# Direct excitation strategy for radical generation in organic synthesis

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Direct excitation strategy for radical generation in organic synthesis

Yuto Sumida,*a and Hirohisa Ohmiya **a,b

Visible-light-mediated chemical processes have been vigorously studied and have led to state-of-the-art synthetic chemistry since they enable the control of radical generation and excited-state-based transformations. The essential process is the generation of a radical species via single electron transfer (SET) between the substrate and catalyst. While photoredox chemistry is an important methodology, these systems essentially require photocatalysts and involve redox processes of the catalyst in the catalytic cycle, which often complicates the reaction. Hence, a seminal contribution in the area of photoredox chemistry is the development of a system free of a photoredox catalyst. In this tutorial review, we summarise the chronology of C-centred radicals, including photoredox chemistry, and shed light on the direct excitation strategy that enables the generation of radical species without exogenous photocatalysts. This strategy provides more straightforward methods, which are energetically efficient in principle, with the potential to open a new window into organic synthesis.

Key learning points

(1) Generation, reactivity, and application of C-centred radicals
(2) Mechanistic overview of radical generation in photoredox chemistry
(3) EDA complex strategy for photoredox catalyst-free radical processes
(4) Direct photo-excitation in radical chemistry

1. Introduction

Carbon-centred radicals are generally highly reactive species derived from unpaired electrons, and provide synthetically useful intermediates in organosynthetic chemistry.1 The thermodynamically or kinetically stabilised C-centred radicals have a long half-life and are persistent radicals, while short-lived C-centred radicals are transient (lifetime less than 10^{-3}s), as defined by Ingold et al.2 Radical reactions in organic synthesis such as Kolbe electrolysis,3 pinacol coupling4 and the Borodin-Hundsdiecker reaction5 have existed since the 19th century. In contrast, the C-centred radical was only unambiguously confirmed by Gomberg's discovery of the persistent trityl radical (half-life of 10^{-2.2}s) in 1900.6 C-centred radicals impart peculiar reactivity and chemoselectivity according to single-electron based chemistry, different from the conventional ionic (two electron) chemical reactions of carbanions, carbocations and carbenes. The chemoselectivity of radical reactions is mainly governed by the bond dissociation energy (BDE) and electronic polarity of the reaction substrates.7 Radical chemistry allows reactions with protic functional groups and solvents such as alcohols, carboxylic acids and water, which generally disturb ionic reactions. Despite their synthetic utility, C-centred radicals have not been a key player in synthetic chemistry, with few exceptions such as the Birch reduction8 and Kharasch reaction (atom transfer radical addition, ATRA).9 This is likely because synthetic chemists have had no standard generation method of transient C-centred radicals, making it challenging to design rational synthesis to apply alkyl radicals to molecular construction. The recent remarkable progress in photoredox chemistry is based on the ability to generate C-centred radicals under exceptionally mild conditions using photoredox catalysts with visible light. Stimulated by this, electron donor-acceptor (EDA) complex chemistry, which has been studied in theoretical chemistry and physical chemistry for decades, has been re-investigated from the viewpoint of organic synthesis. Additionally, direct photo-excitation, in which the radical source itself is excited to harness the acquired energy of light for bond cleavage to generate radicals, has emerged in recent years. This tutorial review will discuss the generation of alkyl radicals based on classical methods and photoredox catalysis. It will also focus on radical generation demanding only visible light, which involves EDA complexes and direct photo-excitation strategies (Figure 1).

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2. Establishment of Radical Chemistry

Radical chemistry evolved when van der Kerk reported a method for generating alkyl radicals using stannane.10 Around the same time, Walling reported radical polar effects11 and Barton nitrite photolysis to enhance steroid chemistry.12 As typical radical additions, the Giese13 and Minisci14 reactions are synthetically useful and thus still applied to the synthesis of natural products, pharmaceuticals, and polymers. In parallel with alkyl radical-based transformations, numerous pioneering works for alkyl radical generation have built systematical knowledge of radical chemistry (Figure 2). Although tin hydride promoting alkyl radical generation is an excellent method,8a,15 the residual highly toxic tin compounds are concerning in the synthesis of pharmaceuticals and other applications, which called for improvement of methodologies for radical chemistry. In 1967, Davies reported that the reaction of oxygen with an organoboron compound results in homolysis and alkyl radical formation, which was later developed into a catalytic amount (as an initiator),17 making it a more versatile method. A xanthate-based process, the Barton-McCombie reaction, enabled alkyl radical generation using an alcohol as a foothold.18 Similarly, Barton reported alkyl radical formation by decarboxylation from a redox active ester, a so-called Barton ester, derived from N-hydroxythiopyridone and carboxylic acid thermally or by Sn or UV irradiation.19 The generation of alkyl radicals is closely connected to polymer chemistry. Sawamoto12a and Matyjaszewski20b independently reported ATRP on the basis of the Kharasch reaction, while xanthate chemistry led to the development of reversible addition-fragmentation chain-transfer (RAFT) polymerisation21 based on the addition/fragmentation of alkyl radicals, both of which are still under active study as living radical polymerisations that realise a narrow molecular weight distribution.

In 1988, Okada and Oda reported visible-light-mediated alkyl radical generation from N-(acyloxy)phthalimide 1a, 1,6-Bis(dimethylamino)pyrene promoted photosensitised electron transfer (ET)22a to form a reduced intermediate I. Immediately afterwards, they developed a catalytic system using Ru(bpy)_3Cl_2 complex and 1-benzyl-1,4-dihydronicotinamide (BNAH) as a single-electron reductant,22b affording Giese addition product 2, which has become a cornerstone for the ensuing fruitfulness of photoredox chemistry in recent years (Scheme 1).

3. The Rise of Photoredox Chemistry

As countless radical reactions and generation methods for alkyl radicals have been developed over the past half-century, radical chemistry has gradually evolved with the accumulation of knowledge and improvement of versatility. However, radical chemistry has held a subordinate position to ionic chemistry because it assumes that radical species are difficult to control and the reactions are challenging to predict. In the 1980s, pioneering works in photoredox chemistry from Kellogg,23a Pac,24b Fukuzumi and Tanaka,23c in addition to Okada and Oda (vide supra), were reported. Nevertheless, visible-light radical-based chemistry was still far from the limelight, probably because the visible-light reaction setup was
less common in organic synthesis, in addition to the notorious nature of radicals. After two decades, Yoon, MacMillan, and Stephenson independently described three types of photoredox chemistry,24 which marked the beginning of modern photoredox chemistry. The basic principle of photoredox chemistry is that a photoredox catalyst excited under irradiation of visible light induces a single electron transfer (SET) to either an acceptor or a donor. The SET causes the catalyst to lose an electron (an oxidative quenching cycle) or to acquire an electron from the substrate (reductive quenching cycle). The catalyst then undergoes the exact opposite process, resulting in a SET with another substrate (often the original substrate), thus completing the catalytic cycle (Figure 3A).25 The process is driven by the conversion of visible light into chemical energy and requires neither strong bases nor acids, producing alkyl radicals under unprecedentedly mild conditions at ambient room temperature. The SET process between catalyst-to-substrate or substrate-to-substrate can be easily predicted from the redox potential of the excited or ground state, allowing precise catalytic reaction design. In addition to Ru(bpy)₃Cl₂ complexes, many Ru and Ir complexes have been synthesised as photoredox catalysts, and these are currently the most widely used in this field.26 More recently, the development of organophotoredox catalysts has also progressed energetically. The design and synthesis of novel organophotoredox catalysts have advanced in parallel with the application of well-known organic fluorescent dyes as photoredox catalysts27 (Figure 3B). Additionally, photoredox chemistry has incorporated various radical precursors, including oxidative quenching-type22–27 (e.g., redox active esters and Katritzky pyridinium salts) or reductive quenching-type28 (e.g., silicates, dihdropyridines, and borates). Depending on the redox potential of each radical precursor, oxidative or reductive quenching can occur to produce alkyl radicals. Based on the intrinsic redox potential of each photoredox catalyst and radical precursor, chemists can design the desired catalytic reaction (Figure 3C).

Hydrogen atom transfer (HAT) and energy transfer (EnT) separate from the SET event have also been recognised as significant processes in photo-mediated synthetic chemistry. HAT provides a potent approach. Similar to other radical processes, HAT is profoundly affected by BDE. Thus, HAT of tertiary C(sp³)–H bonds occurs preferentially to that of secondary or primary C(sp³)–H bonds, enabling late-stage C–H functionalisation that is difficult in two-electron chemistry.28 The EnT process can also occur via the excited state of the photoredox catalyst to the ground state of the substrate.24a,30 While this photophysical process is still underdeveloped, it allows unique and thermally challenging transformations.

**Figure 3.** A. General catalytic mechanism of photoredox catalysis. B. Widely used photoredox catalysts and their photophysical properties. C. Widely used radical precursors in photoredox catalysis and their redox potentials.

### 4. EDA complexes in synthetic photochemistry

An electron-donating molecule with an electron-accepting molecule can be assembled to form a charge-transfer (CT) complex in the ground state. The produced molecular assembly is described as an electron donor-acceptor (EDA) complex, which often absorbs visible light, even when the two original molecules can absorb only in the UV region. Synthetic strategies based on EDA complexes have emerged as an attractive approach in recent years because the strategy enables inherent synthetic photochemistry without an exogenous photoredox catalyst.31 Although the photophysical
properties of EDA complexes have been extensively explored since the 1950s, their application to chemical synthesis has been limited. In 1949, Benesi and Hildebrand reported spectroscopic changes due to iodihe interaction with aromatic hydrocarbons.32 Subsequently, Mulliken proposed a theory for the formation of EDA complexes in quantum mechanics.33 Stable charge-transfer complexes formed in the ground state generally have an immense contribution from the non-bonded structure and a small contribution from the charge-transfer structure. In contrast, photo-excitation of EDA complexes leads to polarised charge-transfer states that cannot be reached thermally, from which the SET process affords a radical ion pair (Scheme 2A). Alternatively, Leonhart and Weller described that while no charge-transfer interaction is observed in the ground state, an EDA complex called an exciplex34 can be formed in the excited state of a donor or acceptor (Scheme 2B). Both processes produce radical species that can participate in diverse reactions. However, even though the SET event occurs successfully and forms a radical ion pair from an EDA complex, back electron transfer (BET) often hampers the generation of radical species as an ideal path and, consequently, the application of EDA complexes to organic synthesis.

Scheme 2. Schematic pathway of EDA complex (A) and exciplex (B).

This restriction derived from BET was alleviated by using a leaving group (LG)-installed acceptor. Elimination of the leaving group competes with BET, preventing the return to the original EDA complex. If the efficiency of the elimination, an irreversible process, is sufficiently high, the equilibrium is broken to generate the radical species, which is then involved in chemical synthesis (Scheme 3). Several groups conducted pioneering works on this approach of an EDA complex formed from a donor substrate with LG-installed acceptors, however, there was no distinct experimental evidence of the EDA complex.

Scheme 3. A radical generation strategy based on LG-installed EDA complex.

These pioneering transformations demonstrated the potential of the EDA complex as an efficient method of radical formation and a unique protocol in chemical synthesis. Nonetheless, the EDA complex strategy received little fanfare from organic chemists, as in the case of photoredox chemistry in the 1980s, for similar reasons. In 2013, Melchiorre and coworkers reignited the EDA complex strategy.35 They formed a coloured EDA complex from an electron-deficient benzyl bromide 4 with a chiral enamine generated in situ from aldehyde 3 with an amine catalyst. This chiral EDA complex A can be excited under visible-light irradiation, and SET occurs to form a radical ion pair A. Elimination of the leaving group, Br anion, from the acceptor affords the alkyl radical followed by eventual radical–radical coupling to give product 5 (Scheme 4). In the same period, Tobisu and Chatani discovered another coloured EDA complex formed from diaryliodonium salt 6 with pyrrole 7, in which the absorption reached the visible-light region.36 Photoirradiation of the EDA complex B facilitated SET to yield an aryl radical with the liberation of iodobenzene and a pyrrole radical cation via the radical ion pair B. The recombination of the aryl radical and the pyrrole radical cation provided a cationic adduct, which led to the product 8 after deprotonation (Scheme 5).

Scheme 4. Enantioselective catalytic α-alkylation of aldehydes.

Scheme 5. EDA complex-mediated arylation of heteroarenes using diaryliodonium salts.

Research on the EDA complex has accelerated and it has now been recognised as a relevant strategy in photoredox chemistry, with the above-mentioned reports as triggers. A wide variety of EDA complexes, including enzyme-based formation thereof, have been described in association with corresponding mechanistic rationales. The catalytic EDA complex strategy is also an attractive option due to increased reports related to the various methodologies based on EDA complexes. The general plan for such a catalytic system is that the reaction of a catalyst and a substrate having a foothold, such as
a carbonyl group, provides the electron donor to facilitate the formation of the EDA complex, as exemplified by Melchiorre et al. In this context, the Shang and Fu group found that the combination of triphenylphosphine (PPh₃) and an alkali iodide (MI) works as a catalytic electron donor to give an EDA complex with an electron acceptor (Scheme 6).³⁷ Mixing PPh₃ and NaI with redox active ester 1 as an acceptor generates a visible-light absorbable EDA complex C from the three components. The EDA complex gives an alkyl radical and a persistent radical PPh₃⁺ via intermediate II under photoirradiation, affording the product 10. The reaction without a radical trap substrate 9 resulted in simple iodination of the generated alkyl radical to form product 11. This protocol does not require interaction with a radical trap substrate nor a foothold for catalytic activation. Enantioselective Minisci reaction of lepined with 1b was also feasible with the addition of a chiral phosphoric acid catalyst (PA). Moreover, the combination of PPh₃ and NaI activated not only the redox active ester, but the Katritzky salt 13 and Togni reagent 14, to obtain the products 15 and 16, which makes the strategy more versatile. An N-heterocyclic carbene (NHC) worked similarly to form ternary EDA complex D. The Wang and Chen group reported that iodination of N-alkenoxyypyridinium salt 17 proceeded in the presence of the NHC catalyst via generation of an α-carbonyl radical to afford the iodinated product 18 (Scheme 6).

Bosque and Bach reported another catalytic EDA complex formation without the interaction of a radical trap substrate (Scheme 7).³⁸ 3-Acetoxyquinuclidine (q-OAc) catalytically activates tetrachloro-N-phthalimide (NCIPth) redox active ester 19 to form the EDA complex. Interestingly, while the bright yellow solution caused by the coloured EDA complex E was observed from q-OAc with 19, a colourless solution was obtained with the corresponding N-phthalimide. The main reason for this difference is that the SET reduction potential of 19 (E_red = −0.70 to −0.54 V vs SCE) is much higher compared to the N-phthalimide redox ester (E_red = −1.24 to −1.38 V vs SCE). Photoirradiation promoted the formation of radical ion pair E involving the quinuclidyl radical cation (q-OAc⁺⁺) from the EDA complex E. The α-amino radical was further oxidised by q-OAc⁺⁺ to give iminium cation 21 with the regeneration of the catalyst q-OAc and the eventual amidation of 21 to afford the product 20.

Scheme 6. PPh₃ or NHC-catalysed radical generation based on catalytic formation of a three-component EDA complex.

Scheme 7. Catalytic formation of EDA complex-mediated decarboxylative α-amidation using quinuclidine as a catalyst.
In 2020, Stephenson developed a catalytic EDA complex strategy using \( \pi \)-stacking interactions (Scheme 8).\(^{39}\) The reaction of 2-MeO-naphthalene (2-MeONp) as a catalyst with \( N \)-(trifluoroacetoxyl)-pyridinium as an electron acceptor, generated by treating pyridine \( N \)-oxide 22 with trifluoroacetic acid anhydride (TFAA), results in a coloured EDA complex F, SET of which gives a radical ion pair F. The decarboxylation affords a CF\(_3\) radical and the 2-MeONp radical cation. The addition of the CF\(_3\) radical to heteroarene 23 then occurs followed by the SET oxidation of the CF\(_3\)-adduct with the 2-MeONp radical cation to yield the product 24 with regeneration of the catalyst.

Nagao and Ohmiya developed an organophotoredox-catalysed decarboxylative etherification (Scheme 9).\(^{40}\) In their catalytic system, the organophotoredox catalyst, a phenothiazine (PTH), organises the EDA complex G with redox active ester 1c. The radical ion pair G derived from the EDA complex G via SET under photoirradiation gave the alkyl radical and radical cation PTH\(^{**}\). Recombination of the alkyl radical with PTH\(^{**}\) provided cationic species IV followed by nucleophilic attack of alcohol 25 to afford ether 26.

As a potent strategy with an EDA complex, an enzymatic system has also been advanced based on directed evolution.\(^{41}\) The proximity effect in the active site of a biological cofactor has expanded the catalytic and enantioselective radical processes.

Scheme 8. A catalytic EDA complex strategy using \( \pi \)-stacking interactions.

5. Direct Photo-Excitation of Reaction Substrates

While the EDA complex strategy is a splendid methodology and has contributed considerably to the recent growth of photosynthetic chemistry, the methodology for direct excitation of a reaction substrate under visible-light irradiation is the most straightforward to generate an alkyl radical, since it does not require a precious photoredox catalyst in addition to the formation of an EDA complex. Classically, vitamin B12 is the earliest and most studied molecule that can be directly excited under visible light to generate alkyl radicals via homolytic cleavage of the carbon-cobalt bond (Scheme 10A).\(^{42}\)

Vitamin B12 plays a crucial role as a coenzyme involved in many biological events. The family containing Co-C bonds includes cyano, methyl, and 5'-deoxyadenosyl cobalamins (27a–c). Among them, the relatively high reactive C–Co bond contained in 27b and c can serve as the radical source in enzymatic reactions,\(^{42b}\) and this radical formation is facilitated by photoirradiation. A vast number of papers have been reported on photo-excited cobalamins over a broad field, including structural characterisation, reactivity, and applications to organic synthesis, polymer synthesis, and caged probes. Furthermore, based on cobalamin as a structural model, organocobalt complexes directly excited by visible light have been reported (Scheme 10B). For example, the reaction of (pyridine)bis(dimethylglyoximato)cobalt(III), \( \text{Co(dmgH)}_2\text{py} \),\(^{41c}\) bearing an alkyl group 28 with olefin 29 gave a Mizorogi-Heck type product 30 under visible-light irradiation (Scheme 10C).\(^{42d}\) The direct photo-excitation of \( \text{R-Co(dmgH)}_2\text{py} \) 28 initiates the reaction, causing homolytic C–Co cleavage to form a transient carbon-centred radical with a persistent Co(II) complex. The reverse reaction between the generated alkyl radical and the Co(II) complex to reproduce the alkyl Co(III) complex also occurs smoothly, due to the persistent radical effect (PRE) derived from the Co(II) complex. The selective radical addition to olefin 29 proceeds prior to homocoupling. The recombination of benzyl radical V with Co(III) forms benzyl Co(III)
complex VI as an intermediate, allowing β-hydride elimination to afford the product 30. The most fundamental requirement to trigger photochemistry is that only the molecule, intermediate, or catalyst absorbing the light can initiate the photochemical change, according to the Grotthuss-Draper law. In direct photo-excitation, the reaction substrate or in situ generated intermediate absorbs light by itself and the acquired energy is involved in bond cleavage. Thus, the bond cleavage results in photo-induced generation of the radical species (Figure 4).

**Figure 4.** Jablonski diagram of bond cleavage following direct excitation.

An as early example of non-transition metal, N-acyloxy-pyridine-2-thiones, Barton ester 31 gave 2-pyridyl sulfide 32 via decarboxylative rearrangement under the irradiation of a tungsten lamp (Scheme 11).\(^{19,43}\) The photo-excited Barton ester undergoes homolytic N–O bond cleavage followed by decarboxylation to generate the corresponding alkyl radical, which is recombined with thiopyridyl radical VII to afford the product. In addition to the simple synthesis of sulfide 32, the system has been applied to various radical chemistries, such as vicinal alkyl thiolation of an olefin to form 33,\(^{43a}\) halogenation to form 34,\(^{43b}\) and Minisci reaction to form 35.\(^{43c}\)

**Scheme 10.** Direct photo-excitation of bioinspired cobalt-based complexes.

**Scheme 11.** Alkyl radical generation from direct photo-excitation of Barton ester.

A photo-triggered alkyl radical generation from an alkylborate was described by Schuster and coworkers, based on C–B bond cleavage of the borate following SET oxidation.\(^{44}\) They found that the reaction of 1,4-dicyanonaphthalene 36 with alkyl(triaryl)borate 37 resulted in decyanoalkylation under 350 nm irradiation to form regioisomeric mixture 38. The products indicated that the photoirradiation activated 36, the excited state of which was reduced by SET with the alkylborate to generate the alkyl radical (Scheme 12A).\(^{44a}\) In this context, Schuster proposed that by exchanging the alkylborate...
counteraction with a visible-light absorbable unit, it could be directly excited to generate the corresponding alkyl radical. Indeed, when the butylborate 39 was prepared by exchanging the counteraction with indocarboxyanine (Cy+), direct excitation of the borate occurred under 430 nm laser pulse irradiation. The excited Cy+BuBPh3 was converted to cyanine radical cation Cy+ and boranyl radical anion VIII via an intra-ion pair ET (Scheme 12).44b The fragmentation of the boranyl radical anion afforded the butyl radical with triphenylborane, which could initiate polymerisation in the presence of an appropriate monomer.

Direct excitation of rationally designed amides inducing N–X homolytic cleavage enables hydrogen atom transfer (HAT). Alexanian prepared a series of N-halo or N-xanthylamides 40, which could be directly excited under photoirradiation.45a–c Homolytic cleavage of the excited amide gave amidy radical IX, which induced intermolecular HAT with an aliphatic C–H bond. Consequently, C–H bromination, chlorination, or xanthylation progressed by the reaction of an alkyl radical with heteroatom-centred radical X• (Scheme 13A). Additionally, the direct excitation of N-dithiocarbamate amide 42 converted it to alkyl dithiocarbamate product 43 via Hofmann–Löffler–Freytag type transformation.45d Photo-excited amide 42 similarly produced amidy radical X with xanthyl radical XI, which promoted intramolecular 1,5-HAT, enabling site-specific functionalisation of an aliphatic C–H bond (Scheme 13B).

Despite 4-alkyl-1,4-dihydropyridines (alkyl-DHPs) being recognised as reductive radical sources for photoredox catalysis (Figure 3C), Melchiorre and coworkers found that alkyl-DHPs can be directly excited under visible-light irradiation to generate the corresponding alkyl radicals.45e Direct excitation of Bn-DHP 44a in MeCN under irradiation of HP single LED (405 nm) resulted in the formation of toluene 45 (85%), 1,2-diphenylethane 46 (7%), and the quantitative pyridine derivative 47 from oxidation of DHP radical intermediate XII (Scheme 14A). The observation of 1,2-diphenylethane 46, albeit in low yield, indicated the intervention of a benzyl radical. Although this protocol requires a high-powered light source, the Ni-catalysed cross-coupling of aryl bromide 48 with alkyl-DHP 44 proceeds based on single electron transmetalation45b without an external photoredox catalyst (Scheme 14B). The photo-excited alkyl-DHP can work as a strong reductant (E(44+/44−) ≈ −1.6 V vs. Ag/Ag+ in CH3CN) and thus, active Ni0 catalyst XIII would be produced via SET reduction (Ep(Ni0/NiII) = −1.2 V vs. SCE in DMF) by the excited state of alkyl-DHP 44, giving the alkyl radical. The generated alkyl radical leads to alkyl Ni0 complex XIV followed by oxidative addition of aryl bromide 48 to form XV. The reductive elimination from XV provides the cross-coupling product with Ni0-Br complex XVI, the SET reduction of which regenerates the active Ni0 catalyst XIII and alkyl radical. This pioneering work demonstrated that the direct photo-excitation system allows construction of a surrogate reaction system for metallaphotoredox catalysis without the photoredox catalyst.

Scheme 12. A. Radical generation from single electron oxidation of alkylborate. B. Exchanging the borate counteraction enabled direct excitation under visible-light irradiation.

Scheme 13. A. HAT reagents generated from direct photo-excitation of N-halo or N-xanthylamide. B. Intramolecular 1,5-HAT via direct excitation of N-xanthylamide.
Melchiorre and coworkers applied their methodology to several transformations (Scheme 15).\textsuperscript{47} Enantioselective acyl-alkyl cross-coupling proceeded using a secondary benzyl group-substituted DHP \textsuperscript{44b} with alkyl carboxylic anhydride \textsuperscript{50} under visible-light irradiation in the presence of a catalytic amount of Ni complex with bis(oxazoline) as a chiral ligand to provide the enantio-enriched product \textsuperscript{51} (Scheme 15A).\textsuperscript{46a} Subsequently, Giese addition based on the direct excitation of acyl-DHP \textsuperscript{44c} has been reported, which was enhanced by an electron mediator. Ni(bpy)\textsubscript{4}BF\textsubscript{4} worked as the catalytic electron mediator in this system. While the Ni complex minimally absorbs visible light (405 nm), it can be reduced by photo-excited alkyl-DHP (E\textsubscript{h}(NiII/NiI) = −1.35 V vs. SCE) (Scheme 15B).\textsuperscript{47b} They also found that acyl-DHPs are directly excited at 460 nm, which is a longer wavelength than that of alkyl-DHPs. When applying the acyl-DHP \textsuperscript{44d} to the reaction with isocyanoline \textsuperscript{54} under visible-light irradiation at 460 nm, the unusual Minisci reaction proceeds to give the hydroxyalkylated product \textsuperscript{55} (Scheme 15C).\textsuperscript{47h} The reaction of protonated isocyanoline with the acyl radical generated from directly photo-excited acyl-DHP afforded the radical cation \textsuperscript{XVII}, followed by deprotonation, converting it to the relatively stable α-amino radical \textsuperscript{XVIII}. A spin centre shift then occurred to form \textsuperscript{XIX} driven by rearomatisation. SET reduction of \textsuperscript{XIX} by the DHP radical (DHP\textsuperscript{+}) gave the corresponding pyridinium cation pyr-H\textsuperscript{+} with anion \textsuperscript{XX}, of which proton transfer and deprotonation led to the final product \textsuperscript{55}. 

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The direct excitation of acyl- or alkyl-DHPs enabling radical generation under visible-light irradiation can apply to a Co-catalysed enantioselective Giese addition or a late-stage modification of an oligopeptide via histidine-selective Minisci reaction (Scheme 16). The Lu and Xiao group reported that the octahedral Co\textsuperscript{III} complex coordinated by chiral N4 ligand catalysed the radical addition of bleomycin (Scheme 16B).\textsuperscript{44d} Although this transformation can be carried out under conditions using a photoredox catalyst or stoichiometric oxidant for simple amino acids with protecting groups, the direct excitation strategy is more straightforward, and suitable for targeting oligopeptides bearing many functional groups, such as saralasin and bleomycin (Scheme 16B).
Direct photo-excitation of alkyl borates, which enables the universal generation of alkyl radicals, has been developed. Sumida, Hosoya and Ohmiya described the direct photo-excitation of designed boron molecule 58-derivable alkylborate complex 59 to generate tertiary, secondary, and primary alkyl radicals, and initially applied them to the Giese addition (Scheme 17). The boracene 58, 8,9-dixao-8a-borabenzof[fg] tetracene, has a highly planar and robust structure based on the benzof[fg]tetracene skeleton partially replaced by O–B–O bonds. The series of borates 59 prepared from boracene with alkyl Li or Grignard reagents shows substantial air and moisture stabilities. The photo-excited borate provides an exceptionally strong red-shift (\(E_n = \sim 2.2 \text{ eV} \) vs. SCE in MeCN). Thus, the borate-based direct excitation strategy applies to Ni-catalysed carbon–carbon bond-forming reactions. When the reaction of alkylborate with aryl halides was carried out in the presence of Ni catalyst under visible-light irradiation, the system resulted in the cross-coupling products 61a–c (Scheme 17B). The protocol permitted the cross-coupling with electron-rich aryl bromides, which is significant to apply under Ni/Ir photoredox cocatalysis. The generation of a methyl radical was achieved to obtain the methyl group-installed products, which is significant in medical science as the ‘magic methyl effect’. The three-component vicinal alkylarylation of olefin 62 was also accomplished via a radical relay pathway based on the direct photo-excitation of alkylborate 59a.
under visible-light irradiation. The hypervalent iodine 67, which has obvious absorption at less than 300 nm, was directly excited under 450 nm to generate an azido radical. Subsequent regioselective HAT of 68 occurred, followed by azidation to give the product 69 (Scheme 19).

6. Conclusions

Photoredox chemistry allows the conversion of visible light into chemical energy, enabling the generation of carbon-centred radicals under exceptionally mild conditions. In particular, metallaphotoredox chemistry, in combination with transition metals, is a methodology that has revolutionised modern organic synthesis. Although EDA complex chemistry has been studied for a long time, its significance has been reaffirmed with the rise of photoredox chemistry. The direct excitation strategy is a cutting-edge system in synthetic photochemistry, realising the most straightforward transformations. This approach has more to offer than a photoredox catalyst-free system. It provides energetically efficient chemical reactions due to direct electron transfer between substrates. The protocol operates via a different reaction pathway from chemistry in the ground-state, can couple with transition metal catalysis, and thus has the potential to open another door of photoredox chemistry.

Conflicts of interest

There are no conflicts to declare.

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