

## Contents

### Preface xi

<b>1</b>	<b>Substitution-type Electrophilic Amination Using Hydroxylamine-Derived Reagents</b>	<b>1</b>
	<i>Zhe Zhou and László Kürti</i>	
1.1	Introduction	1
1.2	Cu-Catalyzed Reactions	2
1.3	Electrophilic Amination Reactions Catalyzed by Other Transition Metals	15
1.4	Electrophilic Amination with Hydroxylamine-derived Metallanitrenes	18
1.5	Transition-Metal-Free Electrophilic Amination Reactions	22
1.6	Conclusion	28
	References	28
<b>2</b>	<b>Remote Functionalizations Using Nitrogen Radicals in H-Atom Transfer (HAT) Reactions</b>	<b>31</b>
	<i>Ji Hye Kim, Elizabeth M. Dauncey and Daniele Leonori</i>	
2.1	Introduction	31
2.2	Intramolecular 1,5-H-Atom Transfer (1,5-HAT)	31
2.3	Photoinduced Strategies	34
2.3.1	Reductive Strategies	34
2.3.1.1	1,5-HAT via Iminyl Radicals	34
2.3.1.2	1,5-HAT via Amidyl and Sulfamidyl Radicals	37
2.3.2	Oxidative Strategies	39
2.3.2.1	1,5-HAT via Iminyl Radicals	39
2.3.2.2	1,5-HAT via Amidyl and Sulfamidyl Radicals	40
2.3.3	Photoinduced Bond Homolysis	43
2.4	Thermal Strategies	46
2.5	Summary and Conclusions	50
	References	50

<b>3</b>	<b>Radical-Based C–N Bond Formation in Photo/Electrochemistry</b>	<b>53</b>
	<i>Binbin Huang, Yating Zhao and Wujiong Xia</i>	
3.1	Introduction	53
3.2	C–N Bond Formation via N-radical Species Addition	54
3.2.1	Radical Addition to C–C Double/Triple Bonds	55
3.2.1.1	Amidyl Radical Addition	55
3.2.1.2	Hydrazonyl Radical Addition	62
3.2.1.3	Aminium Radical Cation Addition	64
3.2.2	Radical Species Addition to Aromatic Rings	71
3.3	Amination via N-atom Nucleophilic Addition	77
3.3.1	Aromatic C(sp <sup>2</sup> )—H Bond Amination	77
3.3.2	Olefinic C(sp <sup>2</sup> )—H Bond Amination	82
3.3.3	Activated C(sp <sup>3</sup> )—H Bond Amination	85
3.3.3.1	Benzylidic C(sp <sup>3</sup> )—H Bond Amination	85
3.3.3.2	N- $\alpha$ -C(sp <sup>3</sup> )—H Bond Amination	87
3.4	Amination via Radical Cross-coupling	90
3.4.1	Aryl C(sp <sup>2</sup> )—N Bond Formation via Radical Cross-coupling	90
3.4.1.1	Aryl C(sp <sup>2</sup> )—N Bond Formation Using Diarylamines	91
3.4.1.2	Aryl C(sp <sup>2</sup> )—N Bond Formation Using Azoles	94
3.4.2	Other C–N Bond Formation via Radical Cross-coupling	96
3.5	Summary and Conclusions	98
	References	100
<b>4</b>	<b>Propargylamines: Recent Advances in Asymmetric Synthesis and Use as Chemical Tools in Organic Chemistry</b>	<b>103</b>
	<i>Fei Zhao, Seong-Heun Kim and Daniele Castagnolo</i>	
4.1	Introduction	103
4.2	Metal-Catalyzed Asymmetric Synthesis of Propargylamines	104
4.2.1	Enantioselective A <sup>3</sup> Coupling	104
4.2.1.1	Enantioselective A <sup>3</sup> Coupling Involving Primary Amines	106
4.2.1.2	Enantioselective A <sup>3</sup> Coupling Involving Secondary Amines	108
4.2.2	Enantioselective Propargylic Amination of Propargylic Esters with Amines	112
4.2.3	Cu-Catalyzed Enantioselective Ring Opening of Alkynyl-Substituted Epoxides/Lactones/Carbonates	116
4.2.4	Enantioselective Addition of Terminal Alkynes to Enamines/Enamides	118
4.2.5	Rh/Ru-Catalyzed Enantioselective Hydrogenation of Alkynyl-Substituted Enamines/Imines	120
4.2.6	Enantioselective C–H Activation: Synthesis of Cyclic Propargylamines	123
4.3	Enzymatic Synthesis of Propargylamines	126
4.4	Photoredox Synthesis of Propargylamines	130
4.5	Organocatalyzed Asymmetric Synthesis of Propargylamines	134
4.6	Propargylamines as Building Blocks in the Synthesis of Heterocycles	137
4.6.1	Synthesis of Pyrroles from Propargylamines	138
4.6.2	Synthesis of Pyrrolines from Propargylamines	139

4.6.3	Synthesis of Pyridines from Propargylamines	140
4.6.4	Synthesis of Quinolines from Propargylamines	142
4.6.5	Synthesis of Oxazoles from Propargylamines	145
4.6.6	Synthesis of Thiazoles from Propargylamines	148
4.7	Conclusions	150
	References	150
<b>5</b>	<b>Transition-Metal-Catalyzed Chiral Amines Synthesis</b>	<b>155</b>
	<i>Anton Cunillera, Carmen Claver, Cyril Godard, Martine Urrutigoity and Philippe Kalck</i>	
5.1	Introduction	155
5.2	Asymmetric Reductive Amination	156
5.3	Asymmetric Hydroamination	162
5.4	Asymmetric Hydroaminoalkylation	168
5.5	Asymmetric Hydroaminomethylation	171
5.6	Coupling on a Chiral Metal Center	176
5.7	Conclusion	177
	References	178
<b>6</b>	<b>Industrial Relevance of Asymmetric Organocatalysis in the Preparation of Chiral Amine Derivatives</b>	<b>187</b>
	<i>Luca Bernardi, Armando Carbone and Francesco Fini</i>	
6.1	Introduction	187
6.2	Organocatalysis in Manufacture: Representative Examples	189
6.3	Case Studies	200
6.3.1	Pregabalin	200
6.3.1.1	Pathway A: Desymmetrization of Glutaric Anhydride 53	202
6.3.1.2	Pathway B: Addition of an Amino $\alpha$ -Carbanion 55 to Michael Acceptors	204
6.3.1.3	Pathway C: Addition of Acetate Enolate Equivalents to Nitroalkene 56	206
6.3.2	Bicyclic $\alpha$ -Amino Acid Core of Telaprevir	214
6.3.3	5-(Trifluoromethyl)-2-isoxazolines as Antipest Agents	223
6.4	Summary and Conclusions	230
	References	231
<b>7</b>	<b>Biocatalytic Synthesis of Chiral Amines Using Oxidoreductases</b>	<b>243</b>
	<i>Sebastian C. Cosgrove, Jeremy I. Ramsden, Juan Mangas-Sánchez and Nicholas J. Turner</i>	
7.1	Introduction	243
7.2	Amine Oxidases	243
7.2.1	Introduction	243
7.2.2	(S)-Selective Amine Oxidases	244
7.2.2.1	Monoamine Oxidase from <i>Aspergillus niger</i>	244
7.2.2.2	Directed Evolution of MAO-N	244
7.2.2.3	Synthetic Applications and Cascades	247
7.2.2.4	Monoamine Oxidase from <i>Pseudomonas monteili</i> ZMU-T01	249

7.2.2.5	Cyclohexylamine Oxidase from <i>Brevibacterium oxydans</i> (CHAO)	249
7.2.3	(R)-Selective Amine Oxidases	252
7.2.3.1	D-Amino Acid Oxidase (pkDAO)	252
7.2.3.2	6-Hydroxy-D-nicotine Oxidase (6-HDNO) from <i>Arthrobacter nicotinovorans</i>	252
7.3	Amine Dehydrogenases	252
7.3.1	Introduction	252
7.3.2	Discovery and Engineering of AmDH	253
7.3.2.1	Leucine Dehydrogenase	253
7.3.2.2	Phenylalanine Dehydrogenase and Chimeric Amine Dehydrogenase	254
7.3.2.3	Native Amine Dehydrogenase	254
7.3.3	Synthetic Applications of AmDH	256
7.3.3.1	Primary Amine Synthesis with Engineered AmDH	256
7.3.3.2	Primary Amine Synthesis with Natural AmDH	258
7.3.3.3	Substrate Promiscuity in AmDH	259
7.3.3.4	Cascade Reactions that Use AmDH	260
7.4	Imine Reductases	262
7.4.1	From Biosynthesis to Biocatalysis	262
7.4.2	Biocatalytic Application of Imine Reductases	264
7.4.2.1	IREDs in Cascade and Chemoenzymatic Synthesis	265
7.4.3	IRED Engineering	267
7.4.4	Imine Reductases Catalyzing Reductive Amination	267
7.4.5	Imine Reductase-Catalyzed Amine Alkylation Cascades	270
7.4.6	Engineering of Reductive Aminases	270
7.5	Engineered Cytochrome P450s	270
7.6	Conclusions and Perspectives	274
	References	274
<b>8</b>	<b>Engineering Functional Nanomaterials Through the Amino Group</b>	<b>285</b>
	<i>Giacomo Filippini, Paolo Pengo, Susanna Bosi, Giulio Ragazzon, Lucia Pasquato and Maurizio Prato</i>	
8.1	Abbreviations	285
8.1	Introduction	287
8.2	Quantification of Nanomaterial-Bound Amino Groups	288
8.3	Exploiting Amino Compounds for the Functionalization of Carbon-Based Nanomaterials	290
8.3.1	Historical Backgrounds: Allotropes of Carbon	290
8.3.2	Use of Amines for the Functionalization of Carbon Nanostructures	290
8.3.3	Other Functionalization Procedures of Common Carbon Nanostructures	297
8.3.4	Exfoliation of Graphite with Melamine	299
8.3.5	Other Carbon Nanomaterials	301
8.3.5.1	Carbon Nanohorns	301
8.3.5.2	Carbon Nanodiamonds	305
8.3.5.3	Carbon Nano-onions	307

8.3.6	Amino-Functionalized Carbon-Based Nanomaterials for Analytical Applications	308
8.4	Amines in the Synthesis and Functionalization of Carbon Dots	309
8.4.1	Amines as CD Constituents	310
8.4.2	Amine-Rich CDs from Arginine and Ethylenediamine (NCDs)	312
8.4.2.1	One-Pot Functionalization of NCDs	312
8.4.2.2	Postfunctionalization of NCDs	313
8.4.2.3	Use of CD-Supported Amines in Organocatalysis	315
8.5	Amines for the Engineering of Hybrid Organic-Inorganic Nanomaterials	316
8.5.1	Amines as Head Groups or End Groups on Self-assembled Monolayers on Flat Surfaces	316
8.5.2	Alkylamines in the Preparation of Semiconductor Quantum Dots	319
8.5.2.1	Sulfur-Amine and Selenium-Amine Systems	319
8.5.2.2	Capping Ligands for Quantum Dots and Ligand Exchange by Amines	321
8.5.3	Alkylamines as Reagents for the Synthesis and Passivation of Metal Nanoparticles	322
8.5.3.1	Alkylamines as Capping Agents for Metal Nanoparticles	322
8.5.3.2	Displacement of Amines from the Surface of Metal Nanoparticles	325
8.5.4	Amines on the Outer Surface of Organic-inorganic Hybrid Nanoparticles	325
8.5.5	Postfunctionalization of Amine-Terminated Organic-Inorganic Hybrid Nanoparticles	328
	References	329
<b>9</b>	<b>Recent Advances in the Synthesis of Nitrogen Compounds from Biomass Derivatives</b>	<b>341</b>
	<i>Ana C. Fernandes</i>	
9.1	Introduction	341
9.2	Synthesis of Nitrogen Compounds from Chitin and Its Derivatives	341
9.3	Synthesis of Amines and Formamides from $\alpha$ -Amino Acids	345
9.4	Synthesis of Nitrogen Compounds from Cellulosic Biomass Derivatives	348
9.5	Synthesis of Nitrogen Compounds from Lignin Derivatives	366
9.6	Synthesis of Nitrogen Compounds from Triglycerides and Fatty Alcohols	370
9.7	Conclusion	373
	References	373
<b>10</b>	<b>Recent Advances in the Synthesis of Arylamines in the Light of Application in Pharmaceutical and Chemical Industry</b>	<b>377</b>
	<i>Dino Berthold, Alexander M. Haydl, Joyce C. Leung, Ulrich Scholz, Qing Xiao and Zhibin Zhu</i>	
10.1	Modern Approaches to Transition-Metal-Catalyzed C–N Coupling in Industry	377
10.1.1	Introduction	377
10.1.2	Transition-Metal-Catalyzed C—N-Bond Formation	377
10.1.2.1	Ullmann-Type Amination	378
10.1.2.2	Buchwald–Hartwig Amination	383

10.2	New Methodologies in the Synthesis of Arylamines on the Brink of Industrial Application	388
10.2.1	Introduction	388
10.2.2	Catalytic C–H Amination	389
10.2.2.1	Catalytic C–H Amination under Standard Conditions	389
10.2.2.2	Photoredox Catalysis	399
10.2.2.3	Electrochemical Approaches	402
10.2.3	Decarboxylative Aryl Amination	405
10.2.4	Nickel-Catalyzed C–N Coupling	407
10.2.5	Other Metal-Catalyzed Cross-Couplings	414
10.2.6	Reductive Amination	417
10.2.7	Hydroamination	419
10.2.8	Summary and Conclusions	424
10.3	Advances to Arylamine Formation Using Intensified and More Sustainable Process Technologies	424
10.3.1	Introduction	424
10.3.2	Flow Chemistry	425
10.3.2.1	Pd-Catalyzed C–N Bond Forming Reaction	425
10.3.2.2	Nucleophilic Aromatic Substitution	426
10.3.2.3	Telescoped Sequence of Nitration and Hydrogenation in Flow Synthesis	428
10.3.2.4	Chan–Lam Coupling	428
10.3.3	Immobilization of Catalysts/Supported Catalysts	429
10.3.4	Personal Accounts from Contract Manufacturing Companies on Utility of Modern Flow Amination Methods	431
10.4	Miscellaneous Aspects of Aromatic Amination Reactions in the World of Active Pharmaceutical Ingredients	431
10.4.1	Cohort of Concerns and its Regulatory Impact on Amine-Based Active Pharmaceutical Compounds	431
10.4.2	Role of Control of Elemental Impurities in Human Pharma Applications	432
10.4.3	Transition Metal Accounting	433
10.4.4	Recycling of Metals, Ligands, and Other Cost Drivers of Aromatic Amination	434
10.4.5	Regulatory Requirements for the Submission of a Catalytic Reaction in a New Drug Application	434
	References	435