J. Chem. Sci. (2021)133:5
https://doi.org/10.1007/s12039-020-01868-0

REVIEW ARTICLE

How to train free radicals for organic synthesis? A modern approach

AANKHI KHAMRAI and VENKATARAMAN GANESH*
Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur, West Bengal 721 302, India
E-mail: ganesh.v@chem.iitkgp.ac.in

MS received 24 August 2020; revised 19 October 2020; accepted 24 October 2020

Abstract. In this review, the journey of free radicals, from being shrewdly untamable until its emergence as a powerful tool in chemistry, has been tracked. A modern perspective on the generation of radicals has been offered through the lens of photoredox, metal mediation, redox-active scaffolds, and EDA complexes. Spotlight has been on the catalysis of radical reactions harboring unique strategies like smart initiation, electron and hole catalysis, and polarity reversal catalysis.

1. Introduction

Free radicals are known for their chaotic behavior and controlling them is challenging. In the past, radical chemistry had been sidetracked by ionic chemistry due to their uncontrollable nature leading to various side reactions. To perform a radical reaction, it required stringent conditions, an elaborate experimental setup, and a specially trained workforce, keeping the chemistry out of reach for general applications. Nevertheless, over the years, radical chemistry has fought this long battle and various misconceptions to earn a significant place showing its versatility and elegance. Apart from establishing synergy with organic synthesis, the versatility of radicals has had a profound impact on material science, agrochemicals, fine-chemical manufacturing, and drug discovery. Their 'translational' potential has been in the spotlight thereafter. Although limited by elaborate setup, a few classical and reliable radical methods such as Kolbe decarboxylation and Hunsdiecker reaction were the torchbearers: Gone are those days. Modern science has brought about a plethora of smarter methodologies for the generation of radicals and catalysis of radical reactions. The radical paradox has been addressed, i.e., although they are invisible, it has become possible to detect their presence and predict the course of action of these otherwise notorious species. Radicals want things done fast; the question now is not just to make them react controllably but also to do so in a selective manner. Let us take a tour of the recent developments made in this diverse field. The basics and various applications of radical chemistry have been highlighted elsewhere.[1] This article adds a significant amount of modern perspective to the existing ones.

2. Radicals

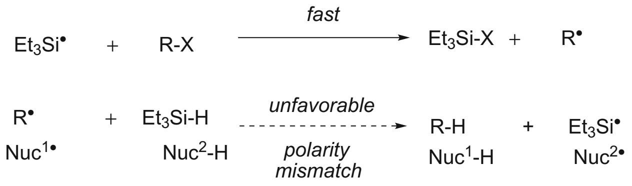
Free radicals have a single unpaired electron housed in a SOMO (Singly Occupied Molecular Orbital). A low barrier for a pyramidal inversion drive reactions involving chiral radical intermediates towards undesired racemization. On top of that, rapid diffusion-controlled radical-radical recombination made enantioselective radical-mediated reactions a daunting task in the past. They can be stabilized by neighboring groups offering *viz.,* hyperconjugation, conjugative resonance, and captodative stabilization. They exhibit paramagnetism and thus are widely characterized by Electron Spin Resonance (ESR). Radicals can also be detected chemically *via* trapping experiments with TEMPO or with radical scavengers like BHT. Fleeting radicals can be seen by ring-opening of cyclopropyl methyl radical and 1,2-migration type rearrangements, which are unimolecular radical reactions with known reaction rates. Such reactions function as molecular "clocks" in competition experiments with bimolecular radical reactions to measure unknown rates. Thus, famously called radical clock experiments, they are used as chemical diagnostic tools for detecting free-radical intermediates and the reaction rates.

---

*For correspondence

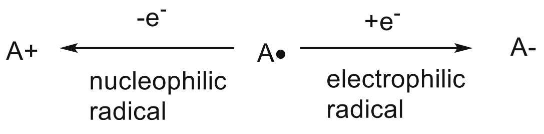
3. Radical polarity

In 1934, Ingold first coined the term ‘nucleophile’ for electron-rich species and ‘electrophile’ for electron-deficient ones. Since then, rigorous efforts have been made to gauge charged species, atoms, and molecules on empirical scales of ‘*philicity*’. However, do electrically neutral free radicals fall under such category?



The rate and selectivity of atom abstraction by these radicals are governed by the polar effects operating in the transition state. Therefore, the nature of the radical determines which reactive sites of the substrate are prone to attack: An electrophilic radical prefers an electron-rich reaction site; a nucleophilic radical prefers an electron-poor reaction site. In terms of energy, a radical having high ionization energy (IE) and electron affinity (EA) will be electrophilic, while low IE and EA would convey nucleophilic properties.

To determine the *philicity* of a radical A•, a qualitative analysis of the stability of oxidized (cationic) and reduced (anionic) forms of A• can be made. For example, if A+ is more stable than A-, then A• is a nucleophilic radical because it wants to lose an e–. However, if the reverse is true, then A• is an electrophilic radical because it wants to gain an e–. Thus, *t*BuO• is electrophilic, whereas *t*Bu• is nucleophilic. There are other qualitative approaches, like comparing the acidity of A-H. The higher the acidity of A-H, the higher is the electrophilicity of A•.



4. Radical generation

4.1 *Classical methods*

Radicals have been generated in the past, mainly through thermal, photochemical (UV light), or redox activation. Thermolysis of intrinsically weak bonds as in dialkyl peroxides or nitrogen-rich compounds that evolve N_2 upon fragmentation, like AIBN, generate free-radicals upon heating. While these methods have made free radicals more accessible, the explosive nature of peroxides, the toxicity of tetramethyl succinonitrile generated from the 2-cyanopropyl radicals upon pyrolysis of AIBN, and poisoning from organotin reagents (used as initiators) have unpopularized these classical methods of free radical generation. Despite its vast potential, the radical chemistry of stannanes is limited due to the inadequate management of effluents and challenges faced in removing organotin residues during purification.

Light can trigger fragmentation in a molecule once its wavelength corresponds to energy higher than that of the bond to be cleaved. Generally, this process requires shining high-intensity UV light, and the bond cleavage is non-selective. Such is the case for the formation of alkoxy radicals from alkyl nitrite or hypochlorite. Lastly, covalent bonds can be broken by electron transfer processes either by accepting an electron from a donor molecule or donating its electron to an acceptor.

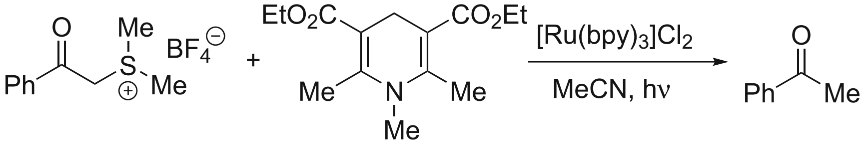
In the upcoming sections, we will see how extensive research in radical chemistry has created alternative solutions in surmounting these obstacles and developed unique methods in taming the impatient radicals in recent years.

4.2 *Modern approaches to radical generation*

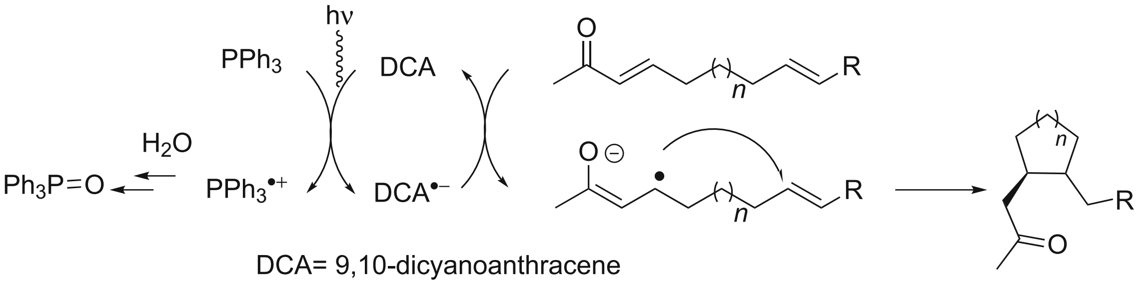
4.2.1 *Visible light mediated radical generation: organic and metallophotoredox catalysis*: In 1978, Kellogg achieved the light-mediated reduction of sulfonium ions to the corresponding alkanes using 1,4 dihydropyridine, in 99% yield, and at surprising rates with just catalytic amount of $[Ru(bpy)_3]Cl_2$.[2] How did $[Ru(bpy)_3]Cl_2$ accelerate this reductive desulfuration? The answer has been sought after by a few researchers over the years since then. Pioneering contributions from Pandey’s group in the ’90s in the field of organophotoredox is noteworthy.[3] Later in 2008, pioneering works published by Yoon on the photoredox catalyzed [2+2] cycloaddition of enones[4] and MacMillan on the enantioselective α-alkylation of aldehydes,[5] had kick-started a renaissance in radical-mediated methodologies – this time without the toxicity caused by stannanes (Scheme 1).

Photoredox chemistry succumbs to non-traditional bond formation under mild conditions, using a simple household light source to excite a photocatalyst and bench-stable precursors like carboxylic acid or halides, thereby expanding the repertoire of organic synthesis.

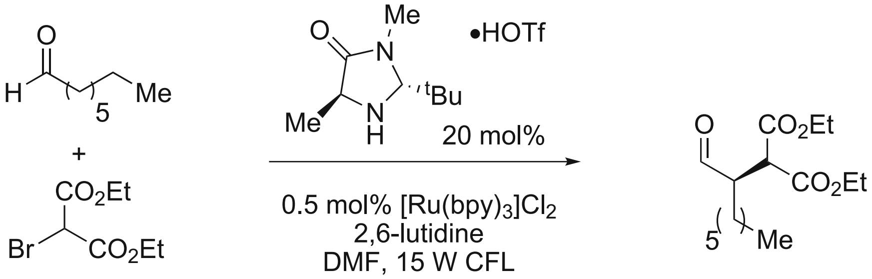
(a) Kellog,1978 - Reductive Desulfuration



(b) Pandey, 1996 - Photoinduced electron-transfer using PPh_3 as sacrificial electron-donor



(c) MacMillan, 2008 - Asymmetric catalytic α-alkylation of aldehydes



Scheme 1. Pioneering works in the field of photoredox catalysis.

What is a photocatalyst? In simple words, a photocatalyst (PC) converts light energy into chemical energy. A ground state (S_0) of a specially designed catalyst is excited by light by various generic activation modes to its singlet excited state (S_1). Now, this excited state complex performs inter-system crossing (ISC) to achieve the triplet excited state (T_1) - the catalytically active state (PC*). PC*, our protagonist in photoredox, can, in turn, induce reactivity in another substrate or a secondary catalyst either by single electron transfer event (SET) or by energy transfer event (EnT) (Figure 1). This process leads to low barrier unique reaction pathways resulting in the formation of open-shell radical intermediates.

Organic dyes (Eosin Y, Rose Bengal, etc.), metal polypyridyl complexes, and carbazoyl dicyanobenzene (CDCBS, electron donor-acceptor type molecules) are powerful PCs with wide redox window, long-lived excited states, and high fluorescence quantum yield. The excited organic PCs possess enhanced oxidizing/reducing capabilities compared to their ground state counterpart. In metallophotocatalysts, such excitations with visible light trigger Metal to Ligand Charge Transfer (MLCT), resulting in excited Ir or Ru pyridyl complexes. Like organic photocatalysts, these excited state species get involved in redox chemistry. The Gibbs free energy of the triplet state of $Ir(ppy)_3$ is 56 kcal mol^{-1} higher than the ground state – such is the enormous capacity of the power device, PC.

It is rewarding to find the photon absorbing PCs to get excited chemoselectively by visible light, in the range inaccessible to common organic molecules. Our protagonist, PC*, can act both as a strong oxidant and

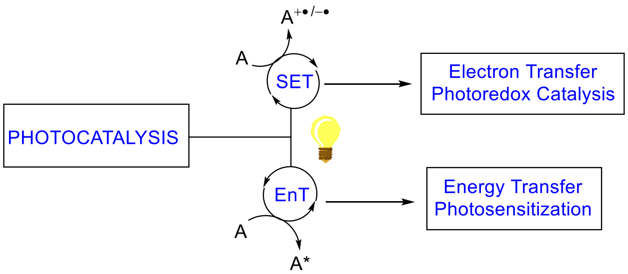


Figure 1. Simplified terminologies in photocatalysis.

a reductant, independently as well as simultaneously (Figure 2). SET with organic (and organometallic) substrates provide easy access to a radical cation or a radical anion. In an oxidative quenching cycle, PC* loses an electron to give oxidized ground state catalyst [PC•+], with simultaneous reduction of the substrate to form a radical anion. After the desired transformation of the formed radical anion, the cycle closes by a subsequent SET back to [PC•+] regenerating the ground state PC. Similarly, a reductive quenching cycle can be explained by using an electron by PC* from the substrate.

The field of EnT catalysis has comparatively been overlooked. Energy transfer can be formally defined as "the photophysical process in which an excited state of one molecular entity (the donor D) is deactivated to a lower-lying state by transferring energy to a second molecular entity (the acceptor A), which is thereby raised to a higher energy state." [D* + A →D + A*]. The photocatalyst (the donor) undergoes excitation with visible light, subsequently transfers the energy to the respective substrate (the acceptor). As a suitable example, the intramolecular [2+2] photocycloaddition of alkene-tethered styrenes has been described by Yoon and co-workers[6] (Scheme 2). Here, the triplet state of styrenes was accessed through EnT from an excited iridium photocatalyst. Excited styrenes then react intramolecularly to afford the cyclobutane products.

Flow Photochemistry – Industrial Applications

Traditional 'start and stop' batch chemistry: We are familiar with small scale reactions in a round-bottomed flask and of a larger scale in jacketed reactors. The parameters that control such reactions are temperature, mixing rate, reaction time, and concentration. After the reaction, the recovery involves work-up and filtration.

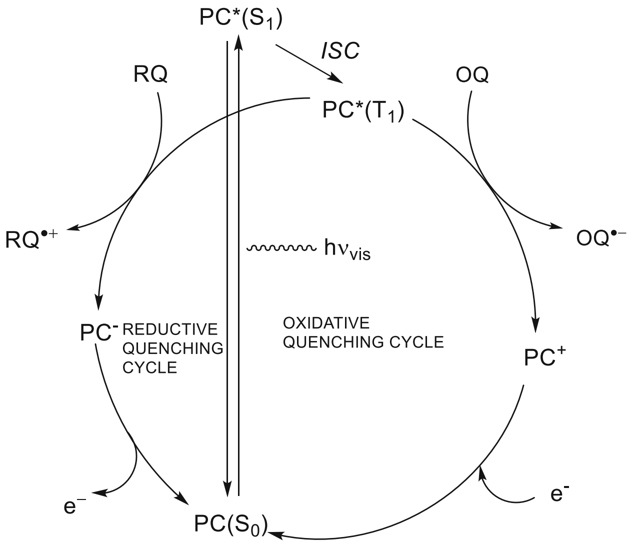
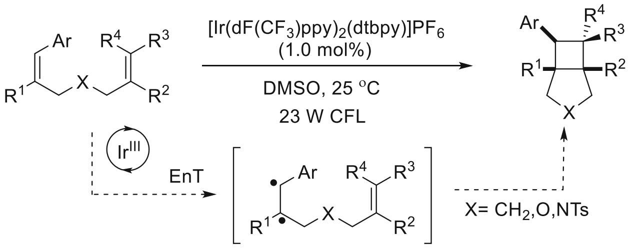


Figure 2. Electron transfer mechanism of photoredox catalysis.



Scheme 2. Intramolecular [2+2] cycloaddition of styrenes.

New age Flow Chemistry: It promises continuity, from pumping of the starting materials into the microreactor at a specific flow rate, exposure to reaction parameters, till the release of the product in a continuous stream. In addition to all the parameters in a batch setup, adjusting the flow rate provides an additional handle to control the reaction yields.

Conducting transformations in-flow has caused a paradigm shift in synthetic chemists' perspective towards photoredox transformations of organic molecules. The commencement of flow photoreactors has brought about a range of benefits, including predictable scale-up, improved reproducibility, and decreased safety hazards. The high surface area to volume ratio in these reactors ensures enhanced photon flux density. This design results in more effective exposure of reaction mixture to incident radiation, thereby accelerating such photochemical transformations. A viable laboratory design includes commercially available PFA (PerfluoroAlkoxyAlkane) tubing due to its chemical inertness and optical transparency, a peristaltic pump, and an LED assembly, and a silver-mirrored Erlenmeyer flask as a collector to reflect any stray light (Figure 3).[7] The flow microreactors can be of glass with etched channels of about 100 mm diameter, glass columns packed with solid or tube reactors of fluoropolymer with the entire length of metal tube enveloped around a heat exchanger. The narrow diameter ensures the homogeneity of the intensity of light throughout the reaction mixture under photochemical transformations. Such parity is difficult in flasks, where the intensity of the light absorbed decreases on traveling from one wall of the flask to the other end, following the Lambert-Beer law.

The advent of multi-catalytic platforms such as dual photoredox metal/organocatalytic methodologies (covalent or non-covalent interactions, Hydrogen Atom Transfer HAT, C-C, and C-X bond formation) have enabled high regio- and enantioselective radical

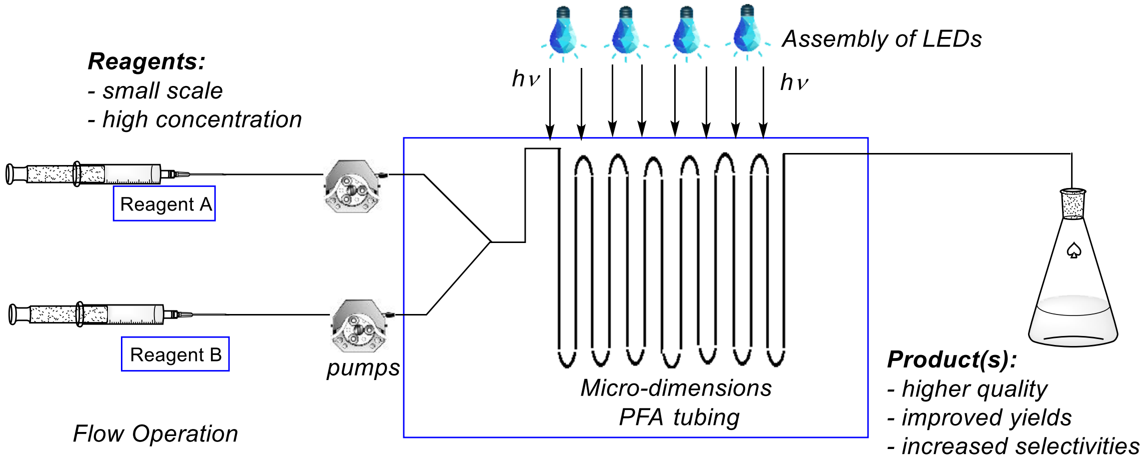


Figure 3. A schematic representation of a flow photoreactor.

transformations. Photoredox continues to grow and lend its hand in medicinal and process chemistry, synthesis of natural products, late-stage functionalization of drug molecules, and streamlining organic synthesis.

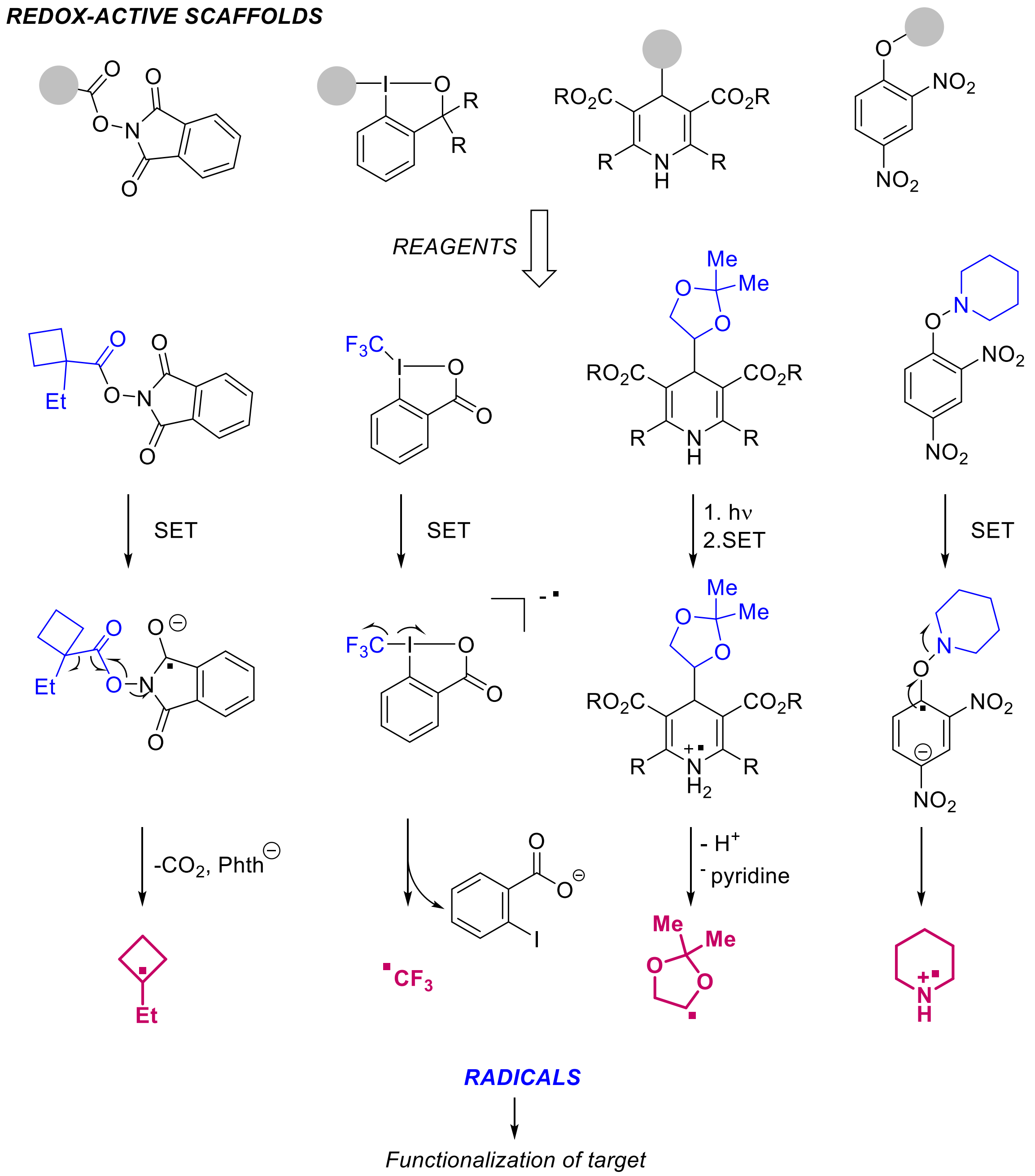
4.2.2 *Redox-active groups as radical precursors – the pseudohalides of radical chemistry*: In recent years, functional group transfer reagents bearing redox-active groups have proved to be excellent precursors for generating reactive radical intermediates under mild conditions. These modular and adaptable reagents are much like the synthetic equivalents of highly reactive radical synthons. The redox-active scaffolds provide an 'antenna' for SET processes to occur (e.g.: first-row transition metal catalysis and photoredox catalysis) and facilitate the homolytic scission of a C-C or C-X (X= heteroatom, halogen) bonds. Synthetic manipulation of these scaffolds ensures the release of the radical species, including previously inaccessible, nascent ones, in a chemoselective and predictable manner.

As given in Scheme 3, *N*-acyloxyphthalimides belong to the class of 'Redox-Active Esters' (RAEs). Apart from being surrogates of carboxylic acids, they are excellent oxidants. RAEs that deliver alkyl radicals are thought to be a suitable proxy to alkyl halides in SET based cross-couplings. The other examples of redox-active groups yielding radical intermediates include hypervalent iodine reagents (Togni's Reagent), 1,4-dihydropyridine derivatives (Hantzsch esters), and electron-poor O-aryl oximes, respectively. Xanthates and related derivatives (trithiocarbonates and dithioesters) can increase the lifetimes of reactive radicals in solution by storing them in a dormant state. By scission of C-S bonds, the released radicals can undergo intermolecular addition even to unactivated alkenes – a process known as degenerative xanthate addition-transfer.

4.2.3 *Metal mediated radical generation*: The recent surge in transition metal promoted radical reactions usually observes the product with a new or modified functionality at termination. Thus, transition metal-mediated free-radical reactions have become increasingly crucial as synthetic tools. Mechanistically, they can be classified based on the nature of the radical generation: Oxidative or reductive.

For an oxidative process, the metal acts as the oxidant. Under this class, C-centered radicals from the scission of a metal-carbon bond are formed upon electron transfer (ET) from the radical precursor to the organometallic complex. For example, substituted α-tetralones can be constructed from Mn(III) assisted olefin addition to aromatic methyl ketone (Scheme 4a).[8] At first, Mn(III) oxidizes the methyl ketone to the corresponding α-acyl radical to be intermolecularly added to an olefin. Next, the intramolecular addition of the newly generated C-centered radical to the aromatic ring produces a radical stabilized by conjugation. Finally, oxidation with Mn(III) aromatizes the ring to yield the desired product.

Similarly, the metal acts as the reductant for a reductive process where the metal complex transfers an atom or an electron to the radical precursor to initiate the reaction. For example, Cp_2TiCl promotes epoxy C-O bond cleavage in epoxy olefins. The

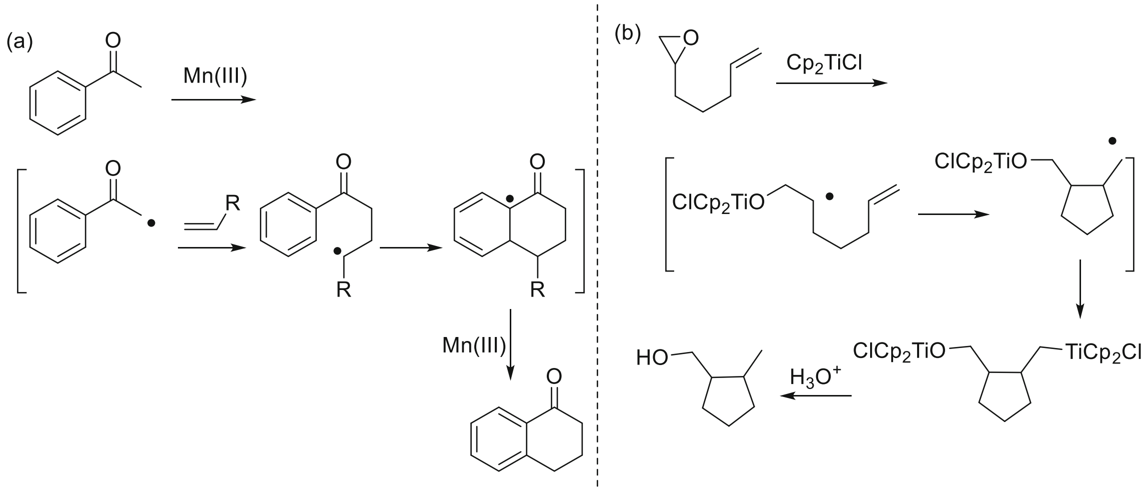


Scheme 3. Generation of radicals based on redox-active groups

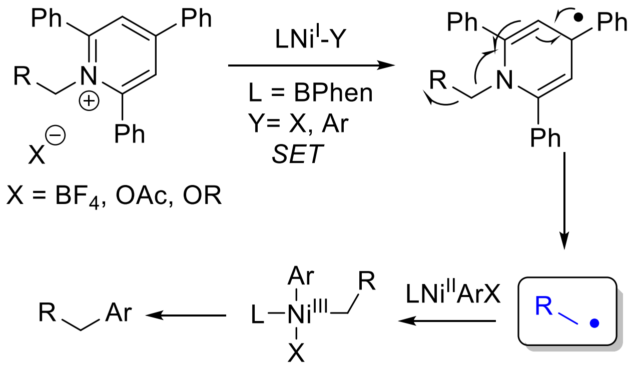
C-centered radical adds to the alkene in a *cis*-fashion intramolecularly to generate thermodynamically stable endo derivatives of cyclopentanemethanol (Scheme 4b).[9] The above methods are stoichiometric on the metal used. Several catalytic methods are being developed to achieve similar reactivity.

The Watson group's recent work illustrates how Ni mediated SET can fragment an alkyl pyridinium salt to give an alkyl radical.[10] A Ni(II) aryl intermediate recombines with this alkyl radical to give an alkyl aryl Ni(III) intermediate. The cross-coupled product is obtained on subsequent reductive elimination (Scheme 5).

4.2.4 *Electron donor-acceptor complexes (EDA)*: Another powerful strategy to expand light-mediated radical chemistry is the use of EDA complexes. Mulliken charge-transfer theory proposes that an electron acceptor molecule, A (with high electron affinity), and an electron-rich substrate, D (with low ionization potential) can associate in their ground states to form a molecular aggregate - capable



Scheme 4. Metal-mediated radical generation (a) oxidative process (b) reductive process.



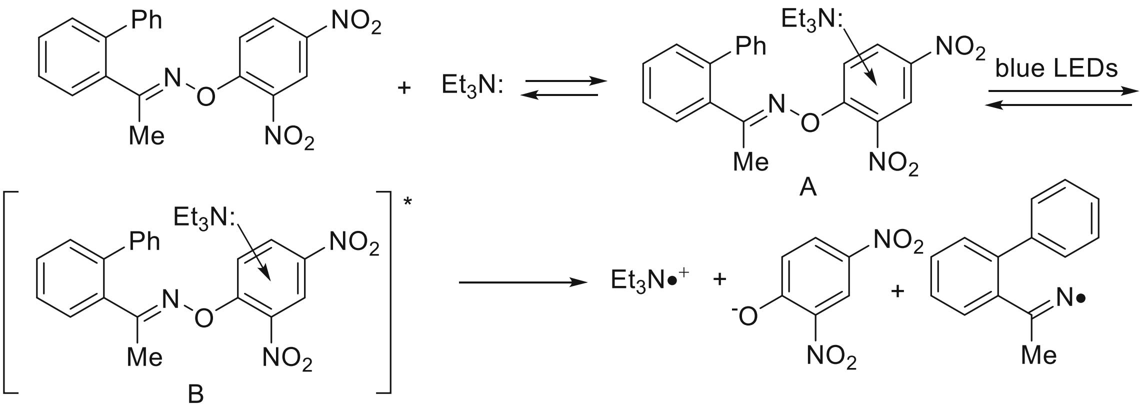
Scheme 5. Ni catalyzed fragmentation of alkyl pyridinium salts.

of harvesting visible light energy. A and D individually may not absorb light in the visible region, but together with the formation of new molecular orbitals, their physical properties become entirely different. Upon irradiation, the excited state of the EDA complex is populated, which triggers D to perform an intra-complex electron transfer to A, generating a radical ion pair with net separation of charges. Ultimately, reactive radicals are furnished under mild conditions without the aid of a photocatalyst.[11a–c]

In Scheme 6, O-aryl oxime associates with Et_3N reversibly, giving the EDA complex A to be subsequently excited to B upon visible light irradiation. A SET process is initiated, and the excited state radical ion pair collapses to yield the iminyl radical.[11d]

5. Catalyzing a radical reaction

A suitable mode of initiation in the absence of any kind of inhibition can sustain a radical chain reaction innately, without the aid of a catalyst. For such a system to operate, the propagation steps should be fast enough. Other areas of catalysis are fundamentally different from the catalysis of radical reactions in two aspects. Unlike others, in radical chemistry, the catalytic cycles have catalyst-free intermediates operating in the innate steps. Secondly, radical cycles cannot tolerate even a single slow endothermic step. A catalyst in a radical chain reaction supervises the chain transfer step or bridges the generation and return of the reactive intermediates to closed-shell species. The aim is to keep the potential innate radical cycle intact while assisting the slower cycle to give the same outcome. In the following sections, we will explore some of the modern catalysis techniques applied to radical chemistry.



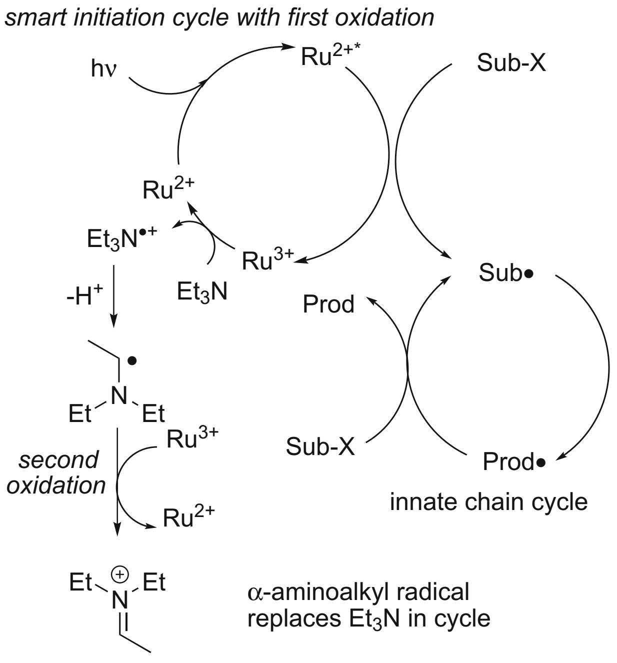
Scheme 6. Iminyl radical formation from O-aryl oxime-Et_3N EDA complex.

In a radical chain reaction if the rate of propagation step is

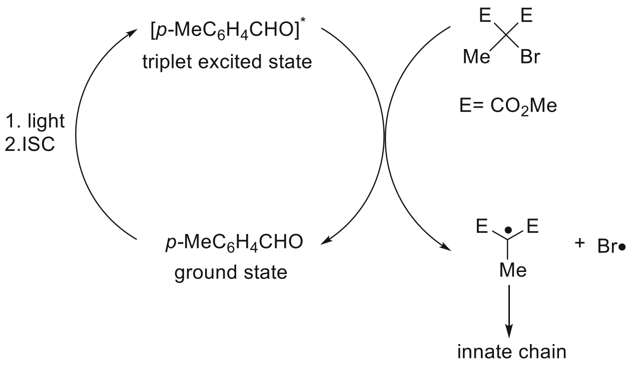
$\geq 10^5$ s^{-1} → good innate chain

~ 10^4 s^{-1} → short chains are still possible

< 10^3 s^{-1} → the chain cannot propagate because the termination steps are faster



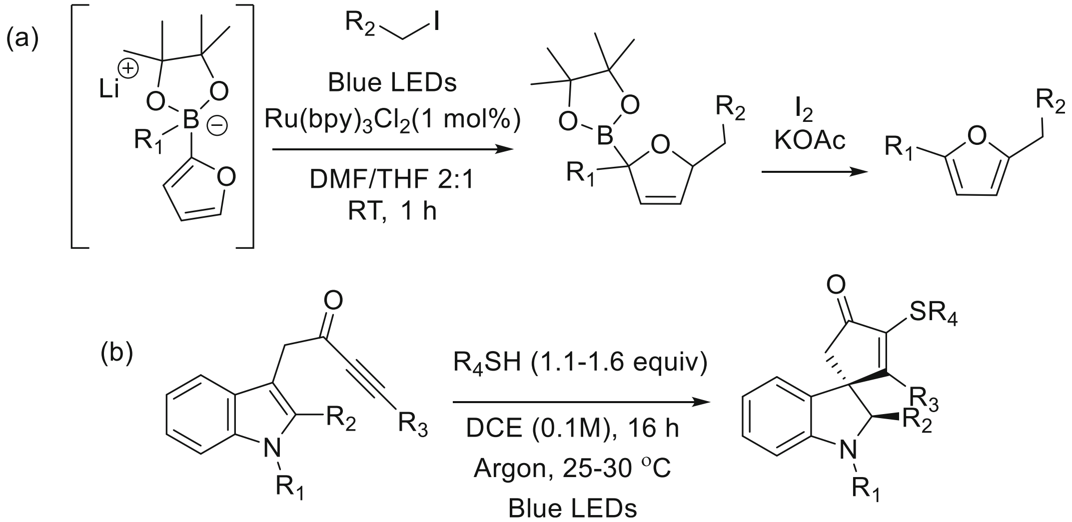
Scheme 7. Photoredox catalysis with smart initiation.



Scheme 8. Photocatalysis of initiation by an energy-transfer mechanism.

5.1 *Smart initiation*

It is generally easier to get an initiator to work more efficiently in a radical chain reaction than a catalyst. All that an initiator must worry about is a single step, while a catalyst must responsibly coordinate at least two. An initiation is 'smart' when the initiator catalytically provides a radical species involved in the chain-reaction and is regenerated. 'Smart initiation'

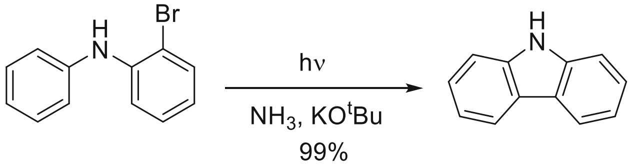


Scheme 9. Recent examples of catalysis by smart initiation.

would require a co-initiator (in electron-transfer reactions) or a photon (in energy-transfer reactions) to close the catalytic cycle. Although valuable for short chains, the initiator's controlled and continuous supply throughout the reaction is required through the catalytic cycle (**A**), thus enabling the use of expensive initiators in minute quantities (~1 g of initiator for >1 Kg of the substrate).[1g,12a–d]

In the generic example given in Scheme 7, irradiation excites Ru^{2+}(catalyst) to Ru^{2+*}. Ru^{2+*} then reduces the substrate (Sub-X) to provide Sub•, which starts the innate chain cycle and the metal going to ground state Ru^{3+}. Ru^{3+}, a potent oxidizing agent, oxidizes Et_3N (co-initiator) to the corresponding radical cation (Et_3N•+). This species further participates in a second oxidation step ending up in an iminium ion. The convenience and safety of such smart initiators have earned them an upper hand over traditional peroxides and azo compounds.

Photocatalysis of initiation can even occur by an energy transfer mechanism[1g] (Scheme 8). Triplet excited state of 4-methoxybenzaldehyde can sensitize the halomalonate causing it to homolyze the C-Br bond while regenerating the ground state photocatalyst. The malonyl radical thus produced initiates the innate cycle – smart!



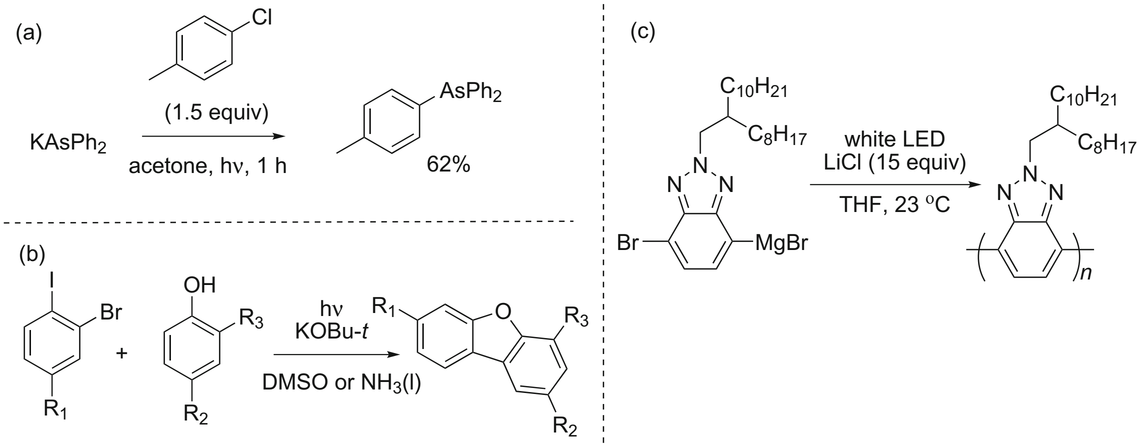
Scheme 10. Photochemical formation of carbazole from diarylamine.

The interesting reactivity of Ru^{2+*} has been exploited in recent literature. It acts as a smart initiator in the stereospecific three-component alkylation reaction between alkyl iodides and furan-derived boronate complexes under photoredox conditions.[12e] Another strategic initiation has been demonstrated by Ho and coworkers in the construction of sulfur-containing spirocyclic indolines. Here, in the absence of a catalyst, indole-tethered ynones form an intramolecular EDA complex and trigger thiyl radical generation from thiols (Scheme 9).[13]

5.2 *$S_{RN}1$ reaction*

The $S_{RN}1$ (Unimolecular Radical Nucleophilic Substitution) opened the gates to new C-C and C-X bond formation with those aromatic and aliphatic compounds for which nucleophilic substitution via polar $2e^-$ pathways are inaccessible or very slow. Since its inception in 1996, the scope of the reaction has enhanced. It started with the inclusion of vinyl halides, perfluoroalkyl halides, and heteroaromatic compounds as substrates, and a whole host of substrates from other classes.

t-BuOK is not only a strong base but also a single electron donor. (2-Bromo-N-phenylbenzenamine) on treatment with *t*-BuOK and ammonia in the presence of light gave the corresponding carbazole (Scheme 10).[14] The mechanism of this transformation is rather intriguing since the $2e^-$ pathways could be slow. It has been proposed that an electron transfer (ET) to the aryl halide from *t*-BuOK initiates a radical chain, generating a radical anion (R-X)•–. The



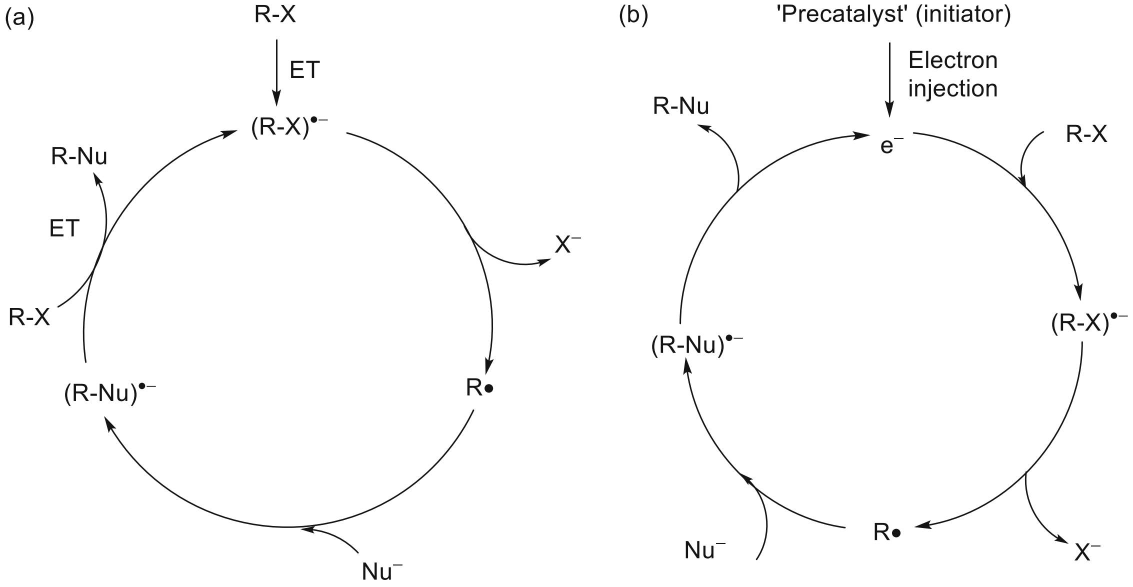
Scheme 11. $S_{RN}1$ reaction mediated (a) As-C aryl bond construction (b) synthesis of dibenzofurans (c) polymerization of Grignard monomers.

corresponding R• obtained from the radical anion fragmentation reacts with a nucleophile (intramolecular C-C arylation), producing conjugated radical anion (R–Nu)•–. (R–Nu)•– transfers electron (ET) to the radical precursor, yielding the R–Nu coupling product (carbazole). Nevertheless, there could be other interpretations of the mechanism, which is discussed in the following section below.

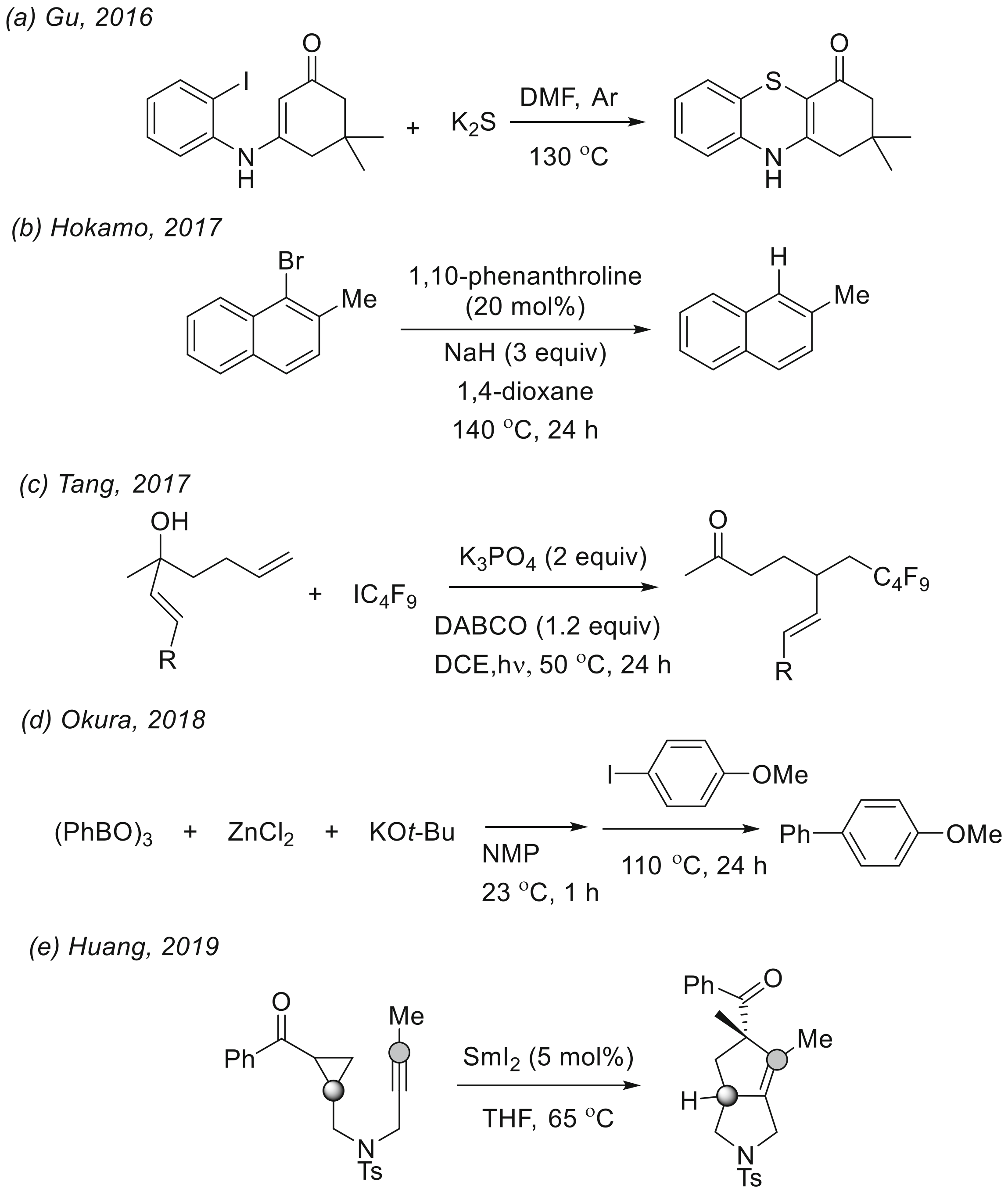
In 1980, Rossi *et al.,* constructed the challenging As-C(aryl) bond via light-mediated $S_{RN}1$ reaction between aryl halides and potassium arsenide.[15] Recent work by Solòrzano and coworkers exhibits the formation of substituted dibenzofurans from a light-induced coupling between 2-bromo-1-iodobenzene derivatives and substituted phenols proceeding through the $S_{RN}1$ pathway.[16] The chemistry has been applied successfully in radical polymerization of electron-deficient Grignard monomers (Scheme 11).[17]

5.3 *An Analogue of Proton Catalysis – An Electron Catalysis?*

An electron being omnipresent, often chain reactions initiated with transition metal salts or organic donor molecules, are mistakenly thought to be catalyzed by the initiator or metal, while the real catalyst is a tiny electron. Surprisingly, parallelism can be drawn between catalysis by acid/proton, H^+ (1.0 g mol^{-1}), and catalysis by an electron (0.00055 g mol^{-1}). A counterion accompanies both the charged species in



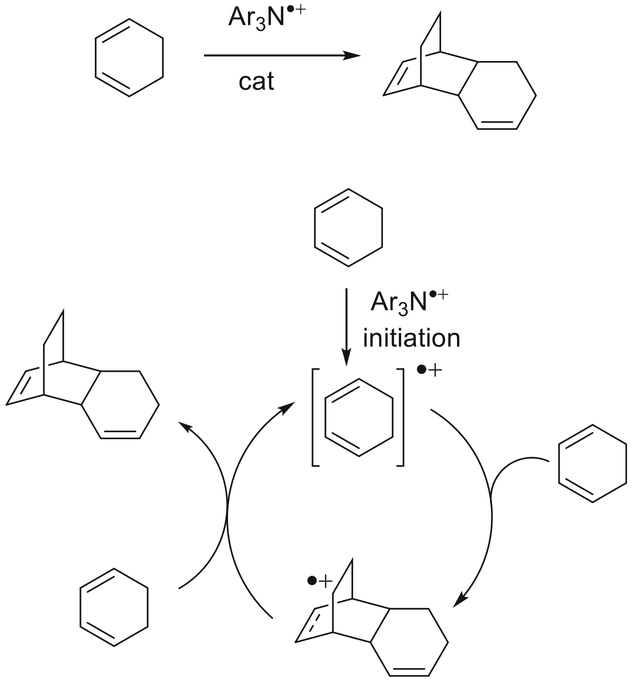
Scheme 12. (a) Classical view of the $S_{RN}1$-mechanism (b) $S_{RN}1$ reaction with the electron as the catalyst.



Scheme 13. A glimpse of electron catalyzed radical transformations in recent literature.

solution, and they practically do not appear in their respective catalytic cycle. Mechanistically, for both classes of reactions, a reactive intermediate is formed on either removing or adding a charged subatomic particle. The path to the product involves one or several in-between reactions, and finally, the reversal of the original particle closes the catalytic cycle to balance the charges.

If the reaction mechanism provided for the $S_{RN}1$ reaction can be re-imagined through the lens of electron catalysis – a convincing story stands out. The mechanism for the same example given in Scheme 10 can be investigated in the angle of the electron. The electron, released from a suitable donor (*t*-BuOK), is injected into the cycle to reduce R-X. The initiator is the ‘precatalyst’ that renders the real catalyst, the electron. The radical anion formed upon fragmentation releases R• that traps the nucleophile. The resultant (R–Nu)•– functions as an electron transfer reagent to furnish the product R–Nu and simultaneously sustains



Scheme 14. Hole-catalyzed Diels-Alder reaction.

the reaction by restoring the electron into the catalytic cycle (Scheme 12). Electron catalysis reactions can be initiated photochemically or electrochemically. Apart from S$_{RN}$1, several other radical cascades like radical Heck-type reactions, base-promoted homolytic aromatic substitutions (BHAS), and radical cross-dehydrogenative couplings (CDC) can be viewed through this paradigm.[18]

Identification of the electron as a catalyst candidate has caused a storm of research activities to harness its full potential (Scheme 13). Synthesis of benzothiazines *via* S$_{RN}$1 type electron catalysis in the presence of K_2S initiating sulfur insertion in enaminones is one such example from recent literature.[19] Studer and coworkers had disclosed the hydrodehalogenation of aryl bromides with NaH and 1,4 dioxane.[20] Another significant advancement from his group is the regioselective α-perfluoroalkylation of unactivated alkenes accompanying 1,4 alkenyl migration.[21] The Shirakawa group has popularized an electron-catalyzed cross-coupling between aryl iodides and aryl boroxines in presence of $ZnCl_2$ and KO^{t}Bu to gain access to biaryls.[22] Procter and coworkers have disclosed the synthesis of complex cyclic ketones in a SmI_2 catalyzed pathway: Radical relay cascade followed by electron catalysis.[23]

5.4 *Hole catalysis*

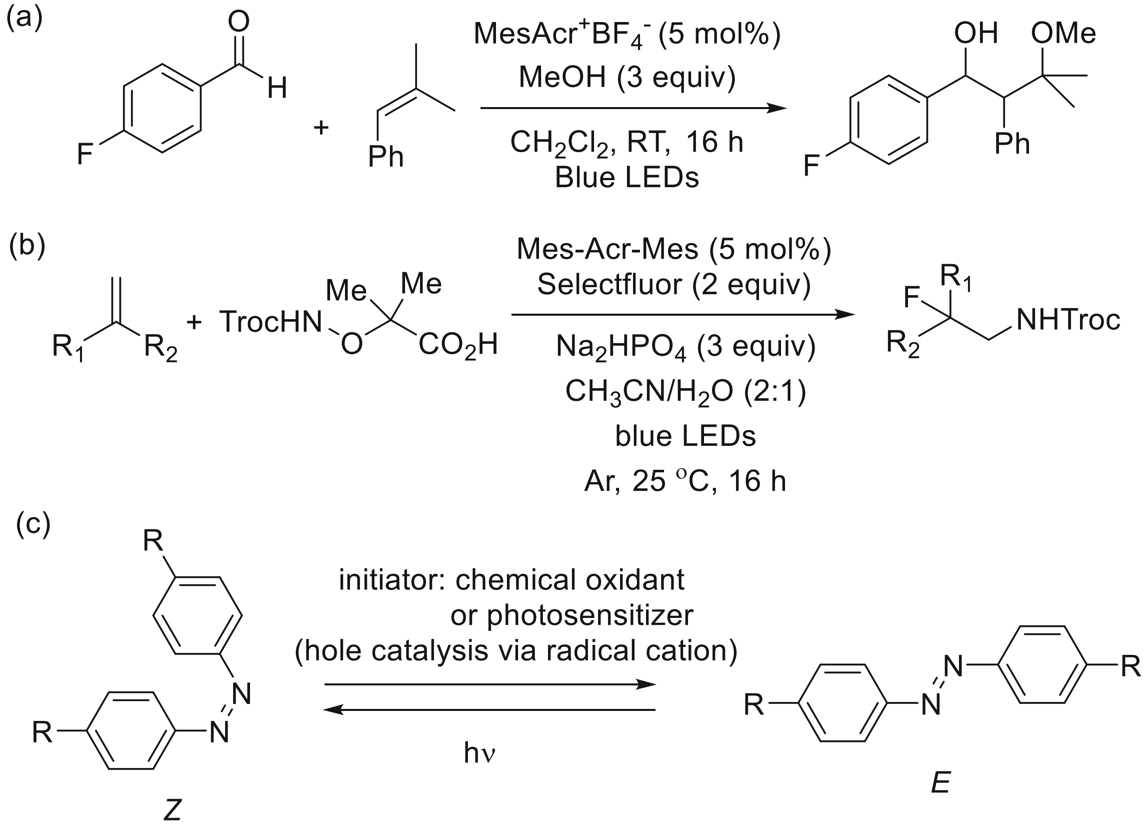
Hole catalysis is the converse of electron catalysis, as well as the redox analog of base catalysis. At the initiation step, an electron is withdrawn from the substrate rather than added. This signifies the creation of a *hole* in the valence shell of the substrate.

In Scheme 14, 1,3-cyclohexadiene transfers an electron to triarylammonium radical cation furnishing the corresponding radical cation. [24] This open-shell species initiates the chain and reacts with another molecule of 1,3-cyclohexadiene in an endo fashion to release the product radical cation (reduced conjugation). The cycloaddition step is indeed exothermic as σ-bonds are formed at the cost of π-bonds. Before closing the catalytic cycle, the product radical drives the final electron transfer to yield the dimer product while regenerating the cyclohexadienyl radical cation. Diels-Alder dimerization of cyclopentadiene happens spontaneously at room temperature. However, it is a lot difficult to dimerize 1,3-cyclohexadienes.

This unconventional mode of catalysis has been embraced by the synthetic community (Scheme 15). The activation of 4-fluorobenzaldehyde *in situ* by Brønsted acid and the subsequent trapping of alkyl radicals under photochemical conditions is a recent example.[25] Jiang and co-workers demonstrated how unactivated alkenes could be amido-fluorinated using α-amido-oxy acids as amidyl radical precursors.[26] The final addition of the alkene to the derived N-centered radical justifies the operation of hole catalysis. Another exemplary contribution of this strategy is the catalysis of Z to E isomerization of azobenzene derivatives.[27]

5.5 *Polarity reversal catalysis*

Previously, the concept of radical polarity was introduced. It would only be wise to expect that polarities of radicals should be matched for reactivity. Here comes the role of Polarity Reversal Catalysis (PCR) in taming the dragon, i.e., lowering the activation energy barrier or creating an alternate reaction pathway. Assuming a hydrogen atom transfer reaction (HAT), a radical of certain philicity would prefer to produce a resulting radical with opposite philicity. This transfer is kinetically favorable. Likewise, a radical of certain philicity to produce a radical with similar philicity is very slow and disfavored. However, PCR promises to replace the one step slow unfavorable reaction due to mismatched polarities with a shunted two-step polarity



Scheme 15. Participation of hole catalysis in (a) intermolecular radical addition to carbonyls (b) amido-fluorination of unactivated alkenes (c) isomerization of azobenzenes.

slow, mismatched reaction

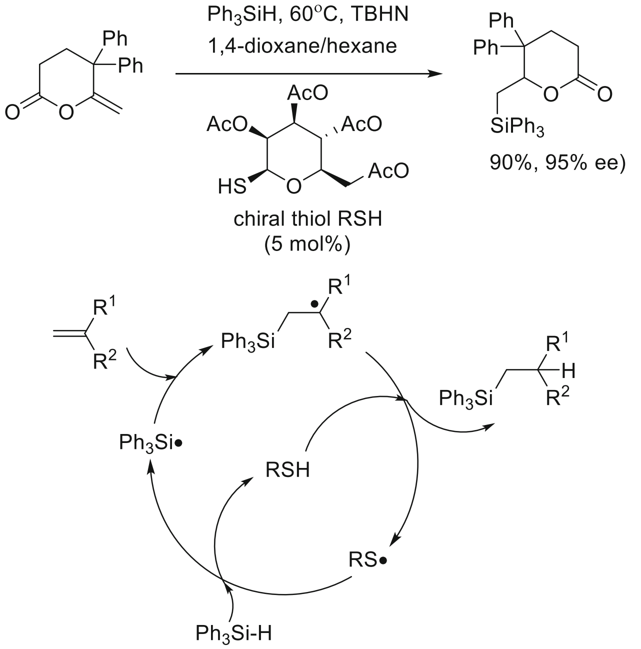
$$A^{\bullet nuc} + B\text{-}H^{nuc} \xrightarrow{\text{slow}} A\text{-}H^{nuc} + B^{\bullet nuc}$$

two fast, matched reactions to achieve the transformation

$$A^{\bullet nuc} + X\text{-}H^{elec} \xrightarrow{\text{fast}} A\text{-}H^{nuc} + X^{\bullet elec}$$

$$X^{\bullet elec} + B\text{-}H^{nuc} \xrightarrow{\text{fast}} X\text{-}H^{elec} + B^{\bullet nuc}$$

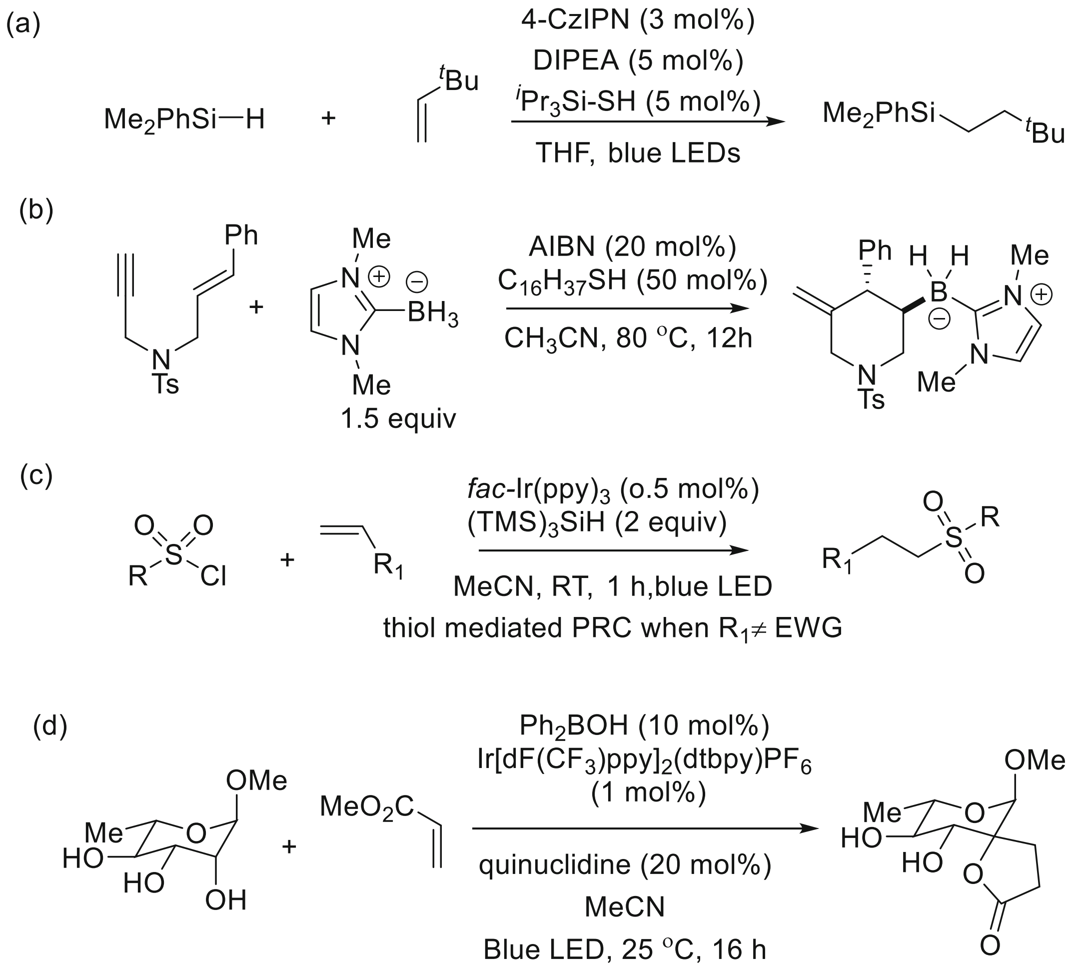
Scheme 16. Polarity reversal catalysis in hydrogen-transfer reactions.



Scheme 17. Asymmetric hydrosilylation reaction applying Polarity reversal catalysis.

matched process between the radicals and the substrates (Scheme 16).

For example, let us look at the thiol catalyzed asymmetric hydrosilylation reaction (Scheme 17).[28] In the presence of di-tert-butylhyponitrile (TBHN) and a mannose-derived chiral thiol catalyst, the lactone affords the enantioselective hydrosilylation product. TBHN is a source of tert-butoxy radical and reacts with the thiol to generate RS•, thus initiating the cycle. Perfect polarity matched addition happens when the electrophilic thiyl radical RS• abstracts H from Ph_3SiH to furnish the nucleophilic silyl radical, Ph_3Si•. The alkene adds to this silyl radical to generate a nucleophilic carbon radical, incapable of H-abstraction from Ph_3Si-H (Polarity mismatch). The carbon radical waits to abstract H-atom from the chiral thiol face-selectively giving the desired product in high enantiomeric excess. It must be noted that the silane



Scheme 18. (a) to (c) Recent reports which involve thiol mediated PRC (d) Polarity matched Hydrogen Atom Transfer in C-H alkylation of carbohydrates.

concentration is 20 times higher than the thiol. Still, the polarity match-mismatch effect runs the show dominantly. The resulting RS• then returns into the catalytic cycle. In the absence of chiral thiol, the reduction of the nucleophilic carbon radical by Ph_3SiH directly would be a polarity-mismatched reaction - rendering the reaction very slow.

Literature has encountered the appearance of thiol as a polarity reversal catalyst time and again. The recurrence has been established in the hydrosilylation of alkenes with electron-donating substituents under photoredox conditions.[29] Also, 1,6-enynes have undergone borylation and subsequent cyclization cascade to yield cyclic structures with an alkenyl or alkyl boron handles.[30] An NHC-boryl reagent induces such a transformation under the supervision of dodecanethiol as an additive. Hell *et al.*, have illustrated the assistance of thiol in hydrosulfonylation of unactivated alkenes in the presence of sulfonyl chloride.[31] Contrastingly, alkenes with electron-withdrawing substituents were self-sufficient. Stereoselective C-H alkylation of carbohydrates under dual photoredox and HAT catalysis has been reported.[32] Polarity matched HAT with the radical cation derived from quinuclidine accelerates such reactions (Scheme 18).

In summary, we have come a long way, from groping in the dark to call the free radical unwieldy and unpredictable to embracing it as essential chemistry in the synthetic community. Mild and neutral reaction conditions; compatibility with numerous functional groups; lesser tendency towards rearrangements and β-eliminations; reaction rates spanning several orders of magnitudes; and remarkable chemoselectivity: Free radical transformations are no longer optional, but an absolute necessity in the synthetic toolbox. Modern methodologies for the generation of radicals like photoredox chemistry, employment of redox-active scaffolds or EDA complexes, and metal-assisted generation have surmounted the challenges faced in classical ways. A better understanding of radical polarity has lifted the fog over the specifics of the transition state and related intermediates. This interpretation has made catalysis of radical reactions more viable. The gradual percolation of this unique chemistry into the industrial sector through flow photoreactors is commendable. The 'plug-and-play' aspect of radical chemistry continues to intrigue experimentalists and theoreticians alike. We still have a long way to go.

Acknowledgements

VG thanks Ramanujan Fellowship (RJN-2018/085) for the financial support. The authors thank IIT Kharagpur for the infrastructure provided.

References

1. (a) Romero K J, Galliher M S, Pratt D A and Stephenson C R 2018 Radicals in natural product synthesis *Chem. Soc. Rev.* **47** 785; (b) Plesniak M P, Huang H-M and Procter D J 2017 Radical Cascade Reactions Triggered by Single Electron Transfer *Nat. Rev. Chem.* **1** 0077; (c) Motherwell W B and Crich D 2013 *Free Radical Chain Reactions in Organic Synthesis* (London: Elsevier); (d) Gibian M and Corley R C 1973 Organic Radical-Radical Reactions. Disproportionation vs. Combination *Chem. Rev.* **73** 441; (e) Curran D P 1988 The design and application of free radical chain reactions in organic synthesis. Part 1 *Synthesis* **6** 417; (f) Gao Y, Zhou D, Lyu J, Sigen A, Xu Q, Newland B, Matyjaszewski K, Tai H and Wang W 2020 Complex Polymer Architectures through Free-Radical Polymerization of Multivinyl Monomers *Nat. Rev. Chem.* **4** 194; (g) Studer A and Curran D P 2016 Catalysis of Radical Reactions: A Radical Chemistry Perspective *Angew. Chem. Int. Ed.* **55** 58
2. Hedstrand D M, Kruizinga W H and Kellogg R M 1978 Light Induced and Dye Accelerated Reductions of Phenacyl Onium Salts by 1,4-Dihydropyridines *Tetrahedron Lett.* **19** 1255
3. Pandey G, Ghorai M K and Hajra S 1996 Design of a Photosystem to Harvest Visible-Light into Electrons: Photosensitised One Electron Redox Reactions in Organic Synthesis *Pure Appl. Chem.* **68** 653
4. Ischay M A, Anzovino M E, Du J and Yoon T P 2008 Efficient Visible Light Photocatalysis of [2+2] Enone Cycloadditions *J. Am. Chem. Soc.* **130** 12886
5. Nicewicz D A and MacMillan D W C 2008 Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes *Science* **322** 77
6. Lu Z and Yoon T P 2012 Visible Light Photocatalysis of [2+2] Styrene Cycloadditions by Energy Transfer *Angew. Chem. - Int. Ed.* **51** 10329
7. Tucker J W, Zhang Y, Jamison T F and Stephenson C R J 2012 Visible-Light Photoredox Catalysis in Flow *Angew. Chem.* **124** 4220
8. Iqbal J, Bhatia B and Nayyar N K 1994 Transition Metal-Promoted Free-Radical Reactions in Organic Synthesis: The Formation of Carbon-Carbon Bonds *Chem. Rev.* **94** 519
9. Nugent W A and RajanBabu T V 1988 Transition-Metal-Centered Radicals in Organic Synthesis. Titanium(III)-Induced Cyclization of Epoxyolefins *J. Am. Chem. Soc.* **110** 8561
10. Basch C H, Liao J, Xu J, Piane J J and Watson M P 2017 Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C-N Bond Activation *J. Am. Chem. Soc.* **139** 5313
11. (a) Crisenza G E, Mazzarella D and Melchiorre P 2020 Synthetic Methods Driven by the Photoactivity of Electron Donor–Acceptor Complexes *J. Am. Chem. Soc.* **142** 5461; (b) Lima C G, de M Lima T, Duarte M, Jurberg I D and Paixao M W 2016 Organic synthesis enabled by light-irradiation of EDA complexes: theoretical background and synthetic applications *ACS Catal.* **6** 1389; (c) Yuan Y Q, Majumder S, Yang M H and Guo S R 2020 Recent advances in catalyst-free photochemical reactions via electron-donor-acceptor (EDA) complex process *Tetrahedron Lett.* **61** 151506; (d) Sun J, He Y, An X De, Zhang X, Yu L and Yu S 2018 Visible-Light-Induced Iminyl Radical Formation: Via Electron-Donor-Acceptor Complexes: A Photocatalyst-Free Approach to Phenanthridines and Quinolines *Org. Chem. Front.* **5** 977
12. (a) Narayanam J M and Stephenson C R 2011 Visible light photoredox catalysis: applications in organic synthesis *Chem. Soc. Rev.* **40** 102; (b) Majek M, Filace F and von Wangelin A J 2014 On the mechanism of photocatalytic reactions with eosin Y *Beilstein J. Org. Chem.* **10** 981; (c) Cismesia M A and Yoon T P 2015 Characterizing chain processes in visible light photoredox catalysis *Chem. Sci.* **6** 5426; (d) Kärkäs M D, Matsuura B S and Stephenson C R 2015 Enchained by visible light-mediated photoredox catalysis *Science* **349** 1285; (e) Silvi M, Schrof R, Noble A and Aggarwal V K 2018 Enantiospecific Three-Component Alkylation of Furan and Indole *Chem. - A Eur. J.* **24** 4279
13. Ho H E, Pagano A, Rossi-Ashton J A, Donald J R, Epton R G, Churchill J C, James M J, O'Brien P, Taylor R J K and Unsworth W P 2020 Visible-Light-Induced Intramolecular Charge Transfer in the Radical Spirocyclisation of Indole-Tethered Ynones *Chem. Sci.* **11** 1353
14. Budén M E, Vaillard V A, Martin S E and Rossi R A 2009 Synthesis of Carbazoles by Intramolecular Arylation of Diarylamide Anions *J. Org. Chem.* **74** 4490
15. Rossi R A, Alonso R A and Palacios S M 1981 Photostimulated Reactions of Potassium Diphenylarsenide with Haloarenes by the $S_{RN}1$ Mechanism *J. Org. Chem.* **46** 2498
16. Camargo Solórzano P, Brigante F, Pierini A B and Jimenez L B 2018 Photoinduced Synthesis of Dibenzofurans: Intramolecular and Intermolecular Comparative Methodologies *J. Org. Chem.* **83** 7867
17. Woods E F, Berl A J and Kalow J A 2020 Photocontrolled Synthesis of N-Type Conjugated Polymers *Angew. Chemie - Int. Ed.* **59** 6062
18. Studer A and Curran D P 2014 The Electron is a Catalyst *Nat. Chem.* **6** 765
19. Gu Z Y, Cao J J, Wang S Y and Ji S J 2016 The involvement of the trisulfur radical anion in electron-catalyzed sulfur insertion reactions: facile synthesis of

benzothiazine derivatives under transition metal-free conditions *Chem. Sci.* **7** 4067

20. Hokamp T, Dewanji A, Lübbesmeyer M, Mück-Lichtenfeld C, Würthwein EU and Studer A 2017 Radical Hydrodehalogenation of Aryl Bromides and Chlorides with Sodium Hydride and 1, 4-Dioxane *Angew. Chem. Int. Ed.* **56** 13275
21. Tang X and Studer A 2018 Alkene 1, 2-Difunctionalization by Radical Alkenyl Migration *Angew. Chem. Int. Ed.* **130** 822
22. Okura K, Teranishi T, Yoshida Y and Shirakawa E 2018 Electron-Catalyzed Cross-Coupling of Arylboron Compounds with Aryl Iodides *Angew. Chem. Int. Ed.* **57** 7186
23. Huang H M, McDouall J J and Procter D J 2019 SmI_2-catalysed cyclization cascades by radical relay *Nat. Catal.* **2** 211
24. Pabon R A, Bellville D J and Bauld N L 1983 Cation radical Diels-Alder reactions of electron-rich dienophiles *J. Am. Chem. Soc.* **105** 5158
25. Pitzer L, Sandfort F, Strieth-Kalthoff F and Glorius F 2017 Intermolecular Radical Addition to Carbonyls Enabled by Visible Light Photoredox Initiated Hole Catalysislena *J. Am. Chem. Soc.* **139** 13652
26. Jiang H and Studer A 2018 Amidyl Radicals by Oxidation of α-Amido-Oxy Acids: Transition-Metal-Free Amidofluorination of Unactivated Alkenes *Angew. Chem. Int. Ed.* **57** 10707
27. Goulet-Hanssens A, Rietze C, Titov E, Abdullahu L, Grubert L, Saalfrank P and Hecht S 2018 Hole Catalysis as a General Mechanism for Efficient and Wavelength-Independent Z → E Azobenzene Isomerization *Chem.* **4** 1740
28. Haque M B and Roberts B P 1996 Enantioselective radical-chain hydrosilylation of prochiral alkenes using optically active thiol catalysts *Tetrahedron Lett.* **37** 9123
29. Zhou R, Goh Y Y, Liu H, Tao H, Li L and Wu J 2017 Visible-Light-Mediated Metal-Free Hydrosilylation of Alkenes through Selective Hydrogen Atom Transfer for Si—H Activation *Angew. Chem. Int. Ed.* **56** 16621
30. Ren S C, Zhang F L, Qi J, Huang Y S, Xu A Q, Yan H Y and Wang Y F 2017 Radical Borylation/Cyclization Cascade of 1,6-Enynes for the Synthesis of Boron-Handled Hetero- and Carbocycles *J. Am. Chem. Soc.* **139** 6050
31. Hell S M, Meyer C F, Misale A, Sap J B I, Christensen K E, Willis M C, Trabanco A A and Gouverneur V 2020 Hydrosulfonylation of Alkenes with Sulfonyl Chlorides under Visible Light Activation *Angew. Chem. Int. Ed.* **59** 11620
32. Dimakos V, Su H Y, Garrett G E and Taylor M S 2019 Site-Selective and Stereoselective C-H Alkylations of Carbohydrates via Combined Diarylborinic Acid and Photoredox Catalysis *J. Am. Chem. Soc.* **141** 5149