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TUTORIAL REVIEW

Direct excitation strategy for radical generation in organic synthesis

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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 coupling[4] and the Borodin-Hundsdiecker reaction[5] 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 reduction[8] 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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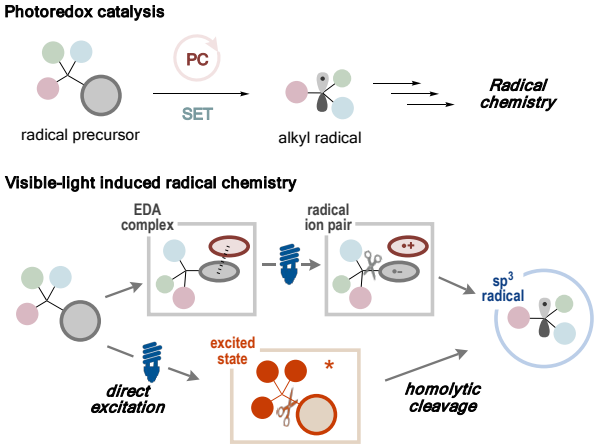


Figure 1. General scheme of photoredox catalysis, EDA complex, and direct photo-excitation.

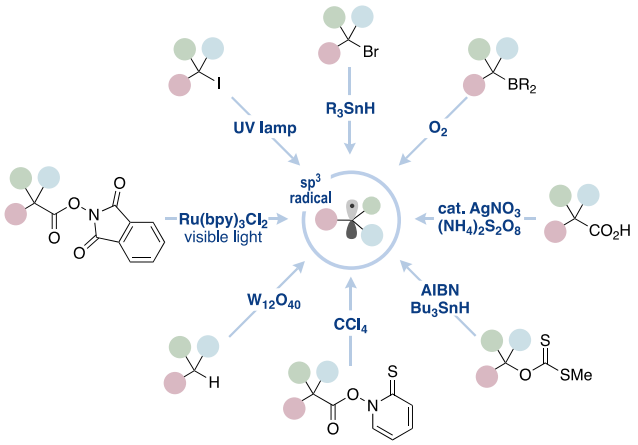
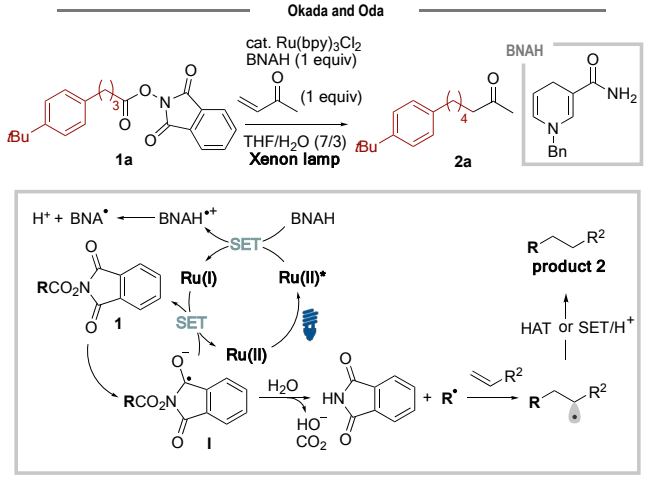


Figure 2. Selected conventional alkyl radical generation methods.

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 effects[11] and Barton nitrite photolysis to enhance steroid chemistry.[12] As typical radical additions, the Giese[13] and Minisci[14] 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,[16] 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. Sawamoto[20a] and Matyjaszewski[20b] independently reported ATRP on the basis of the Kharasch reaction, while xanthate chemistry led to the development of reversible addition-fragmentation chain-transfer (RAFT) polymerisation[21] 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).



Scheme 1. Ru-catalysed decarboxylative alkyl radical generation.

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,[23b] 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 $Ru(bpy)_3Cl_2$ 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 catalysts[26f] (Figure 3B). Additionally, photoredox chemistry has incorporated various radical precursors, including oxidative quenching-type[22,27] (e.g., redox active esters and Katritzky pyridinium salts) or reductive quenching-type[28] (e.g., silicates, dihydropyridines, 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 $C(sp^3)$–H bonds occurs preferentially to that of secondary or primary $C(sp^3)$–H bonds, enabling late-stage C–H functionalisation that is difficult in two-electron chemistry.[29] 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.

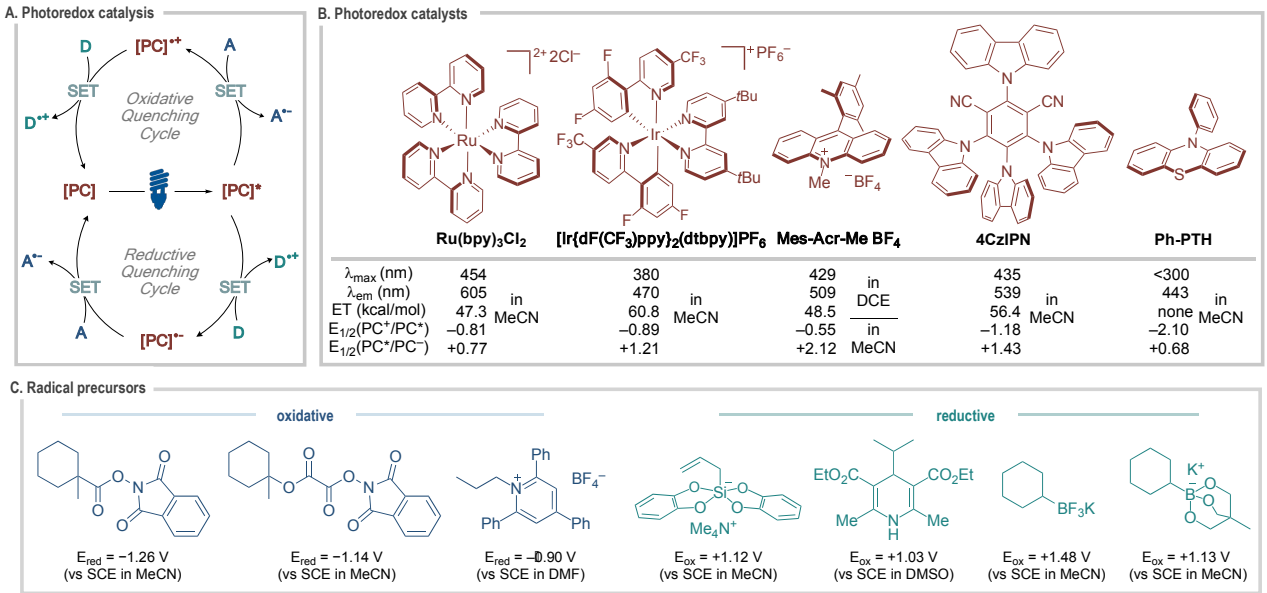
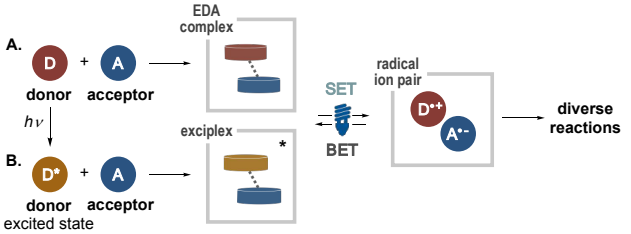


Figure 3. **A**. General catalytic mechanism of photoredox catalysis. **B**. Widely used photoredox catalysts and their photophysical properties. **C.** Widely used radical precursors in photoredox catalysis and their redox potentials.

4. EDA complexes in synthetic photochemistry

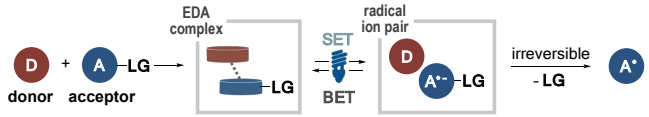
An electron-donating molecule with an electron-accepting molecule can be assembled to form a charge-transfer (CT) complex in the ground state. The produced molecular assembly is described as an electron donor-acceptor (EDA) complex, which often absorbs visible light, even when the two original molecules 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 Hildebland reported spectroscopic changes due to iodine 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 exciplex[34] 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.



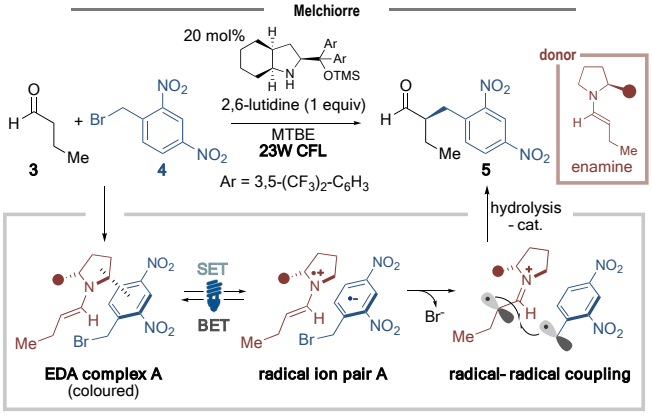
Scheme 2. Schematic pathway of EDA complex (A) and exciplex (B).

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.

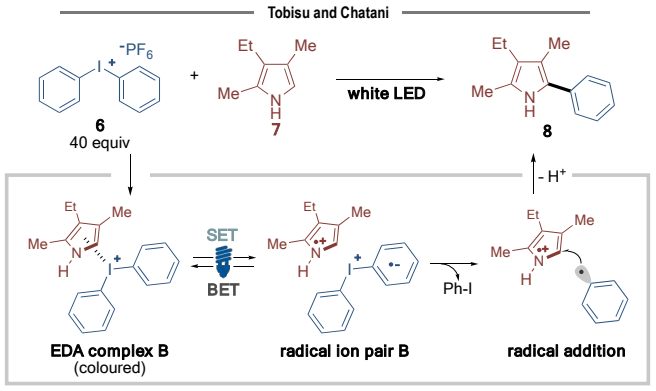


Scheme 3. A radical generation strategy based on LG-installed EDA complex.

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, based on asymmetric organocatalysis enabling α-alkylation of aldehydes.[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.

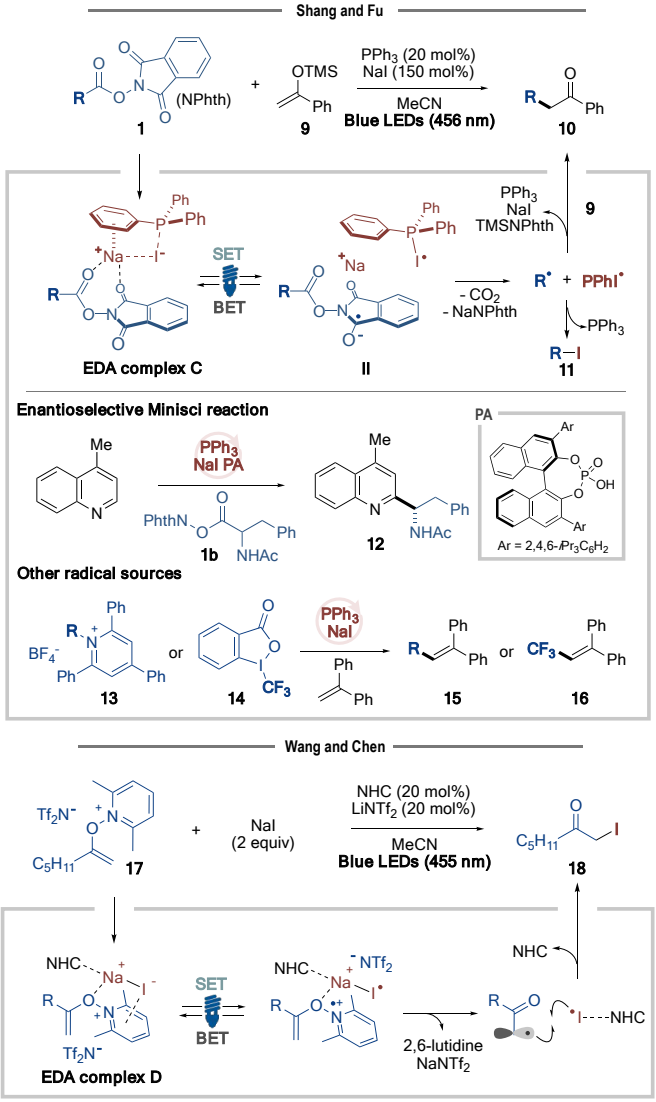


Scheme 5. EDA complex-mediated arylation of heteroarenes using diaryliodonium salts.

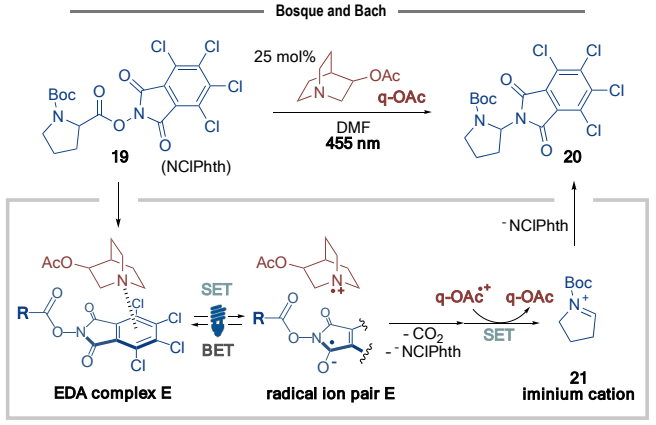
Research on the EDA complex has accelerated and it has now been recognised as a relevant strategy in photoredox chemistry, with the above-mentioned reports as triggers. A wide variety of EDA complexes, including enzyme-based formation thereof, have been described in association with corresponding mechanistic 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 (PPh_3) and an alkali iodide (MI) works as a catalytic electron donor to give an EDA complex with an electron acceptor (Scheme 6).[37] Mixing PPh_3 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 $PPh_3I^{\bullet}$ 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 lepidine with **1b** was also feasible with the addition of a chiral phosphoric acid catalyst (**PA**). Moreover, the combination of PPh_3 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*-alkenoxypyridinium 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 (NClPhth) 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**$^{\bullet+}$) from the EDA complex **E**. The α-amino radical was further oxidised by **q-OAc**$^{\bullet+}$ 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. PPh_3 or NHC-catalysed radical generation based on catalytic formation of a three-component EDA complex.

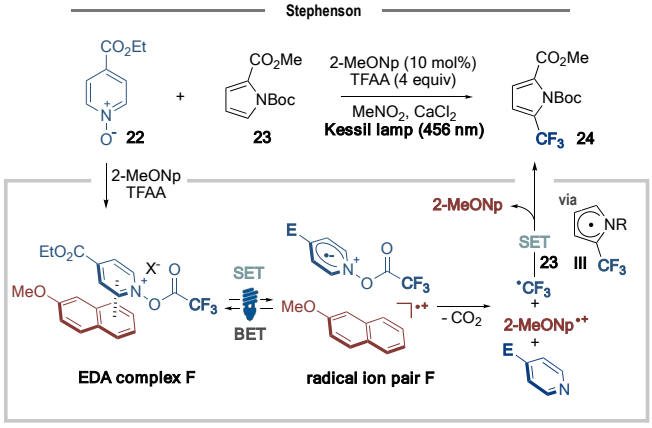


Scheme 7. Catalytic formation of EDA complex-mediated decarboxylative α-amidation using quinuclidine as a catalyst.

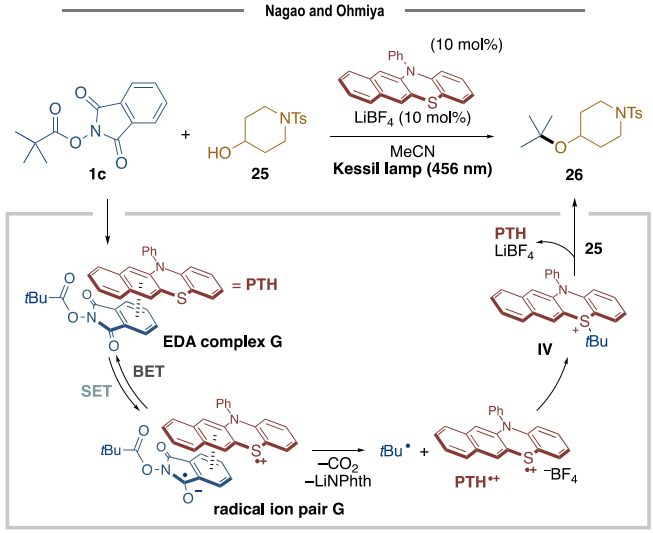
In 2020, Stephenson developed a catalytic EDA complex strategy using π-stacking interactions (Scheme 8).[39] The reaction of 2-MeO-naphthalene (2-MeONp) as a catalyst with *N*-(trifluoroacetoxy)-pyridinium as an electron acceptor, generated by treating pyridine *N*-oxide **22** with trifluoroacetic acid 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**$^{\bullet+}$. Recombination of the alkyl radical with **PTH**$^{\bullet+}$ 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 π-stacking interactions.



Scheme 9. Organophotoredox catalyst enabling radical polar crossover via π-stacking-driven formation of an EDA complex.

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), **Co(dmgH)$_2$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 **R-Co(dmgH)$_2$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(II) 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).

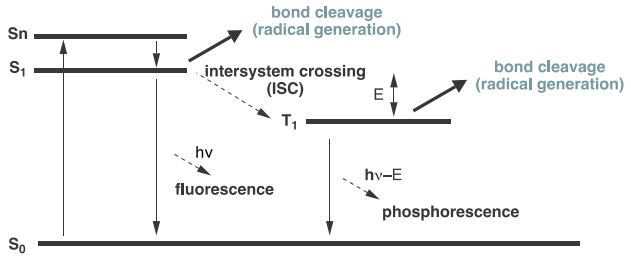
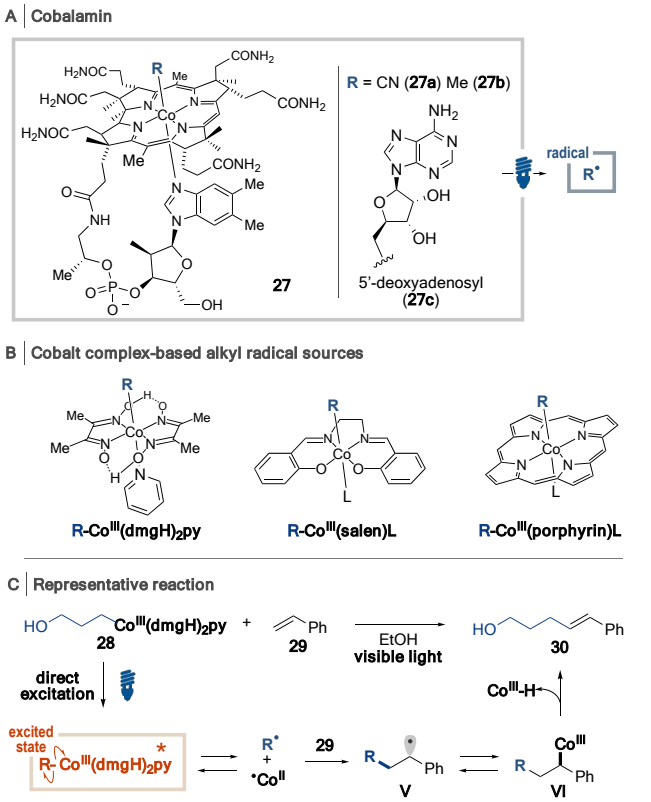
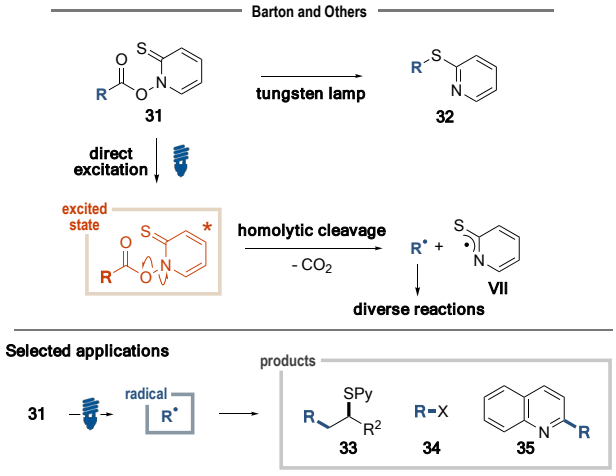


Figure 4. Jablonski diagram of bond cleavage following direct excitation.

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.

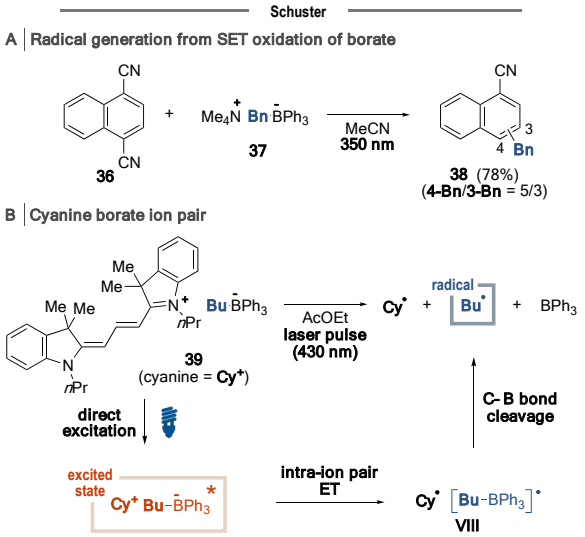


Scheme 11. Alkyl radical generation from direct photo-excitation of Barton ester.

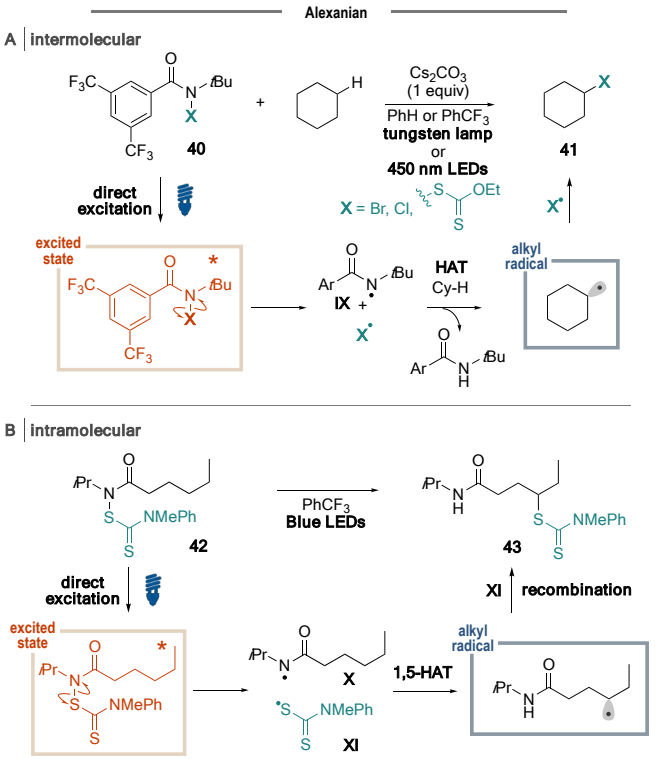
A photo-triggered alkyl radical generation from an alkylborate was described by Schuster and coworkers, based on C–B bond cleavage of the borate following SET oxidation.[44] They found that the reaction of 1,4-dicyanonaphthalene **36** with alkyl(triaryl)borate **37** resulted in decyanoalkylation under 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

countercation 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 countercation with indocarbocyanine (**Cy**$^+$), direct excitation of the borate occurred under 430 nm laser pulse irradiation. The excited **Cy**$^+$**[BuBPh$_3$]**$^-$ was converted to cyanine radical cation **Cy**$^\bullet$ and boranyl radical anion **VIII** via an intra-ion pair ET (Scheme 12B).[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 amidyl 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**$^\bullet$ (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 amidyl radical **X** with xanthyl radical **XI**, which promoted intramolecular 1,5-HAT, enabling site-specific functionalisation of an aliphatic C–H bond (Scheme 13B).

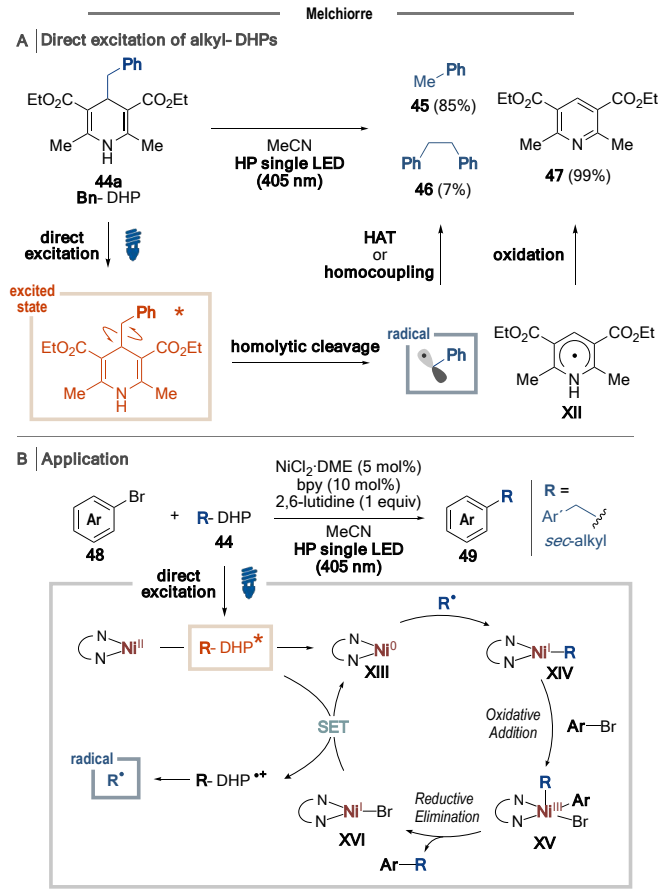


Scheme 12. **A**. Radical generation from single electron oxidation of alkylborate. **B**. Exchanging the borate countercation enabled direct excitation under visible-light irradiation.



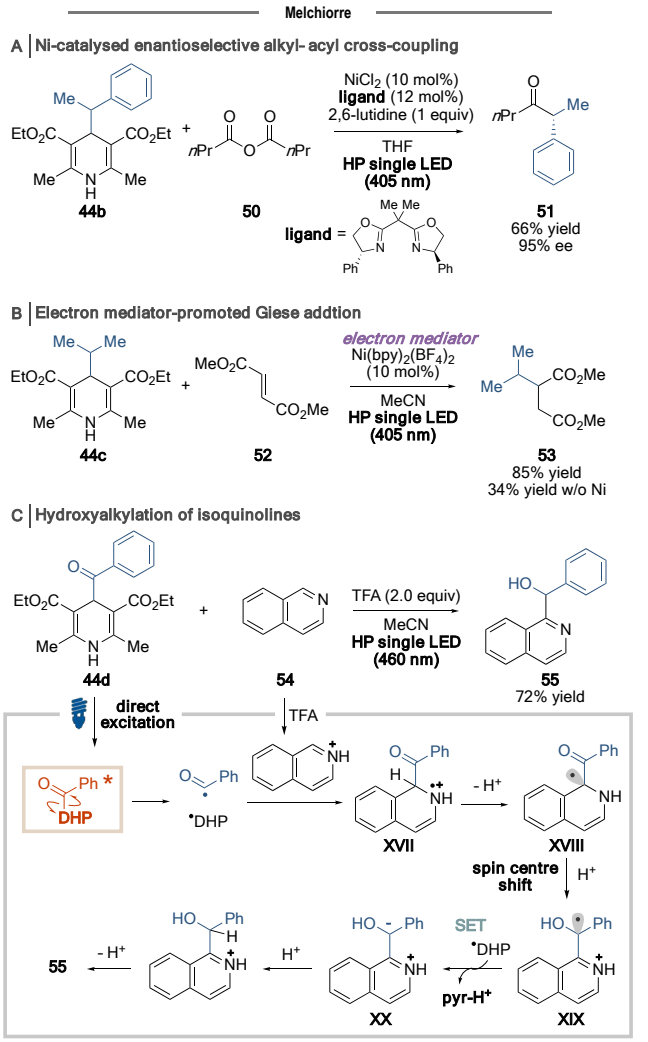
Scheme 13. **A**. HAT reagents generated from direct photo-excitation of *N*-halo or *N*-xanthylamide. **B**. Intramolecular 1,5-HAT via direct excitation of *N*-xanthylamide.

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.[46a] 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 transmetalation[45b] without an external photoredox catalyst (Scheme 14B). The photo-excited alkyl-DHP can work as a strong reductant ($E(\mathbf{44}^{\bullet+}/\mathbf{44}^*) \approx -1.6$ V vs. Ag/Ag$^+$ in CH_3CN) and thus, active Ni^0 catalyst **XIII** would be produced via SET reduction ($Ep(Ni^{II}/Ni^0) = -1.2$ V vs. SCE in DMF) by the excited state of alkyl-DHP **44**, giving the alkyl radical. The generated alkyl radical leads to alkyl Ni^I complex **XIV** followed by oxidative addition of aryl bromide **48** to form **XV**. The reductive elimination from **XV** provides the cross-coupling product with Ni^I-Br complex **XVI**, the SET reduction of which regenerates the active Ni^0 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.



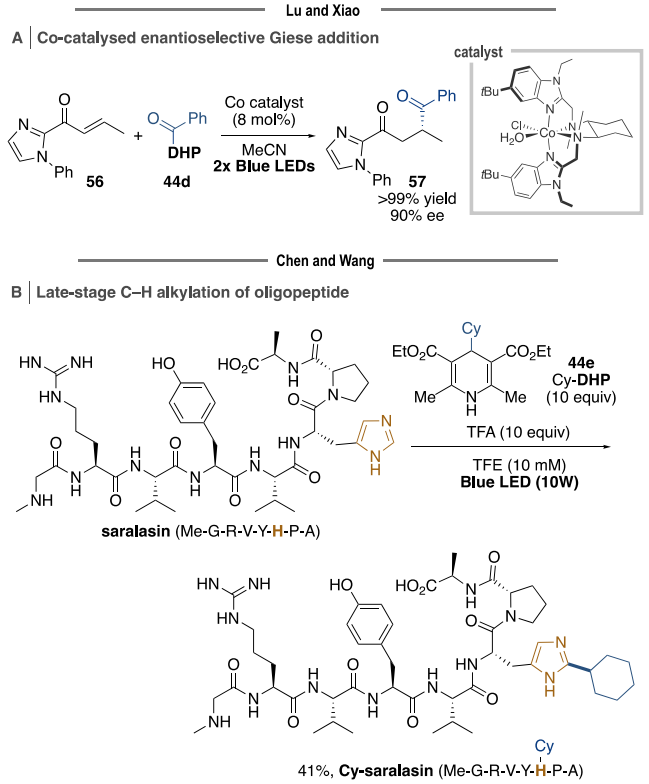
Scheme 14. **A**. Radical generation via direct excitation of alkyl-DHPs. **B**. Ni-catalysed cross-coupling based on direct excitation of alkyl-DHP.

Melchiorre and coworkers applied their methodology to several transformations (Scheme 15).[47] Enantioselective acyl-alkyl cross-coupling proceeded using a secondary benzyl group-substituted DHP **44b** with alkyl carboxylic anhydride **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 **51** (Scheme 15A).[46a] Subsequently, Giese addition based on the direct excitation of alkyl-DHP **44c** has been reported, which was enhanced by an electron mediator. $Ni(bpy)_3BF_4$ 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 ($E_p(Ni^{II}/Ni^{I})$ = –1.35 V vs. SCE) (Scheme 15B).[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 **44d** to the reaction with isoquinoline **54** under visible-light irradiation at 460 nm, the unusual Minisci reaction proceeds to give the hydroxyalkylated product **55** (Scheme 15C).[47c] The reaction of protonated isoquinoline with the acyl radical generated from directly photo-excited acyl-DHP afforded the radical cation **XVII**, followed by deprotonation, converting it to the relatively stable α-amino radical **XVIII**. A spin centre shift then occurred to form **XIX** driven by rearomatisation. SET reduction of **XIX** by the DHP radical (**DHP•**) gave the corresponding pyridinium cation **pyr-H⁺** with anion **XX**, of which proton transfer and deprotonation led to the final product **55**.

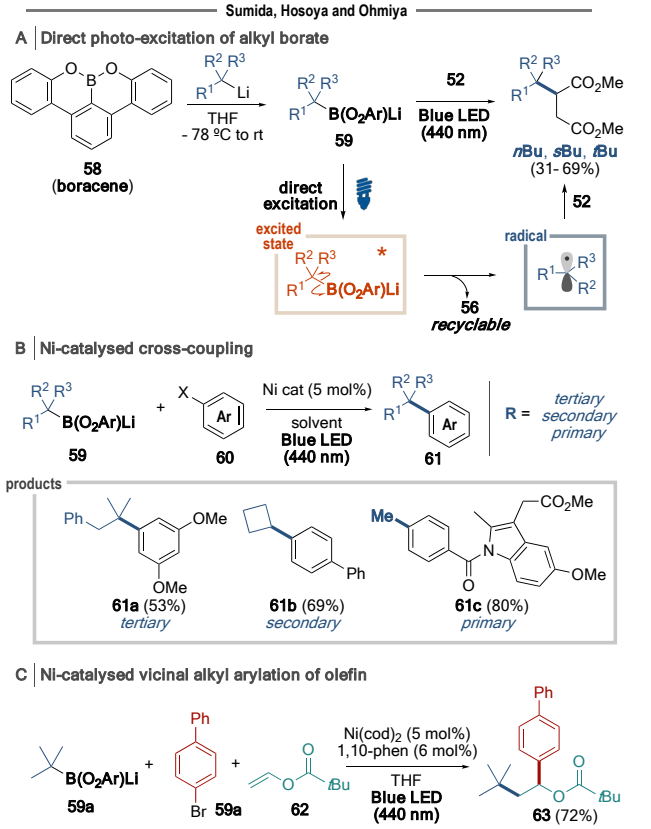


Scheme 15. Applications of alkyl-DHP protocol. **A**. Ni-catalysed enantioselective alkylation of carbonate ester. **B**. Electron mediator-promoted Giese addition. **C**. Hydroxyalkylation of isoquinoline via spin centre shift.

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^{II} complex coordinated by chiral N4 ligand catalysed the radical addition of **56** having an aryl imidazole unit as the directing group, which indicated that the direct excitation strategy of acyl-DHP **44d** was compatible with the Co^{II}-catalysis (Scheme 16A).[48a] Chen and Wang demonstrated a highly chemoselective modification of peptides via C–H alkylation of a histidine residue based on the direct excitation of alkyl-DHP **44e**.[48b] 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).



Scheme 16. **A**. Enantioselective Giese acylation using chiral Co catalyst. **B**. Late-stage alkylation of highly functionalised molecules.



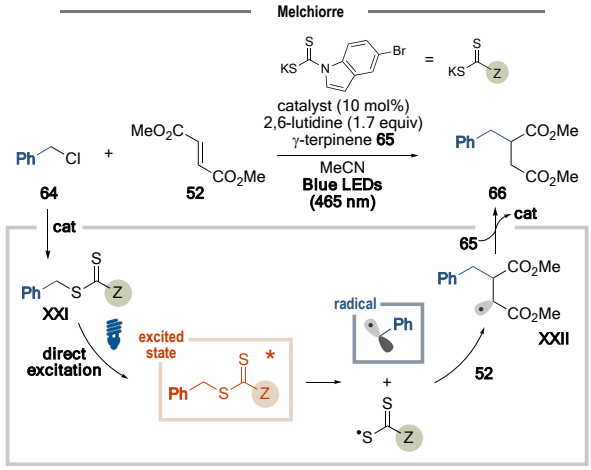
Scheme 17. A broad range of alkyl radical generations based on direct photo-excitation of alkylborates. **A**. General scheme for direct excitation of borate applied to Giese addition. **B**. Ni-catalysed cross-coupling of alkylborate with aryl halide. **C**. Ni-catalysed *vicinal* alkylarylation of olefins.

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**-derived alkylborate complex **59** to generate *tertiary*, *secondary*, and *primary* alkyl radicals, and initially applied them to the Giese addition (Scheme 17).[49] The boracene **58**, 8,9-dioxa-8a-borabenzo[*fg*] tetracene,[49a] has a highly planar and robust structure based on the benzo[*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 reductant (E_p = –2.2 V vs. SCE in MeCN).[49b] 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 introduction of *tertiary*, *secondary*, and *primary* alkyl units to yield the cross-coupling products **61a–c** (Scheme 17B). The protocol permitted the cross-coupling with electron-rich aryl bromides, which were difficult to apply under Ni/Ir photoredox cocatalysis.[49d] 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**.

In recent years, a catalytic direct excitation system has been designed based on *in situ* formation of direct excitable species. Melchiorre reported that a chromophore having the dithiocarbonyl anion as the nucleophilic part provided a radical source by the reaction with an alkyl electrophile, such as benzyl chloride **64** (Scheme 18).[50] *In situ*-formed intermediate **XXI** could be directly excited under photoirradiation to provide the corresponding benzyl radical with dithiocarbonyl radical. The turnover event of the dithiocarbonyl anion catalyst progressed by SET with a cyclohexadienyl radical, which was formed by the HAT process of γ-terpinene **65** with the radical adduct **XXII**. This protocol was demonstrated by Giese addition, tandem radical addition/cyclisation of *N*-arylacrylamides, and functionalisation of electron-rich (hetero)arenes.

Finally, a different mode of direct excitation was introduced. Recently, several groups reported that some molecules containing heavy atoms were not restricted by the Grotthuss-Draper law.[51] Despite no well-marked absorption in the visible-light region, hypervalent iodine-based compounds afforded radical species via homolytic bond cleavage following direct excitation under visible light (Figure 5). Nemoto and Nakajima have shown that this phenomenon arises from the direct S_0–T_n transition, which has been recognised as a forbidden process.[51c] Based on this property, they developed radical reactions using various hypervalent iodine species

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).



Scheme 18. Catalytic system for direct excitation.

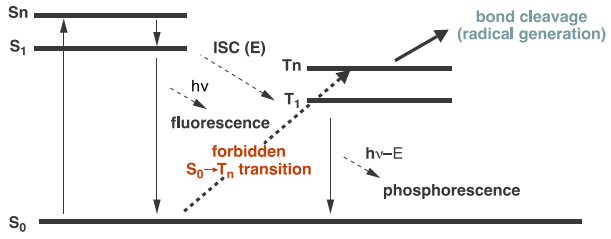
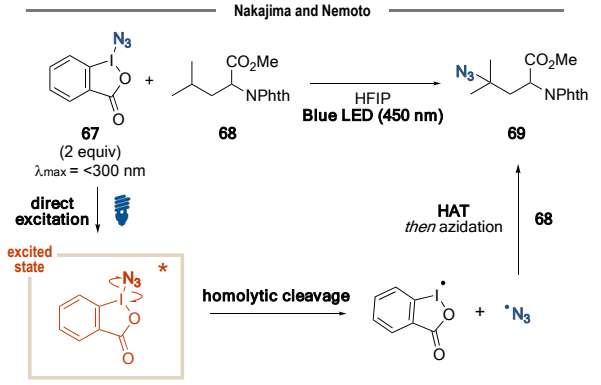


Figure 5. Jablonski diagram of direct S_0–T_n transition.



Scheme 19. Direct S_0–T_n transition of hypervalent iodine compound.

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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References

1 (a) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press, 2003. (b) M. Yan, J. C. Lo, J. T. Edwards and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 12692-12714. (c) A. Studer and D. P. Curran, *Angew. Chem. Int. Ed.*, 2016, **55**, 58-102. (d) S. Crespi and M. Fagnoni, *Chem. Rev.*, 2020, **120**, 9790-9833.
2 D. Griller and K. U. Ingold, *Acc. Chem. Res.*, 1976, **9**, 13-19.
3 H. Kolbe, *Ann. Chem. Pharm.* 1848, **64**, 339-341.
4 R. Fittig, *Ann. Chem*. 1859, **110**, 17.
5 (a) A. Borodin, *Ann. Chem. Pharm*. 1861, **119**, 121. (b) H. Hunsdiecker and C. Hunsdiecker, *Ber. Dtsch. Chem. Ges. B* 1942, **75**, 291.
6 (a) M. Gomberg, *J. Am. Chem. Soc.*, 1900, **22**, 757-771. (c) D. Leifert and A. Studer, *Angew. Chem. Int. Ed.*, 2020, **59**, 74-108.
7 (a) C. Galli and T. Pau, *Tetrahedron*, 1998, **54**, 2893-2904. (b) Luo, Y.-R. (2007). *Comprehensive Handbook of Chemical Bond Energies* (1st ed.). CRC Press.
8 a) A. J. Birch, *J. Chem. Soc*. 1944, 430. (b) A. J. Birch, *J. Chem. Soc.* 1945, 809. (c) A. J. Birch, *J. Chem. Soc.* 1946, 593.
9 (a) M. S. Kharasch and F. R. Mayo, *J. Am. Chem. Soc.*, 1933, **55**, 2468-2496. (b) M. S. Kharasch, E. V. Jensen and W. H. Urry, *Science*, 1945, **102**, 128-128.
10 G. J. M. van der Kerk, J. G. Noltes, J. G. A. Luijten, *J. Appl. Chem*. 1957, **7**, 356-374.
11 (a) C. Walling, *Pure Appl. Chem.*, 1967, **15**, 69-80. (b) B. P. Roberts, *Chem. Soc. Rev.*, 1999, **28**, 25-35.
12 D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, 1960, **82**, 2640-2641.
13 B. Giese, *Angew Chem Int Ed*, 1983, **22**, 753-764.
14 F. Minisci, R. Bernardi, F. Bertini, R. Galli and M. Perchinummo, *Tetrahedron*, 1971, **27**, 3575-3579.
15 K. J. Hale, S. Manaviazar and H. A. Watson, *Chem. Rec.*, 2019, **19**, 238-319.
16 A. G. Davies and B. P. Roberts, *J. Chem. Soc. B:* 1967, 17-22.

17 (a) M. Katsukiyo, I. Yoshifumi, N. Kyoko, F. Keigo, O. Koichiro and U. Kiitiro, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 143-147. (b) C. Ollivier and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415-3434.
18 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574-1585.
19 (a) D. H. R. Barton, H. A. Dowlatshahi, W. B. Motherwell and D. Villemin, *J. Chem. Soc., Chem. Comm.*, 1980, 732-733. (b) D. H. R. Barton, D. Crich and W. B. Motherwell, *J. Chem. Soc., Chem. Comm.*, 1983, 939-941.
20 (a) M. Kato, M. Kamigaito, M. Sawamoto and T. Higashimura, *Macromolecules*, 1995, **28**, 1721-1723. (b) J.-S. Wang and K. Matyjaszewski, *J. Am. Chem. Soc.*, 1995, **117**, 5614-5615.
21 J. Chiefari, Y. K. Chong, F. Ercole, J. Krstina, J. Jeffery, T. P. T. Le, R. T. A. Mayadunne, G. F. Meijs, C. L. Moad, G. Moad, E. Rizzardo and S. H. Thang, *Macromolecules*, 1998, **31**, 5559-5562.
22 (a) K. Okada, K. Okamoto and M. Oda, *J. Am. Chem. Soc.*, 1988, **110**, 8736-8738. (b) K. Okada, K. Okamoto, N. Morita, K. Okubo and M. Oda, *J. Am. Chem. Soc.*, 1991, **113**, 9401-9402.
23 (a) D. M. Hedstrand, W. H. Kruizinga and R. M. Kellogg, *Tetrahedron Letters*, 1978, **19**, 1255-1258. (b) C. Pac, M. Ihama, M. Yasuda, Y. Miyauchi and H. Sakurai, *J. Am. Chem. Soc.*, 1981, **103**, 6495-6497. (c) K. Hironaka, S. Fukuzumi and T. Tanaka, *J. Chem. Soc., Perkin Trans.* 1984, 1705-1709.
24 (a) J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2009, **131**, 14604-14605. (b) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77-80. (c) . M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2009, **131**, 8756-8757.
25 M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898-6926.
26 (a) S. P. Pitre, C. D. McTiernan, W. Vine, R. DiPucchio, M. Grenier and J. C. Scaiano, *Sci. Rep.*, 2015, **5**, 16397. (b) M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras and S. Bernhard, *Chem. Mater.*, 2005, **17**, 5712-5719. (c) D. J. Wilger, J.-M. M. Grandjean, T. R. Lammert and D. A. Nicewicz, *Nat. Chem.*, 2014, **6**, 720-726. (d) E. Speckmeier, T. G. Fischer and K. Zeitler, *J. Am. Chem. Soc.*, 2018, **140**, 15353-15365. (e) N. J. Treat, H. Sprafke, J. W. Kramer, P. G. Clark, B. E. Barton, J. Read de Alaniz, B. P. Fors and C. J. Hawker, *J. Am. Chem. Soc.*, 2014, **136**, 16096-16101. (f) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075-10166.
27 (a) **Oxalate**: G. L. Lackner, K. W. Quasdorf, G. Pratsch and L. E. Overman, *J. Org. Chem.*, 2015, **80**, 6012-6024. (b) **Katritzky salt**: S. M. James Grimshaw, Jadwiga Trocha-Grimshaw *Acta Chem. Scand.*, 1983, **37b**, 485-489. (c) F. J. R. Klauck, M. J. James and F. Glorius, *Angew. Chem. Int. Ed.*, 2017, **56**, 12336-12339.
28 (a) **Si**: D. Matsuoka and Y. Nishigaichi, *Chem. Lett.*, 2014, **43**, 559-561. (b) V. Corcé, L.-M. Chamoreau, E. Derat, J.-P. Goddard, C. Ollivier and L. Fensterbank, *Angew. Chem. Int. Ed.*, 2015, **54**, 11414-11418. (c) **DHP**: K. Nakajima, S. Nojima and Y. Nishibayashi, *Angew. Chem. Int. Ed.*, 2016, **55**, 14106-14110. (d) J.-P. Cheng, Y. Lu, X.-Q. Zhu, Y. Sun, F. Bi and J. He, *J. Org. Chem.*, 2000, **65**, 3853-3857. (e) **B**: Y. Yasu, T. Koike and M. Akita, *Adv. Synth. Catal.*, 2012, **354**, 3414-3420. (f) J. C. Tellis, D. N. Primer and G. A. Molander, *Science*, 2014, **345**, 433-436. (g) F. Lima, M. A. Kabeshov, D. N. Tran, C. Battilocchio, J. Sedelmeier, G. Sedelmeier, B. Schenkel and S. V. Ley, *Angew. Chem. Int. Ed.*, 2016, **55**, 14085-14089.
29 (a) L. Capaldo and D. Ravelli, *Eur. J. Org. Chem.*, 2017, **2017**, 2056-2071. (b) S. Sarkar, K. P. S. Cheung and V. Gevorgyan, *Chem. Sci.*, 2020, **11**, 12974-12993.
30 F. Strieth-Kalthoff and F. Glorius, *Chem*, 2020, **6**, 1888-1903.
31 G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461-5476.
32 H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc.*, 1949, **71**, 2703-2707.
33 R. S. Mulliken, *J. Am. Chem. Soc.*, 1952, **74**, 811-824.
34 H. Leonhardt and A. Weller. *Ber. Bunsenges. Phys. Chem*., 1963, 67. 791.
35 E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem.*, 2013, **5**, 750-756.
36 M. Tobisu, T. Furukawa and N. Chatani, *Chem. Lett.*, 2013, **42**, 1203-1205.
37 (a) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, **363**, 1429-1434. (b) Y.-T. Wang, M.-C. Fu, B. Zhao, R. Shang and Y. Fu, *Chem. Comm.*, 2020, **56**, 2495-2498. (c) M.-C. Fu, J.-X. Wang and R. Shang, *Org. Lett.*, 2020, **22**, 8572-8577. (d) H. Sheng, Q. Liu, X.-D. Su, Y. Lu, Z.-X. Wang and X.-Y. Chen, *Org. Lett.*, 2020, **22**, 7187-7192.
38 I. Bosque and T. Bach, *ACS Catal.*, 2019, **9**, 9103-9109.
39 E. J. McClain, T. M. Monos, M. Mori, J. W. Beatty and C. R. J. Stephenson, *ACS Catal.*, 2020, **10**, 12636-12641.
40 (a) S. Shibutani, T. Kodo, M. Takeda, K. Nagao, N. Tokunaga, Y. Sasaki and H. Ohmiya, *J. Am. Chem. Soc.*, 2020, **142**, 1211-1216. (b) S. Shibutani, K. Nagao and H. Ohmiya, *Org. Lett.*, 2021, **23**, 1798-1803.
41 (a) M. A. Emmanuel, N. R. Greenberg, D. G. Oblinsky and T. K. Hyster, *Nature*, 2016, **540**, 414-417. (b) K. F. Biegasiewicz, S. J. Cooper, X. Gao, D. G. Oblinsky, J. H. Kim, S. E. Garfinkle, L. A. Joyce, B. A. Sandoval, G. D. Scholes and T. K. Hyster, *Science*, 2019, **364**, 1166-1169. (c) X. Huang, B. Wang, Y. Wang, G. Jiang, J. Feng and H. Zhao, *Nature*, 2020, **584**, 69-74.
42 (a) J. Demarteau, A. Debuigne and C. Detrembleur, *Chem. Rev.*, 2019, **119**, 6906-6955. (b) P. M. Kozlowski, T. Kamachi, T. Toraya and K. Yoshizawa, *Angew. Chem. Int. Ed.*, 2007, **46**, 980-983. (c) G. N. Schrauzer and R. J. Windgassen, *J. Am. Chem. Soc.*, 1966, **88**, 3738-3743. (d) B. P. Branchaud, M. S. Meier and Y. Choi, *Tetrahedron Lett.*, 1988, **29**, 167-170.
43 (a) C. Ollivier and P. Renaud, *Angew. Chem. Int. Ed.*, 2000, **39**, 925-928. (b) D. H.R. Barton, B. Lacher and S. Z. Zard, *Tetrahedron*, 1987, **43**, 4321-4328. (c) D. H. R. Barton, B. Garcia, H. Togo and S. Z. Zard, *Tetrahedron Lett.*, 1986, **27**, 1327-1330.
44 (a) J. Y. Lan and G. B. Schuster, *J. Am. Chem. Soc.*, 1985, **107**, 6710-6711. (b) S. Chatterjee, P. Gottschalk, P. D. Davis and G. B. Schuster, *J. Am. Chem. Soc.*, 1988, **110**, 2326-2328.
45 (a) V. A. Schmidt, R. K. Quinn, A. T. Brusoe and E. J. Alexanian, *J. Am. Chem. Soc.*, 2014, **136**, 14389-14392. (b) W. L. Czaplyski, C. G. Na and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 13854-13857. (c) R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 696-702. (d) C. G. Na and E. J. Alexanian, *Angew. Chem. Int. Ed.*, 2018, **57**, 13106-13109.
46 (a) L. Buzzetti, A. Prieto, S. R. Roy and P. Melchiorre, *Angew. Chem. Int. Ed.,* 2017, **56**, 15039-15043. (b) J. C. Tellis, D. N. Primer and G. A. Molander, *Science*, 2014, **345**, 433-436. (c) SET oxidation of the directly excited substrate followed by radical reaction was also proposed: L. Candish, M. Teders and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 7440-7443.
47 (a) E. Gandolfo, X. Tang, S. Raha Roy and P. Melchiorre, *Angew. Chem. Int. Ed.,* 2019, **58**, 16854-16858. (b) T. van Leeuwen, L. Buzzetti, L. A. Perego and P. Melchiorre, *Angew. Chem. Int. Ed.,* 2019, **58**, 4953-4957. (c) B. Bieszczad, L. A. Perego and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2019, **58**, 16878-16883.
48 (a) K. Zhang, L. Q. Lu, Y. Jia, Y. Wang, F. D. Lu, F. Pan and W. J. Xiao, *Angew. Chem. Int. Ed.*, 2019, **58**, 13375-13379. (b) X. Chen, F. Ye, X. Luo, X. Liu, J. Zhao, S. Wang, Q. Zhou, G. Chen and P. Wang, *J. Am. Chem. Soc.*, 2019, **141**, 18230-18237.
49 (a) Y. Sumida, R. Harada, T. Kato-Sumida, K. Johmoto, H. Uekusa and T. Hosoya, *Org. Lett.*, 2014, **16**, 6240-6243. (b) Y. Sato, K. Nakamura, Y. Sumida, D. Hashizume, T. Hosoya and H. Ohmiya, *J. Am. Chem. Soc.*, 2020, **142**, 9938-9943. (c) Y. Sato,

Y. Miyamoto, Y. Sumida, T. Hosoya and H. Ohmiya, *Org. Biomol. Chem.*, 2020, **18**, 6598-6601. (d) D. N. Primer and G. A. Molander, *J. Am. Chem. Soc.*, 2017, **139**, 9847-9850.

50 (a) B. Schweitzer-Chaput, M. A. Horwitz, E. de Pedro Beato and P. Melchiorre, *Nat. Chem.*, 2019, **11**, 129-135. (b) D. Spinnato, B. Schweitzer-Chaput, G. Goti, M. Ošeka and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2020, **59**, 9485-9490.

51 (a) R. Sakamoto, H. Kashiwagi and K. Maruoka, *Org. Lett.*, 2017, **19**, 5126-5129. (b) S. Yang, H. Tan, W. Ji, X. Zhang, P. Li and L. Wang, *Adv. Synth. Catal.*, 2017, **359**, 443-453. (c) M. Nakajima, S. Nagasawa, K. Matsumoto, T. Kuribara, A. Muranaka, M. Uchiyama and T. Nemoto, *Angew. Chem. Int. Ed.*, 2020, **59**, 6847-6852.