

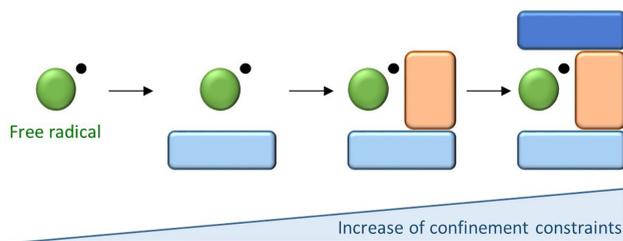
Abstracts

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1.1 Improving Radical Persistence through Confinement: A Survey

M. P. Bertrand, E. Besson, and S. Gastaldi

Most organic radical species are transient and were long considered to be beyond control. Tremendous progress in the knowledge and understanding of their reactivity has enabled their use as standard intermediates in organic synthesis. In this review, strategies implemented to increase radical lifetimes, without modifying fundamentally their structural features, are presented. A wide array of systems has been designed that allow modulation of the level of confinement constraints. The ability of these systems to increase radical lifetime has now reached the point where a transient radical can become persistent, which opens up many new prospects for future applications.



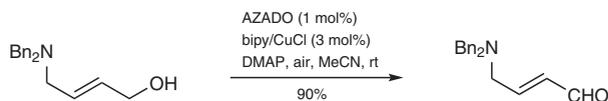
Keywords: transient radicals • persistent radicals • confinement • supramolecular interactions • covalent organic frameworks • metal–organic frameworks • cucurbiturils • cyclodextrins • cyclophanes • zeolites • mesoporous silicas • periodic mesoporous organic silicas • layered structures • lamellar polysilsesquioxanes • single-walled carbon nanotubes • self-assembled systems.

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1.2 Nitroxides in Organic Synthesis

G. Casano and O. Ouari

This review describes selected methods using nitroxides such as TEMPO and AZADO for selective oxidative transformations including oxidation of alcohols and diols, N-alkylation of amines, C–H activation, C–C bond formation, and cross-coupling radical reactions.

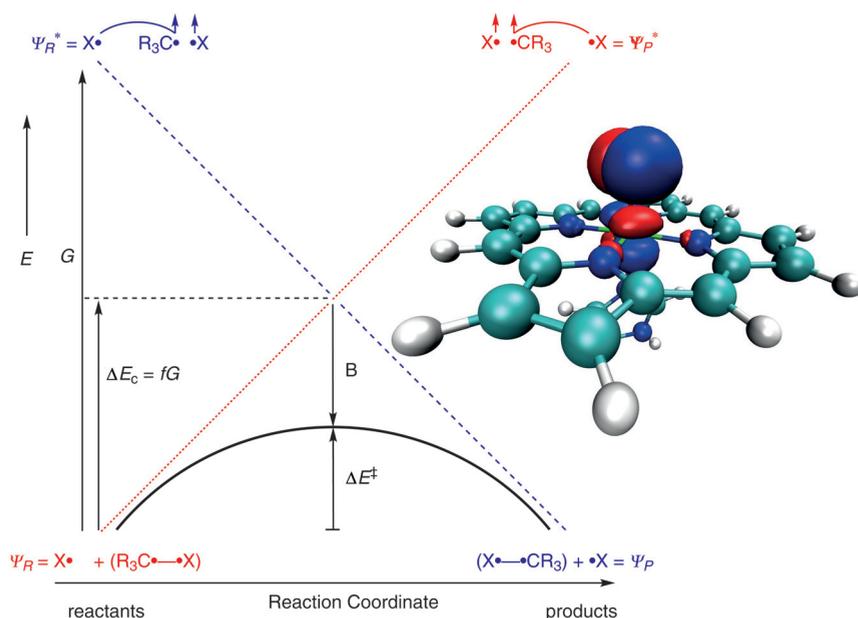


Keywords: radicals • nitroxides • oxidation • oxoammonium • alcohol oxidation • chemo-selective oxidation • TEMPO • copper(I)/TEMPO catalyzed aerobic oxidation • Anelli protocol • persistent radical effect • C–C bond formation

1.3 Modelling Radicals and Their Reactivities

E. Derat and B. Braïda

In this chapter, the application of computational quantum mechanical methods to the understanding of radical reactions is introduced. For radical reactions, access to electronic configurations through quantum chemical calculations allows rationalization of unusual reactivities. Using the valence bond approach, the nature of bonding in three-electron bonds can be characterized by large resonance interactions. Similarly, some simple reactions that are commonly believed to be radical-free, such as [3 + 2] cycloadditions, are in fact governed by a high-lying biradical intermediate that helps to stabilize the transition state. More complex radical and enzymatic reactions can also be modelled, as illustrated by the example of horseradish peroxidase. These case studies show that computational analysis can complement experimental investigations and fill in the blanks to enable a more complete understanding of radical reactions.

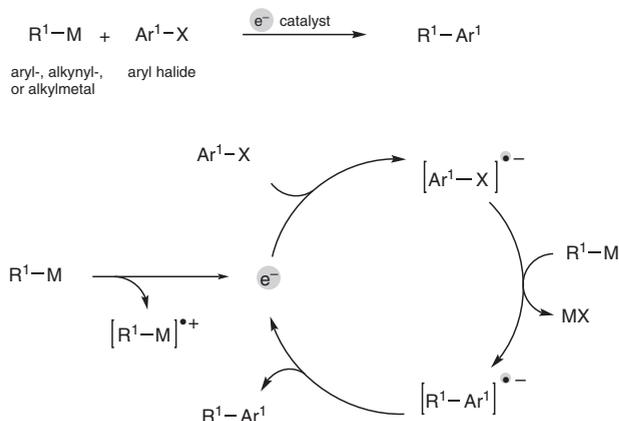


Keywords: radicals · modelling · computational chemistry · quantum mechanics · density functional theory (DFT) · radical stability · valence bond methods · two-center, three-electron bonds · enzyme catalysis · cycloaddition · electron transfer · iron catalysts · radical ions

1.4 Electron Catalysis

E. Shirakawa 

An electron acts as a catalyst in the substitution reaction of aryl halides with diverse nucleophiles. Aryl halides, on receiving an electron, are activated as the radical anions, which react with aryl-, alkynyl-, and alkylmetals to give the cross-coupling products.

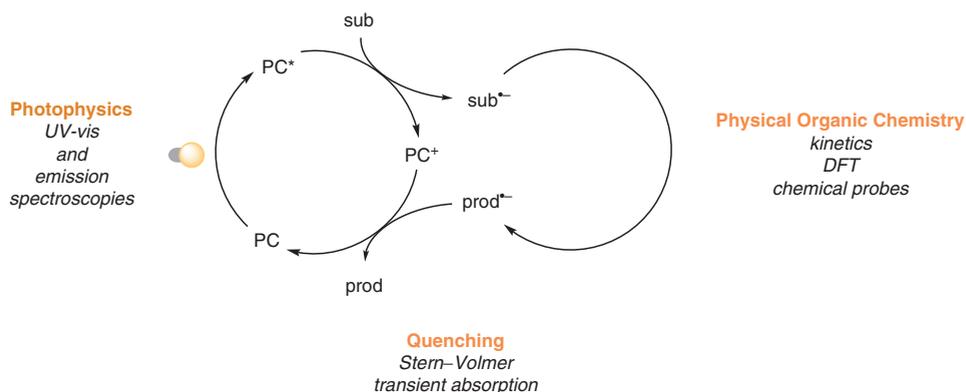


Keywords: electron catalysis • radicals • radical ions • arylation • aryl compounds • carbon-carbon coupling • cross-coupling reactions • radical reactions

1.5 Photochemistry and Radical Generation: Approaches in Mechanism Elucidation

S. B. Cahoon and T. P. Yoon

The development of photocatalytic reactions has reemerged as an active area of research in organic synthesis. A large variety of synthetically valuable transformations have now been developed that take advantage of the ease by which photocatalysts generate a variety of open-shelled reactive intermediates. The study of the mechanisms of these reactions, however, is a challenge, especially in increasingly sophisticated reactions that often involve multiple steps and complex reaction mixtures. Multiple complementary techniques often need to be utilized in tandem in order to develop a detailed understanding of these reactions. The first part of this review outlines many of the most common techniques that are used to interrogate the initiation and product-formation steps of a photocatalytic transformation. The second part describes case studies that provide contextual examples of how photophysical, electrochemical, physical organic, and computational investigations can be used together to provide insights into the mechanisms of complex photocatalytic reactions.



Keywords: radicals · photochemistry · photochemical · mechanism · quenching · absorption · emission · electrochemistry · excited-state potential · UV-vis · transient absorption · time resolved · Stern–Volmer · quantum yield · hydrogen-atom transfer (HAT) · proton-coupled electron transfer (PCET) · metallaphotoredox · EDA complexes · enantioselectivity · chiral photocatalysts · cycloaddition · initiation · propagation

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1.6 Sulfur-, Selenium-, and Silicon-Centered Radicals

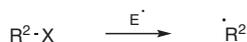
A. Kaga and H. Yorimitsu

Sulfur-, selenium-, and silicon-centered radicals are versatile reaction intermediates in modern synthetic organic chemistry. These radicals are capable of adding to carbon–carbon multiple bonds such as alkene and arenes, thus introducing the corresponding elements into the products. These radicals can also serve as mediators of free-radical reactions, including as polarity-reversal catalysts, asymmetric catalysts, and halogen-atom abstraction agents, without these elements being incorporated into the products of the reactions. This chapter describes the utility of sulfur-, selenium-, and silicon-centered radicals in two sections. The first covers reactions involving incorporation of the corresponding elements into the products, while the second describes reactions using these radicals as catalysts or reagents to prepare products that do not contain the corresponding elements.

incorporation of S, Se, or Si into the products



S, Se, or Si radicals as catalysts/reagents



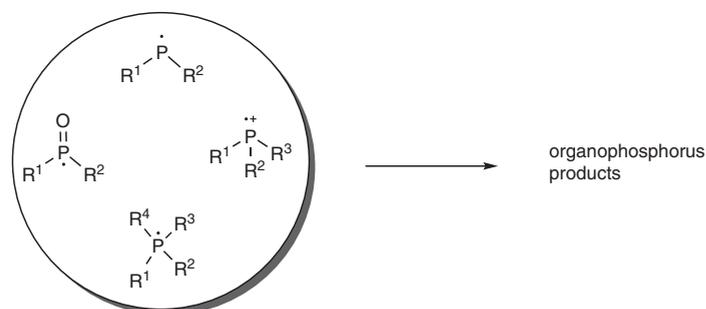
X = H, Br; E = SR³, SeR³, or SiR³₃

Keywords: radicals · sulfur · selenium · silicon · radical addition · arylation · hydrogen-atom abstraction · halogen-atom abstraction · polarity-reversal catalysis · asymmetric catalysis · photoredox catalysis

1.7 Phosphorus-Centered Radicals

C. Bellanger, S. Chelli, and S. Lakhdar 

Organophosphorus compounds are one of the most important classes of organic products because of their applications as ligands for transition-metal catalysts, as organocatalysts, as biologically active molecules, and as building blocks for material sciences. This review discusses recent approaches for the generation of four types of synthetically useful phosphorus-centered radicals and their use for the formation of carbon–phosphorus bonds. Emphasis is placed on the scope and limitations of the reactions reported.

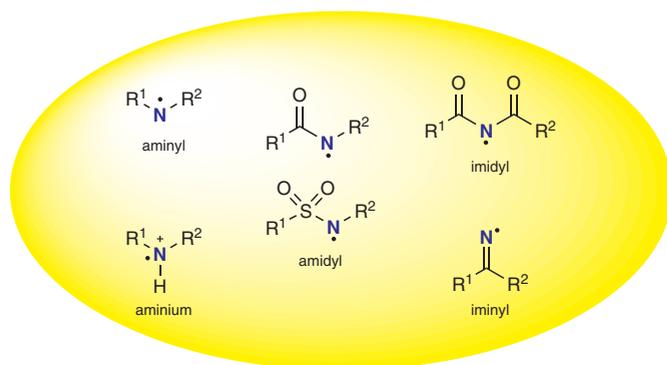


Keywords: radicals · phosphinyl · phosphinoyl · phosphoniumyl · phosphoranyl · radical reactions · carbon–phosphorus bonds

1.8 Nitrogen-Centered Radicals

X.-L. Lu, B. Wang, and S. Chiba 

Nitrogen-containing compounds are prevalent in the key components of various functional materials and compounds such as pharmaceutical drugs. Therefore, it is extremely important to develop versatile synthetic methodologies capable of constructing C–N bonds in an efficient manner under milder reaction conditions. Apart from common ionic C–N bond-forming reactions (i.e., nucleophilic and electrophilic amination, as well as transition-metal-catalyzed C–N cross-coupling processes), leveraging of nitrogen-centered radicals for C–N bond-forming process has created another dimension to the modern synthesis of nitrogen-containing compounds. In particular, recent development of novel catalytic strategies and the design of new nitrogen-radical precursors have rendered their generation and use for C–N bond formation more practical and user-friendly for synthesis of wider array of nitrogen-containing compounds of potential use. This chapter highlights the latest developments in synthetic methods for C–N bond construction using nitrogen-centered radicals by showing selected reactions, mostly reported in the last five years, based on their structural and reactivity features as well as the method of radical generation.



- radical addition to π -systems
- 1,5-hydrogen transfer
- β -carbon elimination

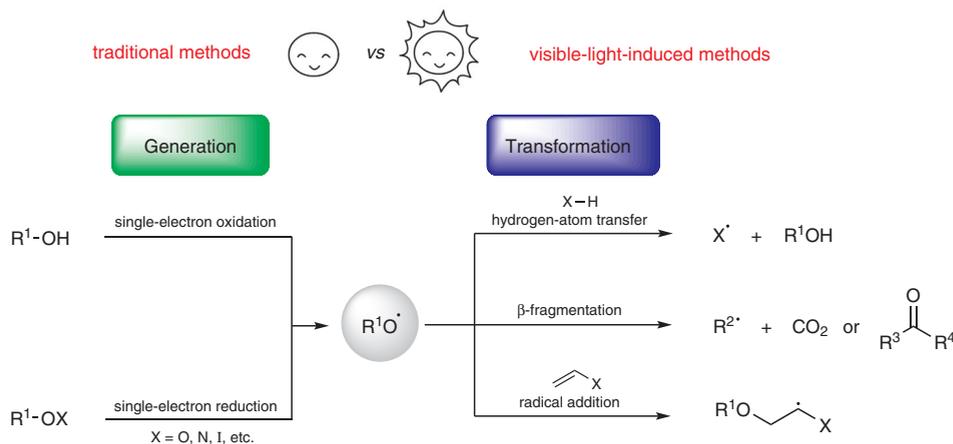
Keywords: radicals • nitrogen-centered radicals • C–N bond formation • radical addition • 1,5-hydrogen shift • β -carbon elimination

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1.9 Oxygen-Centered Radicals

J. Zhang, D. Liu, and Y. Chen

Oxygen-centered radicals ($R^1O\cdot$) are reactive intermediates in organic synthesis, with versatile synthetic utilities in processes such as hydrogen-atom transfer (HAT), β -fragmentation, radical addition to unsaturated carbon–carbon bonds, and rearrangement reactions. In this review, we focus on recent advances in the generation and transformation of oxygen-centered radicals, including (alkyl-, α -oxo-, aryl-) carboxyl, alkoxy, aminoxyl, phenoxyl, and vinyloxy radicals, and compare the reactivity of oxygen-centered radicals under traditional reaction conditions with their reactivity under visible-light-induced reaction conditions.



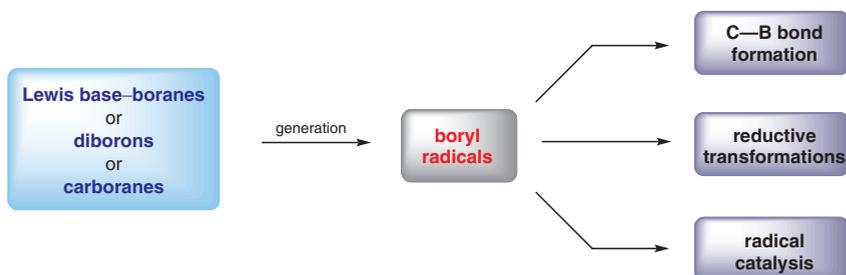
R^1 = acyl, alkyl, aryl, vinyl, etc.

Keywords: radicals • oxygen-centered radicals • visible-light photoredox catalysis • carboxyl radicals • alkoxy radicals • C–C bond formation

1.10 Boron-Centered Radicals

F.-L. Zhang and Y.-F. Wang

Boryl radicals have emerged as powerful radical intermediates in organic synthesis. This review summarizes recently developed transformations involving boryl radical species, including C–B bond formation reactions, reduction reactions, and radical catalysis.

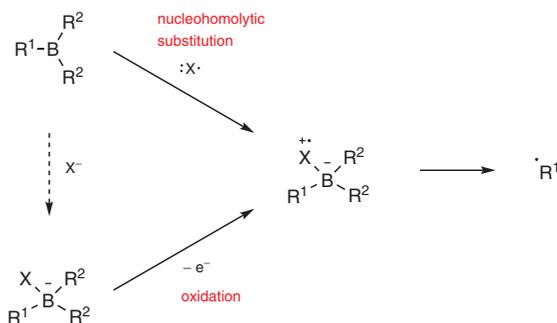


Keywords: radicals · boryl radicals · borylation · reduction · organoboron compounds · radical catalysis · C–C bond formation

1.11 Generation of Radicals from Organoboranes

E. André-Joyaux, L. Gnägi, C. Meléndez, V. Soulard, and P. Renaud 

Radicals can be generated by the cleavage of the C–B bond of alkylboranes or boronic acid derivatives. The fragmentation process may result from a nucleohomolytic substitution process or from a redox process. The nucleohomolytic substitution is ideal for the generation of alkyl radicals and is usually part of a chain-reaction process. Redox processes (mainly oxidative reactions) have been used to generate both alkyl and aryl radicals. The use of stoichiometric oxidizing agents can be avoided by employing photoredox catalysis. A broad range of synthetic applications such as radical cascade processes, multicomponent reactions, and cross-coupling reactions in the presence of suitable metal catalysts are now possible. In their diversity, organoboron compounds represent one of the most general sources of radicals. The merging of radical chemistry with the classical chemistry of organoboron derivatives opens tremendous opportunities for applications in organic synthesis.

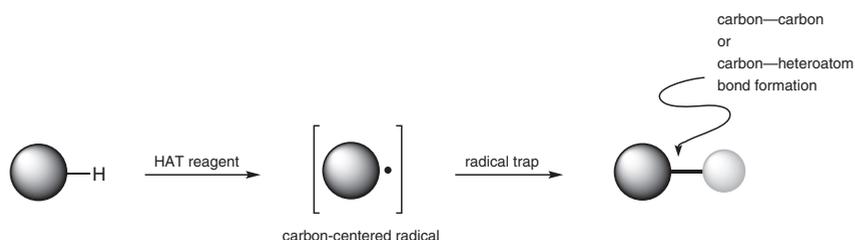


Keywords: radicals · organoboranes · boronic esters · chain reactions · photoredox catalysis

1.12 Intermolecular Radical C–H Functionalization

M. Bietti and F. Dénès 

The generation of carbon-centered radicals via intermolecular hydrogen-atom transfer (HAT) from C–H bonds to an abstracting species (HAT reagent) represents a significant challenge in terms of reactivity, site-selectivity and stereoselectivity. The radical species resulting from such a transfer can then engage in carbon–carbon or carbon–heteroatom bond formation, possibly through the intervention of transition-metal catalysts, leading to a variety of functionalized products. This chapter aims to provide the reader with useful guidelines to understand, predict, and design selective radical transformations based upon initial HAT from a C–H bond coupled to different radical-capture strategies. A selection of examples that illustrate different approaches to implement HAT reactions in synthetically useful procedures are presented.

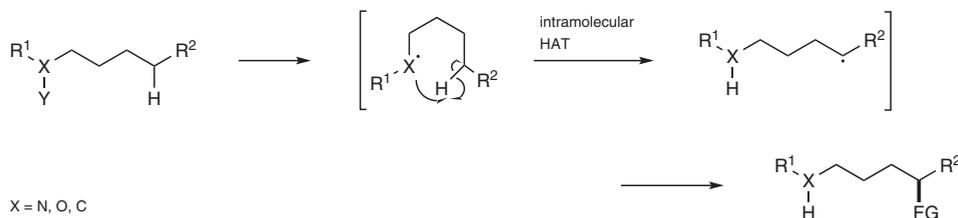


Keywords: radicals • C–H bond activation • radical reactions • hydrogen-atom transfer (HAT) • regioselectivity • halogenation • hydroxylation • amination • carbon–carbon coupling • iridium complexes • iron complexes • nickel complexes • hydrocarbons

1.13 Intramolecular Hydrogen-Atom Transfer

S. M. Treacy, X. Zhang, and T. Rovis

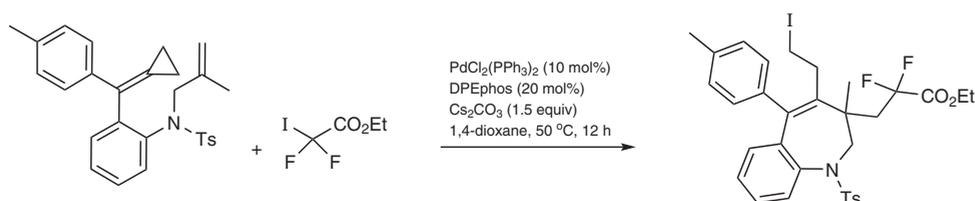
Recent advances in intramolecular hydrogen-atom transfer (HAT) have demonstrated significant utility in C–H functionalization through highly reactive open-shell intermediates. The intramolecular transposition of radical reactivity from select functional groups to generate more stable carbon-centered radicals often proceeds with high regioselectivity, providing novel bond disconnections at otherwise inert and largely indistinguishable positions. This chapter explores the functional groups capable of intramolecular HAT to generate remote radicals and the transformations currently available to the synthetic chemist.



Keywords: radicals • hydrogen-atom transfer • intramolecular hydrogen-atom transfer • amidyl radicals • alkoxy radicals • homolysis • [1,5]-hydrogen-atom transfer • alkyl radicals • remote functionalization

1.14 Palladium(I)-Mediated Reactions*G. Maestri and A. Serafino*

Several elegant reactivities can be observed in reactions involving palladium(I) species, allowing access to molecular architectures that are often beyond the capabilities of popular diamagnetic palladium complexes. This review presents three main axes of research in this context, which have mostly emerged in the last decade. Reactions promoted by visible light enable synthetic methods that are unusual in their mild experimental conditions coupled with remarkably broad functional group tolerance. The use of discrete palladium(I) dimers as precatalysts allows one to perform a wide set of cross-coupling protocols, such as Kumada and Negishi reactions, and chalcogenation reactions, with a surgical precision on the carbon–halogen bond that is initially activated. The generation of alkyl radicals and palladium(I) species through a thermal strategy proves useful for the elaboration of substrates with several polyfluorinated fragments, which are otherwise elusive coupling partners for more common two-electron processes.



Keywords: alkenes · alkynes · alkyl halides · aryl compounds · cyclization · electron transfer · heterocycles · palladium catalysts · photochemistry · radicals · radical cyclization · reductive elimination