

Reinhard Bruckner

Advanced Organic Chemistry

Reaction Mechanisms



A Harcourt Science and Technology Company

San Diego • San Francisco • New York • Boston • London • Sydney • Tokyo

Contents

Foreword	xv
Preface to the English Edition	xvii
Preface to the German Edition	xix
Acknowledgments	xxiii
1 Radical Substitution Reactions at the Saturated C Atom	1
1.1 Bonding and Preferred Geometries in C Radicals, Carbenium Ions and Carbanions	1
1.1.1 Preferred Geometries	2
1.1.2 Bonding	3
1.2 Stability of Radicals	5
1.2.1 Reactive Radicals	5
1.2.2 Unreactive Radicals	8
1.3 Relative Rates of Analogous Radical Reactions	9
1.3.1 The Bell–Evans–Polanyi Principle	10
1.3.2 The Hammond Postulate	11
1.4 Radical Substitution Reactions: Chain Reactions	13
1.5 Radical Initiators	15
1.6 Radical Chemistry of Alkylmercury(II) Hydrides	16
1.7 Radical Halogenation of Hydrocarbons	19
1.7.1 Simple and Multiple Chlorinations	19
1.7.2 Regioselectivity of Radical Chlorinations	22
1.7.3 Regioselectivity of Radical Brominations Compared to Chlorinations	24
1.7.4 Rate Law for Radical Halogenations; Reactivity/Selectivity Principle	26
1.7.5 Chemoselectivity of Radical Brominations	28
1.8 Autoxidations	32
1.9 Defunctionalizations via Radical Substitution Reactions	34
1.9.1 Simple Defunctionalizations	34
1.9.2 Defunctionalization via 5-Hexenyl Radicals: Competing Cyclopentane Formation	37
References	40
2 Nucleophilic Substitution Reactions at the Saturated C Atom	43
2.1 Nucleophiles and Electrophiles; Leaving Groups	43
2.2 Good and Poor Nucleophiles	44

2.3	Leaving Groups and the Quality of Leaving Groups	46
2.4	S_N2 Reactions: Kinetic and Stereochemical Analysis— Substituent Effects on Reactivity	49
2.4.1	Energy Profile and Rate Law for S_N2 Reactions: Reaction Order	49
2.4.2	Stereochemistry of S_N2 Substitutions	51
2.4.3	A Refined Transition State Model for the S_N2 Reaction; Crossover Experiment and Endocyclic Restriction Test	52
2.4.4	Substituent Effects on S_N2 Reactivity	54
2.5	S_N1 Reactions: Kinetic and Stereochemical Analysis; Substituent Effects on Reactivity	57
2.5.1	Energy Profile and Rate Law of S_N1 Reactions; Steady State Approximation	57
2.5.2	Stereochemistry of S_N1 Reactions; Ion Pairs	61
2.5.3	Solvent Effects on S_N1 Reactivity	62
2.5.4	Substituent Effects on S_N1 Reactivity	65
2.6	When Do S_N Reactions at Saturated C Atoms Take Place According to the S_N1 Mechanism and When Do They Take Place According to the S_N2 Mechanism?	69
2.7	Unimolecular S_N Reactions That Do Not Take Place via Simple Carbenium Ion Intermediates: Neighboring Group Participation	69
2.7.1	Conditions for and Features of S_N Reactions with Neighboring Group Participation	69
2.7.2	Increased Rate through Neighboring Group Participation	71
2.7.3	Stereoselectivity through Neighboring Group Participation	72
2.8	Preparatively Useful S_N2 Reactions: Alkylations References	76 81
3	Additions to the Olefinic C=C Double Bond	85
3.1	The Concept of <i>cis</i> and <i>trans</i> Addition	86
3.2	Vocabulary of Stereochemistry and Stereoselective Synthesis I	87
3.2.1	Isomerism, Diastereomers/Enantiomers, Chirality	87
3.2.2	Chemoselectivity, Diastereoselectivity/Enantioselectivity, Stereospecificity/Stereoconvergence	88
3.3	Additions That Take Place Diastereoselectivity as <i>cis</i> Additions	91
3.3.1	A Cycloaddition Forming Three-Membered Rings	92
3.3.2	Additions to C=C Double Bonds That Are Related to Cycloadditions and Form Three-Membered Rings, Too	93
3.3.3	<i>cis</i> -Hydration of Olefins via the Hydroboration/Oxidation/Hydrolysis Reaction Sequence	95
3.3.4	Heterogeneously Catalyzed Hydrogenation	104
3.4	Enantioselective <i>cis</i> Additions to C=C Double Bonds	105
3.4.1	Vocabulary of Stereochemistry and Stereoselective Synthesis II: Topicity, Asymmetric Synthesis	106

3.4.2	Asymmetric Hydroboration of Achiral Olefins	107
3.4.3	Thought Experiment I on the Hydroboration of Chiral Olefins with Chiral Boranes: Mutual Kinetic Resolution	109
3.4.4	Thought Experiments II and III on the Hydroboration of Chiral Olefins with Chiral Boranes: Reagent Control of Diastereoselectivity, Matched/Mismatched Pairs, Double Stereodifferentiation	110
3.4.5	Thought Experiment IV on the Hydroboration of Chiral Olefins with Chiral Dialkylboranes: Kinetic Resolution	112
3.4.6	Catalytic Asymmetric Synthesis: Sharpless Oxidations of Allyl Alcohols	113
3.5	Additions That Take Place Diastereoselectively as <i>trans</i> Additions (Additions via Onium Intermediates)	116
3.5.1	Addition of Bromine	117
3.5.2	The Formation of Halohydrins; Halolactonization and Haloetherification	118
3.5.3	Solvomercuration of Olefins: Hydration of C=C Double Bonds through Subsequent Reduction	121
3.6	Additions That Take Place or Can Take Place without Stereocontrol Depending on the Mechanism	123
3.6.1	Additions via Carbenium Ion Intermediates	123
3.6.2	Additions via "Carbanion" Intermediates	126
	References	126
4	β-Eliminations	129
4.1	Concepts of Elimination Reactions	129
4.1.1	The Concept of α,β - and 1, <i>n</i> -Elimination	129
4.1.2	The Terms <i>syn</i> - and <i>anti</i> -Elimination	130
4.1.3	When Are Stereogenic <i>syn</i> - and <i>anti</i> -Selective Eliminations Stereoselective?	131
4.1.4	Formation of Regioisomeric Olefins by β -Elimination: Saytzeff and Hofmann Product(s)	134
4.1.5	The Synthetic Value of Het ¹ /Het ² in Comparison to H/Het Eliminations	135
4.2	β -Eliminations of H/Het via Cyclic Transition States	136
4.3	β -Eliminations of H/Het via Acyclic Transition States: The Mechanistic Alternatives	140
4.4	E2 Eliminations of H/Het and the E2/S _N 2 Competition	141
4.4.1	Substrate Effects on the E2/S _N 2 Competition	141
4.4.2	Base Effects on the E2/S _N 2 Competition	143
4.4.3	A Stereoelectronic Effect on the E2/S _N 2 Competition	144
4.4.4	The Regioselectivity of E2 Eliminations	146
4.4.5	One-Pot Conversion of an Alcohol to an Olefin	148

4.5	E1 Elimination of H/Het from R _{tert} -X and the E1/S _N 1 Competition	149
4.5.1	Energy Profiles and Rate Laws for E1 Eliminations	150
4.5.2	The Regioselectivity of E1 Eliminations	152
4.5.3	E1 Eliminations in Protecting Group Chemistry	155
4.6	E1 _{cb} Eliminations	156
4.6.1	Unimolecular E1 _{cb} Eliminations: Energy Profile and Rate Law	156
4.6.2	Nonunimolecular E1 _{cb} Eliminations: Energy Profile and Rate Law	157
4.6.3	E1 _{cb} Eliminations in Protecting Group Chemistry	158
4.7	β -Eliminations of Het ¹ /Het ²	160
4.7.1	Fragmentation of β -Heterosubstituted Organometallic Compounds	161
4.7.2	Julia-Lythgoe Synthesis of <i>trans</i> -Olefins	161
4.7.3	Peterson Olefination	163
4.7.4	Oxaphosphetane Fragmentation, Last Step of Wittig and Horner-Wadsworth-Emmons Reactions	163
4.7.5	Corey-Winter Reaction	165
	References	166
5	Substitution Reactions on Aromatic Compounds	169
5.1	Electrophilic Aromatic Substitutions via Wheland Complexes ("Ar-S _E Reactions")	169
5.1.1	Mechanism: Substitution of H ⁺ vs <i>ipso</i> -Substitution	169
5.1.2	Thermodynamic Aspects of Ar-S _E Reactions	171
5.1.3	Kinetic Aspects of Ar-S _E Reactions: Reactivity and Regioselectivity in Reactions of Electrophiles with Substituted Benzenes	176
5.2	Ar-S _E Reactions via Wheland Complexes: Individual Reactions	182
5.2.1	Ar-Hal Bond Formation by Ar-S _E Reaction	182
5.2.2	Ar-SO ₃ H Bond Formation by Ar-S _E Reaction	184
5.2.3	Ar-NO ₂ Bond Formation by Ar-S _E Reaction	186
5.2.4	Ar-N=N Bond Formation by Ar-S _E Reaction	188
5.2.5	Ar-Alkyl Bond Formations by Ar-S _E Reaction	189
5.2.6	Ar-C(OH) Bond Formation by Ar-S _E Reactions and Associated Secondary Reactions	196
5.2.7	Ar-C(=O) Bond Formation by Ar-S _E Reaction	197
5.2.8	Ar-C(=O)H Bond Formation through Ar-S _E Reaction	199
5.3	Electrophilic Substitution Reactions on Metallated Aromatic Compounds	200
5.3.1	Electrophilic Substitution Reactions of <i>ortho</i> -Lithiated Benzene and Naphthalene Derivatives	201

5.3.2	Electrophilic Substitution Reactions in Aryl Grignard and Aryllithium Compounds That Are Accessible from Aryl Halides	203
5.3.3	Electrophilic Substitutions on Arylboronic Acids and Arylboronic Esters	206
5.4	Nucleophilic Substitution Reactions in Aryldiazonium Salts	207
5.5	Nucleophilic Substitution Reactions via Meisenheimer Complexes	211
5.5.1	Mechanism	211
5.5.2	Examples of Reactions of Preparative Interest	213
5.3.3	A Special Mechanistic Case: Reactions of Aryl Sulfonates with NaOH/KOH in a Melt	215
5.6	Nucleophilic Aromatic Substitution via Arynes, <i>cine</i> Substitution	216
	References	217
6	Nucleophilic Substitution Reactions on the Carboxyl Carbon (Except through Enolates)	221
6.1	C=O-Containing Substrates and Their Reactions with Nucleophiles	221
6.2	Mechanisms, Rate Laws, and Rate of Nucleophilic Substitution Reactions at the Carboxyl Carbon	224
6.2.1	Mechanism and Rate Laws of S _N Reactions on the Carboxyl Carbon	224
6.2.2	S _N Reactions on the Carboxyl Carbon: The Influence of Resonance Stabilization of the Attacked C=O Double Bond on the Reactivity of the Acylating Agent	230
6.2.3	S _N Reactions on the Carboxyl Carbon: The Influence of the Stabilization of the Tetrahedral Intermediate on the Reactivity	234
6.3	Activation of Carboxylic Acids and of Carboxylic Acid Derivatives	236
6.3.1	Activation of Carboxylic Acids and Carboxylic Acid Derivatives in Equilibrium Reactions	237
6.3.2	Conversion of Carboxylic Acids into Isolable Acylating Agents	238
6.3.3	Complete <i>in Situ</i> Activation of Carboxylic Acids	240
6.4	Selected S _N Reactions of Heteroatom Nucleophiles on the Carboxyl Carbon	244
6.4.1	Hydrolysis of Esters	246
6.4.2	Lactone Formation from Hydroxycarboxylic Acids	250
6.4.3	Forming Peptide Bonds	254
6.4.4	S _N Reactions of Heteroatom Nucleophiles with Carbonic Acid Derivatives	256
6.5	S _N Reactions of Hydride Donors, Organometallics, and Heteroatom-Stabilized "Carbanions" on the Carboxyl Carbon	260
6.5.1	When Do Pure Acylations Succeed, and When Are Alcohols Produced?	260

6.5.2	Acylation of Hydride Donors: Reduction of Carboxylic Acid Derivatives to Aldehydes	263
6.5.3	Acylation of Organometallic Compounds and Heteroatom-Stabilized "Carbanions": Synthesis of Ketones	265
	References	268
7	Additions of Heteroatom Nucleophiles to Heterocumulenes. Additions of Heteroatom Nucleophiles to Carbonyl Compounds and Follow-up Reactions	271
7.1	Additions of Heteroatom Nucleophiles to Heterocumulenes	271
7.1.1	Mechanism of the Addition of Heteroatom Nucleophiles to Heterocumulenes	271
7.1.2	Examples of the Addition of Heteroatom Nucleophiles to Heterocumulenes	272
7.2	Additions of Heteroatom Nucleophiles to Carbonyl Compounds	279
7.2.1	On the Equilibrium Position of Addition Reactions of Heteroatom Nucleophiles to Carbonyl Compounds	279
7.2.2	Hemiacetal Formation	281
7.2.3	Oligomerization/Polymerization of Carbonyl Compounds	286
7.3	Addition of Heteroatom Nucleophiles to Carbonyl Compounds in Combination with Subsequent S_N1 Reactions: Acetalizations	288
7.3.1	Mechanism	288
7.3.2	Formation of <i>O,O</i> -Acetals	290
7.3.3	Formation of <i>S,S</i> -Acetals	295
7.3.4	Formation of <i>N,N</i> -Acetals	297
7.4	Addition of Nitrogen Nucleophiles to Carbonyl Compounds in Combination with Subsequent $E1$ Eliminations: Condensation Reactions of Nitrogen Nucleophiles with Carbonyl Compounds	299
	References	303
8	Addition of Hydride Donors and Organometallic Compounds to Carbonyl Compounds	305
8.1	Suitable Hydride Donors and Organometallic Compounds and a Survey of the Structure of Organometallic Compounds	305
8.2	Chemoselectivity of the Addition of Hydride Donors to Carbonyl Compounds	307
8.3	Diastereoselectivity of the Addition of Hydride Donors to Carbonyl Compounds	309
8.3.1	Diastereoselectivity of the Addition of Hydride Donors to Cyclic Ketones	310

8.3.2	Diastereoselectivity of the Addition of Hydride Donors to α -Chiral Acyclic Carbonyl Compounds	313
8.3.3	Diastereoselectivity of the Addition of Hydride Donors to β -Chiral Acyclic Carbonyl Compounds	322
8.4	Enantioselective Addition of Hydride Donors to Carbonyl Compounds	323
8.5	Addition of Organometallic Compounds to Carbonyl Compounds	327
8.5.1	Simple Addition Reactions of Organometallic Compounds	328
8.5.2	Enantioselective Addition of Organozinc Compounds to Carbonyl Compounds: Chiral Amplification	333
8.5.3	Diastereoselective Addition of Organometallic Compounds to Carbonyl Compounds	335
8.6	1,4-Additions of Organometallic Compounds to α,β -Unsaturated Ketones	339
	References	342
9	Reaction of Ylides with Saturated or α,β-Unsaturated Carbonyl Compounds	347
9.1	Ylides/Ylenes	347
9.2	Reactions of S Ylides with Saturated Carbonyl Compounds or with Michael Acceptors: Three-Membered Ring Formation	349
9.2.1	Mechanism for the Formation of Cyclopropanes and Epoxides	349
9.2.2	Stereoselectivity and Regioselectivity of Three-Membered Ring Formation from S Ylides	351
9.3	Condensation of P Ylides with Carbonyl Compounds: Wittig Reaction	353
9.3.1	Nomenclature and Preparation of P Ylides	354
9.3.2	Mechanism of the Wittig Reaction	355
9.4	Horner–Wadsworth–Emmons Reaction	360
9.4.1	Horner–Wadsworth–Emmons Reactions with Achiral Substrates	361
9.4.2	Horner–Wadsworth–Emmons Reactions between Chiral Substrates: A Potpourri of Stereochemical Specialties	364
	References	372
10	Chemistry of the Alkaline Earth Metal Enolates	373
10.1	Basic Considerations	373
10.1.1	Notation and Structure of Enolates	373
10.1.2	Preparation of Enolates by Deprotonation	377
10.1.3	Other Methods for the Generation of Enolates	386

10.1.4	Survey of Reactions between Electrophiles and Enolates and the Issue of Ambidoselectivity	388
10.2	Alkylation of Quantitatively Prepared Enolates and Aza-Enolates; Chain-Elongating Syntheses of Carbonyl Compounds and Carboxylic Acid Derivatives	391
10.2.1	Chain-Elongating Syntheses of Carbonyl Compounds	391
10.2.2	Chain-Elongating Syntheses of Carboxylic Acid Derivatives	400
10.3	Hydroxyalkylation of Enolates with Carbonyl Compounds (“Aldol Addition”): Synthesis of β -Hydroxyketones and β -Hydroxyesters	406
10.3.1	Driving Force of Aldol Additions and Survey of Reaction Products	406
10.3.2	Stereocontrol	408
10.4	Condensation of Enolates with Carbonyl Compounds: Synthesis of Michael Acceptors	414
10.4.1	Aldol Condensations	414
10.4.2	Knoevenagel Reaction	418
10.4.3	A Knoevenagel Reaction “with a Twist”	419
10.5	Acylation of Enolates	422
10.5.1	Acylation of Ester Enolates	422
10.5.2	Acylation of Ketone Enolates	425
10.6	Michael Additions of Enolates	428
10.6.1	Simple Michael Additions	428
10.6.2	Tandem Reactions Consisting of Michael Addition and Consecutive Reactions	430
	References	432
11	Rearrangements	435
11.1	Nomenclature of Sigmatropic Shifts	435
11.2	Molecular Origins for the Occurrence of [1,2]-Rearrangements	436
11.3	[1,2]-Rearrangements in Species with a Valence Electron Sextet	438
11.3.1	[1,1]-Rearrangements of Carbenium Ions	438
11.3.2	[1,2]-Rearrangements in Carbenes or Carbenoids	453
11.4	[1,2]-Rearrangements <i>without</i> the Occurrence of a Sextet Intermediate	458
11.4.1	Hydroperoxide Rearrangements	459
11.4.2	Baeyer–Villiger Rearrangements	459
11.4.3	Oxidation of Organoborane Compounds	462
11.4.4	Beckmann Rearrangement	464
11.4.5	Curtius Rearrangement	464
11.5	Claisen Rearrangement	467
11.5.1	Classical Claisen Rearrangement	467
11.5.2	Claisen–Ireland Rearrangements	468
	References	474

12	Thermal Cycloadditions	477
12.1	Driving Force and Feasibility of One-Step [2 + 4]- and [2 + 2]-Cycloadditions	477
12.2	Transition State Structures of Selected One-Step [2 + 4]- and [2 + 2]-Cycloadditions	478
12.2.1	Stereostructure of the Transition States of One-Step [2 + 4]-Cycloadditions	478
12.2.2	Frontier Orbital Interactions in the Transition States of One-Step [2 + 4]-Cycloadditions	480
12.2.3	Frontier Orbital Interactions in the Transition States of the Unknown One-Step Cycloadditions of Alkenes or Alkynes to Alkenes	486
12.2.4	Frontier Orbital Interactions in the Transition State of One-Step [2 + 2]-Cycloadditions Involving Ketenes	486
12.3	Diels–Alder Reactions	488
12.3.1	Stereoselectivity of Diels–Alder Reactions	489
12.3.2	Substituent Effects on Reaction Rates of Diels–Alder Reactions	493
12.3.3	Orientation Selectivity of Diels–Alder Reactions	497
12.3.4	Simple Diastereoselectivity of Diels–Alder Reactions	500
12.4	[2 + 2]-Cycloadditions with Dichloroketene	502
12.5	1,3-Dipolar Cycloadditions	504
12.5.1	1,3-Dipoles	504
12.5.2	Frontier Orbital Interactions in the Transition States of One-Step 1,3-Dipolar Cycloadditions; Sustmann Classification	505
12.5.3	1,3-Dipolar Cycloadditions of Diazoalkanes	507
12.5.4	1,3-Dipolar Cycloadditions of Nitrile Oxides	510
12.5.5	1,3-Dipolar Cycloadditions and 1,3-Dipolar Cycloreversions as Steps in the Ozonolysis of Alkenes	513
12.5.6	A Tricky Reaction of Inorganic Azide	515
	References	516
13	Transition Metal-Mediated Alkenylations, Arylations, and Alkynylations	519
13.1	Alkenylation and Arylation of Copper-Bound Organyl Groups	520
13.2	Alkenylation and Arylation of Grignard Compounds	522
13.3	Palladium-Catalyzed Alkenylation and Arylation of Organometallic Compounds	526
13.3.1	A Prelude: Preparation of Haloalkenes and Alkenylboronic Acid Derivatives, Important Building Blocks for Palladium-Mediated C,C Couplings	526

13.3.2	Alkenylation and Arylation of Boron-Bound Groups	529
13.3.3	Alkenylation and Arylation of Zinc-Bound Functionalized Groups	534
13.3.4	Alkenylation and Arylation of Copper Acetylides	535
13.4	Alkynylation of Copper Acetylides	538
13.5	Heck Reactions	539
	References	542
14	Oxidations and Reductions	545
14.1	Oxidation States of Organic Chemical Compounds, Oxidation Numbers in Organic Chemical Compounds, and Organic Chemical Redox Reactions	545
14.2	Cross-References to Redox Reactions Already Discussed in Chapters 1–13	550
14.3	Oxidations	555
14.3.1	Oxidations in the Series Alcohol → Aldehyde → Carboxylic Acid	555
14.3.2	Oxidative Cleavages	562
14.3.3	Oxidations at Heteroatoms	573
14.4	Reductions	576
14.4.1	Reductions $R_{sp^3}-X \rightarrow R_{sp^3}-H$ or $R_{sp^3}-X \rightarrow R_{sp^3}-M$	576
14.4.2	One-Electron Reductions of Carbonyl Compounds and Esters; Reductive Coupling	583
14.4.3	Reductions of Carboxylic Acid Derivatives to Alcohols or Amines	588
14.4.4	Reductions of Carboxylic Acid Derivatives to Aldehydes	593
14.4.5	Reductions of Carbonyl Compounds to Alcohols	593
14.4.6	Reductions of Carbonyl Compounds to Hydrocarbons	594
14.4.7	Hydrogenation of Alkenes	599
14.4.8	Reductions of Aromatic Compounds and Alkynes	604
	References	608
	Index	613