Florencio Zaragoza Dörwald

Metal Carbenes in Organic Synthesis

WILEY-VCH

Weinheim · New York · Chichester
Brisbane · Singapore · Toronto

This Page Intentionally Left Blank

Florencio Zaragoza Dörwald

Metal Carbenes in Organic Synthesis

WILEY-VCH

This Page Intentionally Left Blank

Florencio Zaragoza Dörwald

Metal Carbenes in Organic Synthesis

WILEY-VCH

Weinheim · New York · Chichester
Brisbane · Singapore · Toronto

Dr. Florencio Zaragoza Dörwald
Novo Nordisk A/S MedChem Research
Novo Nordisk Park
DK-2760 Måløv – Denmark

Library of Congress Card No. applied for.

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

Deutsche Bibliothek Cataloguing-in-Publication Data:
Zaragoza Dörwald, Florencio:
Metal carbenes in organic synthesis / Florencio Zaragoza Dörwald. –
Weinheim ; New York ; Chichester ; Brisbane ; Singapore ; Toronto :
Wiley-VCH, 1999
ISBN 3-527-29625-5

Printed on acid-free and chlorine-free paper.

Composition: Fa. Richarz Publikations-Service GmbH., D-53734 Sankt Augustin.
Printing: betz-druck GmbH, D-64291 Damstadt
Bookbinding: J. Schäffer GmbH & Co. KG., D-67269 Grünstadt
Printed in the Federal Republic of Germany.

Foreword

In the period between the discovery in the late 1950s that copper catalyzed the addition of diazo compounds to olefins to yield cyclopropanes and the recent introduction of olefin metathesis into the synthesis of fine chemicals, a wide variety of useful organic transformations that involve metal carbene intermediates has been discovered. Since most of the reactions of metal carbenes result in the formation of carbon-carbon bonds, the reactions have played a major role in the organometallic revolution in organic synthetic technology during the past few years. Zaragoza-Dörwald has assembled this large array of reactions into a system that allows the common feature of the reactions to be recognized. After outlining the bonding description of the types of complexes, he uses the simple structure types to divide an amazing array of reactions that range from cyclopropanation to the olefination of carbonyls into groups that follow a general mechanistic pathway. The book follows a consistent outline that efficiently provides the active chemist with the information needed to follow up a reaction type. Each section starts with a definition of the metal carbene structure along with a general mechanistic scheme for the preferred reactions of that type of carbene. A few specific examples are discussed to demonstrate the key features, and then a large number of examples are tabulated. At the end of each section an experimental procedure is presented that provides the details of a representative reaction. I found the progression from general to specific examples an extremely efficient presentation of important ideas without excessive details. For example, his treatment of the Dötz and related reactions allowed him to introduce many of the subtle features of this complex reaction in a concise fashion. This approach also allows the book to be read at many levels. The brief introduction and the array of tables allow for a rapid overview of the field, while the extensive references and experimental procedures provide ample detail for an in-depth study of specific reactions. Along a number of reviews have been written on specific aspects of metal carbene complex chemistry, this book describes in one place the array of reactions involving these intermediates and provides the structural basis that ties them together. Although some parts of the book might quickly become out of date, this concise presentation of all the aspects of the use of carbene complexes in synthesis will help provide the impetus for even more rapid developments in this field of research.

Pasadena, October 1998

Robert H. Grubbs
(California Institute of Technology, Pasadena)

This Page Intentionally Left Blank

Preface

To the memory
of my friend and colleague
Lutz Richter

In recent decades there has been an exponential increase in the use of transition metals in organic synthesis. Among the different types of transition-metal-based reagent described, carbene complexes are among the most versatile. The applications of carbene complexes include both their use as catalysts for a number of important synthetic transformations and their utilization as stoichiometric reagents. The aim of this book is to give the reader a well-structured overview of the most important applications of carbene complexes in organic synthesis. Special emphasis has been given to recent innovations, in an attempt to pinpoint new and promising research areas. Hopefully this will give plenty of inspiration for the development of new research projects.

As an organic chemist I consider reaction mechanisms of crucial importance, both for the classification of reactions and for synthesis-planning. For this reason mechanisms are proposed for almost all the reactions described herein. Most of these mechanisms have not yet been rigorously proven, however, and should be considered as preliminary.

The subject of this book has been organized in three main sections: preparation and applications of heteroatom-substituted carbene complexes (Fischer-type carbenes), non-heteroatom-substituted carbene complexes, and acceptor-substituted carbene complexes. In each section the different types of reaction have been ordered either according to the mechanism or according to the type of product. In addition to a selection of illustrative examples, several experimental procedures have been included. These were chosen taking into account safety, availability of starting materials, relevance of the products, and general interest.

I would like to thank my colleagues and supervisors at Novo Nordisk A/S, in particular Jesper Lau and Behrend F. Lundt, for their support and encouragement. It is also a pleasure to acknowledge Kilian W. Conde-Friboes, Robert Madsen, and Thomas Redemann for proofreading various sections of the manuscript and for their helpful comments and suggestions.

This Page Intentionally Left Blank

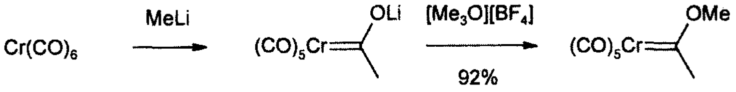
Table of Contents

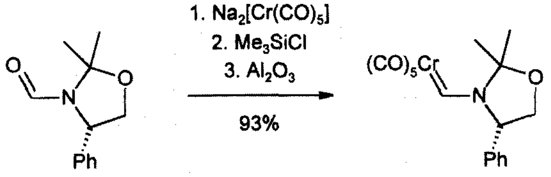
Abbreviations

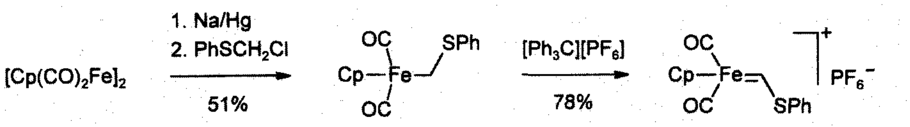
Ac	acetyl
acac	acetylacetonato
ADMET	acyclic diene metathesis
All	allyl
BHT	2,6-di(*tert*-butyl)-4-methylphenol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
Bu	butyl
CAN	ceric ammonium nitrate, $(NH_4)_2Ce(NO_3)_6$
Cap	caprolactam
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
COT	1,3,5-cyclooctatriene
Cp	η^5-cyclopentadienyl
Cp’	pentamethyl-η^5-cyclopentdienyl
Cy	cyclohexyl
DCE	1,2-dichloroethane
de	diastereomeric excess
dec.	decomposition
DMAD	dimethyl acetylenedicarboxylate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
ee	enantiomeric excess
eq.	equivalents
Hex	hexyl
hfacac	hexafluoroacetylacetonato
HMPA	hexamethylphosphoric triamide
L	ligand
M	metal
MCPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl

MS	molecular sieves
mp	melting point
MTO	methylrhenium trioxide, CH_3ReO_3
mwt	molecular weight
Np	neopentyl, 2,2-dimethylpropyl
Ns	(trimethylsilyl)methyl
Pht	phthaloyl
piv	pivalate, 2,2-dimethylpropionate
PMP	4-methoxyphenyl
PNB	4-nitrobenzyl
Pol	polymeric support
Pr	propyl
Pyr	pyridine
RCM	ring-closing metathesis
ROMP	ring-opening metathesis polymerization
salen	bis(salicylaldehyde)ethylenediimine
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	4-methylphenyl
Tp'	hydrotris(3,5-dimethyl-1-pyrazolyl)borato
Tr	trityl
Ts	*p*-toluenesulfonyl, tosyl

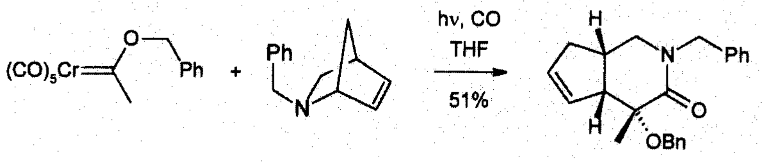
Experimental Procedures





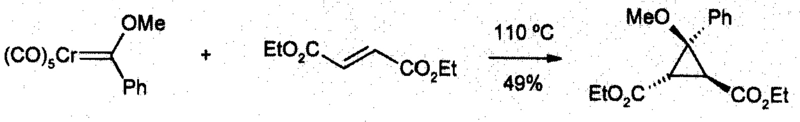


Experimental Procedure 2.2.1. Photolysis of a Chromium Carbene Complex: 2-Benzyl-4-benzyloxy-4-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-3-one



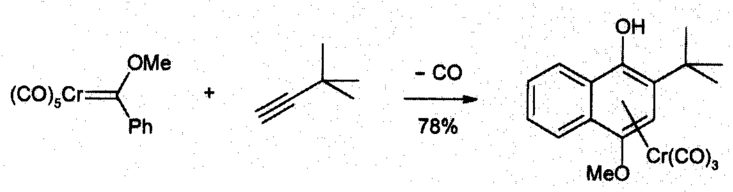
45

Experimental Procedure 2.2.2. Cyclopropanation with a Chromium Carbene Complex: Diethyl *trans*-3-Methoxy-3-phenylcyclopropane-1,2-dicarboxylate



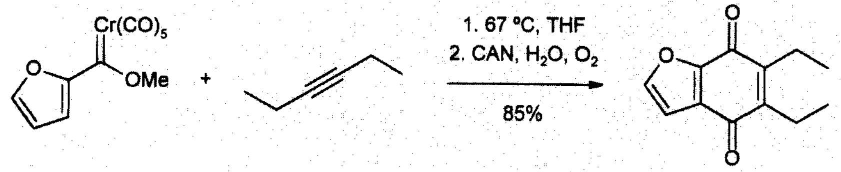
48

Experimental Procedure 2.2.3. Benzannulation with a Chromium Phenylcarbene Complex: [1-4:4a,8a-η^6-2-(*tert*-Butyl)-4-methoxy-1-naphthol]tricarbonylchromium



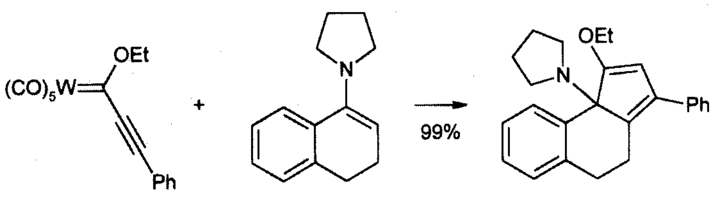
52

Experimental Procedure 2.2.4. Benzannulation with a Chromium Furylcarbene Complex: 5,6-Diethyl-4,7-dihydrobenzo[*b*]furan-4,7-dione



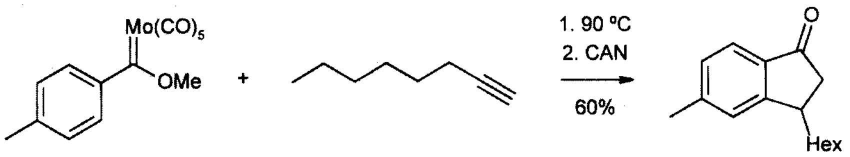
54

Experimental Procedure 2.2.5. Cyclopentannulation with a Tungsten Alkynylcarbene Complex: 1-(1-Ethoxy-3-phenyl-5,9b-dihydro-4*H*-cyclopenta[*a*]naphthalen-9-yl)pyrrolidine



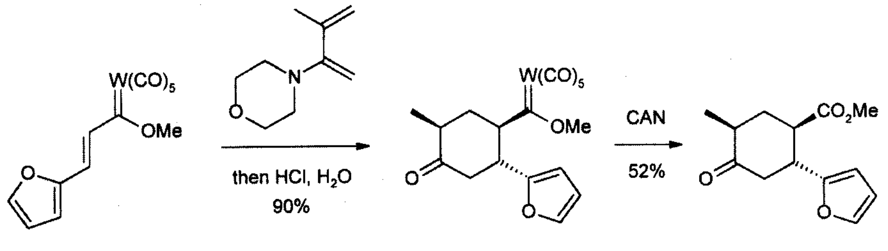
59

Experimental Procedure 2.2.6. Cyclopentannulation with a Molybdenum Arylcarbene Complex: 3-Hexyl-5-methyl-1-indanone



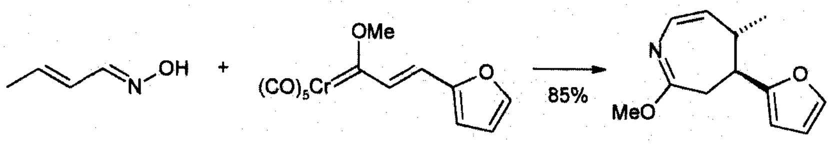
61

Experimental Procedure 2.2.7. Diels–Alder Reaction of a Tungsten Vinylcarbene Complex: Methyl 2-(2-Furyl)-5-methyl-4-oxo-1-cyclohexanecarboxylate



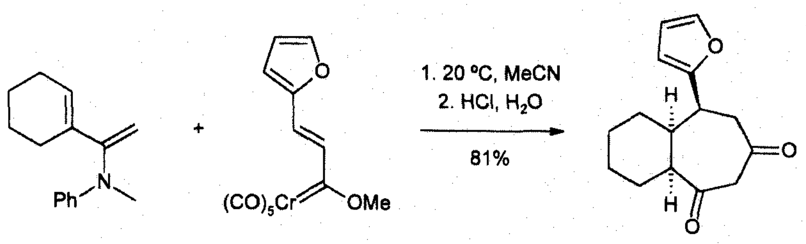
70

Experimental Procedure 2.2.8. [4 + 3] Cycloaddition of a Chromium Vinylcarbene Complex to a 1-Azadiene: *trans*-4-(2-Furyl)-2-methoxy-5-methyl-4,5-dihydro-3*H*-azepine



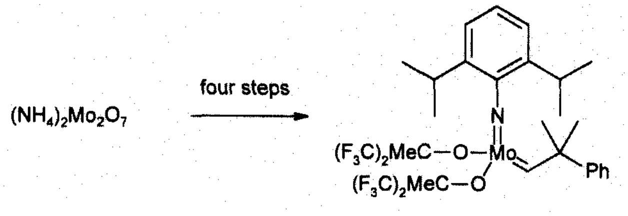
71

Experimental Procedure 2.2.9. [4 + 3] Cycloaddition of a Chromium Carbene Complex to a 2-Aminodiene: 6-(2-Furyl)bicyclo[5.4.0]undecan-2,4-dione



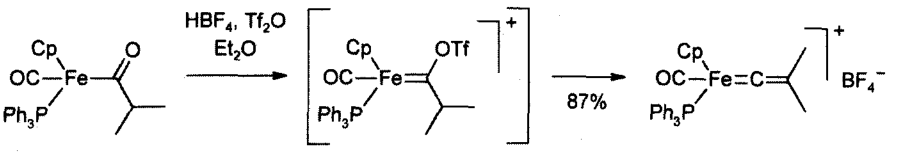
73

Experimental Procedure 3.1.1. Preparation of a Molybdenum Carbene Complex by Nucleophilic Abstraction: (2,6-Diisopropylphenylimido)bis[1,1-bis(trifluoromethyl)ethoxy](2-methyl-2-phenyl-1-propylidene)molybdenum



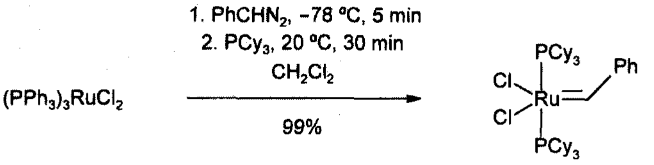
80

Experimental Procedure 3.1.2. Preparation of an Iron Vinylidene Complex by Electrophilic Abstraction: Carbonyl(η^5-cyclopentadienyl)(dimethylvinylidene)-(triphenylphosphine)iron tetrafluoroborate



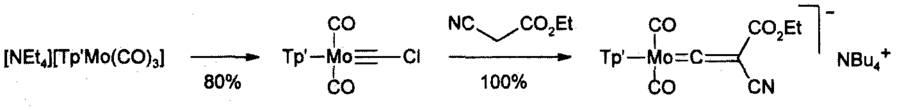
86

Experimental Procedure 3.1.3. Preparation of a Ruthenium Carbene Complex from a Diazoalkane: Dichloro-bis(tricyclohexylphosphine)benzylideneruthenium



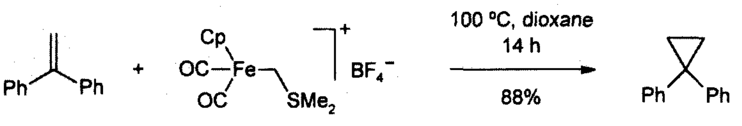
91

Experimental Procedure 3.1.4. Preparation of a Molybdenum Vinylidene Complex from a Carbyne Complex: Tetrabutylammonium {Cyano(ethoxycarbonyl) vinylidene}(dicarbonyl){hydro-tris(3,5-dimethyl-1-pyrazolyl)borato}molybdenum



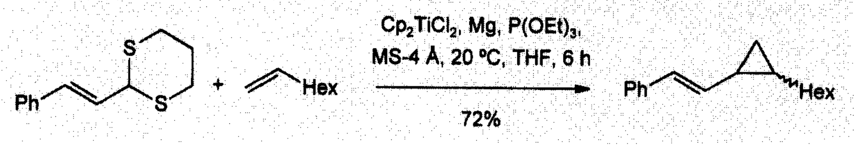
95

Experimental Procedure 3.2.1. Cyclopropanation with an Iron Carbene Complex: 1,1-Diphenylcyclopropane



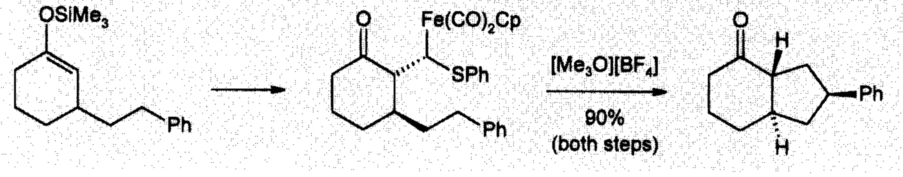
106

Experimental Procedure 3.2.2. Cyclopropanation with a Titanium Carbene Complex: (*E*)-1-Hexyl-2-(2-phenylethenyl)cyclopropane



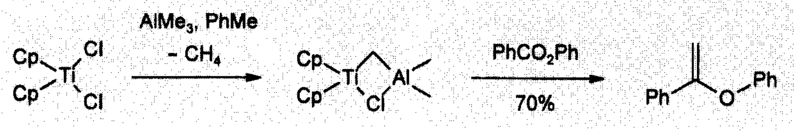
113

Experimental Procedure 3.2.3. Intramolecular C–H Insertion of an Iron Carbene Complex: 8-Phenylbicyclo[4.3.0]nonan-2-one



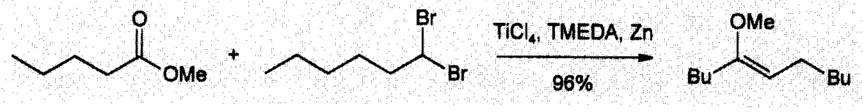
124

Experimental Procedure 3.2.4. Methylenation of an Ester with the Tebbe Reagent: 1-Phenoxy-1-phenylethene



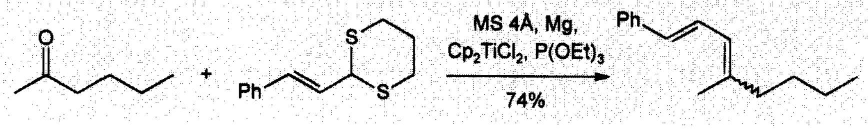
129

Experimental Procedure 3.2.5. Alkylidenation of an Ester: 5-Methoxy-5-undecene



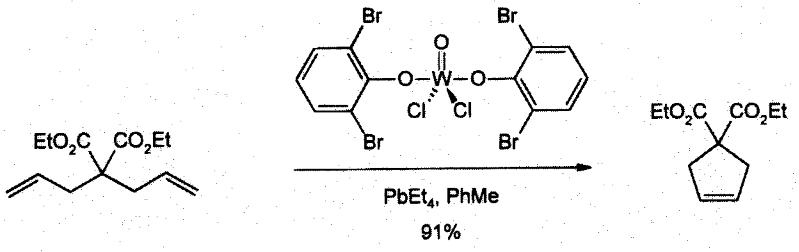
133

Experimental Procedure 3.2.6. Alkylidenation of a Ketone: 4-Methyl-1-phenyl-octa-1,3-diene



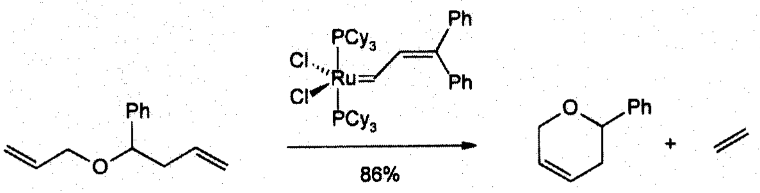
133

Experimental Procedure 3.2.7. RCM with a Tungsten Catalyst in Homogeneous Phase: Diethyl 3-Cyclopentene-1,1-dicarboxylate



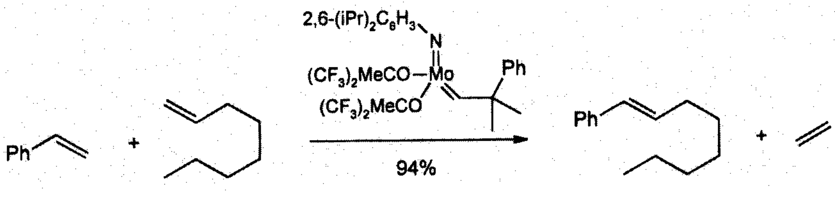
150

Experimental Procedure 3.2.8. RCM with a Ruthenium Catalyst in Homogeneous Phase: 2-Phenyl-3,6-dihydro-2*H*-pyran



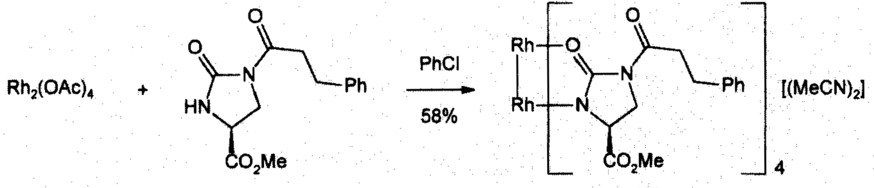
156

Experimental Procedure 3.2.9. Cross Metathesis with a Molybdenum Catalyst in Homogeneous Phase: (*E*)-1-Phenyl-1-octene



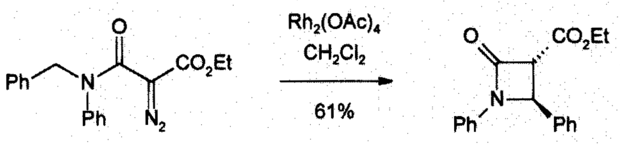
161

Experimental Procedure 4.1.1. Preparation of an Enantiomerically Pure Rhodium(II) Complex: Dirhodium(II) Tetrakis[methyl 2-oxo-1-(3-phenylpropanoyl)-4(*S*)-imidazolidinecarboxylate]; $Rh_2(4S\text{-}MPPIM)_4(MeCN)_2$



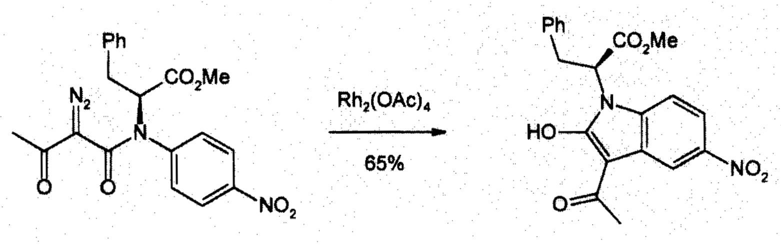
175

Experimental Procedure 4.2.1. Preparation of a β-Lactam by Intramolecular C–H Insertion: Ethyl *trans*-2-Oxo-1,4-diphenyl-3-azetidinecarboxylate



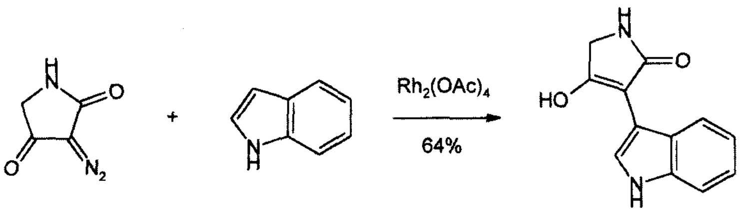
182

Experimental Procedure 4.2.2. Preparation of an Indole by Intramolecular C–H Insertion: Methyl (2*S*)-2-(3-Acetyl-2-hydroxy-5-nitro-1*H*-1-indolyl)-3-phenylpropanoate



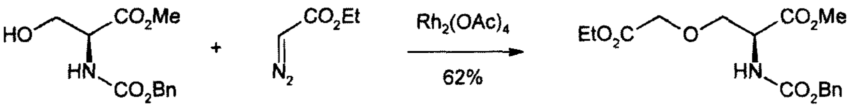
187

Experimental Procedure 4.2.3. Alkylation of Indole by Intermolecular C–H Insertion: 3-(1*H*-3-Indolyl)-2,4-pyrrolidinedione



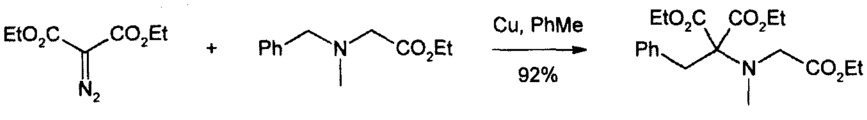
192

Experimental Procedure 4.2.4. Etherification of a Serine Derivative by Intermolecular O–H Insertion: Methyl (2*S*)-3-[(Ethoxycarbonyl)methoxy]-2-(benzyloxycarbonylamino)propanoate



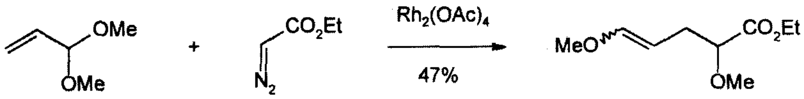
197

Experimental Procedure 4.2.5. Ammonium Ylide Formation and Stevens Rearrangement: Diethyl 2-Benzyl-2-{[(ethoxycarbonyl)methyl](methyl)amino}malonate



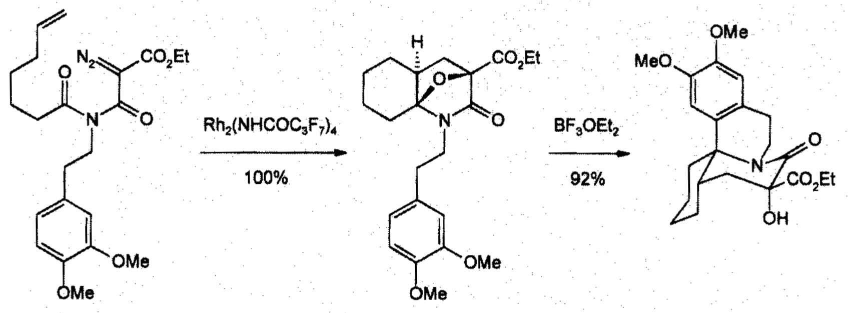
200

Experimental Procedure 4.2.6. Oxonium Ylide Formation and 2,3-Sigmatropic Rearrangement: Ethyl 2,5-Dimethoxy-4-pentenoate



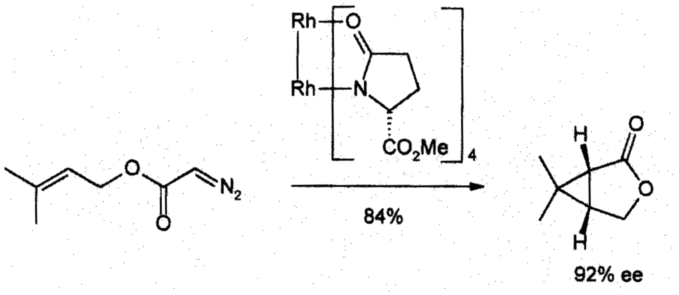
205

Experimental Procedure 4.2.7. Carbonyl Ylide Formation and Intramolecular 1,3-Dipolar Cycloaddition: Ethyl 2-Hydroxy-8,9-dimethoxy-3-oxo-1,2,3,5,6,11,12,13,14,14a-decahydroisoquino[1,2-*f*]quinoline-2-carboxylate



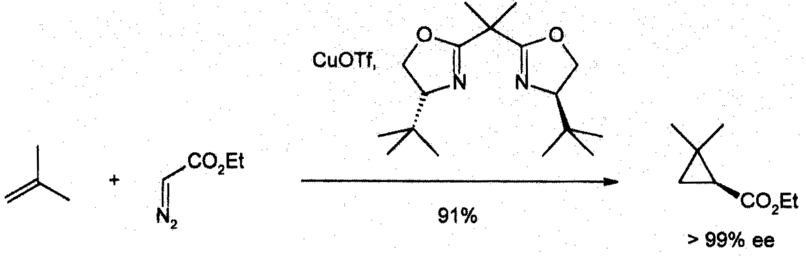
210

Experimental Procedure 4.2.8. Enantioselective, Intramolecular Cyclopropanation: 6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one



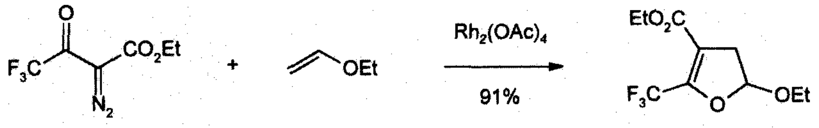
221

Experimental Procedure 4.2.9. Enantioselective, Intermolecular Cyclopropanation: Ethyl (1*S*)-2,2-Dimethyl-1-cyclopropanecarboxylate



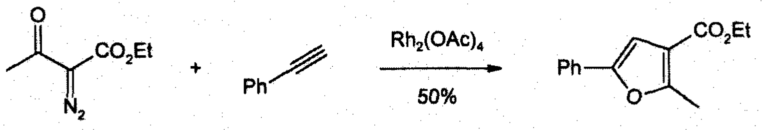
224

Experimental Procedure 4.2.10. Cycloaddition of an Acylcarbene Complex to an Enol Ether: Ethyl 5-Ethoxy-2-trifluoromethyl-4,5-dihydro-3-furoate



227

Experimental Procedure 4.2.11. Cycloaddition of an Acylcarbene Complex to an Alkyne: Ethyl 2-Methyl-5-phenyl-3-furoate



227

The experimental procedures in this text are intended for use only by persons skilled in organic synthesis, and are conducted at ones own risk. WILEY–VCH and the author disclaim any liability for any injuries or damages claimed to have resulted from the experimental procedures described herein. In many of the reactions presented benzene is used as solvent. The replacement of benzene by a less toxic solvent, such as, e.g., toluene, might in many instances lead to comparable results, and is strongly recommended.

1 The Carbon–Metal Double Bond

When the development of carbene-complex chemistry began in the mid seventies, two different patterns of reactivity emerged and led to a, maybe overemphasized, division of these compounds into (electrophilic) Fischer-type and (nucleophilic) Schrock-type carbene complexes (Figure 1.1).

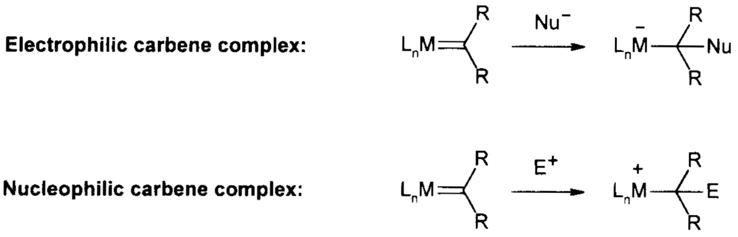


Fig. 1.1. Reactivity of carbene complexes towards electrophiles (E^+) and nucleophiles (Nu^-).

Today, however, carbene complexes covering a broad range of different reactivities have been prepared. Often it is no longer possible to predict whether a carbene complex will behave as an electrophile or as a nucleophile. Thus, a reactivity-based nomenclature would be difficult to apply consistently. For this reason in this book compounds with a carbon–metal double bond will be called 'carbene complexes' or 'alkylidene complexes', terms not associated with any specific chemical behavior.

1.1 Reactivity of Carbene Complexes

Carbenes are electron-deficient intermediates, capable of reacting with organic compounds in several ways. Typical reactions of uncomplexed carbenes include cyclopropanation, C–H insertion, and reaction with lone pairs to yield ylides (Figure 1.2).

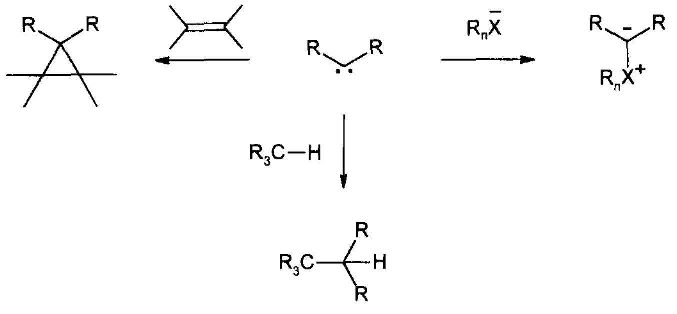


Fig. 1.2. Typical reactions of free carbenes.

The reactivity of carbenes is strongly influenced by the electronic properties of their substituents. If an atom with a lone pair (e.g. O, N, or S) is directly bound to the carbene carbon atom, the electronic deficit at the carbene will be compensated to some extent by electron delocalization, resulting in stabilization of the reactive species. If both substituents are capable of donating electrons into the empty p orbital of the carbene, isolable carbenes, as e.g. diaminocarbenes (Section 2.1.6), can result. The second way in which carbenes can be stabilized consists in complexation. The shape of the molecular orbitals of carbenes enable them to act towards transition metals as σ-donors and π-acceptors. The chemical properties of the resulting complexes will also depend on the electronic properties of the metallic fragment to which the carbene is bound. Particularly relevant for the reactivity of carbene complexes are the ability of the metal to accept σ-electrons from the carbene, and its capacity for back-donation into the empty p orbital of the carbene.

Four different types of metallic fragment can now be considered:

(a) good σ-acceptor, good π-back-donator;
(b) poor σ-acceptor, good π-back-donator;
(c) good σ-acceptor, poor π-back-donator;
(d) poor σ-acceptor, poor π-back-donator.

In situation (a) a strong carbon–metal bond results. To this group belong the typical Schrock-type carbenes [e.g. $Np_3Ta{=}CH(tBu)$], many of which are nucleophilic at carbon. Situation (b) should also lead to nucleophilic carbene complexes, albeit with a weaker carbon–metal bond. Typical reactions of nucleophilic carbene complexes include carbonyl olefination (Section 3.2.4) and olefin metathesis (Section 3.2.5).

Metallic groups as in case (c) lead to electrophilic or even carbocation-like carbene complexes. Typical examples are Fischer-type carbene complexes [e.g. $(CO)_5Cr{=}C(Ph)OMe$] and the highly reactive carbene complexes resulting from the reaction of rhodium(II) and palladium(II) carboxylates with diazoalkanes. Also platinum ylides [1,2], resulting from the reaction of diazoalkanes with platinum(II) complexes, have a strong Pt–C σ bond but only a weak Pt–C π bond. In situation (d) the interaction between the metal and the carbene is very weak, and highly reactive complexes showing carbene-like behavior result. Similar to uncomplexed carbenes,