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Acyloxy, sulfate, and phosphate radicals as hydrogen atom transfer (HAT) agents for direct C(sp^3)–H functionalization

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Selective activation of inert and ubiquitous C(sp^3)–H bonds has long been a challenging task in organic synthesis, through which chemists can directly synthesize value-added compounds from inexpensive and readily available alkane feedstocks. By means of modern photochemistry, electrochemistry, as well as traditional thermochemistry, diverse hydrogen atom transfer (HAT) protocols have been established, employing various radicals, especially oxygen-centered ones, as the HAT agents. This review focuses on three unique classes of oxygen radicals, namely acyloxy, sulfate, and phosphate radicals, which have demonstrated significant potential for achieving direct intermolecular C(sp^3)–H bond functionalization *via* HAT pathways. By focusing on the key developments from 2014 to 2024, this review discusses the generation mechanisms, reactivity characteristics and applications of these acid-related oxygen radicals, aiming to provide researchers with insights to further advance the techniques and innovations in the future C(sp^3)–H functionalization strategy development.

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Sustainability spotlight

In recent years, C(sp^3)–H activation has emerged as a crucial area in organic synthesis, allowing for the direct utilization of unprefunctionalized alkane feedstocks to construct complex molecules. Hydrogen atom transfer (HAT), representing a sustainable approach for C–H activation under relatively mild conditions, has seen significant development in the last decades. This review highlights the use of acyloxy, sulfate, and phosphate radicals as three unique classes of oxygen-based radicals as HAT reagents for achieving direct C(sp^3)–H functionalization. This research contributes to UN Sustainable Development Goals: industry, innovation, and infrastructure (SDG 9), responsible consumption and production (SDG 12), and climate action (SDG 13).

1. Introduction

Selective C(sp^3)–H activation stands as a pivotal yet challenging domain in organic synthesis, which significantly broadens the repertoire of synthetic methodologies, enabling the direct construction of value-added compounds from readily available alkane feedstocks, thereby avoiding the tedious pre-functionalization procedures.[1]

Throughout the development of direct C(sp^3)–H bond functionalization, intermolecular hydrogen atom transfer (HAT) processes enabled by organic photocatalysis[2] (involving photosensitizers such as decatungstate,[3] eosin Y and its close relatives,[4] ketones,[5] and metal chlorides[6]), electrochemical or photo-electrochemical methods,[7] and traditional thermally-promoted reactions have played significant roles. Taking advantage of various reactive radicals as the HAT agents, including chlorine radical,[6,7d–g,8] bromine radical,[9] carbon-centered radicals,[10] nitrogen-centered radicals,[7b,c,11] oxygen-centered radicals,[4,5,12] *etc.*, these protocols have provided diversified and more sustainable options for achieving direct C(sp^3)–H functionalization. Among these, oxygen radical-mediated HAT processes have become one of the most extensively studied subjects.

Apart from the "direct HAT" mediated by eosin Y and its close relatives[4] and ketones (mainly diaryl ketones and anthraquinone)[5] under light irradiation, most of the oxygen radical-mediated transformations can be classified as "indirect HAT" (wherein the real HAT species are generated *in situ* from certain oxygen-containing precursors).[2] Some representative oxygen-based precursors, as well as radicals for indirect HAT processes are highlighted in Scheme 1:

(a) Peroxides, such as *tert*-butyl hydroperoxide (TBHP) and di-*tert*-butyl peroxide (DTBP), can undergo cleavage under light irradiation, heating, or single-electron transfer (SET), to yield alkoxy radicals as HAT agents (Scheme 1a).[13]

(b) *N*-Oxides, such as pyridine *N*-oxide and its derivatives, are competent of generating oxygen radicals for HAT processes upon single-electron oxidation (Scheme 1b).[14]

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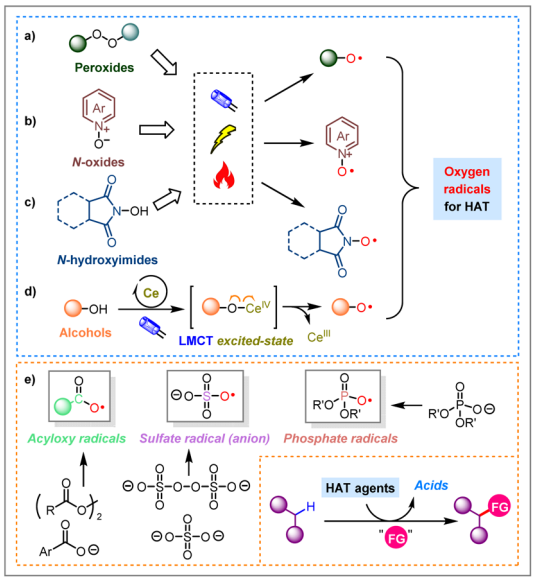
(c) *N*-Hydroxyimides, such as *N*-hydroxyphthalimide (NHPI) and *N*-hydroxyimide (NHI), serve as highly efficient indirect HAT reagents, which are capable of generating reactive oxygen radicals upon photo-irradiation or electrochemical activation (Scheme 1c).[12e,15]

(d) Alcohols, can engage in photo-induced ligand-to-metal charge transfer (LMCT) mechanism with cerium salts (Scheme 1d), or be oxidized by excited-state photosensitizers to access alkoxy radicals.[12b,16]

Beyond the above well-established categories, this review will shed light on three classes of acid-related oxygen-centered radicals, whose roles as unique HAT agents are often overlooked: (1) acyloxy radicals (mainly aryl substituted ones), (2) sulfate radical (anion), and (3) phosphate radicals (Scheme 1e).

(1) Aryl substituted acyloxy radicals (Ar–COO$^{\bullet}$) exhibit slow decarboxylation rates, which are nearly a thousand times slower than those of alkyl counterparts (Alk–COO$^{\bullet}$).[17] Their high stability against decarboxylation renders them ideal HAT reagents, particularly for hydrogen atom abstraction from C(sp^3)–H bonds, to form aromatic carboxylic acids (Ar–COOH).[18] Common generation methods for these radicals include thermal or photolytic decomposition of peroxides (*e.g.*, benzoyl peroxide, BPO),[19] and photo-/electro-chemical conversion of carboxylic acids (salts) or derivatives.[20,20a,20b] In 2016, a seminal publication from the Glorius group demonstrated the use of tetrabutylammonium or sodium benzoate ($Bu_4N^+PhCOO^-$ or Na^+PhCOO^-) as an HAT reagent for the selective trifluoromethylthiolation of unactivated C(sp^3)–H bonds under visible-light induced photoredox catalysis.[20c] Later in 2017, the same group further developed a visible-light induced alkynylation of Csp2(O)–H bonds of aldehydes, wherein the aryl carboxyl radical derived from sodium 2-iodobenzoate acts as an HAT reagent.[20d]



Scheme 1 Representative oxygen-centered radicals as HAT reagents. (a) Peroxides as oxygen radical precursors; (b) *N*-oxides as oxygen radical precursors; (c) *N*-hydroxyimides as oxygen radical precursors; (d) alcohols as oxygen radical precursors; (e) the focus of this review: acyloxy, sulfate, and phosphate radicals as HAT agents for direct C(sp^3)–H functionalization.

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Binbin Huang

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(2) Sulfate radical anion ($SO_4^{\bullet -}$) can be generated from persulfates ($S_2O_8^{2-}$) through thermo- or photochemically-promoted homolytic cleavage, as well as single-electron reduction events enabled by photochemistry, electrochemistry, among others.[21] It was not until recent years did the academic community conduct more in-depth explorations of utilizing sulfate radical anion as an HAT reagent in alkane C(sp^3)–H functionalization.[22] Notably, in 2023, Ye, Ma, and colleagues reported an innovative protocol to achieve Ritter-type amination of C(sp^3)–H bonds, using sulfate radical anion as an HAT agent that is electrochemically generated from cost-effective sulfuric acid (SO_4^{2-}).[23]

(3) It is noteworthy that phosphate radicals as HAT reagents have been observed in nature, particularly in the photolysis of DNA, where phosphate radicals generated by high-energy light can abstract hydrogen atoms from the deoxyribose moiety.[24] Photo-induced single-electron oxidation of phosphates ($(RO)_2P(O)O^-$) readily generates phosphate radicals ($(RO)_2P(O)O^{\bullet}$) to serve as HAT agents for achieving direct C(sp^3)–H functionalization. In 2018, the teams of Alexanian and Nicewicz,[25a] and Kanai and Oisaki,[25b] independently reported their studies on the functionalization of C(sp^3)–H bonds using phosphate

derivatives as HAT reagents. These strategies have further expanded the repertoire of sustainable organic synthesis.

To advance the research of HAT-based C(sp^3)–H activation, this review will dissect the generation mechanisms, reaction characteristics, and potential applications of the aforementioned three types of oxygen-centered radicals in HAT processes, with a focus on the developments from 2014 to 2024. Our aim is to provide researchers with a systematic understanding and strategic toolkit, thereby propelling the development of C–H activation techniques in modern organic synthesis.

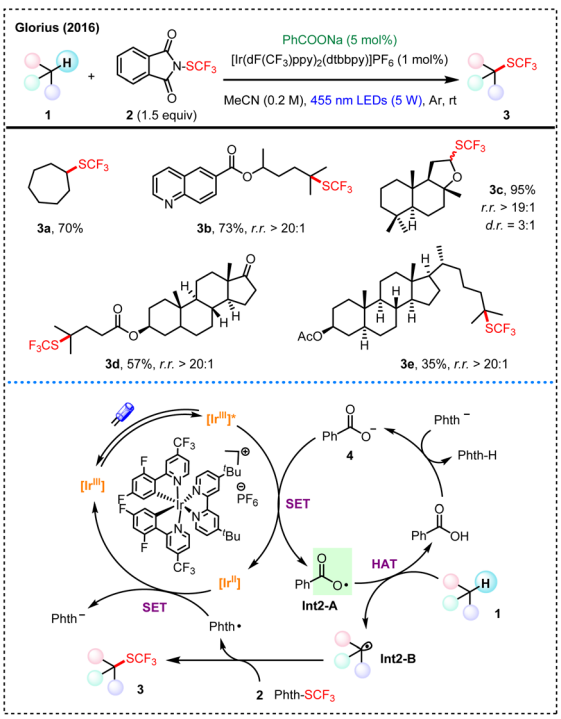
2. Acyloxy radicals as HAT reagents

2.1. Visible-light induced generation of acyloxy radicals

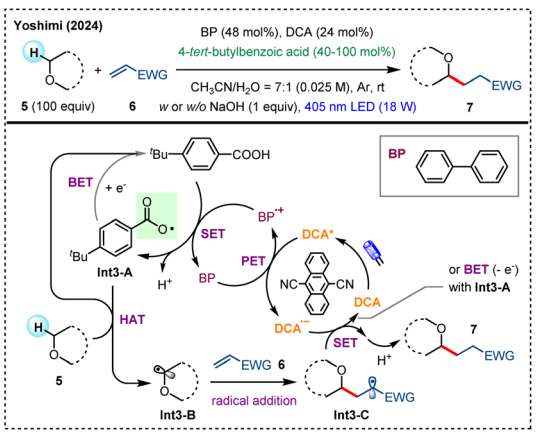
Visible-light photocatalysis, as an emerging strategy in organic synthesis, has garnered widespread attention from the chemical community in recent years.[26] This technique utilizes visible-light as a clean and renewable energy source to excite photosensitizers under mild conditions, thereby initiating a series of synthetically useful transformations.[27] Compared to reactions controlled by traditional thermodynamics or kinetics, visible-light photocatalysis offers chemists a new mode of molecule activation, enabling transformations that are elusive under conventional thermal conditions.

Trifluoromethylthiolation is an important functionalization strategy, which can significantly improve the chemical, physical, and biological properties of molecules by modifying them with trifluoromethylthio group (–SCF_3), a functionality with high electronegativity and lipophilicity.[28] In 2016, Glorius and colleagues disclosed a groundbreaking visible-light-promoted photoredox catalytic system for the selective trifluoromethylthiolation of unactivated C(sp^3)–H bonds with Phth–SCF_3 **2** (Scheme 2).[20c] Employing Ir(dF(CF_3)ppy)$_2$(dtbbpy)PF_6 as the photocatalyst and easily available sodium benzoate (which is equally effective to tetrabutylammonium benzoate) as the HAT catalyst, this reaction proceeds efficiently under the irradiation of 455 nm blue LEDs, exhibiting excellent selectivity in introducing –SCF_3 group at the most electron-rich C(sp^3)–H bond positions. Notably, high regioselectivity is also observed for the trifluoromethylthiolation of substrates containing multiple tertiary C(sp^3)–H bonds. One obvious superiority of this approach is the application of alkane substrates as the limiting reagents, which greatly improves its practicability and potential in the late-stage modification of complex molecules. The proposed reaction mechanism involves the excited state photocatalyst *Ir(III) being reductively quenched by benzoate **4**, generating radical **Int2-A** as a potent HAT agent to abstract a hydrogen atom from **1**. The resulting carbon-centered radical **Int2-B** then reacts with the trifluoromethylthiolating reagent **2** to yield the final product **3**. The simultaneously generated Phth$^\bullet$ is sequentially engaged in SET with Ir(II) and protonation with benzoyl acid, for the regeneration of both ground state photocatalyst Ir(III) and benzoate anion.

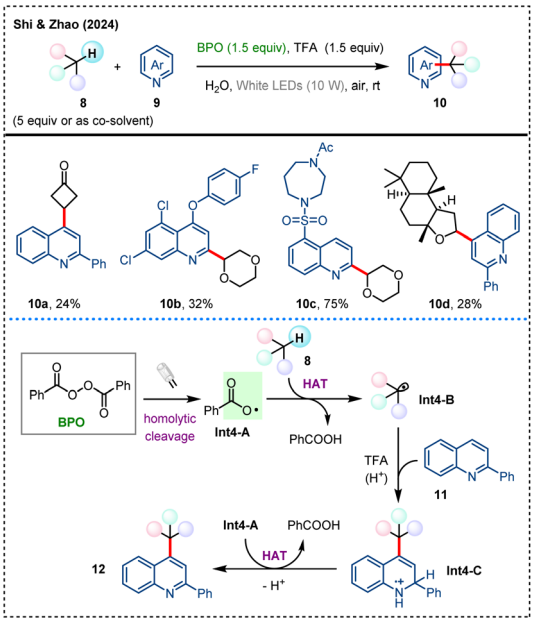
Photocatalytic Giese-type radical addition represents an important strategy for the construction of C(sp^3)–C(sp^3) bonds under mild conditions.[29] Recently, Yoshimi and coworkers developed a photoredox HAT system for the direct alkylation of *O*-α-C(sp^3)–H bonds using 4-*tert*-butylbenzoic acid as the HAT reagent, along with biphenyl (BP) as an electron donor and 9,10-dicyanoanthracene (DCA) as an electron acceptor (Scheme 3).[20e] Upon exposure to visible-light, a photoinduced electron transfer (PET) process between excited DCA* and BP enables efficient production of aryl acyloxy radical **Int3-A**, which selectively abstracts a hydrogen atom from *O*-containing substrate **5** (including acetals, ethers and alcohols), to generate carbon-centered radical **Int3-B**. The subsequent addition of **Int3-B** to electron-deficient alkene **6** forges a new C–C bond (**Int3-C**), and the following SET with DCA$^{\bullet-}$ furnishes final product **7**. Notably, along with the alkylation products, the additive 4-*tert*-



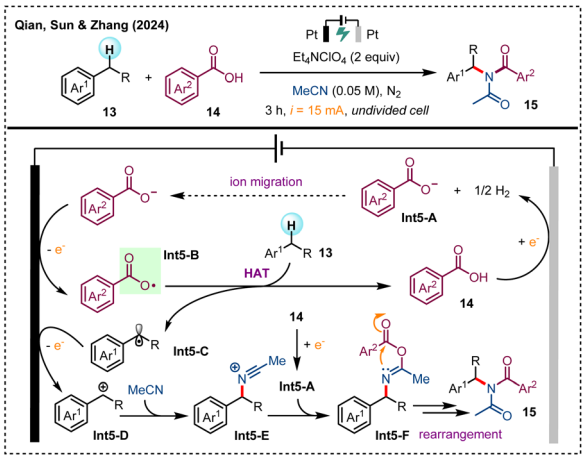
Scheme 2 Selective trifluoromethylthiolation of unactivated C(sp^3)–H bonds *via* visible-light enabled benzoyloxy radical HAT mechanism.



Scheme 3 Visible-light induced, benzoic acid-facilitated HAT for C–C bond formation.



Scheme 4 Visible-light-mediated dehydrogenative coupling of *N*-heteroarenes with inert C(sp^3)–H bonds *via* BPO-initiated HAT.



Scheme 5 Electrochemical amidation of benzylic C(sp^3)–H bonds *via* HAT with anodically generated benzoyloxy radicals.

butylbenzoic acid can also be recovered in high yield after reaction.

N-Heteroaromatic compounds, known for their pronounced bioactivity, have long been a focal point in pharmaceutical and agrochemical research, and the efficient construction and functionalization of these compounds are of great significance in organic synthesis.[30] In 2024, Shi, Zhao, and coworkers reported a visible-light induced intermolecular HAT process with BPO as a precursor for benzoyloxy radical (Scheme 4).[31] This approach avoids the application of hazardous chemicals and high temperature that are typically associated with such reactions, enabling the Minisci-type dehydrogenative coupling of *N*-heteroarenes **9** with inert C(sp^3)–H substrates **8** in water. This reaction system is compatible with a variety of six-membered *N*-heterocyclic compounds such as quinolines, isoquinolines and *etc.*, as well as C(sp^3)–H compounds, including cyclic ethers, esters, aldehydes, ketones, and even silanes (Si–H). Mechanistically, the reaction initiates with the decomposition of BPO under visible-light irradiation, to generate benzoyloxy radical **Int4-A** that is capable of abstracting hydrogen atoms from inert C(sp^3)–H bonds, resulting in the formation of key alkyl radical **Int4-B**. This alkyl radical then couples with TFA-protonated *N*-heteroarene **11** to form an *N*-radical cationic intermediate **Int4-C**, which upon further HAT and deprotonation yields the Minisci coupling product **12**.

2.2. Electrochemical generation of acyloxy radicals

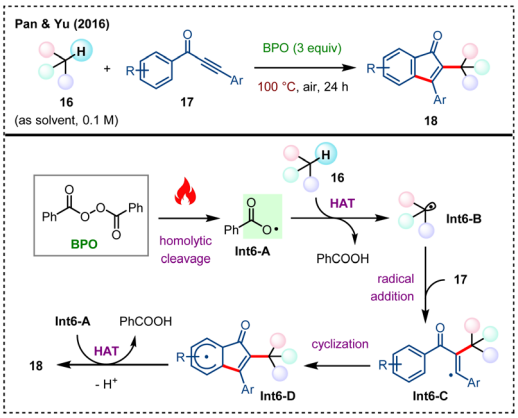
Organic electrosynthesis has been increasingly favored in recent years due to its innate advantages that eliminates the reliance on external chemical oxidants/reductants, thereby minimizing side reactions and waste production, which is in accordance with the aim of sustainable chemistry.[32] By altering the reaction components (such as electrode materials, electrolytes, solvents, *etc.*), and precisely adjusting the parameters (such as current and voltage), the conditions can be optimized to enhance the efficiency as well as selectivity of both electro-oxidative and electro-reductive transformations.[33]

Oxidative C–N bond formation under chemical oxidant-free electrochemical conditions is an attractive strategy for accessing amine derivatives.[34] In 2024, the team of Qian, Sun, and Zhang utilized anodic oxidation for acyloxy radical generation from aromatic carboxylic acids **14** to achieve a three-component amidation of C(sp^3)–H bonds at benzylic position (Scheme 5).[35] The reaction mechanism is proposed as follows: initially, acid **14** is reduced at the cathode to form hydrogen gas and acyloxy anion **Int5-A**, which then migrates to the anode surface for oxidation to access oxygen-centered radical **Int5-B**. The following HAT process of **Int5-B** with substrate **13** results in the formation of benzylic radical **Int5-C**, which is readily oxidized at the anode to generate cation **Int5-D**. The next interaction with solvent MeCN and **Int5-A**, followed by a Mumm rearrangement yield the final product **15**.

2.3. Thermochemical generation of acyloxy radicals

Under heating conditions, benzoyl peroxide (BPO) can decompose to produce reactive benzoyloxy radicals *via* homolytic O–O bond cleavage, allowing for subsequent HAT processes with C(sp^3)–H bonds.[19] In the following section, some representative and significant works reported in the past decade are introduced.

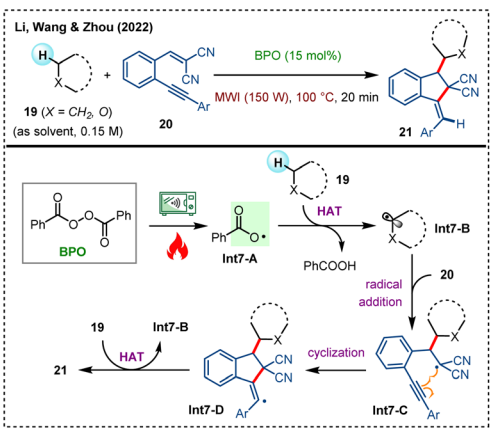
Internal alkynes represent an important moiety for cyclization to access five-membered ring systems.[36] In 2016, the team led by Pan and Yu disclosed a BPO-enabled oxidative radical cyclization of ynones with alkanes for the synthesis of a series of 2-alkyl-3-aryl indenones **18** (Scheme 6).[37] The substrate scope includes diverse alkanes **16** which are used as reaction solvent, and diversely substituted 1,3-diaryl-2-propyn-1-ones **17**. The possible mechanism for the reaction is proposed as follows: initially, BPO undergoes homolytic cleavage under heating



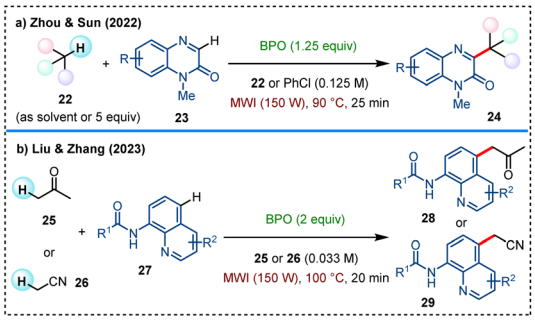
Scheme 6 Metal-free radical oxidative annulation of ynones with alkanes to access indenones.

conditions to generate benzoyloxy radical **Int6-A**. This radical abstracts a hydrogen atom from alkane **16**, forming alkyl radical **Int6-B**, which then adds onto the C–C triple bond of ynone **17** to reach **Int6-C**. Next, the intramolecular radical addition of **Int6-C** results in another radical intermediate **Int6-D**, which further has a hydrogen atom abstracted by **Int6-A** to afford the target indenone product **18.**

Microwave dielectric heating shows advantage to dramatically elevate the conversion rates of organic synthetic transformations, thereby reducing reaction times from days and hours to minutes and seconds.[38] In 2022, Li, Wang, Zhou, and colleagues developed a BPO-initiated microwave-accelerated cyclization of 1,5-enynes with cycloalkanes, providing an efficient approach to exocyclic indane derivatives **21** (Scheme 7).[39] Through deuterium labeling experiments, radical trapping experiments, and mass spectroscopy studies, a reasonable reaction mechanism is proposed. Under heating and microwave irradiation, BPO readily generates benzoyloxy radical **Int7-A**, which acts as an initiator to abstract a hydrogen atom from cycloalkane **19** to form alkyl radical **Int7-B**. This alkyl radical then selectively attacks the carbon–carbon double bond of the



Scheme 7 Microwave-accelerated synthesis of exocyclic indane derivatives *via* C–H activation and 1,5-enyne cyclization.



Scheme 8 Microwave-accelerated CDC reactions for direct C(sp^3)–C(sp^2) bonds formation.

1,5-enyne **20** to form a tertiary carbon radical **Int7-C**, which subsequently cyclizes with the adjacent internal alkyne moiety to afford intermediate **Int7-D.** Ultimately, cyclization product **21** is formed through an HAT event with cycloalkane **19**, meanwhile generating another **Int7-B.**

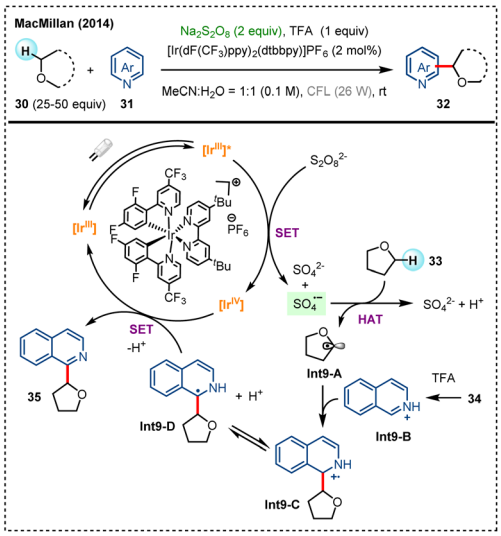
Cross dehydrogenative coupling (CDC) reactions for direct C(sp^3)–C(sp^2) bonds formation have garnered considerable research attention in recent years.[40] In 2022, Zhou and Sun *et al.* developed a microwave-accelerated CDC reaction of quinoxalin-2(1*H*)-ones with alkanes under metal-free conditions (Scheme 8a).[41] A wide range of simple alkanes **22** are applied as alkyl radical precursors under microwave-assisted BPO-promotion to achieve C–H alkylation of diversely substituted quinoxalin-2(1*H*)-ones **23** and some other nitrogen-containing heteroaromatics. Later in 2023, Liu, Zhang and colleagues reported another metal-free microwave-accelerated CDC reaction for the C5-alkylation of *N*-(quinolin-8-yl)amides **27** with acetone **25** or acetonitrile **26**, using BPO as a benzoyloxy radical source (Scheme 8b).[42]

3. Sulfate radical anion as an HAT reagent

3.1. Visible-light induced generation of sulfate radical anion

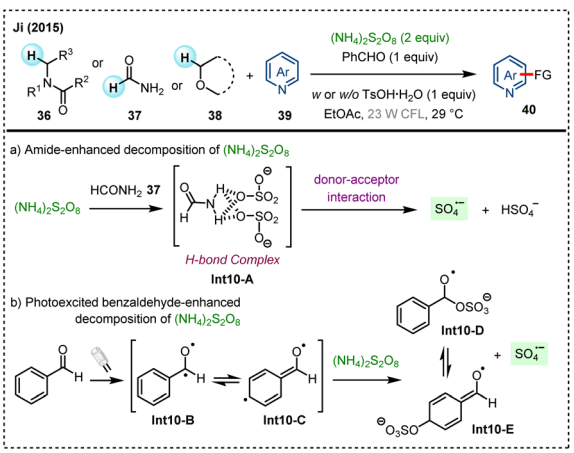
Persulfate salts (*e.g.*, $K_2S_2O_8$, $Na_2S_2O_8$, and $(NH_4)_2S_2O_8$), commonly serving as an oxidizing reagent in chemical reactions,[21,43] begins to demonstrate unique potential in achieving direct functionalization of unactivated hydrocarbons when combined with organic photocatalysis, by forming sulfate radical anion ($SO_4^{\bullet-}$) as a powerful HAT species.[22]

In 2014, the MacMillan group reported an innovative photocatalytic CDC reaction for achieving α-heteroarylation of ethers (Scheme 9).[44] In the mechanistic proposal, sulfate radical anion generated by SET between excited-state photocatalyst and $Na_2S_2O_8$ acts as the HAT reagent, extracting hydrogen atom from *O*-α-C(sp^3)–H of ethers **33** to form α-oxyalkyl radicals **Int9-A.** This radical intermediate then couples with protonated heteroarene **Int9-B** to build a new C–C bond (**Int9-C**). This method exhibits a broad substrate scope, applicable to a variety of cyclic and acyclic ethers, as well as diverse heteroarenes, including pyridines, quinolones, and their derivatives, demonstrating excellent functional group tolerance and regioselectivity.

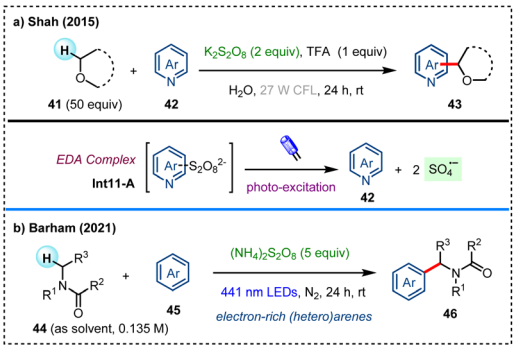


Scheme 9 Photocatalytic α-heteroarylation of ethers with sulfate radical anion as an HAT agent.

In 2015, Ji and colleagues developed a photo-induced CDC reaction mediated by benzaldehyde, achieving α-heteroarylation of amides and ethers without the need for metal photocatalyst (Scheme 10).[45] The photo-excited benzaldehyde is used to promote a unique decomposition mechanism of ammonium persulfate, generating sulfate radical anion as an powerful HAT reagent. Two possible pathways for the generation of sulfate radical anion are proposed: (a) in the absence of benzaldehyde, the formation of complex **Int10-A** through hydrogen bonding between $(NH_4)_2S_2O_8$ and amide **37**, followed by a donor–acceptor interaction, produce sulfate radical anion ($SO_4^{\bullet-}$), which is primarily enabled by thermal chemistry; (b) the excited-state benzaldehyde generated under visible-light irradiation facilitates the decomposition of $(NH_4)_2S_2O_8$ to produce $SO_4^{\bullet-}$, a process that is part of photochemistry. Regardless of whether the sulfate radical anion is generated through thermal or photochemical pathways, it serves as an



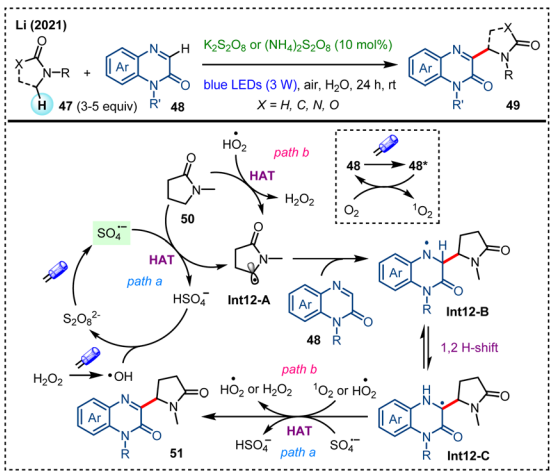
Scheme 10 Photo-induced CDC for α-heteroarene functionalization of amides and ethers without metal catalysts.



Scheme 11 Visible-light-mediated EDA complex formation for C(sp^3)–H bond functionalization.

HAT agent capable of abstracting hydrogen atoms from diverse amides and ethers. Throughout the reaction process, benzaldehyde may participate in a catalytic cycle, ultimately being regenerated to sustain the catalytic process.

Electron donor–acceptor (EDA) complexes are molecular aggregates of electron donors and acceptors, which upon light-irradiation can undergo photo-excitation to facilitate the following chemical processes.[46] In 2015, Shah *et al.* developed an external photocatalyst-free CDC reaction, facilitating the activation of C(sp^3)–H bonds in ethers to couple with electron-deficient *N*-heteroarenes under visible-light irradiation (Scheme 11a).[47] In this method, *N*-heteroarenes **42** form EDA complexes (**Int11-A**) with $K_2S_2O_8$, which upon visible-light excitation generates sulfate radical anion *via* homolytic cleavage as the HAT agent for direct C(sp^3)–H functionalization of ethers **41**. In 2021, Barham's group described a photocatalyst-free, visible-light-mediated direct C(sp^3)–H arylation of amides (Scheme 11b).[48] In this reaction, solvent-caged EDA complexes are formed between electron-rich (hetero)arenes **45** and persulfate in amides **44** (as solvent), which upon photoexcitation produces sulfate radical anion as the hydrogen abstractor for the activation of *N*-α-C(sp^3)–H bonds.



Scheme 12 Visible-light-mediated regioselective amidoalkylation of *N*-heteroaromatics with γ-lactams/amides in aqueous medium.

In 2021, Li and coworkers developed a persulfate-catalyzed photocatalytic CDC reaction of *N*-heteroaromatics with γ-lactams/amides in water (Scheme 12).[49] In the presence of catalytic $K_2S_2O_8$ or $(NH_4)_2S_2O_8$ under air atmosphere, this protocol enables smooth amidoalkylation of various *N*-heteroaromatics such as quinoxalin-2(1*H*)-ones (**48**), quinolines, isoquinolines, phthalazines, and benzothiazoles in high regioselectivity. Upon visible-light irradiation, $S_2O_8^{2-}$ decomposes to $SO_4^{\bullet-}$, while substrate **48** is also excited to form excited-state **48***. This excited-state molecule (**48***) undergoes energy transfer with triplet oxygen to generate singlet oxygen ($^1O_2$). The sulfate radical anion ($SO_4^{\bullet-}$) then undergoes HAT with γ-lactam **50** to form a carbon-centered radical **Int12-A** (path a), which selectively adds onto the C3-position of **48**, establishing a new C–C bond. Finally, the desired product **51** is obtained through an HAT process followed by dehydrogenation steps. Hydrogen peroxide produced during the reaction may undergo homolytic cleavage under visible-light irradiation to generate hydroxyl radical (HO$^\bullet$), which may participate in the cycle of persulfate. In addition, intermediate $HO_2^\bullet$ may extract hydrogen from **50** to produce H_2O_2 (path b).

3.2. Electrochemical generation of sulfate radical anion

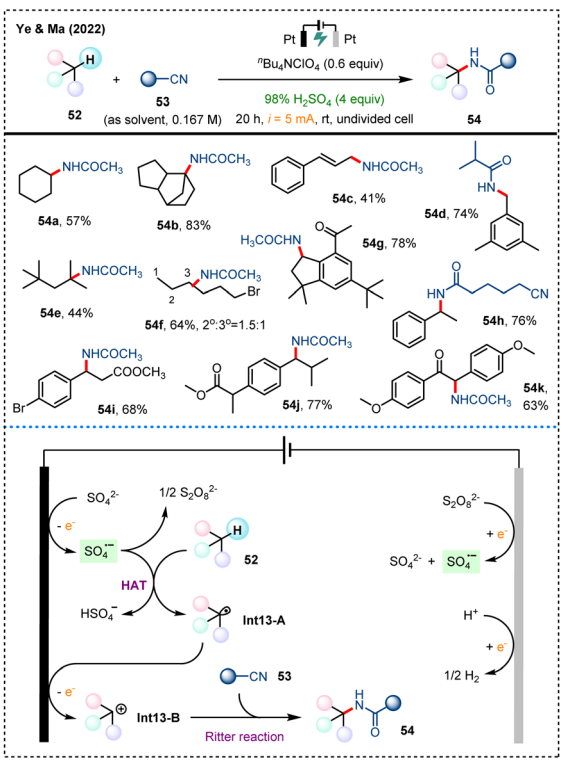
Ritter-type reaction of organonitriles represents an important method for the synthesis of amide compounds.[50] In 2022, Ye, Ma and their colleagues developed an innovative electrosynthetic strategy that utilizes sulfate ions (SO_4^{2-}) of cost-effective sulfuric acid as a key additive to achieve Ritter-type amination of inert C(sp^3)–H bonds (Scheme 13).[23] Upon anodic oxidation of SO_4^{2-}, sulfate radical anion $SO_4^{\bullet-}$ is readily generated to serve as an HAT reagent, facilitating the direct amination of C(sp^3)–H bonds of common alkanes with diverse organonitriles with excellent site selectivity.

In terms of the mechanism for this electrochemical Ritter-type amination,[23] the single-electron oxidation of SO_4^{2-} at the anode to form sulfate radical anions ($SO_4^{\bullet-}$) serves as the key step. This radical anion is capable of abstracting a hydrogen atom from substrate **52**, generating carbon radical **Int13-A**, which is further oxidized at the anode to form carbocation intermediates **Int13-B**. Subsequently, nitrile **53** attack the carbocation **Int13-B**, leading to the formation of the final amination product **54** through a Ritter reaction pathway. Additionally, the dimerization of sulfate radical anions forms persulfate ions ($S_2O_8^{2-}$), which are transferred to the cathode and reduced back to SO_4^{2-} and $SO_4^{\bullet-}$. This method paves a convenient and flexible pathway for realizing synthetically useful transformations of C(sp^3)–H bonds mediated by sulfate radical anion generated *via* electrochemistry.

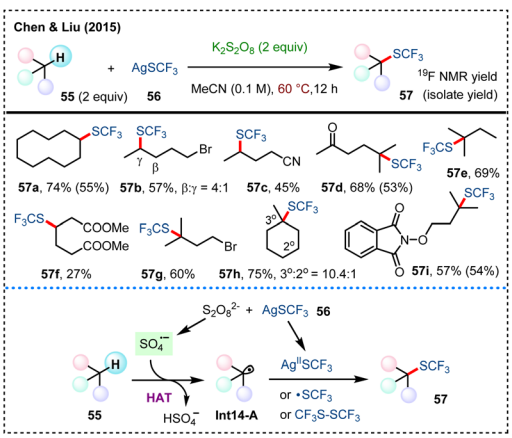
3.3. Thermochemical generation of sulfate radical anion

In 2015, the team led by Chen and Liu developed a potassium persulfate-mediated direct C(sp^3)–H trifluoromethylthiolation, utilizing silver(I) trifluoromethanethiolate ($AgSCF_3$, **56**) as the –SCF_3 source (Scheme 14).[51] Under relatively mild conditions at 60 °C, this reaction demonstrates a broad substrate scope, including a variety of unactivated alkanes. $K_2S_2O_8$ is proposed to play a dual role in this system: on one hand, it decomposes to produce sulfate radical anion that abstracts hydrogen atoms from C(sp^3)–H bonds to form key alkyl radical **Int14-A**; on the other hand, it is also responsible for the oxidation of $AgSCF_3$, generating radical $^\bullet SCF_3$, Ag(II)SCF_3 or CF_3S–SCF_3 intermediates, which are key to the formation of the final trifluoromethylthiolation product **57**.

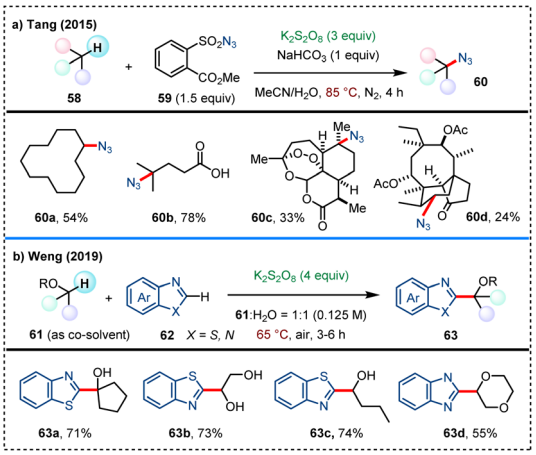
The homolytic cleavage of $S_2O_8^{2-}$ triggered by heating at certain temperature generates sulfate radical anion to enable HAT processes, thereby facilitating C–N and C–C bonds formation *via* direct C(sp^3)–H functionalization. In 2015, Tang



Scheme 13 Electrochemical synthesis of amides *via* sulfate-mediated Ritter-type C(sp^3)–H amination.



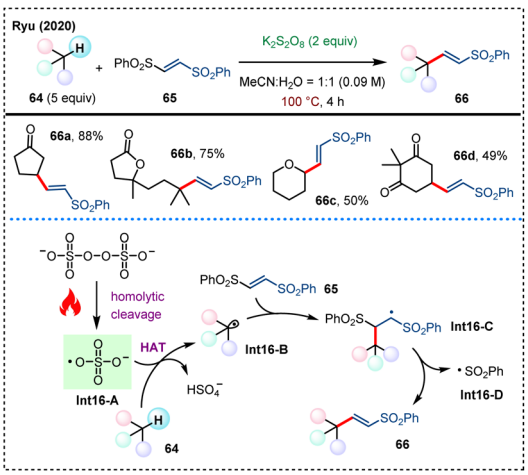
Scheme 14 Direct trifluoromethylthiolation of unactivated C(sp^3)–H bonds under thermal conditions.



Scheme 15 Sulfate radical-mediated direct C(sp^3)–H azidation and heteroarylation.

and coworkers developed an sulfate radical-mediated azidation of unactivated aliphatic C–H bonds (Scheme 15a).[52] This transition-metal-free method utilizes an easily handled sulfonyl azide **59** as the azide source, showcasing practicability for scale-up reactions and late-stage azidation of natural product derivatives. In 2019, Weng and coworkers reported a hydroxyalkylation of benzothiazoles with alcohols/ethers in aqueous solution that is mediated by sulfate radicals (Scheme 15b).[53] This method takes advantage of the high solubility of inorganic salts in water with simplified post-treatment process, showing good substrate applicability and functional group compatibility.

Later in 2020, Ryu's group developed a site-selective alkenylation of alkanes in the presence of persulfate (Scheme 16).[54] Using 1,2-bis(phenylsulfonyl)ethane **65** as the alkenylating reagent, this method is capable of directly modifying C(sp^3)–H bonds to access diverse (*E*)-2-alkylvinylphenylsulfones **66**, with new C(sp^3)–C(sp^2) bonds forged. Notably, direct alkenylation of some steric hindered C(sp^3)–H bonds can also be achieved due to the compact size of sulfate radicals. This strategy offers a broad substrate scope and excellent site selectivity, providing an effective tool for complex molecule synthesis.

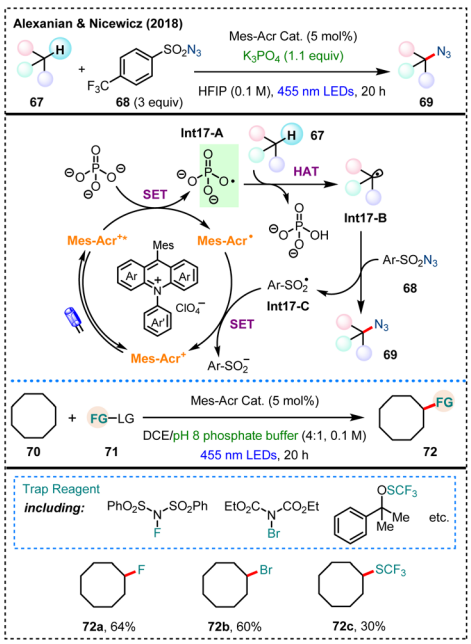


Scheme 16 Compact sulfate radical-mediated C(sp^3)–H alkenylation under heating conditions.

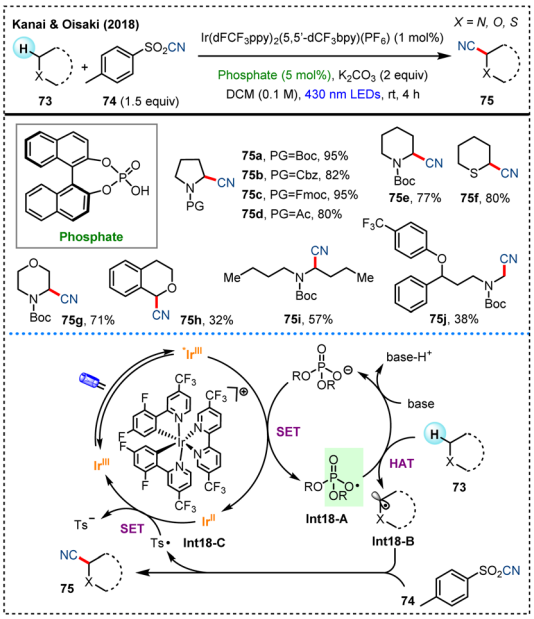
4. Phosphate radicals as HAT reagents

Compared with acyloxy and sulfate radicals, phosphate radicals have been relatively underexplored in the application of mediating HAT processes. The current transformations have mainly relied on visible-light photocatalytic methods.

In 2018, Alexanian, Nicewicz and their colleagues reported a general strategy combining photoredox catalysis with phosphate salts to achieve direct azidation of aliphatic C–H bonds (Scheme 17).[25a] Initially, the researchers hypothesized that the highly oxidizing acridinium salts (Mes–Acr$^+$) could be used to oxidatively generate heteroatom-centered radicals with HAT ability, facilitating the functionalization of C(sp^3)–H bonds with a sulfonyl group transfer reagent. A system combining K_3PO_4 with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is then screened out to effectively facilitating the C–H azidation, using **68** as the azide source. The mechanism is proposed as follows: under the excitation of 455 nm LEDs, the acridinium salt photosensitizer undergoes SET with the phosphate salt, generating an oxygen-centered radical **Int17-A** which upon HAT with alkane **67** results in carbon-centered radical **Int17-B**. This radical is then trapped by the sulfonyl azide **68** to form the desired product **69**, while also generating a sulfonyl radical **Int17-C**. Notably, using different radical acceptors, a variety of C(sp^3)–H functionalizations have also been realized, including fluorination, bromination and trifluoromethylthiolation, among others. These transformations demonstrate the versatility of this photoredox catalytic system, allowing for the modular incorporation of



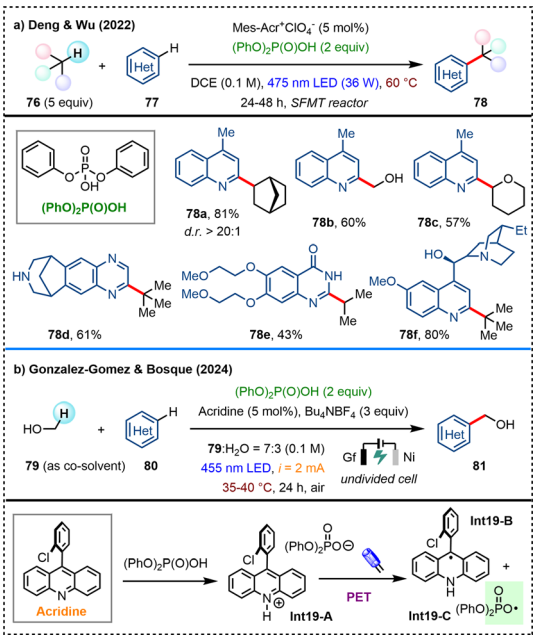
Scheme 17 A general strategy for aliphatic C–H functionalization enabled by organic photoredox catalysis.



Scheme 18 Phosphate-radical-mediated visible-light photoredox cyanation of C(sp^3)–H bonds.

diverse functional groups through the application of different radical trapping agents.

In the same year, the research team led by Kanai and Oisaki developed an innovative cyanation for C(sp^3)–H bonds under visible-light photoredox catalysis in the presence of a phosphate catalyst (Scheme 18).[25b] Under the irradiation of 430 nm blue light, the phosphate salt produces a phosphorus-based oxygen radical **Int18-A** through single-electron oxidation, which acts as an HAT agent to efficiently activate C(sp^3)–H bonds with relatively high bond dissociation energies (BDEs). The resulting radical **Int18-B** then react with the cyanide source **74** to form cyanation product **75.** This method showcases excellent functional group compatibility, along with large potential in the late-stage modification of complex molecules, broadening the horizon for pharmaceutical synthesis.



Scheme 19 Phosphate radical enabled visible-light induced CDC reaction of heteroarenes with alkanes/alcohols.

In 2022, the team of Deng and Wu developed a photo-induced Minisci-type CDC reaction between alkanes and heteroarenes in a metal- and external oxidant-free manner (Scheme 19a).[55] The success of this transformation lies in the use of an elegantly designed stop-flow microtubing (SFMT) reactor to enhance the light penetration while stabilizing volatile and gaseous reagents and intermediates. The key additive diphenyl phosphate plays a dual role both in activating heteroarene substrates and in generating phosphate radicals to promote the HAT process triggered by photoredox catalysis. Later in 2024, Gonzalez-Gomez, Bosque, and coworkers also reported a highly selective hydroxymethylation of azaarenes with methanol, employing chlorine or phosphate radicals as the HAT reagents with a acridine photocatalyst under photo-electrochemical conditions (Scheme 19b).[56] Under irradiation of 455 nm blue light, the PET process of acridinium intermediate **Int19-A** provides the key phosphate radical **Int19-C** as a selective HAT reagent. Instead of chemical oxidants, electrochemical oxidation is applied for the regeneration of the photocatalyst, thereby further improving the sustainability of this transformation.

5. Summary and outlook

This review delves into the innovative applications of acyloxy, sulfate, and phosphate radicals in intermolecular HAT reactions for achieving direct C(sp^3)–H bond functionalization. Methods such as organic photocatalysis, electrosynthesis, and thermochemistry-enabled reactions have been utilized for the generation of these acid-related radicals as unique and promising categories of HAT species. Specifically, acyloxy radicals, mainly the aryl substituted ones, exhibit remarkable stability, offering high efficiency and selectivity for the hydrogen abstraction from C(sp^3)–H bonds. Sulfate radical (anion), generated from easily available persulfates or sulfates through thermo-, photo- or electrochemical methods, provides a cost-effective and sustainable choice for C(sp^3)–H functionalization. Phosphate radicals, as inspired by natural processes, provide a novel strategy for C(sp^3)–H activation, which exhibits remarkable potential for further exploration. The generation mechanisms, reactivity characteristics and the applications in selective HAT processes of these oxygen-centered radicals are discussed, underscoring their potential to advance C–H activation methodologies in modern organic synthesis.

Looking ahead, future research may focus on establishing more sustainable reaction conditions for the facile generation of these radicals, broadening the range of substrates that these radicals can effectively engage with, as well as exploring their potential in asymmetric C(sp^3)–H functionalization. As the field of C–H activation continues to evolve, these acid-related radicals are anticipated to play increasingly prominent roles,

offering new strategies and tools for chemists to innovate the synthetic methodologies.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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