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REVIEW

Controlling Radical Reactivity for Visible-Light Bioorthogonal Chemistry

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ABSTRACT

Bioorthogonal chemistry enables selective reactions within complex biological environments. Visible-light photocatalysis expands this toolbox by generating carbon-centered radicals through single-electron transfer under mild conditions, enabling selective bond-forming transformations with spatiotemporal control. Unlike broader photocatalytic transformations in biology, bioorthogonal radical reactions that selectively couple exogenous partners without reacting with native biological functionalities have not been systematically examined from the perspective of radical reactivity control. The central challenge is to control radical reactivity such that productive coupling outcompetes biological quenching while maintaining chemoselectivity. This review examines two complementary strategies to address this challenge: kinetic trapping of transient alkyl radicals and thermodynamic stabilization of persistent ketyl radicals. Framing representative systems through physical-organic principles—including radical lifetime, polarity, and reaction kinetics—we highlight applications in nucleic acid and protein modifications, protein–protein cross-linking, and live-cell labeling. Finally, we discuss emerging opportunities in biocompatible photocatalysts, long-wavelength activation, and in vivo applications, providing a conceptual framework for the design of next-generation visible-light bioorthogonal chemistries.

1 | Introduction

Bioorthogonal chemistry encompasses chemical reactions that proceed selectively within complex biological environments without interfering with endogenous biochemical processes [1–4]. These reactions enable the selective modification, visualization, and manipulation of biomolecules in living systems [5–7]. Established platforms, including strain-promoted alkyne–azide cycloaddition (SPAAC) and inverse electron-demand Diels–Alder (IEDDA) reactions, have become indispensable tools for chemical biology [8–11]. Nevertheless, their reliance on a relatively limited set of two-electron reaction pathways can limit the accessible bond-forming chemistry and, in many cases, does not provide direct temporal control over reaction initiation. These limitations have motivated the development of alternative reaction manifolds that combine broad chemical reactivity with biological compatibility and externally controlled activation.

Radical chemistry offers a particularly attractive opportunity in this context. Radicals have long served as versatile intermediates in synthetic and polymer chemistry, and their distinct reactivity provides access to bond constructions that are difficult to achieve through conventional two-electron processes [12–15]. Of particular interest for chemical biology is the formation of C—C bonds, which can directly connect biomolecules with diverse synthetic partners. Historically, however, the application of radical chemistry in biological settings was constrained by the harsh conditions often required for radical generation, including elevated temperatures, toxic initiators, and ultraviolet irradiation. The development of visible-light photoredox catalysis has changed this landscape by enabling radical generation through single-electron transfer (SET)

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under mild conditions and, in many cases, in aqueous or cellular environments [16–18]. Light activation further provides an external means of controlling when radical generation occurs, offering a basis for spatiotemporal regulation [19].

Early studies demonstrated that transient alkyl radicals, generated photocatalytically from precursors such as organoborates and carboxylic acid derivatives, can undergo productive radical addition in aqueous environments, enabling DNA modification and site-selective protein functionalization [20–22]. These systems illustrate a fundamental challenge of radical bioorthogonal chemistry: short-lived radicals must undergo productive capture before encountering competing quenchers or undergoing unproductive side reactions in biological environments. More recently, stabilized diaryl ketyl radicals have emerged as a complementary radical platform. Generated through visible-light photocatalysis of benzophenone derivatives, these radicals differ fundamentally from the transient alkyl radicals discussed above. Unlike conventional UV-induced benzophenone photochemistry [23, 24], photocatalytic ketyl generation proceeds under mild visible-light conditions [25] and can access persistent radical species whose extended lifetimes and thermodynamic stabilization enable selective radical–radical coupling [26, 27]. This strategy has enabled applications including protein labeling, protein–protein cross-linking, and cell-surface modification in primary neuronal cultures [28].

These contrasting examples suggest that the key challenge in biological radical chemistry is not simply the generation of radicals but the control of their reactivity. While recent reviews have comprehensively surveyed visible-light photocatalysis in biology [29, 30], including radical and non-radical approaches for modification of native biomolecules [31–33], proximity labeling [34], prodrug activation [35, 36], and synthetic chemistry in living cells [18, 37–40], a focused analysis of photocatalytic radical reactions that selectively couple exogenous partners without undesired reactions with native biological functionalities remains lacking.

Here, we examine visible-light photocatalytic radical chemistry for bioorthogonal applications through the framework of radical reactivity control. We focus on two representative classes of carbon-centered radicals—transient alkyl radicals and thermodynamically stabilized ketyl radicals—that illustrate complementary strategies for achieving selective reactivity in biological environments: kinetic trapping and thermodynamic stabilization. We discuss their applications in DNA and protein modifications, protein–protein cross-linking, and live-cell labeling while examining how radical lifetime, polarity, redox properties, and reaction kinetics govern their behavior. By placing these representative systems within a unified physical-organic framework, this review seeks to identify emerging principles for controlling radical reactivity in biological environments and to provide a basis for the rational design of next-generation visible-light bioorthogonal chemistry (Figure 1).

2 | Bioorthogonal Photocatalytic Reactions via Alkyl Radicals

Alkyl radicals are highly reactive carbon-centered open-shell intermediates with generally short lifetimes, making their controlled use in biological environments particularly challenging [45]. Their high reactivity also renders them susceptible

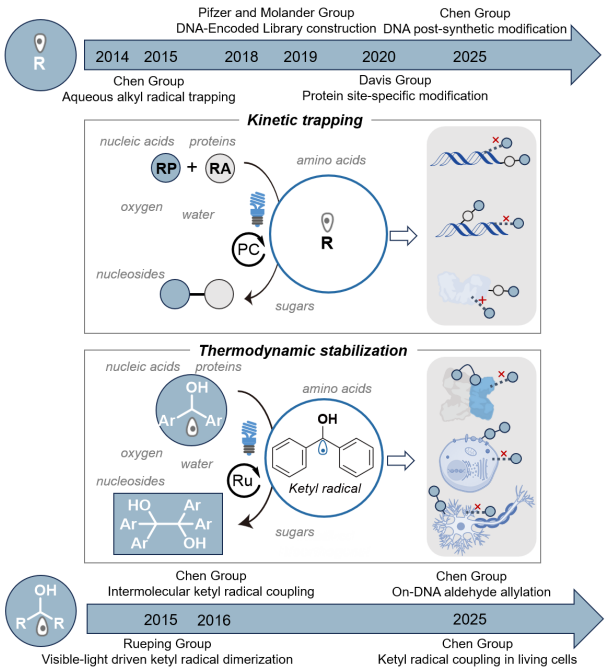

FIGURE 1 | Overview of visible-light photocatalytic bioorthogonal radical reactions. This timeline specifically tracks photocatalytic radical bioorthogonal reactions that proceed selectively between exogenous partners without reacting with endogenous biomolecules. Two distinct strategies for controlling radical reactivity are illustrated: kinetic trapping of transient alkyl C-radicals (top) and thermodynamic stabilization of persistent ketyl radicals (bottom), with representative biological applications across DNA, protein, and cell-surface scaffolds. PC, photocatalysts; RP, Radical precursor; RA, Radical acceptor [20, 21, 25, 28, 41–44].

to rapid quenching by molecular oxygen, thiols, and other endogenous biomolecules before productive bond formation can occur [46–48]. Successful implementation therefore relies on kinetic control: transient radicals must be generated and intercepted rapidly by highly reactive acceptors before competing quenching pathways become significant. Polarity matching between the radical and its reaction partner can further enhance selectivity, as exemplified by the addition of nucleophilic alkyl radicals to electron-deficient acceptors.

The central requirement is thus for productive radical capture to outcompete biological quenching through favorable reaction kinetics. Although visible-light photoredox chemistry involving alkyl radicals was initially developed primarily for synthetic applications, a limited number of platforms have been adapted to neutral aqueous and biomolecule-compatible conditions [49]. These studies establish the fundamental principles of kinetic trapping that underpin photocatalytic alkyl radical bioorthogonal chemistry [50].

2.1 | Photocatalytic Generation and Trapping of Alkyl Radicals in Aqueous Media

Visible-light photoredox catalysis provides a mild platform for generating alkyl radicals under conditions increasingly compatible with biological environments. In 2014, Chen and coworkers reported a redox-neutral, visible-light-induced deboronative

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alkynylation that operated under air in water/organic biphasic media with blue-light irradiation (468 nm) (Figure 2A) [41]. Using $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and cyclic iodine(III) reagent hydroxybenziodoxole (BI-OH) as the essential additive, alkyl-BF_3K salts were converted into alkyl radicals that underwent addition to the alkynylbenziodoxole (BI-alkyne) π-system, enabling C(sp^3)—C(sp) bond formation. The reaction tolerated a broad range of functional groups and, importantly, remained effective in neutral aqueous buffers containing amino acids, nucleosides, oligosaccharides, nucleic acids, proteins, and cell lysates.

This oxidative radical platform was subsequently expanded to C(sp^3)—C(sp^2) bond formation through deboronative/decarboxylative alkenylation [51]. In this system, acetoxybenziodoxole (BI-OAc) served not only as an essential additive for photocatalytic turnover but also as a covalent activator by forming an isolable BI–vinyl carboxylic acid complex prior to radical addition. This preorganization enhanced radical capture and enabled efficient coupling in a pH 7.4 aqueous buffer, highlighting the importance of controlling radical reactivity in biological settings.

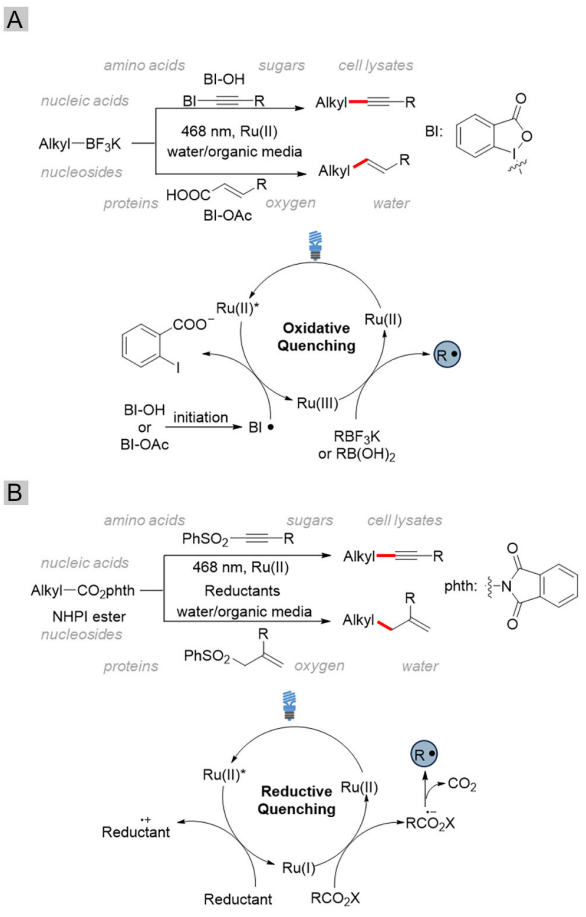

FIGURE 2 | Photocatalytic generation and kinetic trapping of alkyl radicals under aqueous, biomolecule-compatible conditions. (A) Oxidative quenching pathways for generating alkyl radicals from alkyltrifluoroborates (R–BF_3K) or alkylboronic acids [R–$B(OH)_2$], enabling C(sp^3)—C bond formation through radical addition [41]. (B) Reductive quenching pathways for generating alkyl radicals from *N*-acyloxyphthalimide (NHPI) esters, enabling chemoselective C(sp^3)—C cross-coupling under mild aqueous conditions [42].

Collectively, these studies established that successful aqueous alkyl radical chemistry requires simultaneous optimization of radical generation and radical capture: redox matching ensures efficient radical formation, whereas acceptor preorganization accelerates productive bond formation over competing biological quenching pathways.

Although these oxidative approaches established the feasibility of alkyl radical generation in aqueous conditions, their dependence on hypervalent iodine reagents and relatively slow reaction rates motivated the development of complementary reductive strategies. *N*-Acyloxyphthalimide (NHPI) esters emerged as versatile radical precursors by enabling direct conversion of abundant carboxylic acids into photocleavable radical handles (Figure 2B) [52]. Under reductive quenching conditions with blue-light irradiation (468 nm), photoexcited $[Ru(bpy)_3]^{2+}$ generates Ru(I), which transfers an electron to the NHPI ester to induce decarboxylation and generate the corresponding alkyl radical. Addition of this radical to alkynyl sulfones afforded the desired coupling products under mild conditions. Notably, the transformation showed minimal interference with the activity of human carbonic anhydrase II, demonstrating compatibility with protein enzymes.

The reductive strategy was further advanced through chemoselective decarboxylative allylation optimized for biomolecular applications (Figure 2B) [42]. Using allyl sulfones as radical acceptors, this system achieved rapid conversion within minutes under blue-light irradiation (468 nm), operated efficiently at low micromolar concentrations relevant to biomolecular studies, and employed ascorbate as a water-soluble reductant. The biomolecular compatibility was demonstrated by direct modification of an oligosaccharide conjugate in an 83% yield within 1 min, illustrating a key conceptual advance: visible-light-generated alkyl radicals can be harnessed for covalent modification of biomolecules rather than merely tolerated in biomolecule-containing reaction mixtures.

More broadly, these studies establish the fundamental principle of kinetic trapping in alkyl radical bioorthogonal chemistry. Rapidly activated radical precursors (e.g., alkyl-BF_3K salts and NHPI esters) must be paired with highly SOMOphilic acceptors capable of capturing transient radicals faster than competing endogenous quenching pathways, including molecular oxygen and cellular thiols. This strategy provides a general blueprint for translating highly reactive alkyl radicals into selective chemical tools for aqueous and biological environments.

Complementary to these catalyst–iodine/NHPI platforms, Mascareñas, Mato, and coworkers developed green- and red-light photoredox systems for generating alkyl radicals from redox-active phthalimide esters and their subsequent Giese-type trapping. Using biocompatible nicotinamide reductants, these reactions proceeded under air and were compatible with aqueous media, cell-culture media, and cell lysates [53]. Related photocatalytic arylations of diazonium salts in aqueous media further demonstrate biorelevant C—C bond formation under SET conditions [54]. Together, these studies expand the kinetic-trapping toolbox beyond hypervalent iodine/NHPI-derived radical precursors.

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2.2 | Alkyl Radical-Mediated Modification of Nucleic Acids and Proteins

Reactions involving DNA require aqueous conditions, ambient temperature, neutral pH, and preservation of nucleic acid integrity, as even minor damage can compromise downstream amplification or sequencing [55, 56]. Visible-light photocatalytic radical chemistry provides an attractive solution by enabling mild, aqueous, and light-controlled C—C bond formation on DNA. When combined with carefully engineered radical acceptors capable of rapidly capturing transient radicals, these reactions have become powerful tools for DNA-encoded library (DEL) synthesis and DNA modification, allowing the expansion of chemical space while maintaining DNA compatibility (Figure 3A) [58].

Early advances demonstrated that alkyl radicals generated under photoredox conditions could be effectively incorporated into DNA-compatible transformations. The Baran group reported a radical Giese addition on DNA using alkyl radicals derived from redox-active esters, enabling the addition to DNA-conjugated acrylates [59]. Shortly thereafter, Pfizer demonstrated that α-amino acid-derived alkyl radicals could be generated by visible-light photocatalysis and coupled with DNA-tagged Michael acceptors to form $C(sp^3)$—$C(sp^3)$ bonds (Figure 3A) [57]. The Molander group further expanded this strategy through Ni/photoredox dual catalysis, employing radical–polar crossover pathways to introduce diverse $C(sp^3)$ fragments onto DNA under mild, open-air conditions. DNA integrity was rigorously validated by qPCR and sequencing analyses, confirming the compatibility of radical chemistry with DNA-encoding technologies [44]. Subsequent developments incorporating α-silylamines, alkyl bromides, and alkyl iodides as radical precursors further broadened the accessible chemical space, establishing visible-light radical chemistry as a versatile approach for DEL diversification [60–62].

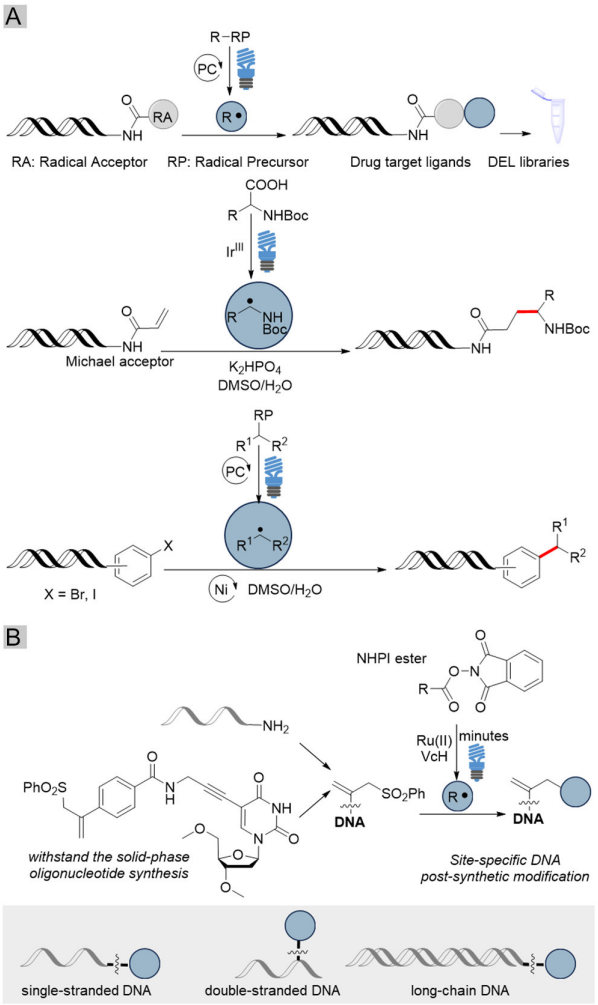

FIGURE 3 | Photocatalytic alkyl radical strategies for nucleic acid functionalization. (A) Visible-light-driven alkyl radical reactions enabling $C(sp^3)$—$C(sp^3)$ bond construction in DNA-encoded library (DEL) synthesis [57]. (B) Site-specific post-synthetic modification of single- and double-stranded DNA through alkyl radical-mediated allylation. RA, Radical Acceptor; RP, Radical Precursor; DEL, DNA-encoded library [21].

Beyond DEL synthesis, where DNA primarily functions as a molecular barcode, alkyl radical chemistry has also enabled the direct post-synthetic modification of DNA itself. The Chen group developed a visible-light-catalyzed decarboxylative allylation strategy for site-specific DNA modification using alkyl radicals generated from NHPI esters (Figure 3B) [21]. A key challenge in this approach was identifying radical acceptors that could simultaneously withstand the conditions of solid-phase oligonucleotide synthesis and efficiently capture transient radicals under aqueous conditions. The allyl sulfone acceptor satisfied these requirements: it remained stable during DNA synthesis while retaining high reactivity toward photogenerated alkyl radicals. By incorporating allyl sulfone handles through terminal amide coupling or modified nucleoside building blocks, internal and terminal DNA modification sites could be accessed [55].

Using $Ru(bpy)_3Cl_2$ and ascorbic acid as the photocatalytic system, NHPI-derived alkyl radicals were efficiently coupled with allyl sulfones within minutes under open-air aqueous conditions at blue light irradiation (468 nm). The reaction tolerated a broad range of functional groups, including primary, secondary, and tertiary alkyl groups, alcohols, carboxylic acids, phenols, indoles, aryl iodides, aldehydes, alkynes, and azides, while preserving DNA integrity. This strategy enabled site-specific modification of single-stranded DNA, double-stranded DNA, and PCR-amplified long-chain DNA, demonstrating the feasibility of visible-light radical chemistry for programmable DNA functionalization.

The compatibility of alkyl radicals with protein environments was first established through radical addition to dehydroalanine (DHA) residues. Davis and coworkers demonstrated that alkyl radicals could undergo polarity-matched $C(sp^3)$—$C(sp^3)$ bond formation with DHA, a highly effective SOMOphilic handle that can be introduced at defined protein sites through genetic, or biosynthetic, or by chemical conversion of cysteine [63]. This approach enabled the installation of diverse side chains onto multiple protein scaffolds and highlighted the potential of radical chemistry for protein functionalization.

Building on this foundation, the Davis group developed visible-light photocatalytic strategies for controlled radical generation in proteins (Figure 4) [20]. An oxidative boronic acid catechol ester (BACED) pathway enabled alkyl radical generation

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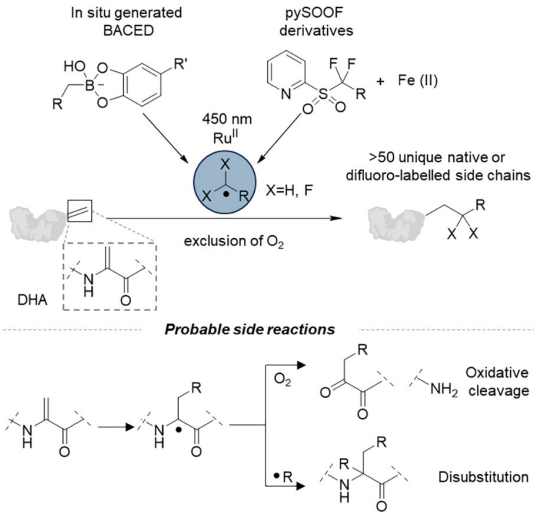

FIGURE 4 | Photocatalytic alkyl radical strategies for protein functionalization [20]. Representative single-electron-transfer (SET) pathways enabling site-selective modification of amino acid residues and protein scaffolds through radical-mediated C—C bond formation under aqueous, biocompatible conditions. DHA, dehydroalanine; BACED, boronic acid catechol ester; pySOOF, pyridyl sulfone fluoride.

from alkyl boronic acids through oxidation by photoexcited $[Ru(bpy)_3]^{2+}$, whereas a complementary reductive pyridyl sulfone fluoride (pySOOF) pathway employed Ru(I)-mediated activation (450 nm) to generate difluoromethyl radicals. Unlike conventional radical reactions that rely solely on reagent reactivity, these photocatalytic approaches introduced an additional level of control through light-mediated regulation of radical production. Temporal control of irradiation minimized excessive radical accumulation and reduced undesired overfunctionalization, whereas rigorous oxygen exclusion (<6 ppm O_2) prevented oxidative radical degradation and preserved protein integrity.

Under these optimized conditions, more than 50 chemically diverse side chains—including olefins, azides, halides, sulfoxides, sulfones, sulfates, esters, and amides—were incorporated into diverse protein scaffolds. Difluorinated modifications further enabled real-time monitoring of protein modification by ^{19}F NMR, while electrophilic halide-containing side chains provided opportunities for proximity-driven protein–protein crosslinking. Together, these studies demonstrate how kinetic control of radical generation and selective radical capture can transform highly reactive alkyl radicals into versatile tools for protein engineering and chemical biology.

Beyond noncanonical handles, visible-light photoredox chemistry also enables radical functionalization of canonical amino acid residues. As comprehensively reviewed by Professor Davis, Nappi, and Gaunt groups, representative examples include photoredox-catalyzed site-selective modification of tyrosine and tryptophan [33, 64], as well as methionine and C-terminal residues [32, 65], via radical pathways under biocompatible conditions [17, 31]. It should be emphasized, however, that direct functionalization of canonical residues constitutes modification of the biomolecule itself and is therefore mechanistically distinct from the exogenous partner bioorthogonal reactions that constitute the central focus of this review.

3 | Bioorthogonal Photocatalytic Reactions via Ketyl Radicals

In contrast to short-lived alkyl radicals, ketyl radicals offer an alternative strategy for controlling radical reactivity through stabilization. Generated by single-electron reduction of carbonyl compounds, ketyl radicals are resonance-stabilized radical anions in which the unpaired electron is delocalized across the carbonyl group and adjacent π-systems (Figure 5). Their persistence depends strongly on the substitution and conjugation surrounding the radical center: simple alkyl ketyl radicals are generally short-lived and prone to disproportionation or dimerization, whereas diaryl ketyl radicals benefit from extensive conjugation across the aromatic rings, resulting in substantially longer radical lifetimes [66, 67]. This increased persistence provides a wider kinetic window for productive encounter with selected reaction partners while reducing the relative contribution of competing biological quenching pathways.

Unlike alkyl radicals, whose reactivity is primarily controlled through rapid kinetic trapping, persistent ketyl radicals provide a complementary strategy based on thermodynamic stabilization. By extending radical lifetime through delocalization, the reaction can be directed toward selective radical addition or radical–radical coupling while limiting unproductive reactions with endogenous biomolecules [68, 69]. The reaction is also O_2-tolerant: although O_2 initially retards the reaction by quenching radicals, continued irradiation restores standard yields through ketyl regeneration.

3.1 | Visible-Light Generation of Ketyl Radicals: Development of a Bioorthogonal Platform

Ketyl radicals have a long history as photoactive intermediates in benzophenone-based cross-linking chemistry. Upon ultraviolet (UV) irradiation (350–360 nm), benzophenone undergoes efficient intersystem crossing to generate a triplet excited state with a substantial n → π* character [67]. This triplet diradical acts as a potent hydrogen-atom abstractor, preferentially reacting with weak and electron-rich C—H bonds in biomolecules. Following hydrogen abstraction, recombination between the resulting ketyl radical and the carbon-centered radical affords covalent crosslink products (Figure 6A) [70]. The relative stability of the benzophenone triplet state in protic solvents and its limited reactivity toward water have contributed to its widespread use in photoaffinity labeling for mapping protein–ligand interactions, identifying protein complexes, and labeling nucleic acids and lipids

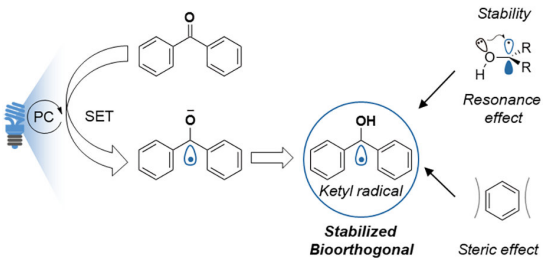

FIGURE 5 | Visible-light photocatalysis produces stabilized diaryl ketyl radicals via steric/resonance effects [66, 67]. SET, single-electron transfer.

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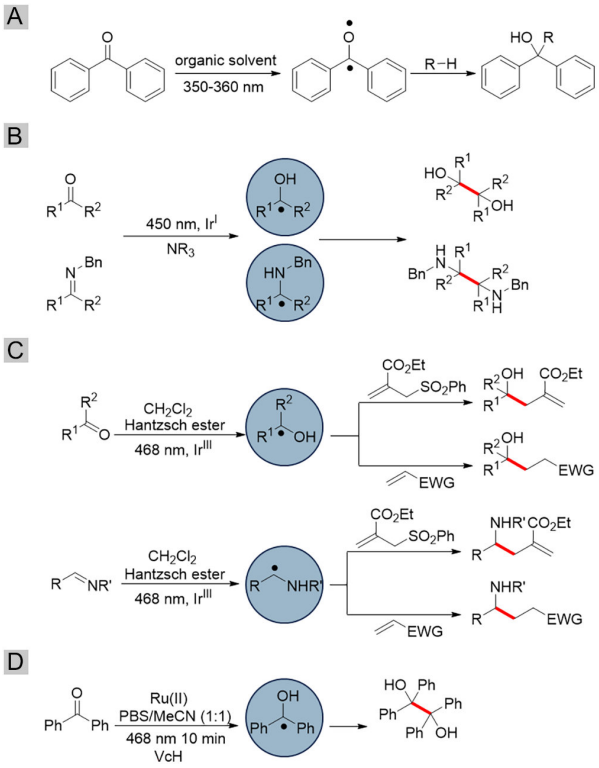

FIGURE 6 | Evolution of visible-light-driven ketyl radical chemistry from synthetic transformations to bioorthogonal applications. (A) UV excitation of benzophenone generates triplet diradical intermediates that undergo hydrogen-atom transfer (HAT)-mediated C—H activation, resulting in nonspecific protein crosslinking [70]. (B) Visible-light photoredox catalysis enables single-electron reduction of carbonyl compounds and imines to generate ketyl and α-aminoalkyl radicals for selective radical coupling reactions [25]. (C) Expansion of ketyl radical chemistry to intermolecular C—C bond formation through polarity-reversed allylation and related additions of aldehydes, ketones, and imines [43]. (D) Development of thermodynamically stabilized diaryl ketyl radicals that undergo selective radical–radical coupling under aqueous, biologically compatible conditions [28].

[71, 72]. However, the intrinsic HAT reactivity of the triplet diradical results in limited chemoselectivity as any accessible C—H bond may serve as a reaction site.

Moreover, the requirement for prolonged UV irradiation introduces additional phototoxicity concerns, restricting applications in living systems [73].

A conceptual shift occurred with the emergence of visible-light photoredox strategies for ketyl radical generation, which replaced direct excitation of benzophenone triplets with the single-electron reduction of carbonyl compounds. Rueping and coworkers reported a general visible-light-driven ketyl radical coupling strategy in 2015 based on the reductive activation of carbonyl compounds and imines (Figure 6B) [25]. Under blue-light irradiation (450 nm), an iridium photocatalyst and a tertiary amine cocatalyst cooperatively reduced aldehydes, ketones, and imines to generate ketyl or α-aminoalkyl radicals, which subsequently underwent radical–radical dimerization to form vicinal diols or diamines. This transformation overcame the challenging reduction potentials of carbonyl compounds through a dual catalytic mechanism, in which the amine served both as a sacrificial electron donor and as a hydrogen-bonding activator that facilitated proton-coupled electron transfer (PCET). Unlike UV-generated triplet diradicals, which undergo nonspecific HAT chemistry, photoredox-generated ketyl radicals exhibit a distinct reactivity profile dominated by radical coupling. This work demonstrated that ketyl radicals could be generated under visible-light irradiation with excellent functional group tolerance, providing the foundation for subsequent biological applications. However, these early examples remained largely restricted to organic solvents, and their compatibility with complex biological environments remained unexplored [74].

Subsequent advances expanded ketyl radical chemistry beyond radical dimerization toward intermolecular C—C bond formation. In 2016, Chen and coworkers reported a polarity-reversed allylation strategy in which photoredox-generated ketyl radicals underwent coupling with allyl sulfones to furnish homoallylic alcohols (Figure 6C) [43]. Mechanistically, reductive quenching of the photocatalyst generated the Hantzsch ester (HE) radical cation, which interacted with the carbonyl substrate through hydrogen bonding to facilitate proton-coupled electron transfer and ketyl radical formation. The resulting ketyl radical underwent addition to allyl sulfones, followed by elimination of phenylsulfinate to yield the allylated product. The reaction tolerated diverse functional groups, including thiophenes, furans, esters, and amides, and could also be extended to imines for the synthesis of α-branched amines. Although initially developed in organic solvents, the transformation maintained high efficiency in the presence of water and under aerobic conditions, suggesting potential compatibility with biological settings [22, 43].

Building on these advances, Chen and coworkers established a fully aqueous, visible-light-driven ketyl radical coupling platform designed specifically for bioorthogonal applications (Figure 6D) [28]. Unlike traditional benzophenone photochemistry, this strategy avoided triplet diradical formation and instead exploited resonance stabilization and steric protection to extend ketyl radical lifetimes while suppressing competing HAT and [2+2] pathways [67–69]. Critically, the resulting diaryl ketyl radicals underwent ultrafast homocoupling ($k = 5.9 \times 10^7\,M^{-1}\,s^{-1}$), allowing productive radical coupling to outcompete biological quenching processes and enabling protein modification and cross-linking in aqueous environments.

Through systematic optimization of photocatalyst–reductant combinations, the $Ru(bpy)_3Cl_2$/ascorbate pair was identified as an effective system for generating stabilized ketyl radicals in PBS under blue-light irradiation. NMR titration confirmed hydrogen-bonding interactions between ascorbate and the benzophenone scaffold through characteristic O–H···O=C chemical shift perturbations. Under optimized conditions, the pinacol coupling product was obtained in a 92% yield with minimal side products. Mechanistically, ascorbate acts as a biocompatible reductant that reductively quenches the excited *Ru(II) catalyst to generate Ru(I), which transfers an electron to the diaryl ketone substrate. The resulting ketyl radical is stabilized through the combined effects of resonance delocalization across the carbonyl and aromatic π-systems and steric protection that suppresses undesired radical pathways. This system therefore established a visible-light-driven catalytic ketyl radical manifold compatible with biologically relevant aqueous environments.

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More broadly, this work established thermodynamic stabilization as a distinct strategy for controlling radical reactivity in bioorthogonal chemistry. By extending radical lifetime through resonance delocalization and steric gating while maintaining selective radical–radical coupling, stabilized ketyl radicals provide a blueprint for transforming highly reactive open-shell intermediates into selective biological tools. This principle may be broadly applicable beyond diaryl ketyl radicals to other stabilized radical classes, including α-amino, α-oxy, and polarity-tuned carbon-centered radicals, thereby expanding the scope of radical chemistry in complex biological environments.

3.2 | Biomolecular and Cellular Applications of Bioorthogonal Ketyl Radical Chemistry

The evolution of ketyl radical chemistry from UV-induced benzophenone photochemistry to visible-light-driven photocatalysis in aqueous media has established a distinct bioorthogonal platform that combines mild reaction conditions with high chemoselectivity and cytocompatibility. The extended lifetime of stabilized diaryl ketyl radicals enables controlled diffusion and selective radical–radical coupling while minimizing undesired interactions with endogenous biomolecules. These unique reactivity features have enabled applications ranging from DNA functionalization to protein labeling, cross-linking, and live-cell manipulation. Collectively, these studies demonstrate that visible-light photocatalytic ketyl radical chemistry provides a distinct strategy to classical photoaffinity labeling by achieving both spatiotemporal control and biological compatibility that are difficult to attain with UV-driven benzophenone chemistry.

3.2.1 | *DNA Functionalization Through Photocatalytic Ketyl Radical-Mediated Aldehyde Coupling*

Aldehyde functionalities, particularly those present in epigenetic DNA modifications such as 5-formylcytosine (5fC) and 5-formyluracil (5fU), represent valuable chemical handles for DNA functionalization [75]. However, their derivatization often relies on acidic conditions, elevated temperatures, or reactions that perturb native nucleobase structures, limiting compatibility with intact biological samples [76–78]. Photocatalytic ketyl radical chemistry provides an alternative strategy by enabling selective aldehyde transformation under neutral aqueous conditions while preserving DNA integrity.

Using this approach, Chen and coworkers developed a photocatalytic on-DNA aldehyde allylation strategy for precise DNA functionalization (Figure 7A) [22]. In this system, aldehyde groups were introduced as synthetic DNA handles or generated endogenously from 5fC residues within genomic DNA. Under visible-light irradiation (468 nm, 3 h) in 50% aqueous DMF at room temperature, an iridium photocatalyst and an allyl sulfone acceptor promoted a radical addition–elimination cascade, installing allylic groups onto aldehyde sites through the formation of new $C(sp^3)$—$C(sp^3)$ bonds in 94% yield. Subsequent qPCR and LC–MS analyses confirmed that DNA integrity was maintained throughout the transformation, highlighting the compatibility of ketyl radical chemistry with nucleic acid substrates.

The modularity of this approach further enabled DNA-templated cross-linking through proximity-driven radical coupling. Hybridization of an aldehyde-functionalized DNA strand with a complementary strand containing an allyl sulfone acceptor generated covalent interstrand linkages, providing a strategy

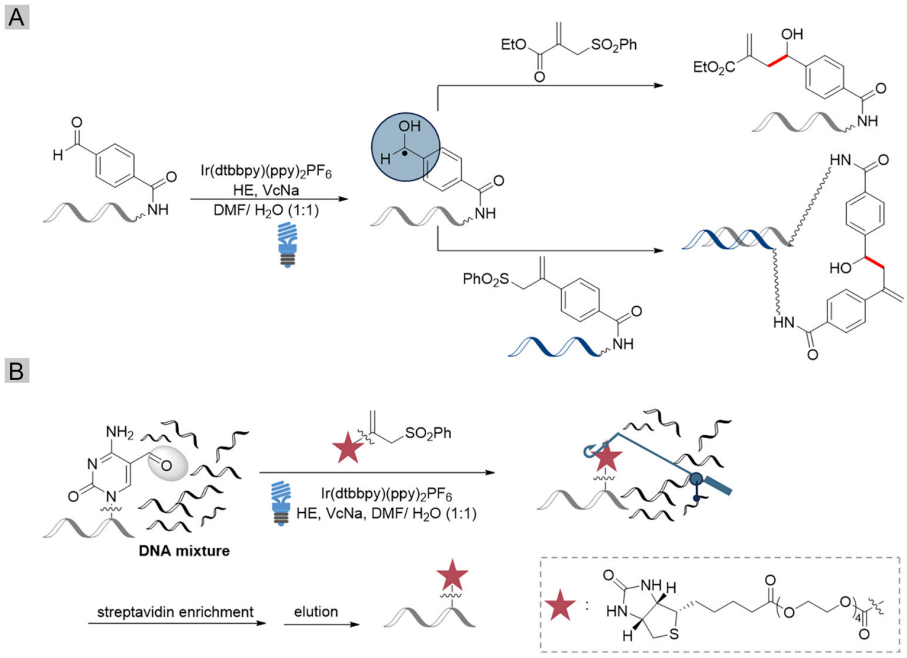

FIGURE 7 | Photocatalytic ketyl radical-mediated aldehyde allylation for DNA functionalization and epigenetic profiling [22]. (A) Visible-light-driven aldehyde allylation enables site-specific modification and proximity-induced crosslinking of aldehyde-functionalized DNA through ketyl radical intermediates and allyl sulfone acceptors. (B) Selective photocatalytic labeling and enrichment of 5-formyl-2′-deoxycytidine (5fC) epigenetic marks from complex genomic DNA samples. HE, Hantzsch ester; VcNa, Vitamin C sodium.

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for constructing DNA nanostructures and programmable DNA conjugates.

Beyond synthetic DNA modification, this chemistry also provides a mild analytical method for profiling epigenetic aldehyde modifications. By employing a biotinylated allyl sulfone probe, 5fC-containing DNA strands could be selectively labeled and enriched using streptavidin-coated magnetic beads from complex cellular DNA samples (Figure 7B). Compared with conventional approaches such as bisulfite sequencing or oxidative tagging strategies, which may alter or damage DNA templates, this photocatalytic method enables selective chemical capture while maintaining the DNA structural integrity. Thus, stabilized ketyl radical chemistry extends beyond biomolecular modification to provide a nondestructive tool for studying endogenous epigenetic DNA marks.

3.2.2 | Protein Labeling and Interrogation of Protein–Protein Interactions via Stabilized Diaryl Ketyl Radicals

The photocatalytic ketyl radical platform developed by Chen and coworkers enabled visible-light-driven protein labeling and cross-linking with a level of selectivity unattainable by conventional UV-based benzophenone photocrosslinking [28]. In this strategy, proteins containing benzophenone handles—introduced either through *N*-hydroxysuccinimide (NHS) ester modification of lysine residues or genetic incorporation of 4-benzoylphenylalanine (Bpa)—undergo selective coupling with functionalized benzophenone probes under photocatalytic conditions (468 nm) [79]. Labeling of the nanobody 7D12 demonstrated the broad adaptability of this approach across different protein scaffolds. Moreover, the compatibility with diverse reporter groups, including coumarin, fluorescein, and tetramethylrhodamine (TAMRA), as well as enrichment handles such as biotin, alkynes, dibenzocyclooctyne (DBCO), and desthiobiotin, highlights its versatility for downstream biological analysis (Figure 8A) [80].

Beyond single-protein modification, the stabilized ketyl radical platform enables proximity-driven interrogation of protein–protein interactions through covalent cross-linking for precise analysis of protein complex structures [81]. By positioning Bpa residues at protein interfaces, photocatalytic activation generates ketyl radicals that undergo selective radical–radical coupling to form covalent pinacol linkages between interacting partners (Figure 8B). Using

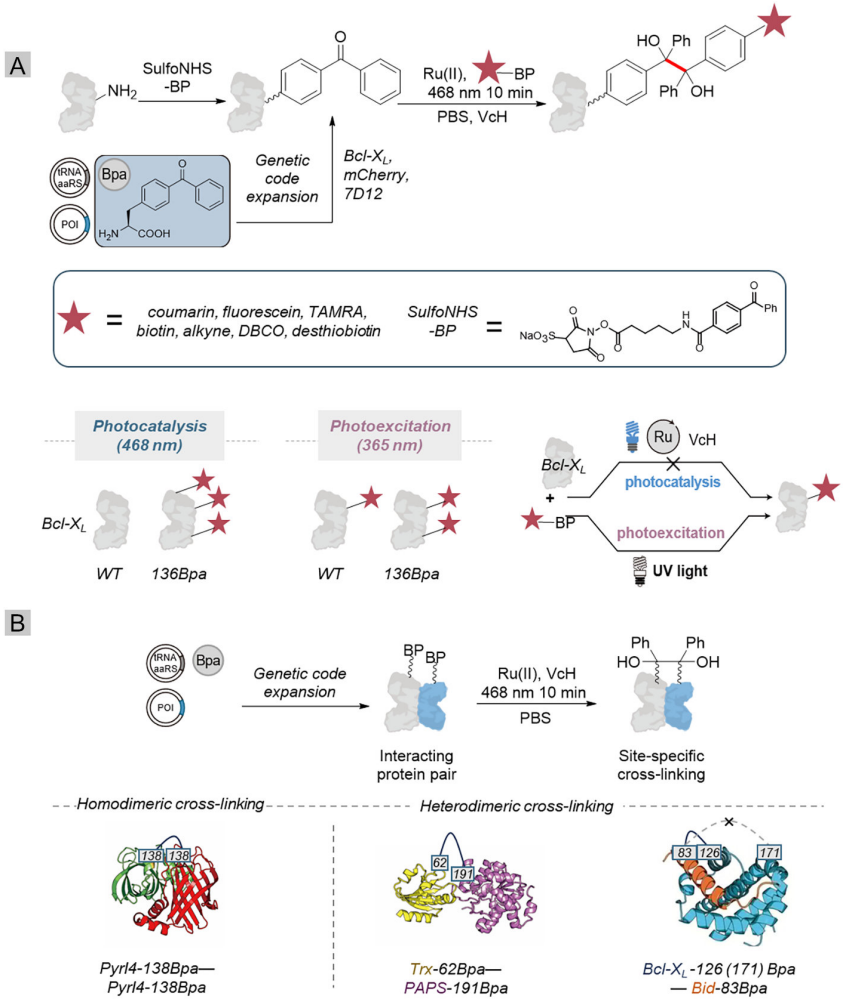

FIGURE 8 | Stabilized diaryl ketyl radical chemistry for site-specific protein labeling and protein–protein cross-linking [28]. (A) Photocatalytic benzophenone coupling enables selective incorporation of functional probes onto target proteins through visible-light-generated ketyl radicals, overcoming the nonspecific labeling associated with UV activation. (B) Proximity-driven ketyl radical coupling enables covalent capture and residue-level mapping of protein–protein interaction interfaces. BP, benzophenone; WT, wild type; VcH, Vitamin C; Bpa, 4-benzoylphenylalanine.

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the PyrI4 homodimer as a model system, this strategy captured the native dimerization interface, with tandem mass spectrometry enabling identification of the crosslinked amino-acid residues. Extension to heterodimeric complexes, including Trx/PAPS and Bcl-X_L/Bid systems, further demonstrated the generality of this approach. Control experiments confirmed the requirement for molecular proximity, as distal Bpa incorporation or disruption of native protein interactions abolished crosslink formation.

Molecular dynamics simulations and bio-layer interferometry measurements further indicated that Bpa incorporation preserved the protein structure and binding affinity, establishing photocatalytic ketyl radical coupling as a selective approach for protein–protein cross-linking at residue-level resolution.

3.2.3 | Live-Cell Applications: From Cell-Surface Modification to Primary Neuronal Systems

A critical benchmark for bioorthogonal photocatalytic chemistry is the ability to maintain selectivity and compatibility within intact cellular environments [6, 7]. Visible-light generation of stabilized diaryl ketyl radicals enables site-specific protein labeling in living cells while minimizing the phototoxicity and background modification associated with UV-driven benzophenone chemistry [28]. In HeLa cells, surface benzophenone installation using SulfoNHS-BP followed by $Ru(bpy)_3Cl_2$/ascorbate-mediated photocatalysis with biotin-BP under blue-light irradiation (468 nm) produced efficient, light-dependent surface biotinylation with minimal background labeling, as confirmed by confocal microscopy and flow cytometry (Figure 9A) [82]. Importantly, the method was compatible with primary neuronal cultures, which are particularly sensitive to photochemical stress. Biotin labeling detected by streptavidin–TAMRA colocalized with the neuronal marker microtubule-associated protein 2 (MAP-2), demonstrating selective modification of neuronal cell surfaces, while MTT assays showed cell viability above 84% under standard conditions. Control experiments further confirmed that individual components of the photocatalytic system exhibited minimal cytotoxicity (Figure 9A) [83].

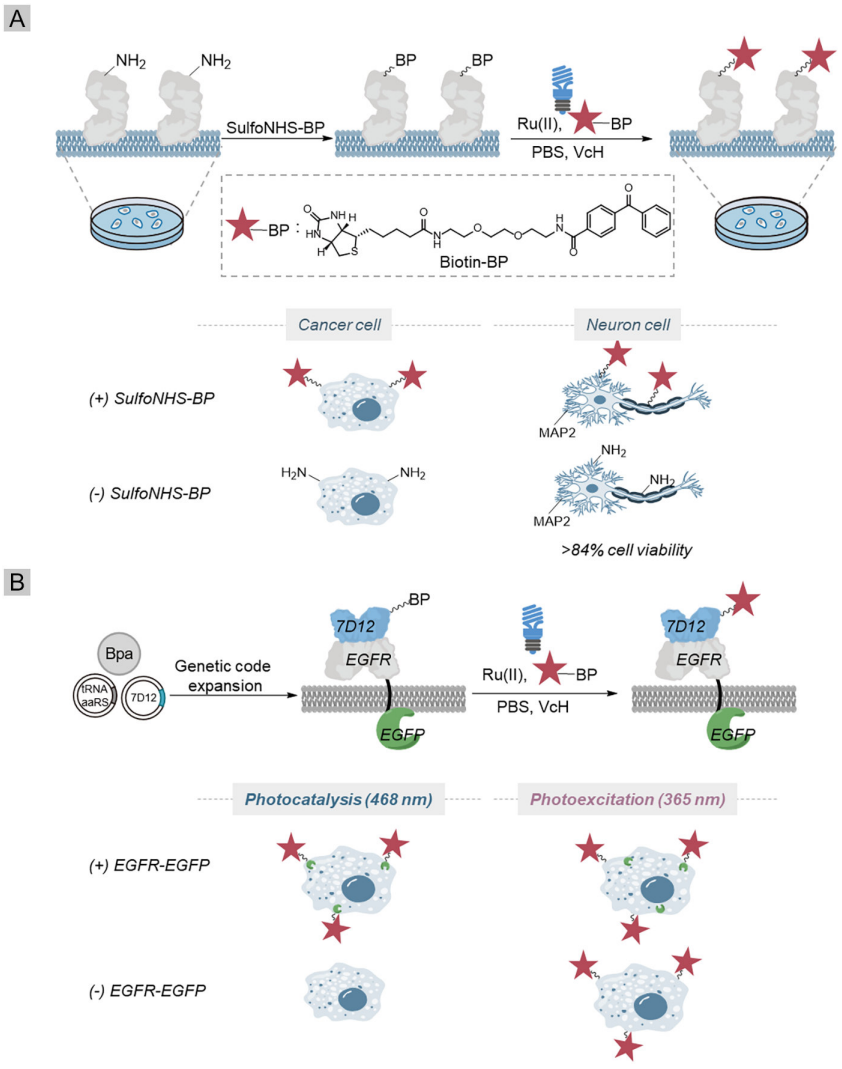

FIGURE 9 | Live-cell applications of photocatalytic ketyl radical chemistry: surface labeling and cytocompatibility [28]. (A) Visible-light-driven photocatalytic ketyl radical coupling enables cell-surface protein modification in immortalized cell lines and primary neuronal cultures through sulfo-NHS-mediated benzophenone installation and bioconjugation. (B) Comparison of labeling selectivity and cellular compatibility between visible-light photocatalytic ketyl radical coupling and conventional UV-activated benzophenone photoaffinity labeling.

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The platform also enabled genetically encoded, site-specific protein modification on live cells through the incorporation of the benzophenone-derived unnatural amino acid Bpa. The anti-EGFR nanobody 7D12 was engineered to contain Bpa at a position distal to its antigen-binding region [84, 85]. Following selective binding to EGFR–EGFP-expressing HEK 293T cells, photocatalytic coupling with biotin-BP generated strong target-associated signals with minimal nonspecific labeling [86]. In contrast, direct UV irradiation of the same system produced extensive background modification, demonstrating that visible-light-driven ketyl radical chemistry provides superior selectivity compared with traditional benzophenone photochemistry (Figure 9B).

The improved cytocompatibility of this approach arises not simply from the use of visible light but from a fundamental mechanistic transformation: replacing UV-generated triplet diradicals, which promote hydrogen-atom transfer and competing [2 + 2] pathways, with photocatalytically generated ketyl radicals that undergo selective radical–radical coupling [67–69]. By suppressing dominant off-target reaction channels while maintaining efficient covalent bond formation, this strategy establishes design principles for photoactivated bioorthogonal chemistry: biological selectivity is achieved not by maximizing radical generation but by rationally controlling radical reactivity.

Collectively, these studies—from chemical surface labeling in immortalized cell lines to protein engineering in primary neuronal cultures and genetically encoded site-specific modification—demonstrate that photocatalytic ketyl radical chemistry provides a robust and versatile platform for biomolecular manipulation in living systems. More broadly, they illustrate how physical organic control of radical lifetime and reactivity can transform reactive open-shell intermediates into selective chemical tools for interrogating biomolecules within their native cellular environments.

4 | Summary and Discussion

Visible-light photocatalysis has expanded bioorthogonal chemistry by enabling the controlled generation of carbon-centered radicals under mild conditions. Unlike classical cycloaddition-based reactions, photocatalytic radical chemistry provides access to selective C—C bond formation while offering spatiotemporal control through light activation. The central challenge, however, is not simply radical generation but controlling radical reactivity so that productive bond formation outcompetes the numerous quenching pathways present in biological environments.

This review highlights two complementary strategies for addressing this challenge. Transient alkyl radicals exemplify kinetic control, in which rapid radical generation, highly reactive acceptors, and optimized photocatalytic conditions enable productive capture before competing quenching occurs. This approach has enabled applications ranging from DNA-encoded library synthesis to site-specific DNA modification and protein functionalization. In contrast, stabilized diaryl ketyl radicals illustrate thermodynamic control, in which resonance delocalization and steric protection increase radical persistence and favor selective radical–radical coupling over competing pathways. These examples demonstrate that radical selectivity in biological environments can be rationalized through a small set of interconnected physical-organic parameters.

Among these parameters, radical lifetime (τ) defines the kinetic window for productive reaction, spanning many orders of magnitude from nanoseconds for unstabilized alkyl radicals to microseconds or longer for persistent species [26, 27]. Radical philicity, determined by the electronic environment surrounding the unpaired electron, influences chemoselectivity by favoring reactions with polarity-matched (SOMOphilic) partners [87]. The redox potential of the radical precursor must be appropriately matched to the photocatalyst to enable efficient radical generation under mild conditions, while catalyst identity and excited-state properties further influence the rates and selectivities of downstream reactions [88]. Together, these parameters define the mechanistic space within which radical reactivity can be tuned.

These principles become particularly important in biological environments, where radicals encounter abundant endogenous quenchers, including molecular oxygen, thiols, and other redox-active biomolecules. For short-lived radicals, productive capture must outcompete these competing processes, requiring highly reactive and polarity-matched reaction partners [45, 69]. For persistent radicals, extending τ through resonance stabilization and steric protection can increase the opportunity for productive radical–radical encounters, consistent with the persistent radical effect (PRE) [26, 27]. The resulting design principle is therefore conditional rather than universal: when a transient radical can be intercepted rapidly by a suitable SOMOphilic partner, kinetic trapping is favored; when a sufficiently persistent radical can be generated and selectively coupled, thermodynamic stabilization provides an alternative route to reactivity control.

Together, these strategies provide a mechanistic framework for understanding radical behavior in biological environments. More broadly, they suggest that selective radical bioorthogonal chemistry can be approached by deliberately engineering three interconnected properties—radical lifetime, polarity, and reaction kinetics—rather than by optimizing individual reactions empirically. Extending this framework to additional radical classes and reaction modes will be an important step toward establishing more general principles for controlling open-shell reactivity in biological systems.

5 | Outlook

Visible-light bioorthogonal chemistry has expanded beyond classical photoclick reactions to encompass photocatalytic uncaging, proximity labeling, and radical-mediated C—C bond formation [89–94]. Among these approaches, photocatalytic radical chemistry offers a distinct strategy for direct covalent bond construction through a single-electron transfer and carbon-centered radical intermediates. As discussed throughout this review, the key challenge is not simply generating radicals but controlling their lifetime, reactivity, and selectivity in complex biological environments. Although alkyl and ketyl radicals provide two illustrative cases, the principles of kinetic trapping and thermodynamic stabilization offer a broader framework for engineering open-shell reactivity in bioorthogonal chemistry.

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Future progress will depend on moving from the discovery of individual radical transformations toward the deliberate control of radical properties. In particular, radical lifetime, polarity, and reaction kinetics provide complementary handles for tuning chemoselectivity. Polarity matching between radicals and reaction partners may offer an additional dimension of selectivity beyond conventional kinetic control. Extending these principles to other open-shell intermediates—including heteroatom-centered radicals, nitrogen-centered radicals, polarity-tuned carbon radicals, and other persistent radical systems—could further expand the scope of bioorthogonal radical chemistry.

An important challenge is to establish whether these principles remain predictive in increasingly complex biological settings. Recent photocatalytic radical reactions in cells demonstrate that radical chemistry can operate in biological environments, but many such transformations involve endogenous substrates rather than selective coupling between exogenous partners [35, 39]. Truly bioorthogonal radical reactions therefore remain comparatively scarce, and the relationships between radical properties and biological reactivity are still insufficiently defined. The kinetic-trapping and thermodynamic-stabilization strategies discussed here provide starting points for addressing this gap, but broader validation will require systematic comparisons of radical lifetime, polarity, redox properties, and reaction kinetics across structurally diverse systems. Such studies could establish quantitative relationships between radical properties and productive reactivity in biological environments.

Photocatalyst design will be equally important. Catalysts for biological applications should combine aqueous compatibility, low dark toxicity, efficient single-electron transfer, long-wavelength activation, and minimal nonspecific interactions with biomolecules. Organic dyes, protein-confined photocatalysts, genetically encoded photocatalytic systems, and catalysts coupled to endogenous metabolic processes represent promising directions. Beyond the catalyst itself, engineering the local environment surrounding the photocatalytic center may provide an additional means of controlling radical generation, lifetime, and selectivity.

Several challenges will determine whether radical bioorthogonal chemistry can approach the versatility of classical cycloaddition-based approaches. First, reversible radical transformations under physiological conditions remain rare, limiting the use of radical chemistry for the dynamic manipulation of biomolecules. Second, multiplex orthogonality will require independent control over multiple radical reactions through variables such as wavelength, redox potential, catalyst identity, and radical polarity. Classical bioorthogonal chemistry achieves multiplexing through orthogonal functional-group pairs; for example, the mutual orthogonality of IEDDA and SPAAC has enabled dual- and triple-labeling schemes [8–11]. Radical reactions are more difficult to orthogonalize because selectivity depends simultaneously on the redox potential, radical polarity, lifetime, and catalyst identity. These parameters are not readily decoupled, making multiplex radical chemistry a particularly demanding design problem. Finally, translation from cellular models to intact tissues and living organisms will require coordinated advances in photocatalyst design, light delivery, and biological targeting.

Ultimately, the development of radical bioorthogonal chemistry will depend on establishing general relationships between radical properties and biological reactivity. Rather than expanding the reaction repertoire solely through empirical discovery, future efforts should seek to predict when a given radical will survive, where it will react, and which competing biological pathways will dominate. Such a predictive control would transform photocatalytic radical chemistry from a collection of specialized reactions into a general strategy for manipulating covalent chemistry in living systems, with potential applications in biomolecular engineering, chemical biology, diagnostics, and therapeutics.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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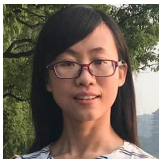

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