

Advanced Organic Chemistry

Part B: Reactions and Synthesis

Francis A. Carey
and Richard J. Sundberg

University of Virginia, Charlottesville, Virginia

PLENUM PRESS • NEW YORK AND LONDON

Advanced Organic Chemistry

Part B: Reactions and Synthesis

Preface to Part B

In Part A, the structural and mechanistic groundwork of organic chemistry was considered. Part B assumes that the student possesses a mastery of these areas and emphasizes the synthetic application of organic reactions. Mechanisms are discussed in sufficient detail to allow the student to understand the basis for the selectivity of the reaction and its stereochemistry, but fine points of mechanistic detail are not emphasized. Many of the most general synthetic reactions are illustrated by referenced examples included in the schemes.

The organization is along the lines of reaction type rather than functional groups. The first nine chapters discuss most of the important reactions presently in use in organic synthesis. Although the emphasis here is on synthesis, the reactions that are discussed in each chapter are usually members of related mechanistic families. Chapter 10 discusses synthetic tactics and strategy in general. Chapter 11 considers some of the special features of macromolecular synthesis.

As in Part A, the majority of the references are to English language journals that are widely accessible. References have been chosen primarily because they are illustrative of a given point or are useful leading references. No attempt has been made to consider authors' priority in the selection of references.

A number of problems are given with each chapter. An attempt has been made in those dealing with synthesis to make the problems cumulative in the sense that reactions discussed in preceding chapters may be involved, while reactions that have yet to be discussed are avoided. Of course, synthetic problems have numerous "correct answers"; therefore, although literature references to the synthetic problems are given, there may in many instances be other, perhaps preferable, alternatives. Many of the problems will be quite challenging, and the student should not feel discouraged at not being able to match the solutions to synthetic challenges reported in the literature. Indeed, it may be most useful to treat the more difficult problems as takeoff points for in-class discussion and analysis.

Contents of Part B

List of Figures	xi
List of Tables	xiii
List of Schemes	xv
Contents of Part A	xix
Chapter 1. Alkylation of Carbon via Enolates and Enamines	1
1.1. Generation of Carbon Nucleophiles by Proton Abstraction	1
1.2. Kinetic Versus Thermodynamic Control in Formation of Enolates	3
1.3. Other Means of Generating Enolates	7
1.4. Alkylations of Enolates	8
1.5. Generation and Alkylation of Dianions	12
1.6. Solvent Effects in Enolate Alkylations	12
1.7. Oxygen Versus Carbon as the Site of Alkylation	15
1.8. Alkylations of Aldehydes, Esters, Nitriles, and Nitro Compounds	19
1.9. The Nitrogen Analogs of Enols and Enolates—Enamine Alkylations	21
1.10. Alkylation of Carbon by Conjugate Addition	24
General References	28
Problems	28
Chapter 2. Reactions of Nucleophilic Carbon Species with Carbonyl Groups	33
2.1. Aldol Condensation	33
2.2. Related Condensation Reactions	42
2.3. The Mannich Reaction	44
2.4. Acylation of Nucleophilic Carbon	47
2.5. The Wittig Reaction	53

2.6. Sulfur Ylides as Nucleophiles	59
2.7. Nucleophilic Addition–Cyclization	63
General References	64
Problems	65
Chapter 3. Addition Reactions of Carbon–Carbon Multiple Bonds	73
3.1. Addition of Hydrogen	73
3.2. Addition of Hydrogen Halides	81
3.3. Hydration and Other Acid-Catalyzed Additions	85
3.4. Oxymercuration	87
3.5. Addition of Halogens to Olefins	90
3.6. Addition of Other Electrophilic Reagents	95
3.7. Electrophilic Substitution Alpha to Carbonyl Groups	98
3.8. Hydroboration	100
3.9. Additions to Allenes and Alkynes	112
General References	121
Problems	122
Chapter 4. Reduction of Carbonyl and Other Functional Groups	129
4.1. Hydride-Transfer Reagents	129
4.2. Hydrogen-Atom Donors	143
4.3. Dissolving-Metal Reductions	145
General References	152
Problems	152
Chapter 5. Organometallic Compounds	163
5.1. Organic Derivatives of Group I and II Metals	163
5.1.1. Preparation and Properties	163
5.1.2. Reactions	170
5.2. Organic Derivatives of Group IIb Metals	180
5.3. Organic Derivatives of Transition Metals	182
5.4. Catalysis of Rearrangements by Metal Ions and Complexes	191
5.5. Organometallic Compounds with π -Bonding	193
General References	197
Problems	198
Chapter 6. Cycloadditions and Unimolecular Rearrangements and Eliminations	205
6.1. Cycloaddition Reactions	205
6.1.1. Diels–Alder Reaction	206
6.1.2. Dipolar Cycloaddition Reactions	212
6.1.3. 2 + 2 Cycloadditions and Other Reactions Leading to Cyclobutanes	219
6.2. Photochemical Cycloadditions	222

6.3. Sigmatropic Rearrangements	226
6.4. Unimolecular Thermal Elimination Reactions	234
6.4.1. Cycloreversions and Related Eliminations	235
6.4.2. β -Eliminations Involving Cyclic Transition States	242
General References	247
Problems	248

Chapter 7. Aromatic Substitution Reactions 257

7.1. Electrophilic Aromatic Substitution	257
7.1.1. Nitration	257
7.1.2. Halogenation	260
7.1.3. Friedel-Crafts Alkylations and Acylations	261
7.1.4. Electrophilic Metalation	272
7.2. Nucleophilic Aromatic Substitution	275
7.2.1. Nucleophilic Aromatic Substitution via Diazonium Ions	275
7.2.2. Nucleophilic Aromatic Substitution by Addition-Elimination	280
7.2.3. Nucleophilic Aromatic Substitution by Elimination-Addition	282
7.2.4. Copper-Catalyzed Nucleophilic Aromatic Substitution	288
7.3. Substitutions Involving Aryl Free Radicals	288
7.4. Reactivity of Polycyclic Aromatics	292
General References	294
Problems	295

Chapter 8. Reactions Involving Carbenes, Nitrenes, and Other Electron-Deficient Intermediates 301

8.1. Carbenes	302
8.1.1. Structure	302
8.1.2. Generation of Carbenes	304
8.1.3. Reactions	311
8.2. Nitrenes	320
8.3. Rearrangements of Electron-Deficient Intermediates	322
8.3.1. Migration to Carbon	322
8.3.2. Migration to Nitrogen	328
8.4. Fragmentation Reactions	333
8.5. Some Synthetically Useful Carbonium-Ion Reactions	336
General References	343
Problems	343

Chapter 9. Oxidations 351

9.1. Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids	351
9.1.1. Transition-Metal Oxidants	351
9.1.2. Oxygen, Ozone, and Peroxides	356
9.1.3. Other Oxidants	356
9.2. Addition of Oxygen at Carbon-Carbon Double Bonds	359

9.2.1. Transition-Metal Oxidants	359
9.2.2. Epoxides from Olefins and Peroxidic Reagents	362
9.3. Cleavage of Carbon–Carbon Double Bonds	371
9.3.1. Transition-Metal Oxidants	371
9.3.2. Ozonolysis	373
9.4. Selective Oxidative Cleavages at Other Functional Groups	377
9.4.1. Cleavage of Glycols	377
9.4.2. Oxidative Decarboxylation	379
9.5. Oxidations of Ketones and Aldehydes	381
9.5.1. Transition-Metal Oxidants	381
9.5.2. Oxidation of Ketones and Aldehydes by Peroxidic Compounds and Oxygen	383
9.5.3. Oxidations with Other Reagents	386
9.6. Allylic Oxidation of Olefins	387
9.6.1. Transition-Metal Oxidants	387
9.6.2. Oxygen, Ozone, and Peroxides	388
9.6.3. Other Oxidants	390
9.7. Oxidations at Unfunctionalized Carbon Atoms	393
General References	396
Problems	396
Chapter 10. Multistep Syntheses	407
10.1. Protective Groups	407
10.1.1. Hydroxyl-Protecting Groups	408
10.1.2. Amino-Protecting Groups	414
10.1.3. Carbonyl-Protecting Groups	416
10.1.4. Carboxylic Acid Protecting Groups	417
10.2. Synthetic Equivalent Groups	418
10.3. Asymmetric Syntheses	423
10.4. Synthetic Strategy	429
General References	449
Problems	450
Chapter 11. Synthesis of Macromolecules	459
11.1. Polymerization	460
11.1.1. Chain-Addition Polymerization	460
11.1.2. Step-Growth Polymerization	467
11.2. Peptide and Protein Synthesis	472
11.3. Nucleosides, Nucleotides, and Polynucleotides	482
General References	491
Problems	491
References for Problems	497
Subject Index	509

List of Figures

1.1. Enhanced reactivity of unsolvated enolates	15
1.2. O-versus C-alkylation	17
2.1. Transition states for base-catalyzed dehydration in Claisen–Schmidt condensations	41
2.2. Stereochemistry of the Wittig reaction as a function of the reaction-energy profile	57
3.1. Relative reaction energy in partial protonation of primary versus tertiary carbon atoms	83
3.2. Electronic versus steric control of ring-opening	97
5.1. Representation of π -bonding in olefin–transition-metal complexes . .	194
5.2. Structures of some π -organometallic compounds containing allyl groups as ligands	195
6.1. <i>Endo</i> and <i>exo</i> addition in Diels–Alder addition	207
11.1. Amino acid sequence of bovine insulin	473

List of Tables

1.1. Approximate pK values for some carbon acids and basic catalysts	3
1.2. Compositions of enolate mixtures	6
1.3. Relative alkylation rates of sodium diethyl <i>n</i> -butylmalonate in various solvents	13
3.1. Conditions for catalytic reduction of various groups	78
3.2. Homogeneous hydrogenation catalysts	80
3.3. Stereochemistry of addition of hydrogen halides to olefins	84
3.4. Relative reactivity of some alkenes in oxymercuration	88
3.5. Addition of electrophilic reagents to olefins	96
3.6. Orientation in hydroboration reactions	103
3.7. Relative reactivity of alkenes and alkynes	114
4.1. Reactivity of hydride-transfer reducing agents	130
4.2. Stereochemistry of hydride reductions	136
6.1. Relative reactivity of substituted alkenes toward 1,3-dipoles	217
7.1. Relative activity of Friedel-Crafts catalysts	265
8.1. Relative rates of addition to alkenes	304
10.1. Stereoselectivity in some hydroboration-oxidations of alkenes with di-3-pinanylborane	426
10.2. Stereoselectivity in some Diels-Alder reactions of chiral acrylate esters	427

3.8. Alkylation of trialkylboranes with haloesters, haloketones, and halonitriles	111
3.9. Ketones from acid-catalyzed and mercuric-ion-catalyzed hydration of terminal alkynes	115
3.10. Reductions of alkynes to alkenes	117
3.11. Syntheses using aluminum alkyls	120
4.1. Reduction of other functional groups by complex metal hydrides	140
4.2. Dehalogenations with stannanes	144
4.3. Dissolving-metal reductions	146
4.4. Carbonyl-to-methylene reductions	149
5.1. Organolithium compounds by metalation	167
5.2. Synthetic procedures involving Grignard reagents	174
5.3. Conjugate additions of Grignard reagents	177
5.4. Synthesis of ketones from carboxylate salts	178
5.5. Preparation of ketones via organocadmium reagents	181
5.6. Condensation of α -halocarbonyl compounds using zinc—the Reformatsky reaction	182
5.7. Reactions of lithium copper reagents	184
5.8. Preparation of biaryls by the Ullmann coupling reaction	190
5.9. Metal-ion-catalyzed isomerizations	192
5.10. Reactions of cyclobutadiene	196
5.11. Electrophilic substitution reactions of ferrocene	197
6.1. Representative dienophiles	210
6.2. Some examples of Diels–Alder reactions	212
6.3. 1,3-Dipolar compounds	214
6.4. Typical 1,3-dipolar cycloaddition reactions	218
6.5. Generation of dipolar intermediates from small rings	219
6.6. 2 + 2 Cycloadditions of ketenes	220
6.7. Formation of cyclobutanes in thermal addition reactions	221
6.8. Intramolecular cyclization of dienes	224
6.9. Intermolecular photocycloadditions of enones and alkenes	225
6.10. Photocycloaddition of carbonyl compounds with alkenes	227
6.11. Claisen rearrangements	232
6.12. Photochemical and thermal decomposition of cyclic azo compounds	241
6.13. Eliminations via cyclic transition states	243
6.14. Thermal eliminations via cyclic transition states	244
7.1. Some examples of aromatic nitration	259
7.2. Aromatic halogenation	262
7.3. Friedel–Crafts alkylation reactions	266
7.4. Friedel–Crafts acylation reactions	270
7.5. Synthetic reactions related to the Friedel–Crafts reaction	272

7.6. Substitution reactions of diazonium salts	278
7.7. Nucleophilic aromatic substitution	283
7.8. Some syntheses via benzyne intermediates	287
7.9. Preparation of aryl cyanides from haloaromatics	289
7.10. Aromatic substitution involving radical intermediates	290
8.1. General methods for generation of carbenes	305
8.2. Synthesis of cyclopropanes by carbene–olefin-addition reactions	314
8.3. Intramolecular carbene-insertion reactions	317
8.4. Conversion of ketones to olefins via sulfonylhydrazones	319
8.5. Wolff rearrangement of α -diazoketones	325
8.6. Base-catalyzed rearrangements of α -haloketones	327
8.7. Beckmann rearrangement reactions	330
8.8. Curtius reactions	332
8.9. Schmidt reactions	334
8.10. Fragmentation reactions	335
8.11. Some examples of pinacol rearrangements	338
8.12. Polyolefin cyclizations	342
9.1. Oxidations with Cr(VI)	354
9.2. Oxidations of alcohols with manganese dioxide	356
9.3. Oxidations of alcohols based on sulfur reagents	358
9.4. Oxidations involving addition of oxygen at carbon–carbon double bonds	361
9.5. Epoxidation of alkenes	364
9.6. Ring-opening of epoxides	366
9.7. Alcohols by reduction of epoxides	368
9.8. Base-catalyzed epoxide ring-opening	370
9.9. Oxidative cleavage of alkenes	373
9.10. Generalized ozonolysis mechanism	374
9.11. Ozonolysis reactions	378
9.12. Baeyer–Villiger oxidations	385
9.13. Generation of singlet oxygen	389
9.14. Oxidation of olefins with singlet oxygen	391
9.15. Selenium dioxide oxidations	393
9.16. Side-chain oxidations of aromatic compounds	395
10.1. Protection of hydroxyl groups	412
10.2. Nucleophilic acyl synthetic equivalents	421
10.3. Examples of masked functionalities in synthesis	422
10.4–10.10. Juvabione syntheses	432
10.11. Synthesis of fumagillo	439
10.12. Synthesis of caryophyllene	441
10.13. Synthesis of sirenin	442
10.14–10.17. Syntheses of prostaglandin intermediates	444

11.1.	Some major polymers	470
11.2.	Normal sequence for peptide synthesis	475
11.3.	Summary of protecting groups and activation techniques employed in some polypeptide syntheses	480
11.4.	Syntheses of some nucleosides	487
11.5.	Syntheses of some oligonucleotides	490

Contents of Part A

List of Figures	xiii
List of Tables	xvii
List of Schemes	xxi
Contents of Part B	xxiii
Chapter 1. Chemical Bonding and Molecular Structure	1
Introduction	1
1.1. Valence-Bond Approach to Chemical Bonding	2
1.2. Bond Energies, Lengths, and Dipoles	10
1.3. Molecular Orbital Theory	15
1.4. Hückel Molecular Orbital Theory	26
General References	32
Problems	32
Chapter 2. Stereochemical Principles	39
Introduction	39
2.1. Enantiomeric Relationships	40
2.2. Diastereomeric Relationships	45
2.3. Dynamic Stereochemistry	53
2.4. Prochiral Relationships	61
General References	66
Problems	66
Chapter 3. Conformational and Other Steric Effects	71
Introduction	71

3.1.	Steric Strain and Molecular Mechanics	72
3.2.	Conformations of Acyclic Molecules	78
3.3.	Conformations of Cyclohexane Derivatives	83
3.4.	Carbocyclic Rings Other Than Six-Membered	94
3.5.	Heterocyclic Conformational Analysis	98
3.6.	Molecular Orbital Methods Applied to Conformational Analysis	103
3.7.	Conformational Effects on Reactivity	107
3.8.	Other Steric Effects on Reactivity	111
	General References	119
	Problems	119
Chapter 4. Study and Description of Organic Reaction Mechanisms		125
	Introduction	125
4.1.	Thermodynamic Data	125
4.2.	Kinetic Data	127
4.3.	Substituent Effects and Linear Free-Energy Relationships	139
4.4.	Isotope Effects	149
4.5.	Characterization of Reaction Intermediates	152
4.6.	Catalysis	154
4.7.	Solvent Effects	158
4.8.	Basic Mechanistic Concepts: Kinetic Versus Thermodynamic Control, Hammond's Postulate, the Curtin-Hammett Principle	163
4.9.	Isotopes in Labeling Experiments	170
4.10.	Stereochemistry	171
	General References	172
	Problems	173
Chapter 5. Nucleophilic Substitution		183
	Introduction	183
5.1.	The Limiting Cases—Substitution by the Ionization (S_N1) Mechanism	184
5.2.	The Limiting Cases—Substitution by the Direct Displacement (S_N2) Mechanism	187
5.3.	Alternative Mechanistic Hypotheses	190
5.4.	Carbonium Ions	195
5.5.	Nucleophilicity	206
5.6.	Leaving-Group Effects	212
5.7.	Steric and Other Substituent Effects on Substitution and Ionization Rates	215
5.8.	Stereochemistry of Nucleophilic Substitution	219
5.9.	Secondary Kinetic Isotope Effects in Substitution Mechanisms	227
5.10.	Neighboring-Group Participation	229
5.11.	Carbonium Ion Rearrangements	236
5.12.	Nonclassical Carbonium Ions and the Norbornyl Cation Problem	242

5.13. Synthetic Applications of Nucleophilic Substitution Reactions	249
General References	257
Problems	257
Chapter 6. Polar Addition and Elimination Reactions	265
Introduction	265
6.1. Addition of Hydrogen Halides to Alkenes	266
6.2. Acid-Catalyzed Hydration of Alkenes	271
6.3. Addition of Halogens	272
6.4. The E2, E1, and E _{1cB} Mechanisms	278
6.5. Orientation Effects in Elimination Reactions	282
6.6. Stereochemistry of E2 Elimination Reactions	286
6.7. Dehydration of Alcohols	290
6.8. Eliminations Not Involving C–H Bonds	291
General References	294
Problems	294
Chapter 7. Carbanions and Other Nucleophilic Carbon Species	299
Introduction	299
7.1. Acidity of Hydrocarbons	299
7.2. Carbanions Stabilized by Functional Groups	307
7.3. Enols and Enamines	315
General References	319
Problems	319
Chapter 8. Reactions of Carbonyl Compounds	325
Introduction	325
8.1. Hydration and Addition of Alcohols to Aldehydes and Ketones	326
8.2. Addition–Elimination Reactions of Ketones and Aldehydes	329
8.3. Reactivity of Carbonyl Compounds Toward Addition	334
8.4. Ester Hydrolysis and Related Reactions	335
8.5. Amide Hydrolysis	341
8.6. Acylation of Nucleophilic Oxygen and Nitrogen Groups	343
8.7. Intramolecular Catalysis	347
General References	352
Problems	352
Chapter 9. Aromaticity and Electrophilic Aromatic Substitution	361
9.1. Aromaticity	361
9.1.1. The Concept of Aromaticity	361
9.1.2. The Annulenes	365
9.1.3. Aromaticity in Charged Rings	372
9.1.4. Fused-Ring Systems	376