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Visible-light induced direct C(sp^3)–H functionalization: recent advances and future prospects

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The direct activation of inert saturated C–H bonds for selective functionalization has long been a significant challenge in organic synthesis. The past few decades have witnessed the emergence of visible-light-induced synthesis, which also offers a new platform for achieving direct C(sp^3)–H functionalization under mild conditions. Due to the tremendous research effort devoted to this, various novel visible-light-driven protocols have been established, enabling the efficient and sustainable preparation of value-added molecules from readily available alkane feedstocks. Inspired by the recent breakthroughs, herein we summarize the latest methodologies reported from the second half of 2021 to the first half of 2024, with a particular emphasis on the formation of C–P, C–B, C–S bonds, *etc.*, along with some efforts in asymmetric C–H functionalization, to reveal the current trends and the existing challenges in this rapid-developing field.

1. Introduction

The selective activation of inert C(sp^3)–H bonds poses a significant challenge in organic synthesis, due to the high bond dissociation energies (BDEs) of saturated C–H bonds and their ubiquity in organic molecules (Scheme 1a).[1] The precise conversion of alkanes into value-added products in a more sustainable and step-economical way is always of paramount appeal, and therefore, direct C–H activation is often dubbed the "Holy Grail" of organic synthesis.[2] The development of efficient methodologies for C–H activation holds the potential to profoundly influence the field of organic synthesis, by which chemists can streamline the synthesis of complex molecules, reduce the reliance on prefunctionalized starting materials, and minimize the waste generation.[3]

Over the past few decades, visible-light-induced organic synthesis has attracted considerable research attention and is regarded as an emerging green, efficient, and economical synthetic methodology,[4] which also offers a new avenue for achieving direct C(sp^3)–H functionalization.[5] In 2021, Wu[5a] and Fagnoni[5b] independently disclosed their own comprehensive accounts on the advances in visible-light-induced C–H functionalization, showcasing the prospects for overcoming

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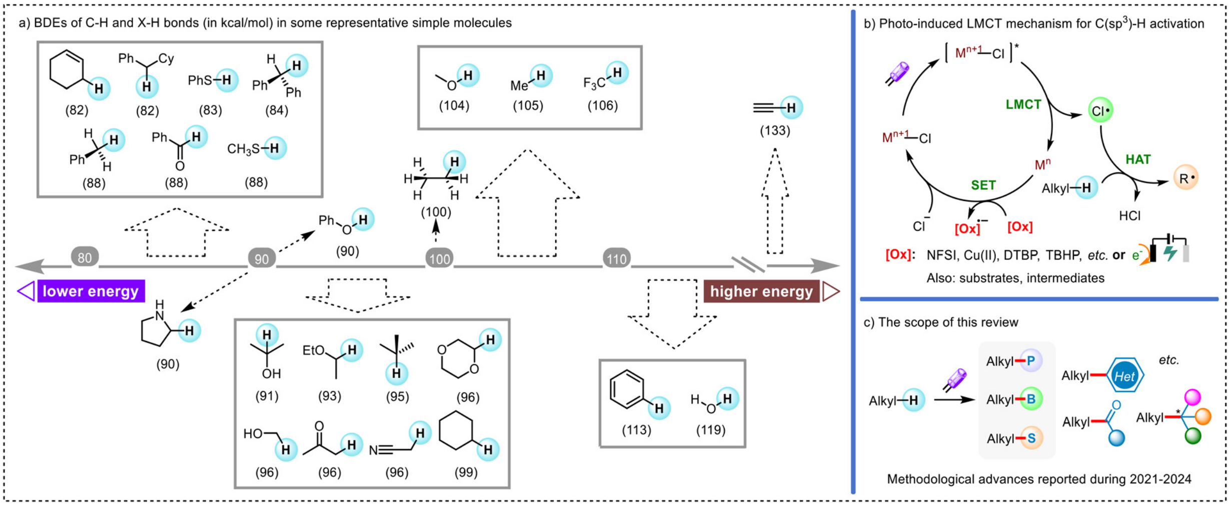

Scheme 1 Background information for this review.

the inherent challenges *via* hydrogen atom transfer (HAT) processes. Based on the pathways leading to the generation of HAT reagents (generally induced by visible light irradiation), the related C–H activation research can be classified into two broad categories:[5] direct HAT processes (exemplified by photosensitizers such as eosin Y,[6] TBADT,[7] and benzophenone,[8] which upon photoexcitation and intersystem crossing can directly abstract hydrogen atoms from alkanes) and indirect HAT processes (*e.g.*, the visible-light-excited iron chloride species could not abstract the hydrogen atom, but the chlorine radical generated *via* a ligand-to-metal charge transfer process serves as the real powerful HAT reagent).[9]

Despite the significant progress in visible-light-induced $C(sp^3)$–H activation that has been documented in these elegant reviews, the field continues to evolve rapidly, and promising new discoveries and advancements have been reported.[10] From the second half of 2021 to the first half of 2024, breakthroughs in visible-light-induced $C(sp^3)$–H functionalization have been achieved, particularly with the rise of photoinduced ligand-to-metal charge transfer (LMCT) processes[11] and photoelectrocatalytic systems,[12] which are also the catalytic patterns to be highlighted in this review (Scheme 1b). Photocatalytic C–H functionalization using inexpensive metals such as iron,[9] copper,[13] cerium,[14] bismuth[15] and titanium[16] has been deepened. Apart from the homolytic cleavage of metal chlorides under photoinduced LMCT or single-electron oxidation of chlorides, Shi's group pioneered the generation of chlorine radicals using electron donor–acceptor complexes.[10b] For direct $C(sp^3)$–H phosphorylation, Hu[17a] and Xia[17b] independently reported their photocatalytic systems to address the long-standing challenge, producing trivalent phosphines direct from economical hydrocarbons, which hold the potential to serve as versatile ligands in organic synthesis.[18] Alkyl boronates are widely utilized as practical synthetic intermediates in cross-coupling reactions, which can be accessed by Aggarwal's metal-free photoinduced

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C(sp^3)–H borylation.[19] Building on Aggarwal's pioneering work, several groups have made notable advancements in this challenging transformation by means of visible-light photocatalysis or photoelectrocatalysis.[20] Furthermore, progress has also been achieved in C(sp^3)–H sulfurization through different visible-light-mediated pathways,[20a,21] which is driven by the ubiquitous presence of sulfur-containing moieties in pharmaceutical compounds and natural products.[22]

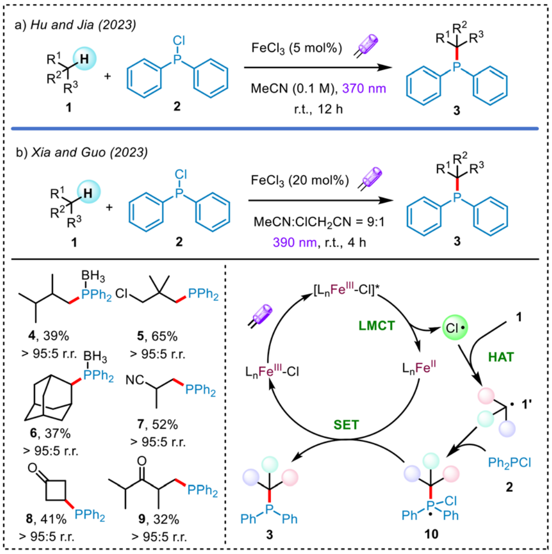
To further propel the development of this field and complement the earlier reviews,[5] this review will systematically summarize the recent advances in visible-light (mainly purple light around 370–390 nm) induced C(sp^3)–H functionalization over the past three years, and several UV-light (<370 nm) enabled strategies are also included. It is noteworthy that while the remote C(sp^3)–H activation strategies represent significant strides in visible-light-enabled organic synthesis, these reactions often require tailored substrate structures to facilitate radical migration,[23] which therefore would only be briefly addressed in the subsequent discussions. The review is categorized by the diverse C–X (X = hetero atom) bonds formed directly from unactivated C(sp^3)–H, with a particular emphasis on the formation of C–P, C–B, and C–S bonds, among others. Additionally, concerning the significance of asymmetric synthesis,[5g] we also highlight some of the latest achievements (mainly reported after 2023) in visible-light-enabled enantioselective C(sp^3)–H functionalization in an independent section. The scope of this review is presented in Scheme 1c. We believe that these recent examples along with the discussion will not only underscore the transformative potential of visible-light-induced organic synthesis in C(sp^3)–H activation, but also provide crucial perspectives for advancing sustainable and efficient chemical processes.

2. C(sp^3)–H phosphorylation

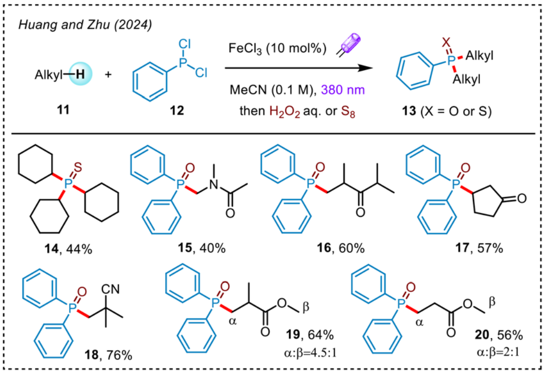
The construction of C–P bonds is of immense importance in organic synthesis and the pharmaceutical chemistry.[24] From a synthetic perspective, phosphorus ligands play a crucial role in catalytic reactions, and phosphorus-containing compounds are pivotal in drug development,[25] as exemplified by certain antibiotics[26] and anticancer agents.[27] Moreover, phosphorus-containing compounds find extensive applications as pesticides and herbicides, bolstering agricultural productivity.[28] Recent methods for C–P bond formation primarily involve transition metal catalysis using copper,[29] nickel,[30] or palladium.[31] Moreover, systems for radical phosphorylation have been developed using highly reactive radical precursors such as alkyl halides, *N*-hydroxyphthalimide (NHPI) esters, and Katritzky salts, to react with diphosphates or chlorophosphates.[32] However, these methods are ineffective for the direct phosphorylation of inert C(sp^3)–H bonds, and their photocatalytic counterparts typically work on specific positions, such as benzylic positions[33] and α-positions adjacent to nitrogen atoms.[34] In late 2023, Wu *et al.* developed a visible-light-induced remote C(sp^3)–H phosphonylation of aliphatic amines,[35] but this substrate-specific method lacks generality for broader applications. Consequently, developing a robust method for the phosphorylation of simple alkane C(sp^3)–H bonds remains a significant endeavor.

In 2023, Hu[17a] and Xia[17b] *et al.* almost simultaneously reported the first visible-light-induced, iron-catalyzed direct C(sp^3)–H phosphorylation of unactivated alkanes (Scheme 2). Exemplified by the work of Xia and Guo (Scheme 2b),[17b] the reaction is facilitated by a photoinduced Fe-LMCT process under 390 nm light irradiation, and demonstrates a broad substrate scope, showing compatibility with simple alkanes containing halide, ketone, ester, nitrile, ether, thioether, and silane moieties. The visible-light-mediated C(sp^3)–H phosphorylation reaction proceeds through a series of key steps. Upon visible-light excitation, the iron(III) complex undergoes an intramolecular LMCT process, generating a reduced iron(II) complex and a highly reactive chlorine radical ($Cl^•$). The chlorine radical then engages in an HAT process with the C–H bond of alkane **1**, producing an alkyl radical intermediate **1′**. This carbon-centered radical subsequently adds onto chlorodiphenylphosphine **2** to form intermediate **10**, which rapidly undergoes a single-electron-transfer (SET) process with the iron(II) complex, yielding the desired C(sp^3)–H phosphorylation product **3** and completing the catalytic cycle of the iron catalyst.

Shortly thereafter, Huang and Zhu *et al.* reported a similar photoinduced, iron-LMCT catalyzed C(sp^3)–H phosphorylation reaction (Scheme 3).[36] Apart from monochlorophenyl phosphines, dichlorophenyl phosphines **12** and even phosphorus trichloride can be used as the phosphating reagents, resulting in dialkylated or trialkylated trivalent phosphorus derivatives. By adding hydrogen peroxide or elemental sulfur after the reaction, pentavalent phosphorus compounds can be obtained with O- or S-incorporation.



Scheme 2 Visible-light-induced C(sp^3)–H phosphorylation of hydrocarbons.

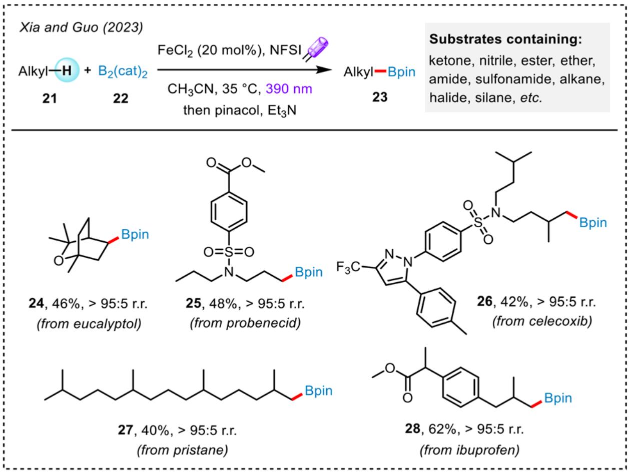


Scheme 3 Iron-catalyzed C(sp^3)–H phosphorylation *via* photoinduced LMCT.

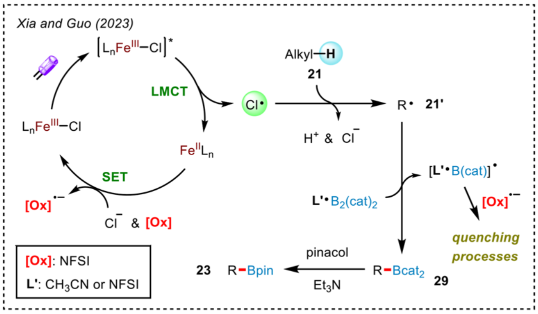
3. C(sp^3)–H borylation

The vacant p-orbital of boron atoms enables the formation of stable σ bonds with carbon atoms. This imparts unique reactivity to boron-containing compounds, rendering them invaluable in organic synthesis,[37] particularly as substrates in Suzuki coupling reactions,[38] which have significantly advanced the related fields. Significant strides have been made in transition metal/iridium-catalyzed C–H borylation[39] and radical pathways for C–B bond formation.[40] Notably, the Aggarwal group has contributed to the metal-free, visible-light-induced C–H borylation of alkanes, employing a reactive reagent B-chlorocatecholborane (Cl-Bcat) as the chloride source in combination with an alkoxyphthalimide.[19] Subsequently, visible-light-mediated remote C(sp^3)–H borylation has also emerged, albeit relying on specialized precursors, thus posing certain limitations in generality.[41] Consequently, developing a general, mild and cost-effective catalytic system for the construction of C–B bonds from inert alkanes still remains a formidable challenge.

In 2023, Xia and Guo *et al.* reported an visible-light-mediated, iron-catalyzed C(sp^3)–H borylation reaction, wherein the direct photoexcitation of ferrous chloride ($FeCl_2$) enables the generation of reactive chlorine radicals by LMCT (Scheme 4).[20a] These radicals undergo intermolecular HAT processes with simple alkanes for following functionalization with bis(catecholato)diboron (B_2cat_2, **22**). The reaction shows broad substrate compatibility, accommodating functionalities such as halides, carbonyls, nitriles, amides, and sulfonamides, making it applicable for the late-stage modification of pharmaceutical molecules and natural products. Notably, this strategy exhibits excellent terminal selectivity.



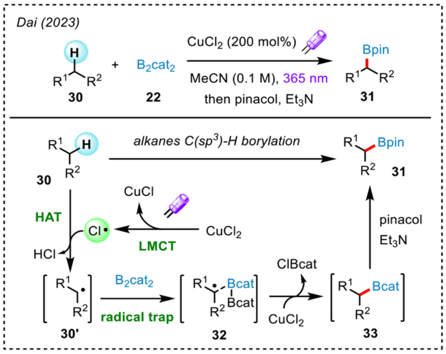
Scheme 4 C(sp^3)–H borylation *via* photoinduced LMCT.



Scheme 5 Mechanism of the C(sp^3)–H borylation *via* photoinduced LMCT.

The mechanism of this photoinduced iron-catalyzed C(sp^3)–H borylation is proposed as follows (Scheme 5):[20a] upon excitation, ferric chloride undergoes an intramolecular LMCT process, generating reduced iron(II) species and a chlorine radical. The latter rapidly undergoes HAT with the C(sp^3)–H substrate **21**, releasing alkyl radical **21′**. This intermediate reacts with the ligand-stabilized $B_2(cat)_2$ to form the desired alkyl boronic ester **29**, which is further transformed into the final stabilized product **23** by treatment with pinacol and triethylamine. The *N*-fluorobenzene sulfonamide (NFSI) serves as a single-electron oxidant to convert iron(II) to iron(III) complex.

In 2023, the Dai research group reported a photoinduced, copper-mediated alkane C(sp^3)–H borylation reaction using ultraviolet light (365 nm) and stoichiometric cupric chloride, offering an alternative method for the synthesis of alkyl boronic esters (Scheme 6).[20b] The reaction mechanism is pro-



Scheme 6 Photoinduced C(sp^3)–H borylation of alkanes *via* copper(II) chloride.

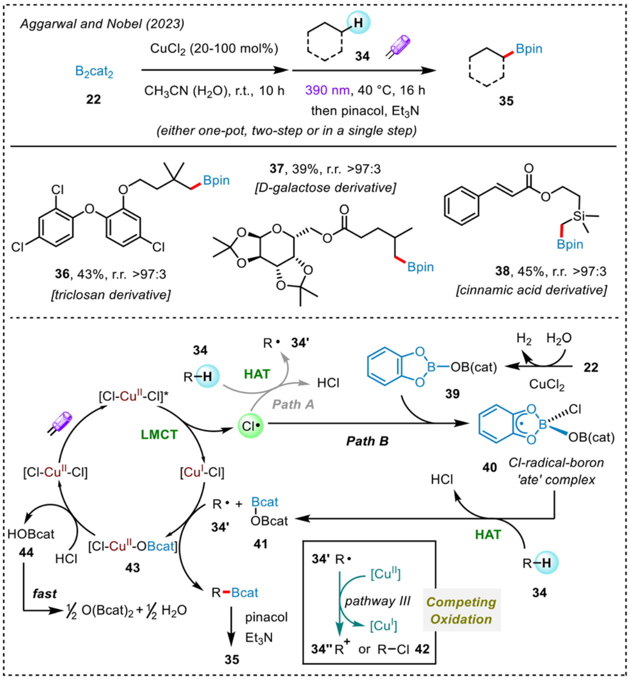
posed as follows: upon excitation, the excited state $CuCl_2$ undergoes an LMCT process to generate chlorine radicals. These radicals then undergo HAT with alkane **30**, generating alkyl radical **30′**. The alkyl radical interacts with B_2cat_2 to form intermediate **32**, which further reacts with $CuCl_2$ to produce unstable borylated product **33**. The next treatment with Et_3N and pinacol affords the stable product **31**.

Shortly thereafter, the group of Aggarwal and Nobel reported a copper-catalyzed C(sp^3)–H borylation of non-activated alkanes under visible-light irradiation and external oxidant-free conditions (Scheme 7).[20c] Notably, the authors discovered that under $CuCl_2$ catalysis, B_2cat_2 and H_2O undergo a dehydrogenation process to generate the key intermediate $O(Bcat)_2$ **39**, an efficient alkyl radical borylating reagent. The reaction demonstrates excellent generality, is applicable to a variety of complex alkane structures, and provides alkyl boronic esters with outstanding selectivity. The authors conducted detailed mechanistic studies, confirming the presence of the hypothesized electrophilic borylating reagent **39** during the reaction. They proposed that the HAT agent is either chlorine radicals or a Cl-radical-boron 'ate' complex **40** formed by the interaction of chlorine radical with **39**. This finding serves as crucial evidence for explaining the reaction's excellent regioselectivity.

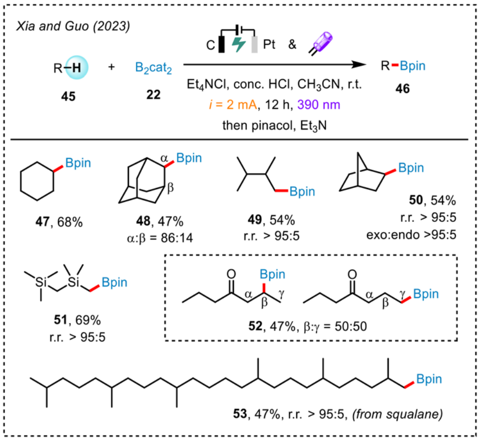
In recent years, driven by the rapid development of both organic photocatalysis[4,5] and electrocatalysis,[42] organic photoelectrocatalysis has garnered increasing attention, providing a new paradigm for achieving selective and sustainable transformations.[12] For example, in 2020, the Xu research group developed a photoelectrocatalytic dehydrogenative cross-coupling of heteroarenes with aliphatic C–H bonds.[43] This reaction utilized electrical energy to oxidize chloride ions to molecular chlorine, and light energy to further generate chlorine radicals for the desired C–H activation process. Building upon this work, the group of Xia and Guo developed a photoelectrochemical C(sp^3)–H borylation, providing a significant extension of chloride-mediated C–H functionalization in photoelectrochemical systems (Scheme 8).[44]

In 2024, Lu[20d] and Ackermann[20e] independently reported their protocols of photoelectrochemically driven iron-catalyzed C(sp^3)–H borylation (Scheme 9). These reactions merge iron photochemistry with electrochemical systems, conveniently transforming inexpensive alkanes into high-value alkyl boronic ester derivatives without the need for external chemical oxidants.

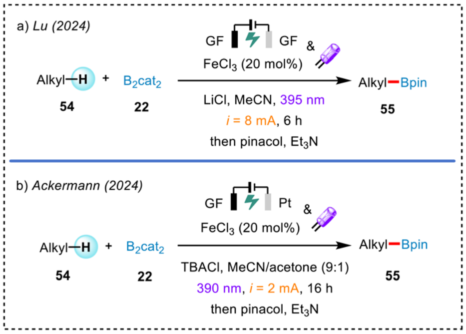
Exemplified by Lu's work,[20d] the proposed mechanism involves the formation of $[FeCl_4]^-$ from $FeCl_3$ and chloride anions in solution. When exposed to purple LED light, the excited $*[FeCl_4]^-$ undergoes an LMCT process, resulting in the generation of a chloride radical, which then abstracts a hydrogen atom from alkane **54**, forming alkyl radical **54′** and regenerating $[FeCl_4]^-$ by anodic oxidation. At the same time, B_2cat_2 is reduced at the cathode, forming a radical anion, which then



Scheme 7 Copper-mediated photocatalytic dehydrogenative C(sp^3)–H borylation of alkanes.



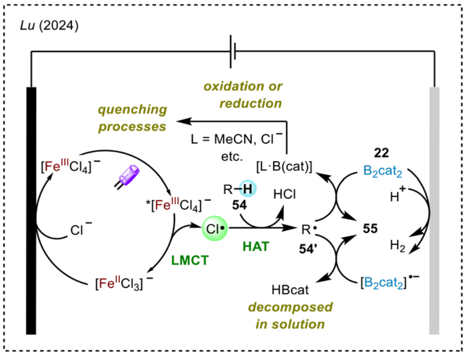
Scheme 8 Photoelectrochemical C(sp^3)–H borylation of alkanes.



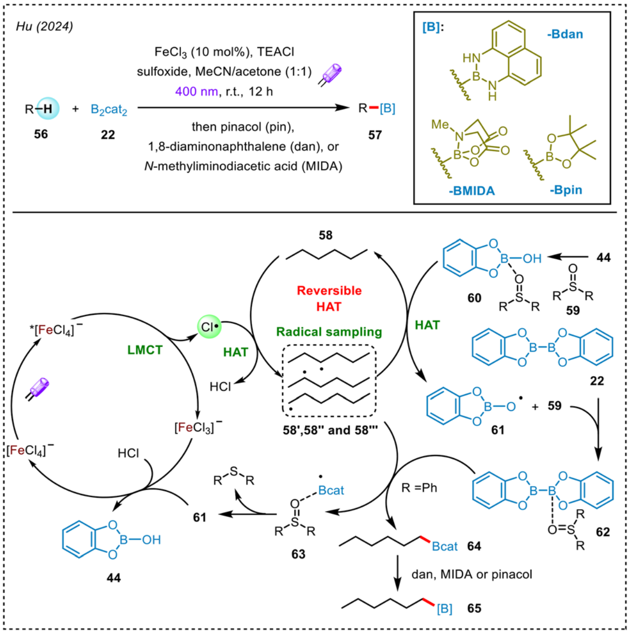
Scheme 9 Photoelectrochemically driven, iron-catalyzed C(sp^3)–H borylation of alkanes.

reacts with the alkyl radical to yield the C(sp^3)–H borylation product **55**. Additionally, direct interaction between the alkyl radical and B_2cat_2 can also produce the borylated product with H_2 evolution (Scheme 10).

Traditional HAT reactions typically require stoichiometric HAT precursors or harsh conditions, and the site-selective modifications of simple alkanes are generally elusive. Recently, Hu *et al.* reported a novel photocatalytic strategy for direct C(sp^3)–H borylation (Scheme 11).[20f] This iron-catalyzed reaction enables a highly selective borylation of terminal C(sp^3)–H bonds in substrates with small steric hindrance, including unbranched alkanes, offering a new avenue for selective C–H bond functionalization. A reversible HAT process is revealed by the mechanistic studies, and a key boron-sulfoxide complex **62** is proposed to contribute to the regioselectivity. The selectivity can be primarily attributed to two major aspects: (1) steric hindrance plays a crucial role, where di-phenyl sulfoxide (**59**, R = Ph) facilitates the preferential borylation of terminal radicals due to their lower steric hindrance. Reactions at secondary positions are completely suppressed, due to the obstructive nature of the phenyl ring structure towards radical attacks, making terminal radicals **58‴** more easily accessible to the reaction center. (2) The reversible HAT process is another key factor. During the process, BcatOH-sulfoxide **60** undergoes a reversible reaction with unreacted secondary alkyl radicals **58′** or **58″** to regenerate alkane **58**, preventing them from reacting with B_2cat_2, thereby enhancing the selectivity.



Scheme 10 Mechanism of photoelectrochemically driven C(sp^3)–H borylation.



Scheme 11 Terminal-selective C(sp^3)–H borylation through intermolecular radical sampling.

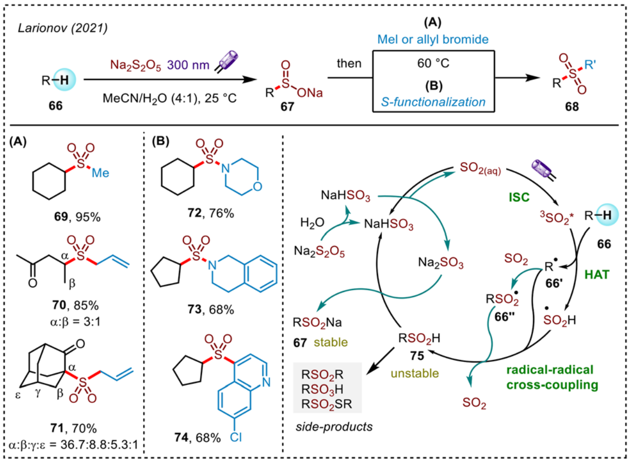
4. C(sp^3)–H sulfurization

Sulfur is an essential element for life, and is widely present in various crucial biomolecules, such as amino acids (cysteine and methionine),[45] coenzyme A,[46] and vitamins (biotin).[47] The formation and cleavage of C–S bonds play a pivotal role in enzyme-catalyzed reactions, serving as the core of numerous biological processes.[48] By constructing and manipulating C–S bonds, molecules with specific biological activities can be developed, which holds significant potential for drug design and biochemical research.[49]

In recent years, driven by the emergence of organic photocatalysis, significant advancements have been made in the construction of C–S bonds.[50] However, direct C(sp^3)–H sulfurization reactions have only recently emerged in the studies of simple alkanes.[51] The following content will provide a detailed overview of these research developments, primarily focusing on C(sp^3)–H thioetherification, C(sp^3)–H sulfinylation, and C(sp^3)–H sulfonylation.

In 2021, Larionov and coworkers reported a novel photo-induced C(sp^3)–H sulfinylation reaction mediated by sodium metabisulfite ($Na_2S_2O_5$), enabling the direct installation of sulfinates onto inert aliphatic C–H bonds under the irradiation of 300 nm UV-light in aqueous media (Scheme 12).[52] This method exhibits excellent selectivity for monosulfination by keeping a low SO_2 concentration and forming stable sulfinate salts *in situ*. The mechanism of the C(sp^3)–H sulfination reaction proceeds as follows: upon photon absorption, the dissolved sulfur dioxide undergoes an intersystem crossing (ISC) to the reactive triplet state $^3SO_2$*. It then abstracts a hydrogen atom from alkane **66**, generating an alkyl radical **66′** and a hydroxy sulfonyl radical. The alkyl radical is subsequently trapped by SO_2 to form intermediate **66″**, which then reacts with the hydroxy sulfonyl radical to produce an alkyl sulfinic acid **75**. This unstable compound is further converted to the corresponding alkyl sulfinate sodium salt **67** in the presence of Na_2SO_3. By one more facile step, this protocol enables the direct conversion of aliphatic C–H bonds to other classes of organosulfur compounds, including sulfonamides, sulfonyl fluorides, and sulfones.

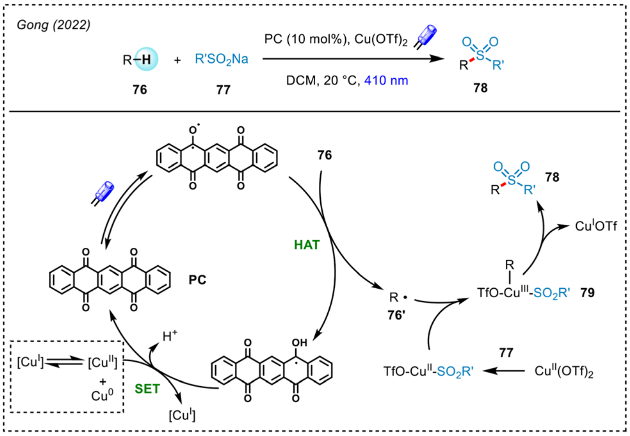
In 2022, Gong *et al.* reported a novel C(sp^3)–H sulfonylation method employing a conjugated polycyclic quinone as a direct HAT photocatalyst, inexpensive copper salt as oxidant, and sul-



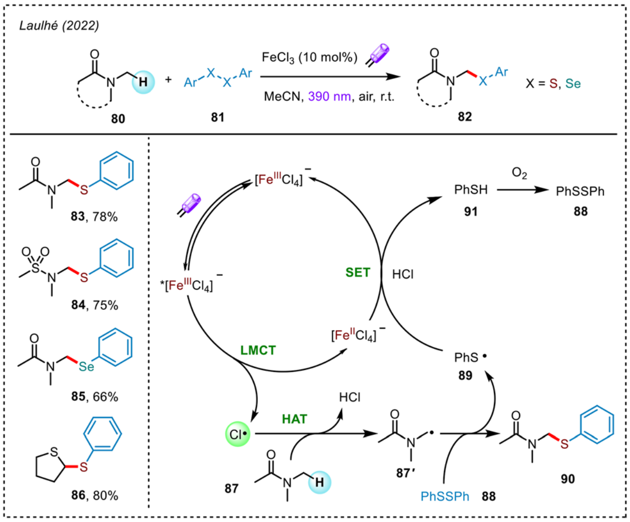
Scheme 12 Photoinduced C(sp^3)–H sulfinylation and further sulfonylation.

finate salts as the sulfonylating reagents (Scheme 13).[53] This approach efficiently converts various toluene derivatives and cycloalkanes into value-added sulfone products **78**. The proposed mechanism unfolds as follows: upon photoexcitation, the conjugated quinone chromophores undergo an intersystem crossing to their triplet excited state, which exhibits ambiphilic radical characteristics. In this activated form, the quinone can engage in an HAT process from C(sp^3)–H bonds in alkane substrates **76**, thereby generating alkyl radical intermediates **76′**. Meanwhile, the copper catalytic cycle facilitates the formation of sulfone products **78** *via* a sequence of ligand exchange, oxidative addition and reductive elimination steps.

Over the past several decades, the synthesis of organochalcogen compounds has aroused great interest in the synthetic community.[54] In 2022, Laulhé *et al.* reported a photoinduced C–H chalcogenation (thioetherification and selenoetherification) reaction using readily available dichalcogenides *via* an Fe-LMCT process (Scheme 14).[55] This method is applicable to



Scheme 13 Photoinduced C(sp^3)–H sulfonylation using conjugated quinone and copper salt.

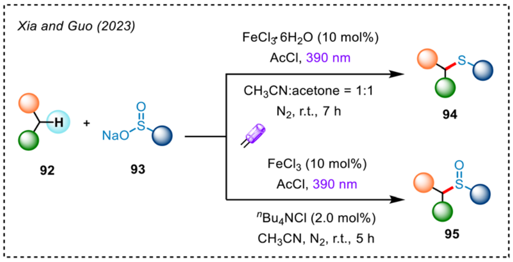


Scheme 14 Photoinduced C(sp^3)–H chalcogenation of amide derivatives and ethers *via* Fe-LMCT.

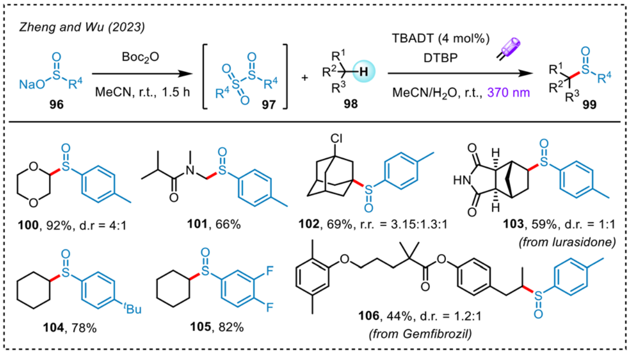
Boc- and mesyl-protected amines, nitriles, halides, and sulfonylamides, exhibiting moderate to excellent yields for secondary and tertiary amides, offering a complementary strategy for the sulfurization of *N*-alkylamides and (thio)ethers in current synthetic chemistry.

The synthesis of sulfoxides has long been challenging. In 2021, Bi and co-workers discovered an intriguing transformation: in the presence of acyl chlorides, sodium benzenesulfinate can be converted into sulfinyl sulfones.[56] By means of such a strategy, Larionov reported the first visible-light-enabled decarboxylative sulfinylation.[57] Furthermore, the direct C(sp^3)–H sulfinylation of inert alkanes has seen developments. In 2023, Xia and Guo *et al.* developed an iron-induced selective C(sp^3)–H thioetherification and C(sp^3)–H sulfinylation using sodium benzenesulfinate/acyl chloride systems (Scheme 15).[20a]

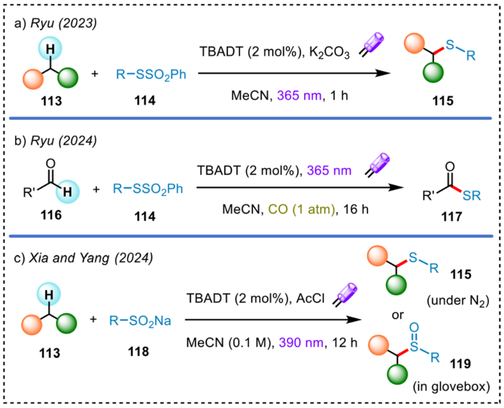
In the same year, Zheng and Wu reported a photoinduced direct C(sp^3)–H sulfinylation mediated by tetrakis(tetrabutylammonium) decatungstate (TBADT), which exhibits excellent site-selectivity and is applicable to the late-stage modification of complex molecules (Scheme 16).[58] The sulfone intermediate **97** in this reaction originates from the reaction between



Scheme 15 Iron-photocatalyzed C(sp^3)–H thioetherification and sulfinylation.



Scheme 16 Photocatalytic C(sp^3)–H sulfinylation mediated by decatungstate salts.



Scheme 18 Decatungstate as an HAT reagent for the photochemical synthesis of thioethers and thioesters.

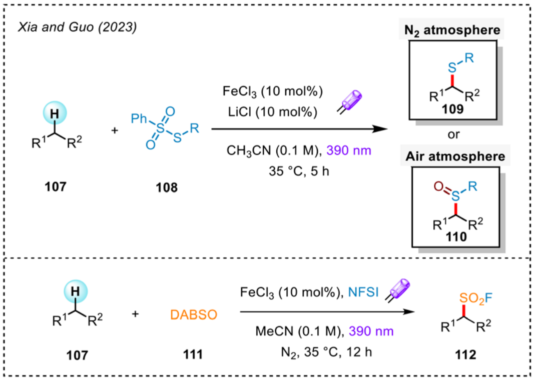
sodium arylsulfinate **96** and (Boc)$_2$O. Additionally, it is also demonstrated in this work that secondary and tertiary aldehydes can be converted to the corresponding sulfone products through decarbonylative sulfonylation.

Meanwhile, building upon their previous research, Xia, Guo and coworkers reported another advancement in iron photocatalysis (Scheme 17).[21] By altering the reaction atmosphere (N$_2$ or air), they successfully utilized sulfinyl sulfones **108** to achieve selective C(sp^3)–H thioetherification or sulfinylation of inert alkanes. Additionally, the introduction of a 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO)/NFSI combination during the reaction facilitated the transformation of alkanes into the corresponding sulfonyl fluorides **112**.

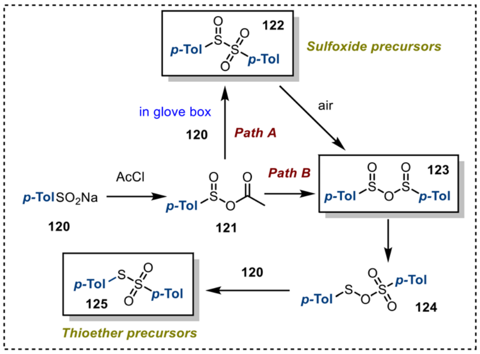
At the end of 2023, the Ryu research group reported a photocatalytic C(sp^3)–H thiolation by a double S$_H$2 strategy using sulfinyl sulfones **114** as sulfur sources and TBADT as the photocatalyst (Scheme 18a).[59] Subsequently, they expanded the substrate scope to aldehydes, in which they found that a CO atmosphere can effectively limit the extent of decarbonylation of acyl radicals (Scheme 18b).[60] Soon after, Xia and Yang *et al.* also reported similar reactions using more easily available sulfinate salts **118** and acetyl chloride as reagents (Scheme 18c).[61] Interestingly, under a standard nitrogen atmosphere, thioether products **115** are obtained as the major products, while under glovebox conditions, this reaction predominantly yields sulfoxide products **119**.

The proposed mechanism for this selective precursor formation in Xia and Yang's work is presented in Scheme 19.[61] Initially, sodium *p*-toluenesulfinate **120** reacts with acetyl chloride to generate mixed anhydride **121**, which further converts into the sulfoxide precursor **122** under glovebox conditions with an extremely low oxygen and moisture content (Path A).[56] However, in less rigorously moisture- and oxygen-free conditions, the unstable intermediate **122** would readily transform into **123**, which undergoes subsequent steps to deliver the thioether precursor **125** (Path B). Next, these precursors are further engaged in the corresponding C(sp^3)–H sulfurization reactions.

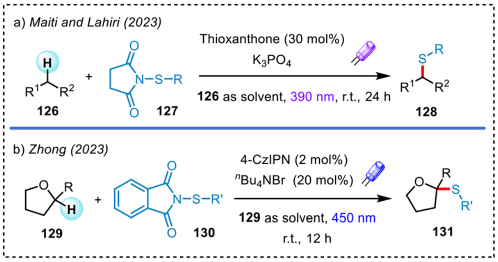
In 2023, Maiti and Lahiri developed a transition-metal-free C(sp^3)–H thiolation using thioxanthone as the photosensitizer, which plays a dual role of both hydrogen atom transfer and a photoinduced energy transfer agent, enabling the smooth conversion of various toluenes as well as unactivated alkanes (Scheme 20a).[62a] Concurrently, Zhong *et al.* employed 4-CzIPN as the photosensitizer for the oxidative generation of bromine radical under 450 nm visible-light irradiation, which serves as



Scheme 17 Selective C(sp^3)–H sulfinylation *via* photomediated Fe-catalysis.



Scheme 19 Proposed mechanism for the selective formation of thioether and sulfoxide precursors.

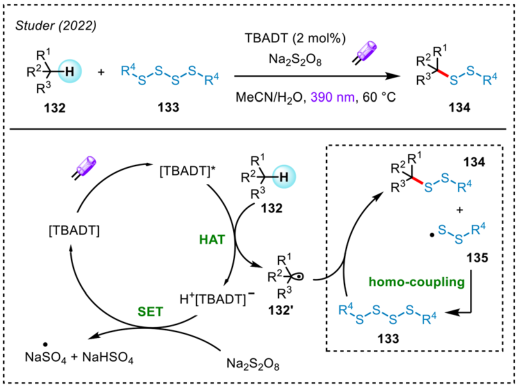


Scheme 20 Transition-metal-free photoinduced hydrogen atom transfer-assisted C(sp^3)–H thiolation.

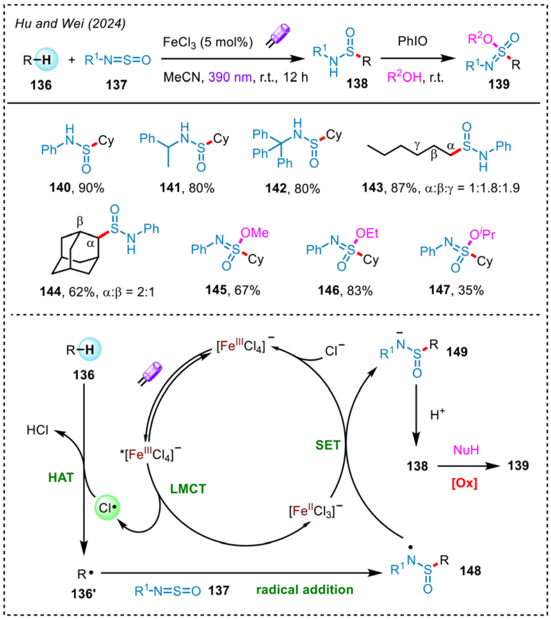
the HAT reagent for selectively activating the α-C–H bonds of ethers **129** for thioetherification with reagent **130** (Scheme 20b).[62b]

Disulfide bonds are of significant biological importance in maintaining a protein structure, regulating protein aggregation, and drug delivery.[63] The synthesis of asymmetric disulfides is challenging and often requires harsh conditions. In 2022, the Studer group developed a protocol utilizing decatungstate photocatalysis and tetrasulfides **133** as radical disulfurization agents to transform aliphatic C(sp^3)–H bonds and aldehyde C(sp^2)–H bonds into the corresponding –C–S–S– moieties (Scheme 21).[64] By using this strategy, a series of valuable asymmetric dialkyl disulfides **134** as well as acyl alkyl disulfides were successfully prepared. Furthermore, the application of this method in the late-stage modification of drugs and natural products is elegantly demonstrated.

Sulfinamide structures are prevalent in pharmacologically active molecules,[65] yet examples of the sulfinamidation *via* direct C–H activation of inert alkanes are still lacking. Recently, Hu and Wei *et al.* reported the application of iron photocatalysis in the direct sulfinamidation of alkanes, enabling the rapid synthesis of high-value sulfonamides **138** from simple hydrocarbons and sulfinylamines **137** (Scheme 22).[66] The proposed mechanism proceeds as follows: the photoexcited *[Fe(III)Cl_4]$^-$ undergoes LMCT to form a reduced Fe(II) species and a chlorine radical. The chlorine radical serves as an HAT reagent to interact with the C(sp^3)–H bond of **136**, generating alkyl radical **136′**, which is subsequently trapped by sulfinylamine **137** to form aminosulfinyl radical **148.** This intermediate then undergoes SET with the Fe(II) species to generate intermediate **149**, completing the Fe-catalytic cycle. Finally, intermediate **149** undergoes protonation to yield the corresponding target product **138.** Further transformation to sulfonimidate esters **139** with alcohol nucleophiles is also demonstrated viable using PhIO as the oxidant.



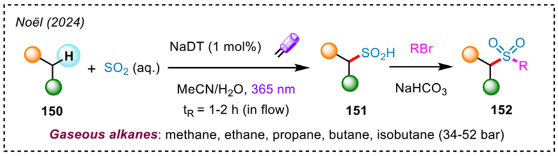
Scheme 21 Synthesis of asymmetric disulfides *via* photoinduced C(sp^3)–H activation.



Scheme 22 Iron photocatalysis for sulfinamide synthesis from alkanes.

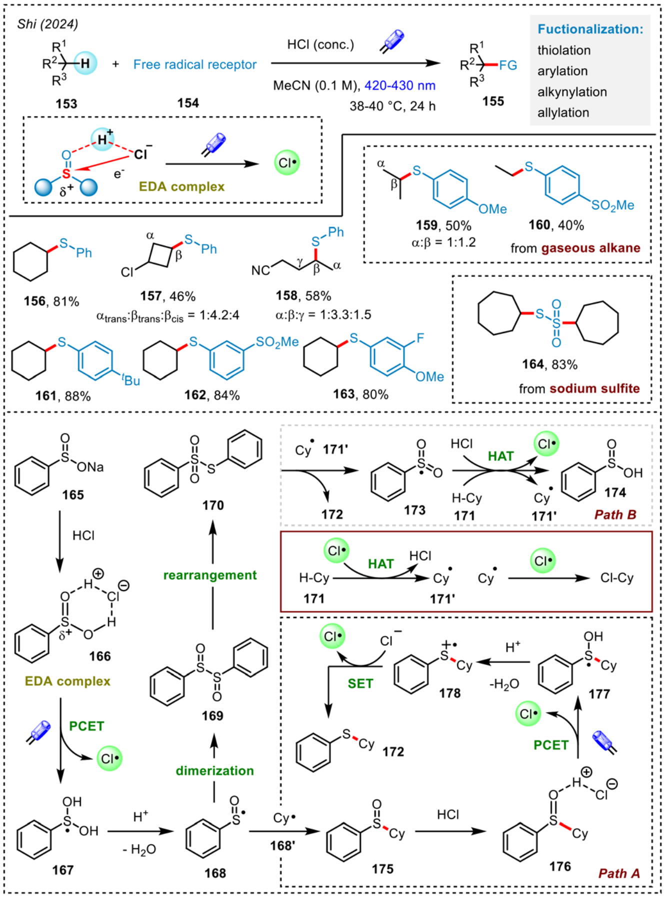
Very recently, Noël's group introduced a photomediated approach to harness an HAT process for the activation of volatile alkanes under flow conditions (Scheme 23).[67] Gaseous alkanes such as isobutane, butane, propane, ethane, and methane can be activated under the standard conditions in 34–52 bar pressure, forming nucleophilic radicals to react with SO_2 to produce the corresponding sulfinates **151**, which are further converted into sulfones **152** upon treatment with alkyl bromide and base.

Chlorine radical has been recognized as a potent HAT reagent for inert C–H bond activation.[68] The established methods for photoinduced chlorine radical generation primarily involve three approaches: photoinduced LMCT processes of



Scheme 23 C(sp^3)–H sulfinylation of light hydrocarbons with sulfur dioxide *via* HAT photocatalysis in flow.

metal chlorides,[11] oxidation of chloride ions by excited-state photosensitizers[69] and the photochemical decomposition of hydrochloric acid to produce molecular chlorine, which subsequently yields chlorine radicals.[43,44] Recently, Shi's group introduced a new strategy for generating chlorine radicals through an electron donor–acceptor (EDA) complex formed by hydrochloric acid and the S(IV)═O group of sulfinates (Scheme 24).[10b] By means of this approach, chlorine radicals effectively activate C(sp^3)–H bonds and react with diverse radical acceptors. In the case of sodium benzenesulfinate **165** as the acceptor, under visible-light irradiation, chloride ions undergo a proton-coupled electron transfer (PCET) process with the internal S(IV)═O group of EDA complex **166**, generating chlorine radicals and simultaneously producing sulfur radical intermediate **167**. The protonation and dehydration of intermediate **167** forms radical **168**, which undergoes subsequent dimerization and rearrangement to deliver sulfinylsulfone intermediate **170**. On the other hand, the chlorine radical can also abstract hydrogen atoms from alkane **171** to generate alkyl radical **171′**, which then attacks sulfinylsulfone **170** to yield the desired thioetherification product **172** *via* two possible pathways. Additionally, when heterocyclic compounds are employed as the radical acceptors, the reaction solvent is replaced with dimethyl sulfoxide (DMSO), utilizing its S(IV)═O structure to form similar key EDA complexes.



Scheme 24 Photoinduced versatile aliphatic C–H functionalization *via* an electron donor–acceptor complex.

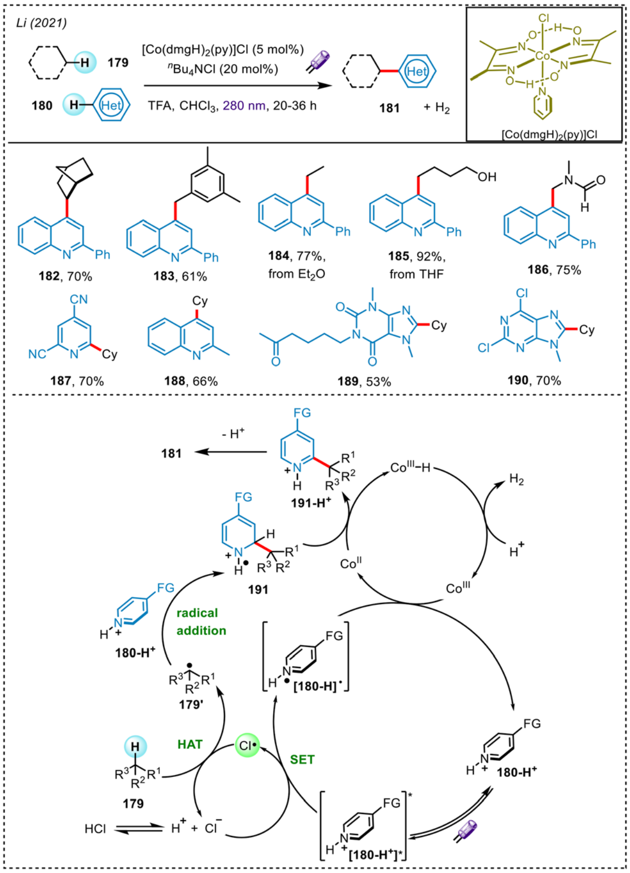
5. C(sp^3)–H heteroarylation

Different from traditional C(sp^2)–H functionalization reactions,[70] C(sp^3)–H heteroarylation reactions directly link the C(sp^3) of alkanes with hetero aromatic groups containing nitrogen, oxygen, sulfur, and other heteroatoms, effectively constructing diverse heterocyclic compounds.[71] Minisci-type reactions, as a versatile tool for synthesizing substituted N-heteroarenes, have advanced with the development of photoredox catalysis and the emergence of a wider range of radical precursors, providing new opportunities for the functionalization of complex heteroaromatic frameworks.[72] Achieving C(sp^3)–H Minisci reactions with unactivated alkanes is an especially appealing goal.[73] Moreover, sulfonyl-substituted pyrimidine and benzothiazole derivatives can act as radical acceptors for arylation, offering novel approaches for incorporating heterocyclic fragments into molecules.[74] Furthermore, exploiting the oxidation of carbon radicals at the α-position of an oxygen atom to carbocation centers enables nucleophilic attack by nitrogen-containing heterocycles,[75] thereby constructing a variety of N-containing heterocyclic compounds. In the following sections, we will highlight the recent advancements in C(sp^3)–H heteroarylation using these strategies.

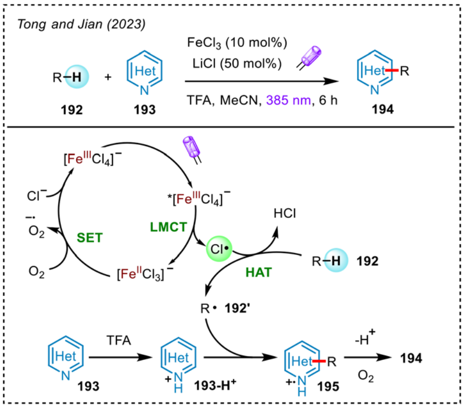
In 2021, the Li research group developed a UV-light-mediated dehydrogenative Minisci alkylation, enabling the coupling of various heterocyclic compounds with strong aliphatic C–H bonds, demonstrating its applicability to access various complex heterocycles (Scheme 25).[69c] This study employed cobaloxime complex [Co(dmgH)$_2$(py)]Cl as a terminal oxidant and heterocyclic substrates **180** as photosensitizers. In the mechanistic proposal, the protonated heterocycle (**180-H$^+$**) first undergoes excitation under visible light, facilitating the oxidation of chloride ions to chlorine radicals *via* an SET process. The chlorine radical serves as the HAT reagent, activating alkane **179** to alkyl radical **179′**, while simultaneously forming radical intermediate **[180-H]$^•$**. Subsequently, alkyl radical **179′** adds onto intermediate **180-H$^+$** to form intermediate **191**. Concurrently, the trivalent Co-complex oxidizes radical intermediate **[180-H]$^•$** back to its initial state, reducing itself to a divalent cobalt species. This cycle promotes the catalytic turnover of cobalt and facilitates the formation of the target product **181** through interaction with intermediate **191** and subsequent deprotonation.

In 2023, Tong, Jian and coworkers developed a green method using iron trichloride as a photoinduced LMCT catalyst for the direct functionalization of unactivated C(sp^3)–H alkanes (Scheme 26).[76] The reaction proceeds smoothly under an air atmosphere, and is compatible with a variety of heterocycles including quinolines, benzothiazoles, and quinoxalines.

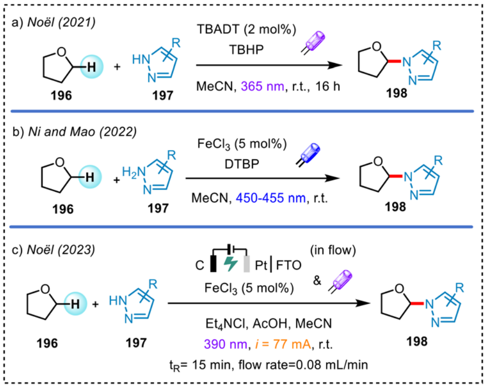
To further propel advances in HAT photocatalysis for C(sp^3)–heteroarylation, Noël's group reported the employment of decatungstate to enable the selective hydrogen abstraction



Scheme 25 Photoinduced dehydrogenative Minisci alkylation.



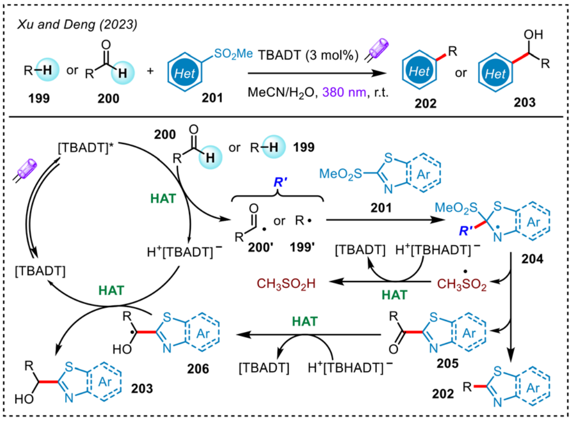
Scheme 26 Minisci alkylation *via* photo-induced Fe-LMCT.



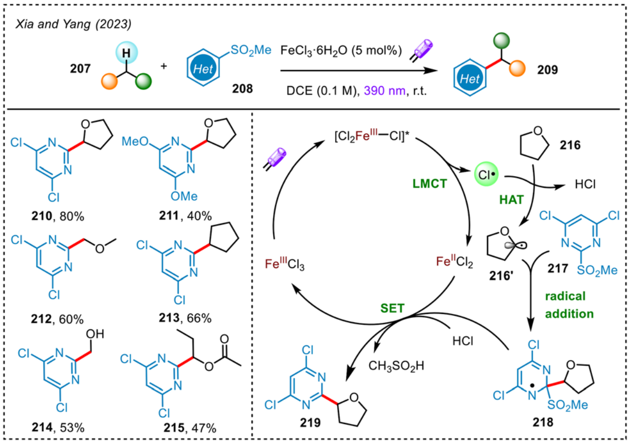
Scheme 27 Nucleophilic approaches to achieve $C(sp^3)$–H heteroarylation.

of $C(sp^3)$–Hs at the α-position to oxygen or nitrogen atoms, thereby generating carbon-centered radical intermediates (Scheme 27a).[75a] These carbon radicals are subsequently oxidized to carbocations by *tert*-butyl hydroperoxide (TBHP), which are then engaged in nucleophilic addition by N-heteroaryl coupling partners. In 2022, the group of Ni and Mao disclosed a similar strategy utilizing chlorine radicals generated *via* photoinduced Fe-LMCT as the HAT reagent, with an external oxidant di-*tert*-butyl peroxide (DTBP) to facilitate the reaction (Scheme 27b).[75b] Building upon these precedents, in 2023, Noël and colleagues incorporated the photoinduced Fe-LMCT manifold into an electrochemical setup in flow. This chemical oxidant-free photoelectrochemical LMCT approach not only enables the catalytic turnover of the iron species through anodic oxidation, but also facilitates the oxidation of α-oxy radical intermediates (Scheme 27c).[75c] Notably, this reaction manifests broad substrate scope, permitting the incorporation of diverse nitrogen-containing heterocycles at the α-position of ethers, thereby providing a promising strategy for sustainable $C(sp^3)$–H heteroarylation.

In 2023, Xu and Deng *et al.* reported a novel TBADT-catalyzed method for the hydroxyalkylation or alkylation of N-heteroaromatics with aldehydes or alkanes in aqueous solution (Scheme 28).[77] This reaction employs methanesulfonyl-substituted benzothiazoles **201** as the radical acceptors. Notably, when aldehydes **200** are used as the reaction partners, the formation of ketones **205** does not terminate the reaction. Instead, it further proceeds into another HAT process with $H^+[TBADT]^-$, ultimately yielding the desired hydroxyalkylated heteroaromatic product **203**.



Scheme 28 Photoinduced hydroxyalkylation of N-heteroaromatics with alkanes and aldehydes.



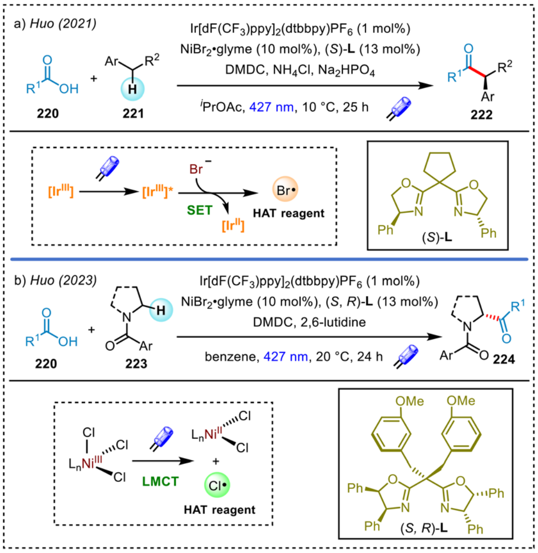
Scheme 29 C(sp^3)–H heteroarylation *via* photoinduced Fe-LMCT.

Given the importance of pyrimidine as a component of genetic material and its widespread presence in pharmaceutical molecules, introducing pyrimidine rings into inert alkanes possesses a significant appeal.[78] In 2017, Murafuji *et al.* reported a visible-light-induced C–H pyrimidination reaction using benzophenone as an HAT catalyst, but the substrate scope seems to be limited to saturated heterocycles containing O, N, and S heteroatoms.[78d] At the end of 2023, Xia and Yang *et al.* reported a visible-light-driven, iron-catalyzed C(sp^3)–H pyrimidination reaction (Scheme 29).[79] This method is applicable not only to simple alkanes but also to ethers, esters, and even free alcohols, exhibiting a significantly broadened scope.

6. C(sp^3)–H acylation

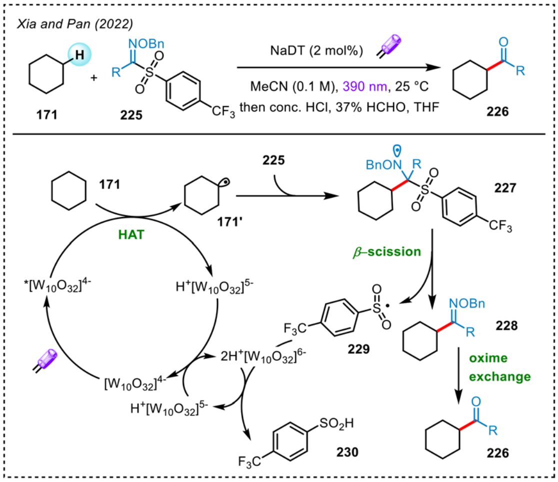
Ketones are prevalent in nature, existing among many significant biomolecules, including steroid hormones and fragrances.[80] Apart from conventional redox synthesis, reagents such as β-keto acids[81] and α-keto acids[82] facilitate the incorporation of carbonyl groups into molecular frameworks. Recently, the integration of N-heterocyclic carbene (NHC) catalysis with photoredox catalysis for the synthesis of ketones *via* acyl radical cross-coupling has garnered considerable attention.[83] However, achieving the acylation of simple alkanes remains a formidable challenge. The following section will focus on some recent research progress in this area.

In 2021, Huo's group disclosed an asymmetric benzylic C–H acylation for the synthesis of chiral α-aryl ketones **222**, utilizing an Ir/Ni dual catalytic system under mild photoirradiation conditions (Scheme 30a).[84a] Dimethyl dicarbonate (DMDC) is employed as the activating agent for carboxylic acids **220** to generate mixed anhydride *in situ*. The key step of this reaction is the generation of bromine radicals from bromide anions through single-electron oxidation enabled by iridium photoredox catalysis, which act as HAT reagents for the subsequent activation of benzylic C–H bonds. In 2023, they further developed a regio- and enantioselective *N*-α-acylation reaction for saturated N-heterocycles with a dual catalytic system, for the construction of chiral α-acylated amine derivatives **224** under blue-light irradiation (Scheme 30b).[84b] In this reaction, chlorine radicals generated through a photoinduced LMCT process with high-valent nickel chloride act as the HAT reagent. These two methods represent convenient and efficient approaches for the straightforward synthesis of enantioenriched carbonyl compounds.



Scheme 30 Direct enantioselective acylation of benzylic C(sp^3)–H bonds with carboxylic acids.

In 2022, Xia and Pan *et al.* reported a direct acylation of inert C(sp^3)–H bonds (Scheme 31).[85] This strategy utilizes decatungstate NaDT to activate alkanes and employs CF_3-modified phenylsulfonyl ketone oximes **225** as the acylating reagents. The CF_3-modified phenylsulfonyl group is found to significantly enhance the electrophilicity of the imine and lower the



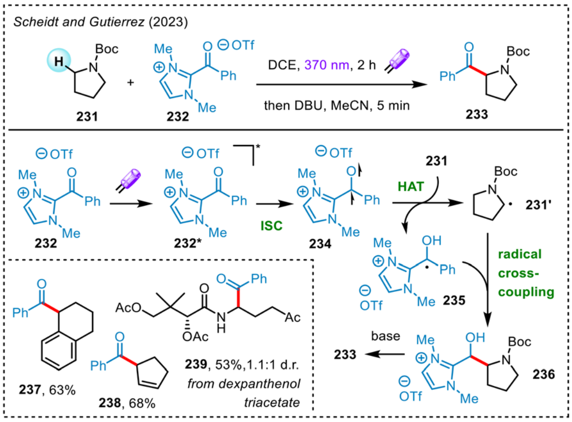
Scheme 31 Direct acylation of inert C(sp^3)–H bonds using decatungstate and phenylsulfonyl ethanone oximes.

C–S bond cleavage energy, thereby facilitating the transformation. This method exhibits excellent site selectivity and a broad substrate scope, including late-stage functionalization of complex natural products.

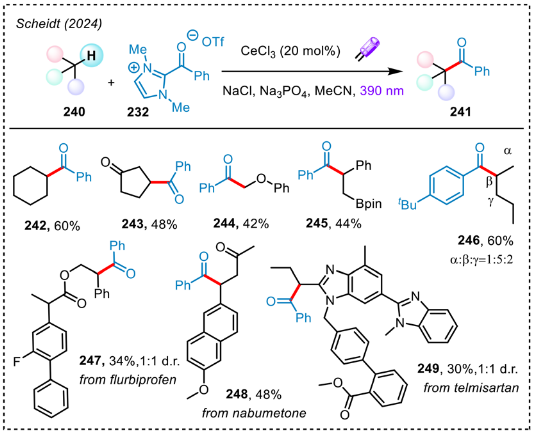
Radical imidazolium ions as substitutes of stable acyl radicals have attracted considerable attention, and the related studies have shown significant progress.[86] In 2023, Scheidt and Gutierrez's research group discovered that, upon visible-light excitation, acyl imidazolium ions **232*** readily undergo intersystem crossing to generate triplet diradical species **234** (Scheme 32).[87] This species can serve as an HAT agent, activating the specific C–H bonds (such as α-C–Hs of nitrogen atoms and benzylic C–Hs) to form alkyl radicals. Alkyl radical **231′** is then engaged in selective cross-coupling with radical intermediate **235** to produce the desired acylated products **233** upon further treatment with a base.

As an inexpensive and abundant rare earth element, cerium has opened up new avenues for its applications in sustainable chemical synthesis.[88] At the end of 2023, based on their previous work, Scheidt and co-workers disclosed a novel photoinduced, cerium-catalyzed acylation employing azolium salts **232** as the acyl sources, enabling the direct functionalization of unactivated $C(sp^3)$–H bonds (Scheme 33).[89] This protocol is successfully applied to a variety of C–H bonds, including cyclic and acyclic alkanes, demonstrating its potential utility in practical synthesis.

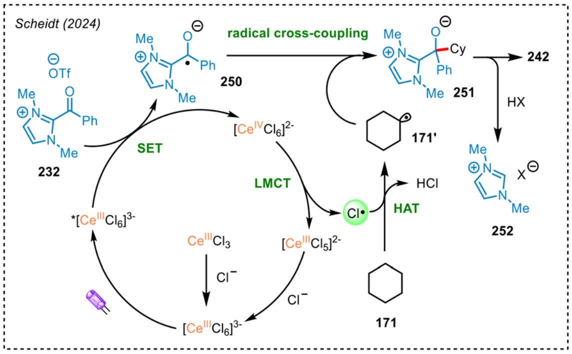
The proposed reaction mechanism is illustrated in Scheme 34.[89] The whole process begins with the photoexcitation of $[Ce^{III}Cl_6]^{3-}$ formed from $Ce^{III}Cl_3$, generating a potent single-electron reductant species $*[Ce^{III}Cl_6]^{3-}$, which subsequently reduces the acyl azolium salt **232** to form radical intermediate **250**. Meanwhile, the high-valent $[Ce^{IV}Cl_6]^{2-}$ species is also produced, which undergoes an LMCT process, leading to the formation of the $[Ce^{III}Cl_5]^{2-}$ complex and a highly reactive chlorine radical. The chlorine radical efficiently abstracts a hydrogen atom from alkane **171**, producing alkyl radical **171′** to couple with radical **250** to form the tertiary azolyl intermediate **251**. Under basic conditions, **251** ejects carbine **252** to finally yield the desired ketone product **242**.



Scheme 32 Photoinduced $C(sp^3)$–H acylation *via* azolium-promoted intermolecular HAT.



Scheme 33 Photoinduced cerium-catalyzed $C(sp^3)$–H acylation.

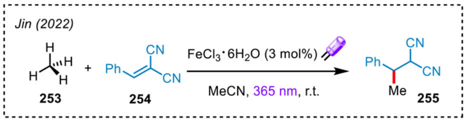


Scheme 34 The mechanism of photoinduced cerium-catalyzed $C(sp^3)$–H acylation.

7. Other types of $C(sp^3)$–H functionalization

In this section, we will introduce the recent advances in $C(sp^3)$–H activation for the construction of $C(sp^3)$–$C(sp^3)$ bonds, $C(sp^3)$–N bonds, and some other related transformations.[90] Some of this work is derived from earlier seminal studies, while other portions represent pioneering efforts. We will selectively highlight several representative and significant developments.

It is well-known that methane is an abundant and inexpensive organic carbon source in nature, while also being one of the major contributors to the global greenhouse effect. Consequently, the activation of the C–H bonds in methane holds significant economic and environmental value.[91] However, the high bond dissociation energy of 105 kcal mol^{-1} for the C–H bonds in methane, coupled with the poor solubility of gaseous alkanes in most solvents, has made methane activation a formidable challenge.[92] In 2022, the research group led by Jin employed an iron-catalyzed strategy for generating chlorine radicals, achieving the direct functionalization of methane, and some heavier gaseous alkanes (Scheme 35).[93]

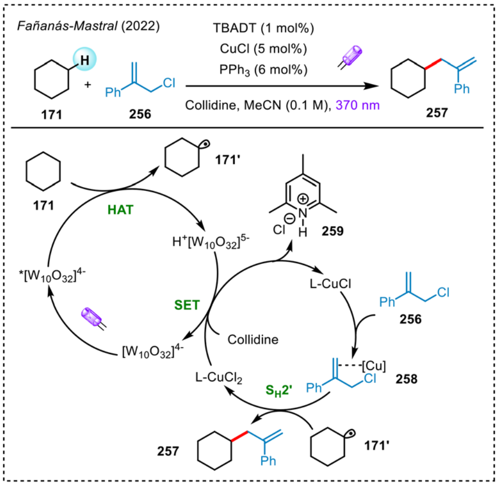


Scheme 35 UV-light-enabled, iron-catalyzed methane functionalization.

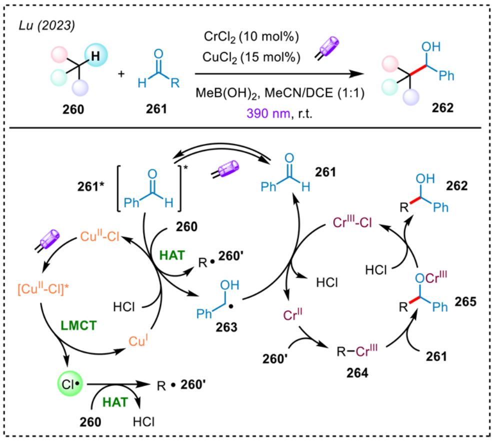
The theoretical calculations reveal that the photoexcitation of the acetonitrile complex of iron chloride is the "rate-determining step", while the C–H activation process is merely the "product-determining step". This work may bring novel ideas for feedstock upgrading and catalyst design.

Allylation represents an important and practical transformation for the construction of C(sp^3)–C(sp^3) bonds.[94] In 2022, Fañanás-Mastral *et al.* reported a light-driven, decatungstate and copper cooperatively catalyzed allylation of alkanes with simple allylic chlorides (Scheme 36).[95] The photoexcited decatungstate anion acts as an HAT agent, activating alkane **171** to generate nucleophilic carbon-centered radical **171′**, which subsequently engages in a nucleophilic substitution (S_H2') reaction with activated allylic π-olefin-copper complexes **258** to afford the desired products **257**. This strategy enables an efficient allylation of various chemical feedstocks and natural products.

In 2023, Lu's group developed a Cu/Cr dual-catalytic system for converting aliphatic C–H bonds into nucleophiles under visible-light irradiation, which then interact with aldehydes **261** to access aryl alkyl alcohols **262** (Scheme 37).[96] The mechanistic studies indicate that the direct redox reaction between Cu(I) and Cr(III) seems unfavorable. In their proposed mechanism, aromatic aldehyde **261** acts not only as a substrate but also as a photosensitizer to undergo photoexcitation, and the excited **261*** participates in the following HAT process to produce radical **260′** and facilitate the copper catalytic cycle, meanwhile generating intermediate **263**. On the other hand, ketyl radical **263** reduces Cr(III) to Cr(II), enabling its rapid coupling with alkyl radical **260′** to form organometallic intermediate **264** for subsequent nucleophilic addition process.

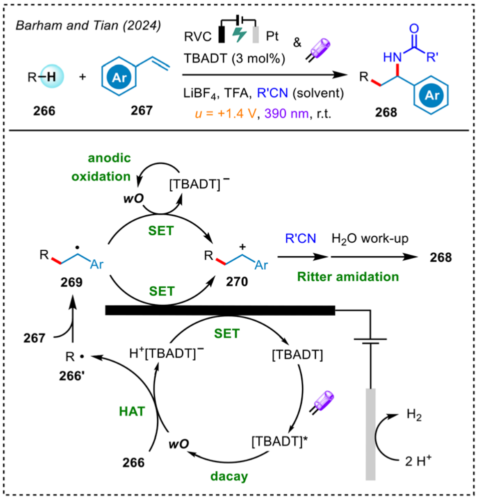


Scheme 36 Photoinduced, decatungstate-copper co-catalyzed allylation of alkanes.

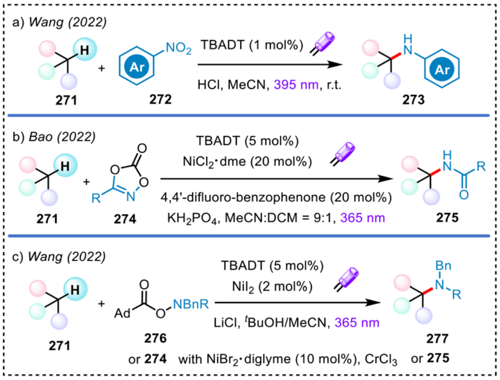


Scheme 37 Coupling reaction between aldehydes and alkanes *via* photoinduced LMCT.

Recently, Barham and Tian *et al.* developed a novel photoelectrochemical carboamidation reaction utilizing styrenes and unactivated alkanes without the need for external oxidants (Scheme 38).[97] TBADT is employed as the photocatalyst, generating the active species ***w*O** by photoexcitation and subsequent decay, which is a strong HAT reagent for the C(sp^3)–H activation of alkane **266**. The resulting alkyl radical **266′** adds onto styrene **267** to afford benzylic radical **269**, which is then oxidized *via* either direct or indirect anodic oxidation to access benzylic cation **270**. The further Ritter-type amidation provides final product **268**. The reaction exhibits good functional group tolerance for both styrenes and alkanes, addressing limitations in prior reports to electron-poor olefin trapping partners and mono-functionalization.



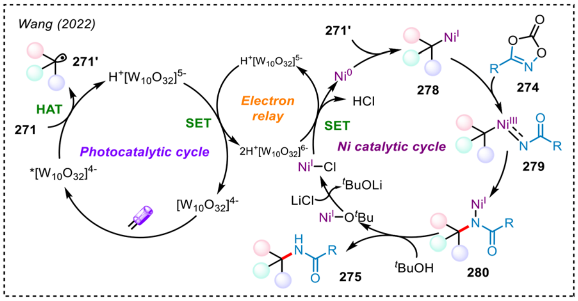
Scheme 38 Photoelectrochemical carboamidation of styrenes using unactivated alkanes.



Scheme 39 Decatungstate-mediated photochemical C(sp^3)–N bond construction.

In 2022, Wang *et al.* reported a novel method employing a cost-effective tungsten photocatalyst for the C(sp^3)–N coupling reaction between unactivated simple hydrocarbons and nitrobenzenes (Scheme 39a).[98a] In parallel, advancements in C(sp^3)–H amidation reactions have also been made. In 2020, König *et al.* developed an innovative photoinduced copper(II)-peroxide catalytic system to achieve N–H bond alkylation, enabling the activation of stable C(sp^3)–H bonds to react with a wide range of (sulfon)amides and N-heterocyclic nucleophiles.[98b] In 2021, Murakami's group applied iridium photoredox catalysis combined with nickel catalysis for the synthesis of amides from inert alkanes and isocyanates.[98c] In 2022, Bao *et al.* reported a photoinduced decatungstate/nickel catalytic strategy for the direct intermolecular C(sp^3)–H amidation of unactivated alkanes, ketones, ethers, amines, and aldehydes, with dioxazolones **274** as the sources of amide moieties (Scheme 39b).[98d] Concurrently, Wang and colleagues described a similar photodriven tungsten/nickel dual-catalytic system that enables both C(sp^3)–H amination and amidation of inert alkanes (Scheme 39c).[98e]

The reaction mechanism of Wang's work is proposed as follows (Scheme 40):[98e] under UV-light irradiation, decatungstate undergoes intersystem crossing to generate an excited triplet state, which acts as an HAT reagent to activate the inert C–H bond of alkane **271**, forming a reduced photosensitizer and alkyl radical **271′**. The alkyl radical **271′** is then captured by Ni^0 to form alkyl–Ni^I species **278**, which, upon coordination with oxazolones **274**, forms complex **279**. Further nitrene insertion and protonation of **279** ultimately yield the desired amide product **275**.



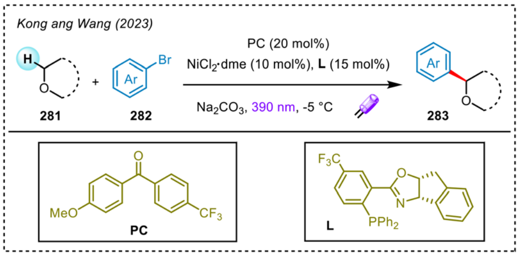
Scheme 40 Proposed mechanism for decatungstate-mediated C(sp^3)–N bond construction.

8. Asymmetric C(sp^3)–H functionalization

The selective functionalization of C–H bonds has long been an appealing yet challenging task in organic synthesis. Of particular interest are methods that directly convert the ubiquitous C(sp^3)–H bonds into new C–C or C–X bonds with high chemoselectivity, regioselectivity, and especially stereoselectivity.[99] In recent years, significant advancements have been made in asymmetric photocatalytic C(sp^3)–H bond activation, which circumvent the need for harsh reaction conditions or pre-functionalization, thereby enabling more step-economical and atom-economical synthesis.[5g,84,100] The latest research progress in this field has showcased the powerful capability of C–H activation chemistry in constructing molecular complexity and has provided opportunities for developing new efficient and sustainable synthetic strategies. In this section, we will highlight the latest representative work (mainly studies reported after 2023) on asymmetric photocatalytic C(sp^3)–H functionalization for the reference of researchers in related fields.

In 2023, Kong, Wang, and colleagues reported an enantioselective C(sp^3)–H arylation/alkenylation of saturated oxygen-containing heterocycles **281** at their *O*-α-positions (Scheme 41).[101] A diaryl ketone which upon photoexcitation acts as a direct HAT agent is employed as the photocatalyst, along with a nickel catalyst and a chiral PHOX ligand, to achieve this directing-group-free asymmetric C(sp^3)–H functionalization. This method is applicable to various saturated O-heterocyclic systems and a wide range of aryl and alkenyl bromides, providing an efficient route to high-value chiral oxygen heterocycles **283**, and demonstrating the immense potential and broad prospects of synergistic photocatalysis and nickel catalysis in asymmetric C–H functionalization reactions.

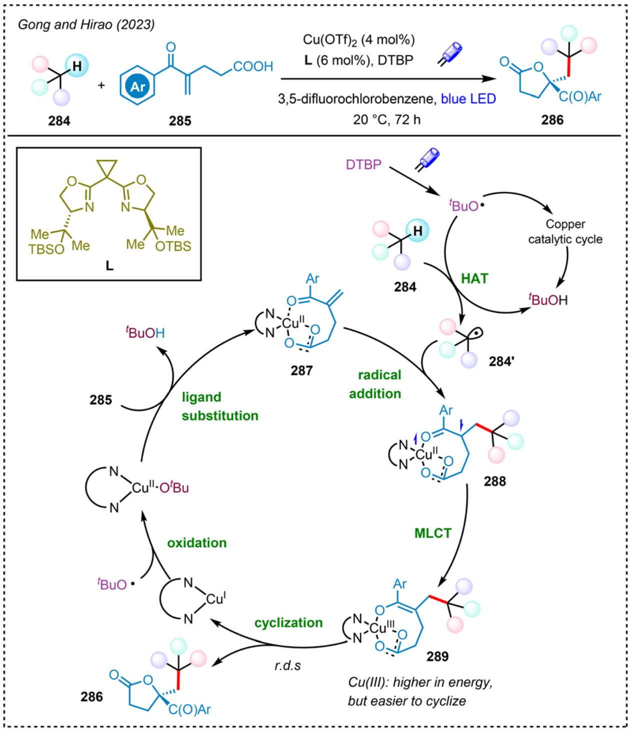
In 2023, Gong and Hirao *et al.* developed a visible-light-induced, copper-catalyzed atom transfer radical coupling



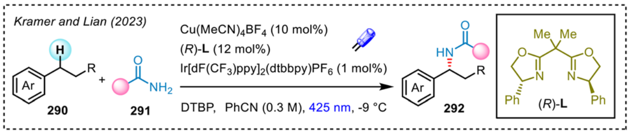
Scheme 41 Synergistic nickel and photocatalysis strategies in asymmetric C(sp^3)–H arylation and alkenylation.

(ATRC) that enables the asymmetric oxidative functionalization of alkenes, facilitating the effective synthesis of diverse chiral lactones with high enantioselectivity *via* aliphatic C–H activation (Scheme 42).[102] The proposed mechanism is initiated with the photoinduced homolysis of DTBP to generate *tert*-butoxy radicals, which abstract a hydrogen atom from alkane **284**, affording alkyl radical **284′**. This radical subsequently undergoes radical addition to the copper(II) complex **287**, yielding key intermediate **288**. A series of cyclization steps ultimately furnish the lactone product **286** while simultaneously releasing the copper(I) species. Regeneration of the active copper(II) complex **287** occurs through oxidation of copper(I) by another *tert*-butoxy radical, followed by ligand exchange with substrate **285**, thereby closing the catalytic cycle. As revealed by density functional theory (DFT) calculations and mechanistic experiments, the enantioselectivity originates from the asymmetric C–O bond formation, and the rate-determining step is the cyclization step from **289** to **286**.

In 2023, Kramer, Lian and colleagues disclosed a dual copper and photocatalytic system for the enantioselective radical amidation and amination of benzylic C–H bonds (Scheme 43).[103] This catalytic system integrates a Cu-catalyst with a chiral ligand, an Ir-photocatalyst, and peroxide DTBP oxidant, demonstrating a broad substrate scope with excellent functional group tolerance.



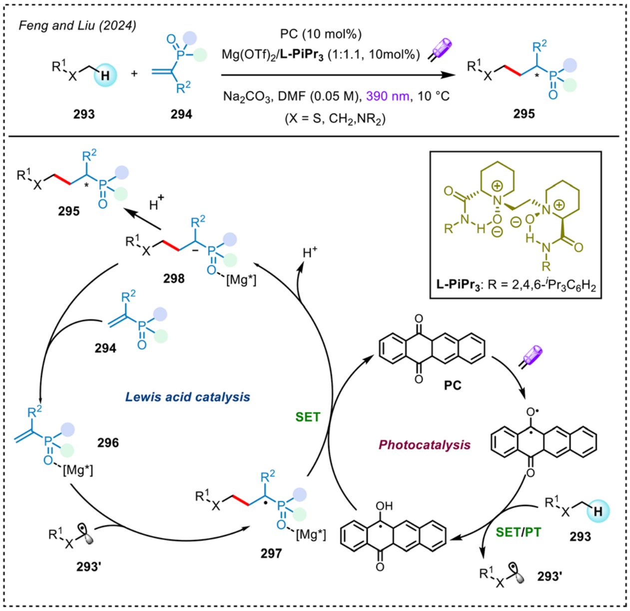
Scheme 42 Photoinduced copper-catalyzed ATRC for the asymmetric synthesis of chiral lactones.



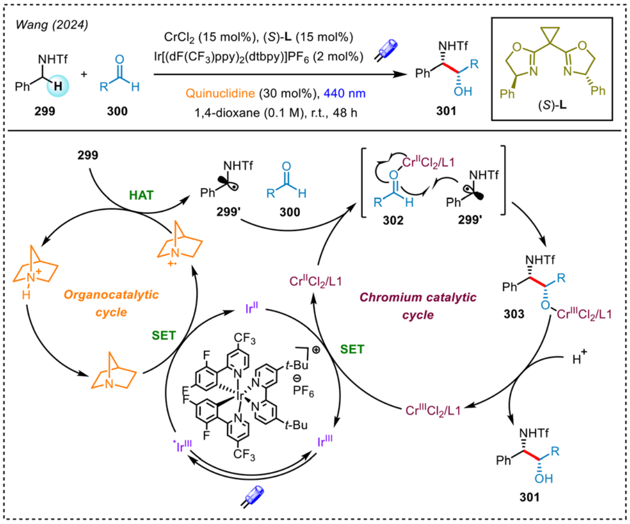
Scheme 43 Enantioselective intermolecular radical amidation and amination of benzylic C–H bonds *via* dual copper and photocatalysis.

Recently, Feng, Liu, and colleagues developed an innovative photocatalytic C(sp^3)–H functionalization for the asymmetric synthesis of privileged α-chiral alkyl phosphines **295** (Scheme 44).[104] This protocol employs a synergistic catalytic system combining an organic photocatalyst with a chiral Lewis acid catalyst. Under visible-light irradiation, the asymmetric addition of various C(sp^3)–H containing reagents, including sulfides, amines, alkenes, and toluene derivatives, to α-substituted vinylphosphine oxides **294** is efficiently realized. Through this approach, structurally diverse α-chiral alkyl phosphine compounds can be synthesized, exhibiting excellent chemoselectivity, regioselectivity, and stereoselectivity. Mechanistic studies reveal that the excited-state photocatalyst oxidizes C(sp^3)–H substrate **293** *via* single-electron transfer, generating a radical cation, which subsequently forms radical **293′** through proton transfer (PT). This carbon radical then adds onto Lewis acid-activated vinylphosphine oxide **296**, followed by single-electron reduction and protonation steps to yield the final product **295**.

In 2024, the Wang group reported a visible-light-induced asymmetric α-amino C(sp^3)–H functionalization of *N*-sulfonyl benzylic amines **299** with aldehydes **300** to access enantioenriched β-amino alcohols **301** (Scheme 45).[105] A triple catalytic system is adopted involving photoredox catalysis, HAT catalysis, and chromium catalysis. Upon irradiation, the excited-state Ir(III)* undergoes SET with quinuclidine, generating a



Scheme 44 Visible-light-induced C(sp^3)–H radical functionalization for asymmetric synthesis of α-chiral alkyl phosphine.

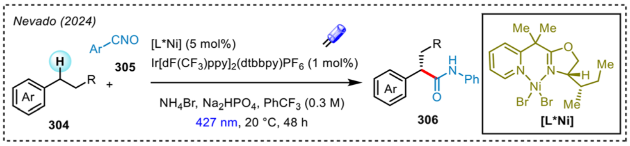


Scheme 45 Asymmetric α-amino C(sp^3)–H functionalization *via* photoredox and chromium catalysis.

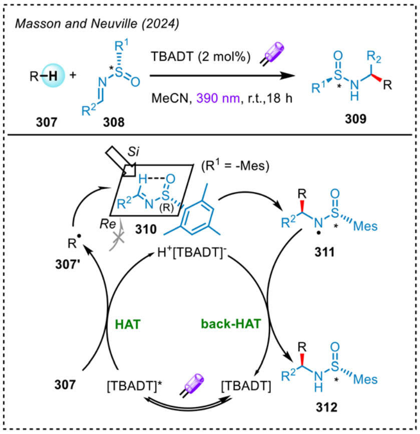
nitrogen radical cation with HAT capability. Due to H-bonding interaction, this radical cation would selectively abstract a hydrogen atom from the α-position of the nitrogen atom in **299**, forming radical intermediate **299′**. This radical intermediate then adds onto the aldehyde-Cr(II)/**L** complex **302**, forming enantioenriched alkoxy intermediate **303**. The dissociation of the Cr–O bond releases the desired product **301** and the Cr(III)/**L** complex, which can oxidize Ir(II) back to Ir(III), thereby closing both the iridium and chromium catalytic cycles.

In early 2024, Nevado and colleagues introduced a dual nickel/photoredox catalysis strategy that employs a chiral nickel complex with pyridine-oxazoline ligands as a catalyst under mild conditions (Scheme 46).[106] This approach facilitates the direct coupling of simple alkyl arenes **304** with isocyanates **305**, yielding chiral α-aryl amides with high yields and excellent enantioselectivity. The proposed reaction mechanism encompasses three synergistic catalytic cycles: the photoredox cycle, bromine radical HAT cycle and nickel catalytic cycle.

Chiral sulfoxides and the related compounds are important chemical reagents with excellent asymmetric induction capabilities, which have been employed to enable the synthesis of various chiral compounds.[107] In 2024, Masson and Neuville *et al.* reported a sustainable visible-light-mediated method for the stereoselective radical alkylation of chiral *N*-sulfinyl imines **308** with simple alkanes **307**, utilizing TBADT as the photocatalyst (Scheme 47).[108] The chiral sulfoxide not only serves as a substrate but also acts as a chiral inducer: the hydrogen bond between the sulfinyl-oxygen and the imine hydrogen of **310** (R^1 = mesityl) shields the *Re*-face, and therefore, alkyl radical **307′** would attack from the less-hindered *Si*-face to form the enantioenriched *N*-centered radical intermediate **311**.



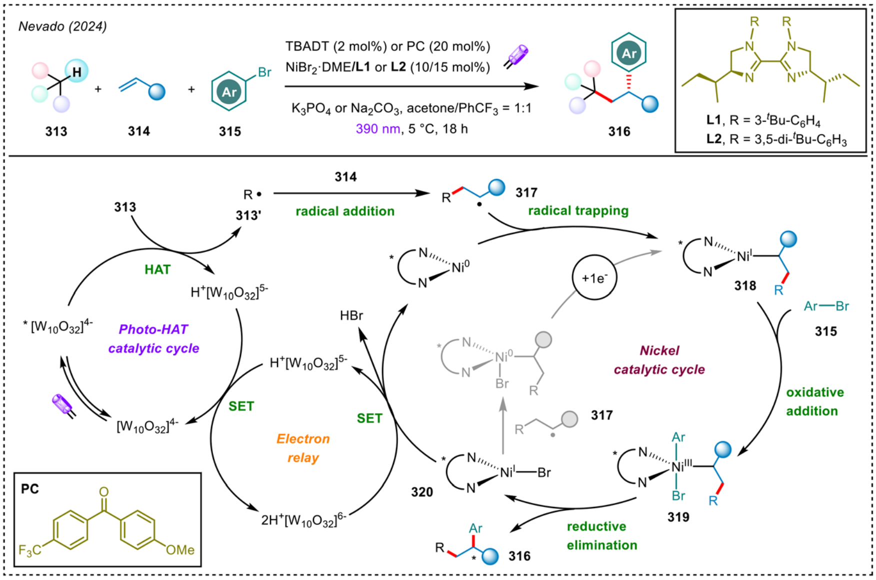
Scheme 46 Direct asymmetric functionalization of benzylic C–H bonds *via* dual nickel/photoredox catalysis for the synthesis of chiral α-aryl amides.



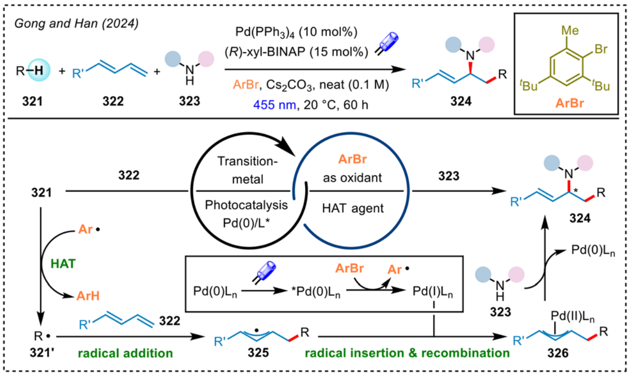
Scheme 47 TBADT-mediated photocatalytic stereoselective radical alkylation of chiral *N*-sulfinyl imines.

Recently, Nevado and colleagues reported a novel asymmetric three-component dicarbofunctionalization reaction of alkenes, which combines photomediated hydrogen atom transfer with nickel-catalyzed radical relay (Scheme 48).[109] The proposed reaction mechanism goes as follows: under 390 nm light irradiation, TBADT is excited to the excited state TBADT*, which then abstracts a hydrogen atom from alkane **313**, generating carbon-centered radical **313′** and singly reduced decatungstate species. Subsequently, this carbon-centered radical adds onto olefin **314**, forming radical intermediate **317**, which is further captured by Ni(0), forming an alkyl–Ni(I) species **318**. Next, this alkyl–Ni(I) intermediate undergoes oxidative addition with aryl bromide **315**, yielding an alkyl–Ni(III)–aryl intermediate **319**. In the next reductive elimination step, the target difunctionalized product **316** is delivered, along with a Ni(I) species. Finally, the Ni(I) species undergoes single-electron transfer with the singly reduced decatungstate to regenerate Ni(0) and decatungstate, completing the entire catalytic cycle. The alternative pathway *via* the combination of **320** and **317**, and subsequent single-electron reduction to access **318** is also proposed. This protocol provides important insights for the future development of asymmetric multicomponent reactions involving C(sp^3)–H activation.

Studies employing aryl radicals as HAT reagents in C–H activation have been relatively unexplored.[110] Recently, Gong, Han, and co-workers have reported a breakthrough in this area, by developing a photoinduced palladium-catalyzed three-component enantioselective carboamination reaction of dienes with a modified BINAP-type chiral ligand (Scheme 49).[111] In this novel strategy, 2-bromo-1,5-di-*tert*-butyl-3-methylbenzene (**ArBr**) is screened out to serve as both an oxidant to oxidize the photoexcited Pd(0) species, and a pre-



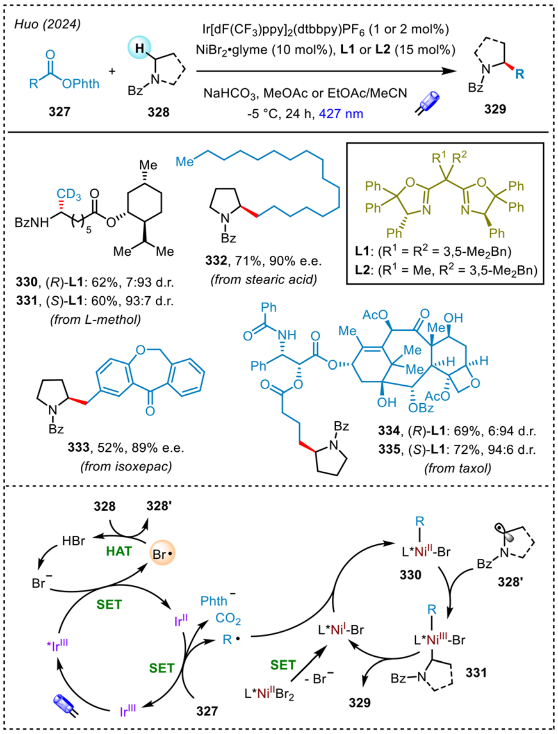
Scheme 48 Asymmetric three-component difunctionalization *via* photomediated HAT and nickel catalysis.



Scheme 49 Photoinduced Pd-catalyzed enantioselective carboamination of dienes.

cursor of aryl radical as an HAT reagent for C(sp^3)–H activation. Remarkably, this protocol can accommodate a diverse array of alkane substrates, including toluene derivatives, ethers, amines, esters, and ketones, enabling the efficient synthesis of various pivotal chiral allylamines with exceptional enantioselectivitiy (up to 99% ee).

Very recently, Huo and colleagues reported an important breakthrough, wherein photoredox and nickel catalysis are combined to achieve the enantioselective alkylation of α-amino C(sp^3)–H bonds (Scheme 50).[112] This reaction employs two independent catalytic cycles for the activation of C–H bonds and subsequent asymmetric coupling, and exhibits a broad substrate scope, enabling methylation, deuteromethylation, and other alkylation reactions on various cyclic and acyclic amine compounds while tolerating a wide range of functional groups. The use of *in situ* generated bromine radicals as HAT reagents avoids the potential compatibility issues associated with external HAT reagents and harsh conditions.



Scheme 50 Enantioselective α-amino C(sp^3)–H alkylation *via* dual photoredox and nickel catalysis.

Bromine radicals herein are produced through the single-electron oxidation of bromide anions by the excited photocatalyst, which subsequently abstract hydrogen atoms from amine substrate **328** to generate α-amino radical **328′**. Concurrently, the photocatalyst reduces carboxylic acid derivative **327** to form another alkyl radical. These two carbon radicals undergo asymmetric cross-coupling under the effect of the chiral nickel catalyst to yield C(sp^3)–C(sp^3) coupling product **329**. This modular design allows for the independent control of radical generation and asymmetric cross-coupling, thereby achieving high efficiency and selectivity.

9. Summary and outlook

Photoinduced direct C(sp^3)–H functionalization has seen rapid development in recent years, providing a novel pathway for the straightforward synthesis of complex organic molecules from readily available alkane feedstocks under sustainable conditions. Researchers have expanded the repertoire of both reaction types and substrate scopes within this field through the development of new photosensitizers, catalytic cycles, as well as reaction systems. Particularly noteworthy is the increasing application of cost-effective metals such as iron and copper as photoinduced LMCT catalysts, laying a solid foundation for more economical synthetic processes. Additionally, the emerging photoelectrochemical synthesis offers a promising opportunity for achieving more selective and sustainable transformations by replacing chemical oxidants with a precisely controlled electric current. Furthermore, photochemical strategies have made it possible to directly construct carbon–heteroatom bonds (such as C–P, C–B, C–S) under very mild conditions, which is elusive by means of traditional methods, providing new avenues for the sustainable synthesis of value-added molecules containing these important linkages.

While the scope of alkane partners has been greatly expanded, the high addition amount greatly limits the application of these protocols in practical synthesis, particularly in the functionalization of complex C(sp^3)–H sources. Therefore, developing new methods which employ alkanes as the limiting reagents are highly desirable. In addition to pursuing reaction universality, realizing photocatalytic enantioselective C(sp^3)–H functionalization is also a key objective, which has still been in its infancy. Currently, the application of chiral ligands and pre-installation of auxiliaries are the major strategies for achieving stereoselectivity control, while the innovative design of new chiral photosensitizers/catalysts can also be anticipated. Looking ahead, the future research will likely continue to focus on developing new photocatalytic systems to expand reaction types and substrate scopes, and on further exploring the mechanisms for novel reaction discovery.

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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