

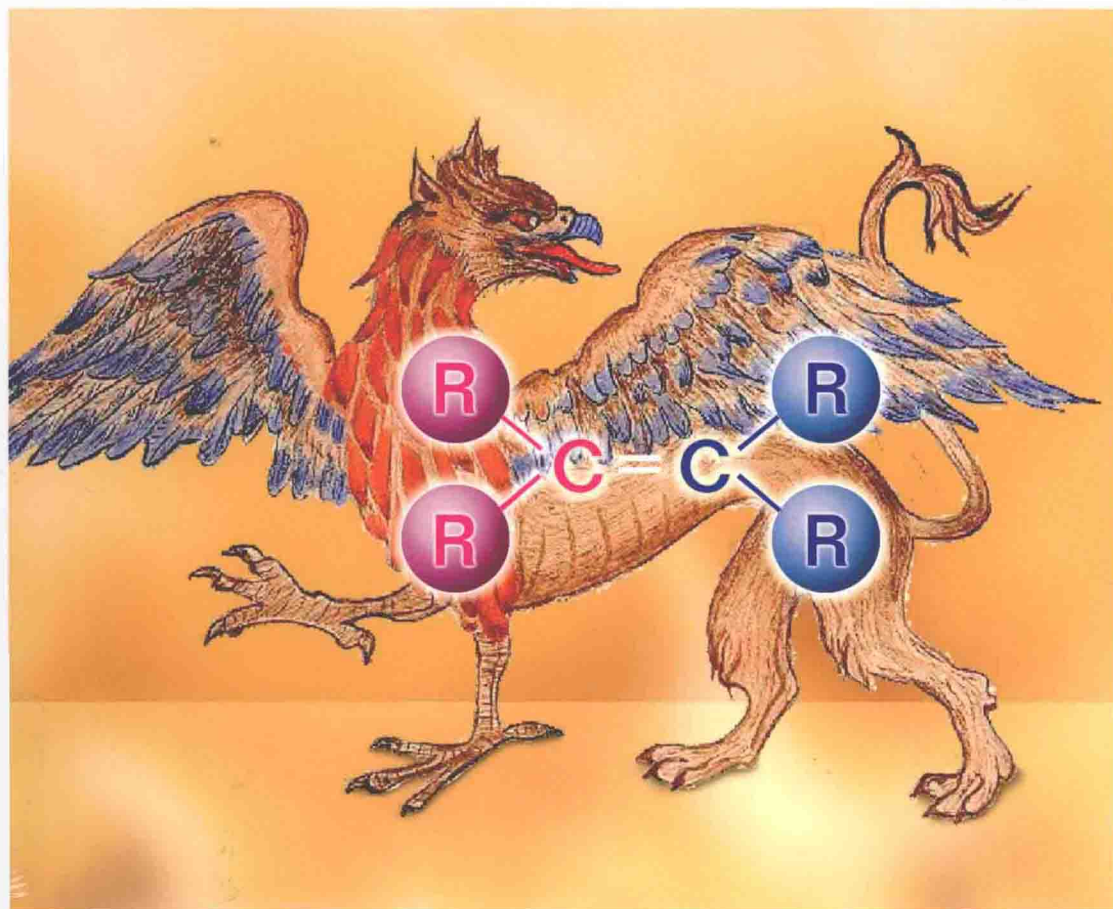
Edited by Janine Cossy,
Stellios Arseniyadis, and Christophe Meyer

 WILEY-VCH

Metathesis in Natural Product Synthesis

Strategies, Substrates and Catalysts

With a Foreword by Robert H. Grubbs



Metathesis in Natural Product Synthesis

Strategies, Substrates and Catalysts

Edited by

Janine Cossy, Stelios Arseniyadis, and Christophe Meyer

With a Foreword by Robert H. Grubbs



WILEY-VCH Verlag GmbH & Co. KGaA

The Editors

Prof. Janine Cossy

Laboratoire de Chimie
Organique, ESPCI
10 Rue Vauquelin
75231 Paris Cedex 05
France

Dr. Stellos Arseniyadis

Laboratoire de Chimie
Organique, ESPCI
10 Rue Vauquelin
75231 Paris Cedex 05
France

Dr. Christophe Meyer

Laboratoire de Chimie
Organique, ESPCI
10 Rue Vauquelin
75231 Paris Cedex 05
France

Cover

The gryffon painting being part of the front cover picture has been kindly provided by Dominique Escortell

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>.

© 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

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.

Cover Adam Design, Weinheim

Typesetting Laserwords Private Limited, Chennai, India

Printing and Binding Strauss GmbH, Mörlenbach

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32440-8

Foreword

In the last few decades, metathesis has been among the key reactions that have revolutionized the synthesis of complex molecules. Many organic chemists in academic and industrial laboratories, in the field of natural products, have used this reaction as a very practical, versatile, and selective synthetic tool. Olefin metathesis has helped to elevate the art and science of chemical synthesis to its present high level.

The examples in this book will demonstrate that organic chemists, with the metathesis reaction in hand, have a new way to consider the connections that are required for efficient access to natural products. This book assembles the most important and interesting examples in the synthesis of natural products using metathesis. Owing to the possibilities opened by olefin and acetylenic metathesis, a great variety of carbocyclic – nitrogen-, oxygen-, sulfur-containing heterocycles – natural products with small-, medium-, and macrocyclic size can be obtained rapidly. The synthetic transformations that couple metathesis steps in cascade reactions are particularly elegant. Emphasis has been put on the metathesis step showing the importance of the catalysts that are tolerant of a large variety of functional groups, very regio-, stereoselective, and even enantioselective. The power of the catalysts and of the metathesis reaction can be appreciated when alternative pathways are considered.

Every reaction and catalyst can always be improved. In the area of metathesis, the development of more active and robust catalysts, catalysts that can control the *E* and *Z* stereoselectivity of the formed olefins, particularly the stereoselectivity of trisubstituted olefins, or catalysts that can control the enantioselectivity remains a challenge. As has been demonstrated in the past, improvements of the catalysts give rise to increasingly exciting applications in the field of complex molecules and particularly in the field of natural products synthesis. This book will be a good source of inspiration for those planning future developments of metathesis reactions in the field of natural and non-natural products.

Robert H. Grubbs

Preface

In the 1960s, the ring-opening polymerization of cycloalkenes and the disproportionation of linear alkenes, both used by the polymer and the petroleum industry, were the first reported examples of “olefin metathesis reactions.” Whereas those transformations were generally carried out with ill-defined catalysts, the mechanism of olefin metathesis proposed by Chauvin and H  risson in 1971 identified metal carbenes as catalytically active species with reactions proceeding through metallacyclobutane intermediates. The mid-1970s saw the emergence of the first well-defined alkylidene–metal complexes for olefin metathesis initially based on tantalum and tungsten. However, in the late 1980s, the quest for higher functional group tolerance resulted in the development of the molybdenum complex, also known as *Schrock’s catalyst*, which was later used by Grubbs and Fu in ring-closing metathesis (RCM) to access oxygen and nitrogen heterocycles. Up to now, several applications of RCM to natural products synthesis have been reported using Schrock’s catalyst as the initiator; however, its air- and moisture sensitivity, which implies the use of a glove box or Schlenk techniques, has certainly hampered its more widespread use by organic chemists. In 1992, Grubbs and coworkers reported the first stable vinylidene ruthenium catalyst to be active in both ring-opening metathesis (ROM) and RCM. In 1995, further refinements led to the development of an air- and moisture-stable as well as highly functional group-tolerant benzylidene ruthenium complex also known as *Grubbs first-generation catalyst*. The latter became the first user-friendly metathesis catalyst and has allowed numerous synthetic applications. The replacement of one phosphine by a strongly σ -donating *N*-heterocyclic carbene ligand to further improve the stability of the active species and accelerate the initiation phase stimulated the discovery of the second-generation catalysts. To date, many catalysts have been devised with the goal of improving the rate of initiation and the stability of the catalytic propagating species to enable the metathesis of sterically hindered substrates. This was attained by fine-tuning the steric and/or electronic properties of the benzylidene part or the *N*-heterocyclic carbene of the ruthenium complexes, and/or other subtle ligand exchange. For the tremendous impact of metathesis in the science of organic synthesis, Chauvin, Grubbs, and Schrock received the Nobel Prize in Chemistry in 2005.

The aim of the book is to emphasize the impact of metathesis on the synthesis of natural products and/or biologically active compounds, and highlight how they

have provided new and elegant solutions to many synthetic puzzles. As RCM has been the first class of metathesis reactions routinely used in natural products chemistry, the first three chapters of the book will highlight its applications to the synthesis of small- to medium-size carbocycles (Chapter 1, N. Blanchard and J. Eustache), nitrogen heterocycles (Chapter 2, L. van Delft and Floris P. J. T. Rutjes), and oxygen heterocycles (Chapter 3, J. D. Rainier). Phosphorus and sulfur heterocycles synthesized *via* RCM also deserved a section since they have found useful applications in the stereoselective synthesis of acyclic subunits found in various natural products (Chapter 4, C.D. Thomas and P.R. Hanson). The use of RCM for the synthesis of macrocyclic compounds has also been covered (Chapter 5, A. Gradillas and J. Pérez-Castells) since it constitutes an attractive alternative to traditional routes such as macrolactonization or macrolactamization. Alkynes can also be used as reacting partners in metathesis reactions as illustrated in the two following chapters of the book. Indeed, while ene-yne metathesis catalyzed by alkylidene ruthenium complexes allows a convenient access to conjugated dienes (Chapter 6, M. Mori), ring-closing alkyne metathesis using a well-defined tungsten-alkylidyne complex or molybdenum precatalysts activated *in situ* offers a convenient route toward cycloalkynes (Chapter 7, P. Davies). As for many reactions, there are situations where a planned metathesis event was found to be either unsuccessful or did not operate with high efficiency, stereoselectivity, and/or chemoselectivity. Silicon-tethered metathesis (Chapter 8, P. A. Evans) and the use of an unsaturated relay allowing initiation of metathesis at an appropriate reactive site (Chapter 9, T. R. Hoyer and J. Jeon) are two strategies that have been used to circumvent some of these problems. More recently, cross-metathesis (CM) has emerged as a useful catalytic and chemoselective alternative to traditional olefination methods. Applications in the context of natural product synthesis have therefore been covered (Chapter 10, J. Prunet and L. Grimaud). After disclosing the synthetic potential of each of the different metathesis reactions, it appeared important to illustrate how their combination in cleverly designed cascades has led to some impressive and elegant synthesis of structurally complex natural products (Chapter 11, M. Porta and S. Blechert). The development of chiral molybdenum or ruthenium catalyst has also enabled the achievement of enantioselective metathesis reactions whose applications yet reported to the synthesis of natural products have been listed in one chapter (Chapter 12, A. H. Hoveyda, S. J. Malcolmson, S. J. Meek, and A. R. Zhugralin). Finally, the last section of the book is devoted to solid-phase metathesis, which constitutes a useful tool in diversity-oriented synthesis for chemical biology while also simplifying the purification stages (Chapter 13, S. Barluenga, P.-Y. Dakas, R. Jogireddy, G. Valot, and N. Winssinger).

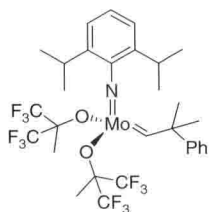
We would like to warmly thank all the authors for contributing to this book and acknowledge their expertise on the different topics that have been covered. We also thank the team at Wiley-VCH and especially Stefanie Volk for her helpful assistance during the preparation of this book.

We sincerely hope that this book will be a valuable source of information for researchers working in both academic and industrial laboratories and that it will

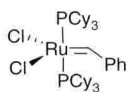
stimulate new applications and developments of metathesis in the field of natural product synthesis.

Janine Cossy, Stelios Arseniyadis, and Christophe Meyer.

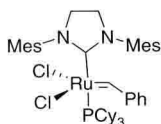
List of Catalysts



[Mo]-I



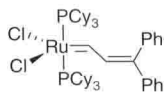
[Ru]-I



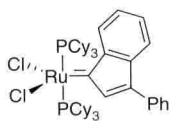
[Ru]-II



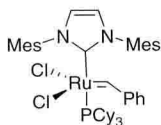
[Ru]-III



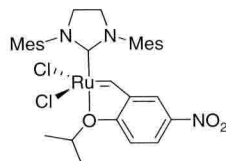
[Ru]-IV



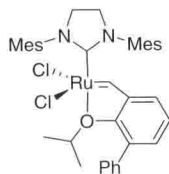
[Ru]-V



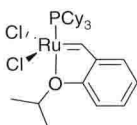
[Ru]-VI



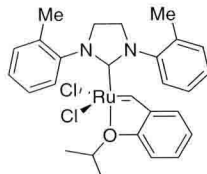
[Ru]-VII



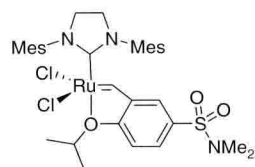
[Ru]-VIII



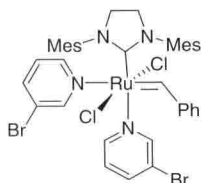
[Ru]-IX



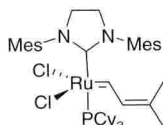
[Ru]-X



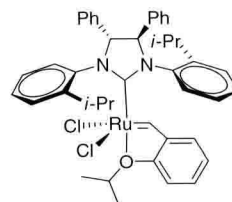
[Ru]-XI



[Ru]-XII



[Ru]-XIII



(R,R)-[Ru]-XIV

List of Contributors

Sofia Barluenga

Université Louis Pasteur de
Strasbourg
Organic and Bioorganic
Chemistry Laboratory
Institut de Science et Ingénierie
Supramoléculaire
8 Allée Gaspard Monge
67000 Strasbourg
France

Nicolas Blanchard

Université de Haute-Alsace
Ecole Nationale Supérieure de
Chimie de Mulhouse
Laboratoire de Chimie Organique
et Bioorganique associé au CNRS
3 Rue Alfred Werner
68093 Mulhouse Cedex
France

Siegfried Blechert

Technische Universität Berlin
Institute of Chemistry
Straße des 17. Juni 135
10623 Berlin
Germany

Pierre-Yves Dakas

Université Louis Pasteur de
Strasbourg
Organic and Bioorganic
Chemistry Laboratory
Institut de Science et Ingénierie
Supramoléculaire
8 Allée Gaspard Monge
67000 Strasbourg
France

Paul W. Davies

University of Birmingham
School of Chemistry
Birmingham
B15 2TT
United Kingdom

Jacques Eustache

Université de Haute-Alsace
Ecole Nationale Supérieure de
Chimie de Mulhouse
Laboratoire de Chimie Organique
et Bioorganique associé au CNRS
3 Rue Alfred Werner
68093 Mulhouse Cedex
France

P. Andrew Evans

The University of Liverpool
Department of Chemistry
Crown Street
Liverpool L69 7ZD
UK

Ana Gradillas

Universidad CEU-San Pablo
Departamento de Química
Facultad de Farmacia
Urb. Montepríncipe
28668 Boadilla del Monte
Madrid
Spain

Laurence Grimaud

Ecole Nationale Supérieure des
Techniques Avancées
Unité Chimie et Procédés
32 boulevard Victor
75739 Paris Cedex 15
France

Paul R. Hanson

University of Kansas
Department of Chemistry
1251 Wescoe Hall Drive
Malott Hall
Lawrence, KS 66045
USA

Amir H. Hoveyda

Boston College
Department of Chemistry
Eugene F. Merkert
Chemistry Center
Chestnut Hill
MA 02467
USA

Thomas R. Hoye

University of Minnesota
Department of Chemistry
207 Pleasant Street
SE
Minneapolis
Minnesota 55455
USA

Junha Jeon

University of Minnesota
Department of Chemistry
207 Pleasant Street
SE
Minneapolis
Minnesota 55455
USA

Rajamalleswaramma Jogireddy

Université Louis Pasteur de
Strasbourg
Organic and Bioorganic
Chemistry Laboratory
Institut de Science et Ingénierie
Supramoléculaire
8 Allée Gaspard Monge
67000 Strasbourg
France

Steven J. Malcolmson

Boston College
Department of Chemistry
Eugene F. Merkert
Chemistry Center
Chestnut Hill
MA 02467
USA

Simon J. Meek

Boston College
Department of Chemistry
Eugene F. Merkert
Chemistry Center
Chestnut Hill
MA 02467
USA

Silvie A. Meeuwissen

Radboud University Nijmegen
Institute for Molecules and
Materials
Heyendaalseweg 135
6525 ED Nijmegen
The Netherlands

Miwako Mori

Health Sciences University of
Hokkaido
Ishikari-Tobetsu
Hokkaido
061-0293
Japan

Marta Porta

Technische Universität Berlin
Institute of Chemistry
Straße des 17. Juni 135
10623 Berlin
Germany

Joëlle Prunet

Ecole Polytechnique
Laboratoire de Synthèse
Organique
UMR CNRS 7652
DCSO
91128 Palaiseau
France

Javier Pérez-Castells

Universidad CEU-San Pablo
Departamento de Química
Facultad de Farmacia
Urb. Montepríncipe
28668 Boadilla del Monte
Madrid
Spain

Jon D. Rainier

University of Utah
Department of Chemistry
315 East 1400 South
Salt Lake City
UT 84112
USA

Floris P. J. T. Rutjes

Radboud University Nijmegen
Institute for Molecules and
Materials
Heyendaalseweg 135
6525 ED Nijmegen
The Netherlands

Christopher D. Thomas

University of Kansas
Department of Chemistry
1251 Wescoe Hall Drive
Malott Hall
Lawrence, KS 66045
USA

**Sebastiaan (Bas) A. M. W.
van den Broek**

Radboud University Nijmegen
Institute for Molecules and
Materials
Heyendaalseweg 135
6525 ED Nijmegen
The Netherlands

Floris L. van Delft

Radboud University Nijmegen
Institute for Molecules and
Materials
Heyendaalseweg 135
6525 ED Nijmegen
The Netherlands

Gaële Valot

Université Louis Pasteur de
Strasbourg
Organic and Bioorganic
Chemistry Laboratory
Institut de Science et Ingénierie
Supramoléculaire
8 Allée Gaspard Monge
67000 Strasbourg
France

Nicolas Winssinger

Université Louis Pasteur de
Strasbourg
Organic and Bioorganic
Chemistry Laboratory
Institut de Science et Ingénierie
Supramoléculaire
8 Allée Gaspard Monge
67000 Strasbourg
France

Adil R. Zhugralin

Boston College
Department of Chemistry
Eugene F. Merkert
Chemistry Center
Chestnut Hill
MA 02467
USA

Abbreviations

Ac	acetyl
acac	acetylacetonato
AIBN	azobisisobutyronitrile
Ar	aryl
AROM	asymmetric ring-closing metathesis
BBN	9-borabicyclononane
9-BBN	9-borabicyclo[3.3.0]nonan-9-yl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOM	benzyloxymethyl
BQ	1,4-benzoquinone
Bz	benzoyl
CAN	ceric ammonium nitrate
Cat.	catalytic
Cbz	benzyloxycarbonyl
CM	cross-metathesis
COD	cycloocta-1,5-diene
Cp	cyclopentadienyl
Cp [*]	1,2,3,4,5-pentamethylcyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIAD	diisopropyl azodicarboxylate
DIPEA	diisopropylethylamine
DMAP	<i>N,N</i> -dimethylaminopyridine
DMB	3',5'-dimethoxybenzoin
dmdba	bis(3,5-dimethoxybenzylidene)acetone
DMDO	dimethyldioxirane
DMF	<i>N,N</i> -dimethylformamide

DMP	Dess-Martin periodinane
DMP	dimethoxypropane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
Fmoc	9-fluorenylmethoxycarbonyl
Grubbs II	benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro(tricyclohexylphosphine) ruthenium
HMDS	hexamethyldisilazane
HPMA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
<i>i</i> -pr	isopropyl
IBX	2-iodoxybenzoic acid
dIcr	(+)- β -caranyl
Im	imidazole
Ipc	diisopinocampheyl
KHMDS	potassium hexamethyldisilazide
LDA	lithium N,N-diisopropylamide
LiHMDS	lithium bistrimethylsilylamide
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
MEM	2-methoxyethoxymethoxy
Mes	mesityl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
NMO	N-methylmorpholine N-oxide
PCC	pyridinium chlorochromate
Ph	phenyl
Phth	phthalyl
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
PMP	4-methoxyphenyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>p</i> Ts	<i>para</i> -toluenesulfonyl
Py	pyridine
Quant.	quantitative
RCAM	ring-closing alkyne metathesis

RCEYM	ring-closing ene-yne metathesis
RCM	ring-closing metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
RRCM	relay ring-closing metathesis
RRM	ring-rearrangement metathesis
rt	room temperature
<i>t</i> -Bu	tertiary butyl
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TCE	trichloroethoxymethoxy
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
2-Th	2-thienyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol-BINAP	2,2'-bis(ditolylphosphino)-1,1'-binaphthalene
TPAP	tetra(<i>n</i> -propyl)ammonium perruthenate
Tr	triphenylmethyl (trityl)
Trt	trityl
Ts	<i>p</i> -toluenesulfonyl
TS	transition state

Contents

	Foreword	V
	Preface	XV
	List of Catalysts	XIX
	List of Contributors	XXI
	Abbreviations	XXV
1	Synthesis of Natural Products Containing Medium-size Carbocycles by Ring-closing Alkene Metathesis	1
	<i>Nicolas Blanchard and Jacques Eustache</i>	
1.1	Introduction	1
1.2	Formation of Five-membered Carbocycles by RCM	11
1.3	Formation of Six-membered Carbocycles by RCM	11
1.4	Formation of Seven-membered Carbocycles by RCM	22
1.5	Formation of Eight-membered Carbocycles by RCM	30
1.6	Formation of Nine-membered Carbocycles by RCM	33
1.7	Formation of 10-membered Carbocycles by RCM	34
1.8	Conclusion	39
	References	40
2	Natural Products Containing Medium-sized Nitrogen Heterocycles Synthesized by Ring-closing Alkene Metathesis	45
	<i>Sebastiaan (Bas) A. M. W. van den Broek, Silvie A. Meeuwissen, Floris L. van Delft, and Floris P. J. T. Rutjes</i>	
2.1	Introduction	45
2.2	Five-membered Nitrogen Heterocycles	47
2.2.1	Dihydropyrroles	47
2.2.2	Pyrrolidine Alkaloids	47
2.2.2.1	Pyrrolidines	47
2.2.2.2	Dipyrrolidines	49
2.2.2.3	Polyhydroxypyrrolidines	49
2.2.3	Indolizidine Alkaloids	52
2.2.3.1	Polycyclic Indolizidines	52

2.2.3.2	Polyhydroxyindolizidines	55
2.2.4	Pyrrolizidine Alkaloids	59
2.3	Six-membered Nitrogen Heterocycles	61
2.3.1	Piperidine Alkaloids	61
2.3.1.1	Piperidines	61
2.3.1.2	Piperidine Carboxylic Acids	66
2.3.1.3	Piperidones	68
2.3.1.4	Polyhydroxypiperidines	69
2.3.2	Indolizidine Alkaloids	70
2.3.3	Quinolizidine Alkaloids	73
2.4	Seven-membered Nitrogen Heterocycles	78
2.5	Eight-membered Nitrogen Heterocycles	81
2.6	Conclusion	82
	References	83
3	Synthesis of Natural Products Containing Medium-size Oxygen Heterocycles by Ring-closing Alkene Metathesis	87
	<i>Jon D. Rainier</i>	
3.1	Introduction	87
3.2	General RCM Approaches to Medium Rings	89
3.3	Laurencin	95
3.4	Eunicellins/Eleutherobin	102
3.5	Helianane	104
3.6	Octalactin A	105
3.7	Microcarpalide and the Herbarums	106
3.8	Marine Ladder Toxins	109
3.8.1	Ciguatoxin	109
3.8.2	Brevetoxin	117
3.8.3	Gambierol, Gambieric Acid, Olefinic-ester Cyclizations	120
3.9	Conclusion	124
	Acknowledgments	124
	References	124
4	Phosphorus and Sulfur Heterocycles via Ring-closing Metathesis: Application in Natural Product Synthesis	129
	<i>Christopher D. Thomas and Paul R. Hanson</i>	
4.1	Introduction	129
4.2	Synthesis and Reactivity of Sultones Derived from RCM	129
4.3	Total Synthesis of the Originally Proposed Structure of (±)-Mycothiazole	132
4.4	Synthesis and Reactivity of Phosphates from RCM	134
4.5	Applications of Phosphate Tethers in the Synthesis of Dolabelide C	140
4.6	Conclusion	144