Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS

ACCEPTED MANUSCRIPT

Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. **00(0)** 1-29 (2026)
JSCS–14130
Survey
Published DD MM, 2026

Radical leaps in radical chemistry. Part 1

MILENA TRMCIC[1], FILIP BIHELOVIC[2], BOJAN VULOVIC[2], AND RADOMIR N. SAICIC[2,3]*

[1]*University of Belgrade – Innovative Centre Faculty of Chemistry Belgrade, Studentski trg 12, 11158 Belgrade, Serbia,* [2]*University of Belgrade – Faculty of Chemistry, Studentski trg 12, 11158 Belgrade, Serbia,* [3]*Serbian Academy of Sciences and Arts, Kneza Mihaila 35, 11000 Belgrade, Serbia.*

(Received 10 August; revised 21 August; accepted 28 August 2026)

Abstract: Since the final decade of the twentieth century, radicals – once regarded as highly reactive and difficult-to-control intermediates – have become indispensable tools of modern synthetic organic chemistry. Classical methods of radical generation, including tributyltin hydride chemistry, the Barton reaction, and atom- or group-transfer processes, have matured into standard synthetic methodologies. More recently, however, new radical precursors, mechanistic insights, and catalytic strategies have dramatically expanded both the scope and the synthetic potential of radical reactions, fundamentally reshaping their role in retrosynthetic planning. This Review highlights some of the most significant conceptual and methodological advances in carbon–carbon bond-forming radical reactions achieved during the past two decades. Electrochemical methods are beyond the scope of this article. Owing to its length, the Review is presented in two consecutive parts. Part 1 comprises the Introduction, six topics illustrating recent advances in "classical" radical chemistry, and five topics describing conceptual developments associated with visible-light photocatalysis. Part 2 covers twelve additional visible-light-photocatalytic transformations together with applications of radical chemistry in total synthesis.

Keywords: organic synthesis; catalysis; photoredox; visible light photocatalysis; persistent radical effect; cross coupling.

* Corresponding author. E-mail: rsaicic@chem.bg.ac.rs
https://doi.org/10.2298/JSC260810052T

CONTENTS

1. INTRODUCTION

For almost 80 years after Gomberg's seminal discovery of the triphenylmethyl radical (and his expressed wish to preserve this topic of research for himself),[1] radicals were regarded more as exotic reactive intermediates than as a platform for the development of synthetic methodology. The prevailing perception of their high reactivity and, consequently, low selectivity discouraged their widespread application in laboratory synthesis, with notable exceptions such as allylic bromination, Kochi hydrobromination of alkenes, and remote functionalizations exemplified by the Hunsdiecker, Hofmann–Löffler–Freytag, and Barton reactions. Continuous mechanistic studies and the accumulation of physicochemical data on radical species gradually changed this perception. The famous 1985 *Tetrahedron* Symposium in Print, which gathered contributions from many pioneers of synthetic radical chemistry,[2] symbolized this change of paradigm and the emergence of radical reactions as reliable tools of synthetic organic chemistry. During the following decades, methods based on tributyltin hydride, Barton thiohydroxamic esters, tris(trimethylsilyl)silane, manganese(III) acetate, samarium(II) iodide, and atom/group-transfer reactions of halides and xanthates became established synthetic tools, particularly for carbon–carbon bond formation, as demonstrated by their numerous applications in the total synthesis of complex natural products.[3]

Since the beginning of the 21st century, however, the development of radical chemistry has undergone a qualitative rather than merely quantitative change. Many of the limitations traditionally associated with radical reactions have been progressively overcome through the introduction of new and readily accessible radical precursors, milder and more efficient methods of radical generation, and greater control over radical reactivity, lifetime, and selectivity. At the same time, the merger of radical chemistry with other modes of activation and catalysis has opened reaction pathways that have no straightforward counterpart in classical radical chemistry. Visible-light photocatalysis has been particularly transformative in this respect, enabling radicals to be generated under mild conditions by single-electron transfer and allowing radical processes to be integrated with organocatalytic and transition-metal catalytic cycles. Other developments – including hydrogen-atom-transfer processes, radical–polar crossover, radical cross-coupling and radical sorting, as well as increasingly effective stereochemical control – have further expanded the range of structures and bond constructions accessible through radical intermediates. Consequently, radicals are no longer employed merely as highly reactive intermediates capable of performing a limited repertoire of characteristic transformations, but as species whose generation and subsequent reaction pathways can increasingly be designed and controlled.

These developments have also changed the role of radicals in synthetic planning. Transformations involving radical intermediates can provide bond

disconnections complementary to those derived from conventional polar chemistry,[4] permit direct use of abundant functional groups as radical precursors, and enable rapid increases in molecular complexity through cascade reactions, cross-couplings, and skeletal reorganizations. Thus, the recent renaissance of radical chemistry is characterized not simply by an increasing number of radical reactions, but by a substantial expansion of the mechanistic and strategic space available to synthetic chemists.[5-7]

This Review highlights some of the most important advances in carbon–carbon bond formation *via* radical intermediates that have emerged during the past two decades. Rather than providing a systematic account of the state of the art, our intention is to identify conceptual and methodological advances that have significantly expanded the synthetic capabilities of radical chemistry and to illustrate them with representative examples. The selection is necessarily influenced by the authors' judgement, and some important contributions will inevitably have been omitted.

For the purposes of discussion, the developments reviewed here are provisionally divided into two broad groups. The first comprises advances that extend the scope and overcome important limitations of "classical" radical chemistry through improved radical precursors, reagents, initiation methods, and control of radical reactivity. The second encompasses new mechanistic manifolds that have emerged from visible-light photocatalysis (VLP) and its combination with other catalytic modes. The boundary between these categories is necessarily permeable, but the distinction provides a useful framework for tracing the evolution from classical radical methodology to the increasingly diverse reaction networks of contemporary radical chemistry.

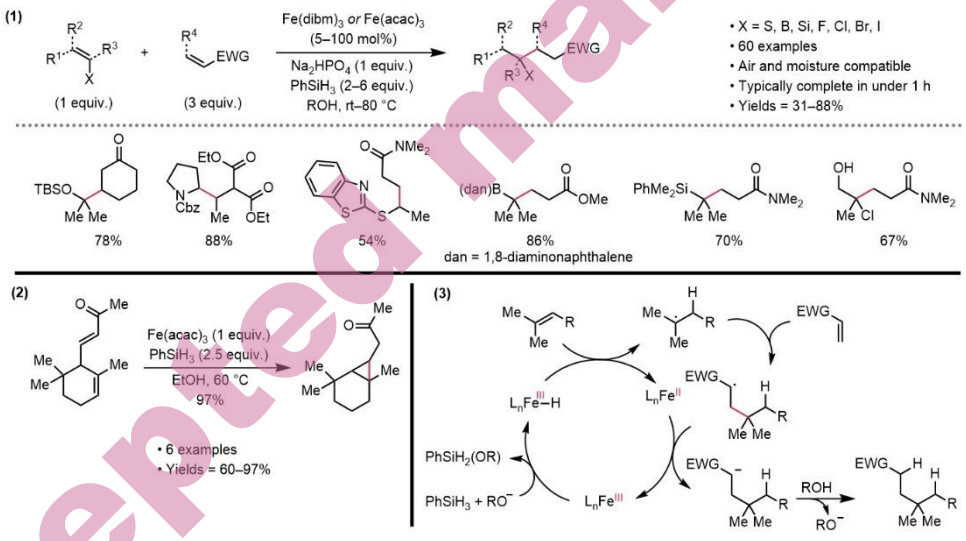
The reader is assumed to be familiar with the basic principles of radical chemistry and the principal methods of radical generation for synthetic purposes. Excellent books[8,9] and review articles[4-7,10,11] are available that cover these subjects in greater detail and provide extensive illustrations of the application of free radicals in the synthesis of natural products,[12] pharmaceuticals,[13] agrochemicals, and other structurally complex targets.

2. WHAT'S NEW IN "CLASSICAL" RADICAL CHEMISTRY

2.1. New reagent: $Fe(acac)_3/PhSiH_3$

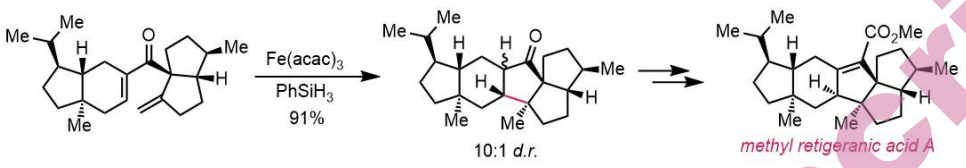
Reagents are at the core of synthetic efficiency. The scope, and hence the applicability, of synthetic transformation largely depends on the availability of precursors. "Traditional" radical precursors encompass alkyl (alkenyl, aryl) halides (iodides and bromides; rarely chlorides – only activated ones), selenides, carbonyl compounds (reductively – *via* the corresponding ketyls, or oxidatively – at the α-position), and carboxylic acids (through decarboxylation). The drawback of these methods is that the appropriate functional group has to be introduced at

the proradical carbon atom of the precursor, which will subsequently be „lost" (sacrified) in order to generate a radical intermediate. Alkenes and alkynes are ubiquitous feedstock for synthetic chemistry, and it would be highly desirable to use them as direct radical precursors. Stork discovered early on that reversible addition of tributyltin radicals to alkynes can be used for such purpose; however no analogous, comparably efficient method for alkenes was available. This changes dramatically with the discovery of Baran and collaborators, that iron complex-mediated reaction of alkenes with silanes offers a general method of radical generation, for both inter- and intramolecular reactions (Scheme 1, examples 1 and 2).[14,15] Remarkably, the reaction tolerates a broad range of functional groups



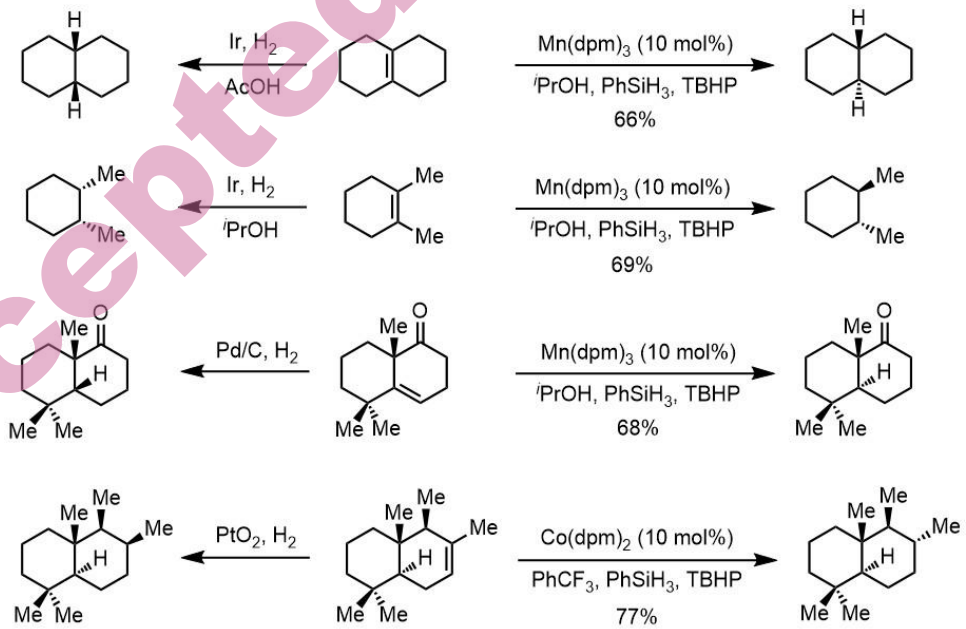
Scheme 1

(even halides!), is not sensitive to oxygen or moisture, and can be performed on a gram scale. Even cyclopropane ring formation – a notoriously difficult transformation in free radical chemistry – proceeds very well. The reaction mechanism is represented in Scheme 1 (example 3); note that the radical center is created at the more substituted alkene end, and that the method is suitable for the creation of quaternary carbon atoms. Not surprisingly, it has already found extensive synthetic application, including the most complex synthetic targets, such as retigeranic acid A, where the key step in the synthesis involves notoriously difficult 5-*endo*-cyclization (Scheme 2).[16] A related reagent disclosed by Shenvy and



Scheme 2

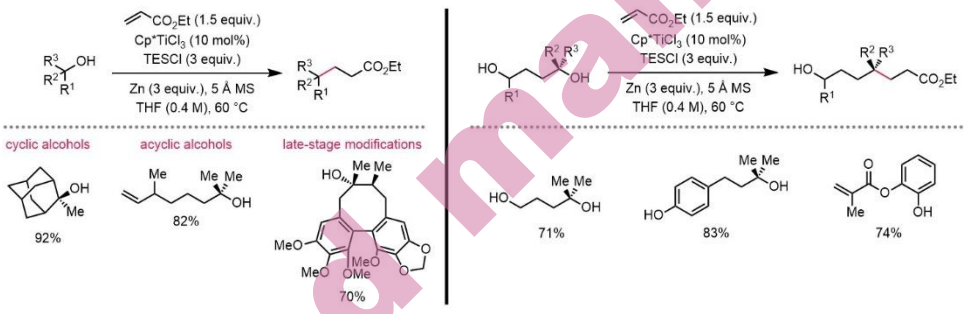
coworkers – $Mn(dpm)_3/PhSiH_3/TBHP$ – allows for hemoselective hydrogenation of alkenes with thermodynamic control: substituted cyclohexene substrates afford more stable di-equatorial isomers, much alike dissolving metal reductions, but with remarkably broad functional group tolerance (Scheme 3).[17] The stereoselectivity of the reaction may be explained by the fact that it proceeds *via* the tertiary cyclohexyl radical. These radicals are known to pyramidalize in the transition state, and react with tributyltin deuteride with high axial selectivity; HAT from phenylsilane follows the same stereochemical pathway. An interesting reagent for radical difunctionalization of styrenes is the combination of Togni reagent and chiral Cu(I) catalyst, which provides trifluoromethylated products with high *ee*.[18] The use of iron, manganese and cobalt reagents in synthetic radical chemistry,[19] notably hydrofunctionalization of alkenes,[20] has been reviewed.



Scheme 3

2.2. Alcohols as direct carbon radical precursors (1)

The use of alcohols as carbon radical precursors requires activation, *i.e.*, their conversion into xanthates, thiocarbamates, mixed esters, or other active derivatives capable of C–O bond homolysis. Obviously, it would be much more convenient to use alcohols directly.[21,22] Shu, Wang and coworkers found that tertiary alcohols undergo direct deoxygenative functionalization in the presence of low valent titanium species generated *in situ*.[23] The resulting radicals participate in Giese addition, and, notably, tertiary alcohols are selectively transformed in the presence of primary alcohols (Scheme 4). Oxorhenium catalyst enables Giese addition of benzyl radicals generated from the corresponding alcohols.[24]

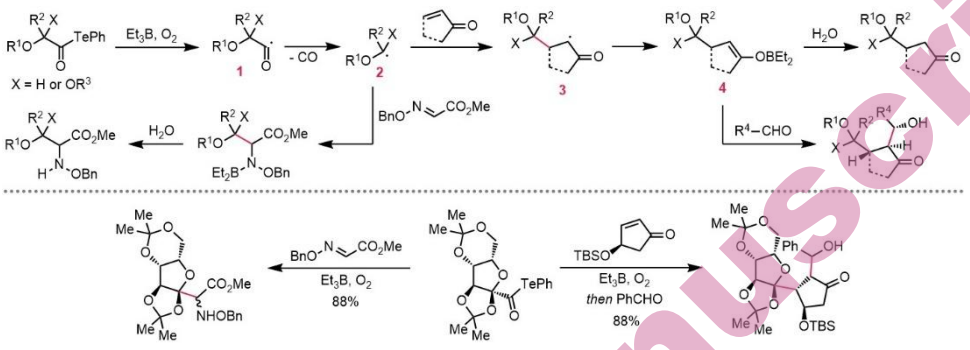


Scheme 4

Other variants of the reaction have been reported,[25-27] and this topic has been reviewed.[28] Other methods for carbon radical generation directly from alcohols are displayed in section dedicated to photoredox reactions (*vide infra*).

2.3. Acyl telluride/Et3B system of radical generation: Additions to non-terminal alkenes

In intermolecular radical additions (Giese reactions), the most widely used methods of radical generation, such as the tributyltin hydride or Barton methods, are generally limited to terminal alkenes as radical acceptors, apart from doubly activated alkenes and a few other exceptions. Inoue and coworkers overcame this long-standing limitation by developing a method based on α-alkoxyacyl tellurides as radical precursors in combination with triethylborane, which serves both as the chain initiator and as the kinetic trapping reagent.[29] The reaction is initiated by generation of the Et radical from the Et_3B/O_2 system, which induces homolytic cleavage of the C–Te bond. The resulting acyl radical **1** undergoes rapid decarbonylation, as the corresponding alkoxyalkyl radical **2** is stabilized. This last species subsequently adds to electron-deficient alkene, a transformation that proceeds efficiently even with substituted alkenes, because this method allows radicals a relatively long lifetime (in contrast to TBTH method, where a fast hydrogen abstraction results in premature reduction of alkoxyalkyl intermediate). Et_3B rapidly reacts with adduct radical **3**, converting it into boron

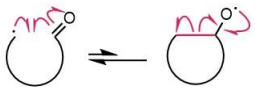


Scheme 5

enolate **4**, which can be either undergo protodeborylation or be further exploited in an aldol reaction. Accordingly, both two- and three-component coupling reactions become possible, providing highly oxygenated products (Scheme 5).

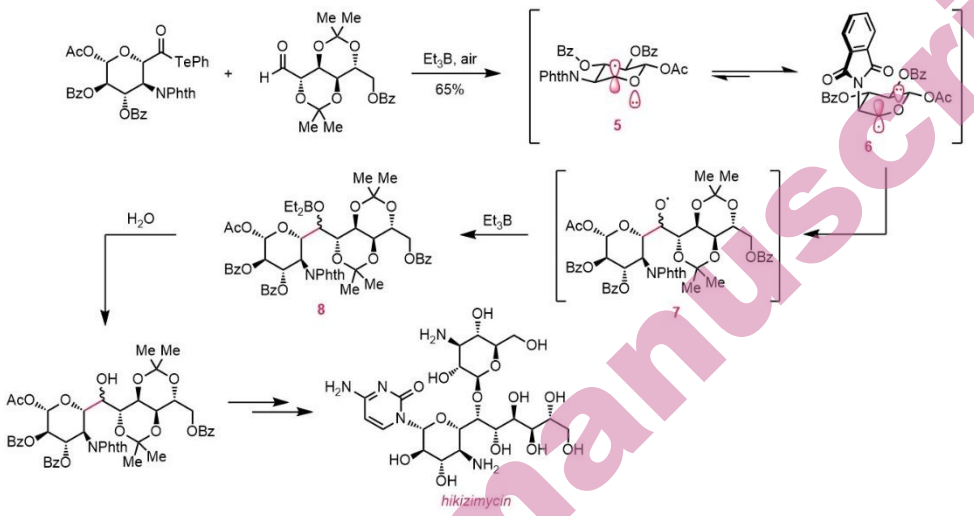
2.4. Acyl telluride/Et₃B system of radical generation: Intermolecular additions of carbon radicals to aldehydes

For a long time, additions of carbon-centered radicals to carbonyl groups have been considered synthetically unfeasible, due to unfavorable overal thermodynamics of such a transformation, where the equilibrium is strongly shifted towards thermodynamically more stable fragmented radical (Scheme 6).[30] In 1986 it was found that 6-*exo*-cyclization can be



Scheme 6

accomplished under kinetic control in the presence of TBTH, which rapidly quenches cyclic alkoxy radical;[31-34] however, intermolecular variant of this reaction remained elusive. In the preceding study (Scheme 5), Inoue and collaborators found that acyl telluride/Et₃B method of radical generation can be successfully applied for additions to C=N bonds, and illustrated the applicability of this reaction in their unified total synthesis of important nucleoside antibiotics polyoxins.[35] This methodology was further extended to additions to aldehydes and elegantly exploited in the remarkable total synthesis of hikizimycin (Scheme 7).[36,37] The initial radical can adopt two conformations: **5** and **6**. Although **5** places all substituents in the more favorable equatorial positions, conformer **6** presents the C-1 radical in a stereoelectronically more favorable orientation for addition, which therefore proceeds preferentially from the α-face.



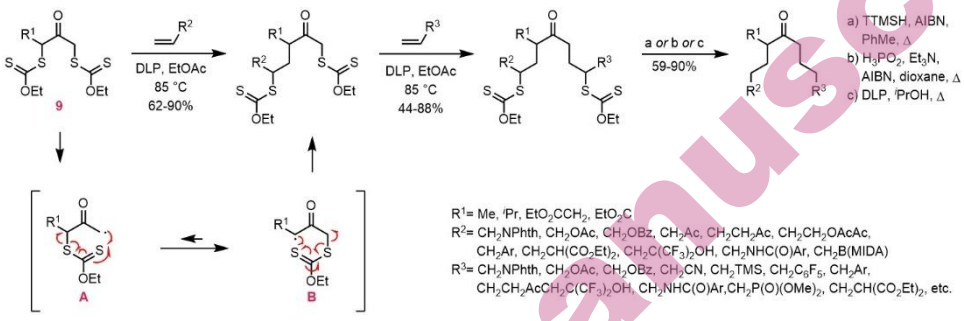
Scheme 7

Here again, triethylborane acts as a kinetic trapping agent by rapidly converting the final alkoxy radical intermediate **7** into borinate **8**. Fast trapping suppresses the reverse β-fragmentation and thereby renders an otherwise thermodynamically unfavorable intermolecular radical addition synthetically viable.

2.5. Regioselectivity in reactions of xanthates

Group-transfer reactions of xanthates have long been established as a classical method for the generation of synthetically useful carbon-centered radicals.[38] More recently, however, an impressive level of regiocontrol has been achieved through the development of regiodivergent radical reactions. The example shown in Scheme 8 addresses the long-standing problem of regioselective alkylation of unsymmetrical acyclic ketones.[39] Zard and coworkers demonstrated that unsymmetrical xanthates of type **9** undergo regioselective addition to alkenes with inverse electron demand. Precursor **9** can give rise to two radicals – **A** and **B** – which rapidly interconvert *via* intramolecular xanthate transfer, and which react with alkene with the same rate. More substituted radical (**B**) is thermodynamically favored (~3-4 kcal mol^{-1}) and dominates in the equilibrium (>100 : 1), hence the regioselectivity of the addition. The resulting adducts can subsequently be reduced to furnish dialkylated products with essentially complete regioselectivity. Overall, the transformation provides the radical equivalent of enolate alkylation with simple alkenes while tolerating a wide range of functional groups that would require protection under conventional enolate chemistry. Ironically, radicals – once regarded as highly reactive and inherently unselective intermediates – here provide a solution to one of the long-standing problems of selective organic synthesis. The

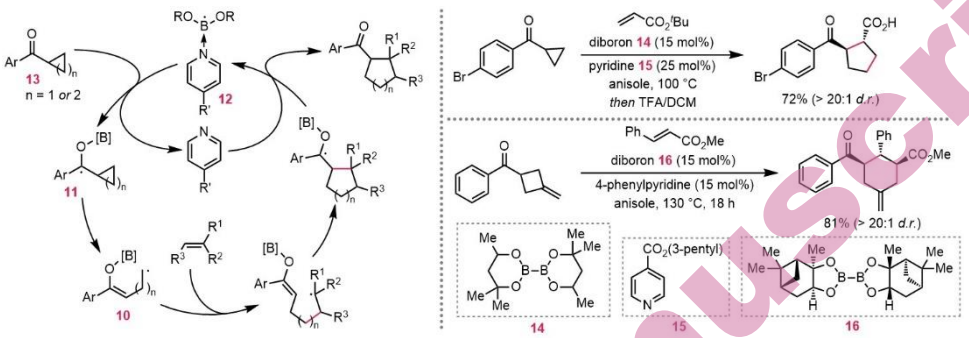
same group subsequently reported additional examples of regioselective additions to strained boronates, where the reaction outcome is governed by subtle control of both kinetic and thermodynamic factors.[40,41]



Scheme 8

2.6. B-promoted radical reactions

Some may regard the choice of initiator as a minor issue, since its role is merely to trigger the propagation cycle.[42] However, it may have a profound influence on the success of a radical reaction. The Et_3B/O_2 system provides steady initiation even at temperatures as low as −78 °C, a feature that is particularly advantageous for stereoselective reactions.[43] Even more importantly, boron-mediated radical catalysis can provide sufficiently long-lived radical intermediates to enable otherwise prohibitively slow radical processes. The annulation method presented in Scheme 9 illustrates this concept. The first example shows a formal free radical 3+2 annulation reaction, where the requisite 3-butenyl radical **10** (n = 1) is generated by fragmentation of cyclobutylmethyl radical **11**, on its turn created by the action of pinacolatoboron/pyridine complex **12** on phenyl cyclopropylketone **13** (n = 1).[44] Whereas this fragmentation/addition/cyclization sequence can be performed with other reagents (as disclosed by Feldman and coworkers),[45,46] the analogous reaction with cyclobutylmethyl radicals was not possible, as the fragmentation of cyclobutylmethyl radical to 4-pentenyl radical is slow. The boron-mediated methodology overcomes this limitation by allowing sufficient time for the fragmentation to occur, and the second example proves the feasibility of such a transformation as a useful method to access substituted cyclohexane derivatives *via* a formal 4+2 cycloaddition (Scheme 9).[47]

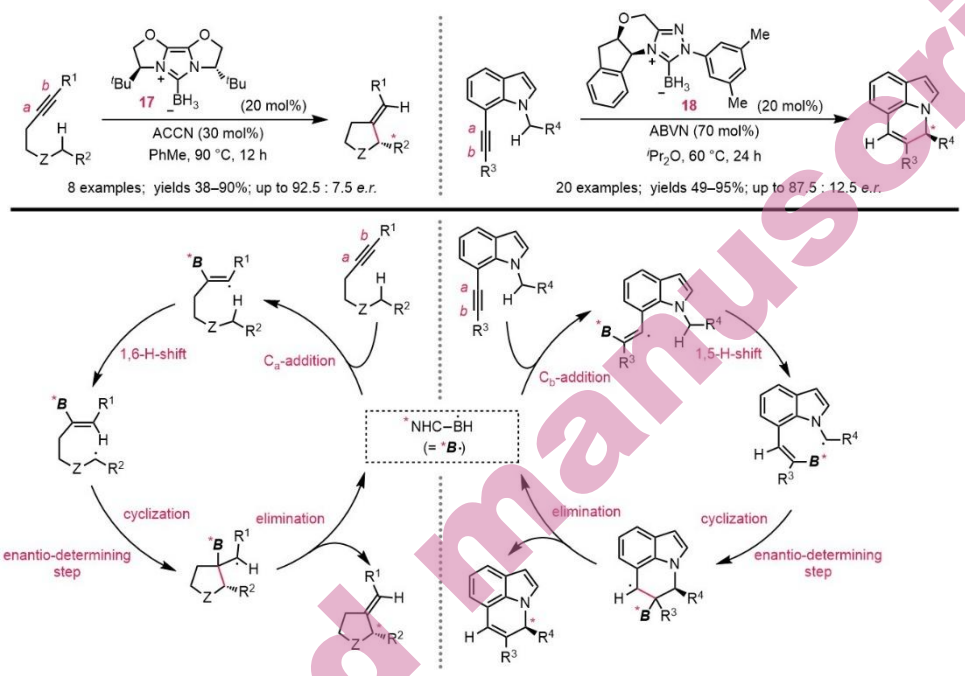


Scheme 9

Another important development concerns ligated boryl radicals (LBRs). Coordination of a Lewis base to the electron-deficient boron centre stabilizes these species, while their electronic and steric properties – and hence their reactivity – can be modulated by the ligand.[48] Particularly important are N-heterocyclic carbene (NHC)-boryl radicals, which combine enhanced stability with pronounced nucleophilic radical character and participate readily in HAT/XAT and bond-forming processes.[49]

NHC-borane complexes are known for some time, and they can act as transfer agents in radical chain reactions.[50] Recently, it was found that these complexes can engage in asymmetric radical cycloisomerization reactions, as exemplified in Scheme 10.[51] Similar transformations have earlier been accomplished with TBTH,[52,53] or with thiophenol,[54] as transfer agents, but the new accomplishment brings about an important difference, as the incorporation of a chiral NHC component, such as in **17**, or **18**, enables asymmetric induction during the cyclization step, thereby transforming a conventional radical sequence into a catalytic asymmetric synthesis. (CAS).

The advances discussed in sections 2.1.–2.6. do not alter the fundamental mechanistic principles of radical chemistry. Rather, they systematically remove the major synthetic limitations of classical radical reactions through improved radical precursors, greater control of radical reactivity and lifetime, and more efficient initiation strategies. The next section illustrates how visible-light photocatalysis went one step further, introducing entirely new mechanistic manifolds that transformed the strategic role of radicals in organic synthesis.



Scheme 10

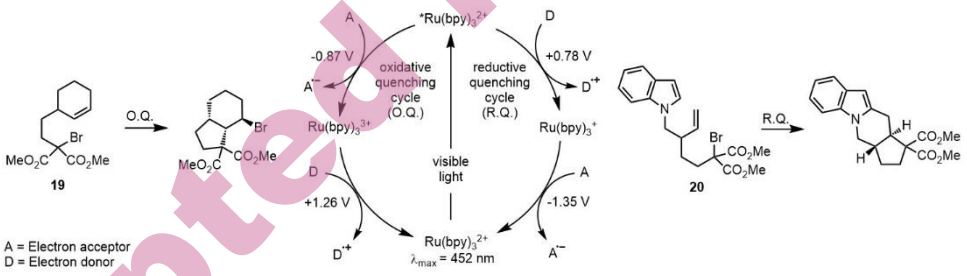
3. THE VISIBLE-LIGHT PARADIGM SHIFT: QUALITATIVELY NEW CONCEPTS AND TRANSFORMATIONS IN RADICAL-BASED ORGANIC SYNTHESIS[55,56]

Traditional methods of free radical generation typically relied on the thermolysis of unstable initiators (such as peroxides or azobis compounds) or photolysis of specific bonds (reagents) using high-energy ultraviolet (UV) light. The seminal reports in 2008-2009[57-59] fundamentally altered this landscape and opened new avenues in synthetic radical chemistry. By leveraging low-energy visible light and photoexcitable catalysts, chemists unlocked a "photon democracy" where reactive intermediates (radicals, radical ions, and excited states) could be generated and tamed under exceptionally mild, ambient conditions. This transition did more than just provide a "greener" alternative to classical initiators; it introduced a suite of qualitatively new concepts and transformations that were previously unimaginable within the constraints of traditional radical generation or two-electron manifold logic.

3.1. Simultaneous electronic duality of the photocatalyst[60]

A fundamental concept introduced by visible light photocatalysis (VLP) to organic synthesis is the ability of a single catalytic species to act simultaneously as both a potent oxidant and a potent reductant. In traditional redox manifolds, such as electrochemistry, the reaction environment is typically bifurcated: the anode serves as an oxidative sink, while the cathode serves as a reductive source. To

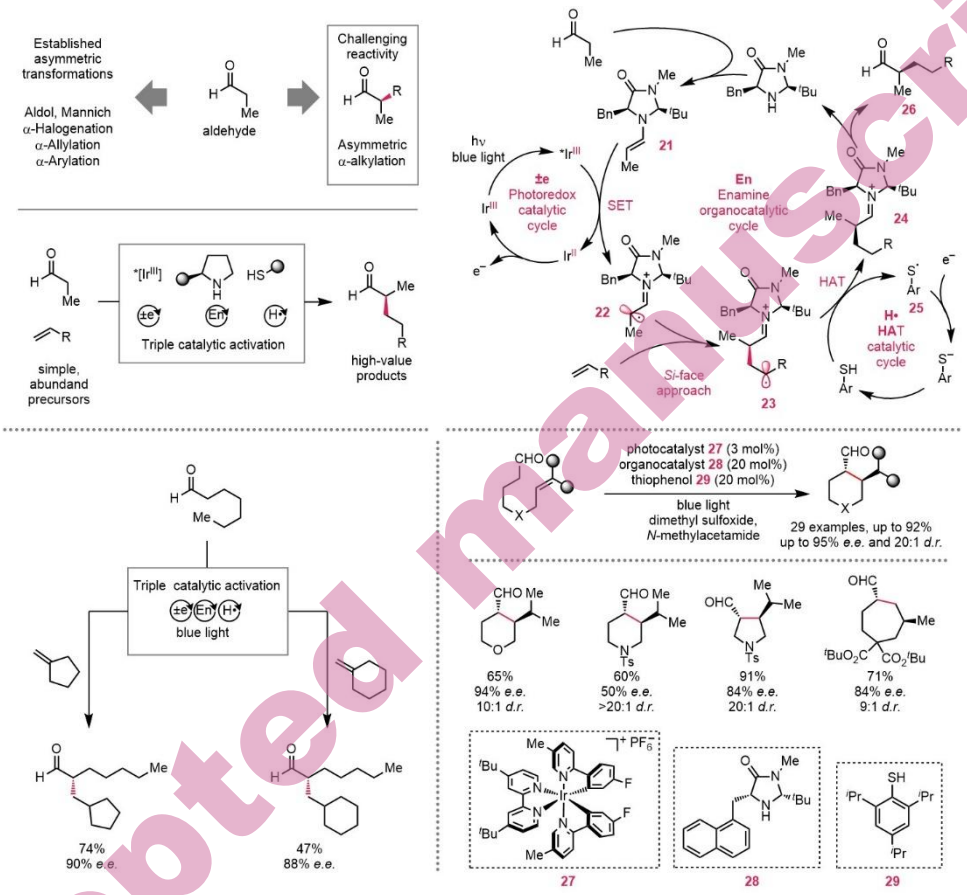
perform a sequence requiring both oxidation and reduction, physical separation or sequential processing is usually required. The photoexcited state of common photocatalysts, such as $[Ir(ppy)_3]^*$ possesses a unique electronic structure. Upon absorption of a visible light photon, an electron is promoted from a metal-centered t_{2g} orbital to a ligand-centered π^* orbital. This excitation creates both a high-energy electron in the π^* orbital (reductive capability) and a corresponding vacancy or "hole," in the t_{2g} orbital (oxidative capability). This electronic duality allows the catalyst to engage in either an oxidative quenching cycle or a reductive quenching cycle, depending on the substrates present. In many modern transformations, this duality is exploited to generate and then resolve radical intermediates within a single flask, maintaining a closed-shell status for the overall reaction without external stoichiometric redox agents. In addition to metal complexes, organic dyes are also useful VLP catalysts. Two examples provided in Scheme 11 are mediated by $Ru(bpy)_3$ complex. The cyclization of bromomalonate **19** proceeds *via* oxidative quenching,[61] whereas the structurally similar indole derivative **20** cyclizes *via* reductive quenching.[62]



Scheme 11

3.2. Compatibility with other catalytic activation modes[63]

Visible-light photocatalysts are exceptionally compatible (perhaps more than any other class of catalysts) with catalytic systems that operate through different activation manifolds (Lewis or Brønsted acids/bases catalysis, organocatalysis, transition-metal catalysis etc.). These dual (or even triple) catalytic systems extend the scope of chemical transformations by introducing unprecedented reactivity (a new mechanism of bond formation) and selectivity (chemo-, regio-, diastereo- and enantioselectivity), not possible by use of either catalyst alone. One such example is enantioselective α-alkylation of aldehydes with simple alkenes, represented in Scheme 12.[64] The overall transformation is a synergistic merger of three catalytic processes: photoredox, enamine organocatalysis and hydrogen-atom transfer (HAT) catalysis. The first step in the reaction sequence is organocatalytic: the formation of enamine from the aldehyde substrate and the organocatalyst. The organocatalytic cycle is followed by a photoredox catalytic cycle: reductive quenching of $[Ir^{III}]^*$ complex which oxidizes enamine



Scheme 12

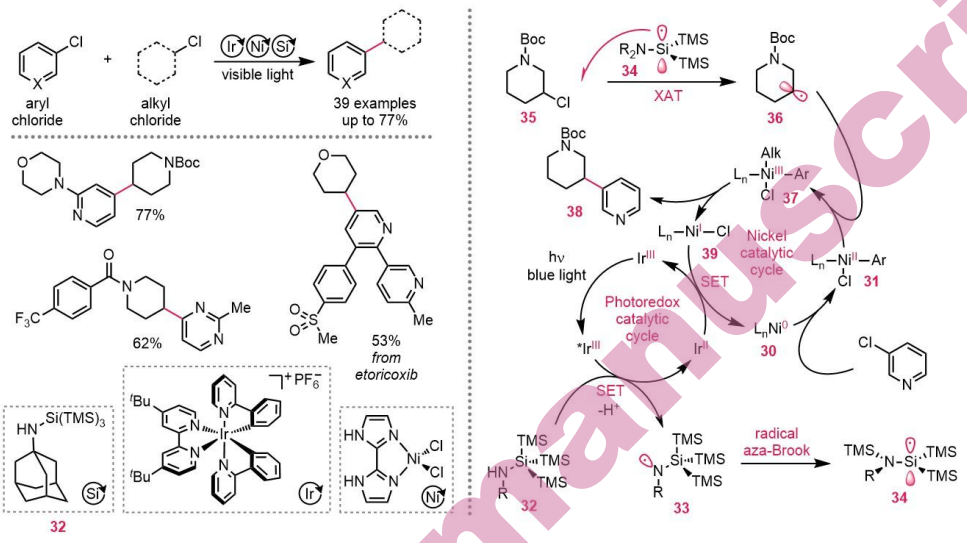
21 into iminium radical-cation **22**. This electrophilic species adds to electron-rich alkene with formation of nucleophilic radical **23** – the substrate for the HAT catalytic cycle accomplished by thiophenol, to provide iminium intermediate **24** and phenylthio radical **25**. The former is hydrolyzed to give the final product **26** and regenerate organocatalyst, whereas phenylthio radical is reduced to the corresponding anion by [Ir^{II}], to regenerate both [Ir^{III}] and ArSH catalysts. Note the atom- and redox-economy of the overall process: no external stoichiometric oxidant, reductant, or hydrogen-atom-transfer reagent is required, despite the fact that the overall transformation involves oxidation, reduction and hydrogen transfer.

Conceptually, each catalyst performs only the elementary step for which it is ideally suited, while the overall transformation emerges from the seamless orchestration of the individual catalytic cycles.

3.3. Single-electron transmetalation: bypassing the C(sp^3) barrier

The merger of transition metal catalysis and photoredox catalysis (termed metallaphotoredox) introduced the revolutionary concept of single-electron transmetalation. For over forty years, the utility of cross-coupling reactions (Suzuki, Negishi, Stille) was largely restricted to C(sp^2) and C(sp) centers. The transmetalation step in these reactions is typically a two-electron process involving the nucleophilic attack of an organometallic species onto a metal-halide complex. The rate of this step follows a strict trend where C(sp^3) centers are significantly less reactive due to their higher activation barriers and poor nucleophilicity. Visible light photocatalysis provided a mechanism to bypass this barrier entirely. Instead of relying on a high-energy, two-electron ionic transmetalation, a photoredox catalyst can be used to generate an alkyl radical *via* single-electron oxidative fragmentation of an organometallic precursor (*e.g.*, potassium alkyltrifluoroborates, or alkylsilicates). This alkyl radical is then "caught" by a low-valent metal center, such as Ni(0) or Ni(I), through a near-barrierless radical combination process.

This shift from two-electron to single-electron transmetalation was first disclosed in 2014 by the Molander group.[65] It fundamentally changed the logic of cross-coupling, enabling the routine use of secondary alkylboron reagents that were previously considered too unreactive or prone to decomposition *via* β-hydride elimination under conventional Pd-catalyzed conditions. Such an example is provided in Scheme 13,[66] which shows cross coupling of unactivated alkyl chlorides – substrates that hitherto were not useful reaction partners in such type of reactions. Here, Ni(0) catalyst **30** undergoes oxidative addition with chloropyridine to provide Ni(II) complex **31**. Alkyl chlorides do not transmetalate, so activation *via* the corresponding radical species is needed. However, unactivated C(sp^3)-Cl bond is inert toward reagents such as TBTH or TTMSH. To solve this problem, the transfer agent is modified in line with another important principle of radical chemistry: polarity matching. Radicals are electron-neutral, but their reactivity much depends on polar factors.[67] Therefore, silane H-donor **32** is designed with π-donating substituent, aiming to decrease the energy of the transition state for the chlorine abstraction and hence accelerate this step (in the transition state, silicon is partially positive, and chlorine – partially negative). This new reagent **32** undergoes [Ir^{II}]* induced electron-transfer to give aminyl radical **33**, which upon aza-Brook rearrangement generates silyl radical **34**, capable of fast chlorine abstraction from **35**. The radical **36** so formed enters the coordination sphere of Ni(II) complex **31** to give Ni(III)(alkyl)(aryl) intermediate **37**, which undergoes reductive elimination to provide the final product **38** and Ni(I) complex **39**. This latter species



Scheme 13

undergoes oxidative quench with [Ir^{II}] complex, to regenerate both Ni(0) and Ir(III) catalysts. Indeed, impressive orchestration of several distinct reactivities into a sophisticated mechanistic manifold which was hardly imaginable under "conventional" conditions for radical reactions. Additional examples of transition-metal catalyzed radical reactions are provided in sections which follow.

Conceptually, metallaphotoredox catalysis extends the accessible redox space of transition-metal catalysis, allowing single-electron elementary steps to be incorporated into otherwise classical organometallic catalytic cycles.

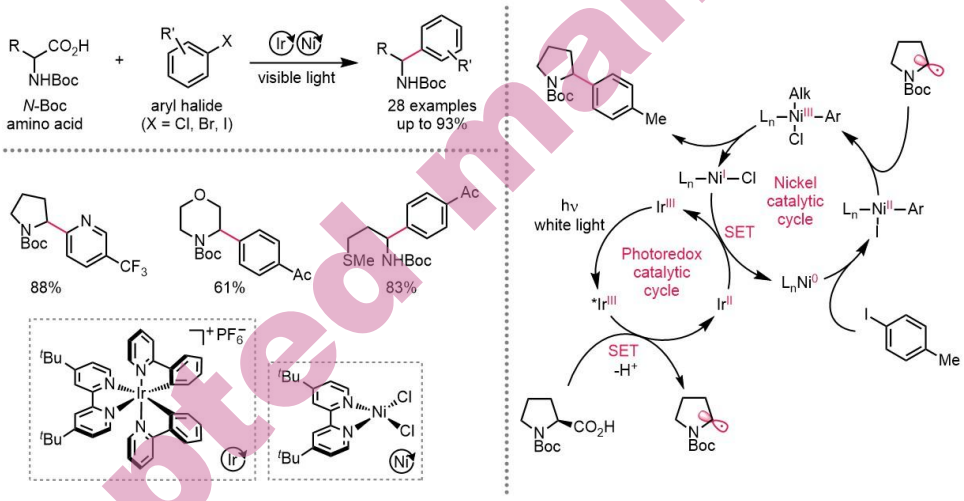
3.4. Carboxylic acids as radical synthons for additions and cross-couplings

A powerful transformation enabled by the metallaphotoredox paradigm is the direct decarboxylative cross-coupling of C(sp^3) carboxylic acids with aryl, vinyl, and even C(sp^3) fragments. Carboxylic acids are among the most abundant, stable, and inexpensive feedstock chemicals in nature and biomass. However, in traditional cross-coupling, they are rarely used as the coupling partners because they do not participate in standard two-electron transmetalation.

The first demonstration that visible light could be used to oxidize carboxylate salts into carboxyl radicals, which rapidly undergo CO_2 extrusion to provide carbon-centered radicals was published in 2014 (Scheme 14).[68] The resulting radical is then funneled into a nickel-catalyzed cross-coupling cycle. This qualitatively new approach enables the modular coupling of α-amino acids and α-oxy acids with aryl halides under conditions that are significantly milder than traditional methods. It effectively transforms a ubiquitous functional group into a

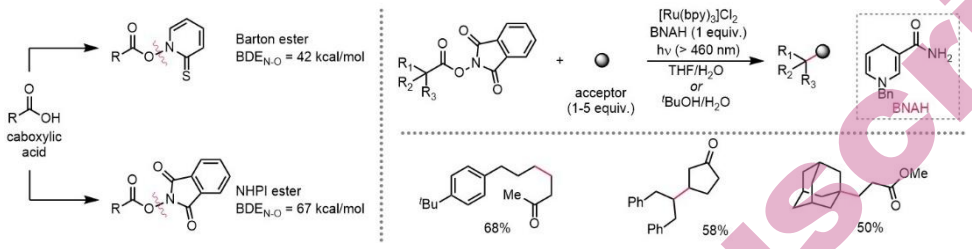
traceless organometallic surrogate, allowing for a "building block" approach to molecule construction that exploits naturally occurring diversity.

Barton method of radical generation *via* thiohydroxamates was a seminal discovery that enabled carbon-carbon bond formation and a broad scope of functional group transformations, starting from carboxylic acids. However, this method has some limitations. Barton esters are thermally and photochemically unstable; in addition, the method only allows for fast radical reactions and is not well poised to combine with transition-metal catalysis, because it produces sulfur containing byproducts. Therefore, *N*-hydroxyphthalimide (NHPI esters) – bench-stable compounds – have been developed as alternative



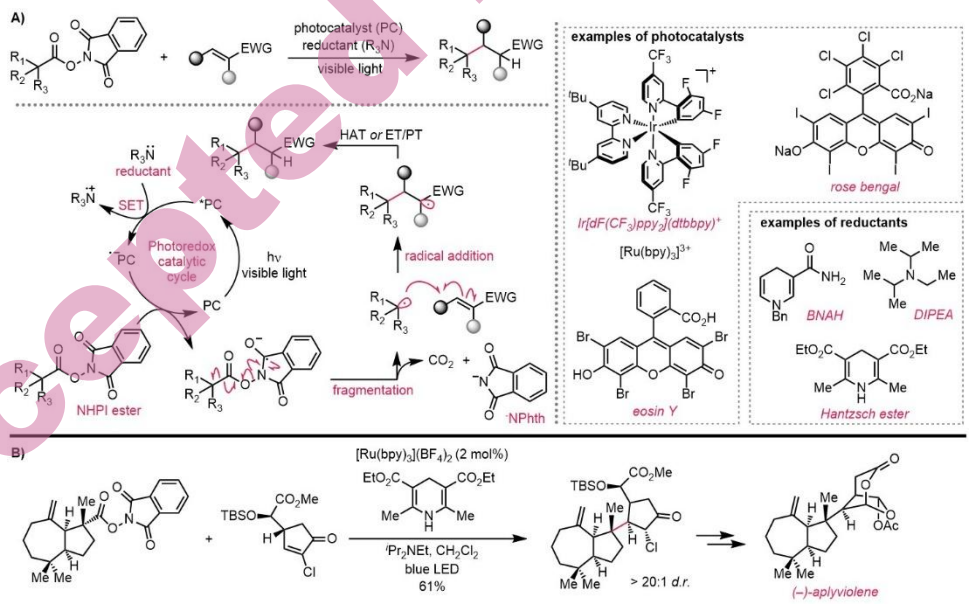
Scheme 14

radical precursors that are more compatible with Ni, Cu, or Pd catalysis, because they avoid sulfur byproducts (Scheme 15).[69-71] Although the N–O bond in NHPI is considerably stronger with respect to Barton esters, the former are redox-active esters (RAE), prone to single electron transfer reduction (SET) which facilitates the N–O bond homolysis. In 1988, Okada and coworkers discovered that NHPI esters undergo decarboxylation under photoredox conditions, which can be exploited for Giese addition, even to nonterminal ones – a long-standing problem in intermolecular radical additions (Scheme 15).[72,73]



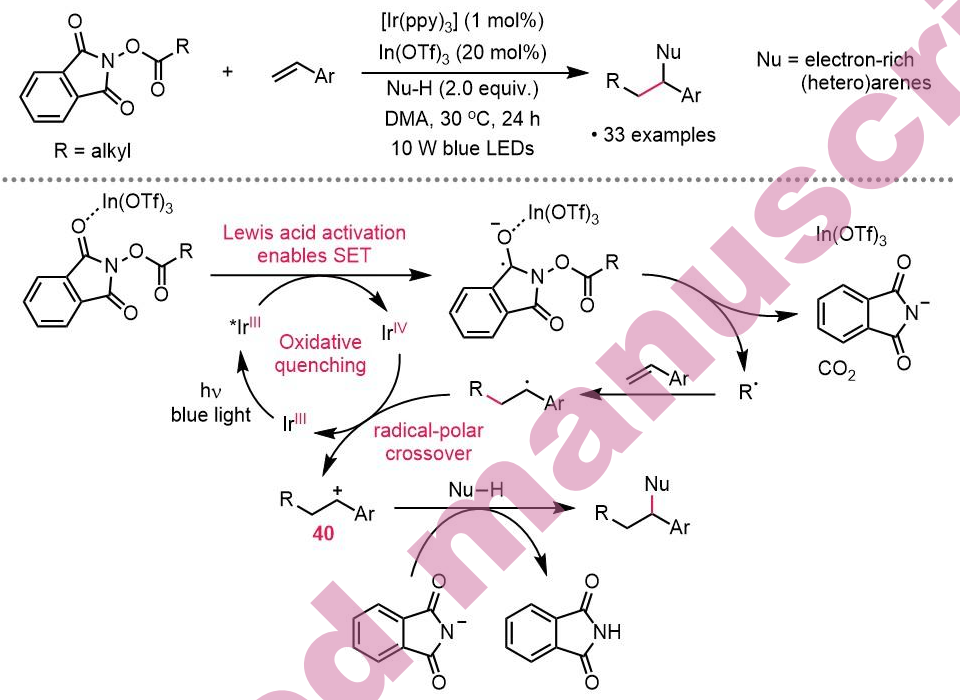
Scheme 15

However, this discovery remained "dormant" for quite some time. Subsequent studies confirmed that, under photoredox conditions, these esters can undergo either reductive or oxidative quenching, providing alkyl radicals suitable for synthetically useful reactions. Thus, in the presence of radicophilic alkenes and reductants, the catalytic cycle represented in Scheme 16A provides Giese adducts, *i.e.*, products of reductive addition.[74,75] Either metal-based or organic photocatalysts can be used.[76] Overman and coworkers exploited this methodology in their concise synthesis of aplyviolene (Scheme 16B).[77,78]



Scheme 16

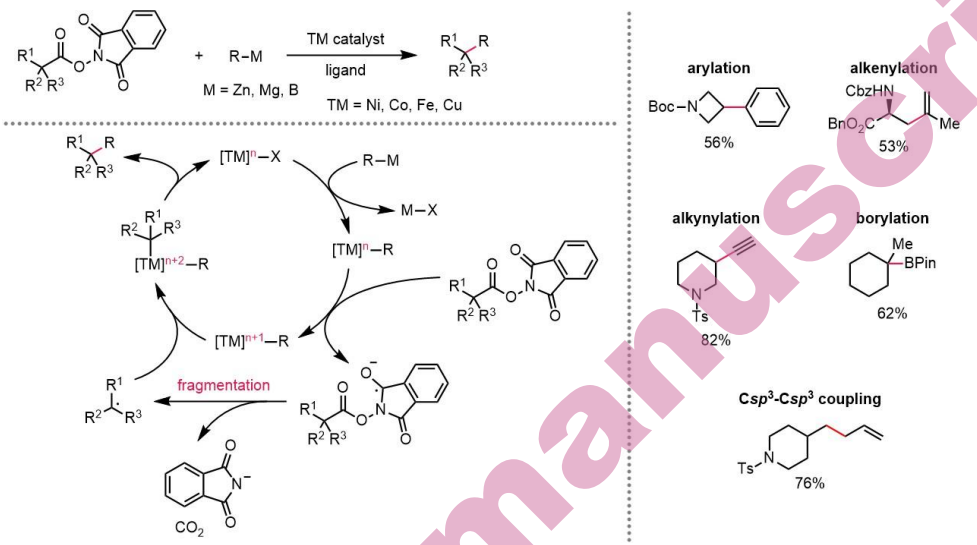
In the presence of nucleophiles and Lewis acids, however, the overall process is redox-neutral and involves nucleophilic attack on carbenium ion **40**, with formation of two carbon-carbon bonds (Scheme 17).[79] Heteronucleophiles can also be used.



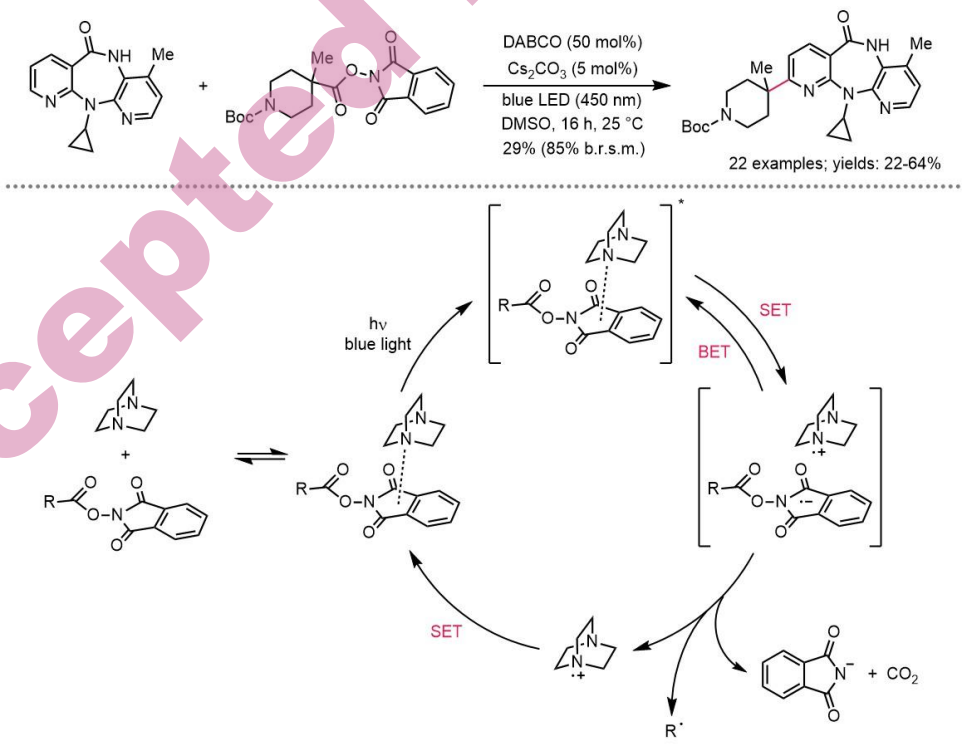
Scheme 17

Baran and coworkers were first to find that NHPI esters enable Ni-mediated cross-coupling of simple carboxylic acids with aryl zinc reagents, even in the absence of a light source, with SET from the Ni-complex initiating the reaction.[80] This method of radical generation (usually employed under photoredox conditions) enables cross couplings of carboxylic acids with organometallic species, as outlined in Scheme 18.[81–85]

NHPI esters can also engage in interesting and useful reactions without transition metal catalysts. Scheme 19 shows an alkylation which proceeds with anti-Friedel–Crafts selectivity.[86] The reaction is based on formation of an electron donor–acceptor (EDA) complex of NHPI with DABCO, which subsequently undergoes light initiated radical generation followed by an autocatalytic chain reaction.[87] The reactive intermediate is a radical, which directs the attack to the most electrophilic position of the aromatic core, thereby accounting for the anti-Friedel–Crafts selectivity. Scheme 19 shows only the mechanism of radical generation; the subsequent transformation may proceed through a more complex mechanistic manifold.



Scheme 18

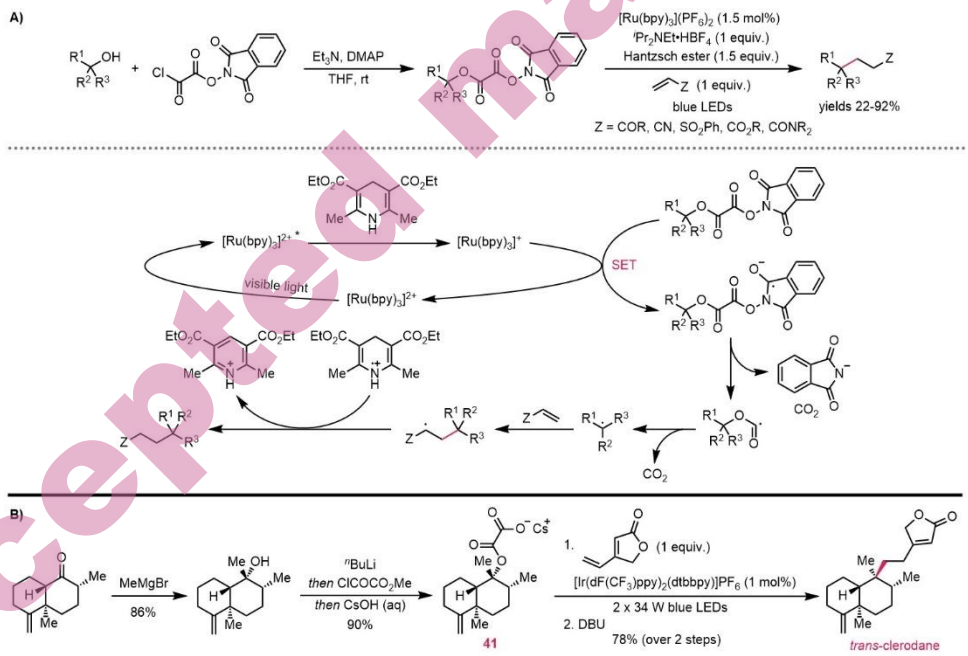


Scheme 19

Additional examples of use of NHPI esters as radical precursors are provided in sections below.

3.5. Alcohols as radical precursors (2)[88,89]

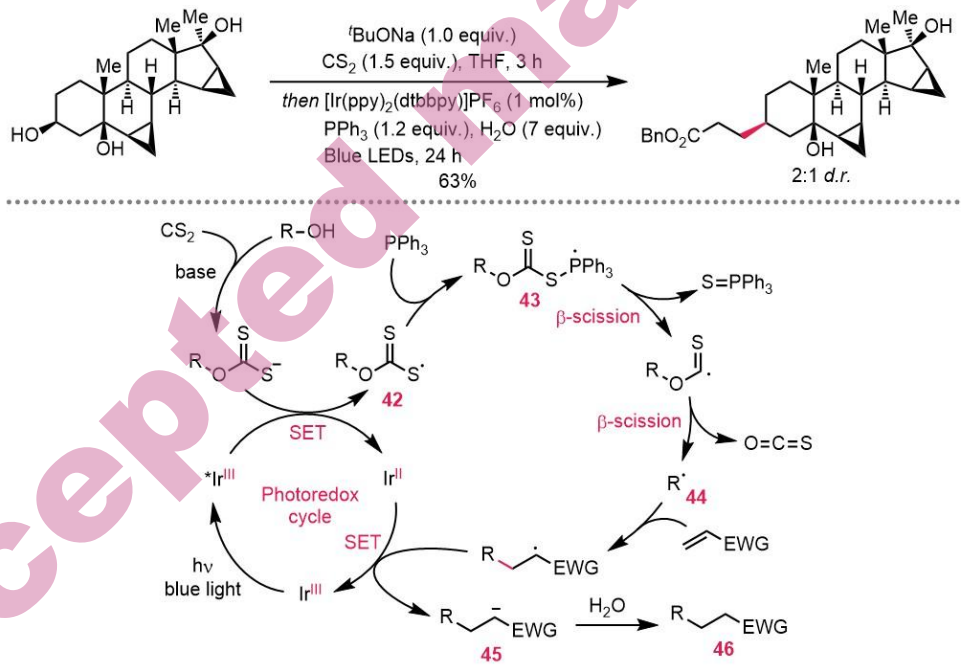
Alcohols are another class of ubiquitous compounds that can serve as radical synthons *via* the intermediacy of NHPI esters. By analogy with the Barton thiohydroxamate approach,[90] Overman developed mixed oxalate esters of NHPI and tertiary alcohols, which are excellent precursors of alkyl radicals under photoredox conditions (Scheme 20A).[91,92] Later, in a collaborative study, MacMillan, Overman and coworkers found that tertiary alkyl oxalate salts of type **41** can be used as radical precursors, without the phthalimide moiety, for redox-neutral couplings with radicophilic alkenes; this methodology was exploited in an efficient synthesis of clerodane (Scheme 20B).[93,74]



Scheme 20

Activation of alcohols for radical reactions *via* xanthates involves treatment of the corresponding alkoxides with carbon disulfide and methyl iodide, followed by isolation of the xanthates prior to the radical reaction. Guo and Wu developed a one-pot strategy that utilizes xanthate salts formed *in situ* (*i.e.*, no methyl iodide is needed). In the presence of PPh_3 and [Ir] catalysts, irradiation with blue light generates alkyl radicals, which undergo synthetically useful carbon-carbon bond-forming reactions (Scheme 21).[94] The small structural change (absence of the

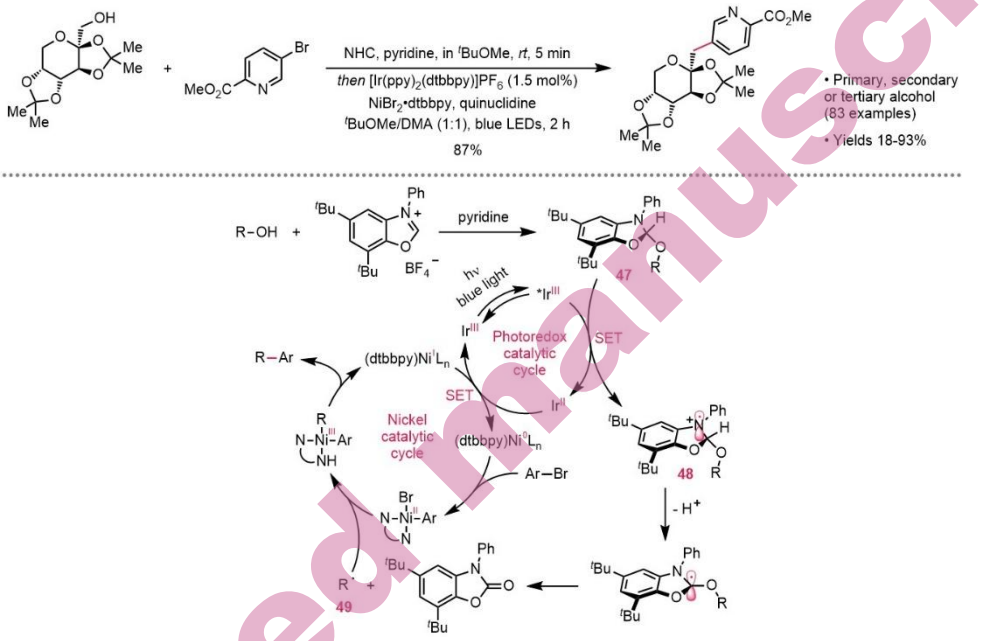
methyl group and the ionic nature of the precursor) brings about a complete change in mechanism compared with the Barton–McCombie reaction. The reaction sequence starts with reductive quenching, followed by rapid addition of radical **42** to PPh_3. The adduct radical **43** undergoes two consecutive β-fragmentations, with expulsion of triphenylphosphine sulfide and carbon oxysulfide, respectively. Alkyl radical **44**, thus generated, undergoes Giese addition, followed by $[Ir^{II}]$-catalyzed reduction to enolate **45**, which is subsequently protonated to afford the final product **46**. Slight modifications of the reaction conditions allow reactions with a variety of substrates, including imines, sulfonyl oxime esters, heteroaryl sulfones, etc.[95–98] Secondary alcohols react preferentially in the presence of tertiary ones; thus, this method provides complementary selectivity to that of titanium-based method shown in Scheme 4.



Scheme 21

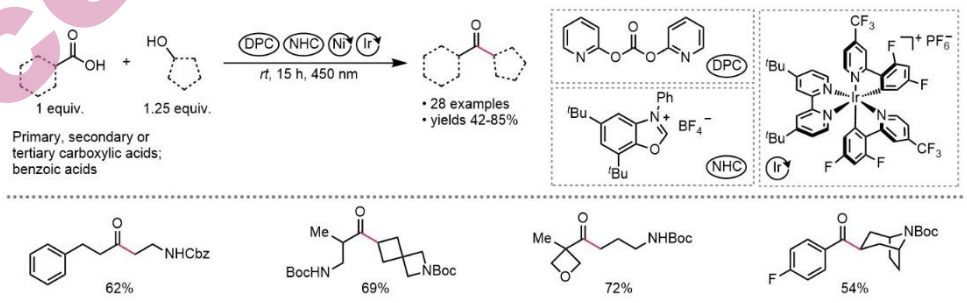
MacMillan and coworkers developed a method for *in situ* activation of alcohols *via* their adducts with NHCs (adducts of type **47**; Scheme 22).[99] Reductive quenching of this intermediate generates the open shell NHC-alcohol intermediate **48**, which undergoes proton transfer, followed by N-O bond homolysis to generate alkyl radical **49**. Further reaction proceeds *via* the pathway described in Scheme 13, to afford the cross-coupling product. This method of radical generation works

well with primary, secondary and tertiary alcohols, and is also suitable for additions to various types of electrophilic alkenes.[100]



Scheme 22

With activated carboxylic acid esters, the analogous catalytic cycle involves acyl-Ni intermediates which couple with radicals to provide ketones – a useful, pH-neutral alternative to the conventional conversion of carboxylic acids to ketones using organolithium reagents (Scheme 23).[101]



Scheme 23

ABBREVIATIONS

A – Electron acceptor; **ABVN** – 2,2′-Azobis(2,4-dimethylvaleronitrile); **ACCN** – 1,1′-Azobis(cyclohexane-1-carbonitrile); **acac** – Acetylacetonate; **AIBN** – 2,2′-Azobis(isobutyronitrile); **BET** – Back electron transfer; **BNAH** – Benzyl nicotinamide; **Boc** – *tert*-Butoxycarbonyl; bpy – 2,2′-Bipyridine; **Cbz** – Carbobenzyloxy; **D** – Electron donor; **DABCO** – 1,4-Diazabicyclo[2.2.2]octane; **dan** – 1,8-Diaminonaphthalene; **DBU** – 1,8-Diazabicyclo[5.4.0]undec-7-ene; **DCM** – Dichloromethane; **DIPEA** – *N,N*-Diisopropylethylamine; **dibm** – Diisobutyrylmethanate; **DLP** – Dilauroyl peroxide; **DMAP** – 4-Dimethylaminopyridine; **DMA** – *N,N*-Dimethylacetamide; **DMSO** – Dimethyl sulfoxide; **dpm** – Dipivaloylmethanate; **DPC** – Di-2-pyridyl carbonate; **dtbbpy** – 4,4′-Di-tert-butyl-2,2′-bipyridine; **EDA** – Electron donor–acceptor; **ET** – Electron transfer; **EWG** – Electron-withdrawing group; **HAT** – Hydrogen atom transfer; **HFL** – Hofmann–Löffler–Freytag; **LED** – Light-emitting diode; **MIDA** – *N*-Methyliminodiacetate; **NHC** – *N*-Heterocyclic carbene; **NHPI** – *N*-Hydroxyphthalimide; **Nu** – Nucleophile; **Phth** – Phthaloyl; **Pin** – Pinacolato; **ppy** – 2-Phenylpyridine; **PT** – Proton transfer; **SET** – Single-electron transfer; **TBHP** – *tert*-Butyl hydroperoxide; **TBS** – *tert*-Butyldimethylsilyl; **TBTH** – Tributyltin hydride; **TES** – Triethylsilyl; **TFA** – Trifluoroacetic acid; **THF** – Tetrahydrofuran; **TM** – Transition metal; **TMS** – Trimethylsilyl; **TTMSH** – Tris(trimethylsilyl)silane; **UV** – Ultraviolet; **VLP** – Visible-light photocatalysis; **XAT** – Halogen atom transfer.

Acknowledgements: The support from the Ministry of Science, Technological Development and Innovation of the Republic of Serbia is acknowledged, contract numbers: 451-03-33/2026-03/ 200168 and 451-03-33/2026-03/ 200288.

И З В О Д

РАДИКАЛНИ ПРОДОРИ У РАДИКАЛСКОЈ ХЕМИЈИ. ПРВИ ДЕО

МИЛЕНА ТРМЧИЋ[1], БОЈАН ВУЛОВИЋ[2], ФИЛИП БИХЕЛОВИЋ[3] И РАДОМИР Н. САИЧИЋ[2,3*]

[1]Универзитет у Београду – Иновациони центар Хемијског факултета, Студентски трг 12-16, 11158 Београд, Србија, 2Универзитет у Београду – Хемијски факултет, Студентски трг 12-16, 11158 Београд, Србија, [3]Српска академија наука и уметности, Београд, Кнеза Михаила 35, 11000 Београд, Србија.

Слободни радикали су током дуго времена сматрани високо реактивним интермедијерима чија се реактивност не може контролисати. Међутим, од деведесетих година наовамо, све је више примера њиховог коришћења у многим важним реакцијама које заузимају значајно место у синтетичкој органској хемији. Неколико метода генерисања слободних радикала, попут трибутилкалајне, Бартонове, или методе преноса атома или групе, постале су важан део методолошког арсенала органске синтезе. Током последњих двадесет година, нови механистички увиди, као и развој нових метода и техника, довели су до значајног напретка у могућностима дизајна, комбиновања и примене радикалских

реакција, и тиме стратешки унапредили њихову улогу у планирању органске синтезе. Овај преглед приказује најважније продоре остварене у синтетичкој радикалској хемији током последње две деценије; ограничен је на стварање веза угљеник–угљеник и не обухвата електрохемијске методе. Преглед излази у два дела, у два узастопна броја. Први део обухвата Секције 1 (Увод), 2 (6 тема о новитетима у „конвенционалној“ радикалској хемији) и део Секције 3 (развој радикалских реакција у светлу фотокатализе видљивом светлошћу – 5 тема). Други део садржи наставак Секције 3 (12 тема о различитим аспектима генерисања радикала фотокатализом видљивом светлошћу) и Секцију 4 (примена радикалских реакција у тоталним синтезама).

(Примљено 10. августа; ревидирано 21. августа; прихваћено 28. августа 2026.)

REFERENCES

1. M. Gomberg, *J. Am. Chem. Soc.* **22**, (1900) 757 (https://doi.org/10.1021/ja02049a006)
2. For the Symposium in print, see: B. Giese, Tetrahedron **41** (1985) (No. 19), p.xiii (preface), and the references that follow from page 2887 to 4368.
3. C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.* **91** (1991) 1237 (https://doi.org/10.1021/cr00006a006)
4. For an excellent review article on Radical retrosynthesis – *i.e.*, the influence of radicals in retrosynthetic analysis, see: J. M. Smith, S. J. Harwood, P. S. Baran, *Acc. Chem. Res.* **51** (2018) 1807 (https://doi.org/10.1021/acs.accounts.8b00209)
5. M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **138** (2016) 12692 (https://doi.org/10.1021/jacs.6b08856)
6. S. Z. Zard, *Org. Lett.* **19** (2017) 1257 (https://doi.org/10.1021/acs.orglett.7b00531), and references therein
7. M. Inoue, L. R. Malins, H. Renata, *Org. Lett*. **26** (2024) 7775 (https://doi.org/10.1021/acs.orglett.4c03159), and the references therein
8. C. Chatgilialoglu, A. Studer, eds. *Encyclopedia of Radicals in Chemistry, Biology and Materials*, Online (2012) John Wiley & Sons, Ltd., Print ISBN: 9780470971253| Online ISBN: 9781119953678| (https://doi.org/10.1002/9781119953678)
9. P. Renaud, M. Sibi, eds. *Radicals in Organic Synthesis*, Wiley VCH, Weinheim (2001) Print ISBN:9783527301607 |Online ISBN:9783527618293 (https://doi.org/10.1002/9783527618293)
10. G. J. Rowland, *Tetrahedron* **65** (2009) 8603 (https://doi.org/10.1016/j.tet.2009.07.001)
11. G. J. Rowland, *Tetrahedron* **66** (2010) 1593 (https://doi.org/10.1016/j.tet.2009.12.023)
12. For the review article on the application of radical reactions in synthesis of terpenes, see: Y. Zhang, Y. Zhang, C. Li, *Chem. Soc. Rev.* **54** (2025) 10427 (https://doi.org/10.1039/d5cs00760g)
13. A. Gupta, J. K. Laha, *Chem. Rec.* **23** (2023) e202300207 (https://doi.org/10.1002/tcr.202300207)
14. J. C. Lo, J. Gui, Y. Yabe, C. Pan, P. S. Baran, *Nature* **516** (2014) 343 (https://doi.org/10.1038/nature14006)

15. J. C. Lo, Y. Yabe, P. S. Baran *J. Am. Chem. Soc.* **136** (2014) 1306 (https://doi.org/10.1021/ja4117632)
16. X. Chen, W. Yao, H. Zheng, H. Wang, P. Zhou, D. Zhu; S. Wang, *J. Am. Chem. Soc.* **145** (2023) 13549 (https://doi.org/10.1021/jacs.3c04850)
17. K. Iwasaki, K.K. Wan, A. Oppedisano, S. W. M. Crossley, R.A. Shenvi, *J. Am. Chem. Soc.* **136** (2014) 1300 (https://doi.org//10.1021/ja412342g)
18. L. Wu, F. Wang, X. Wan, D. Wang, P. Chen, G. Liu, *J. Am. Chem. Soc.* **139** (2017) 2904 (https://doi.org/10.1021/jacs.6b13299)
19. S. H. Kyne, G. Lefèvre, C. Ollivier, M. Petit, V.R. Cladera, L. Fensterbank, *Chem. Soc. Rev.* **49** (2020) 8501 (https://doi.org/10.1039/d0cs00969e)
20. S. W. M. Crossley, C. Obradors, R. M. Martinez, R.A. Shenvi, *Chem. Rev.* **116** (2016) 8912 (https://doi.org/10.1021/acs.chemrev.6b00334)
21. For review articles on deoxygenative radical reactions of alcohols, see: Y. Wu, M. Chang, Z. Guan, R. Chi, J. Yu, X. Wu, Z. Dong, *Sci. China Chem.* **68** (2025) 3494 (https://doi.org/10.1007/s11426-025-2651-2)
22. M. Roy, B. Sardar, I. Mallick, D. Srimani, *Beilstein J. Org. Chem.* **20** (2024) 1348 (https://doi.org/10.3762/bjoc.20.119)
23. H. Xie, J. Guo, Y. Wang, K. Wang, P. Guo, P. Su, X. Wang, X. Shu, *J. Am. Chem. Soc.* **142** (2020) 16787 (https://doi.org/10.1021/jacs.0c07492)
24. C. Bandari, K.M. Nicholas, *J. Org. Chem.* **85** (2020) 3320 (https://doi.org/10.1021/acs.joc.9b03150)
25. T. Suga, Y. Takahashi, C. Miki, Y. Ukaji, *Angew. Chem. Int. Ed.* **61** (2022) e202112533 (https://doi.org/10.1002/anie.202112533)
26. H. Xie, S. Wang, X. Shu, *J. Am. Chem. Soc.* **146** (2024) 32269 (https://doi.org/10.1021/jacs.4c11857)
27. H. Xie, S. Wang, Y. Wang, P. Guo, X. Shu, *ACS Catal.* **12** (2022) 1018 (https://doi.org/10.1021/acscatal.1c05530)
28. X. Pang, P. Su, X. Shu, *Acc. Chem.* **55** (2022) 2491 (https://doi.org/10.1021/acs.accounts.2c00381)
29. M. Nagatomo, D. Kamimura, Y. Matsui, K. Masuda, M. Inoue, *Chem. Sci.* **6** (2015) 2765 (https://doi.org/10.1039/c5sc00457h)
30. S. Wilsey, P. Dowd, K. N. Houk, *J. Org.Chem.* **64** (1999) 8801 (https://doi.org/10.1021/jo990652+)
31. R. Tsang, B. Fraser-Reid, *J. Am. Chem. Soc.* **108** (1986) 102 (https://doi.org/10.1021/ja00285a045)
32. R. Tsang, J. K. Dickson, H. Pak, R. Walton, B. Fraser-Reid, *J. Am. Chem. Soc.* **109** (1987) 3484 (https://doi.org/10.1021/ja00245a063)
33. A. L. J. Beckwith, B. P. Hay, *J. Am. Chem. Soc.* **111** (1989) 2674 (https://doi.org/10.1021/ja00189a049)
34. A. L. J. Beckwith, B. P. Hay, *J. Am. Chem. Soc.* **111** (1989) 230 (https://doi.org/10.1021/ja00183a035)
35. H. Fujino, M. Nagatomo, A. Paudel, S. Panthee, H. Hamamoto, K. Sekimizu, M. Inoue, *Angew. Chem. Int. Ed.* **56** (2017) 11865 (https://doi.org/10.1002/anie.201706671)
36. H. Fujino, T. Fukuda, M. Nagatomo, M. Inoue, *J. Am. Chem. Soc.* **142** (2020) 13227 (https://doi.org/10.1021/jacs.0c06354)
37. Review article on hikizimycin synthesis: H. Fujino, M. Nagatomo, M. Inoue, *J. Org. Chem.* **86** (2021) 16220 (https://doi.org/10.1021/acs.joc.1c01773)

38. S. Zard, *Helv. Chim. Acta* **102** (2019) e1900134 (https://doi.org/10.1002/hlca.201900134)
39. L. Anthore-Dalion, Q. Liu, S. Z. Zard, *J. Am. Chem. Soc.* **138** (2016) 8404 (https://doi.org/10.1021/jacs.6b05344)
40. Q. Huang, J. Michalland, S. Z. Zard, *Angew. Chem. Int. Ed.* **58** (2019) 16936 (https://doi.org/10.1002/anie.201906497)
41. J. Michalland, N. Casaretto, S. Z. Zard, *Angew. Chem. Int. Ed.* **61** (2022) e202113333 (https://doi.org/10.1002/anie.202113333)
42. J. Lalevee, L. P. Fouassier, In *Encyclopedia of Radicals in Chemistry, Biology and Medicine,* (eds C. Chatgilialoglu and A. Stude) Online, (2012) John Wiley & Sons, Ltd., Vol. 1, p. 37 (https://doi.org/10.1002/9781119953678.rad003)
43. For a review on borane-based initiation, see: P. Renaud, In *Encyclopedia of Radicals in Chemistry, Biology and Materials,* Online, (2012) John Wiley & Sons, Ltd. (https://doi.org/10.1002/9781119953678.rad020)
44. Z. Ding, Z. Liu, Z. Wang, T. Yu, M. Xu, J. Wen, K. Yang, H. Zhang, L.Xu, P. Li, *J. Am. Chem. Soc.* **144** (2022) 8870 (https://doi.org/10.1021/jacs.2c03673)
45. K. S. Feldman, M. Parvez, *J. Am. Chem. Soc.* **108** (1986) 1328 (https://doi.org/10.1021/ja00266a051)
46. K. S. Feldman, A. L. Romanelli, R. E. Ruckle, R. F. Miller, *J. Am. Chem. Soc.* **110** (1988) 3300 (https://doi.org/10.1021/ja00218a050)
47. M. Zhao, Z. Ding, S. Perveen, L. Qin, Z. Nie, T. Yu, M. Mao, Y. Cheng, J. Wang, P. Li, *J. Org. Chem.* **91** (2026) 6370 (https://doi.org/10.1021/acs.joc.6c00183)
48. T. Y. Peng, F. L. Zhang, Y. F. Wang, *Acc. Chem. Res.* **56** (2023) 169 (https://doi.org/10.1021/acs.accounts.2c00752)
49. T. Taniguchi, *Chem. Soc. Rev.* **50** (2021) 8995 (https://doi.org/10.1039/D1CS00385B)
50. S. Ueng, M. M. Brahmi, É. Derat, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *J. Am. Chem. Soc.* **130** (2008) 10082 (https://doi.org/10.1021/ja804150k)
51. C. Wang, J. Wang, J. Jin, B. Li, Y. L. Phang, F. Zhang, T. Ye, H. Xia, L. Hui, J. Su, Y. Fu, Y. Wang, *Science* **382** (2023) 1056 (https://doi.org/10.1126/science.adg1322)
52. E. Bosch, M. D. Bachi, *J. Org. Chem*. **58** (1993) 5581 (https://doi.org/10.1021/jo00073a005)
53. B. Alcaide, I. M. Rodriguez-Campos, J. Rodriguez-Lopez, A. Rodriguez-Vicente, *J. Org. Chem.* **64** (1999) 5377 (https://doi.org/10.1021/jo9823994)
54. F. Dénès; F. Beaufils; P. Renaud, *Org. Lett.* **9** (2007) 4375 (https://doi.org/10.1021/ol702017t)
55. C. Stephenson, T. Yoon, D. W. C. MacMillan, Eds. *Visible Light Photocatalysis in Organic Chemistry*, Wiley-VCH Verlag GmbH & Co. Weinheim, 2018 ISBN: 978-3-527-67414-5 (https://onlinelibrary.wiley.com/doi/book/10.1002/9783527674145)
56. C. J. Wallentin, J. D. Nguyen, C. R. J. Stephenson, *Chimia* **66** (2012) 394 (https://doi.org/10.2533/chimia.2012.394)
57. D. Nicewicz, D. W. C. MacMillan, *Science* **322** (2008) 77 (https://doi.org/10.1126/science.1161976)
58. M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **130** (2008) 12886 (https://doi.org/10.1021/ja805387f)
59. J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **131** (2009) 8756 (https://doi.org/10.1021/ja9033582)

60. C. K. Prier; D. A. Rankic; D. W. C. MacMillan, *Chem. Rev.* **113** (2013) 5322 (https://doi.org/10.1021/cr300503r)
61. C. Wallentin, J.D. Nguyen, P. Finkbeiner, C.R.J. Stephenson, *J. Am. Chem. Soc.* **134** (2012) 8875 (https://doi.org/10.1021/ja300798k)
62. J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **12** (2010) 368 (https://doi.org/10.1021/ol902703k)
63. M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem*. **81** (2016) 6898 (https://doi.org/10.1021/acs.joc.6b01449)
64. A. G. Capacci, J. T. Malinowski, N. J. McAlpine, J. Kuhne, D. W. C. MacMillan, *Nat. Chem.* **9** (2017) 1073 (https://doi.org/10.1038/nchem.2797)
65. J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy; N. R. Patel, G. A. Molander, *Acc. Chem. Res.* **49** (2016) 1429 (https://doi.org/10.1021/acs.accounts.6b00214)
66. H. A. Sakai, W. Liu, C. "Chip" Le, D. W. C. MacMillan, *J. Am. Chem. Soc*. **142** (2020) 11691 (https://doi.org/10.1021/jacs.0c04812)
67. A. Ruffoni, R. C. Mykura, M. Bietti, D. Leonori, *Nat. Synth.* **1** (2022) 682 (https://doi.org/10.1038/s44160-022-00108-2)
68. Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **345** (2014) 437 (https://doi.org/10.1126/science.1255525)
69. For review articles on NHPI *esters* and the use of carboxylic acids as radical synthons for cross-coupling reactions, see: C. R Azpilcueta-Nicolas, J. Lumb, *Beilstein J. Org. Chem.* **20** (2024) 346 (https://doi.org/10.3762/bjoc.20.35)
70. G. Laudadio, M. D. Palkowitz, T. E. Ewing, P. S. Baran, *ACS Med. Chem. Lett.* **13** (2022) 1413 (https://doi.org/10.1021/acsmedchemlett.2c00286)
71. S. Murarka, *Adv. Synth. Catal.* **360** (2018) 1735 (https://doi.org/10.1002/adsc.201701615)
72. K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **113** (1991) 9401 (https://doi.org/10.1021/ja00021a034)
73. O. Keiji, O. Kazushige, O. Masaji. *J. Am. Chem. Soc.* **110** (1988) 8736 (https://doi.org/10.1021/ja00234a047)
74. R. Xu, T. Xu, M. Yang, T. Cao, S. Liao, *Nat. Commun.* **10** (2019) 3752 (https://doi.org/10.1038/s41467-019-11805-6)
75. X. Shu, R. Xu, Q. Ma, S. Liao, *Org. Chem. Front.* **7** (2020) 2003 (https://doi.org/10.1039/d0qo00440e)
76. J. Schwarz, B. König, *Green Chem.* **18** (2016) 4743 (https://doi.org/10.1039/c6gc01101b)
77. M. J. Schnermann, L. E. Overman, *Angew. Chem. Int. Ed*. **51** (2012), 9576 (https://doi.org/10.1002/anie.201204977)
78. C.R. Jamison, L. E Overman, *Acc. Chem. Res.* **49** (2016) 1578 (https://doi.org/10.1021/acs.accounts.6b00284)
79. X. Wang, Y. Han, X. Ouyang, R. Song, J. Li, *Chem. Commun.* **55** (2019) 14637 (https://doi.org/10.1039/c9cc07494e)
80. J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **138** (2016) 2174 (https://doi.org/10.1021/jacs.6b00250)
81. C. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **138** (2016) 2174 (https://doi.org/10.1021/jacs.6b00250)
82. F. Toriyama, J. Cornella, L. Wimmer, T. Chen, D. D. Dixon, G. Creech, P. S. Baran, *J. Am. Chem. Soc.* **138** (2016) 11132 (https://doi.org/10.1021/jacs.6b07172)

83. J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D. Bao, F. Wei, T. Zhou, M. D. Eastgate, P. S. Baran, *Nature* **545** (2017) 213 (https://doi.org/10.1038/nature22307)
84. J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S.A. Shaw, M. D. Eastgate, P. S. Baran, *Angew. Chem., Int. Ed.* **56** (2017) 11906 (https://doi.org/10.1002/anie.201705107)
85. T. Qin, J. Cornella, C. Li, L.R. Malins, J.T Edwards, S. Kawamura, B.D. Maxwell, M.D. Eastgate, P. S. Baran, *Science* **352** (2016) 801 (https://doi.org/10.1126/science.aaf6123)
86. D. M. Vahey, M. Mu, S. A. Bonke, T. Sommer, P. Vangal, C. Mallia, M. García-Melchor, E. Reisner, *Nat. Synth.* **5** (2026), 871 (https://doi.org/10.1038/s44160-026-00994-w)
87. For a review article on EDA complexes and their synthetic use, see: G. E. M. Crisenza, D. Mazzarella, P. Melchiorre, *J. Am. Chem. Soc.* **142** (2020) 5461 (https://doi.org/10.1021/jacs.0c01416)
88. For review articles on radical generation from alcohols, see: M. Roy, B. Sardar, I. Mallick, D. Srimani, *Beilstein J. Org. Chem.* **20** (2024) 1348 (https://doi.org/10.3762/bjoc.20.119)
89. Y. Wu, M. Chang, Z. Guan, R. Chi, J. Yu, X. Wu, Z. Dong, *Sci. China Chem.* **68** (2025) 4595 (https://doi.org/10.1007/s11426-025-2651-2)
90. D. H. R. Barton, D. Crich, *J. Chem. Soc., Perkin Trans. 1* **15** (1986) 1603 (https://doi.org/10.1039/P19860001603)
91. G. L. Lackner, K. W. Quasdorf, L. E. Overman, *J. Am. Chem. Soc.* **135** (2013) 15342 (https://doi.org/10.1021/ja408971t)
92. G. L. Lackner, K. W. Quasdorf, G. Pratsch, L. E. Overman, *J. Org. Chem.* **80** (2015) 6012 (https://doi.org/10.1021/acs.joc.5b00794)
93. C. C. Nawrat, C. R. Jamison, Y. Slutskyy, D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **137** (2015) 11270 (https://doi.org/10.1021/jacs.5b07678)
94. H. Guo, X. Wu, *Nat. Commun.* **12** (2021) 5365 (https://doi.org/10.1038/s41467-021-25702-4)
95. W. Zhang, S. Ning, Y. Li; X. Wu, *Chem. Com.* **58** (2022) 12843 (https://doi.org/10.1039/d2cc05098f)
96. H. Guo, X. Wu, *Nat. Commun.* **12** (2021) 5365 (https://doi.org/10.1038/s41467-021-25702-4)
97. W. Baoand, X. Wu, *J. Org. Chem.* **88** (2023) 3975 (https://doi.org/10.1021/acs.joc.2c03043)
98. B. He, X. Wu, *Org. Lett.* **25** (2023) 6571 (https://doi.org/10.1021/acs.orglett.3c02432)
99. Z. Dong, D. W. C. MacMillan, *Nature* **598** (2021) 451 (https://doi.org/10.1038/s41586-021-03920-6)
100. J. Z. Wang, H. A. Sakai, D. W. C. MacMillan, *Angew. Chem. Int. Ed*. **61** (2022) e202207150 (https://doi.org/10.1002/ange.202207150)
101. V. Ciccone, E. Lin; C. N. P. Kullmer, D. W. C. MacMillan; R. E. McNamee, *ACS Catal.* **16** (2026) 12645 (https://doi.org/10.1021/acscatal.6c02684).