

Contents

Preface IX

Glossary and Abbreviations XI

1	Organic Synthesis: General Remarks	1
1.1	Introduction	1
1.2	Synthesis Design	2
1.2.1	Convergent vs Linear Syntheses	2
1.2.2	Retrosynthetic Analysis	3
1.3	Hard and Soft Acids and Bases	9
1.4	The Curtin–Hammett Principle	13
2	Stereoelectronic Effects and Reactivity	17
2.1	Hyperconjugation with σ Bonds	17
2.2	Hyperconjugation with Lone Electron Pairs	19
2.2.1	Effects on Conformation	19
2.2.2	The Anomeric Effect	20
2.2.3	Effects on Spectra and Structure	21
2.3	Hyperconjugation and Reactivity	23
2.3.1	Basicity and Nucleophilicity	23
2.3.2	Rates of Oxidation	25
2.3.3	Rates of Deprotonation	26
2.3.4	Other Reactions	27
2.4	Conclusion	30
3	The Stability of Organic Compounds	35
3.1	Introduction	35
3.2	Strained Bonds	35
3.3	Incompatible Functional Groups	41
3.4	Conjugation and Hyperconjugation of Incompatible Functional Groups	42
3.5	Stability Toward Oxygen	45
3.5.1	Hydrogen Abstraction	45

3.5.2	Oxidation by SET	48
3.5.3	Addition of Oxygen to C–C Double Bonds	51
3.6	Detonations	52
4	Aliphatic Nucleophilic Substitutions: Problematic Electrophiles	59
4.1	Mechanisms of Nucleophilic Substitution	59
4.2	Structure of the Leaving Group	62
4.2.1	Good and Poor Leaving Groups	62
4.2.2	Nucleophilic Substitution of Fluoride	66
4.2.3	Nucleophilic Substitution of Sulfonates	70
4.3	Structure of the Electrophile	72
4.3.1	Steric Effects	72
4.3.2	Conjugation	75
4.3.3	Electrophiles with α -Heteroatoms	79
4.3.4	Electrophiles with β -Heteroatoms	84
4.3.5	Electrophiles with α -Electron-withdrawing Groups	86
4.3.6	Neighboring-group Participation	90
4.3.7	Allylic and Propargylic Electrophiles	93
4.3.8	Epoxides	97
5	The Alkylation of Carbanions	143
5.1	Introduction	143
5.2	The Kinetics of Deprotonations	144
5.3	Regioselectivity of Deprotonations and Alkylations	146
5.3.1	Introduction	146
5.3.2	Kinetic/Thermodynamic Enolate Formation	148
5.3.3	Allylic and Propargylic Carbanions	150
5.3.4	Succinic Acid Derivatives and Amide-derived Carbanions	155
5.3.5	Bridgehead Carbanions	157
5.3.6	Dianions	158
5.3.7	α -Heteroatom Carbanions	161
5.3.8	Vinylic Carbanions	171
5.3.9	Acyl, Imidoyl, and Related Carbanions	173
5.3.10	Aromatic Carbanions	175
5.3.11	Aromatic vs Benzylic Deprotonation	180
5.4	The Stability of Carbanions	182
5.4.1	Introduction	182
5.4.2	α -Elimination	183
5.4.3	β -Elimination	184
5.4.4	Cyclization	190
5.4.5	Rearrangement	193
5.4.6	Oxidation	195
5.4.7	Other Factors which Influence the Stability of Carbanions	196
5.4.8	Configurational Stability of Carbanions	197

6	The Alkylation of Heteroatoms	229
6.1	Alkylation of Fluoride	229
6.2	Alkylation of Aliphatic Amines	231
6.3	Alkylation of Anilines	234
6.4	Alkylation of Alcohols	239
6.5	Alkylation of Phenols	241
6.6	Alkylation of Amides	243
6.7	Alkylation of Carbamates and Ureas	248
6.8	Alkylation of Amidines and Guanidines	250
6.9	Alkylation of Carboxylates	251
7	The Acylation of Heteroatoms	261
7.1	Problematic Carboxylic Acids	261
7.1.1	Sterically Demanding Carboxylic Acids	261
7.1.2	Unprotected Amino and Hydroxy Carboxylic Acids	262
7.1.3	Carboxylic Acids with Additional Electrophilic Groups	265
7.2	Problematic Amines	267
7.2.1	Sterically or Electronically Deactivated Amines	267
7.2.2	Amino Acids	269
7.2.3	Amines with Additional Nucleophilic Groups	270
7.3	Problematic Alcohols	271
7.3.1	Sterically Deactivated and Base-labile Alcohols	271
7.3.2	Alcohols with Additional Nucleophilic Groups	273
8	Palladium-catalyzed C–C Bond Formation	279
8.1	Introduction	279
8.2	Chemical Properties of Organopalladium Compounds	279
8.3	Mechanisms of Pd-catalyzed C–C Bond Formation	282
8.3.1	Cross-coupling	282
8.3.2	The Heck Reaction	285
8.4	Homocoupling and Reduction of the Organyl Halide	287
8.5	Homocoupling and Oxidation of the Carbon Nucleophile	291
8.6	Transfer of Aryl Groups from the Phosphine Ligand	293
8.7	<i>ipso</i> - vs <i>cine</i> -Substitution at Vinylboron and Vinyltin Derivatives	294
8.8	Allylic Arylation and Hydrogenation as Side Reactions of the Heck Reaction	295
8.9	Protodemetalation of the Carbon Nucleophile	296
8.10	Sterically Hindered Substrates	296
8.11	Cyclometalation	298
8.12	Chelate Formation	300
9	Cyclizations	309
9.1	Introduction	309
9.2	Baldwins Cyclization Rules	309
9.3	Structural Features of the Chain	315

VIII | Contents

9.4	Ring Size	319
9.4.1	Formation of Cyclopropanes	321
9.4.2	Formation of Cyclobutanes	325
9.5	Heterocycles	327
10	Monofunctionalization of Symmetric Difunctional Substrates	333
10.1	Introduction	333
10.2	Monofunctionalization of Dicarboxylic Acids	334
10.3	Monofunctionalization of Diols	336
10.4	Monofunctionalization of Diamines	342
10.5	Monoalkylation of C,H-Acidic Compounds	346
10.6	Monoderivatization of Dihalides	348
Index		355