

Contents

Preface *xvii*

Abbreviations *xix*

- 1** **Copper Catalysis: An Introduction** 1
Salim Saranya and Gopinathan Anilkumar
References 4

- 2** **Cu-Catalyst in Reactions Involving Pyridinium and Indolizinium Moieties** 7
Bianca Furdui, Andrea V. Dediu (Botezatu), and Rodica M. Dinica
 - 2.1 Cu-Catalyst in Reactions Involving Pyridinium Moieties 7
 - 2.1.1 Introduction 7
 - 2.1.2 Synthesis and Functionalization of Pyridinium Compounds Catalyzed by Copper 7
 - 2.1.3 Green Methods for Pyridine Synthesis 13
 - 2.2 Cu-Catalyst in Reactions Involving Indolizinium Moieties 15
 - 2.2.1 Introduction 15
 - 2.2.2 Synthesis of Indolizinium Compounds Using a Copper Catalyst 15
 - 2.2.3 Cu-Catalyzed Green Synthesis of Indolizine Moieties 19
 - 2.3 Conclusions 21References 21

- 3** **Copper-Catalyzed Cross-Coupling Reactions of Organoboron Compounds** 23
Jan Nekvinda and Webster L. Santos
 - 3.1 Introduction 23
 - 3.2 Ring Opening Cross-Coupling Reactions 24
 - 3.3 Coupling Reactions with Atoms Other than Carbon 26
 - 3.3.1 Amines, Amides, and Sulfonamides 27
 - 3.3.2 Nitrones 33
 - 3.3.3 Sulfones 35
 - 3.3.4 Silyls 35
 - 3.3.5 Selanyls 36
 - 3.4 Coupling Reactions Involving Carbon 36

3.4.1	Boronic Acid Esters	36
3.4.2	Boronic Acids	41
3.4.3	Single Electron Mechanism	42
3.5	Conclusion	43
	References	43
4	Cu-Catalyzed Homocoupling Reactions	51
	<i>Ganesh C. Nandi, Sundaresan Ravindra, Cholakkaparambil Irfana Jesin, Parameswaran Sasikumar, and Kokkuvayil V. Radhakrishnan</i>	
4.1	Introduction	51
4.2	Synthesis of 1,3-Diynes via Homocoupling Reactions	51
4.2.1	Synthesis of 1,3-Diynes with Homogeneous Cu Catalysis	52
4.2.1.1	Synthesis of Symmetrical 1,3-Diynes with Substrates Other than Terminal Alkynes	54
4.2.2	Synthesis of Symmetrical 1,3-Diynes with Heterogeneous Cu Catalysis	55
4.2.3	Synthesis of Macrocycles Through Intramolecular Coupling of Terminal Alkynes	56
4.3	Cu-Catalyzed Synthesis of Symmetrical Biaryls Through Homocoupling Reactions	57
4.3.1	Homocoupling of Aryl Boronic Acids	58
4.3.1.1	Homogeneous Cu-Catalyzed Homocoupling Reactions	58
4.3.1.2	Heterogeneous Copper-Catalyzed Homocoupling Reactions	58
4.3.2	Synthesis of Symmetrical Biaryls Through C–H Activation	59
4.3.3	Homocoupling of Arylstannane/Silane Derivatives	62
4.3.4	Cu-Catalyzed Homocoupling of Aryl Halides for the Synthesis of Biaryls	62
4.3.4.1	Symmetrical Biaryl Formation Using Homogeneous Copper Catalyst	62
4.3.4.2	Biaryl Formation Using Heterogeneous Cu Catalyst	65
4.3.5	Cu-Catalyzed Homocoupling of Aryl Halides for the Formation of Biaryls in Natural Products	66
4.4	Homocoupling of Alkenes	68
4.5	Summary and Conclusions	69
	References	69
5	Cu-Catalyzed Organic Reactions in Aqueous Media	73
	<i>Noel Nebra and Joaquín García-Álvarez</i>	
5.1	Introduction	73
5.2	Cu-Catalyzed Azide–Alkyne Cycloaddition Reactions (CuAAC)	74
5.2.1	Ligand-Accelerated Cu(I) Catalysts	74
5.2.2	Supported Cu(I) Catalysts	75
5.2.3	Micellar Cu(I) Catalysis	77
5.2.4	Heterogeneous Catalysis: CuNPs	77
5.2.5	Miscellaneous	80
5.3	Cu-Mediated Cross-Coupling Reactions: C–C and C–Heteroatom Bond Formation	81

- 5.3.1 The Ullmann Coupling 81
- 5.3.2 The Chan–Lam–Evans (CEL) Coupling 83
- 5.3.3 Cu-Catalyzed Cyclization Reactions via Cross-Coupling Events 85
- 5.3.4 Cu-Catalyzed C–H Bond Functionalization Reactions 86
- 5.4 Cu-Catalyzed Hydroelementation Reactions of Double and Triple C–C Bonds 89
 - 5.4.1 Michael-Type Additions: Enone Hydrations Enabled by Cu-Based Metallo-Hydratases 89
 - 5.4.2 Cu-Catalyzed Hydroelementation of α,β -Unsaturated Carbonyl Compounds 90
 - 5.4.3 Cu-Catalyzed Hydroelementation of Inactivated C–C Multiple Bonds 92
- 5.5 Miscellaneous 96
- 5.6 Summary and Conclusions 98
 - Acknowledgments 98
 - References 100

- 6 Cu-Catalyzed Organic Reactions in *Deep Eutectic Solvents* (DESs) 103**
Noel Nebra and Joaquín García-Álvarez
 - 6.1 Introduction 103
 - 6.2 Cu-Catalyzed Azide–Alkyne Cycloaddition Reactions (CuAAC) in DESs 106
 - 6.3 Cu-Catalyzed C–C and C–N Bond Formations in DESs 108
 - 6.3.1 Cu-Catalyzed Sonogashira C–C Coupling Using the Eutectic Mixture 1CuCl/1Gly 108
 - 6.3.2 Synthesis of Heterocyclic Compounds via Cu-Catalyzed Cross-Coupling Reactions 110
 - 6.3.3 Cu-Catalyzed C–N Bond Formation in DESs 110
 - 6.4 Cu-Catalyzed Atom Transfer Radical Polymerization Processes in DESs (SARA and ARGET) 112
 - 6.5 Summary and Conclusions 113
 - Acknowledgments 114
 - References 114

- 7 Microwave-Assisted Cu-Catalyzed Organic Reactions 119**
Bogdan Štefane, Helena Brodnik-Žugelj, Uroš Grošelj, Jurij Svete, and Franc Požgan
 - 7.1 Introduction 119
 - 7.2 Ring-Forming Reactions 121
 - 7.2.1 Synthesis of Heterocycles 121
 - 7.2.1.1 Cycloadditions 121
 - 7.2.1.2 Annulation Reactions 123
 - 7.2.1.3 Intramolecular Cyclizations 126
 - 7.2.1.4 Multicomponent Reactions (MCRs) 126
 - 7.2.2 Synthesis of Carbocycles 128
 - 7.3 Cross-Coupling Reactions 130

- 7.3.1 Carbon–Carbon Couplings 130
- 7.3.2 Carbon–Heteroatom Couplings 134
 - 7.3.2.1 C–N Couplings 134
 - 7.3.2.2 C–Chalcogen Couplings 138
- 7.4 Multicomponent Reactions 141
- 7.5 Miscellaneous Reactions 144
- 7.6 Summary and Conclusions 146
 - Acknowledgments 146
 - References 146

- 8 Cu-Catalyzed Asymmetric Synthesis 153**
Hidetoshi Noda, Naoya Kumagai, and Masakatsu Shibasaki
 - 8.1 Introduction 153
 - 8.1.1 Cu-Catalyzed Asymmetric Synthesis: Scope of This Chapter 153
 - 8.1.2 Structures of Chiral Ligands: Trends of the Last Decade 154
 - 8.2 *In Situ* Generation of Cu Nucleophiles from Unsaturated Hydrocarbons 155
 - 8.2.1 Reductive Aldol Reactions 155
 - 8.2.2 Intramolecular Oxy- and Amidocupration 156
 - 8.2.3 Hydrocupration of Unsaturated Compounds 158
 - 8.2.4 Borylcupration of Unsaturated Compounds 163
 - 8.3 Generation of Cu Nucleophiles Under Proton Transfer Conditions 165
 - 8.4 Summary and Conclusions 172
 - References 172

- 9 Cu-Catalyzed Click Reactions 177**
Rajagopal Ramkumar and Pazhamalai Anbarasan
 - 9.1 Introduction 177
 - 9.2 Background 178
 - 9.2.1 Huisgen's Cycloaddition Reaction 178
 - 9.2.2 Copper(I)-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) 178
 - 9.2.3 Mechanistic Study of Copper Azide–Alkyne Cycloaddition Reaction 179
 - 9.3 CuAAC for the Synthesis of Substituted 1,2,3-Triazoles 180
 - 9.4 Heterogeneous CuAAC Reactions 188
 - 9.5 Ligand-Stabilized Cu(I)-Catalyzed Click Reaction 191
 - 9.6 Synthesis of Rotaxanes and Catenanes Using CuAAC 196
 - 9.7 Synthesis of *N*-Sulfonyl-1,2,3-Triazoles and Their Applications 198
 - 9.8 CuAAC and Asymmetric Synthesis 198
 - 9.9 CuAAC for Synthesis of Biologically Active Molecules 202
 - 9.10 Summary 204
 - References 204

- 10 Cu-Catalyzed Multicomponent Reactions 209**
Thachapully D. Suja and Rajeev S. Menon
 - 10.1 Introduction 209

10.2	Cu-Catalyzed MCRs of Alkynes	209
10.2.1	Cu-Catalyzed Multicomponent Alkyne–Azide Cycloadditions	210
10.2.1.1	CuAAC Reactions Initiated by Azide Generation	210
10.2.1.2	CuAAC Reactions Initiated by Alkyne Generation	214
10.2.1.3	Other Multicomponent CuAAC Reactions	214
10.2.2	Cu-Catalyzed Generation and Interception of Ketenimines from Alkynes and Azides	216
10.2.3	Cu-Catalyzed Aldehyde, Alkyne, and Amine (A ³) Coupling	221
10.2.3.1	A ³ -Coupling Reactions That Afford Propargyl Amine Derivatives	222
10.2.3.2	Variation of the Reaction Components in A ³ -Coupling	224
10.2.3.3	Asymmetric A ³ (AA ³)-Coupling Reactions	226
10.2.3.4	Synthetic Applications of Cu-Catalyzed A ³ -Coupling Reactions	227
10.3	Other Cu-Catalyzed Multicomponent Reactions	229
10.4	Summary and Conclusions	233
	References	233
11	Copper-Catalyzed Aminations	239
	<i>Nissy A. Harry and Rajenahally V. Jagadeesh</i>	
11.1	Introduction	239
11.2	Copper-Catalyzed Amination of Aryl and Alkenyl Electrophiles	240
11.2.1	Ammonia as a Nucleophile	240
11.2.2	Sodium Azide as Nucleophile	241
11.2.3	Amines as Nucleophile	242
11.2.4	Mechanism of Cu-Catalyzed Amination of Aryl/Alkyl Halides	244
11.3	Chan–Lam Coupling Reaction	244
11.4	Copper-Catalyzed Hydroaminations	246
11.4.1	Hydroamination of Alkenes	247
11.4.2	Hydroamination of Alkynes	250
11.4.3	Hydroamination of Allenes	251
11.5	Copper-Catalyzed C–H amination Reactions	251
11.6	Conclusion	254
	References	254
12	Cu-Catalyzed Carbonylation Reactions	261
	<i>Parameswaran Sasikumar, Thoppe S. Priyadarshini, Sanjay Varma, Ganesh C. Nandi, and Kokkuvayil V. Radhakrishnan</i>	
12.1	Introduction	261
12.2	Single Carbonylation Reactions	262
12.2.1	Copper-Catalyzed Carbonylative Coupling Reactions	262
12.2.2	Cu-Catalyzed Carboxylation Reaction	268
12.2.3	Cu-Catalyzed Oxidative Carbonylation Reactions	269
12.2.4	Carbonylative Acetylation Reaction	272
12.2.5	Aminocarbonylation Reaction	273
12.2.6	Copper-Catalyzed Oxidative Amidation	275
12.3	Cu-Catalyzed Double Carbonylation Reactions	275
12.4	Summary and Conclusions	278
	References	278

- 13 Ligand-Free, Cu-Catalyzed Reactions 279**
Muhammad F. Jamali, Sanoop P. Chandrasekharan, and Kishor Mohanan
- 13.1 Introduction 279
- 13.2 Heterocycle Synthesis 279
- 13.2.1 Five-Membered Heterocycles 280
- 13.2.2 Six-Membered Heterocycles 280
- 13.2.3 Benzofused Five-Membered Heterocycles Containing One Heteroatom 281
- 13.2.4 Benzofused Five-Membered Heterocycles Containing Two Heteroatoms 283
- 13.2.5 Benzofused Five-Membered Heterocycles Containing Three Heteroatoms 284
- 13.2.6 Benzofused Six-Membered Heterocycles 284
- 13.2.7 Polycyclic Compounds 286
- 13.2.8 Spirocyclic Compounds 286
- 13.3 Carbon–Heteroatom Bond Formations 289
- 13.3.1 C–N Bond Formation 289
- 13.3.2 C–O Bond Formation 291
- 13.3.3 C–S Bond Formation 291
- 13.3.4 C–P Bond Formation 295
- 13.3.5 C–B Bond Formation 295
- 13.3.6 C–Se Bond Formation 295
- 13.4 C–H Activation Reactions 297
- 13.5 Cross-coupling Reactions 299
- 13.6 Azide–Alkyne Cycloaddition Reactions (CuAAC) 301
- 13.7 Trifluoromethylation Reactions 302
- 13.8 Cyanation Reactions 303
- 13.9 Carbonylation Reactions 304
- 13.10 Conclusion 305
- References 305
- 14 Copper-Catalyzed Decarboxylative Coupling 309**
Firas El-Hage and Jola Pospech
- 14.1 Introduction 309
- 14.2 Copper-Catalyzed Decarboxylation of Benzoic Acids 309
- 14.3 Copper-Catalyzed Decarboxylation of Alkenyl Carboxylic Acids 315
- 14.4 Copper-Catalyzed Decarboxylation of Alkynyl Carboxylic Acids 316
- 14.5 Copper-Catalyzed Decarboxylation of Alkyl Carboxylic Acids 320
- 14.6 Summary and Conclusions 325
- References 326
- 15 Copper-Catalyzed C–H Activation 329**
Xun-Xiang Guo
- 15.1 Introduction 329
- 15.2 Carbon–Carbon Bond Formation via Cu-Catalyzed C–H Activation 329
- 15.2.1 Cu-Catalyzed C(sp²)-H Activation 329

- 15.2.2 Cu-Catalyzed C(sp³)-H Activation 332
- 15.3 Carbon-Heteroatom Bond Formation via Cu-Catalyzed C-H Activation 334
 - 15.3.1 C-N Bond Formation 334
 - 15.3.2 C-O Bond Formation 339
 - 15.3.3 C-X Bond Formation 341
 - 15.3.4 C-P Bond Formation 345
 - 15.3.5 C-S Bond Formation 346
- 15.4 Conclusion 347
- References 347

- 16 Aerobic Cu-Catalyzed Organic Reactions 349**
Ahmad A. Almasalma and Esteban Mejía
 - 16.1 Introduction 349
 - 16.2 C-C Bond Formation Reactions 351
 - 16.2.1 Cross-dehydrogenative Couplings Under Thermal Conditions 352
 - 16.2.2 Cross-dehydrogenative Couplings Under Photochemical Conditions 354
 - 16.3 Carbonyl Synthesis via Oxidation of Alcohols 357
 - 16.3.1 "Copper-Only" Biomimetic Catalyst Systems 358
 - 16.3.2 Cu/Nitroxyl "Dual" Systems 360
 - 16.4 Summary and Conclusions 362
 - References 363

- 17 Copper-Catalyzed Trifluoromethylation Reactions 367**
Dzmitry G. Kananovich
 - 17.1 Introduction 367
 - 17.2 Trifluoromethylation of Arenes and Heteroarenes (C(sp²)-CF₃ Bond Formation) 370
 - 17.3 Trifluoromethylation of Alkenes and Alkynes 374
 - 17.4 Trifluoromethylation of Aliphatic Precursors (C(sp³)-CF₃ Bond Formation) 378
 - 17.4.1 Transformations via Functional Group Interconversions 378
 - 17.4.2 Direct C(sp³)-H Trifluoromethylation 382
 - 17.4.3 Ring-opening Trifluoromethylation 386
 - 17.5 Copper-Mediated Formation of CF₃-Heteroatom Bonds 388
 - 17.6 Summary and Conclusions 388
 - References 389

- 18 Cu-Catalyzed Reactions for Carbon-Heteroatom Bond Formations 395**
Govindasamy Sekar, Subramani Sangeetha, Anuradha Nandy, and Rajib Saha
 - 18.1 Introduction 395
 - 18.2 Cu-Catalyzed Reactions for Carbon-Nitrogen Bond Formations 395
 - 18.2.1 Coupling Reactions with Ammonia and its Surrogates 396
 - 18.2.2 Coupling Reactions with Amines 396

- 18.2.3 Coupling Reactions with Amides, Lactams, and Carbamates 398
- 18.2.4 Coupling Reactions with Protected Hydrazines and Hydroxylamines 400
- 18.2.5 Coupling Reactions with Guanidines 400
- 18.2.6 Coupling Reactions with N-Heterocycles 401
- 18.3 Cu-Catalyzed Reactions for Carbon–Oxygen Bond Formations 401
 - 18.3.1 Mechanism and Presence of Cu(I) Intermediate in Ullmann Ether Synthesis 402
 - 18.3.2 Role of Ligands in Copper-Catalyzed Ether Synthesis 403
 - 18.3.3 Copper-Catalyzed C–O Bond Formation for Synthesizing Phenols 404
 - 18.3.4 Copper-Catalyzed C–H Functionalization for C–O Bond Formation 405
 - 18.3.5 Copper-Catalyzed Synthesis of Oxygen Heterocycles 405
 - 18.3.6 Selectivity of Copper-Catalyzed C–O and C–N Bond Formation 406
- 18.4 Cu-Catalyzed Reactions for Carbon–Sulfur Bond Formations 407
- 18.5 Cu-Catalyzed Reactions for Carbon–Selenium and Carbon–Tellurium Bond Formations 413
- 18.6 Cu-Catalyzed Reactions for Carbon–Phosphorous Bond Formations 414
- 18.7 Cu-Catalyzed Reactions for Carbon–Silicon Bond Formations 415
- 18.8 Cu-Catalyzed Reactions for Carbon–Halogen Bond Formations 415
- 18.9 Conclusions 416
- References 416

- 19 Cu-Assisted Cyanation Reactions 423**
Sumanta Garai and Ganesh A. Thakur
- 19.1 Introduction 423
- 19.2 Cyanation Reaction Using CN-Containing Source 423
 - 19.2.1 Metallic Bound CN-Source 423
 - 19.2.1.1 Metal Cyanide 423
 - 19.2.1.2 Potassium Ferrocyanide [K₃Fe(CN)₆] 427
 - 19.2.2 Nonmetallic CN-Source 427
 - 19.2.2.1 Acetone Cyanohydrin 427
 - 19.2.2.2 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) 428
 - 19.2.2.3 2,2'-Azobisisobutyronitrile (AIBN) 429
 - 19.2.2.4 Benzyl Cyanide 429
 - 19.2.2.5 Acetonitrile 432
 - 19.2.2.6 Malononitrile 435
 - 19.2.2.7 Cyanogen Iodide 436
 - 19.2.2.8 α -Cyanoacetate 436
- 19.3 Cyanation Reaction Using Non-CN-Containing Source 437
 - 19.3.1 *N,N*-Dimethylformamide (DMF) 437

- 19.3.2 Ammonium Iodide (NH₄I) and *N,N*-Dimethylformamide (DMF) 439
- 19.3.3 Nitromethane 441
- Acknowledgments 441
- References 441

20 Application of Cu-Mediated Reactions in the Synthesis of Natural Products 443

Anas Ansari and Ramesh Ramapanicker

- 20.1 Introduction 443
- 20.2 Classification 443
- 20.3 Total Synthesis Employing Cu-Catalyzed C–C Coupling Reactions 445
 - 20.3.1 (+)-Nocardioazine B 445
 - 20.3.2 (–)-Rhazinilam 447
 - 20.3.3 Isohericenone and Erinacerin A 447
 - 20.3.4 (+)-Piperarborenine B 449
 - 20.3.5 Macrocarpines D and E 450
- 20.4 Total Synthesis Employing Cu-Catalyzed C–N Coupling Reactions 454
 - 20.4.1 (–)-Aspergilazine A 454
 - 20.4.2 (–)-Psychotriasine 454
 - 20.4.3 (–)-Indolactam V 455
 - 20.4.4 (–)-Palmyrolide A 458
- 20.5 Total Synthesis Employing Cu-Catalyzed C–O Coupling Reactions 458
 - 20.5.1 (±)-Untenone A 458
 - 20.5.2 Coumestrol and Aureol 460
- 20.6 Total Synthesis Employing Cu-Catalyzed Domino Reactions 463
 - 20.6.1 (±)-Sacidumlignan D 463
- 20.7 Conclusion 463
- References 465

Index 469

