

Photocatalytic C(sp³) radical generation via C–H, C–C, and C–X bond cleavage.

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Abstract

Photocatalytic C(sp³) radical generation and functionalization is a powerful and versatile strategy for organic synthesis, as it enables the construction of complex and diverse molecular structures from simple and readily available substrates. In this article, we review some of the recent advances in this field and highlight representative examples of three types of bond cleavages that generate C(sp³) radicals: C–H, C–C, and C–X bond cleavages. We also discuss the general mechanisms and key factors that influence the radical formation and reactivity.

Keywords: Photocatalysis, C(sp³) radicals, bond cleavage, organic synthesis, functionalization

Introduction

Radicals are highly reactive chemical species that have one or more unpaired electrons. They can participate in various types of reactions, such as addition, substitution, elimination, rearrangement, and coupling, to form new bonds and functional groups. Among the different types of radicals, C(sp³) radicals (R[•]) are particularly useful for organic synthesis, as they can be derived from a wide range of substrates and can be used to construct complex and diverse molecular structures. However, generating C(sp³) radicals in a controlled and efficient manner is not trivial, as they are often unstable and prone to side reactions. Traditionally, C(sp³) radicals were produced by thermal or photochemical methods, such as thermolysis of peroxides or persulfates, or direct irradiation of radical precursors. These methods, however, suffer from drawbacks such as high energy consumption, low selectivity, poor atom economy, and environmental hazards. In recent years, photocatalysis has emerged as a powerful and versatile tool for C(sp³) radical generation and functionalization. Photocatalysis involves the use of light to activate a catalyst, which can then transfer electrons or protons to the substrates, resulting in the formation of radicals. Photocatalysis offers several advantages over conventional methods, such as mild reaction conditions, high efficiency, broad substrate scope, and environmental benignity.

In this article, we will review some of the recent advances in photocatalytic C(sp³) radical generation and highlight representative examples in this field. We will focus on three types of bond cleavages that generate C(sp³) radicals: C–H, C–C, and C–X (X ≠ H and C) bond cleavages. We will also discuss the general mechanisms and key factors that influence the radical formation and reactivity.

(A) C–H bond cleavage

C–H bond cleavage is one of the most common and straightforward ways to generate C(sp³) radicals. It involves the abstraction of a hydrogen atom from a C–H bond by a suitable hydrogen atom abstractor (HAA), such as a photocatalyst, a radical initiator, or a sacrificial reagent. The resulting C(sp³) radical can then undergo various transformations, such as radical addition, radical cyclization, radical coupling, or radical cascade reactions.

One of the challenges in C–H bond cleavage is to achieve high selectivity and specificity, as most organic molecules contain multiple C–H bonds with different reactivities and bond strengths. Therefore, the choice of the HAA, the substrate, and the reaction conditions is crucial to control the C–H bond activation and the radical outcome.

Photocatalyst-mediated C–H bond cleavage

One of the most widely used HAAs in photocatalytic C–H bond cleavage is the photocatalyst itself, which can act as both a light absorber and an electron donor. Upon irradiation, the photocatalyst can be excited to a higher energy state, from which it can donate an electron to a suitable electron acceptor (EA), such as oxygen, iodine, or a transition metal complex. The resulting oxidized photocatalyst can then abstract a hydrogen atom from a C–H bond, generating a C(sp³) radical and restoring the photocatalyst to its original state. This process is also known as photoinduced electron transfer (PET) or single-electron transfer (SET) mechanism.

One of the advantages of using the photocatalyst as the HAA is that it can be recycled and reused, making the reaction catalytic and sustainable. Another advantage is that the photocatalyst can be tuned to match the absorption wavelength of the light source and the redox potential of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of photocatalysts that can mediate C–H bond cleavage is the organic dyes, such as eosin Y, rose bengal, methylene blue, and acridine orange. These dyes have strong absorption in the visible region and can undergo facile electron transfer with various EAs. For example, Huang et al. reported a photocatalytic C–H bond cleavage of alcohols using eosin Y as the photocatalyst and oxygen as the EA¹. The resulting alkyl radicals were trapped by styrenes or acrylates, leading to the formation of C–C bonds (Scheme 1).

Another class of photocatalysts that can mediate C–H bond cleavage is the metal complexes, such as iridium, ruthenium, and cobalt complexes. These complexes have strong absorption in the visible or near-infrared region and can undergo facile electron transfer with various EAs. For example, Li et al. reported a photocatalytic C–H bond cleavage of aldehydes using an iridium complex as the photocatalyst and iodine as the EA². The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 2).

Radical initiator-mediated C–H bond cleavage

Another widely used HAA in photocatalytic C–H bond cleavage is the radical initiator, which can generate radicals upon irradiation or thermal decomposition. These radicals can then abstract a hydrogen atom from a C–H bond, generating a C(sp³) radical and a new radical species. The resulting C(sp³) radical can then undergo

various transformations, while the new radical species can either initiate another cycle of C–H bond cleavage or terminate the reaction.

One of the advantages of using the radical initiator as the HAA is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the radical initiator can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of radical initiators that can mediate C–H bond cleavage is the peroxides, such as tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP), and methyl ethyl ketone peroxide (MEKP). These peroxides can generate alkoxy radicals upon irradiation or thermal decomposition, which can then abstract a hydrogen atom from a C–H bond. For example, Zhang et al. reported a photocatalytic C–H bond cleavage of alkanes using TBHP as the radical initiator and oxygen as the EA³. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 3).

Another class of radical initiators that can mediate C–H bond cleavage is the azo compounds, such as azobisisobutyronitrile (AIBN), azodicarboxamide (ADA), and azobenzene. These azo compounds can generate nitrogen-centered radicals upon irradiation or thermal decomposition, which can then abstract a hydrogen atom from a C–H bond. For example, Chen et al. reported a photocatalytic C–H bond cleavage of alcohols using AIBN as the radical initiator and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 4).

Sacrificial reagent-mediated C–H bond cleavage

Another widely used HAA in photocatalytic C–H bond cleavage is the sacrificial reagent, which can donate a hydrogen atom to a radical species, generating a C(sp³) radical and a new radical species. The resulting C(sp³) radical can then undergo various transformations, while the new radical species can either react with another sacrificial reagent or terminate the reaction.

One of the advantages of using the sacrificial reagent as the HAA is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the sacrificial reagent can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of sacrificial reagents that can mediate C–H bond cleavage is the alcohols, such as methanol, ethanol, isopropanol, and tert-butanol. These alcohols can donate an electron to a radical species, such as a halogen atom, a nitroso group, or a sulfonyl group, generating two C(sp³) radicals. For example, Zhang et al. reported a photocatalytic C–H bond cleavage of alkyl halides using methanol as the sacrificial reagent and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–H bonds (Scheme 5).

(B) C–C bond cleavage

C–C bond cleavage is another common and straightforward way to generate $C(sp^3)$ radicals. It involves the homolytic cleavage of a C–C bond by a suitable C–C bond cleaver (CCBC), such as a photocatalyst, a radical initiator, or a sacrificial reagent. The resulting $C(sp^3)$ radicals can then undergo various transformations, such as radical addition, radical cyclization, radical coupling, or radical cascade reactions.

One of the challenges in C–C bond cleavage is to achieve high selectivity and specificity, as most organic molecules contain multiple C–C bonds with different reactivities and bond strengths. Therefore, the choice of the CCBC, the substrate, and the reaction conditions is crucial to control the C–C bond activation and the radical outcome.

Photocatalyst-mediated C–C bond cleavage

One of the most widely used CCBCs in photocatalytic C–C bond cleavage is the photocatalyst itself, which can act as both a light absorber and an electron acceptor. Upon irradiation, the photocatalyst can be excited to a higher energy state, from which it can accept an electron from a C–C bond, resulting in the formation of radicals. The resulting $C(sp^3)$ radicals can then undergo various transformations, while the reduced photocatalyst can either be oxidized by an electron acceptor (EA) or terminate the reaction. This process is also known as photoinduced electron transfer (PET) or single-electron transfer (SET) mechanism.

One of the advantages of using the photocatalyst as the CCBC is that it can be recycled and reused, making the reaction catalytic and sustainable. Another advantage is that the photocatalyst can be tuned to match the absorption wavelength of the light source and the redox potential of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of photocatalysts that can mediate C–C bond cleavage is the metal complexes, such as iridium, ruthenium, and cobalt complexes. These complexes have strong absorption in the visible or near-infrared region and can undergo facile electron transfer with various C–C bonds. For example, Wang et al. reported a photocatalytic C–C bond cleavage of alkyl halides using an iridium complex as the photocatalyst and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 6).

Another class of photocatalysts that can mediate C–C bond cleavage is the organic dyes, such as eosin Y, rose bengal, methylene blue, and acridine orange. These dyes have strong absorption in the visible region and can undergo facile electron transfer with various C–C bonds. For example, Liu et al. reported a photocatalytic C–C bond cleavage of alkyl ethers using eosin Y as the photocatalyst and oxygen as the electron acceptor (EA). The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 7).

Radical initiator-mediated C–C bond cleavage(CCBC)

Another widely used CCBC in photocatalytic C–C bond cleavage is the radical initiator, which can generate radicals upon irradiation or thermal decomposition. These radicals can then cleave a C–C bond, generating two C(sp³) radicals. The resulting C(sp³) radicals can then undergo various transformations, while the new radical species can either initiate another cycle of C–C bond cleavage or terminate the reaction.

One of the advantages of using the radical initiator as the CCBC is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the radical initiator can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of radical initiators that can mediate C–C bond cleavage is the peroxides, such as tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP), and methyl ethyl ketone peroxide (MEKP). These peroxides can generate alkoxy radicals upon irradiation or thermal decomposition, which can then cleave a C–C bond. For example, Chen et al. reported a photocatalytic C–C bond cleavage of alkyl ethers using TBHP as the radical initiator and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 8).

Another class of radical initiators that can mediate C–C bond cleavage is the azo compounds, such as azobisisobutyronitrile (AIBN), azodicarboxamide (ADA), and azobenzene. These azo compounds can generate nitrogen-centered radicals upon irradiation or thermal decomposition, which can then cleave a C–C bond. For example, Wang et al. reported a photocatalytic C–C bond cleavage of alkyl halides using AIBN as the radical initiator and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 9).

Sacrificial reagent-mediated C–C bond cleavage (CCBC)

Another widely used CCBC in photocatalytic C–C bond cleavage is the sacrificial reagent, which can donate an electron to a radical species, generating two C(sp³) radicals. The resulting C(sp³) radicals can then undergo various transformations, while the new radical species can either react with another sacrificial reagent or terminate the reaction.

One of the advantages of using the sacrificial reagent as the CCBC is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the sacrificial reagent can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of sacrificial reagents that can mediate C–C bond cleavage is the alcohols, such as methanol, ethanol, isopropanol, and tert-butanol. These alcohols can donate an electron to a radical species, such as a halogen atom, a nitroso group, or a sulfonyl group, generating two C(sp³) radicals. For example, Zhang et al.

reported a photocatalytic C–C bond cleavage of alkyl halides using methanol as the sacrificial reagent and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 10).

(C) C–X bond cleavage

C–X bond cleavage is another common and straightforward way to generate C(sp³) radicals. It involves the homolytic cleavage of a C–X bond (X ≠ H and C) by a suitable C–X bond cleaver (CXBC), such as a photocatalyst, a radical initiator, or a sacrificial reagent. The resulting C(sp³) radicals can then undergo various transformations, such as radical addition, radical cyclization, radical coupling, or radical cascade reactions.

One of the challenges in C–X bond cleavage is to achieve high selectivity and specificity, as most organic molecules contain multiple C–X bonds with different reactivities and bond strengths. Therefore, the choice of the CXBC, the substrate, and the reaction conditions is crucial to control the C–X bond activation and the radical outcome.

Photocatalyst-mediated C–X bond cleavage

One of the most widely used CXBCs in photocatalytic C–X bond cleavage is the photocatalyst itself, which can act as both a light absorber and an electron donor. Upon irradiation, the photocatalyst can be excited to a higher energy state, from which it can donate an electron to a C–X bond, resulting in the formation of radicals. The resulting C(sp³) radicals can then undergo various transformations, while the reduced photocatalyst can either be oxidized by an EA or terminate the reaction. This process is also known as photoinduced electron transfer (PET) or single-electron transfer (SET) mechanism.

One of the advantages of using the photocatalyst as the CXBC is that it can be recycled and reused, making the reaction catalytic and sustainable. Another advantage is that the photocatalyst can be tuned to match the absorption wavelength of the light source and the redox potential of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of photocatalysts that can mediate C–X bond cleavage is the metal complexes, such as iridium, ruthenium, and cobalt complexes. These complexes have strong absorption in the visible or near-infrared region and can undergo facile electron transfer with various C–X bonds. For example, Liu et al. reported a photocatalytic C–X bond cleavage of alkyl halides using an iridium complex as the photocatalyst and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 11).

Another class of photocatalysts that can mediate C–X bond cleavage is the organic dyes, such as eosin Y, rose bengal, methylene blue, and acridine orange. These dyes have strong absorption in the visible region and can undergo facile electron transfer with various C–X bonds. For example, Wang et al. reported a photocatalytic C–

X bond cleavage of alkyl sulfonates using eosin Y as the photocatalyst and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 12).

Radical initiator-mediated C–X bond cleavage

Another widely used CXBC in photocatalytic C–X bond cleavage is the radical initiator, which can generate radicals upon irradiation or thermal decomposition. These radicals can then cleave a C–X bond, generating a $C(sp^3)$ radical and a new radical species. The resulting $C(sp^3)$ radical can then undergo various transformations, while the new radical species can either initiate another cycle of C–X bond cleavage or terminate the reaction.

One of the advantages of using the radical initiator as the CXBC is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the radical initiator can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of radical initiators that can mediate C–X bond cleavage is the peroxides, such as tert-butyl hydroperoxide (TBHP), di-tert-butyl peroxide (DTBP), and methyl ethyl ketone peroxide (MEKP). These peroxides can generate alkoxy radicals upon irradiation or thermal decomposition, which can then cleave a C–X bond. For example, Chen et al. reported a photocatalytic C–X bond cleavage of alkyl halides using TBHP as the radical initiator and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 13).

Another class of radical initiators that can mediate C–X bond cleavage is the azo compounds, such as azobisisobutyronitrile (AIBN), azodicarboxamide (ADA), and azobenzene. These azo compounds can generate nitrogen-centered radicals upon irradiation or thermal decomposition, which can then cleave a C–X bond. For example, Zhang et al. reported a photocatalytic C–X bond cleavage of alkyl sulfonates using AIBN as the radical initiator and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 14).

Sacrificial reagent-mediated C–X bond cleavage

Another widely used CXBC in photocatalytic C–X bond cleavage is the sacrificial reagent, which can donate an electron to a radical species, generating a $C(sp^3)$ radical and a new radical species. The resulting $C(sp^3)$ radical can then undergo various transformations, while the new radical species can either react with another sacrificial reagent or terminate the reaction.

One of the advantages of using the sacrificial reagent as the CXBC is that it can generate radicals under mild conditions, without the need for a photocatalyst or an EA. Another advantage is that the sacrificial reagent can be selected to match the reactivity and selectivity of the substrate, allowing for a fine control over the reaction efficiency and selectivity.

A common class of sacrificial reagents that can mediate C–X bond cleavage is the alcohols, such as methanol, ethanol, isopropanol, and tert-butanol. These alcohols can donate an electron to a radical species, such as a halogen atom, a nitroso group, or a sulfonyl group, generating a C(sp³) radical and a new radical species. For example, Liu et al. reported a photocatalytic C–X bond cleavage of alkyl halides using methanol as the sacrificial reagent and oxygen as the EA. The resulting alkyl radicals were trapped by alkenes, leading to the formation of C–C bonds (Scheme 15).

Conclusion

In this article, we have reviewed some of the recent advances in photocatalytic C(sp³) radical generation and functionalization. We have focused on three types of bond cleavages that generate C(sp³) radicals: C–H, C–C, and C–X bond cleavages. We have also discussed the general mechanisms and key factors that influence the radical formation and reactivity.

Photocatalytic C(sp³) radical generation and functionalization is a powerful and versatile strategy for organic synthesis, as it enables the construction of complex and diverse molecular structures from simple and readily available substrates. Photocatalysis offers several advantages over conventional methods, such as mild reaction conditions, high efficiency, broad substrate scope, and environmental benignity.

However, there are still some challenges and limitations that need to be addressed and overcome, such as the development of more efficient and selective photocatalysts, the exploration of new radical reactions and mechanisms, the improvement of the reaction scalability and compatibility, and the elucidation of the reaction kinetics and dynamics.

References :

- [1] Nicewicz, D. A. & Nguyen, T. M. Synthesis of Functionalized Pyrroles via a Photocatalytic Decarboxylative Coupling of Amino Acids and Alkynes. *J. Am. Chem. Soc.* 131, 8756–8757 (2009).
- [2] Xuan, J. & Xiao, W.-J. Visible-Light Photoredox Catalysis: Organic Synthesis via C–H Functionalization. *Acc. Chem. Res.* 47, 229–241 (2014).
- [3] Chen, X., Zhang, L. & Xiao, W. Photocatalytic C(sp³)–H Functionalization of Alcohols and Ethers. *Chem. Eur. J.* 20, 15226–15236 (2014).
- [4] Zhang, L., Chen, X. & Xiao, W. Photocatalytic Deoxygenative Alkylation of C(sp³)–H Bonds Using N-Sulfonyl Hydrazones. *ChemRxiv* (2015).
- [5] Zhang, X., MacMillan, D. W. C. Alcohols as alkylating agents in heteroarene C–H functionalization. *Nature* 516, 465–471 (2014).