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Perspective

Photocatalyzed Enantioselective Functionalization of C(sp^3)−H Bonds

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ABSTRACT: Owing to its diverse activation processes including single-electron transfer (SET) and hydrogen-atom transfer (HAT), visible-light photocatalysis has emerged as a sustainable and efficient platform for organic synthesis. These processes provide a powerful avenue for the direct functionalization of C(sp^3)−H bonds under mild conditions. Over the past decade, there have been remarkable advances in the enantioselective functionalization of the C(sp^3)−H bond via photocatalysis combined with conventional asymmetric catalysis. Herein, we summarize the advances in asymmetric C(sp^3)−H functionalization involving visible-light photocatalysis and discuss two main pathways in this emerging field: (a) SET-driven carbocation intermediates are followed by stereospecific nucleophile attacks; and (b) photodriven alkyl radical intermediates are further enantioselectively captured by (i) chiral π-SOMOphile reagents, (ii) stereoselective transition-metal complexes, and (iii) another distinct stereoscopic radical species. We aim to summarize key advances in reaction design, catalyst development, and mechanistic understanding, to provide new insights into this rapidly evolving area of research.

1. INTRODUCTION

Direct functionalization of ubiquitous carbon−hydrogen (C−H) bonds is a captivating goal in modern organic chemistry as it offers concise and adequate access for enhancing the molecular complexity and enabling late-stage functionalization of drug-like molecules, without the need for cumbersome manipulation of functional group transformations.[1−4] However, controlling enantioselectivity in this transformation remains a fundamental yet unsolved challenge. In recent decades, various approaches have been established for the enantioselective transformation of C(sp^3)−H bonds, including biomimetic metal-oxo H atom abstraction[5] as well as transition-metal catalyzed C−H activation,[6−10] C−H insertion with nitrene or carbene,[11−13] and radical reaction.[14−17] The advances, advantages, and limitations of these strategies have been previously discussed in excellent and comprehensive reviews.[5−17]

Photoredox catalysis,[18−28] is an emerging and powerful tool in organic synthesis that offers a unique approach for the direct functionalization of C(sp^3)−H bonds through single-electron transfer (SET) (Scheme 1a),[29,30] direct hydrogen-atom transfer (*d*-HAT) (Scheme 1b) and indirect hydrogen-atom transfer (*i*-HAT) (Scheme 1c).[31−36] Recently, a series of elegant methods that merge photoredox and asymmetric catalysis have been established, providing promising solutions to address the aforementioned challenge of enantioselectivity.[37−39] This perspective aims to showcase significant progress in this burgeoning research field, although it cannot be fully comprehensive.

From this perspective, we present an overview of advancements in enantioselective functionalization of C(sp^3)−H bonds through photocatalysis. Specifically, we focus on elucidating the photoactivation pathway of C(sp^3)−H bonds and the stereocontrolling models of new chemical bond formation. According to reactive intermediates derived from the C(sp^3)−H bond, these reactions can be categorized into two main types. The first category involves reactions that generate carbocation intermediates by the photocatalyzed oxidation process and subsequently capture them enantioselectively using various chiral nucleophile species (Scheme 2a). The second category involves reactions of C−H-derived radical species generated by photocatalyzed SET or HAT processes (Scheme 2b). Depending on the functional partners, the latter category can be further divided into three subsets: (i) enantioselectively capturing radical species with π-SOMOphile reagents; (ii) capture of radical species by chiral transition-metal complexes, followed by formation of cross-coupling products through reductive elimination; (iii) direct cross-coupling between two different radical species with the assistance of chiral catalysts. Another special kind of reaction involves the enantioselective functionalization of the activated α-carbonyl C(sp^3)−H bond via photogenerated-radical addition to the corresponding enamine or enolate intermediates. Although highly significant, these reactions do not involve direct C(sp^3)−H activation via photoredox catalysis, which only produces a variety of functionalized radical species, and thus falls outside of the scope of the Perspective. Additionally, potential remaining challenges and promising future directions will also be addressed.

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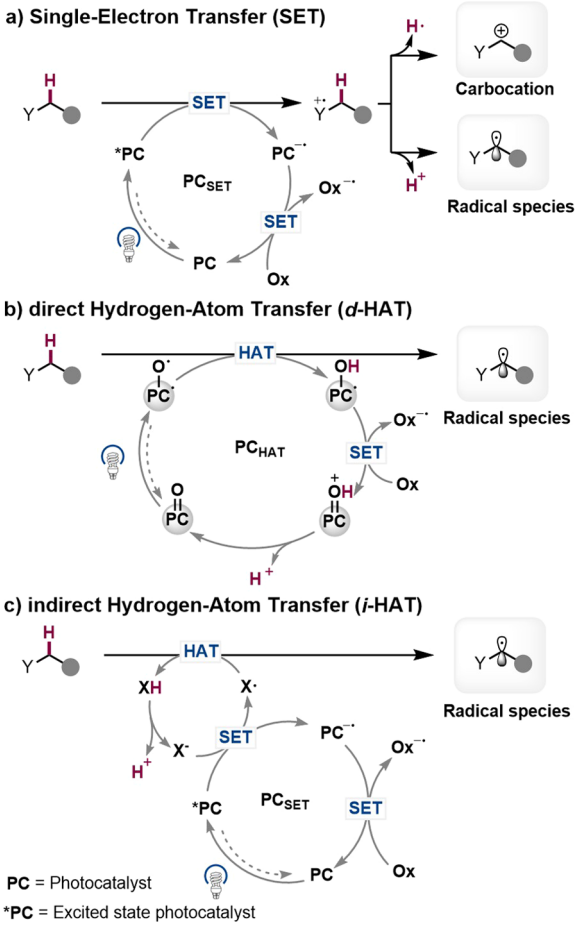
Scheme 1. Photocatalyzed C(sp^3)−H Activation Mechanism



2. ASYMMETRIC FUNCTIONALIZATION OF C(SP^3)−H BOND WITH NUCLEOPHILE REAGENTS

C(sp^3)−H bonds adjacent to heteroatoms can be activated by photoredox catalysis, leading to the formation of a carbocation intermediate. Subsequently, in the presence of a chiral catalyst, these intermediates can react with nucleophilic species under mild conditions to yield a variety of enantiomeric compounds (Scheme 3).

In 2012, the Rovis group demonstrated the catalytic asymmetric α-acylation of tertiary amines with aldehydes by combining chiral *N*-heterocyclic carbene (NHC) catalysis and photoredox catalysis (Scheme 3a).[40] In this transformation, a photoredox catalytic single-electron oxidation of tertiary amine was followed by a hydrogen-atom-abstraction event to form the crucial iminium ion. This intermediate was then intercepted by the nucleophilic Breslow intermediate formed by the interaction of an NHC with an aldehyde, resulting in the formation of a range of α-amino ketones in good yields with excellent enantioselectivities.

Subsequently, Jacobsen and Stephenson presented an enantioselective oxidative C−H alkylation of tetrahydroisoquinoline derivatives by merging asymmetric anion-binding catalysis and photoredox catalysis.[41] The Jiang group described an enantioselective aerobic oxidative C(sp^3)−H olefination of tetrahydro-β-carbolines and tetrahydroisoquinolines through combining an organic photoredox catalyst, a chiral Lewis base catalyst, and an inorganic salt cocatalyst.[42] The Pericàs group reported the asymmetric cross-dehydrogenative coupling (CDC) of aldehydes with xanthenes by integrating photoredox catalysis and enamine catalysis.[43] In 2020, the Zhang group presented a new asymmetric CDC of glycine derivatives with ketones or aldehydes via cooperative photoredox catalysis and organocatalysis, which used air as the terminal oxidant.[44]

Chiral-at-metal complexes can activate 2-acyl imidazoles to form a chiral-coordinated rhodium enolate. In 2015, Meggers and co-workers utilized such a chiral-at-metal rhodium complex to enable the enantioselective catalytic cross-coupling of two C(sp^3)−H groups with molecular oxygen as the terminal oxidant (Scheme 3b).[45] In this process, the catalyst served a dual function, namely as a chiral Lewis acid for catalyzing enantioselective enolate chemistry and simultaneously as a visible-light-mediated photoredox catalyst.

Generally, CDC reactions require a stoichiometric amount of oxidant as the hydrogen acceptor. In 2017, Luo and Wu disclosed a tricatalytic hydrogen-transfer strategy for the enantioselective CDC of tertiary amines and simple ketones by integrating primary amine catalysis, cobalt catalysis, and photoredox catalysis with substoichiometric hydrogen acceptor (Scheme 3c).[46] In this reaction, the coupled Ru/Co catalysis enabled the C−H activation of the tertiary amine to generate an iminium cation intermediate in situ, which was subsequently intercepted by the enamine intermediate formed through the condensation of a simple chiral primary amine with aldehyde, to deliver the corresponding optically pure product.

2,5-Disubstituted tetrahydrofuryl acetals are commonly found in pharmaceuticals, LEDs, and DNA sequencing. However, the enantioselective method for the direct functionalization of cyclic ethers remains scarce. In 2018, the Toste group developed a novel method for stereoselectively functionalizing the C(sp^3)−H bond in cyclic ethers by combining a photochemically active diaryliodonium salt with an anionic phase-transfer catalyst (Scheme 3d).[47] This process involves activating the C(sp^3)−H bond through visible-light photoinduced HAT with diaryliodonium, delivering crucial oxonium species that can be captured by alcohol nucleophiles. The chiral phosphate-paired Lewis acidic diaryliodonium species assist in achieving stereoselective α-C(sp^3)−H acetalization of cyclic ethers.

3. ASYMMETRIC FUNCTIONALIZATION OF C(SP^3)−H BOND WITH π-SOMOPHILE REAGENT

In addition to forming carbocation intermediates, C(sp^3)−H bonds can also be activated by a photoinduced SET or HAT pathway, resulting in the generation of various nucleophilic radical species. These radical species are captured by a diverse variety of π-SOMOphiles with the help of a chiral catalyst, furnishing a wide array of enantioselective C(sp^3)−H functionalized products.

3.1. α-Functionalization of Activated C(sp^3)−H Bond with Electron-Withdrawing Alkene. The first example to realize the enantioselective functionalization of the C(sp^3)−H bond was reported by the Bach group in 2005 (Scheme 4a).[48] In this transformation, the chiral organocatalyst containing an electron-accepting unit bound to the amine substrate through an intermolecular hydrogen bond, followed by a photoinduced electron transfer event with the irradiation of UV light to form α-amino radical species. Finally, the chiral spirocyclic product was obtained in up to 64% yield with 70% ee via a radical-type Michael addition. This reaction demonstrated that the enantioselectivity of photochemical reaction could be well controlled by merging appropriate asymmetric catalysts.

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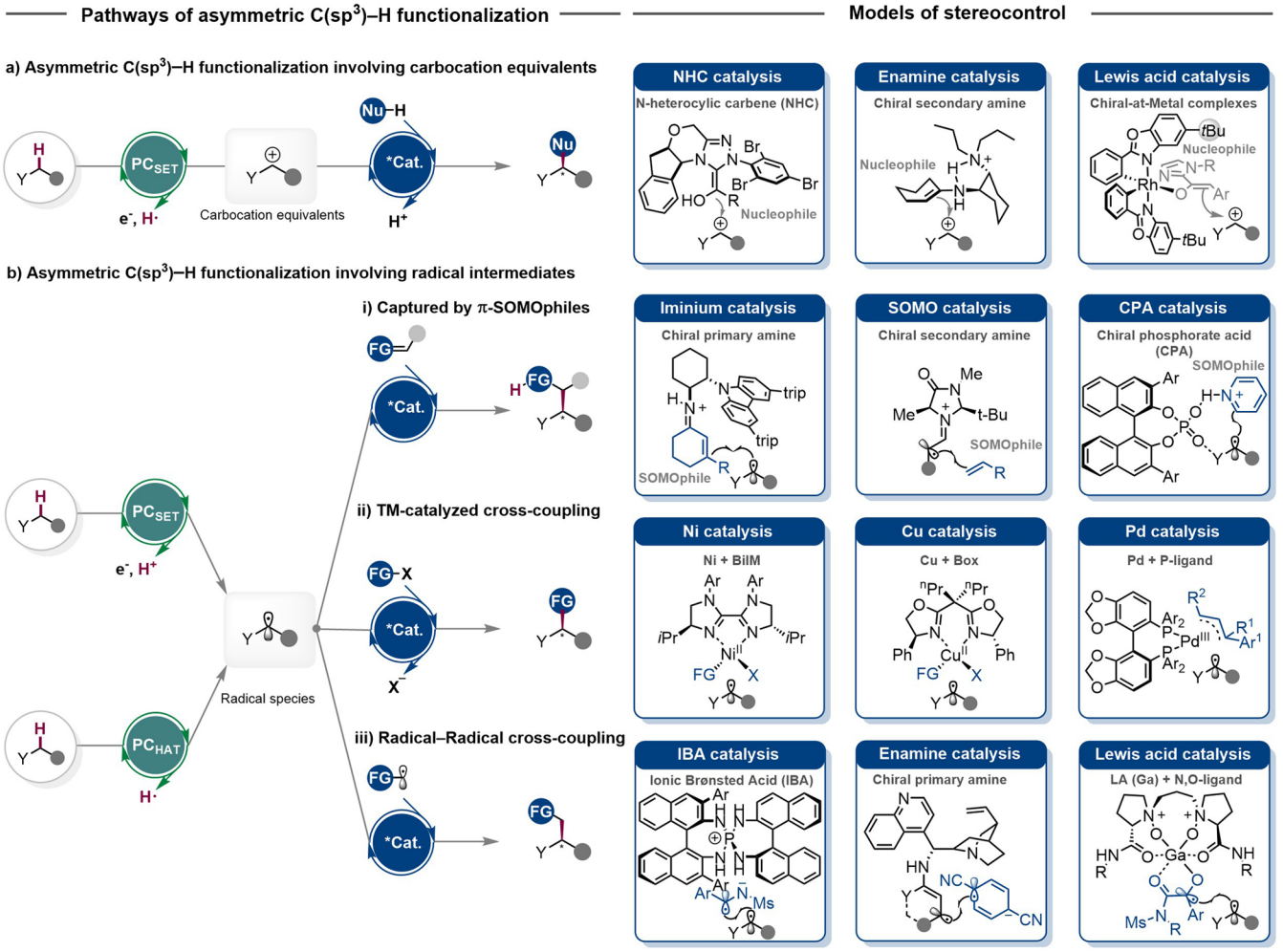
Scheme 2. Overview of Photocatalyzed Enantioselective C(sp^3)−H Functionalization Strategies[a]



[a]FG, functional group; HAT, hydrogen-atom transfer; Nu, nucleophile; PC, photocatalyst; SET, single-electron transfer; and TM, transition metal.

In 2016, the Melchiorre group reported a photoredox-catalyzed radical-type conjugate addition reaction for the enantioselective alkylation of the C(sp^3)−H bond via combining with asymmetric iminium catalysis, providing a concise and effective approach for the construction of chiral quaternary carbon stereocenters (Scheme 4b).[49] In this process, the C(sp^3)−H bond was activated by a photoinduced SET/deprotonation event to deliver the nucleophilic radical intermediate, which was enantioselectively trapped by iminium-ion activated alkenes, furnishing a broad range of *β*,*β*-disubstituted cyclic enones. The key to the success of this reaction was the design of a chiral organic catalyst containing a redox-active carbazole component, which drove the formation of iminium ions and the stereoselective capture of photochemically generated carbon-centered radicals through an electron-relay mechanism. This method was shown to work with two sets of open-shell intermediates, generated through unrelated light-triggered pathways from readily available substrates and photoredox catalysts, representing the application of iminium-ion activation within the realm of radical reactivity.

Later, the Melchiorre group found that the iminium-ion intermediate generated by the condensation of a secondary amine and enal could directly absorb visible light to form an excited-state chiral iminium ion, which possessed an oxidative power and triggered the generation of benzylic radical through a sequential multisite proton-coupled electron-transfer event (Scheme 4c).[50] Applying this novel activation model, they accomplished the direct asymmetric C−H functionalization of toluene derivatives by using a single organocatalyst, affording a wide range of enantioenriched *β*-benzylated aldehydes. This study demonstrated that feedstock chemicals commonly used as solvents, such as toluene and xylene derivatives, could be used as substrates for constructing chiral molecules with high enantioselectivities.

Intramolecular 1,5-hydrogen-atom transfer (1,5-HAT) is an effective way to activate remote C(sp^3)−H bonds through the formation of radical species.[31] In 2016, the Meggers group exploited this 1,5-HAT event to establish a novel photoredox-mediated enantioselective C(sp^3)−H functionalization strategy via radical translocation through merging with asymmetric Lewis acid catalysis (Scheme 4d).[51] A range of *α*,*β*-unsaturated *N*-acylpyrazoles reacted with *N*-alkoxyphthalimides in the presence of a rhodium-based chiral Lewis acid catalyst and the photosensitizer *fac*-[Ir(ppy)$_3$] upon irradiation with visible light, providing C−C bond formation products with high enantioselectivities (up to 97% ee). Mechanical investigations indicated that this transformation underwent a radical translocation (1,5-HAT) from an oxygen-centered to a carbon-centered radical and a subsequent chiral-at-metal rhodium-catalyzed radical alkene addition process.

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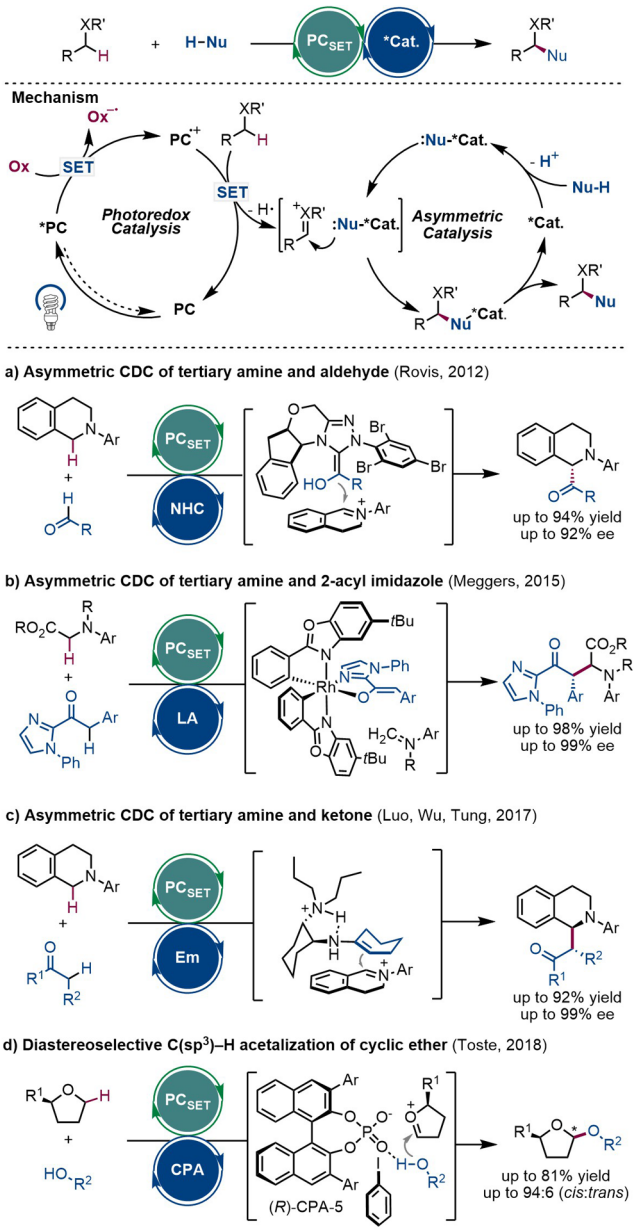
Scheme 3. Asymmetric C(sp^3)−H Functionalization via Photo-Generated Carbocation Intermediate[a]

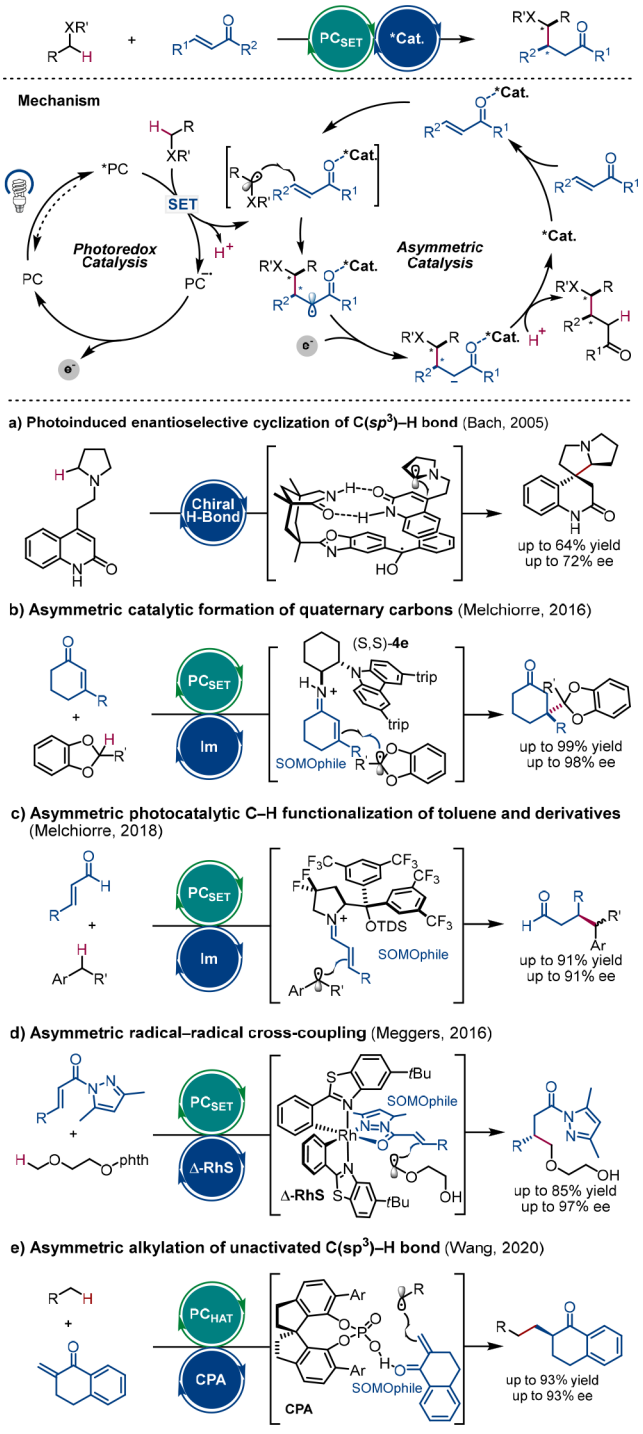


[a]CDC, cross-dehydrogenative coupling; CPA, chiral phosphoric acid; Em, enamine; LA, Lewis acid; NHC, N-heterocyclic carbene; Nu, nucleophile; PC, photocatalyst; and SET, single-electron transfer.

Direct hydrogen-atom transfer (*d*-HAT) via a photoexcited photocatalyst is an alternative tool to activate inert C(sp^3)−H bonds.[33,52,53] In 2020, the Wang group reported a light-mediated enantioselective C−H functionalization of unactivated hydrocarbons with enones in the presence of tetrabutylammonium decatungstate (TBADT) and chiral spiro phosphoric acid (CPA, Scheme 4e).[54] In this protocol, the C(sp^3)−H bond was activated by a TBADT-mediated HAT process to furnish a nucleophilic radical species, followed by a sequential radical addition/hydrogen abstraction/enantioselective protonation process with the assistance of CPA, resulting in the desired products in good yields with excellent enantioselectivities.

Recently, Gong and co-workers developed a three-component asymmetric sulfonylation of the C(sp^3)−H bond in

Scheme 4. Asymmetric Alkylation of (sp^3)−H Bond via Radical-Type Michael Addition[a]



[a]CPA, chiral phosphoric acid; HAT, hydrogen-atom transfer; Im, iminium; PC, photocatalyst; SET, single-electron transfer; and Δ-RhS, chiral-at-Rhodium complexes (a dual function photoredox/chiral Lewis acid catalyst).

cycloalkanes, alkanes, toluene derivatives, and ethers, in which C(sp^3)−H bonds were selectively activated by the direct *d*-HAT process of a commercially available organophotocatalyst.[55] The photogenerated radical was rapidly captured by SO_2 to produce the stabilized sulfonyl radical, which underwent an enantioselective addition to an *α*,*β*-unsaturated carbonyl compound in the

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presence of a chiral nickel catalyst. Protonation delivered a wide range of biologically interesting α-C chiral sulfones in good yields with high regio- and enantioselectivities. This method was utilized to the late-stage functionalization of bioactive molecules, providing appealing access to enantioenriched compounds from abundant hydrocarbon compounds.

3.2. α-Functionalization of Carbonyl Compound with Alkene. Singly occupied molecular orbital (SOMO) catalysis provides an alternative approach for the enantioselective α-functionalization of carbonyl compounds through coupling organocatalysis with a single-electron oxidation event.[56−58] This strategy occurs through stoichiometric oxidation of transiently generated enamines to form 3πe$^-$ enaminyl radical intermediates, which are intercepted by various prefunctionalized olefins and undergo an additional oxidation process to produce enantioenriched α-functionalized adducts. However, this emerging activation model suffers from several limitations: (1) the need for at least two equivalents of a stoichiometric oxidation per bond formation and (2) the requirement for pregenerated-nucleophilic olefin partners, such as silyl ketene acetals, allyl silanes, which can engage the electrophilic 3πe$^-$ enaminyl radical intermediate.

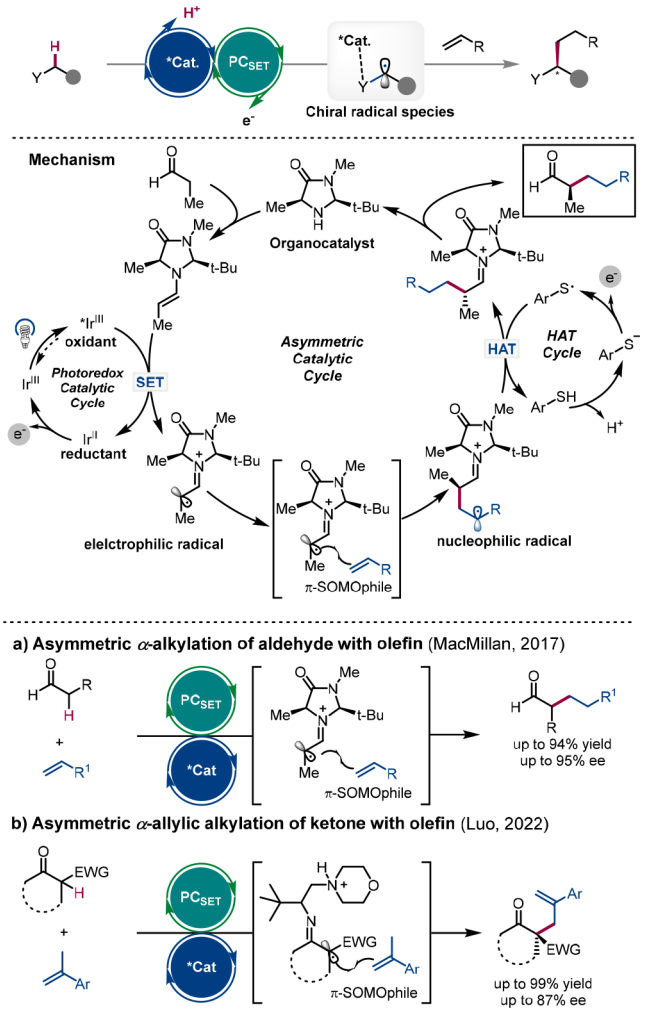
In 2017, the MacMillan group reported a tricatalytic SOMO activation for the direct enantioselective alkylation of aldehydes with simple alkenes through the synergistic merger of photoredox, enamine, and HAT catalysis (Scheme 5a).[59] In this case, the rational combination of SOMO and photoredox activation modes enabled hydrogen atom and electron borrowing to form the crucial 3πe$^-$ enaminyl radicals, captured by simple olefins and hydrogen-atom transfer reagent to deliver a range of alkyl carbonyl adducts in good yields and high enantioselectivities. This multicatalytic approach enabled both intra- and intermolecular coupling of aldehydes to generate cyclic and acyclic carbonyl products, respectively.

In 2022, the Luo group also developed an oxidant-free SOMO catalytic strategy for the asymmetric C(sp^3)−H allylic alkylation of keto carbonyls via the synergistic catalytic system consisting of a chiral primary amine, a photoredox catalyst, and a cobaloxime cocatalyst (Scheme 5b).[60] This transformation was initiated by the single-electron oxidation of the in situ formed enamine intermediate with an excited photoredox catalyst and a cobalt catalyst, forming the chiral imino radical and cobalt radical species. The resulting electrophilic imino radical was captured and further lost a hydrogen atom to deliver a broad range of α-allylic alkylated products in good yields and high enantioselectivities. Mechanistic studies indicated a cooperative radical addition process with the chiral imino radical and metalloradical working in concert to control stereoinduction.

3.3. α-Functionalization of Activated C(sp^3)−H Bond with Electron-Deficient *N*-Heteroarene. Due to the wide distribution of nitrogen-containing heterocycles in natural products, pharmaceuticals, and agrochemicals, the Minisci reaction, which is defined as the addition of open-shell alkyl and perfluoroalkyl radical intermediates to heteroarenes,[61−65] represents one of the most powerful methods for constructing complex and basic heteroarenes and has attracted much attention in the field of photoredox catalysis over the recent decade.[66−68] However, the catalytic asymmetric version remains a great challenge.

In 2018, the Phipps group reported an unprecedented catalytic asymmetric Minisci reaction by merging CPA and photoredox catalysis, using amino acid derivatives as the radical

Scheme 5. Asymmetric α-C(sp^3)−H Functionalization of Carbonyl Compounds via Singly Occupied Molecular Orbital (SOMO) Activation[a]



[a]PC, photocatalyst and SET, single-electron transfer.

precursor.[69] Subsequently, they established the photodriven enantioselective Minisci reaction for the direct coupling of linear amides and heteroarenes (Scheme 6a).[70] In this reaction, the C(sp^3)−H bond of amide was activated by a photopromoted HAT process, resulting in a nucleophilic α-aminoalkyl radical, which was enantioselectively trapped by heteroarenes in the presence of chiral phosphoric acid to deliver the corresponding products in good yields with excellent regioselectivities and enantioselectivities. The key to the success of this reaction was the utility of diacetyl as a directly photoexcitable HAT reagent for in situ generating the α-aminoalkyl radical, which avoided the need of an extraneous photocatalyst. This method presented one of the most economic ways for building complexity around basic heteroarenes.

Alcohol is one of the most readily available materials and is widely distributed in natural products and biologically active molecules. Based on previous research, Phipps and co-workers described a substantial evolution of the asymmetric Minisci reaction (Scheme 6b),[71] in which α-hydroxy radicals were formed via a photoinduced HAT event and enantioselective addition to the heteroarenes with the assistance of chiral phosphorate acid. This method provided a valuable approach for

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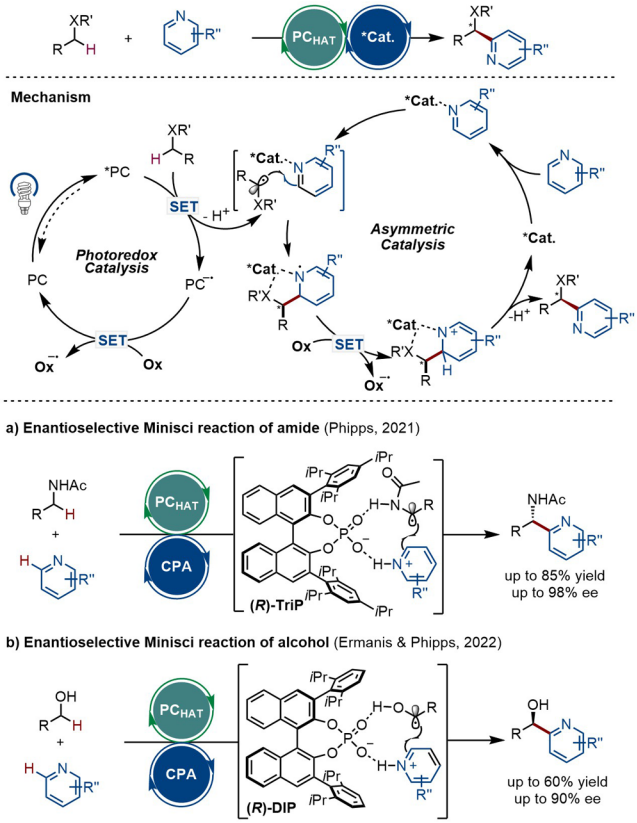
Scheme 6. Asymmetric α-Functionalization of C(sp^3)−H Bond via Minisci Reaction[a]



[a]CPA, chiral phosphoric acid; HAT, hydrogen-atom transfer; PC, photocatalyst; and SET, single-electron transfer.

accessing enantioenriched secondary alcohols through the direct oxidative coupling of two C−H bonds on simple alcohol and pyridine partners. The computational and experimental investigations provided new insight into the origin of this reaction's stereoselectivity, revealing a stereodetermining deprotonation step distinct from the analogous reaction of amide-containing substrates.

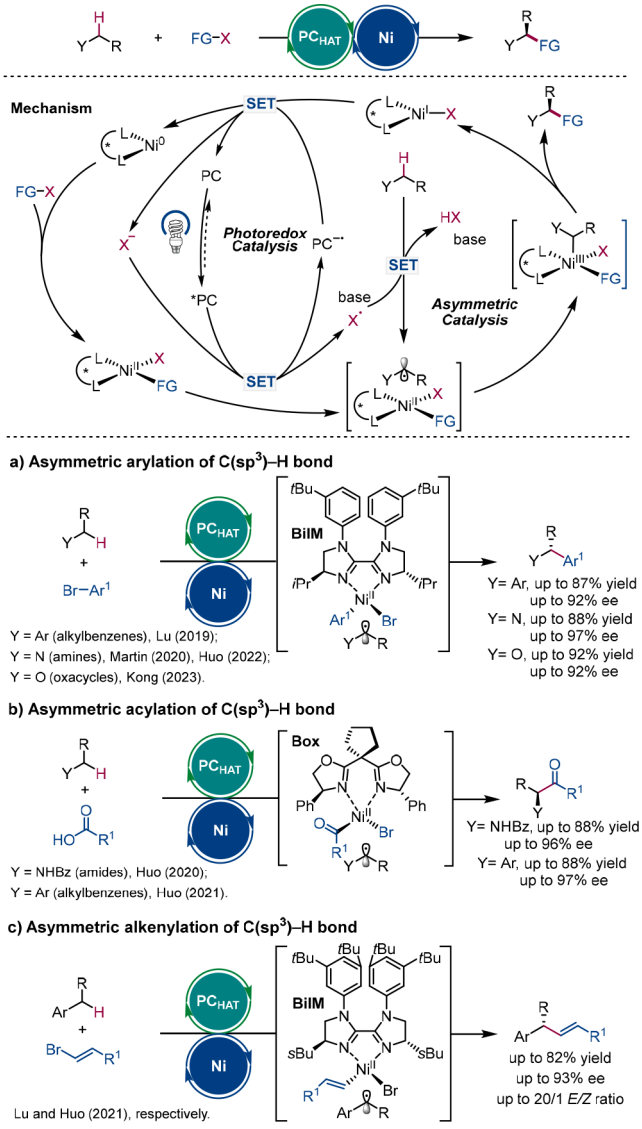
4. ASYMMETRIC FUNCTIONALIZATION OF C(SP^3)−H BOND VIA A METALLAPHOTOREDOX CATALYZED CROSS-COUPLING REACTION

Transition-metal-catalyzed cross-coupling reactions have evolved to be a powerful platform for the rapid construction of C−C and C−heteroatom bonds,[72,73] but they are limited to aryl and olefinic (sp^2) carbons and depend on organometallic compounds, such as aryl or vinyl boronic acids, zinc halides, stannanes, or Grignard reagents. In 2014, the Doyle and MacMillan groups reported an unprecedented cross-coupling of α-carboxyl sp^3-carbons with aryl halides via merging photoredox and nickel catalysis, which also enabled the direct cross-coupling of C(sp^3)−H in dimethylaniline with aryl halides through a C−H functionalization event.[74] This photoredox/nickel catalyzed cross-coupling reaction presents a novel paradigm for the selective functionalization of C(sp^3)−H bond,[75−77] but stereoselective control of this process remains a challenge.

4.1. Asymmetric Ni-Metallaphotoredox Catalysis. By selecting the appropriate ligand, Ni/photoredox catalysis offers a concise and efficient approach for the enantioselective functionalization of C(sp^3)-H bonds with a variety of coupling partners.

4.1.1. Arylation. In 2019, the Lu group developed an asymmetric benzylic C−H arylation strategy by combining photoredox and nickel catalysis, providing a straightforward pathway toward chiral 1,1-diaryl alkanes (Scheme 7a).[78] In this

Scheme 7. Asymmetric α-Functionalization of Activated C(sp^3)−H Bond via Ni-Metallophotocatalysis[a]



[a]FG, functional group; HAT, hydrogen-atom transfer; and PC, photocatalysts.

case, the photoredox catalytic HAT event activated the C(sp^3)−H bond, and the newly designed biimidazoline (BiIM) ligand played a pivotal role in controlling the enantioselectivity of this transformation.

Subsequently, the Huo group employed a similar strategy to accomplish the direct enantioselective α-arylation of saturated aza-cycles and acyclic *N*-alkyl benzamides, in which the commercially available (hetero)aryl chlorides were used as the arylated reagents.[79] In this transformation, the aza-cycles were activated via a HAT event of photoredox-mediated chlorine radicals to generate the corresponding α-amino alkyl radicals.

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These radicals were then enantioselectively coupled with (hetero)aryl chloride partners in the presence of the nickel/BiIM ligand complex. Mechanistic experiments indicated that the nickel catalyst played multiple roles, such as forming chlorine radicals, capturing α-amino radicals, cross-coupling, and asymmetric induction.

Recently, the Kong group employed this photo-HAT/nickel dual catalysis strategy to achieve the enantioselective arylation of C(sp^3)−H in undirected oxacycles.[80] Unlike previous methods, this protocol utilized a diaryl ketone as a photo-HAT catalyst, facilitating hydrogen-atom abstraction from an oxacycle, resulting in a carbon-centered radical species. The capture of these radicals by the nickel/PHOX ligand complex and subsequent reductive elimination furnished a broad range of enantiomerically enriched α-substituted oxacycles. This strategy has also been applied in the late-stage functionalization of natural products and the synthesis of numerous relevant pharmaceutical molecules.

4.1.2. Acylation. α-Amino ketones are widespread privileged motifs in many medically valuable molecules.[81−83] Direct acylation of the C−H bond is one straightforward way to access the diverse set of ketones from feedstock hydrocarbons. In 2020, the Huo group reported a novel strategy for the enantioselective acylation of α-amino C(sp^3)−H bonds through the merger of photoredox and nickel catalysis (Scheme 7b).[84] In this reaction, the C(sp^3)−H bond cleavage proceeded via a HAT process with photoredox catalytically generated bromine radicals. The resulting α-amino alkyl radicals were subsequently trapped by the nickel/Box ligand complex, affording a broad range of enantiomerically enriched α-amino ketones in high yields. This protocol efficiently produces valuable α-amino ketones from bench-stable carboxylic acids using readily available *N*-alkyl benzamides.

Subsequently, they demonstrated this synergistic photoredox/nickel strategy was also suitable for the acylation of benzylic C−H bonds in alkyl arenes, delivering a range of α-aryl ketones in good yield with high enantioselectivities under mild conditions.[85] In this case, a bromine radical in situ generated by photoredox catalysis could perform benzylic C−H cleavage to activate alkylamines as nucleophilic coupling partners, which could be used in a nickel-catalyzed asymmetric acyl cross-coupling reaction. Furthermore, this bromine-radical-mediated C−H activation strategy could also be applied to the enantioselective coupling of alkylamines with chloroformate for the synthesis of chiral α-aryl esters.

4.1.3. Alkenylation. Alkene constitutes the most useful building block for the synthesis of bioactive molecules and functional materials[86−88] and attracts much attention to constructing this motif in organic synthesis.[89−93] In 2021, the Lu group employed the photoredox/nickel dual catalysis strategy to access the direct alkenylation of benzylic C−H bonds (Scheme 7c). This approach offers an effective approach for the stereo- and enantioselective synthesis of chiral allylic compounds from commercially available alkylbenzenes and alkenyl bromides.[94] Soon after, the Huo group also reported a similar method for benzylic C−H alkenylation in a stereo- and enantioselective manner.[95] In both studies, they used the photogenerated bromide-radical to cleave the C(sp^3)−H bond, forming the prochiral benzylic radical coupled with alkenyl bromides in the chiral nickel complex. The tunable Z/E selectivity was achieved by energy transfer catalysis.

4.2. Asymmetric Cu-Metallaphotoredox Catalysis. Copper catalysis provides an alternative method for forming a C−C or C−Heteroatom bond.[96] Coupled with various C−H functionalization processes, photoinduced copper catalysis opens up a novel pathway for the enantioselective functionalization of C(sp^3)−H bonds.

4.2.1. Amination. In 2020, the Nagib group reported an asymmetric C(sp^3)−H functionalization via a radical relay chaperone strategy, which provided a concise access to chiral β-amino alcohols from a variety of alcohols containing alkyl, benzyl, allyl, and propargyl C(sp^3)−H bonds (Scheme 8a).[97] In this protocol, the alcohol was converted into an oxime imidate by condensation with a bench-stable imidoyl chloride. This radical precursor was coordinated and activated by a photoexcited copper complex containing a chiral bisoxazoline ligand and a chiral carboxylate, to form an N-centered radical species, which enabled hydrogen-atom abstraction from a C(sp^3)−H bond and produced an alkyl radical. Finally, through a copper-catalyzed cross-coupling process, the enantioenriched oxazoline was formed and transferred into highly valuable chiral β-amino alcohol by acidic hydrolysis.

4.2.2. Alkylation. C(sp^3)−H alkylation constitutes one of the most valuable transformations in organic synthesis,[98,99] but the enantioselective version continues to pose a significant challenge. In 2021, the Wang and Xu group reported a visible-light-induced Cu-catalyzed asymmetric C(sp^3)−H alkylation of glycine, which provided an effective approach for the synthesis of unnatural α-amino acids under mild conditions (Scheme 8b).[100] In this reaction, a chiral phosphine (Xyl-BINAP) copper complex bound to the substrate and in situ generated a photocatalyst, which mediated the intramolecular photoredox process and controlled the stereoselectivity of this reaction. Furthermore, the success of this strategy enabled the development of other classes of stereoselective alkyl radical coupling reactions. Later, they expanded this visible-light mediated Cu-catalytic system to the stereoselective C-glycosylation of C(sp^3)−H in peptides,[101] offering an efficient way for the direct coupling of medically valuable peptides and saccharide fragments.

4.2.3. Alkynylation. The alkyl group is among the most valuable building blocks in organic synthesis. In 2022, the Zhang group described copper-catalyzed enantioselective C(sp^3)−H alkynylation of unactivated cyclic 2-iodo-benzamide through a photoinduced intramolecular 1,5-HAT event (Scheme 8c).[102] The key to the success of this reaction was the employment of a bisoxazoline diphenylamine ligand coupled with 1,1′-bi-2-naphthol, which improved the reduction potential of the copper complex. Mechanistic and computational studies indicated that the copper complex formed in situ simultaneously served as both a photoredox and coupling catalyst, which drove the photo-mediated intramolecular 1,5-HAT process and controlled the stereoselectivity of C(sp^3)−C(sp) bond formation. In addition to the broad scope of unprecedented benzocyclic amines, this method also showcased excellent diastereoselectivity in the C(sp^3)−H alkynylation of 2-monosubstituted cyclic amines.

4.2.4. Cyanation. Nitrile is a versatile synthon in organic synthesis due to its ability to transform into a variety of other functional groups including carbonyls and amines.[103,104] Direct C−H cyanation is an efficient method for synthesizing nitriles from feedstock carbohydrates and installing the cyano group into complex molecules. Based on their radical relay strategy,[14] the Liu and Wang group described a sustainable method for the enantioselective cyanation of benzylic C−H bonds via merging electrophoto- and copper catalysis (Scheme 8d).[105] By adjusting the electronic properties of anthraquinone-type photocatalysts

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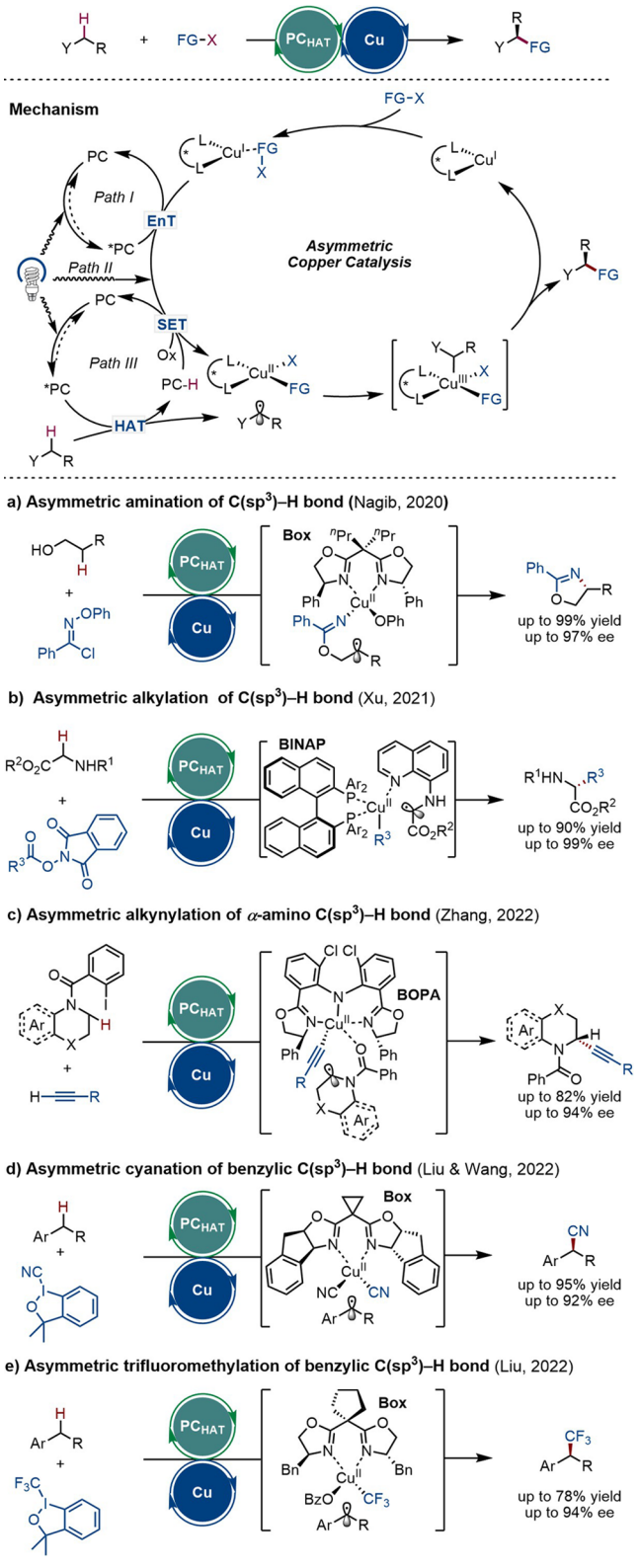
Scheme 8. Asymmetric Functionalization of C(sp^3)−H Bond via Cu-Metallaphotocatalysis[a]



[a]HAT, hydrogen-atom transfer; PC, photocatalyst.

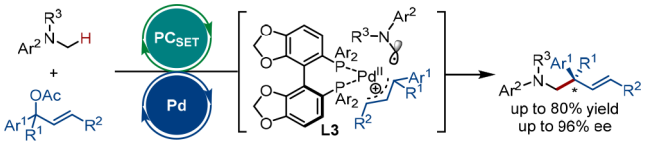
and modulating the applied current, this novel catalytic system effectively regulated the HAT process for producing benzylic radical species and speciation of Cu(II)/Cu(I) to trap the transient radical intermediate, respectively. This multicatalysis-coupled strategy offers a unified approach for the direct benzylic C−H cyanation of diverse alkylarenes with excellent enantioselectivities. Moreover, this protocol is also suitable for the late-stage functionalization of bioactive molecules, such as natural products and pharmaceuticals.

4.2.5. Trifluoromethylation. The installation of a trifluoromethyl (CF_3) group into biologically active molecules has attracted a great deal of attention from the organic community[106−109] because it can significantly enhance their pharmacokinetic properties, especially for optically pure CF_3-containing organofluorines. Recently, the Liu and Wang group employed a cooperative photoredox and copper catalysis system to establish the first enantioselective trifluoromethylation of benzylic C−H bonds, offering straightforward and efficient access to structurally diverse benzylic trifluoromethylation products in good yields with excellent enantioselectivities under mild conditions (Scheme 8e).[110] The merger of photoredox catalysis with copper catalysis was essential for this reaction, where the former was used for the generation of benzylic radicals from alkyl arenes via a photoinduced HAT event, and the latter was used for the enantioselective trifluoromethylation of these benzylic radicals.

4.3. Asymmetric Pd-Metallaphotoredox Catalysis. Palladium (Pd)-catalyzed asymmetric allylic substitutions constitute one of the most powerful and direct tools for the stereoselective construction of carbon−carbon and carbon−heteroatom bonds.[86,111−113]

4.3.1. Allylation. In 2020, Yu and co-workers described an enantioselective α-allylation of *N*-methyl anilines via combining palladium and photoredox catalysis (Scheme 9).[114] In this study,

Scheme 9. Asymmetric Functionalization of C(sp^3)−H Bond via Pd-Metallaphotocatalysis[a]



[a]PC, photocatalyst and SET, single-electron transfer.

the amines were activated by a photoredox catalyzed single-electron oxidation/deprotonation process to form the α-amino alkyl radical intermediates. Subsequent capture by chiral allylPd (III) complex delivered a range of chiral homoallylic amines in moderate to good yields with excellent enantioselectivities and regi-oselectivities.

4.4. Asymmetric Cr-metallaphotoredox catalysis. *4.4.1. Hydroxyalkylation.* In 2019, the Kanai group[115] developed an enantioselective hydroxyalkylation of allylic C−H bonds via cooperative organophotoredox and chiral chromium hybrid catalysis (Scheme 10). The allylic C(sp^3)−H bond was activated by organophotoredox catalysis to generate the allylic radical species, which then engaged with the Cr catalyst to form chiral allyl chromium nucleophiles. Coupling with aldehyde produced a variety of enantioenriched homoallylic alcohols.

5. ASYMMETRIC RADICAL−RADICAL CROSS-COUPLING

5.1. Asymmetric α-Functionalization of C(sp^3)−H Bond via Radical−Radical Cross-Coupling. In 2015, the Ooi group reported an enantioselective radical−radical coupling

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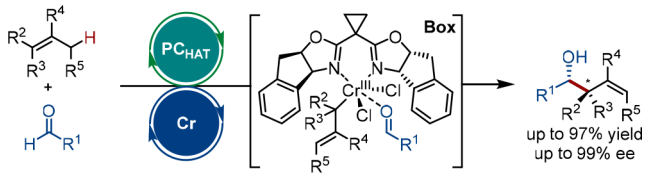
Scheme 10. Asymmetric Functionalization of C(sp^3)−H Bond via Cr-Metallaphotocatalysis[a]



[a]HAT, hydrogen-atom transfer and PC, photocatalyst.

of *N*-arylaminomethanes with *N*-sulfonyl aldimines by combining photoredox catalysis and ionic Brønsted acid catalysis (Scheme 11a).[116] A range of enantioenriched 1,2-diamine derivatives were successfully obtained via this strategy under visible-light irradiation. This mode of synergistic catalysis provides a novel opportunity for the development of photoinduced enantioselective radical transformation.

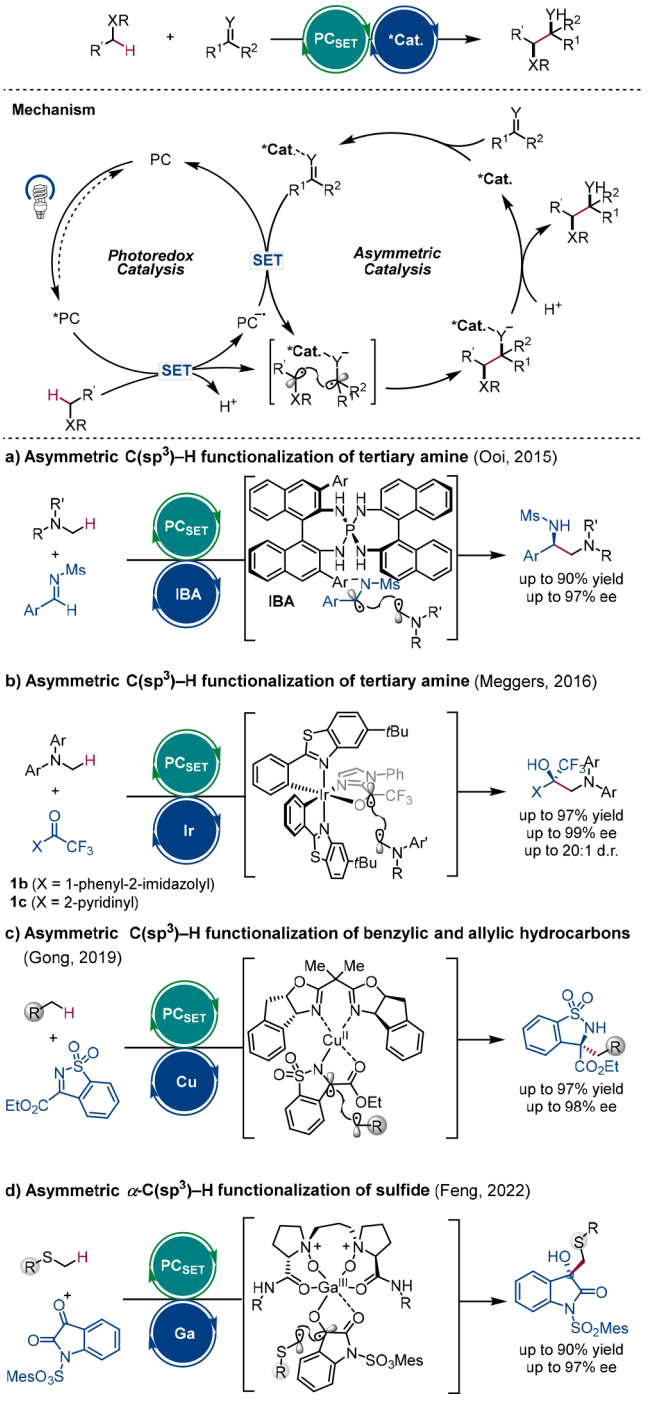
Subsequently, the Meggers group successfully developed an enantioselective radical−radical cross-coupling of trifluoromethyl ketones and tertiary amines via visible-light activated iridium catalysis (Scheme 11b).[117] Utilizing a chiral iridium complex that functions as both a Lewis acid and a photoredox catalyst, a wide range of 1,2-amino alcohols was synthesized with high enantioselectivities reaching up to 99% ee.

In 2019, the Gong group reported a photocatalytic regioselective and stereoselective C(sp^3)−H functionalization of inert C(sp^3)−H bonds through asymmetric radical−radical cross-coupling (Scheme 11c).[118] In this catalytic system, the activation of the C(sp^3)−H bond was accomplished by employing the HAT of an excited photocatalyst to generate alkyl radical intermediates. The imine partner coordinating with the chiral Lewis catalyst was reduced by a reductive photocatalyst to form another radical species. Ultimately, the stereoselective recombination of these radical species furnished a range of functionalized chiral products.

Last year, the Feng and Liu group employed this strategy to accomplish the chemo-, site-, and stereoselective α-C(sp^3)−H functionalization of sulfides (Scheme 11d).[119] In this transformation, isatins simultaneously served as a photoredox catalyst and coupling partner, while the stereocontrol mainly depended on the chiral gallium(III)-*N*,*N*′-dioxide complex. Importantly, this protocol provided an efficient way for the direct late-stage functionalization of methionine-related peptides, regardless of diverse residues, inherent structural similarity, and complexity.

5.2. Asymmetric β-C(sp^3)−H Functionalization of Ketone via Radical−Radical Cross-Coupling. Visible-light induced radical−radical cross-coupling reaction provides an alternative way to directly functionalize C−H bonds,[120] but controlling the stereoselectivity is challenging. In 2013, the MacMillan group first reported the asymmetric C−H arylation of ketones via photoredox catalysis in combination with a cinchona-derived aminocatalyst (Scheme 12a).[121] Mechanistic investigation indicated that the combination of photoredox catalysis and organocatalysis enabled the transient generation of 5-π electron β-enamine radicals from ketones and aldehydes, which could rapidly couple with cyano-substituted aryl rings at the carbonyl β-position. Although a modest enantioselectivity of 50% ee was obtained, this protocol opened a new avenue for the enantioselective functionalization of the aliphatic C−H bond. Henceforth, a range of novel enantioselective C(sp^3)−H functionalization methods have been established over the recent decade.

Scheme 11. Asymmetric α-Functionalization of C(sp^3)−H Bond via Radical−Radical Cross-Coupling[a]



[a]HAT, hydrogen-atom transfer; PC, photocatalyst; and IBA, ionic Brøsted acid.

The Meggers group presented a visible-light-mediated asymmetric β-C(sp^3)−H functionalization of 2-acyl imidazoles and 2-acylpyridines with 1,2-dicarbonyl compounds catalyzed by a chiral-at-rhodium Lewis acid catalyst (Scheme 12b).[122] Mechanistic studies indicated that the photoactivated Rh-enolate transferred a single electron to the 1,2-dicarbonyl compound followed by proton transfer to form alkyl radical and ketyl radical, which then underwent a stereocontrolled radical−radical cross-coupling to form C−H functionalization products

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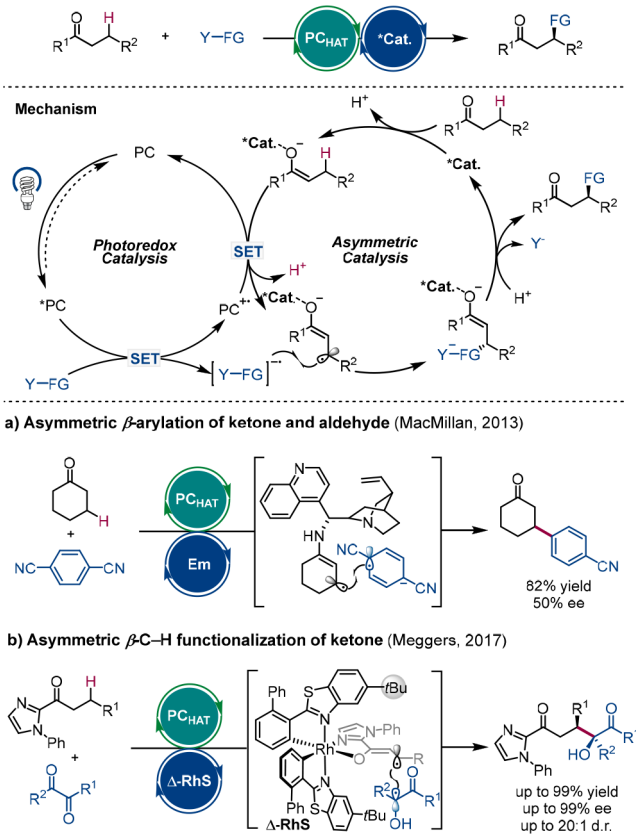
Scheme 12. Asymmetric β-C(sp^3)−H Functionalization of Ketones via Radical−Radical Cross-Coupling[a]



[a]Em, enamine; FG, functional group; HAT, hydrogen-atom transfer; and PC, photocatalyst.

in high yields (up to 99%) with excellent stereoselectivities (up to >20:1 diastereomeric ratio and up to >99% ee).

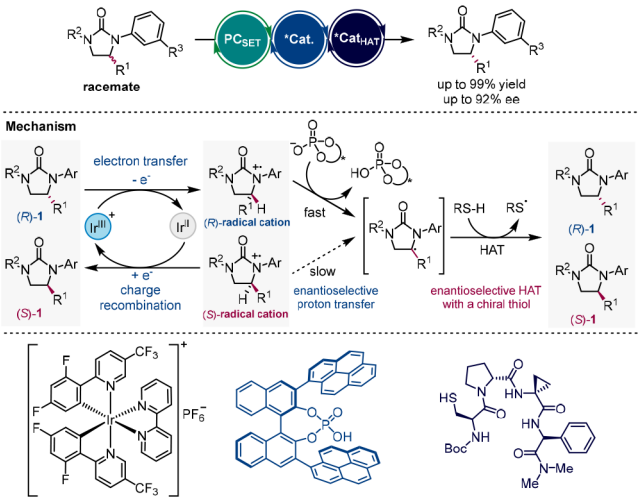
6. PHOTOCATALYZED ASYMMETRIC DERACEMIZATION REACTION

Deracemization, which converts a racemate compound into its single enantiomer, is an attractive strategy for accessing enantioenriched compounds.[123−125] In 2019, the Miller and Knowles group developed an elegant deracemization method that enabled racemic amine derivatives to spontaneously transform into optically enriched amines with the irradiation of visible light in the presence of three different molecular catalysts (Scheme 13).[123] This reaction underwent a sequential photodriven SET/deprotonation/HAT process, which was used to break and reconstruct a stereogenic C(sp^3)−H bond. The key to obtaining enantioenriched products was the ingenious combination of two distinct stereoselective steps, in which the enantioselective deprotonation of radical cation intermediate delivered a chiral radical species and subsequently produced optically pure amine derivatives through the enantioselective HAT event. This study presents a distinct deracemization strategy through the merger of photoredox catalysis, chiral phosphate base, and peptide thiol catalysis.

7. CONCLUSIONS AND PERSPECTIVE

In conclusion, significant advancements have been made in the field of enantioselective functionalization of C(sp^3)−H bonds via visible-light photocatalysis during recent years. These

Scheme 13. Photocatalyzed Asymmetric Deracemization of Amines[a]



[a]HAT, hydrogen-atom transfer and PC, photocatalyst.

developments have opened up new opportunities in organic synthetic chemistry and sparked interest in this emerging area. As illustrated in Scheme 14, numerous elegant methods, distinguished by different C(sp^3)−H substrates and functional reagents, have been established by merging photocatalysis with asymmetric catalysis. This integration enables the generation of a wide range of enantioenriched products directly from readily available C(sp^3)−H substrates without the need for cumbersome prefunctionalization steps. Several methods are particularly suitable for natural products and pharmaceutical molecules, demonstrating great potential for late-stage functionalization. Nevertheless, solutions to the main challenges discussed below are still necessary for the widespread application of these methods.

(1) Enantioselective functionalization of unactivated C-(sp^3)−H bonds for constructing stereocenters on the original carbons has posed a formidable challenge. Unactivated C(sp^3)−H bonds are more widely distributed in the organic compound compared to activated ones. However, the absence of stabilizing interactions from functional groups renders the intermediate species derived from C(sp^3)−H bonds highly unstable. As a result, the enantioselective functionalization of remote and unactivated C(sp^3)−H bonds using this strategy is still scarce.

(2) Enantioselective functionalization of C(sp^3)−H bonds with heteroatom-based functional groups is still in its nascent stages. Heteroatoms (N, O, S, P, and halogens) are fundamental elements in organic chemistry that contribute to the formation of various chiral bioactive or functional compounds when embedded into the carbon skeleton, such as amines and alcohols. Moreover, they can serve as starting functionalities for further transformations to augment molecular complexity and construct compound libraries. However, there are limited methods to enantioselectively construct C−X bonds from C(sp^3)−H bonds by photocatalysis. Therefore, there is an ongoing need for dedicated effort toward efficient enantioselective functionalization of C(sp^3)−H bonds.

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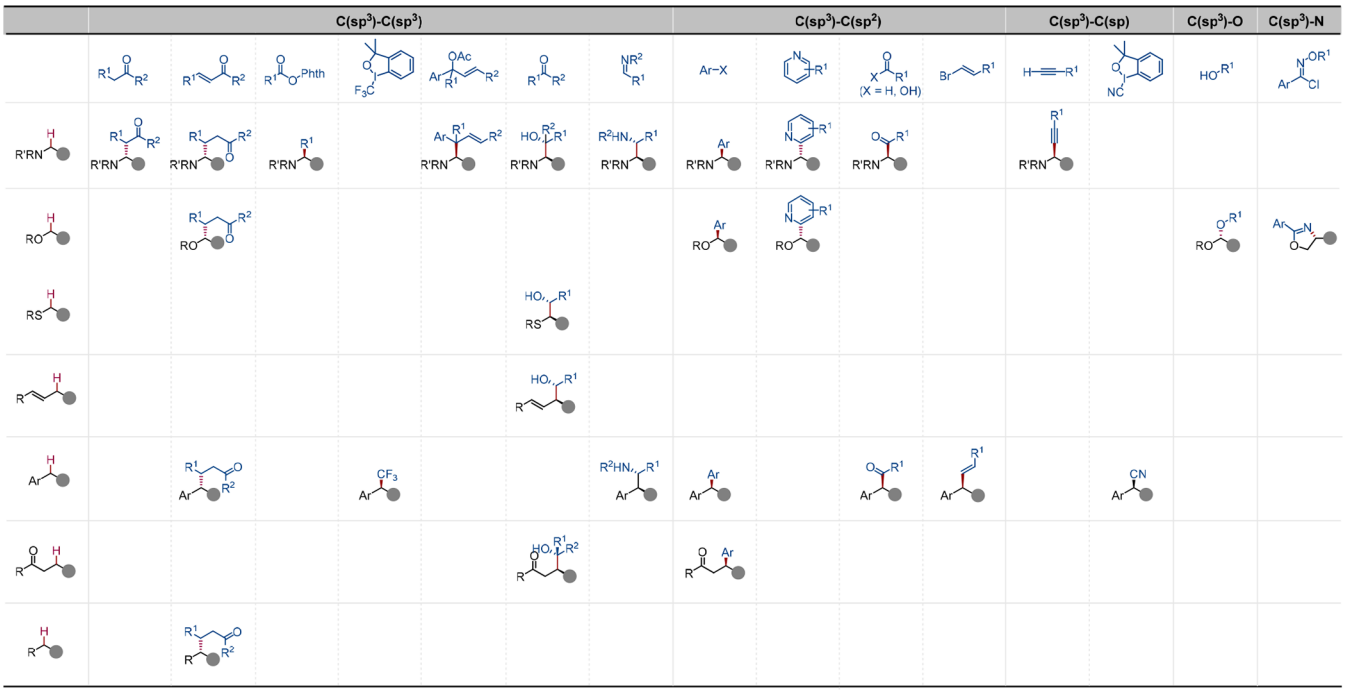
Scheme 14. Overview of Enantioselective C(sp^3)−H Functionalization via Photocatalysis



(3) Enantioconvergent functionalization of racemic tertiary C(sp^3)−H bonds remains largely underexplored. The creation of chiral quaternary carbon centers poses a formidable challenge in organic synthesis.[126] The direct enantioselective functionalization of these racemic tertiary C(sp^3)−H bonds represents an appealing strategy for constructing this valuable skeleton. While the majority of reported methods involving photocatalyzed enantioselective C−H functionalization concentrate on the primary or secondary C(sp^3)−H bonds, successful examples involving tertiary C−H bonds are scarce. Hence, it is imperative to further develop enantioselective functionalization of racemic tertiary C(sp^3)−H bonds.

(4) Enantioselective dual functionalization of C(sp^3)−H bonds has not been reported so far. Dual C−H functionalization offers a straightforward way for constructing cyclic compounds from C−H substrates.[127,128] However, compared to single C(sp^3)−H functionalization, this strategy poses greater challenges due to the requirement of simultaneous activation of two inert C−H bonds with selectivity. Despite a few recent examples, achieving enantioselective versions continues to be a significant challenge.

To address these daunting challenges associated with the enantioselective functionalization of the C(sp^3)−H bond, several promising directions deserve more attention.

First, the development of more efficient and robust photocatalysts, especially chiral ones, is still required to enhance the egio-, diastereo, and enantioselectivity of the C(sp^3)−H functionalization reactions. At present, photocatalysts commonly used in asymmetric functionalization of the C(sp^3)−H bond are achiral. Despite showing promising potential in asymmetric photocatalytic reactions, chiral photocatalysts are rarely used in enantioselective functionalization of the C(sp^3)−H bond, primarily due to the lack of sufficient chiral photocatalysts.[15,129] Consequently, the exploration of novel robust (chiral) photocatalysts for the high regio-, diastereo-, and enantioselective functionalization of the C(sp^3)−H bond is particularly urgent in this field.

Second, there is still a need for the development of novel stereocontrolling models to enable enantioselective functionalization of C(sp^3)−H bonds. For instance, biocatalysis offers several advantages such as high catalytic efficiency, strong substrate specificity, and mild reaction conditions, which are particularly valuable for directly introducing functional groups into complex scaffolds, as well as rapidly diversifying compound libraries.[130−132] Therefore, the merger of photocatalysis with biocatalysis could potentially provide a fresh solution for achieving enantioselective functionalization of C(sp^3)−H bonds in complex molecules.

Third, photoelectrocatalysis offers a more sustainable platform for the enantioselective functionalization of C(sp^3)−H bonds. By harnessing the combined power of light and electrical energy, photoelectrocatalysis allows for the direct functionalization of C−H bonds without relying on external stoichiometric chemical oxidants.[133,134] Recently, several methods based on this emerging technology have been established for the direct functionalization of C−H bonds. However, achieving photoelectrocatalyzed functionalization of inert C(sp^3)−H bonds remains a challenge. Thus, there is also a bright approach for the enantioselective functionalization of C(sp^3)−H bonds via merging photoelectrocatalysis with asymmetric catalysis in the future.

Finally, there is a strong demand for mechanistic insights and selectivity predictions in the enantioselective functionalization of C(sp^3)−H bonds. While several reactions involving the photocatalyzed enantioselective functionalization of C(sp^3)−H bonds have been reported in recent years, predicting the reactive site and enantioselectivity of these reactions remains a formidable challenge. Data science provides an efficient tool for catalysts and ligands design, reaction mechanisms understanding, and new reactions development.[135−137] Therefore, it is imperative to employ data science to gain mechanistic insights

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and predict regio- diastereo-, and enantioselectivity in future enantioselective C(sp^3)−H functionalization.

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Notes

The authors declare no competing financial interest.

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