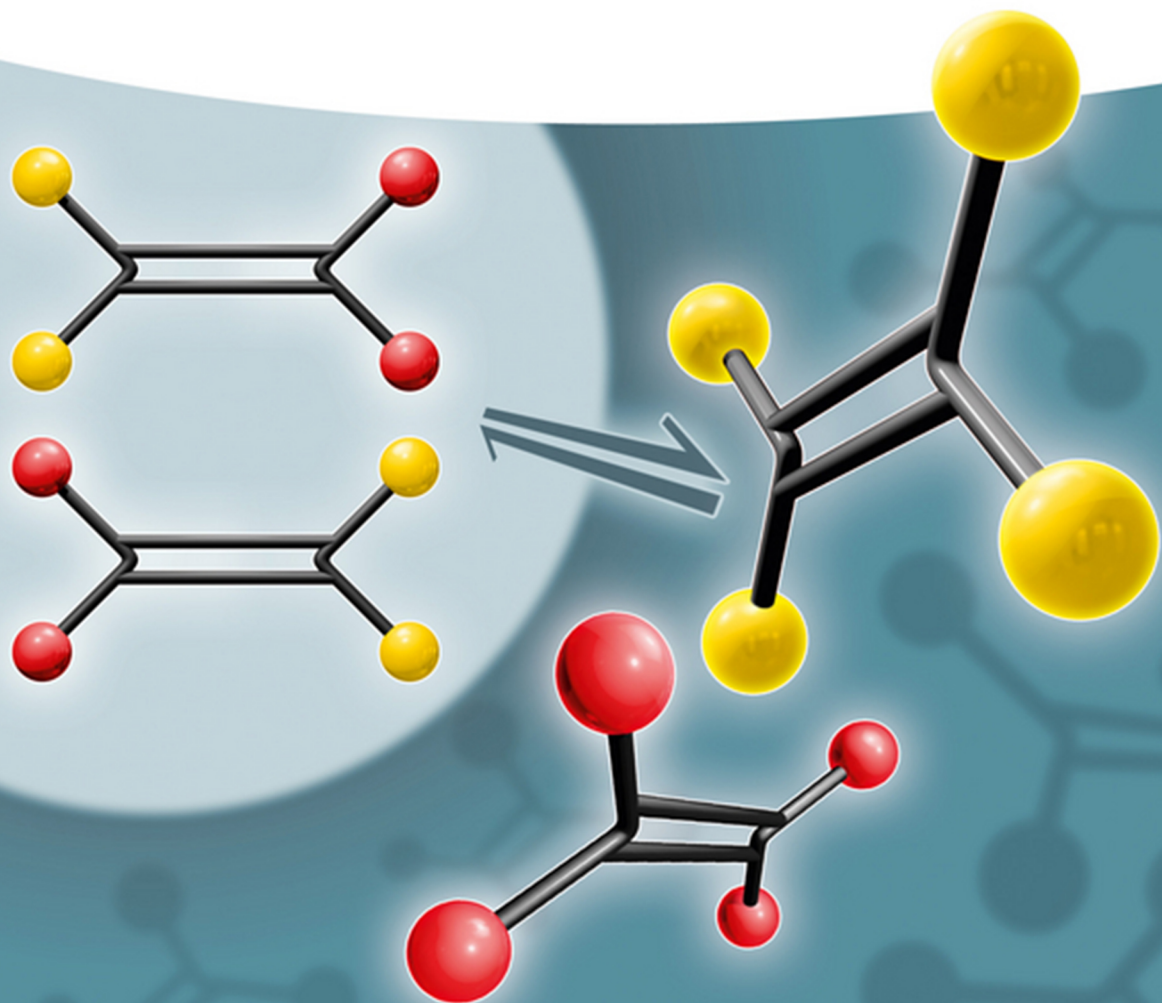


Edited by Robert H. Grubbs and Daniel J. O'Leary

# Handbook of Metathesis

Second Edition

Volume 2: Applications in Organic Synthesis





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and Daniel J. O'Leary*

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Applications in Organic Synthesis*



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# **Handbook of Metathesis**

Volume 2: Applications in Organic Synthesis

*Second Edition*

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## Preface

In 2003, the first edition of the Handbook of Metathesis comprehensively covered the origins of the olefin metathesis reaction and the myriad of applications blossoming from the development of robust, homogeneous transition-metal catalysts. In the intervening 10 years, applications and advances in this field have continued to exponentially increase. To date, 3732 publications regarding olefin metathesis have been reported; of these, 2292 have been reported since 2003!<sup>1)</sup> By 2005, olefin metathesis had become so integral to the field of organic synthesis that the Nobel Prize in Chemistry was awarded to the field (Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock) [1, 2].

In light of these many advancements, a second edition of the Handbook is quite timely. Early on in the planning, it was decided that rather than simply updating the 2003 edition, the second edition would instead emphasize important advancements (e.g., new ligands, diastereoselective metathesis, alkyne metathesis, industrial applications, self-healing polymers) that have occurred during the past decade. In addition, the past 10 years have seen important developments in our understanding of the metathesis mechanism utilizing both computational and mechanistic studies. A greater knowledge of catalyst decomposition, product purification, and the use of supported catalysts and nontraditional reaction media have further enhanced the utility of metathesis systems. A number of new applications are now becoming commercialized based on these new catalyst systems. For example, the first pharmaceutical that uses olefin metathesis in a key step is now commercially available, and a biorefinery that utilizes a homogeneous catalyst is now in production.

Similar to the first edition of this Handbook, contributions have been arranged into three volumes. Volume I (Anna Wenzel, coeditor) emphasizes recent catalyst developments and mechanism and is intended to provide a foundation for the applications discussed throughout the rest of the Handbook. Volume II (Dan O'Leary, coeditor) covers synthetic applications of the olefin metathesis reaction, and polymer chemistry is the topic of Volume III (Ezat Khosravi, coeditor). Chapter topics have been selected to provide comprehensive coverage of these

1) Data obtained from keyword searches conducted within the ISI Web of Science (accessed 1/18/2014).

areas of olefin metathesis. Contributors, many of whom are pioneers in the field, were chosen based on their firsthand experience with the topics discussed.

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## List of Abbreviations

3-CR	three-component reaction
4CC	four-component condensation
Ac	acetyl
ACM	alkyne cross metathesis
ADMAC	acyclic diene metathesis macrocyclization
ADMET	acyclic diene metathesis
ADIMET	acyclic diyne metathesis
Agl	allyl glycine
AIBN	azobisisobutyronitrile
Alloc	allyl carbamate
API	active pharmaceutical ingredient
ARCM	asymmetric ring-closing metathesis
ATRA	atom transfer radical addition
AVM	arylenevinylene macrocycles
B/C/P	build/couple/pair
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di- <i>tert</i> -butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BODIPY	boron-dipyrromethene
BOM	benzyloxymethyl
BOP	benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate
BPS, TBDPS	<i>tert</i> -butyldiphenylsilyl
BRSM, brsm	based on recovered starting material
Bs	brosyl, <i>p</i> -bromobenzenesulfonyl
BTIB	bis(trifluoroacetoxy)iodobenzene
Bz	benzoyl
CAN	ceric ammonium nitrate
CBS	Corey–Bakshi–Shibata
Cbz	benzyloxycarbonyl

CD	circular dichroism
CDI	1,1'-carbonyldiimidazole
CDT	cyclododecatriene
CLPCS	cyclolinear polycarbosilanes
CM	cross-metathesis
CME	carboxymethyl migrastatin ether
CNS	central nervous system
COD	1,5-cyclooctadiene
COGs	cost-of-goods
Cp*	pentamethylcyclopentadienyl
CPA	chiral phosphoric acid
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
DA	Diels-Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
Das	diaminosuberic acid
dba	dibenzylideneacetone
dbcot	dibenzo[a,e]cyclooctatetraene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
DDA	dodecenoate
DDE	dimethyl dodecanedioate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DFT	density functional theory
Dha	dehydroalanine
DIAD	diisopropyl acetylenedicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIEA, DIPEA	<i>N,N</i> -diisopropylethylamine; Hünig's base
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DMBM	3,4-dimethoxybenzyloxymethyl
DMDA	dimethyldiacetylene
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	<i>N,N'</i> -dimethylpropylene urea
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
DOSP	<i>N</i> -(dodecylbenzenesulfonyl)prolinate)
dppp	1,3-bis(diphenylphosphino)propane



DSRCM	diastereoselective ring-closing metathesis
DTBP	2,6-di- <i>tert</i> -butylphenol
DTS	diverted total synthesis
EDA	ethyl diazoacetate
EDC, EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron donor group
ELT	end-of-life tire
EM	effective molarity
ERCM	enantioselective ring-closing metathesis
EROCM	enantioselective ring-opening/cross-metathesis
ERORCM	enantioselective ring-opening/ring-closing metathesis
Ery	erythromycin
EWB	electron withdrawing group
FAME	fatty acid methyl esters
FGP	functional group pairing
Fmoc	fluorenylmethyloxycarbonyl
FRET	fluorescence resonance energy transfer
F-SPE	fluorous-solid-phase extraction
FTO	freedom to operate
GFP	green fluorescent protein
GHRH	growth-hormone-releasing hormone
GSK	GlaxoSmithKline
HBS	hydrogen-bond surrogate
HCV	hepatitis C virus
HDAC	histone deacetylase
HFIP	hexafluoroisopropanol
HH	head-to-head
HMPA	hexamethylphosphoramide
HMSBO	hydrogenated metathesized soybean oil
HNBR	hydrogenated nitrile butadiene rubber
HO-DEAD	hydrogenated oligomeric azodicarboxylate
HPK	hetero-Pauson–Khand
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HT	head-to-tail
HTS	high-throughput screening
HWE	Horner–Wadsworth–Emmons
IMDA	intramolecular Diels–Alder
IMes	1,3-dimesityl-imidazolidin-2-ylidene
iNOS	inducible nitric oxide synthase
IP	intellectual property
Ipc	isopinocampheyl
KHMDS	potassium bis(trimethylsilyl)amide
LACDAC	Lewis acid catalyzed diene-aldehyde cyclocondensation
LCMS	liquid chromatography mass-spectrometry

LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M&M	metathesis and metallocropy
MALDI-MS	matrix-assisted laser desorption/ionization mass spectrometry
MAP	monoaryloxide pyrrolide
mCPBA	<i>m</i> -chloroperbenzoic acid
ME	migrastatin ether
MEM	2-methoxyethoxymethyl
Mes	mesityl
MIDA	<i>N</i> -methyliminodiacetic acid
MM	molecular mechanics
MO	methyl oleate
MOM	methoxymethyl
MPEG	methoxy poly(ethylene glycol)
MPPM, PMB	<i>p</i> -methoxybenzyl
MS	molecular sieve
Ms	methanesulfonyl
MSH	<i>O</i> -mesitylenesulfonylhydroxylamine
MT	metric tons
MVK	methyl vinyl ketone
MW, $\mu$ W	microwave
n.a.	not available
N.R.	no reaction
nAChR	nicotinic acetylcholine receptor
NAP	2-naphthylmethyl
NBR	nitrile-butadiene rubber
NBS	<i>N</i> -bromosuccinimide
NCI	National Cancer Institute
NCS	<i>N</i> -chlorosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NIS	<i>N</i> -iodosuccinimide
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMR	nuclear magnetic resonance
Ns, Nos	nosyl, or 2-nitrobenzenesulfonyl
NXS	<i>N</i> -halosuccinimide (halo = Cl, Br, I)
OBAC	oligomeric bis-acid chloride
ODDE	octadecenedioate
OLEC	olefinic ester cyclization
OM	olefin metathesis
OMAm	oligomeric amine
<i>o</i> -NBSH	<i>o</i> -nitrobenzenesulfonylhydrazide
OTf	trifluoromethanesulfonate
OTPP	oligomeric triphenylphosphine

PAE	poly(arylene ethynylene)
PBB	<i>p</i> -bromobenzyl
PC	phosphatidylcholine
PDI	polydispersity index
PDLA	poly(D-lactide)
PGE	prostaglandin E
phen	phenanthroline
PHOX	phosphinooxazoline
Phth	phthaloyl
Pin	pinacolato
pip	piperidine
Piv	pivaloyl
PKR	Pauson-Khand reaction
PKS	polyketide synthase
plasm	plasmalogen
PLLA	poly(L-lactide)
PMB, MPM	<i>p</i> -methoxybenzyl
pmdba	di( <i>p</i> -methoxybenzylidene)acetone
PMP	<i>p</i> -methoxyphenyl
POSS	polyhedral oligomeric silsesquioxanes
PPTS	pyridinium <i>p</i> -toluenesulfonate
PTSA, <i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
PyBOP	benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
R&D	research and development
RBD	refined, bleached, and deodorized
RCAM	ring-closing alkyne metathesis
RCDM	ring-closing diyne metathesis
RCEM	ring-closing enyne metathesis
RCM	ring-closing metathesis
ROCM	ring-opening cross-metathesis
ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerization
RORCM	ring-opening ring-closing metathesis
RRCM	relay ring-closing metathesis
RRM	ring-rearrangement metathesis
RT	room temperature
s.m.	starting material
Sac	S-allyl cysteine
SAMP	( <i>S</i> )-1-amino-2-methoxymethylpyrrolidine
SBO	soybean oil
SC	silylative coupling
SCLC	small-cell lung carcinoma
SHD	simulated high dilution
Shh	Sonic Hedgehog

SIMes	1,3-dimesityl-4,5-dihydroimidazol-2-ylidene
SI-ROMP	surface-initiated ring-opening metathesis polymerization
SOMO	singly occupied molecular orbital
SPPS	solid-phase peptide synthesis
TADA	transannular Diels-Alder
TAM	terminal alkyne metathesis
TASF	tris(dimethylamino)sulfur trimethylsilyl difluoride
TBAF	tetrabutylammonium fluoride
TBDPS, BPS	<i>tert</i> -butyldiphenylsilyl
TBS, TBDMS	<i>tert</i> -butyldimethylsilyl
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
TCE	1,1,2-trichloroethane
TCPC	tetracarbomethoxy palladacyclopentadiene
TCQ	tetrachloroquinone
TEA	triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
Teoc	trimethylsilylethyl carbamate
TES	triethylsilyl
TFA	trifluoroacetic acid
TFA-N	trifluoroacetamide
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSB	tetramethyldisilacyclobutane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOF	turnover frequency
TON	turnover number
Tr	trityl
TRAM	terminal ring-closing alkyne metathesis
Troc	2,2,2-trichloroethoxycarbonyl
Ts, Tos	tosyl, or <i>p</i> -toluenesulfonyl
UDA	undecenoate
UDDE	undecenedioate
URSM, ursm	unreacted starting material
USDA	United States Department of Agriculture
UV	ultraviolet
VDR	vitamin D receptor
xs	excess

## 1

## General Ring-Closing Metathesis

Paul R. Hanson, Soma Maitra, Rambabu Chegondi, and Jana L. Markley

## 1.1

### Introduction

Olefin metathesis catalyzed by transition-metal–carbene complexes is among the most powerful and important carbon–carbon bond-forming reactions in modern synthetic organic chemistry [1]. Metathesis transformations, including cross-metathesis (CM), ring-closing metathesis (RCM), enyne metathesis, alkyne metathesis, and ring-opening metathesis polymerization (ROMP), have gained prominence due to the high activity, high thermal stability, and excellent functional group compatibility of well-defined transition-metal alkylidene catalysts which have become available over the last two decades (Figure 1.1).

In 1980, the Villemin [2] and Tsuji and Hashiguchi [3] research groups individually reported the first RCM of a diene with tungsten metal complexes (Scheme 1.1, Eq. 1–2). In 1990, Schrock discovered the molybdenum metathesis complex [Mo]-I [4]. In 1992, Grubbs and coworkers employed [Mo]-I in the first transition-metal–carbene-catalyzed RCM of a diene for the synthesis of a cyclic ether (Eq. 3; Scheme 1.1) [5]. In 1995, Grubbs and coworkers developed the more active, thermal, and air-stable, moisture-tolerant ruthenium–carbene complexes termed the Grubbs first-generation catalyst **G-I** [6] and the Grubbs second-generation catalyst **G-II** [7]. Additional metathesis catalysts such as the Hoveyda–Grubbs catalyst **HG-II** [8] followed, with many commercially available at present.

Since its inception, RCM has continued to be a widely utilized metathesis reaction in a variety of settings including materials, small-molecule, and natural-product synthesis [1]. As illustrated in Scheme 1.2, the primary RCM reactions are divided into three general types: (i) ring-closing diene metathesis (RCM); (ii) ring-closing enyne metathesis (RCEM); and (iii) ring-closing alkyne metathesis (RCAM). In 1971, Chauvin and coworkers proposed a mechanism of the general alkene metathesis which involves the initial formation of the metal carbene species **III** as a key propagating intermediate [9]. Subsequent intramolecular [2 + 2] cycloaddition of **III** with a distal olefin forms the metallacyclobutane intermediate **IV**, while retro [2 + 2] reaction affords the final cyclized product (Scheme 1.2). Casey and Burkhardt [10], Katz and McGinnis [11], and

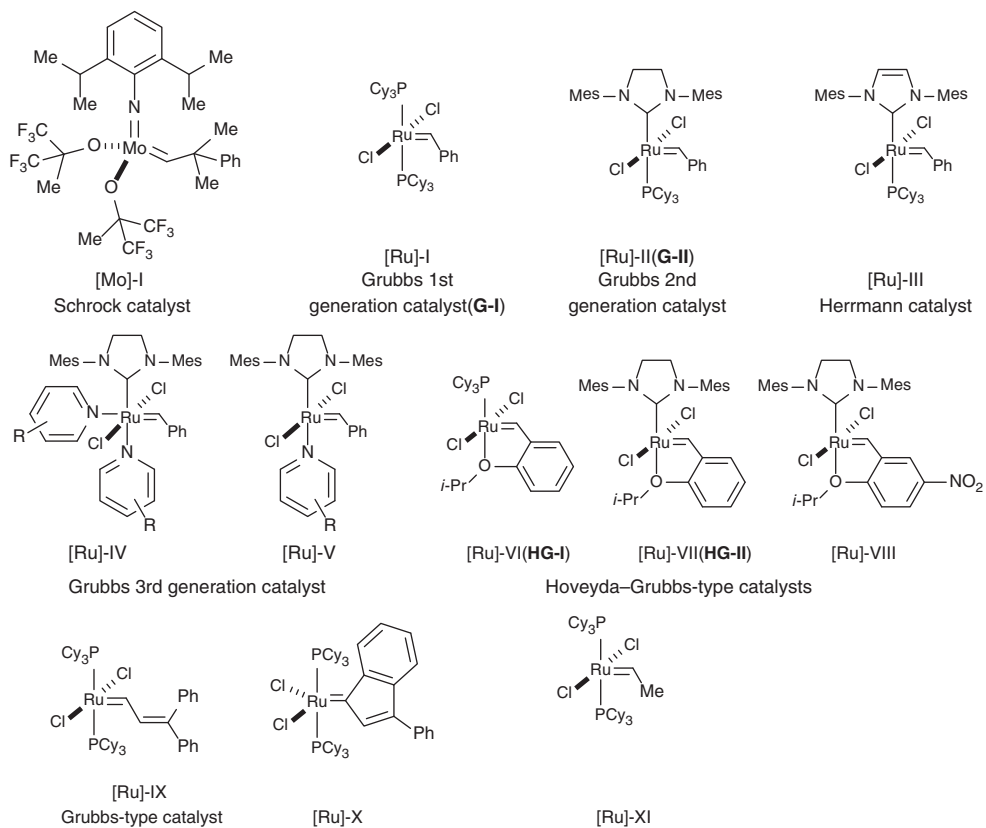
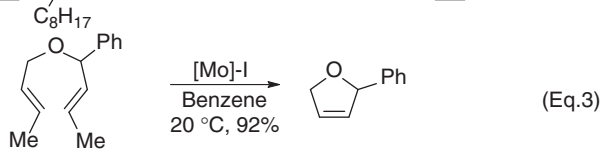
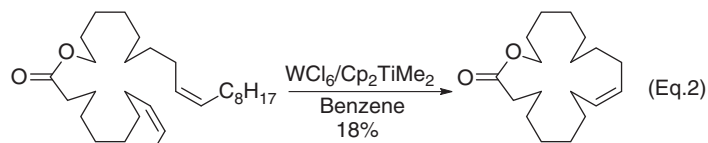
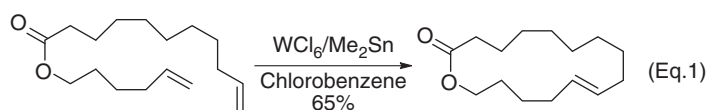


Figure 1.1 List of catalysts.



Scheme 1.1 Early RCM examples.