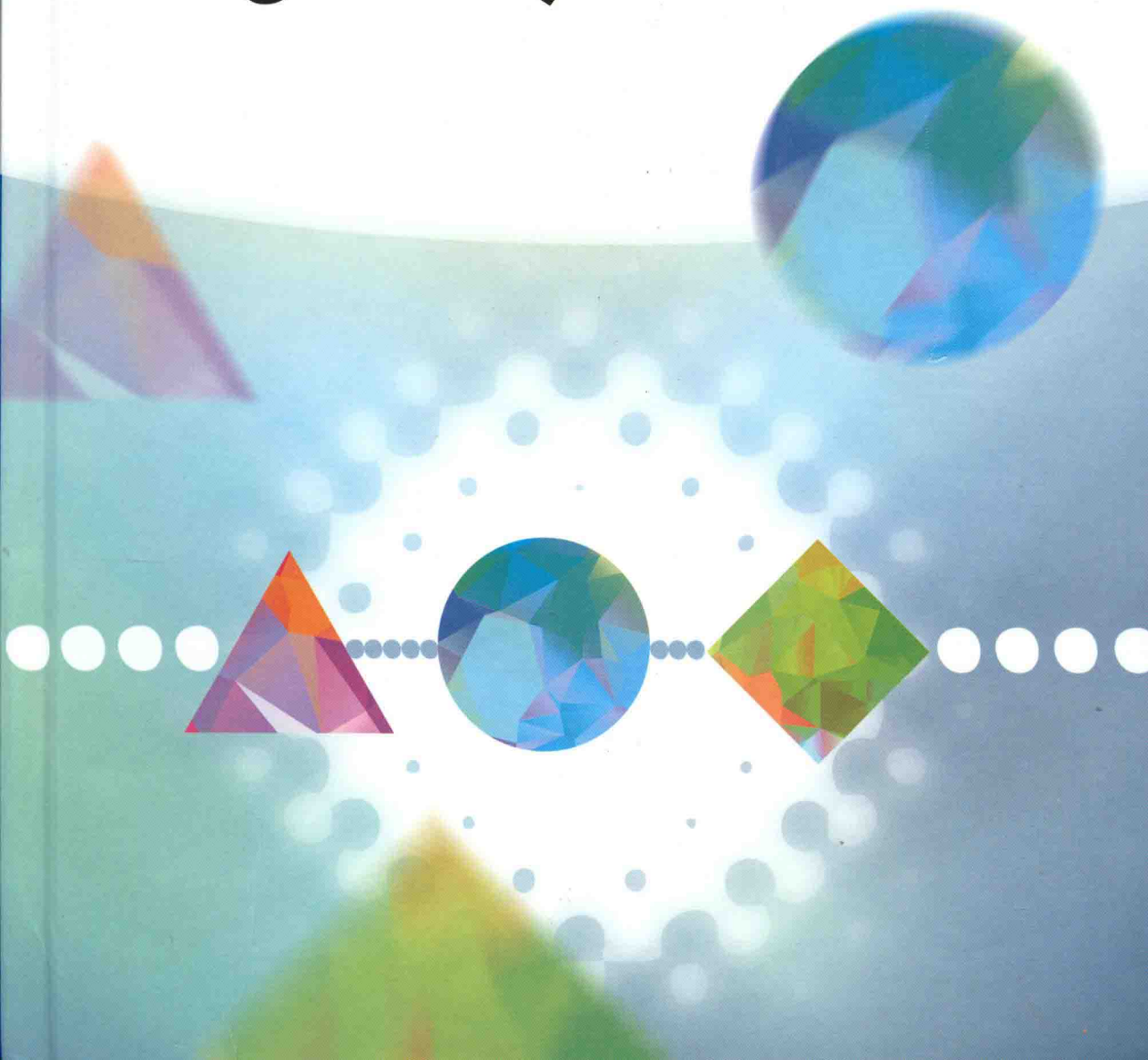


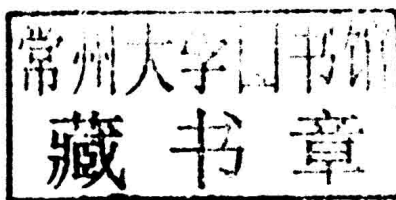
Edited by  
Jieping Zhu, Qian Wang, and Mei-Xiang Wang

# Multicomponent Reactions in Organic Synthesis



*Edited by Jieping Zhu, Qian Wang, and Mei-Xiang Wang*

## **Multicomponent Reactions in Organic Synthesis**



**WILEY-VCH**  
Verlag GmbH & Co. KGaA

## Editors

### **Prof. Jieping Zhu**

Laboratory of Synthesis and Natural  
Products  
Institute of Chemical Sciences and  
Engineering  
École Polytechnique Fédérale de Lausanne  
EPFL-SB-ISIC-LSPN  
BCH5304 (Bat BCH)  
1015 Lausanne  
Switzerland

### **Dr. Qian Wang**

Laboratory of Synthesis and Natural  
Products  
Institute of Chemical Sciences and  
Engineering  
École Polytechnique Fédérale de Lausanne  
EPFL-SB-ISIC-LSPN  
1015 Lausanne  
Switzerland

### **Prof. Mei-Xiang Wang**

MOE Key Laboratory of Bioorganic  
Phosphorus Chemistry & Chemical Biology  
Department of Chemistry  
Tsinghua University  
Beijing 100084  
China

All books published by **Wiley-VCH** are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

**Library of Congress Card No.:** applied for

### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

### **Bibliographic information published by the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2015 Wiley-VCH Verlag GmbH & Co. KGaA,  
Boschstr. 12, 69469 Weinheim, Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

**Print ISBN:** 978-3-527-33237-3

**ePDF ISBN:** 978-3-527-67819-8

**ePub ISBN:** 978-3-527-67820-4

**Mobi ISBN:** 978-3-527-67818-1

**oBook ISBN:** 978-3-527-67817-4

**Cover Design** Adam-Design, Weinheim, Germany

**Typesetting** Thomson Digital, Noida, India

**Printing and Binding** Markono Print Media Pte Ltd.,  
Singapore

Printed on acid-free paper

*Edited by*  
*Jieping Zhu*  
*Qian Wang*  
*Mei-Xiang Wang*

**Multicomponent  
Reactions in Organic  
Synthesis**

## *Related Titles*

Tietze, L.F. (ed.)

### **Domino Reactions** **Concepts for Efficient Organic** **Synthesis**

2014

Print ISBN: 978-3-527-33432-2

Hoz, A.d., Loupy, A. (eds.)

### **Microwaves in Organic** **Synthesis** **3 Edition**

2012

Print ISBN: 978-3-527-33116-1

Zhang, W., Cue, B.W. (eds.)

### **Green Techniques for** **Organic Synthesis and** **Medicinal Chemistry**

2012

Print ISBN: 978-0-470-71151-4

Kappe, C.O., Stadler, A., Dallinger, D.

### **Microwaves in Organic and** **Medicinal Chemistry** **2 Edition**

2012

Print ISBN: 978-3-527-33185-7

Anastas, P.T., Boethling, R., Li, C.,  
Voutchkova, A., Perosa, A., Selva, M.  
(eds.)

### **Handbook of Green** **Chemistry - Green Processes**

2012

Print ISBN: 978-3-527-31576-5

Ding, K., Dai, L. (eds.)

### **Organic Chemistry -** **Breakthroughs and** **Perspectives**

2012

Print ISBN: 978-3-527-33377-6

ISBN: 978-3-527-66480-1

Behr, A., Neubert, P.

### **Applied Homogeneous** **Catalysis**

2012

Print ISBN: 978-3-527-32641-9

Mä, S. (ed.)

### **Handbook of Cyclization** **Reactions**

2010

Print ISBN: 978-3-527-32088-2

Nenajdenko, V. (ed.)

### **Isocyanide Chemistry** **Applications in Synthesis and Material** **Science**

2012

Print ISBN: 978-3-527-33043-0

## List of Contributors

***AlAnod D. AlQahtani***

Anti-Doping Lab Qatar  
Doha  
Qatar

and

University of Groningen  
Department of Pharmacy  
Antonius Deusinglaan 1  
9700 AD Groningen  
The Netherlands

***Bruce A. Arndtsen***

McGill University  
Department of Chemistry  
801 Sherbrooke Street West  
Montreal, QC H3A 0B8  
Canada

***Andrea Basso***

Università degli Studi di Genova  
Dipartimento di Chimica e Chimica  
Industriale  
Via Dodecaneso 31  
16146 Genoa  
Italy

***Xavier Bugaut***

Aix Marseille University  
CNRS  
Centrale Marseille iSm2 UMR 7313  
Service 531 Centre de St Jérôme  
13397 Marseille cedex 20  
France

***Thierry Constantieux***

Aix Marseille University  
CNRS  
Centrale Marseille iSm2 UMR 7313  
Service 531 Centre de St Jérôme  
13397 Marseille cedex 20  
France

***Yoann Coquerel***

Aix Marseille University  
CNRS  
Centrale Marseille iSm2 UMR 7313  
Service 531 Centre de St Jérôme  
13397 Marseille cedex 20  
France

***Konstantin Deilhof***

Heinrich-Heine-Universität  
Düsseldorf  
Institut für Organische Chemie und  
Makromolekulare Chemie  
Universitätsstrasse 1  
40225 Düsseldorf  
Germany

**Alexander Dömling**

University of Groningen  
Department of Pharmacy  
Antonius Deusinglaan 1  
9700 AD Groningen  
The Netherlands

**Laurent El Kaïm**

ENSTA Paris Tech  
UMR 7652  
828 boulevard des Maréchaux  
91 762 Palaiseau Cedex  
France

**Liu-Zhu Gong**

University of Science and  
Technology of China  
Hefei National Laboratory for  
Physical Sciences at the Microscale  
and Department of Chemistry  
No. 96 Jinzhai Road  
Hefei, Anhui 230026  
China

**Laurence Grimaud**

Laboratoire d'électrochimie  
UPMC-ENS-CNRS-UMR 8640  
Ecole Normale  
Supérieure-Département de chimie  
24 rue Lhomond  
75231 Paris cedex 05  
France

**Wenhao Hu**

East China Normal University  
Department of Chemistry  
Shanghai Engineering Research  
Center of Molecular Therapeutics  
and New Drug Development  
3663 Zhongshan Bei Road  
Shanghai 200062  
China

**Nicola Kielland**

University of Barcelona  
Barcelona Science Park  
Baldiri Reixac 10–12  
08028 Barcelona  
Spain

**Yannick Landais**

University of Bordeaux  
Institut des Sciences Moléculaires  
UMR-CNRS 5255  
351, cours de la libération  
33405 Talence Cedex  
France

**Rodolfo Lavilla**

Laboratory of Organic Chemistry  
Faculty of Pharmacy  
University of Barcelona  
Barcelona Science Park  
Baldiri Reixac 10–12  
08028 Barcelona  
Spain

**Virginie Liautard**

University of Bordeaux  
Institut des Sciences Moléculaires  
UMR-CNRS 5255  
351, cours de la libération  
33405 Talence Cedex  
France

**Fabio Lorenzini**

McGill University  
Department of Chemistry  
801 Sherbrooke Street West  
Montreal, QC H3A 0B8  
Canada

**Kevin S. Martin**

University of California  
Department of Chemistry  
One Shields Avenue  
Davis, CA 95616  
USA

**Lisa Moni**

Università degli Studi di Genova  
Dipartimento di Chimica e Chimica  
Industriale  
Via Dodecaneso 31  
16146 Genoa  
Italy

**Micjel C. Morejon**

Department of Bioorganic  
Chemistry  
Weinberg 3  
06120 Halle (Saale)  
Germany

**Thomas J.J. Müller**

Heinrich-Heine-Universität  
Düsseldorf  
Institut für Organische Chemie und  
Makromolekulare Chemie  
Universitätsstrasse 1  
40225 Düsseldorf  
Germany

**Ricardo A.W. Neves Filho**

Department of Bioorganic  
Chemistry  
Weinberg 3  
06120 Halle (Saale)  
Germany

**Romano V.A. Orru**

VU University Amsterdam  
Faculty of Sciences  
Amsterdam Institute for Molecules,  
Medicines & Systems  
Department of Chemistry &  
Pharmaceutical Sciences  
De Boelelaan 1083  
1081 HV Amsterdam  
The Netherlands

**Alfredo R. Puentes**

Department of Bioorganic  
Chemistry  
Weinberg 3  
06120 Halle (Saale)  
Germany

**Jeffrey S. Quesnel**

McGill University  
Department of Chemistry  
801 Sherbrooke Street West  
Montreal, QC H3A 0B8  
Canada

**Hans-Ulrich Reissig**

Freie Universität Berlin  
Institut für Chemie und Biochemie  
Takustrasse 3  
14195 Berlin  
Germany

**Renata Riva**

Università degli Studi di Genova  
Dipartimento di Chimica e Chimica  
Industriale  
Via Dodecaneso 31  
16146 Genoa  
Italy

**Jean Rodriguez**

Aix Marseille University CNRS  
Centrale Marseille iSm2 UMR 7313  
Service 531 Campus Scientifique  
de St Jérôme  
13397 Marseille cedex 20  
France



***Eelco Ruijter***

VU University Amsterdam  
Faculty of Sciences  
Amsterdam Institute for Molecules,  
Medicines & Systems  
Department of Chemistry &  
Pharmaceutical Sciences  
De Boelelaan 1083  
1081 HV Amsterdam  
The Netherlands

***Jared T. Shaw***

University of California  
Department of Chemistry  
One Shields Avenue  
Davis, CA 95616  
USA

***Jevgenijs Tjutrins***

McGill University  
Department of Chemistry  
801 Sherbrooke Street West  
Montreal, QC H3A 0B8  
Canada

***Esther Vicente-García***

University of Barcelona  
Barcelona Science Park  
Baldri Reixac 10–12  
08028 Barcelona  
Spain

***Ludger A. Wessjohann***

Department of Bioorganic  
Chemistry  
Weinberg 3  
06120 Halle (Saale)  
Germany

***Xiang Wu***

University of Science and  
Technology of China  
Hefei National Laboratory for  
Physical Sciences at the Microscale  
and Department of Chemistry  
No. 96 Jinzhai Road  
Hefei, Anhui 230026  
China

***Dong Xing***

East China Normal University  
Department of Chemistry  
Shanghai Engineering Research  
Center of Molecular Therapeutics  
and New Drug Development  
3663 Zhongshan Bei Road  
Shanghai 200062  
China

***Hiroto Yoshida***

Hiroshima University  
Department of Applied Chemistry  
1-4-1 Kagamiyama  
Higashi-Hiroshima 739-8527  
Japan

***Ashkaan Younai***

University of California  
Department of Chemistry  
One Shields Avenue  
Davis, CA 95616  
USA

***Reinhold Zimmer***

Freie Universität Berlin  
Institut für Chemie und Biochemie  
Takustrasse 3  
14195 Berlin  
Germany

## Preface

The quote by Aristotle “the whole is greater than the sum of its parts” nicely reflects the power of multicomponent reactions (MCRs) in which three or more reactants are combined in a single operation to produce adducts that incorporate substantial portions of all the components. Indeed, the ability of MCRs to create value-added molecules from simple building blocks is now well appreciated.

The Wiley-VCH book entitled “Multicomponent Reactions” published in 2005 was warmly received by research communities in academia and industry alike. As predicted in the preface of the very first monograph on the subject, extensive research on the development of new MCRs and their applications in the synthesis of natural products as well as designed bioactive molecules have been continuing at an explosive pace. Nowadays, there is hardly a chemical journal in the broad area of organic chemistry that does not contain papers related to multicomponent reactions. In light of the recent tremendous advances in the field, it became clear to us that a follow-up of this book is needed. While planning the contents of this book, we tried to focus on the synthesis aspects and to make the book complementary rather than an update to the first edition.

The book starts with a general introduction to MCRs (Chapter 1) followed by a detailed discussion on the many facets of discovering novel MCRs (Chapter 2). Inherent to the nature of the reaction, the MCR employs generally at least one substrate with multireactive centers. We therefore classified the MCRs according to the key substrate used, including arynes (Chapter 3), isonitriles (Chapter 4), 1,3-dicarbonyls (Chapter 5), heterocycles (Chapter 6), diazoacetate (Chapter 7), allenes (Chapter 11), alkynes (Chapter 12), and anhydrides (Chapter 13). In a more broad sense, metal-catalyzed (Chapter 8), radical-based (Chapter 14), oxidative (Chapter 10), and enantioselective (Chapter 15) MCRs and synthesis of macrocycles by MCRs (Chapter 9) are subjects of other five chapters. The authors of 15 chapters who outline the essence of the each subject and provide valuable perspectives of the field are all world leaders. It is interesting to point out that some of these subjects were virtually unexplored before 2005, the year the first book was published.

The present monograph, in combination with “Multicomponent Reactions (2005),” is intended to provide an essential reference source for most of the

important topics of the field and to provide an efficient entry point to the key literature and background knowledge for those who plan to be involved in MCRs. We hope that the book will be of value to chemists at all levels in both academic and industrial laboratories. Finally, we hope that this monograph will stimulate the further development and application of this exciting research field.

We would like to express our profound gratitude to the chapter authors for their professionalism, their adherence to schedules, their enthusiasm, their patience, and, most of all, their high-quality contributions. We thank our collaborators at Wiley-VCH, especially Dr. Anne Brennfürher and Dr. Stefanie Volk, for their invaluable help from the conception to the realization of this project, and our project manager, Mamta Pujari, for unifying text and style.

Lausanne, Switzerland  
Beijing, China  
August 2014

*Jieping Zhu, Qian Wang  
Mei-Xiang Wang*

## Contents

List of Contributors XIII

Preface XVII

<b>1</b>	<b>General Introduction to MCRs: Past, Present, and Future</b>	<b>1</b>
	<i>Alexander Dömling and AlAnod D. AlQahtani</i>	
1.1	Introduction	1
1.2	Advances in Chemistry	2
1.3	Total Syntheses	4
1.4	Applications in Pharmaceutical and Agrochemical Industry	4
1.5	Materials	10
1.6	Outlook	10
	References	11
<b>2</b>	<b>Discovery of MCRs</b>	<b>13</b>
	<i>Eelco Ruijter and Romano V.A. Orru</i>	
2.1	General Introduction	13
2.2	The Concept	14
2.3	The Reaction Design Concept	15
2.3.1	Single Reactant Replacement	17
2.3.2	Modular Reaction Sequences	19
2.3.3	Condition-Based Divergence	21
2.3.4	Union of MCRs	23
2.4	Multicomponent Reactions and Biocatalysis	23
2.4.1	Multicomponent Reactions and (Dynamic) Enzymatic Kinetic Resolution	26
2.4.2	Multicomponent Reactions and Enzymatic Desymmetrization	29
2.5	Multicomponent Reactions in Green Pharmaceutical Production	31
2.6	Conclusions	36
	Acknowledgments	36
	References	36

<b>3</b>	<b>Aryne-Based Multicomponent Reactions</b>	<b>39</b>
	<i>Hiroto Yoshida</i>	
3.1	Introduction	39
3.2	Multicomponent Reactions of Arynes via Electrophilic Coupling	41
3.2.1	Multicomponent Reactions under Neutral Conditions	42
3.2.1.1	Isocyanide-Based Multicomponent Reactions	42
3.2.1.2	Imine-Based Multicomponent Reactions	46
3.2.1.3	Amine-Based Multicomponent Reactions	47
3.2.1.4	Carbonyl Compound-Based Multicomponent Reactions	49
3.2.1.5	Ether-Based Multicomponent Reactions	50
3.2.1.6	Miscellaneous	53
3.2.2	Multicomponent Reactions under Basic Conditions	53
3.3	Transition Metal-Catalyzed Multicomponent Reactions of Arynes	60
3.3.1	Annulations	60
3.3.2	Cross-Coupling-Type Reactions	65
3.3.3	Mizoroki–Heck-Type Reactions	65
3.3.4	Insertion into $\sigma$ -Bond	65
3.4	Concluding Remarks	69
	References	69
<b>4</b>	<b>Ugi–Smiles and Passerini–Smiles Couplings</b>	<b>73</b>
	<i>Laurent El Kaïm and Laurence Grimaud</i>	
4.1	Introduction	73
4.1.1	Carboxylic Acid Surrogates in Ugi Reactions	75
4.1.2	Smiles Rearrangements	76
4.2	Scope and Limitations	77
4.2.1	Phenols and Thiophenols	77
4.2.2	Six-Membered Ring Hydroxy Heteroaromatics and Related Mercaptans	84
4.2.3	Five-Membered Ring Hydroxy Heteroaromatic and Related Mercaptans	88
4.2.4	Related Couplings with Enol Derivatives	90
4.2.5	The Joullié–Smiles Coupling	90
4.2.6	The Passerini–Smiles Reaction	91
4.3	Ugi–Smiles Postcondensations	94
4.3.1	Postcondensations Involving Reduction of the Nitro Group	94
4.3.2	Transformations of Ugi–Smiles Thioamides	96
4.3.3	Postcondensations Involving Transition Metal-Catalyzed Processes	97
4.3.4	Reactivity of the Peptidyl Unit	101
4.3.5	Radical Reactions	103
4.3.6	Cycloaddition	103
4.4	Conclusions	105
	References	105

<b>5</b>	<b>1,3-Dicarbonyls in Multicomponent Reactions</b>	<b>109</b>
	<i>Xavier Bugaut, Thierry Constantieux, Yoann Coquerel, and Jean Rodriguez</i>	
5.1	Introduction	109
5.2	Achiral and Racemic MCRs	111
5.2.1	Involving One Pronucleophilic Reactive Site	111
5.2.2	Involving Two Reactive Sites	115
5.2.2.1	Two Nucleophilic Sites	115
5.2.2.2	One Pronucleophilic Site and One Electrophilic Site	120
5.2.3	Involving Three Reactive Sites	134
5.2.4	Involving Four Reactive Sites	139
5.3	Enantioselective MCRs	142
5.3.1	Involving One Reactive Site	143
5.3.2	Involving Two Reactive Sites	146
5.3.3	Involving Three Reactive Sites	149
5.4	Conclusions and Outlook	150
	References	151
 <b>6</b>	 <b>Functionalization of Heterocycles by MCRs</b>	 <b>159</b>
	<i>Esther Vicente-García, Nicola Kielland, and Rodolfo Lavilla</i>	
6.1	Introduction	159
6.2	Mannich-Type Reactions and Related Processes	160
6.3	$\beta$ -Dicarbonyl Chemistry	164
6.4	Hetero-Diels–Alder Cycloadditions and Related Processes	166
6.5	Metal-Mediated Processes	168
6.6	Isocyanide-Based Reactions	171
6.7	Dipole-Mediated Processes	175
6.8	Conclusions	176
	Acknowledgments	178
	References	178
 <b>7</b>	 <b>Diazoacetate and Related Metal-Stabilized Carbene Species in MCRs</b>	 <b>183</b>
	<i>Dong Xing and Wenhao Hu</i>	
7.1	Introduction	183
7.2	MCRs via Carbonyl or Azomethine Ylide-Involved 1,3-Dipolar Cycloadditions	184
7.2.1	Azomethine Ylide	184
7.2.2	Carbonyl Ylide	185
7.3	MCRs via Electrophilic Trapping of Protic Onium Ylides	187
7.3.1	Initial Development	187
7.3.2	Asymmetric Examples	190
7.3.2.1	Chiral Reagent Induction	190
7.3.2.2	Chiral Dirhodium(II) Catalysis	190
7.3.2.3	Enantioselective Synergistic Catalysis	190
7.3.3	MCRs Followed by Tandem Cyclizations	196

7.4	MCRs via Electrophilic Trapping of Zwitterionic Intermediates	198
7.5	MCRs via Metal Carbene Migratory Insertion	199
7.6	Summary and Outlook	203
	References	204
<b>8</b>	<b>Metal-Catalyzed Multicomponent Synthesis of Heterocycles</b>	<b>207</b>
	<i>Fabio Lorenzini, Jevgenijs Tjutris, Jeffrey S. Quesnel, and Bruce A. Arndtsen</i>	
8.1	Introduction	207
8.2	Multicomponent Cross-Coupling and Carbonylation Reactions	208
8.2.1	Cyclization with Alkyne- or Alkene-Containing Nucleophiles	208
8.2.2	Cyclization via Palladium-Allyl Complexes	210
8.2.3	Fused-Ring Heterocycles for <i>ortho</i> -Substituted Arene Building Blocks	211
8.2.4	Multicomponent Cyclocarbonylations	214
8.2.5	Cyclization of Cross-Coupling Reaction Products	216
8.2.6	C–H Functionalization in Multicomponent Reactions	218
8.3	Metallacycles in Multicomponent Reactions	221
8.4	Multicomponent Reactions via 1,3-Dipolar Cycloaddition	223
8.5	Concluding Remarks	227
	References	227
<b>9</b>	<b>Macrocycles from Multicomponent Reactions</b>	<b>231</b>
	<i>Ludger A. Wessjohann, Ricardo A.W. Neves Filho, Alfredo R. Puentes, and Micjel C. Morejon</i>	
9.1	Introduction	231
9.2	IMCR-Based Macrocyclizations of Single Bifunctional Building Blocks	237
9.3	Multiple MCR-Based Macrocyclizations of Bifunctional Building Blocks	245
9.4	IMCR-Based Macrocyclizations of Trifunctionalized Building Blocks (MiB-3D)	256
9.5	Sequential IMCR-Based Macrocyclizations of Multiple Bifunctional Building Blocks	259
9.6	Final Remarks and Future Perspectives	261
	References	261
<b>10</b>	<b>Multicomponent Reactions under Oxidative Conditions</b>	<b>265</b>
	<i>Andrea Basso, Lisa Moni, and Renata Riva</i>	
10.1	Introduction	265
10.2	Multicomponent Reactions Involving <i>In Situ</i> Oxidation of One Substrate	266
10.2.1	Isocyanide-Based Multicomponent Reactions	266
10.2.1.1	Passerini Reactions	266
10.2.1.2	Ugi Reactions with <i>In Situ</i> Oxidation of Alcohols	271
10.2.1.3	Ugi Reaction with <i>In Situ</i> Oxidation of Secondary Amines	273

10.2.1.4	Ugi–Smiles Reaction with <i>In Situ</i> Oxidation of Secondary Amines	275
10.2.1.5	Ugi-Type Reactions by <i>In Situ</i> Oxidation of Tertiary Amines	277
10.2.1.6	Synthesis of Other Derivatives	279
10.2.2	Other Multicomponent Reactions	280
10.3	Multicomponent Reactions Involving Oxidation of a Reaction Intermediate	284
10.3.1	Reactions without Transition Metal-Mediated Oxidation	285
10.3.2	Reactions Mediated by Transition Metal Catalysis	292
10.4	Multicomponent Reactions Involving Oxidants as Lewis Acids	295
10.5	Conclusions	297
	References	297
<b>11</b>	<b>Allenes in Multicomponent Synthesis of Heterocycles</b>	<b>301</b>
	<i>Hans-Ulrich Reissig and Reinhold Zimmer</i>	
11.1	Introduction	301
11.2	Reactions with 1,2-Propadiene and Unactivated Allenes	302
11.2.1	Palladium-Catalyzed Multicomponent Reactions	302
11.2.2	Copper-, Nickel-, and Rhodium-Promoted Multicomponent Reactions	310
11.2.3	Multicomponent Reactions without Transition Metals	314
11.3	Reactions with Acceptor-Substituted Allenes	316
11.3.1	Catalyzed Multicomponent Reactions	316
11.3.2	Uncatalyzed Multicomponent Reactions	318
11.4	Reactions with Donor-Substituted Allenes	323
11.5	Conclusions	329
	List of Abbreviations	329
	References	329
<b>12</b>	<b>Alkynes in Multicomponent Synthesis of Heterocycles</b>	<b>333</b>
	<i>Thomas J.J. Müller and Konstantin Deilhof</i>	
12.1	Introduction	333
12.2	$\sigma$ -Nucleophilic Reactivity of Alkynes	335
12.2.1	Acetylide Additions to Electrophiles	335
12.2.1.1	Alkyne–Aldehyde–Amine Condensation – $A^3$ -Coupling	335
12.2.1.2	Alkyne–(Hetero)Aryl Halide (Sonogashira) Coupling as Key Reaction	337
12.2.2	Conversion of Terminal Alkynes into Electrophiles as Key Reactions	341
12.3	$\pi$ -Nucleophilic Reactivity of Alkynes	345
12.4	Alkynes as Electrophilic Partners	351
12.5	Alkynes in Cycloadditions	356
12.5.1	Alkynes as Dipolarophiles	356
12.5.2	Alkynes in Cu(I)-Catalyzed 1,3-Dipolar Azide–Alkyne Cycloaddition	358



12.5.3	Alkynes as Dienophiles in MCRs	366
12.6	Alkynes as Reaction Partners in Organometallic MCRs	370
12.7	Conclusions	374
	List of Abbreviations	374
	Acknowledgment	375
	References	375
<b>13</b>	<b>Anhydride-Based Multicomponent Reactions</b>	<b>379</b>
	<i>Kevin S. Martin, Jared T. Shaw, and Ashkaan Younai</i>	
13.1	Introduction	379
13.2	Quinolones and Related Heterocycles from Homophthalic and Isatoic Anhydrides	380
13.2.1	Introduction: Reactivity of Homophthalic and Isatoic Anhydrides	380
13.2.2	Imine–Anhydride Reactions of Homophthalic Anhydride	380
13.2.3	MCRs Employing Homophthalic Anhydride	382
13.2.4	Imine–Anhydride Reactions of Isatoic Anhydride	383
13.3	$\alpha,\beta$ -Unsaturated Cyclic Anhydrides: MCRs Involving Conjugate Addition and Cycloaddition Reactions	385
13.3.1	Maleic Anhydride MCRs	385
13.3.2	MCRs of Itaconic Anhydrides	388
13.3.3	Diels–Alder Reactions	390
13.4	MCRs of Cyclic Anhydrides in Annulation Reactions and Related Processes	392
13.4.1	MCR-Based Annulations: Succinic and Phthalic Anhydrides	393
13.5	MCRs of Acyclic Anhydrides	395
13.6	Conclusions	398
	References	399
<b>14</b>	<b>Free-Radical Multicomponent Processes</b>	<b>401</b>
	<i>Virginie Liautard and Yannick Landais</i>	
14.1	Introduction	401
14.2	MCRs Involving Addition Across Olefin C=C Bonds	402
14.2.1	Addition of Aryl Radicals to Olefins	402
14.2.2	MCRs Using Sulfonyl Derivatives as Terminal Trap	404
14.2.3	Carboallylation of Electron-Poor Olefins	406
14.2.4	Carbohydroxylation, Sulfenylation, and Phosphorylation of Olefins	407
14.2.5	Radical Addition to Olefins Using Photoredox Catalysis	410
14.2.6	MCRs Based on Radical–Polar Crossover Processes	414
14.3	Free-Radical Carbonylation	419
14.3.1	Alkyl Halide Carbonylation	419
14.3.2	Metal-Mediated Atom-Transfer Radical Carbonylation	420
14.3.3	Alkane Carbonylation	421
14.3.4	Miscellaneous Carbonylation Reactions	423