

Contents

Foreword *xi*

Preface *xiii*

Abbreviations *xvii*

1	Catalysis and Prerequisites for the Modern Pharmaceutical Industry Landscape	1
1.1	Introduction	1
1.2	Key Historical Moments in Catalysis Development	2
1.3	Key Historical Developments in Catalysis for API Synthesis: Including Catalytic Asymmetric Synthesis	11
1.4	Catalytic Synthesis of APIs in the Twenty-First Century: New Developments, Paradigm Shifts, and Future Challenges	20
1.5	Conclusions	26
	References	26
2	Catalytic Process Design: The Industrial Perspective	31
2.1	Introduction	31
2.2	Process Design	32
2.2.1	Heterogeneous and Homogeneous Catalysts	32
2.2.2	Product Safety and Regulatory Requirements	36
2.2.3	Control of Residual Metals	37
2.2.3.1	Filtration and Adsorption	38
2.2.3.2	Extraction and Scavenging	38
2.2.3.3	Organic Solvent Nanofiltration (OSN)	41
2.2.4	Design of Experiment (DoE)	43
2.2.5	Catalyst Recycling	45
2.2.6	Scalability, Safety, and Environmental Aspects	46
2.3	Examples of Homogeneous and Heterogeneous Catalytic Reactions in API Manufacture	49
2.3.1	Batch Operations	49
2.3.2	Continuous-Flow Operations	63
2.4	Conclusions	67
	References	68

3	Hydrogenation, Hydroformylation, and Other Reductions	75
3.1	Introduction	75
3.2	Hydrogenation	75
3.2.1	Hydrogenation of Alkenes	77
3.2.1.1	Enamides	77
3.2.2	Hydrogenation of Carbonyl Groups	84
3.2.3	Hydrogenation of Imines	87
3.3	Transfer Hydrogenation	88
3.3.1	On Ketones	88
3.3.2	On Imines	92
3.4	Reductions with Oxazaborolidine Catalytic Systems	94
3.5	Hydroformylation	96
3.6	Reductions with Organocatalysts	103
3.7	Other Catalytic Reductions	104
3.7.1	Reduction of Nitro Units	104
3.7.2	Other Reductions	107
3.8	Conclusions	107
	References	108
4	Oxidation: Nobel Prize Chemistry Catalysis	113
4.1	Introduction	113
4.2	Olefin Epoxidation	113
4.2.1	Metal-based Electrophilic Methods	113
4.2.1.1	The Sharpless–Katsuki Asymmetric Epoxidation	113
4.2.1.2	The Jacobsen–Katsuki Asymmetric Epoxidation	116
4.2.2	Nucleophilic Methods	119
4.2.2.1	Nucleophilic Methods with Hydrogen Peroxide	119
4.2.3	Organocatalytic Methods	119
4.3	Olefin Dihydroxylation	121
4.4	Olefin Aminohydroxylation	125
4.5	Sulfur Oxidation	127
4.5.1	Synthesis of Sulfoxides – Use of Titanium, Molybdenum, and Vanadium Catalysts	127
4.5.2	Synthesis of Sulfones – Use of Tungsten Catalysts	132
4.6	Catalytic Oxidation of Carbonyls – Cu/Nitroxyl and Nitroxyl/NO _x Catalytic Systems	133
4.7	Oxidative Dehydrogenations (ODs)	139
4.8	Conclusions	141
	References	142
5	Catalytic Addition Reactions	147
5.1	Introduction	147
5.2	1,2-Additions	148
5.3	1,4-Additions	158
5.4	Conclusions	170
	References	171

6	Catalytic Cross-Coupling Reactions – Nobel Prize Catalysis	175
6.1	Introduction	175
6.2	Heck–Mizoroki Reaction	176
6.3	The Suzuki–Miyaura Reaction	195
6.4	The Buchwald–Hartwig Reaction	210
6.5	The Sonogashira–Hagihara Reaction	224
6.6	The Allylic Substitution Reaction	234
6.7	C–H Activation Processes	239
6.8	Oxidative C–C Bond Formation	248
6.9	Conclusions	251
	References	251
7	Catalytic Metathesis Reactions: Nobel Prize Catalysis	259
7.1	Introduction	259
7.2	Metathesis with Ru-Based Catalysts	264
7.3	Mo-Based Metathesis	283
7.4	Conclusions	286
	References	286
8	Catalytic Cycloaddition Reactions: Coming Full Circle	291
8.1	Introduction	291
8.2	The “Classical” Catalytic Diels–Alder Reaction – Closing the Circle	291
8.3	The Catalytic Hetero-Diels–Alder (hDA) Reaction	299
8.4	The Catalytic [3+2] Cycloaddition Reaction	302
8.4.1	1,3-Dipolar Azomethine Ylide Cycloadditions	302
8.4.2	[3+2] Cycloadditions with Carbonyl Ylides	307
8.4.3	The Azide Catalytic [3+2] Cycloaddition Reaction – The Dawn of <i>Click Chemistry</i>	308
8.5	Other Cycloaddition Reactions	312
8.5.1	[2+2] Cycloaddition	312
8.5.2	[2+2+2] Cycloaddition	313
8.5.3	[5+2] Cycloaddition	315
8.6	Conclusions	316
	References	317
9	Catalytic Cyclopropanation Reactions	321
9.1	Introduction	321
9.2	Metal-Catalyzed Processes	323
9.3	Conclusions	338
	References	338
10	Catalytic C–H Insertion Reactions	341
10.1	Introduction	341
10.2	Metal-Catalyzed Processes	342
10.3	Conclusions	356
	References	357

11	Phase-Transfer Catalysis	359
11.1	Introduction	359
11.2	Achiral Phase-Transfer Catalysis	360
11.3	Asymmetric Phase-Transfer Catalysis	369
11.4	Conclusions	382
	References	382
12	Biocatalysis	387
12.1	Introduction	387
12.2	Hydrolysis and Reverse Hydrolysis	388
12.3	Reduction	394
12.4	Oxidation	399
12.5	C—X Bond Formation	402
12.6	Conclusions	411
	References	411
	Index	415