



**Science of
Synthesis**

Free Radicals: Fundamentals and Applications in Organic Synthesis 2

Volume Editors

L. Fensterbank
C. Ollivier

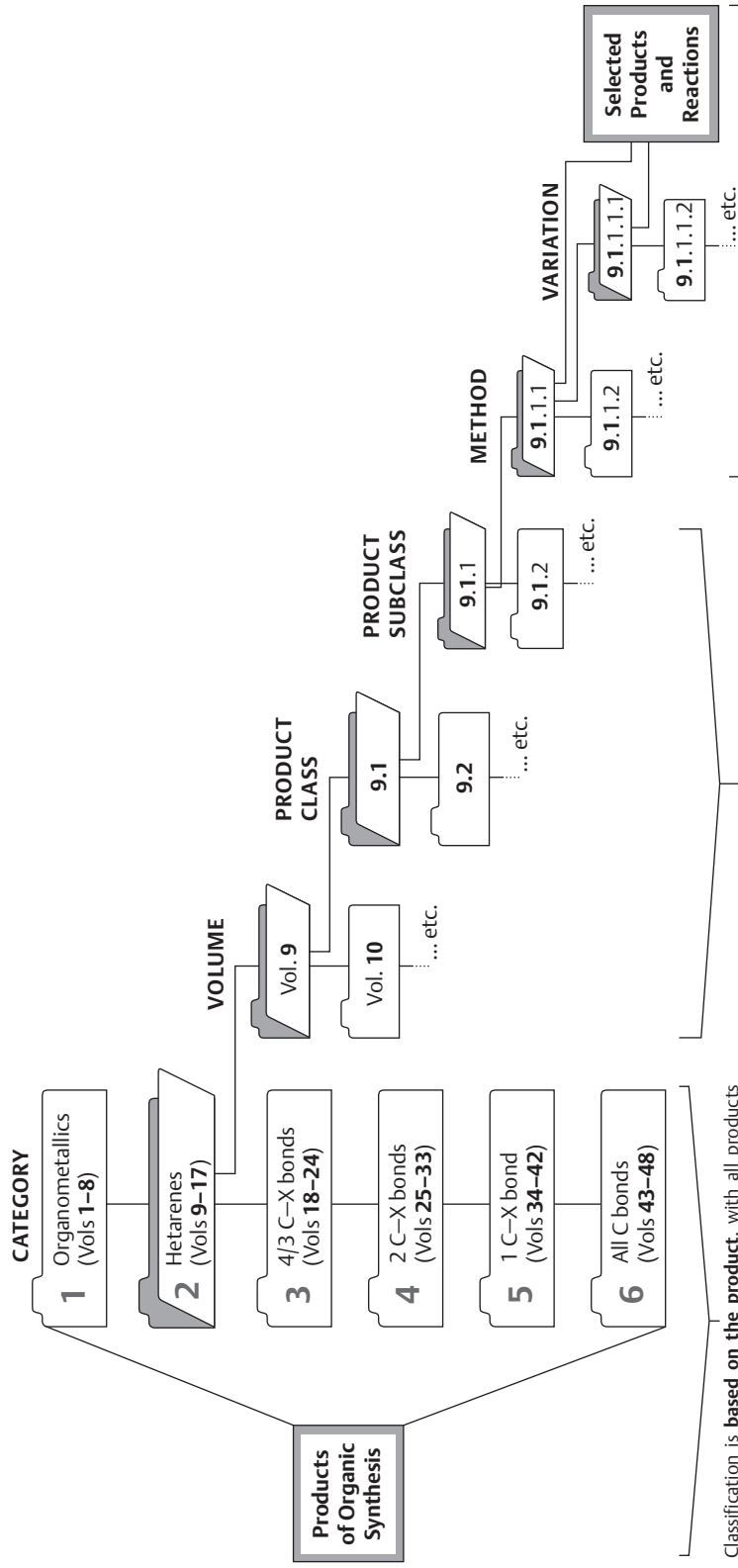
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Organizational Structure of Science of Synthesis*



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C–X) or C–C π -bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

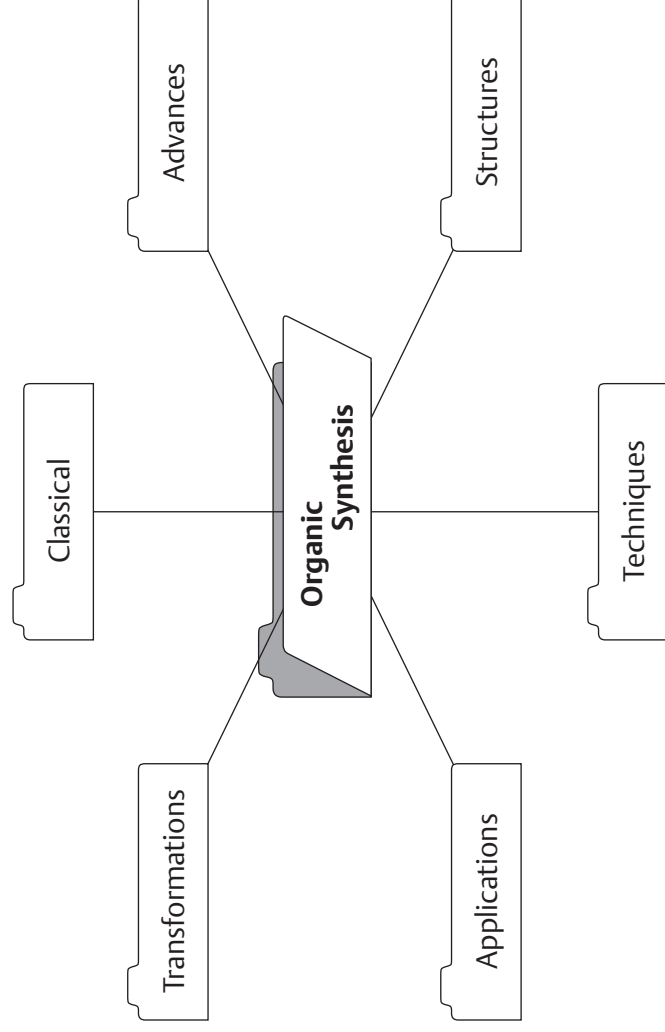
Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., “Thiophenes” is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., “Thiophene 1,1-Dioxides” is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.

* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook**.

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Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

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- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope



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Science of Synthesis

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

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Water in Organic Synthesis

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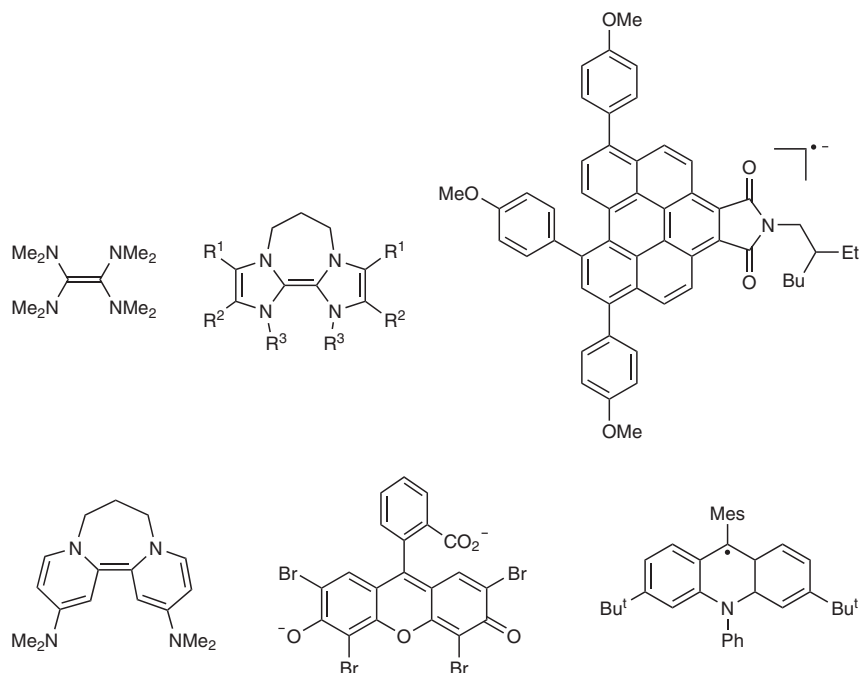
Abstracts

p 1

2.1 Organic Electron Donors in Electron-Transfer Reactions

K. F. Clark, D. Dimitrova, and J. A. Murphy

The field of organic electron donors is large and diverse, both in terms of the structures of the donors and the structures of the acceptors. In the past 15 years, organic donors have been developed that show remarkable strength, with ground-state or excited-state oxidation potentials rivalling even the most reactive metals. At the other end of the scale of reactivity, highly reactive oxidizing agents are now available upon photoactivation of a number of organic structures. The first part of this chapter reviews organic electron donors that are based upon an alkene that is activated by strongly electron-releasing substituents; these donors can be active in the ground and/or excited states. The chapter also covers anionic organic donors that emerged in the field of $S_{RN}1$ and base-induced homolytic aromatic substitution (BHAS) reactions, as well as substrate-based anionic donors including borates and silicates. The use of photoexcited organic dyes as electron donors is described and, finally, some of the recent research with very weak organic donors is highlighted.

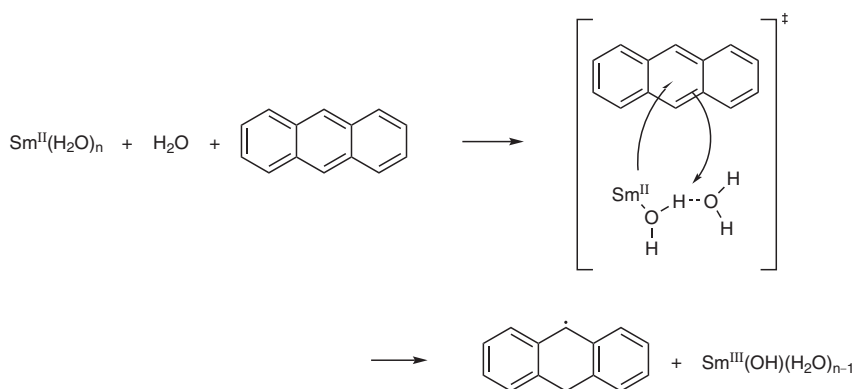


Keywords: organic electron donors • radicals • radical anions • reduction • tetrakis(dimethylamino)ethene (TDAE) • tetrathiafulvalene (TTF) • $S_{RN}1$ reactions • base-induced homolytic aromatic substitution (BHAS) reactions • *tert*-butoxide • organic dyes • eosin Y • rhodamines • acridinium salts • photoexcitation

2.2 Samarium-Mediated Reductions


R. A. Flowers, II, T. V. Chciuk, C. O. Bartulovich

Samarium(II)-based reductants have been shown to be a group of very powerful reagents whose reactivity can be tuned significantly by the use of additives. The use of additives has been shown to greatly impact the rate, diastereoselectivity, chemoselectivity, and mechanism by which these reactions proceed, making these systems extremely useful and versatile. These reagents have been shown to promote several reactions including reductions of a range of functional groups and a variety of carbon-carbon bond forming reactions. More recently, initial work has demonstrated catalytic reactions of samarium(II)-based reductants. This chapter focuses on the chemistry of samarium diiodide (SmI_2) and a few other samarium(II)-based reductants, with examples of the reactions they promote, both with and without the use of additives. Additionally, recent work on the mechanistic understanding of catalytic reactions using terminal reductants and a novel example of an approach employing radical relay that negates the use of a terminal reductant are presented.

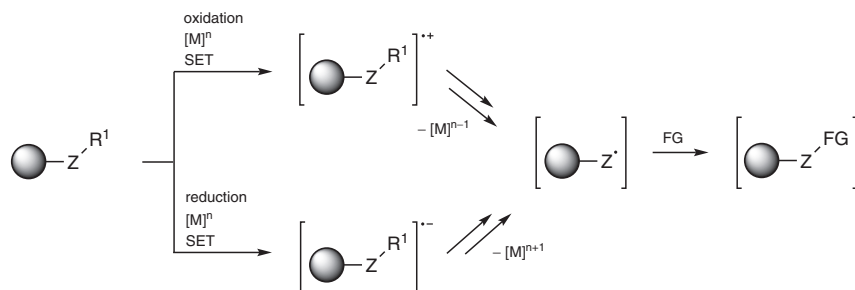


Keywords: samarium · electron transfer · proton donors · hexamethylphosphoric triamide (HMPA) · Lewis bases · additives · lithium halide additives · cyclizations · reductions · reductive coupling · catalysis

2.3 Single-Electron-Transfer Oxidation and Reduction Involving Metal Complexes other than Samarium

M. Cormier and J.-P. Goddard 



Recent advances in the field of radical organic chemistry involving single-electron transfer (SET) are highlighted in this chapter. The focus is on processes between organic molecules and metal complexes that facilitate the creation of challenging covalent bonds. A selection of oxidation and reduction reactions is reported, with special attention paid to enantioselective reactions. Mechanistic discussions are also provided.



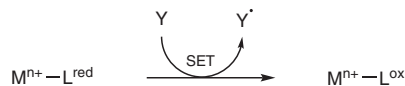
Z = C, N, O, P

Keywords: radical chemistry · organic synthesis · oxidation · reduction · single-electron transfer · metal complexes · enolate coupling · atom-transfer radical addition (ATRA) · C–H oxidation · amination · fluorination · enantioselective reactions · hydrofunctionalization · aryl coupling · phosphorylation

2.4 Redox-Active Ligands in Catalysis for Single-Electron-Transfer Processes

Y. Ren, A. Das, , C. Hessin, and M. Desage-El Murr 

Redox-active ligands are well known for their ability to stabilize electronic density on their scaffolds, and coordination complexes with such ligands are often stable, open-shell species. This property can be used as a means to favor single-electron transfer (SET) with external sources and devise catalytic radical manifolds. This chapter highlights selected representative reactions resulting in efficient and broad-scope catalytic methodologies. It covers nitrene and carbene radical reactivity, as well as radical trifluoromethylation.



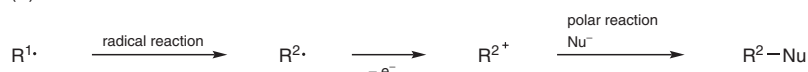
Keywords: redox-active ligands · radicals · single-electron transfer · nitrenes · carbenes · trifluoromethylation · aziridines · cyclopropanes · C–H functionalization · porphyrins · transition-metal complexes

2.5 Radical–Polar Crossover Reactions

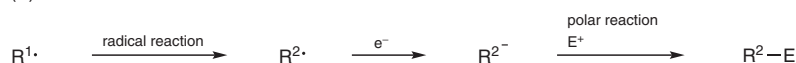
F. Chemla and A. Pérez-Luna

Radical–polar crossover reactions, that is, single-electron redox events allowing for the interconversion between radical and ionic intermediates, make it possible to connect radical and polar processes in the same synthetic transformation. Such a combination is the basis of much original synthetic methodology, which is particularly useful in the context of domino, tandem, or multicomponent reactions. This chapter comprehensively covers the field of radical–polar crossover reactions, with a primary emphasis on transformations wherein both the radical and polar processes provide synthetic elaboration.

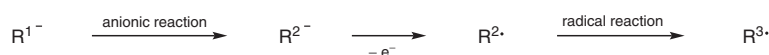
(A) radical-to-cation crossover



(B) radical-to-anion crossover



(C) anion-to-radical crossover

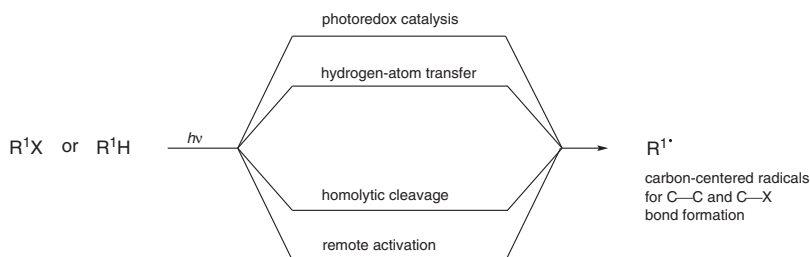


Keywords: radical–polar crossover reactions • anionic reagents • carbocations • domino reactions • multicomponent reactions • organometallic reagents • oxidation • photochemistry • radical addition • radical cyclization • radical reactions • radicals • reduction • tandem reactions

2.6 Generation of Carbon-Centered Radicals by Photochemical Methods

M. Fagnoni, D. Ravelli, and S. Protti

A selection of the recent literature describing the light-driven generation and subsequent exploitation of carbon-centered radicals for synthetic purposes is presented in this chapter. The aim is to showcase to organic (photo)chemistry practitioners the impressive potential of photocatalytic and photochemical strategies in terms of versatility, efficiency, and sustainability.

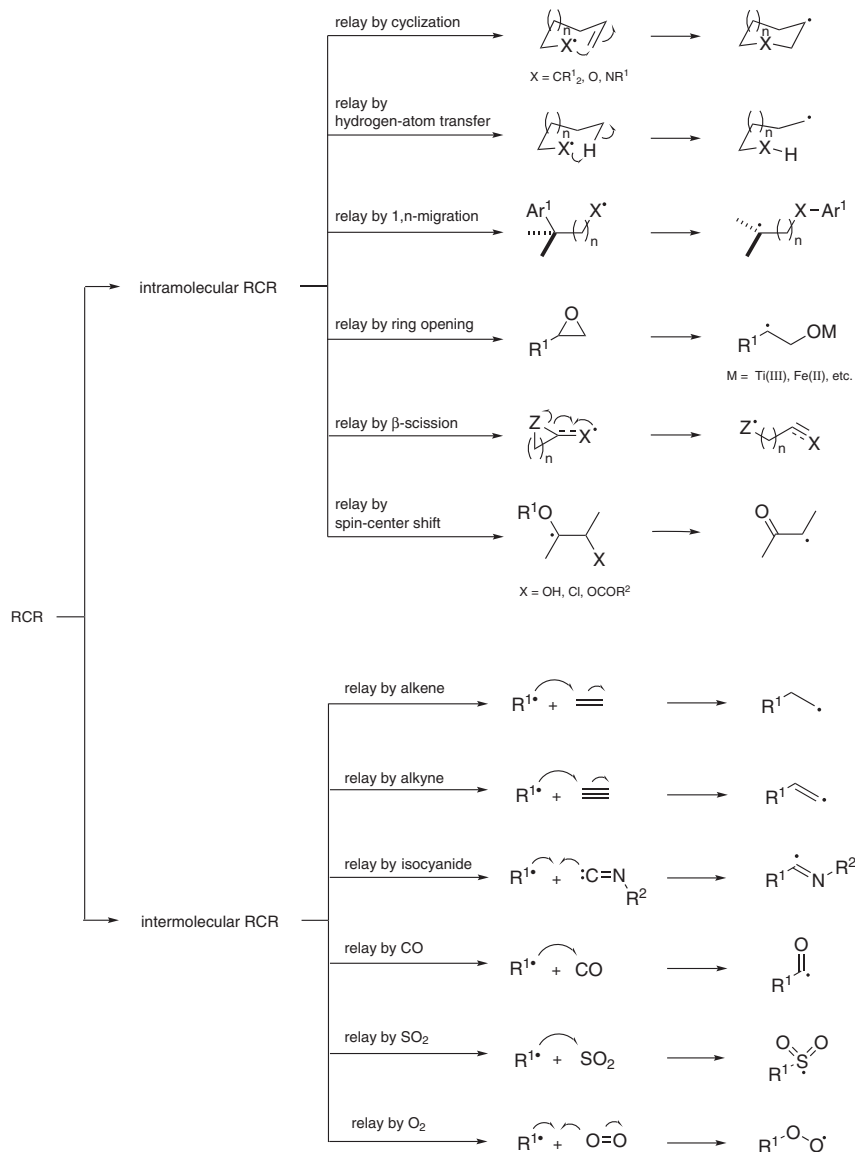


Keywords: C–C bond formation • photocatalysis • photochemistry • radical ions • radicals

2.7 Radical Cascade Reactions

Z.-Q. Liu 

This chapter briefly summarizes the concept of radical cascade reactions (RCR). The chapter is divided into two main parts, describing intramolecular and intermolecular radical cascade reactions, which are further classified based on the six types of relay manner (intramolecular RCR) and six commonly used relay molecules (intermolecular RCR), respectively. This simple classification allows readers to understand this area easily and quickly. Features of radical cascade reactions include step-economy and waste minimization, which endow these radical cascades with a bright future.

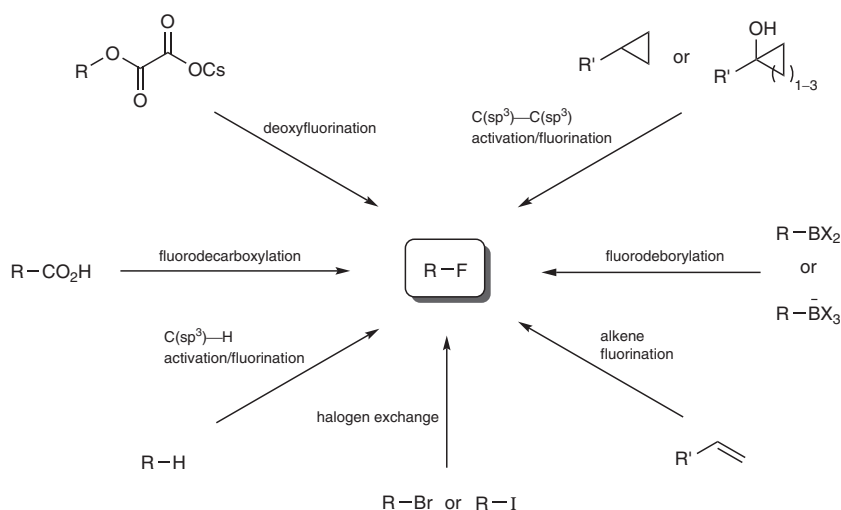


Keywords: free radicals · radical cascade reactions (RCR) · domino reactions · synthetic methods

2.8 Selective Radical Fluorinations

T. G. Bolduc, B. Thomson, and G. M. Sammis

Fluorine atoms are found in numerous industrially relevant materials, including pharmaceuticals, agrochemicals, and plastics. In the pharmaceutical industry alone, more than 20% of all therapeutics and a majority of the top-grossing drugs contain fluorine. The ubiquity of fluorinated compounds in industry has necessitated the development of new methods for selective fluorination. Historically, selective fluorination has relied upon electrophilic or nucleophilic processes. Recently, breakthroughs in the discovery of mild radical fluorine-transfer reagents have led to a renaissance in selective radical fluorinations. This review provides a brief overview of the known fluorine-transfer reagents, including molecular fluorine, hypofluorites, xenon difluoride, electrophilic N-F reagents, and metal-F reagents. A survey of a range of radical fluorination reactions is covered, including fluorodecarboxylation, fluorination of alkenes, fluorination of boronic acid derivatives, C-H activation and fluorination, C-C activation and fluorination, deoxyfluorination, and halogen-exchange reactions. This review primarily focuses on advances in the last ten years, with an emphasis on the most practical methods.

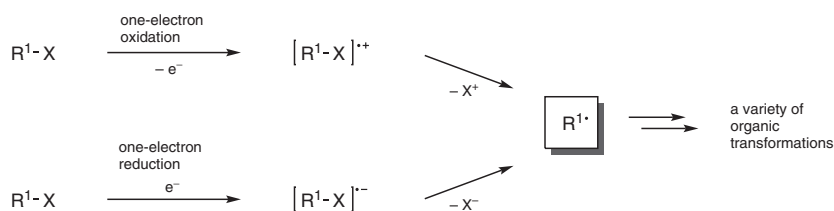


Keywords: selective radical fluorinations · fluorine-atom transfer · Selectfluor · *N*-fluorobenzenesulfonimide (NFSI) · fluorine · hypofluorites · xenon difluoride · metal fluorides · fluorodecarboxylation · fluorination of alkenes · fluorodeborylation · C(sp³)-H fluorination · C(sp²)-H fluorination · C(sp³)-C(sp³) activation and fluorination · deoxyfluorination · halogen exchange · photocatalysis · electrochemistry

2.9 Electrochemical Organic Synthesis via Radical Species

K. Mitsudo and S. Suga

An electrochemical single-electron-transfer reaction is a promising method to generate reactive radical species in organic synthesis. One-electron oxidation of a neutral compound gives a radical cation, which usually breaks down into a radical and a cationic species; conversely, one-electron reduction of a neutral compound affords a radical anion, which forms a radical and an anionic species. The radical species generated in this way can be used for a variety of transformations. In this chapter, selected recent electrochemical transformations that involve electrogenerated radical species are collected and described.



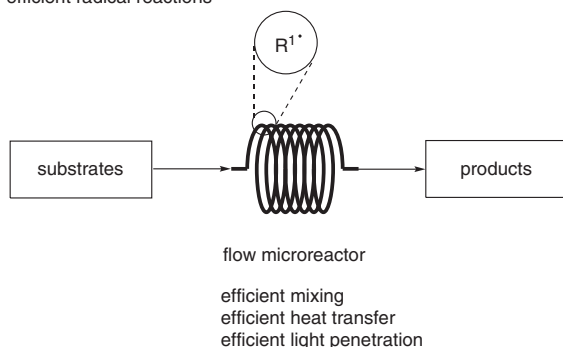
Keywords: electrochemistry · electroorganic chemistry · radical species · single-electron-transfer reaction · one-electron oxidation · one-electron reduction · electrochemical oxidation · electrochemical reduction · nitrogen-centered radicals · sulfur-centered radicals · carbon-centered radicals

2.10 Radical Chemistry in Flow

S. Sumino, T. Fukuyama, and I. Ryu


The past two decades have witnessed a rapid growth in flow-based organic synthesis and synthesis involving radical reactions in flow systems is no exception. Flow microreactors have large surface-to-volume ratios that become available by the employment of tiny channels, and this allows radical reactions to occur with efficient heat transfer and diffusion. Flow photomicroreactors with thin, glass-made channels allow for efficient light penetration, which enables highly efficient photo-radical reactions. This chapter highlights recent advances in both thermal and photo-induced radical reactions, which have achieved increased efficiency by using flow reaction systems.

efficient radical reactions



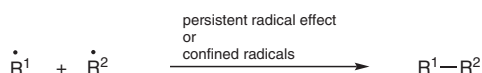
Keywords: radical reaction · flow chemistry · microreactors · radical reduction · radical cyclization · radical carbonylation · radical halogenation · radical C–H functionalization · photo-radical reaction

2.11 Radical–Radical Cross-Coupling Reactions

M. Zhou and T. Qin 

Due to nearly diffusion-limited radical–radical coupling, synthetically useful, selective radical–radical cross-coupling reactions remain challenging. However, different radical lifetimes and various radical initiation approaches now provide the possibility for radical–radical cross-coupling. In this chapter, recent advances in radical–radical cross-coupling reactions are described. In the first part, a basic kinetic phenomenon called the persistent radical effect is briefly reviewed and explained. The remainder of the chapter presents a series of case studies, illustrating several types of radical–radical cross couplings in a variety of disparate settings.

radical–radical cross coupling

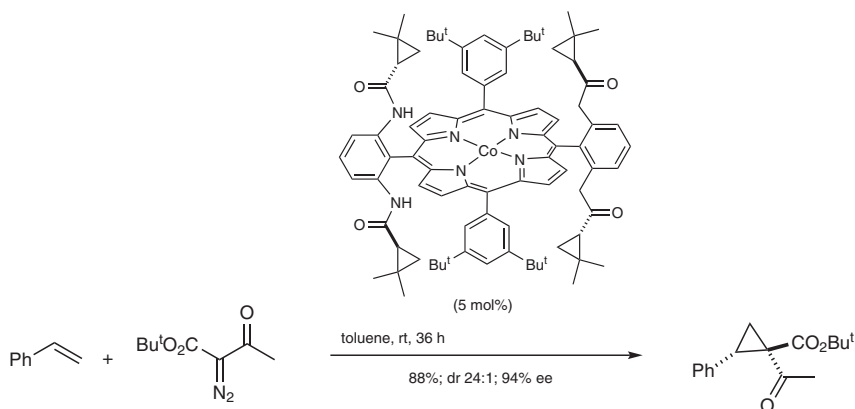


Keywords: radical–radical cross coupling (RRCC) • persistent radicals • transient radicals • persistent radical effect • single-electron transfer • C–C bond formation • metal-free coupling • radical–metal crossover

2.12 Asymmetric Catalysis of Radical Reactions

H. Subramanian and M. P. Sibi

Synthetic methodologies based on radical chemistry are efficient and powerful tools for the construction of carbon–carbon and carbon–heteroatom bonds. This chapter highlights the significance of asymmetric catalysis in free-radical reactions. Several asymmetric catalytic principles, ranging from early chiral Lewis acid and organocatalytic activation to recent photoredox and transition-metal-based asymmetric catalytic systems, are discussed.



Keywords: asymmetric catalysis • radical reactions • chiral Lewis acids • hydrogen-atom transfer • chiral aluminum Lewis acids • chiral Brønsted acids • organocatalysis • photoredox catalysis • transition-metal catalysis • single-electron transfer • chiral porphyrins • chiral N-heterocyclic carbenes


Free Radicals: Fundamentals and Applications in Organic Synthesis 2

	Preface	V
	Abstracts	XI
	Table of Contents	XXI
2.1	Organic Electron Donors in Electron-Transfer Reactions K. F. Clark, D. Dimitrova, and J. A. Murphy	1
2.2	Samarium-Mediated Reductions R. A. Flowers, II, T. V. Chciuk, and C. O. Bartulovich	83
2.3	Single-Electron-Transfer Oxidation and Reduction Involving Metal Complexes other than Samarium M. Cormier and J.-P. Goddard ^{ORCID}	119
2.4	Redox-Active Ligands in Catalysis for Single-Electron-Transfer Processes Y. Ren, A. Das, ^{ORCID} C. Hessin, and M. Desage-El Murr ^{ORCID}	181
2.5	Radical–Polar Crossover Reactions F. Chemla and A. Pérez-Luna ^{ORCID}	209
2.6	Generation of Carbon-Centered Radicals by Photochemical Methods M. Fagnoni, D. Ravelli, ^{ORCID} and S. Protti ^{ORCID}	339
2.7	Radical Cascade Reactions Z.-Q. Liu ^{ORCID}	359
2.8	Selective Radical Fluorinations T. G. Bolduc, B. Thomson, and G. M. Sammis	387
2.9	Electrochemical Organic Synthesis via Radical Species K. Mitsudo and S. Suga	433
2.10	Radical Chemistry in Flow S. Sumino, ^{ORCID} T. Fukuyama, ^{ORCID} and I. Ryu ^{ORCID}	459
2.11	Radical–Radical Cross-Coupling Reactions M. Zhou and T. Qin ^{ORCID}	483

2.12	Asymmetric Catalysis of Radical Reactions	
	H. Subramanian and M. P. Sibi	539
2.13	Recent Developments in Reversible Deactivation Radical Polymerization	
	S. Yamago and Y. Lu	575
	Keyword Index	607
	Author Index	641
	Abbreviations	667

Table of Contents

2.1	Organic Electron Donors in Electron-Transfer Reactions K. F. Clark, D. Dimitrova, and J. A. Murphy	
<hr/>		
2.1	Organic Electron Donors in Electron-Transfer Reactions	1
2.1.1	Electron-Rich Neutral and Anionic Organic Electron Donors	2
2.1.2	Photoexcited Organic Dyes as Electron Donors	42
2.1.3	Electron Transfer with Weak Organic Electron Donors	69
2.1.4	Conclusion	78
2.2	Samarium-Mediated Reductions R. A. Flowers, II, T. V. Chciuk, and C. O. Bartulovich	
<hr/>		
2.2	Samarium-Mediated Reductions	83
2.2.1	Synthesis of Samarium(II) Reductants	83
2.2.1.1	Samarium(II) Iodide	84
2.2.1.1.1	Synthesis in Tetrahydrofuran from Samarium and 1,2-Diiodoethane	84
2.2.1.1.2	Synthesis in Tetrahydrofuran from Samarium and Iodine	85
2.2.1.2	Samarium(II) Bromide	85
2.2.1.2.1	Synthesis from Samarium(II) Iodide and Lithium Bromide/Tetrabutylammonium Bromide	86
2.2.1.2.2	Synthesis from Samarium and 1,1,2,2-Tetrabromoethane	87
2.2.1.3	Samarium(II) Chloride	87
2.2.1.3.1	Synthesis from Samarium(II) Iodide and Lithium Chloride/Tetrabutylammonium Chloride	87
2.2.1.3.2	Synthesis from Samarium(III) Chloride	88
2.2.2	Reductions	88
2.2.2.1	Reduction of Halides	88
2.2.2.2	Reduction of C=C and C≡C Bonds	90
2.2.2.3	Reduction of Carbon–Oxygen Bonds	93
2.2.2.4	Reduction of Nitriles	98
2.2.3	C–C Bond Forming Reactions	99
2.2.3.1	Barbier Couplings	99
2.2.3.2	Halide–Alkene Couplings	101
2.2.3.3	Pinacol Couplings	104
2.2.3.4	Reformatsky Reactions	105
2.2.3.5	Carbonyl–Alkene Coupling and Related Reactions	107

2.2.4	Catalytic Reactions	111
2.2.4.1	Approaches Employing Terminal Reductants	111
2.2.4.2	Radical Relay Reactions	114
2.3	Single-Electron-Transfer Oxidation and Reduction Involving Metal Complexes other than Samarium M. Cormier and J.-P. Goddard 	
2.3	Single-Electron-Transfer Oxidation and Reduction Involving Metal Complexes other than Samarium	119
2.3.1	Single-Electron-Transfer Oxidation Involving Metal Complexes	119
2.3.1.1	Activation of Enols and Enolates	120
2.3.1.1.1	Oxidation of 1,3-Dicarbonyl Derivatives	120
2.3.1.1.2	Oxidation of Enolates	123
2.3.1.1.3	Oxidation of Silyl Enol Ethers	126
2.3.1.1.4	Oxidation of α -Sulfinyl Carbanions	128
2.3.1.2	Hydrofunctionalization of Alkenes	130
2.3.1.2.1	Formation of C—O Bonds	131
2.3.1.2.2	Formation of C—N Bonds	132
2.3.1.2.3	Formation of C—C Bonds	134
2.3.1.3	C—H Activation	137
2.3.1.4	Activation of Aromatics: Arylation	141
2.3.1.5	Oxidation of Nitrogen-Containing Molecules	143
2.3.1.5.1	Oxidation of Amines	144
2.3.1.5.2	Oxidation of Hydrazines and Derivatives	145
2.3.1.6	Phosphorylation	146
2.3.1.6.1	Phosphorylation of Alkenes	146
2.3.1.6.2	Phosphorylation of Arenes	147
2.3.1.7	Activation of Alcohols	148
2.3.1.7.1	Alcohol Activation with Ring Opening	148
2.3.1.7.2	Activation of Acyclic Alcohols	150
2.3.2	Single-Electron-Transfer Reduction Involving Metal Complexes	151
2.3.2.1	Single-Electron-Transfer Reduction of Organohalides and Analogues	151
2.3.2.1.1	Single-Electron-Transfer Reduction of Alkyl Halides	151
2.3.2.1.2	Single-Electron-Transfer Reduction of Fluoro and Perfluoroalkyl Halides	157
2.3.2.1.3	Single-Electron-Transfer Reduction of Aryl Halides and Analogues	159
2.3.2.2	Single-Electron-Transfer Reduction of Epoxides	161
2.3.2.3	Single-Electron-Transfer Reduction of Carbonyl Derivatives and Analogues	163

2.3.3	Asymmetric Reactions Involving Single-Electron Transfer with Metal Complexes	163
2.3.3.1	Chiral Auxiliaries in Reactions Involving Single-Electron Transfer	163
2.3.3.2	Chiral Catalysts in Reactions Involving Single-Electron Transfer	166
2.3.3.2.1	Organocatalysts in Asymmetric Reactions Involving Single-Electron Transfer	166
2.3.3.2.1.1	Enamine Oxidations	167
2.3.3.2.1.2	Brønsted Acid Catalysts	169
2.3.3.2.2	Organometallic Catalysts in Asymmetric Reactions Involving Single-Electron Transfer	171
2.3.3.2.2.1	Copper-Catalyzed Asymmetric Radical Additions	171
2.3.3.2.2.2	Enantioselective Cobalt(II)-Based Metalloradical Catalysis	172
2.3.3.2.2.3	Enantioselective Titanium(III)-Catalyzed Reductive Cyclization	173
2.3.3.2.2.4	Enantioselective BINOL Synthesis	175
2.4	Redox-Active Ligands in Catalysis for Single-Electron-Transfer Processes Y. Ren, A. Das, ^{1b} C. Hessin, and M. Desage-El Murr ^{1b}	
2.4	Redox-Active Ligands in Catalysis for Single-Electron-Transfer Processes	181
2.4.1	Nitrene Radicals and Redox-Active Ligands	181
2.4.1.1	Aziridination via Nitrene Radicals Involving Redox-Active Ligands	182
2.4.1.2	C–H Amination via Nitrene Radicals Involving Redox-Active Ligands	195
2.4.2	Carbene Radicals and Redox-Active Ligands	197
2.4.2.1	Cyclopropanation Using Cobalt Catalysts	198
2.4.2.2	Cyclopropanation Using Copper Catalysts	201
2.4.3	Trifluoromethyl Radicals and Redox-Active Ligands	202
2.4.4	Conclusion	205
2.5	Radical–Polar Crossover Reactions F. Chemla and A. Pérez-Luna ^{1b}	
2.5	Radical–Polar Crossover Reactions	209
2.5.1	Tandem Transformations Relying on Oxidative Radical-to-Cation Crossover Reactions	211
2.5.1.1	Radical-to-Cation Oxidation by Organic Oxidants	212
2.5.1.1.1	Tetrathiafulvalene-Mediated Reactions	212
2.5.1.1.2	Iodine(III)-Mediated Reactions	217
2.5.1.1.3	Radical Oxidation by Dimethyl Sulfoxide	219
2.5.1.1.4	Radical-to-Cation Oxidation in Reactions of “Ate” Complexes of Vinylboronic Esters	220

2.5.1.1.5	Radical Oxidation by Organic Photoredox Catalysts	224
2.5.1.2	Radical-to-Cation Oxidation by Organometallic Oxidants	229
2.5.1.2.1	Reactions Involving Enolizable Carbonyl Compounds as Radical Precursors ...	229
2.5.1.2.2	Reactions Involving α -Halo Ketones, Esters, and Related Compounds as Radical Precursors	239
2.5.1.2.3	Reactions Involving Organometallic Species as Radical Precursors	242
2.5.1.2.4	Reactions Initiated by Fragmentation of Peroxides with Metal Oxidants	250
2.5.1.2.5	Reactions with Azidotrimethylsilane as Radical Precursor	253
2.5.1.2.6	Radical-to-Cation Crossover Reactions in Photocatalytic Processes with Organometallic Catalysts	254
2.5.1.3	Electrochemical Oxidation	267
2.5.2	Tandem Transformations Relying on Reductive Radical-to-Anion Crossover Reactions	267
2.5.2.1	Radical-to-Anion Reduction by Zerovalent Metals	268
2.5.2.1.1	Reduction by Zinc Metal	269
2.5.2.1.2	Reduction by Manganese Metal	272
2.5.2.2	Radical-to-Anion Reduction upon Addition to Metal Centers	274
2.5.2.2.1	Addition to Chromium Complexes	275
2.5.2.2.2	Addition to Samarium(II) Iodide	277
2.5.2.2.2.1	Organic Halide/Alkene Cyclizations	277
2.5.2.2.2.2	Carbonyl/Alkene Cyclizations	281
2.5.2.2.3	Addition to Nickel or Palladium Complexes	289
2.5.2.2.4	Addition to Manganese Complexes	291
2.5.2.2.5	Addition to Iron Complexes	292
2.5.2.3	Radical-to-Anion Reduction upon Homolytic Substitution at Metal Centers ..	294
2.5.2.3.1	Homolytic Substitution at Boron	295
2.5.2.3.1.1	Radical–Polar Crossover Reactions Leading to Boron Enolates	295
2.5.2.3.1.2	Radical–Polar Crossover Reactions Leading to Boron Amides	297
2.5.2.3.2	Homolytic Substitution at Zinc	299
2.5.2.3.2.1	Radical–Polar Crossover Reactions Leading to Zinc Enolates	299
2.5.2.3.2.2	Radical–Polar Crossover Reactions Leading to Alkylzinc Species	304
2.5.2.3.2.3	Radical–Polar Crossover Reactions Leading to Alkenylzinc Species	306
2.5.2.4	Radical-to-Anion Reduction by Photoredox Catalysts	313
2.5.2.4.1	Synthesis of Cycloalkanes by Tandem Radical Addition/Intramolecular Alkylation of Alkenes	314
2.5.2.4.2	Synthesis of Geminal Difluoroalkenes by Tandem Radical Addition/ β -Fluoride Elimination of (Trifluoromethyl)alkenes	319
2.5.2.4.3	Synthesis of Carboxylic Acids by Tandem Radical Reaction/Polar Carboxylation	320

2.5.2.4.4	Synthesis of Saturated Nitrogen Heterocycles by Tandem Radical Addition/ Intramolecular N-Alkylation	321
2.5.3	Tandem Transformations Relying on Oxidative Anion-to-Radical Crossover Reactions	322
2.5.3.1	Anion Oxidation by Ferrocenium Cation	323
2.6	Generation of Carbon-Centered Radicals by Photochemical Methods M. Fagnoni, D. Ravelli, and S. Pratti	
2.6	Generation of Carbon-Centered Radicals by Photochemical Methods	339
2.6.1	Alkynyl Radicals	342
2.6.2	Aryl Radicals	343
2.6.3	Vinyl Radicals	344
2.6.4	Acyl Radicals	344
2.6.5	Carbamoyl Radicals	345
2.6.6	Benzyl Radicals	347
2.6.7	Allyl Radicals	348
2.6.8	Propargyl Radicals	348
2.6.9	Alkyl Radicals	350
2.6.10	α -Amino Radicals	351
2.6.11	α -Oxy Radicals	352
2.6.12	Trifluoromethyl Radicals	353
2.6.13	α -Keto Radicals	354
2.6.14	Conclusion	355
2.7	Radical Cascade Reactions Z.-Q. Liu	
2.7	Radical Cascade Reactions	359
2.7.1	Intramolecular Radical Cascade Reactions	361
2.7.1.1	Relay by Cyclization	361
2.7.1.2	Relay by Hydrogen-Atom Transfer	363
2.7.1.3	Relay by 1,n-Migration	364
2.7.1.4	Relay by Ring Opening	368
2.7.1.5	Relay by β -Scission	369
2.7.1.6	Relay by Spin-Center Shift	373
2.7.2	Intermolecular Radical Cascade Reactions	374
2.7.2.1	Relay by an Alkene	374
2.7.2.2	Relay by an Alkyne	375

2.7.2.3	Relay by an Isocyanide	376
2.7.2.4	Relay by Carbon Monoxide	378
2.7.2.5	Relay by Sulfur Dioxide	379
2.7.2.6	Relay by Oxygen	381
2.7.3	Radical Cascade Reactions Involving Mixed Events	382

2.8 Selective Radical Fluorinations

T. G. Bolduc, B. Thomson, and G. M. Sammis

2.8	Selective Radical Fluorinations	387
2.8.1	Sources of Atomic Fluorine	387
2.8.1.1	Fluorine Gas	387
2.8.1.2	Fluoroxy Reagents and Hypofluorites	388
2.8.1.3	Xenon Difluoride	388
2.8.1.4	N—F Reagents	388
2.8.1.5	Metal Fluoride Reagents	388
2.8.2	Methods of Radical Fluorination	390
2.8.2.1	Fluorodecarboxylations	390
2.8.2.2	Fluorination of Alkenes	394
2.8.2.2.1	Hydrofluorinations of Alkenes	394
2.8.2.2.2	Aminofluorinations of Alkenes	399
2.8.2.2.3	Carbofluorinations of Alkenes	404
2.8.2.3	Fluorination of Boron Derivatives	406
2.8.2.4	C(sp ³)—H Activations	410
2.8.2.4.1	Radical Fluorinations of Aliphatic C(sp ³) Centers	410
2.8.2.4.2	Radical Fluorinations of Benzylic C(sp ³) Centers	416
2.8.2.5	C(sp ³)—C(sp ³) Activations	419
2.8.2.6	Deoxyfluorinations	422
2.8.2.7	Other Fluorination Processes	426
2.8.3	Conclusion	427

2.9 Electrochemical Organic Synthesis via Radical Species

K. Mitsudo and S. Suga

2.9	Electrochemical Organic Synthesis via Radical Species	433
2.9.1	Electrochemical Oxidations	434
2.9.1.1	Transformations via Nitrogen-Centered Radicals	434
2.9.1.2	Transformations via Sulfur-Centered Radicals	442