melvin Calvin first used the term “homogeneous hydrogenation” in 1938 for some non-aqueous, Cu-based systems, and a year later an M. Iguchi was the first to record the use of Rh species for hydrogenations in aqueous media. Jack Halpern was the first to study (in the mid-1950s) the kinetics and detailed mechanisms of such hydrogenations, while notably R.J.P. (Bob) Williams was the first (in 1960) to suggest in an equation the possibility of an $M(H_2)$ species, long before their true characterization in the early 1980s! The majority of the systems studied up to the early 1960s (for homogeneous catalysis generally, as well as hydrogenations) were in aqueous media – a fact frequently overlooked by current researchers – but developments at that time in the isolation and characterization of transition metal hydrides (pioneered especially by Joseph Chatt’s group), including their stabilization by tertiary phosphines, led to increased studies in non-aqueous systems. Cleaner and “greener” aqueous systems are preferred for industrial processes, and intense interest remains in the incorporation of, for example, water-solubility enhancing, polar groups (sulfonate, carboxylate, hydroxide, etc.) into phosphine-containing ligands, protonation of N-atoms in P-N donor ligand, and more general use of cationic or anionic species for catalysis. The completion of the cycle back to aqueous systems is now in progress.

The classic 1961 paper by Halpern *et al.* (the ‘*al.*’ being John Harrod and myself) on the catalytic hydrogenation of unsaturated acids using chlororuthenium(II) species in aqueous acid solutions certainly motivated the work of Geoffrey Wilkinson’s group on Ru- and Rh-triphenylphosphine hydrogenation catalysts; these

findings, published in the mid-1960s, are now legendary. The next highly significant step was the use of chiral phosphines with Rh precursors, first reported in 1968 by the groups of Knowles and Horner, the work providing the first examples of catalytic enantioselective hydrogenation (of unsaturated acids and α -substituted styrenes). Thousands of subsequent publications have recorded the development of catalyst systems containing chiral ligands (such as phosphines, sulfoxides, oxazolines, nitrogen-ligands, combinations of P/N/O/S-donors, carbenes, etc.) for hydrogenation of a wide range of prochiral substrates including alkenes, ketones, and ketimines. Processes reaching close to 100% enantiomeric excess (e.e.) are no longer uncommon, and, in a few cases, a remarkable degree of understanding of the mechanistic pathways has been achieved. About one dozen industrial, catalytic enantioselective homogeneous hydrogenation processes are now operating, and the potential for chiral catalyst systems within fine chemical industries (particularly for pharmaceuticals and agrochemicals) remains enormous. The first such process, that went on-line in 1970, was for the synthesis of L-dopa, a drug for treatment of Parkinson's disease; the system involved hydrogenation of a prochiral enamide using a Rh-chiral phosphine catalyst. In the production of the herbicide Metolachlor, a process that went on-line in 1996, a chiral amine is generated by hydrogenation of a ketimine using an Ir catalyst, and this currently provides the largest scale industrial process for an enantioselective synthesis of any type. The discovery and explanation of non-linear effects in enantioselective reactions, first reported by Kagan's group in 1986, are also noteworthy, and should lead to improved applications in enantioselective synthesis and, more importantly, a better understanding of the origins of enantioselectivity.

Advances thus far in experimental enantioselective hydrogenation have stemmed largely from empirical studies. More trendy and certainly more effective is high-throughput experimentation using ligand libraries, a methodology that is being increasingly promoted by researchers in the fine-chemical industries. Novel attempts to find the best catalyst by purely theoretical work that involves screening virtual catalyst libraries are also being published.

Hydrogenation catalysis in the petrochemical and related industries remains in the domain of heterogeneous systems, because of the practicality of separating and recycling the catalyst, although advances in the use of multiphase systems might find eventually use in relatively small-scale systems where a requirement is high selectivity, a vital property that can be engineered with a homogeneous catalyst. The design of supported metal complexes, including dendrimers, the use of size-exclusion filtration methodology, and the use of biphasic systems with all their ramifications (fluorous solvents, ionic liquids, and supercritical fluids), continue to be areas of intense current interest, and the findings should lead to further industrial uses of homogeneous catalysts, particularly in the small-scale synthesis of high value products.

The classic division between heterogeneous and homogeneous catalysts appears to be becoming increasingly blurred and, in some cases involving colloidal/nanoparticle and metal cluster catalysts, the difference is difficult to determine experimentally. The large majority of reported homogeneous hydrogenation cat-

alysts for aromatic residues now appear to be colloidal systems; in terms of activity within a particular reaction, the true nature of a catalyst may be considered somewhat irrelevant, but this is key when catalyst separation/removal for the purposes of recycling and residual toxicity levels is considered.

The exponential increase in the homogeneous hydrogenation literature over the last three decades shows no sign of abatement, and indeed, with the “replacement” of phosphine ligands by the increasingly popular carbenes, and the use of various two- and multi-phase systems, a further endemic literature expansion in homogeneous catalysis, and especially in the most understood area of hydrogenation, is guaranteed.

There is no question that much general knowledge on homogeneous catalysis has stemmed from studies on homogeneous hydrogenation, and it is fitting that *The Handbook of Homogeneous Hydrogenation* is published about 50 years after Halpern's first reports on the mechanistic aspects of such reactions. The editors have assembled an impressive list of eighty-one international experts that review the field from several aspects noted above. The first six chapters are categorized according to the catalyst metal used (most often the more traditional group 8–10 noble metals, although data on the early transition metals are presented), and there are chapters on the use of metal clusters and nanoparticles. A separate chapter appears on the kinetics commonly observed in hydrogenation systems, and there is one chapter on ionic hydrogenations. Three well-known techniques for studying homogeneous hydrogenation are then each presented in a chapter that discuss: NMR methods in general, the PHIP (parahydrogen induced polarization) NMR method, and the application of mass spectrometry. There are chapters on hydrogenation of organic substrates that are generally assembled according to the nature of the unsaturated function present in the organic, while separate chapters describe hydrogen transfer processes, CO₂ hydrogenation, and Rh-catalyzed, hydrogen-mediated, carbon-carbon bond formation. A large number of the chapters appropriately cover the many aspects of enantioselective hydrogenation, including a synopsis of current industrial applications. The final chapters deal with the fundamental problem associated with applications of homogeneous catalysis: deactivation, separation and recovery of the catalyst, and related engineering aspects.

The editors and authors are to be congratulated on assembling what is destined to become a classic in the area of Homogeneous Hydrogenation, which over the years has earned its title in capital letters.

Brian R. James
(University of British Columbia)

Preface

It is truly astonishing that such a simple reaction as the addition of one molecule of hydrogen to a double or triple bond can have so many facets.

When we had chosen the title of Handbook of Homogeneous Hydrogenation for our book we meant it to be a comprehensive work of reference. In this respect we are quite satisfied. We only had to skip the chapter on dehydrogenations, for which we could not find an author. We are extremely grateful to the other 88 authors for dedicating so much of their valuable time to writing the 81 marvellous chapters included in these volumes. We had envisaged an average of 30 pages per chapter but in the end this was not enough, necessitating an expansion of the two projected volumes to three.

One may wonder how long this handbook remains up-to-date. Indeed many areas are continuously undergoing new developments. In addition, new topics that were hardly emerging five years ago seem to develop at a very fast pace. Colloidal hydrogenation catalysts, for instance, which until recently were seen as the Cinderella of both homogeneous and heterogeneous catalysis – too soluble to be heterogeneous and too ill-defined to be homogeneous – have become quite respectable since they were recognized to be part of nanotechnology. Reductive coupling reactions can be considered as a green method to construct carbon-carbon bonds without taking resort to leaving groups. Indeed, not only this class of reactions, but all hydrogenations are of course extremely environmentally benign. Also the number of substrates is continuously expanding; carboxylic acid derivatives and heteroarenes are good examples of substrates recently added to the existing pool.

Just when everyone thought the chiral-ligand-boom was coming to an end, extremely simple monodentate ligands turned out to be quite effective, also allowing a combinatorial approach using mixtures of ligands. There is now a bewildering choice of chiral ligands available, increasing the chances of application. Indeed, the number of industrial applications is steadily increasing; an important breakthrough in this area was the advent of high throughput experimentation, which allowed for the first time to find a chiral ligand with good performance within a matter of weeks.

Our insight into the mechanisms of hydrogenation reactions has grown tremendously, thanks to advances in spectroscopic techniques, but also thanks to the hard work of many organometallic chemists. Many authors now also recog-

nise the importance of the rate of these reactions. Turnover frequencies of hydrogenations are listed throughout the book.

One aspect that remains underdeveloped is the insight in deactivation pathways. Our knowledge in this area is growing, but the pace is slow. We have devoted an entire chapter to this topic, since the economics of many processes could benefit a lot from more insight in ways to reduce catalyst deactivation.

So far none of the industrial processes recycle the catalyst. Yet the number of ways to do this has grown far beyond simple immobilization. Two-phase catalysis now comes in many flavours.

Looking into the future, we expect that hydrogenation reactions will also be tremendously important for the conversion of renewable resources. Going from carbohydrates to valuable chemicals will require deoxygenating reactions. Thus, hydrogenation of alcohols, aldehydes and carboxylic acids will become very important topics.

We hope the readers will appreciate as well as enjoy the contents of this book. Any comments you may have are of course very welcome.

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