## Contents

### 1 Radical Substitution Reactions at the Saturated C Atom

1.1 Bonding and Preferred Geometries in Carbon Radicals, Carbenium Ions and Carbanions
   - Preferred Geometries
   - Bonding
2
1.2 Stability of Radicals
   - Reactive Radicals
   - Unreactive Radicals
5
1.3 Relative Rates of Analogous Radical Reactions
   - The Bell–Evans–Polanyi Principle
   - The Hammond Postulate
12
1.4 Radical Substitution Reactions: Chain Reactions
15
1.5 Radical Initiators
17
1.6 Radical Chemistry of Alkylmercury(II) Hydrides
18
1.7 Radical Halogenation of Hydrocarbons
   - Simple and Multiple Chlorinations
   - Regioselectivity of Radical Chlorinations
   - Regioselectivity of Radical Brominations Compared to Chlorinations
   - Rate Law for Radical Halogenations; Reactivity/Selectivity Principle and the Road to Perdition
   - Chemoselectivity of Radical Brominations
   - Radical Chain Chlorination Using Sulfuryl Chloride
21
21
23
25
27
29
35
38
41
44
46

### 2 Nucleophilic Substitution Reactions at the Saturated C Atom

2.1 Nucleophiles and Electrophiles; Leaving Groups
2.2 Good and Poor Nucleophiles
2.3 Leaving Groups: Good, Bad and Ugly
2.4 S_N2 Reactions: Kinetic and Stereochemical Analysis—Substituent Effects on Reactivity
   - Energy Profile and Rate Law for S_N2 Reactions: Reaction Order
   - Stereochemistry of S_N2 Substitutions
2.4.1
2.4.2
53
53
54
58
60
60
62
2.4.3  A Refined Transition State Model for the S_N^2 Reaction; Crossover Experiment and Endocyclic Restriction Test ............................. 63
2.4.4  Substituent Effects on S_N^2 Reactivity. ................................. 66

2.5  S_N^1 Reactions: Kinetic and Sterechemical Analysis; Substituent Effects on Reactivity .......................................................... 69
2.5.1  Energy Profile and Rate Law of S_N^1 Reactions; Steady State Approximation ............................................................ 69
2.5.2  Stereochemistry of S_N^1 Reactions; Ion Pairs ......................... 72
2.5.3  Solvent Effects on S_N^1 Reactivity ......................................... 73
2.5.4  Substituent Effects on S_N^1 Reactivity. ................................. 76

2.6  When Do S_N Reactions at Saturated C Atoms Take Place According to the S_N^1 Mechanism and When Do They Take Place According to the S_N^2 Mechanism? ........................................... 83
2.7  Getting by with Help from Friends, or a Least Neighbors: Neighboring Group Participation ...................................................... 83
2.7.1  Conditions for and Features of S_N Reactions with Neighboring Group Participation ......................................................... 83
2.7.2  Increased Rate through Neighboring Group Participation ............ 85
2.7.3  Stereoselectivity through Neighboring Group Participation .......... 86

2.8  S_N^i Reactions ........................................................................... 89
2.9  Preparatively Useful S_N^2 Reactions: Alkylations ....................... 91

3  Electrophilic Additions to the C= C Double Bond ............................ 103

3.1  The Concept of cis- and trans-Addition ...................................... 104
3.2  Vocabulary of Stereochmistry and Stereoselective Synthesis I ........ 104
3.2.1  Isomerism, Diastereomers/Enantiomers, Chirality .................... 104
3.2.2  Chemoselectivity, Diastereoselectivity/Enantioselectivity, Stereoespecificity/Stereocrvconvergence ................................ 106

3.3  Electrophilic Additions that Take Place Diastereoselectively as cis-Additions ................................................................. 109
3.3.1  A Cycloaddition Forming Three-Membered Rings .................... 109
3.3.2  Additions to C= C Double Bonds That Are Related to Cycloadditions and Also Form Three-Membered Rings .................. 114
3.3.3  cis-Hydration of Alkenes via the Hydroboration/Oxidation/ Hydrolysis Reaction Sequence ...................................................... 118
3.3.4  Heterogeneous Hydrogenation ................................................ 126

3.4  Enantioselective cis-Additions to C= C Double Bonds ................. 128
3.4.1  Vocabulary of Stereochemistry and Stereoselective Synthesis II: Topicity, Asymmetric Synthesis ................................. 128
3.4.2  Asymmetric Hydroboration of Achiral Alkenes ......................... 129
3.4.3  Thought Experiment I on the Hydroboration of Chiral Alkenes with Chiral Boranes: Mutual Kinetic Resolution ....................... 131
3.4.4 Thought Experiments II and III on the Hydroboration of Chiral Alkenes with Chiral Boranes: Reagent Control of Diastereoselectivity, Matched/Mismatched Pairs, Double Stereodifferentiation

3.4.5 Thought Experiment IV on the Hydroboration of Chiral Olefins with Chiral Dialkylboranes: Kinetic Resolution

3.4.6 Catalytic Asymmetric Synthesis: Sharpless Oxidations of Allylic alcohols

3.5 Additions that Take Place Diastereoselectively as trans-Additions
(Additions via Onium Intermediates)

3.5.1 Addition of Halogens

3.5.2 The Formation of Halohydrins; Halolactonization and Haloetherification

3.5.3 Solvomercuration of Alkenes: Hydration of C=C Double Bonds through Subsequent Reduction

3.6 Additions that Take Place or Can Take Place without Stereocontrol Depending on the Mechanism

3.6.1 Additions via Carbenium Ion Intermediates

3.6.2 Additions via “Carbanion” Intermediates

4 β-Eliminations

4.1 Concepts of Elimination Reactions

4.1.1 The Concepts of α,β- and 1,ν-Elimination

4.1.2 The Terms syn- and anti-Elimination

4.1.3 When Are syn- and anti-Selective Eliminations Stereoselective?

4.1.4 Formation of Regioisomeric Alkenes by β-Elimination: Saytzeff and Hofmann Product(s)

4.1.5 The Synthetic Value of Het1/Het2 in Comparison to H/Het-Eliminations

4.2 β-Eliminations of H/Het via Cyclic Transition States

4.3 β-Eliminations of H/Het via Acyclic Transition States: The Mechanistic Alternatives

4.4 E2 Eliminations of H/Het and the E2/SN2 Competition

4.4.1 Substrate Effects on the E2/SN2 Competition

4.4.2 Base Effects on the E2/SN2 Competition

4.4.3 A Stereoelectronic Effect on the E2/SN2 Competition

4.4.4 The Regioselectivity of E2 Eliminations

4.4.5 The Stereoselectivity of E2 Eliminations

4.4.6 One-Pot Conversion of an Alcohol to an Alkene

4.5 E1 Elimination of H/Het from R- X and the E1/SN1 Competition

4.5.1 Energy Profiles and Rate Laws for E1 Eliminations

4.5.2 The Regioselectivity of E1 Eliminations

4.5.3 E1 Eliminations in Protecting Group Chemistry

4.6 E1cb Eliminations

4.6.1 Unimolecular E1cb Eliminations: Energy Profile and Rate Law
4.6.2 Nonunimolecular \(E_{1cb}\) Eliminations: Energy Profile and Rate Law ........................................... 190
4.6.3 Alkene-Forming Step of the Julia-Lythgoe Olefination ................................. 191
4.6.4 \(E_{1cb}\) Eliminations in Protecting Group Chemistry .............................. 192
4.7 \(\beta\)-Eliminations of Het\(^1\)/Het\(^2\) ................................................................. 194
4.7.1 Fragmentation of \(\beta\)-Heterosubstituted Organometallic Compounds ............ 194
4.7.2 Peterson Olefination ................................................................................. 195
4.7.3 Oxaphosphetane Fragmentation, Last Step of Wittig and Horner–Wadsworth–Emmons Reactions ............................................................ 196

5 Substitution Reactions on Aromatic Compounds ................................................. 201

5.1 Electrophilic Aromatic Substitutions via Sigma Complexes (‘Ar-SE Reactions’). ............................................................................................................ 201
5.1.1 Mechanism: Substitution of \(H^\oplus vs ipso\)-Substitution. .......................... 201
5.1.2 Thermodynamic Aspects of \(Ar-S_E\) Reactions ........................................... 205
5.1.3 Kinetic Aspects of \(Ar-S_E\) Reactions: Reactivity and Regioselectivity in Reactions of Electrophiles with Substituted Benzenes .................................. 209
5.2 \(Ar-S_E\) Reactions via Sigma Complexes: Individual Reactions .................. 215
5.2.1 \(Ar-Hal\) Bond Formation by \(Ar-S_E\) Reaction ........................................ 215
5.2.2 \(Ar-SO_3H\) Bond Formation by \(Ar-S_E\) Reaction .................................... 218
5.2.3 \(Ar-NO_2\) Bond Formation by \(Ar-S_E\) Reaction ........................................ 219
5.2.4 \(Ar-N=N\) Bond Formation by \(Ar-S_E\) Reaction ....................................... 223
5.2.5 \(Ar-Alkyl\) Bond Formations by \(Ar-S_E\) Reaction ..................................... 225
5.2.6 \(Ar-C(OH)\) Bond Formation by \(Ar-S_E\) Reactions and Associated Secondary Reactions ....................................................................................... 228
5.2.7 \(Ar-C(=O)\) Bond Formation by \(Ar-S_E\) Reaction ................................... 229
5.2.8 \(Ar-C(=O)H\) Bond Formation through \(Ar-S_E\) Reaction ..................... 233
5.3 Electrophilic Substitution Reactions on Metalated Aromatic Compounds .... 234
5.3.1 Electrophilic Substitution Reactions of \(ortho\)-Lithiated Benzene and Naphthalene Derivatives .................................................................................. 234
5.3.2 Electrophilic Substitution Reactions in Aryl Grignard and Aryllithium Compounds That Are Accessible from Aryl Halides .................................. 237
5.3.3 Electrophilic Substitutions of Arylboronic Acids and Arylboronic Esters ........................................................................................................... 242
5.4 Nucleophilic Substitution Reactions of Aryldiazonium Salts ......................... 243
5.5 Nucleophilic Substitution Reactions via Meisenheimer Complexes ............. 247
5.5.1 Mechanism ............................................................................................ 247
5.5.2 Examples of Reactions of Preparative Interest ...................................... 249
5.6 Nucleophilic Aromatic Substitution via Arynes, \(cine\) Substitution ................... 251

6 Nucleophilic Substitution Reactions at the Carboxyl Carbon .................................. 259

6.1 C=O-Containing Substrates and Their Reactions with Nucleophiles ............. 259
6.2 Mechanisms, Rate Laws, and Rate of Nucleophilic Substitution Reactions at the Carboxyl Carbon ............................................................................. 261
6.2.1 Mechanism and Rate Laws of $S_N$ Reactions at the Carboxyl Carbon ........................................... 262
6.2.2 $S_N$ Reactions at the Carboxyl Carbon: The Influence of Resonance Stabilization of the Reacting C=O Double Bond on the Reactivity of the Acylating Agent ............................................... 268
6.2.3 $S_N$ Reactions at the Carboxyl Carbon: The Influence of the Stabilization of the Tetrahedral Intermediate on the Reactivity ................................................................. 272

6.3 Activation of Carboxylic Acids and of Carboxylic Acid Derivatives ....................................................... 274
6.3.1 Activation of Carboxylic Acids and Carboxylic Acid Derivatives in Equilibrium Reactions ................... 274
6.3.2 Conversion of Carboxylic Acids into Isolable Acylating Agents .......................................................... 275
6.3.3 Complete in Situ Activation of Carboxylic Acids ................................................................................. 278

6.4 Selected $S_N$ Reactions of Heteroatom Nucleophiles at the Carboxyl Carbon ........................................... 282
6.4.1 Hydrolysis and Alcoholysis of Esters ..................................................................................................... 287
6.4.2 Lactone Formation from Hydroxycarboxylic Acids ............................................................................. 293
6.4.3 Forming Peptide Bonds ......................................................................................................................... 296
6.4.4 $S_N$ Reactions of Heteroatom Nucleophiles with Carbonic Acid Derivatives ............................................. 300

6.5 $S_N$ Reactions of Hydride Donors, Organometallics, and Heteroatom-Stabilized “Carbanions” on the Carboxyl Carbon .............................................................. 306
6.5.1 When Do Pure Acylations Succeed with Carboxylic Acid (Derivative)s, and When Are Alcohols Produced? 306
6.5.2 Acylation of Hydride Donors: Reduction of Carboxylic Acid Derivatives to Aldehydes ......................... 311
6.5.3 Acylation of Organometallic Compounds and Heteroatom-Stabilized “Carbanions” With Carboxylic Acid (Derivative)s: Synthesis of Ketones .............................................................. 312
6.5.4 Acylation of Organometallic Compounds and Heteroatom-Stabilized “Carbanions” with Carbonic Acid Derivatives: Synthesis of Carboxylic Acid Derivatives ........................................... 317

7 Carboxylic Compounds, Nitriles, and Their Interconversion ................................................................. 321
7.1 Preparation of Nitriles from Carboxylic Acid(Derivative)s ................................................................. 322
7.2 Transformation of Nitriles and Heteroatom Nucleophiles to Carboxylic Acid (Derivative)s ...................... 328

8 Carbonic Acid Derivatives and Heterocumulenes and Their Interconversion ............................................. 339
8.1 Preparation of Heterocumulenes from Carbonic Acid (Derivatives) .......................................................... 341
8.2 Transformation of Heterocumulenes and Heteroatom Nucleophiles into Carbonic Acid Derivatives .................. 348
8.3 Interconversions of Carbonic Acid Derivatives via Heterocumulenes as Intermediates ............................. 356
9 Additions of Heteroatom Nucleophiles to Carbonyl Compounds and Subsequent Reactions—Condensations of Heteroatom Nucleophiles with Carbonyl Compounds

9.1 Additions of Heteroatom Nucleophiles or Hydrocyanic Acid to Carbonyl Compounds

9.1.1 On the Equilibrium Position of Addition Reactions of Heteroatom Nucleophiles to Carbonyl Compounds

9.1.2 Hemiacetal Formation

9.1.3 Formation of Cyanohydrins and $\alpha$-Aminonitriles

9.1.4 Oligomerization of Aldehydes—Polymerization of Formaldehyde

9.2 Addition of Heteroatom Nucleophiles to Carbonyl Compounds in Combination with Subsequent $S_N1$ Reactions of the Primary Product: Acetalizations

9.3 Addition of Nitrogen Nucleophiles to Carbonyl Compounds in Combination with Subsequent $E1$ Eliminations of the Primary Product: Condensation Reactions

10 Addition of Hydride Donors and of Organometallic Compounds to Carbonyl Compounds

10.1 Suitable Hydride Donors and Organometallic Compounds; the Structure of Organolithium Compounds and Grignard Reagents

10.2 Chemoselectivity of the Addition of Hydride Donors to Carbonyl Compounds

10.3 Diastereoselectivity of the Addition of Hydride Donors to Carbonyl Compounds

10.4 Enantioselective Addition of Hydride Donors to Carbonyl Compounds

10.5 Addition of Organometallic Compounds to Carbonyl Compounds

10.5.1 Simple Addition Reactions of Organometallic Compounds

10.5.2 Enantioselective Addition of Organometallic Compounds to Carbonyl Compounds: Chiral Amplification

10.5.3 Diastereoselective Addition of Organometallic Compounds to Carbonyl Compounds
10.6 1,4-Additions of Organometallic Compounds to α,β-Unsaturated Ketones; Structure of Copper-Containing Organometallic Compounds

11 Conversion of Phosphorus- or Sulfur-Stabilized C Nucleophiles with Carbonyl Compounds: Addition-Induced Condensations

11.1 Condensation of Phosphonium Ylides with Carbonyl Compounds:
- Wittig Reaction

11.1.1 Bonding in Phosphonium Ylides
11.1.2 Nomenclature and Preparation of Phosphonium Ylides
11.1.3 Mechanism of the Wittig Reaction

11.2 Wittig–Horner Reaction

11.3 Horner–Wadsworth–Emmons Reaction

11.3.1 Horner–Wadsworth–Emmons Reactions Between Achiral Substrates
11.3.2 Horner–Wadsworth–Emmons Reactions between Chiral Substrates: A Potpourri of Stereochemical Specialties

11.4 (Marc) Julia–Lythgoe- and (Sylvestre) Julia–Kocienski Olefination

12 The Chemistry of Enols and Enamines

12.1 Keto-Enol Tautomerism; Enol Content of Carbonyl and Carboxyl Compounds

12.2 α-Functionalization of Carbonyl and Carboxyl Compounds via Tautomeric Enols

12.3 α-Functionalization of Ketones via Their Enamines

12.4 α-Functionalization of Enol Ethers and Silyl Enol Ethers

13 Chemistry of the Alkaline Earth Metal Enolates

13.1 Basic Considerations

13.1.1 Notation and Structure of Enolates
13.1.2 Preparation of Enolates by Deprotonation
13.1.3 Other Methods for the Generation of Enolates
13.1.4 Survey of Reactions between Electrophiles and Enolates and the Issue of Ambidoselectivity

13.2 Alkylation of Quantitatively Prepared Enolates and Aza-enolates; Chain-Elongating Syntheses of Carbonyl Compounds and Carboxylic Acid Derivatives

13.2.1 Chain-Elongating Syntheses of Carbonyl Compounds
13.2.2 Chain-Elongating Syntheses of Carboxylic Acid Derivatives

13.3 Hydroxyalkylation of Enolates with Carbonyl Compounds (“Aldol Addition”):
- Synthesis of β-Hydroxyketones and β-Hydroxyesters
- Driving Force of Aldol Additions and Survey of Reaction Products
- Stereocontrol
13.4 Condensation of Enolates with Carbonyl Compounds: Synthesis of
Michael Acceptors ........................................... 565
13.4.1 Aldol Condensations .................................. 565
13.4.2 Knoevenagel Reaction ............................... 571
13.5 Acylation of Enolates .................................. 575
13.5.1 Acylation of Ester Enolates .......................... 575
13.5.2 Acylation of Ketone Enolates ....................... 579
13.5.3 Acylation of the Enolates of Active-Methylene Compounds ... 582
13.6 Michael Additions of Enolates ......................... 584
13.6.1 Simple Michael Additions ............................ 584
13.6.2 Tandem Reactions Consisting of Michael Addition and
Consecutive Reactions ........................................ 586

14 Rearrangements ........................................... 595
14.1 Nomenclature of Sigmatropic Shifts .................... 595
14.2 Molecular Origins for the Occurrence of [1,2]-Rearrangements .......... 596
14.3 [1,2]-Rearrangements in Species with a Valence Electron Sextet .......... 598
  14.3.1 [1,2]-Rearrangements of Carbenium Ions ............... 598
  14.3.2 [1,2]-Rearrangements in Carbenes or Carbenoids ........... 615
14.4 [1,2]-Rearrangements without the Occurrence of a Sextet Intermediate ... 622
  14.4.1 Hydroperoxide Rearrangements ....................... 623
  14.4.2 Baeyer–Villiger Rearrangements ....................... 624
  14.4.3 Oxidation of Organoborane Compounds ................... 627
  14.4.4 Beckmann Rearrangement ............................. 629
  14.4.5 Curtius Degradation ................................... 630
14.5 Claisen Rearrangement ................................ 632
  14.5.1 Classical Claisen Rearrangement ....................... 632
  14.5.2 Ireland-Claisen Rearrangements ....................... 634

15 Thermal Cycloadditions ................................ 643
15.1 Driving Force and Feasibility of One-Step [4+2]- and
  [2+2]-Cycloadditions ....................................... 643
15.2 Transition State Structures of Selected One-Step [4+2]- and
  [2+2]-Cycloadditions ....................................... 644
  15.2.1 Stereostructure of the Transition States of One-Step
        [4+2]-Cycloadditions ................................... 644
  15.2.2 Frontier Orbital Interactions in the Transition States of
        One-Step [4+2]-Cycloadditions ......................... 645
  15.2.3 Frontier Orbital Interactions in the Transition States of the
        Unknown One-Step Cycloadditions of Alkenes or Alkynes
        to Alkenes .............................................. 651
  15.2.4 Frontier Orbital Interactions in the Transition State of One-Step
        [2+2]-Cycloadditions Involving Ketenes .................. 652
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.4</td>
<td>Reductions</td>
<td>777</td>
</tr>
<tr>
<td>17.4.1</td>
<td>Reductions $R_{sp^3}-%X \rightarrow R_{sp^3}-H$ or $R_{sp^3}-%X \rightarrow R_{sp^3}-M$</td>
<td>778</td>
</tr>
<tr>
<td>17.4.2</td>
<td>One-Electron Reductions of Carbonyl Compounds and Esters; Reductive Coupling</td>
<td>786</td>
</tr>
<tr>
<td>17.4.3</td>
<td>Reductions of Carboxylic Acid Derivatives to Alcohols or Amines</td>
<td>795</td>
</tr>
<tr>
<td>17.4.4</td>
<td>Reductions of Carboxylic Acid Derivatives to Aldehydes</td>
<td>800</td>
</tr>
<tr>
<td>17.4.5</td>
<td>Reductions of Carbonyl Compounds to Alcohols</td>
<td>800</td>
</tr>
<tr>
<td>17.4.6</td>
<td>Reductions of Carbonyl Compounds to Hydrocarbons</td>
<td>800</td>
</tr>
<tr>
<td>17.4.7</td>
<td>Hydrogenation of Alkenes</td>
<td>806</td>
</tr>
<tr>
<td>17.4.8</td>
<td>Reductions of Aromatic Compounds and Alkynes</td>
<td>815</td>
</tr>
<tr>
<td>17.4.9</td>
<td>The Reductive Step of the Julia–Lythgoe Olefination</td>
<td>819</td>
</tr>
</tbody>
</table>

**Subject Index**                                             827
Organic Mechanisms
Reactions, Stereochemistry and Synthesis
Bruckner, R. - Harmata, M. (Ed.)
2010, XXXII, 855 p., Hardcover
ISBN: 978-3-642-03650-7