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Carbonylation involving organocopper intermediates

Zhi-Peng Bao[ab] and Xiao-Feng Wu *[ab]

Developing economical and environmentally friendly carbonylation synthetic methods is an important and challenging goal. Exploring the application of non-precious metal catalysts in synthetic chemistry has proven to be an ideal choice due to their abundancy, low cost, and low toxicity. In recent years, as copper is one of the cheaper metals, copper catalysts have been widely used in the field of carbonylative transformations. In this review, case-by-case reaction modes and mechanisms are summarized and discussed, along with a personal perspective. Various organocopper intermediates were produced from the single-electron reduction of alkyl halides, capturing radicals from the oxidation of carbon-hydrogen bonds, transmetalation, and active copper species addition to unsaturated bonds (active Cu–H, Cu–Bpin or Cu–Si intermediate), and then, different organocopper intermediates can result from nucleophilic quenching, electrophilic quenching, transmetalation, isomerization to carbene, *etc.*

Broader context

Carbonylative transformation is an important strategy for the preparation of carbonylated compounds with CO as the C1 source. This methodology is usually catalysed by expensive noble metal catalysts. Copper catalysts have been explored as an alternative because of its low cost and to further advance the understanding of catalyst design. In this review, case-by-case reaction modes and mechanisms are summarized and discussed, along with a personal perspective. Various organocopper intermediates were produced from the single-electron reduction of alkyl halides, capturing radical from the oxidation of carbon–hydrogen bonds, transmetalation, and active copper species addition to unsaturated bonds (active Cu–H, Cu–Bpin or Cu–Si intermediate), and then, different organocopper intermediates can result from nucleophilic quenching, electrophilic quenching, transmetalation, isomerization to carbene, *etc.* This review will inspire the further development of carbonylation chemistry.

1. Introduction

Carbonyl-containing compounds are widely present in natural products, pharmaceuticals, agrochemicals, and polymers.[1] As a versatile functional group, the carbonyl moiety can undergo diverse transformations to easily increase molecular complexity, offering a valuable platform for synthetic chemistry.[2] According to FDA statistics from 2015 to 2020, approximately 80% of approved drugs contain carbonyl functional groups.[3] For instance, *Eliquis* (ranked second in 2024 retail drug sales for thrombosis prevention) and *Revlimid* (ranked 28th for multiple myeloma treatment) each contain three or more carbonyl groups, with market values of $20.699 billion and $5.809 billion, respectively.[4] In synthetic chemistry, carbonylation technologies provide one of the most efficient and atom-economical methods for constructing carbonyl compounds.[5] These processes convert carbon monoxide—derived from coal, natural gas, or biomass—into value-added carbonylated products with 100% atom utilization.[6] One of the most renowned examples is the carbonylation of methanol to produce acetic acid, as exemplified by the Monsanto and Cativa processes.[7,8] Notably, a majority of the world's acetic acid is currently produced *via* methanol carbonylation.[9] Another valuable application is the synthesis of methyl methacrylate (MMA), a key monomer for the production of poly(methyl methacrylate) (PMMA), with a global annual production of approximately 4 million tons.[10] Among current technologies, ethylene carbonylation has emerged as one of the most attractive methods due to its high cost-effectiveness and excellent atom economy.[11]

In the historical development of carbonylation technologies, palladium-catalyzed carbonylation has emerged as one of the most mature and well-established systems.[12] As early as 1974, the Heck group reported the first palladium-catalyzed carbonylation of aryl halides and benzyl halogenated compounds.[13] Later, Ryu and co-workers presented their pioneering study on the free-radical-mediated carbonylation of unactivated alkyl halides.[14] Since then, Pd–H catalytic systems have witnessed explosive growth.[15–25] A remarkable example was reported in 2019 by the Beller group, who designed a series of original pyridyl-substituted bidentate phosphine ligands to achieve the highly efficient synthesis of the nylon-66 monomer *via* double carbonylation of 1,3-butadiene, successfully addressing a long-standing scientific challenge that had persisted for nearly a century (Fig. 1).[26]

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[a] *Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, China. E-mail: xwu2020@dicp.ac.cn*

[b] *Leibniz-Institute für Katalyse e. V., 18059 Rostock, Germany*

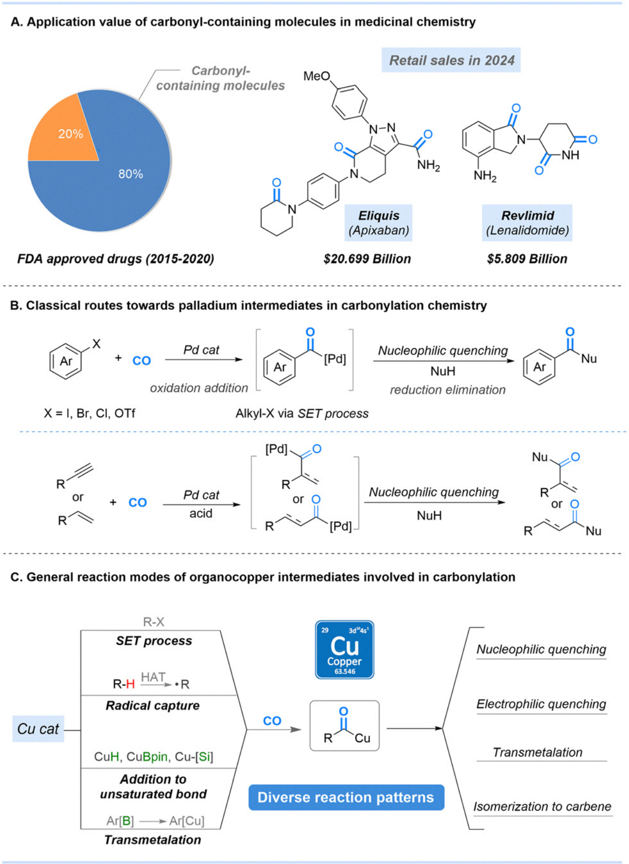

Fig. 1 Importance of carbonyl-containing molecules and diverse reaction modes in carbonylation chemistry by Pd or Cu catalysis.

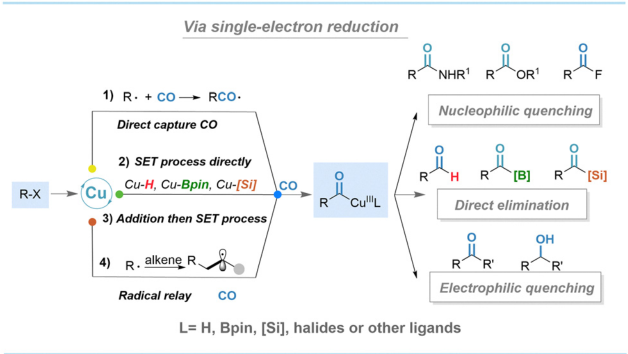

Fig. 2 Diverse types of single-electron reduction processes of organic halides.

In the past decade, copper-catalyzed carbonylation systems have flourished, paralleling the rapid progress seen in palladium-catalyzed carbonylation.[27] These copper-based systems exhibit greater diversity in reaction modes. As a cheap and earth-abundant 3d transition metal—with an estimated crustal abundance of approximately 0.01%—copper has attracted significant interest from the chemical community. Numerous copper-catalyzed carbonylation reactions have been developed. In this work, we categorize these transformations based on their mechanistic features, particularly focusing on the formation and subsequent quenching of organocopper intermediates (Fig. 2). This mechanistic framework facilitates a deeper understanding for readers and may inspire exploration into new areas of chemical space. Overall, these carbonylation pathways can be broadly divided into four types: (I) single-electron reduction processes of organic halides and related compounds; (II) radical capture from the HAT process and other routes; (III) addition of reactive copper species (Cu–H, Cu–Bpin, Cu–[Si], *etc.*) to unsaturated bonds; (IV) transmetalation pathways.

2. Single electron reduction of organic halides

The single-electron reduction of organic halides typically involves activation of C(sp^3)–X and N–X bonds. This strategy

Zhi-Peng Bao

Zhi-Peng Bao was born in Anhui, China, in 1996. He received his MS degree in 2021 from Zhejiang Sci-Tech University. He is currently pursuing his PhD degree in a joint training program at the Leibniz Institute for Catalysis (Germany) and the Dalian Institute of Chemical Physics (DICP) under the supervision of Prof. Xiao-Feng Wu. His current research interests focus on the palladium-catalyzed carbonylation of activated alkyl halides.

Xiao-Feng Wu

Xiao-Feng Wu was born and raised in China. After being educated and trained at China (Zhejiang Sci-Tech University), France (Rennes 1 University) and Germany (Leibniz-Institute for Catalysis), he started his independent research at LIKAT and ZSTU, where he was promoted to professor in 2013. Afterwards, he defended his Habilitation from Rennes 1 University (2017). In 2020, he joined the Dalian Institute of Chemical Physics (DICP) and established a research group focusing on light carbon transformation and practical synthesis. Xiao-Feng Wu has authored more than 660 publications, edited more than 10 books and filed many patents. He has also been honored with various awards.

utilizes a single-electron transfer (SET) process to generate carbon-centered radicals, which then engage in subsequent additions to metal species or carbon monoxide, ultimately forming acyl copper intermediates. These intermediates can undergo either nucleophilic trapping or direct reductive elimination to afford the final products. This reaction mode can be broadly categorized into four types: (1) the carbon radical generated *via* a SET process directly captures CO, followed by nucleophilic trapping to afford amides, esters, or acyl fluorides; (2) a reactive copper species initiates the SET activation of alkyl halides, leading to the formation of acyl copper intermediates, which subsequently undergo reductive elimination to give acylboronates, acylsilanes, aldehyde intermediates, or other products; (3) a reactive copper species facilitates the addition of unsaturated bonds, and then, the SET process takes place; (4) in radical relay processes, a carbon radical is first added to alkenes, generating a new radical that is captured by a copper catalyst. CO is then incorporated either through radical addition or metal coordination, forming an acyl copper intermediate that is ultimately quenched by nucleophiles.

2.1 Nucleophilic quenching of organocopper intermediates

The capture of CO by carbon radicals generated *via* the single-electron reduction of alkyl halides can proceed through different pathways, depending on the mode of quenching and the nature of the nucleophile. These variations will be discussed in detail below. In 2022, our group developed a copper-catalyzed, substrate-controlled mono- and double-carbonylation strategy that efficiently converted alkyl halides and amines into α-keto-amides and amides.[28] This method exhibits excellent selectivity for alkyl bromides, exclusively affording the double-carbonylated products. In contrast, alkyl iodides allow for selective control between mono- and double-carbonylation under specific conditions. As illustrated in Fig. 3, the reaction begins with the coordination of CO to the copper salt, forming a Cu–(CO) species (**3-B**). In the presence of a base, a nucleophilic attack by the amine on the coordinated CO generates intermediate **3-C**. Alternatively, the amine may undergo anionic ligand exchange with **3-B** to yield an aminocopper(I) species (**3-C′**). These intermediates (**3-C** or **3-C′**) then participate in a single-electron reduction of the alkyl bromide, leading to the formation of a radical intermediate and **3-D**, and an acyl radical intermediate is given under a CO atmosphere. Then, the acyl radical reacts with **3-D** to form the key intermediate **3-E**, which undergoes reductive elimination to release the α-ketoamide product and regenerate the catalyst **3-A**. On the other hand, due to the higher reactivity of alkyl iodides compared to bromides, activation of the alkyl iodide may occur prior to nucleophilic attack by the amine, resulting in intermediate **3-F**. This species reacts with the acyl radical to form intermediate **3-G**. In the presence of a base, anionic ligand exchange on copper generates intermediate **3-H**, which undergoes reductive elimination to afford the amide product and regenerate catalyst **3-B**. Additionally, nucleophilic attack of the amine on coordinated CO in **3-G** may occur, forming intermediate **3-E** and leading to the α-ketoamide as a competing product.

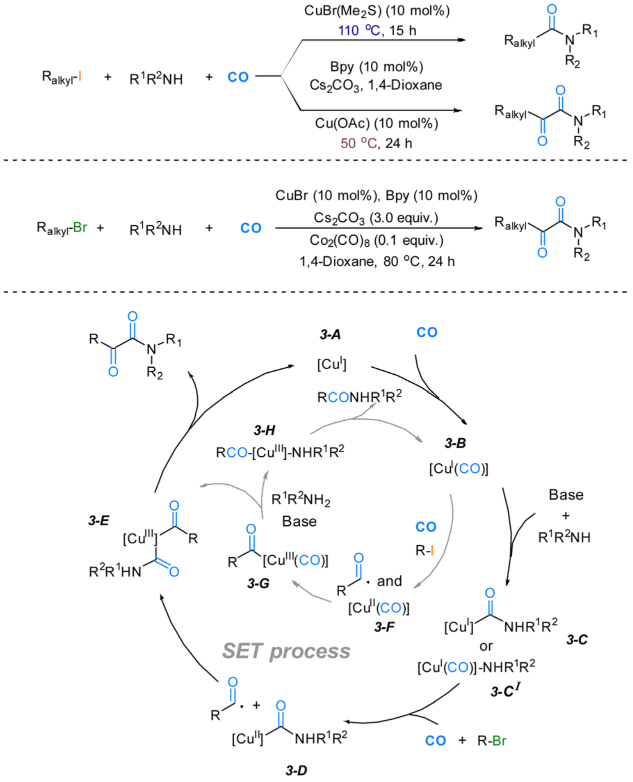

Fig. 3 Copper-catalyzed direct mono- and double-carbonylation reactions.

Anhydrides play a significant industrial role due to their wide applications in the synthesis of polymers, pharmaceuticals, and other commodity chemicals.[29] For example, acetic anhydride (Ac_2O) is especially critical in the wood industry, where its hydrophobic nature makes it an effective protective coating.[30] Therefore, developing convenient and efficient methods for synthesizing commodity anhydrides is of great interest. However, traditional synthetic routes often involve multiple steps and rely on precious metal catalysts. Acetic anhydride is currently produced on an industrial scale *via* a two-step rhodium-catalyzed carbonylation technique, and is widely used in the synthesis of important products like aspirin.[31] In 2023, Mankad reported a copper-catalyzed carbonylation of alkyl halides to aliphatic anhydrides *via* a single-electron transfer (SET) mechanism.[32] The proposed mechanism is illustrated in Fig. 4. Under 390 nm light irradiation, the copper catalyst **4-A** absorbs a photon to generate the excited state **4-B**. This excited [Cu]* species possesses sufficient reducing power to engage in SET with alkyl halides, producing intermediate **4-C** and an alkyl radical. The alkyl radical then reacts with CO to afford an acyl radical. The combination of **4-C** with the acyl radical yields intermediate **4-D**, which undergoes reductive elimination to furnish the corresponding acyl halide. Subsequently, the acyl halide reacts with K_2CO_3, undergoing decarboxylation to generate a carboxylate species. Finally, condensation between the carboxylate and acyl halide results in the formation of the corresponding anhydride product.

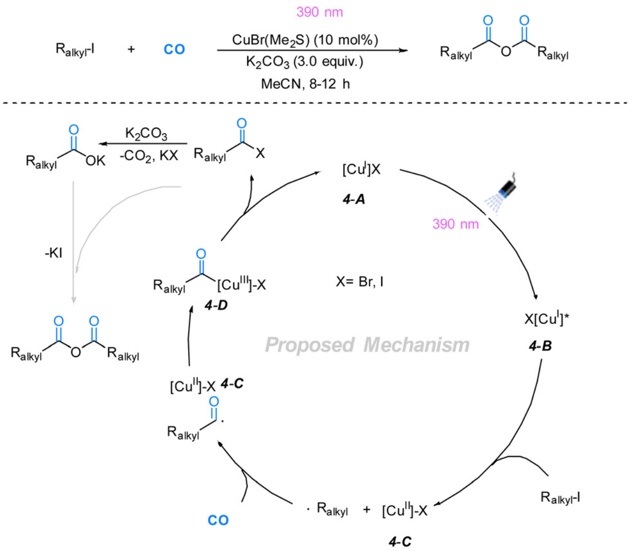

Fig. 4 Copper-catalyzed direct carbonylation for the synthesis of the anhydrides.

In 2024, the same group reported a copper-catalyzed carbonylation for the synthesis of acyl fluorides.[33] It is similar to the mechanism proposed above, as this transformation also proceeds *via* a single-electron reduction pathway. However, the key difference lies in the quenching step, where a fluoride anion is employed as the nucleophile (Fig. 5).

In addition to the novel copper-catalyzed carbonylation pathways of alkyl iodide and alkyl bromide proceeding *via* SET processes described above, other reaction routes have been developed. For example, alkyl fluorides can be transformed into alkyl iodides through halogen exchange, followed by a similar SET-based carbonylation mechanism.[34] Alternatively, the nucleophile in the quenching step can be replaced with alcohols,[35–38] nitroarenes,[39] arylboronic acids[40] and others,[41–43] to access a broader range of carbonyl-containing products (Fig. 6).

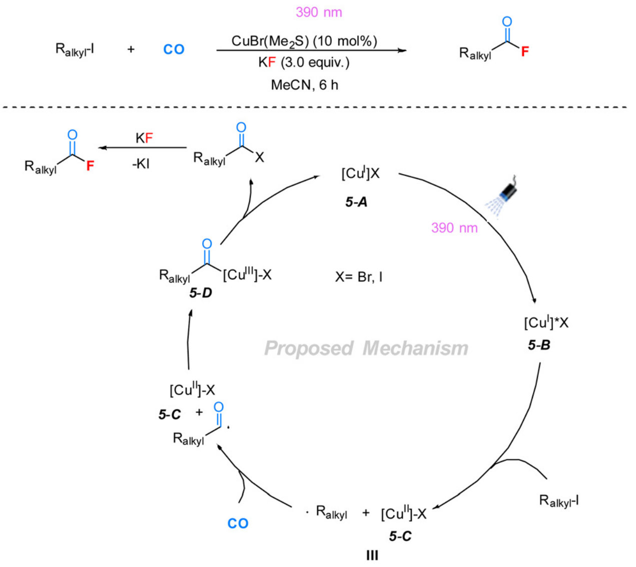

Fig. 5 Copper-catalyzed direct carbonylation for the synthesis of the acyl fluorides.

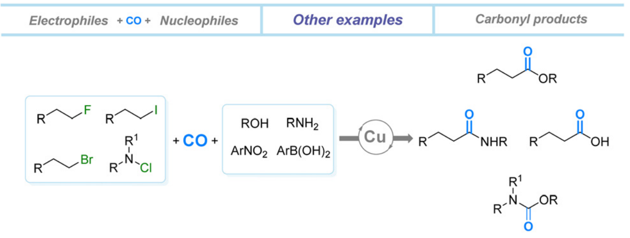

Fig. 6 Other examples of the SET process of organic halides towards carbonyl compounds.

2.2 Active copper species-mediated SET process of halides (direct elimination)

In recent years, active copper species have found widespread applications in organic catalysis. Key reactive intermediates include Cu–Bpin, Cu–[Si], and Cu–H, each of which exhibits distinct reactivity profiles. These species have also demonstrated unique modes of reactivity in the field of carbonylation chemistry. In the following sections, we will discuss carbonylation processes mediated by active copper species, particularly those involving single-electron reduction.

In 2020, the Mankad group developed a novel copper-catalyzed carbonylative silylation of organic halides.[44] The proposed mechanism is illustrated in Fig. 7. Initially, in the presence of a base, $PhMe_2Si$–Bpin undergoes transmetallation with the copper(I) species **7-A** to form a silyl–copper(I) complex **7-B**. Subsequently, **7-B** engages in a single-electron reduction with the alkyl halide, generating the corresponding alkyl radical ($R^\bullet$) and intermediate **7-C**. Under a CO atmosphere, the alkyl radical is rapidly converted into an acyl radical, which then combines with intermediate **7-C** to form the acyl copper species

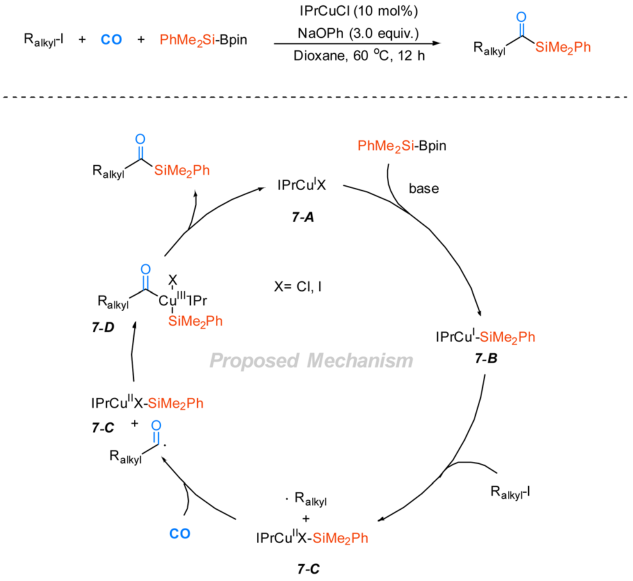

Fig. 7 Copper–silyl intermediate-mediated carbonylation toward acylsilane derivatives.

7-D, which is coordinated with a silicon-containing ligand. This is due to the reactivity of the acyl radical being higher under this condition. Finally, **7-D** undergoes reductive elimination to give the corresponding acylsilane product, regenerating the active copper(I) catalyst **7-A**.

In 2021, Mankad and co-workers developed an interesting copper-catalyzed carbonylative borylation of organic halides.[45] The proposed mechanism is illustrated in Fig. 8. Initially, in the presence of a base, B_2pin_2 undergoes transmetallation with the copper(I) catalyst **8-A** to form an active Cu(I)–Bpin species **8-B**. Subsequently, **8-B** engages in a single-electron reduction of the alkyl halide, generating an alkyl radical ($R^{\bullet}$) and the Cu(II) species **8-C**. Under a CO atmosphere, the alkyl radical rapidly captures CO to form an acyl radical, which then couples with intermediate **8-C** to afford the acyl–copper intermediate **8-D**, coordinated with a Bpin group. Reductive elimination from **8-D**, followed by post-reaction treatment, yields aliphatic potassium acyltrifluoroborates, while regenerating the active copper(I) catalyst **8-A**. An alternative pathway for radical generation may also be involved: LiOtBu reacts with B_2pin_2 to generate a reactive intermediate **8-E**, which can reduce the alkyl halide *via* the SET process to form the corresponding alkyl radical. It is worth noting that the intermediate R–CO–Bpin is not stable under these reaction conditions, and thus requires appropriate post-treatment for successful detection of the product.

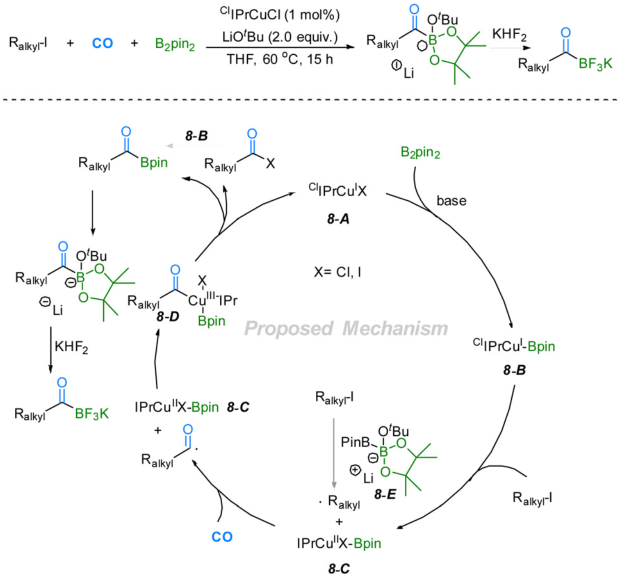

Fig. 8 Carbonylative transformation involving Cu–Bpin intermediates toward acylboron derivatives.

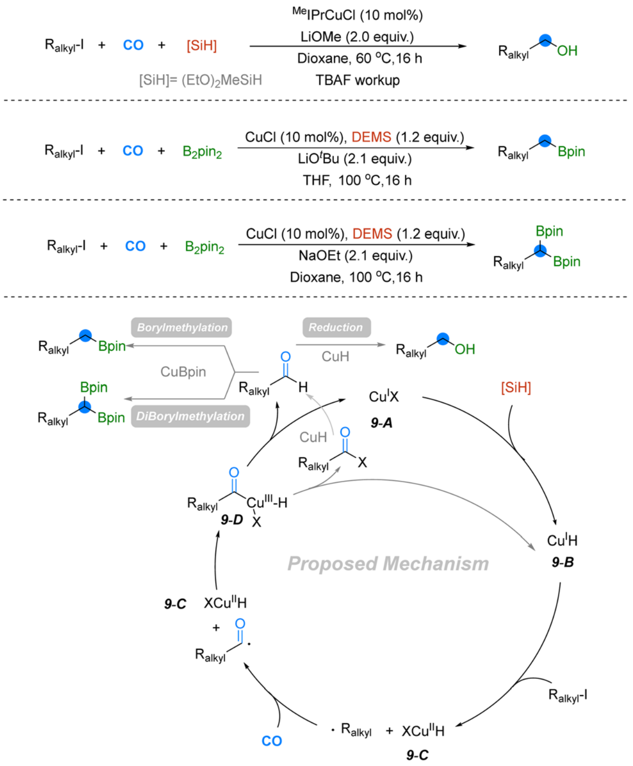

Fig. 9 Carbonylative transformation of alkyl iodides involving Cu–H intermediates.

In addition to Cu–Si and Cu–Bpin intermediates, Cu–H species have emerged as a focal point in carbonylation chemistry. As early as 2018, the Mankad group reported a copper-catalyzed hydroxymethylation of unactivated alkyl iodides.[46] Later, in 2021, Wu and co-workers developed a borylative methylation process that simultaneously employed both Cu–Bpin and Cu–H intermediates.[47] In this catalytic system, the reaction between Cu–H and alkyl iodides proceeds faster than that with Cu–Bpin. A more detailed mechanistic pathway is illustrated as follows: first, in the presence of a silane, the copper catalyst **9-A** reacts to form a Cu–H species **9-B**. This Cu–H species undergoes single-electron reduction of the alkyl iodide, generating a carbon-centered radical and the intermediate **9-C**. Under a CO atmosphere, the carbon radical rapidly captures CO to form an acyl radical, which then couples with **9-C** to afford the acyl-copper intermediate **9-D**. Reductive elimination from **9-D** gives either an acyl halide or an aldehyde, along with regeneration of the active copper species **9-A** or **9-B**. The resulting acyl halide can be further reduced by Cu–H to yield the corresponding aldehyde. This aldehyde may then undergo further transformations, including reduction to one-carbon-extended alcohols, borylmethylation to borane compounds, or diborylmethylation to give diborane derivatives (Fig. 9).

2.3 Addition of unsaturated bonds, then SET process (electrophilic quenching)

Active copper species made their first appearance in carbonylation chemistry in 2017, when Mankad and co-workers reported on the copper-catalyzed hydrocarbonylation of terminal alkynes for the synthesis of unsymmetrical dialkyl ketones and allylic alcohol derivatives.[48,49] By controlling the reaction temperature, they further achieved either 1,4- or 1,2-addition of Cu–H species to the resulting enone intermediate, leading to two distinct types of products. As illustrated in Fig. 10, IPrCuCl first reacts with a base to form IPrCuOMe, which then undergoes

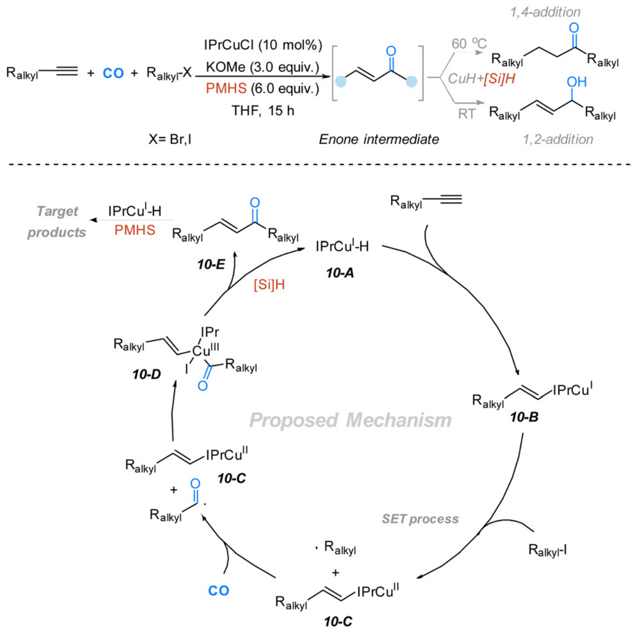

Fig. 10 Copper-catalyzed hydrocarbonylative coupling of alkynes (CuH addition to alkynes).

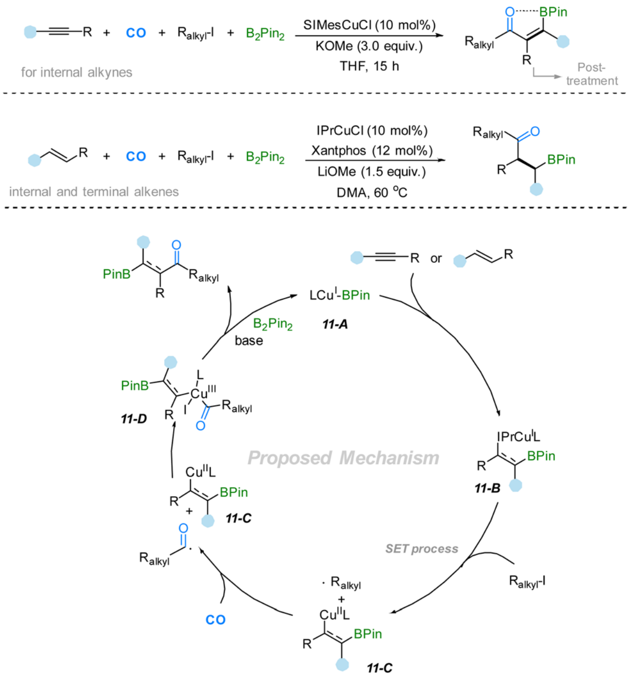

Fig. 11 Copper-catalyzed borocarbonylative coupling of alkynes and alkenes (CuBpin addition to alkynes and alkenes).

transmetallation with a silane to generate the active Cu–H species **10-A**. This species adds across the terminal alkyne to give the alkenyl copper intermediate **10-B**. Subsequently, **10-B** engages in a single-electron reduction of the alkyl iodide, forming intermediate **10-C** and an alkyl radical. In the presence of CO, the alkyl radical rapidly adds CO to form an acyl radical, which then combines with **10-C** to afford the Cu(III) intermediate **10-D**. Reductive elimination from **10-D** yields the α,β-unsaturated ketone **10-E** and regenerates the Cu(I) catalyst, which re-enters the catalytic cycle *via* reaction with a base and silane to form IPrCuH. The enone **10-E** then undergoes further functionalization. At 60 °C, it undergoes 1,4-addition with Cu–H, followed by silane quenching to afford unsymmetrical dialkyl ketones. Alternatively, at room temperature, **10-E** undergoes 1,2-addition with Cu–H, and subsequent quenching with silane gives allylic alcohol derivatives.

Following CuH-mediated hydrocarbonylation, copper-catalyzed borocarbonylative couplings of alkynes and alkenes have also been reported.[50,51] As illustrated in Fig. 11, the reaction begins with the generation of a (L)CuOMe complex *via* the reaction of a Cu(I) catalyst with a base and ligand. This complex then undergoes transmetallation with B_2pin_2 to form the active (L)CuBpin species **11-A**. Next, the (L)CuBpin complex is inserted into the unsaturated bond of an alkyne or alkene, affording the organocopper intermediate **11-B**. Intermediate **11-B** then undergoes single-electron reduction of an alkyl iodide to generate intermediate **11-C** and an alkyl radical. Under a CO atmosphere, the alkyl radical is rapidly converted into an acyl radical, which subsequently couples with **11-C** to form intermediate **11-D**. Reductive elimination from **11-D** obtains boryl ketone derivatives and regenerates the Cu(I) catalyst. Then, the active (L)Cu–Bpin species **11-A** is regenerated *via* ligand exchange with a base and B_2pin_2, thus completing the catalytic cycle.

The selective control of catalytic transformation has attracted the attention of organic synthetic chemists, and has become a long-term goal in synthetic chemistry.[52] Among the four fundamental types of selectivity, regioselectivity—which governs the positional outcome of reactions near the reactive site—has been an active area of research in carbonylation chemistry. For example, in the palladium-catalyzed carbonylation of alkenes or alkynes, the selectivity between linear and branched products can be finely tuned using monodentate and bidentate phosphine ligands,[53] and we can influence *N*- *versus O*-nucleophilic selectivity by the electronic and steric properties of ligands and bases,[54] or the choice of solvent (Fig. 12 and 13).[55]

However, regioselective examples in copper-catalyzed carbonylation reactions remain scarce. Moreover, the reported unsaturated substrates are almost exclusively limited to alkenes and alkynes, and there are few examples for regioselective carbonylation of imines. This scarcity is attributed to the intrinsic electronic polarization of the C═N bond, which places a partial positive charge on the carbon position, rendering it electrophilic and thus prone to nucleophilic attack. This intrinsic polarization makes it challenging to achieve controlled and selective addition.[56]

In 2019, the Hou group reported an intriguing example involving the intramolecular 1,2-migration of a boryl group from carbon to nitrogen in imines.[57] However, regioselectivity in this transformation remained difficult to control. In 2021, Wu and co-workers reported a pioneering example of regioselective carbonylation of imines *via* copper catalysis.[58]

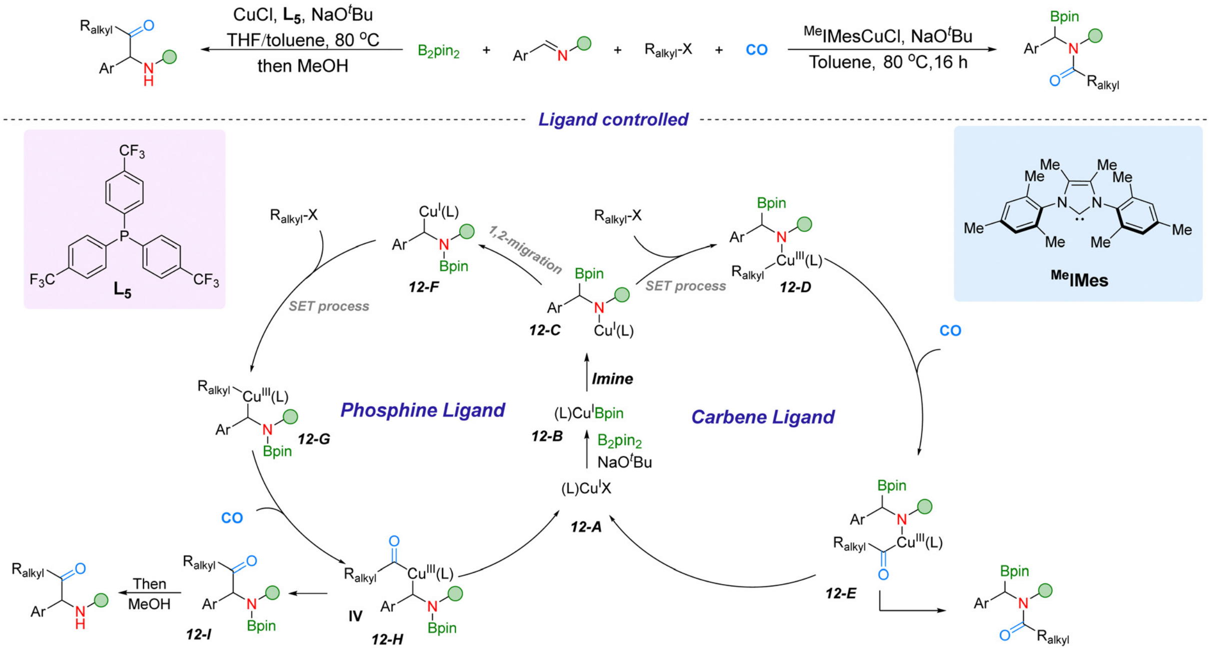

Fig. 12 Phosphine and NHC ligands modulate the formation of organocopper intermediates in the carbonylation chemistry.

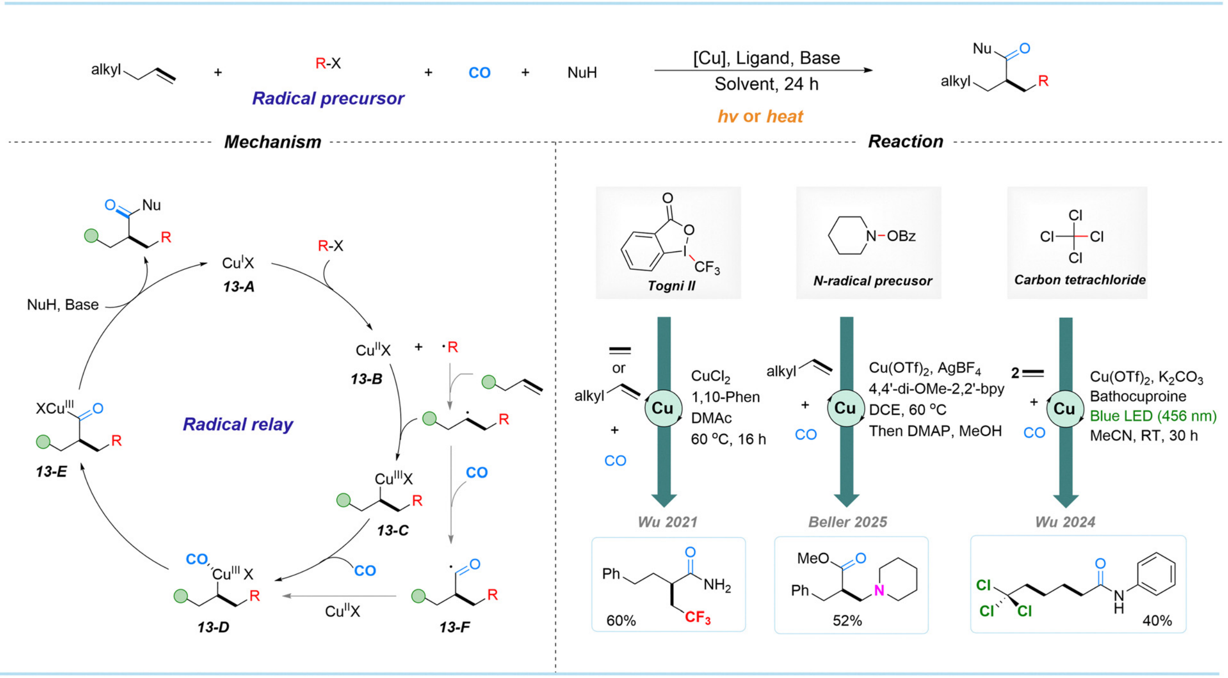

Fig. 13 Diverse copper-catalyzed carbonylation reactions enabled by the radical relay mechanism.

The detailed reaction mechanism is illustrated as follows: initially, the LCu–Bpin species **12-B** is generated from **12-A**, B_2pin_2, and a base, and is subsequently inserted into the C═N bond of the imine to form intermediate **12-C**. In the presence of electron-deficient ligands, the N–Cu bond in **12-C** is relatively weak, favoring an intramolecular 1,2-migration to yield intermediate **12-F**. This rearrangement is likely driven by the formation of a strong B–N bond. Alternatively, it is also possible that **12-F** is directly formed *via* the reaction between **12-B** and the imine. Next, **12-F** undergoes a single-electron process with an alkyl iodide to give intermediate **12-G**. Coordination of CO to **12-G**, followed by migratory insertion, yields the acyl copper species **12-H**. Reductive elimination and subsequent methanol quenching afford the corresponding α-aminoketone product, while regenerating

12-A to re-enter the catalytic cycle. In a parallel catalytic pathway, under the influence of a carbene ligand, the electron-rich copper intermediate **12-C** can directly engage in a single-electron transfer with an alkyl iodide to form intermediate **12-D**. After CO insertion, **12-E** is formed, which undergoes reductive elimination to deliver an alternative product-an α-borylamide.

2.4 Radical relay

Multicomponent reactions (MCRs), which combine three or more reactants in one reaction vessel to produce a single major product, represent an efficient and valuable strategy for constructing highly functionalized molecules from readily available building blocks.[59] Copper-catalyzed radical relay carbonylation reactions constitute a class of four-component transformations involving diverse radical precursors, alkenes, carbon monoxide, and nucleophiles. Representative radical precursors include fluoroalkyl sources such as Togni II reagents[60] or perfluoroalkyl halides,[61] nitrogen-centered radical precursors such as $RR^1N–OBz$,[62] trichloromethyl radical precursors such as carbon tetrachloride,[63] and others.[64,65]

Initially, the copper catalyst undergoes single-electron reduction of the radical precursor to generate the corresponding radical and the Cu(II) intermediate **13-B**. The radical is then added to an alkene, forming a new carbon-centered radical. This radical intermediate can recombine with **13-B** to generate an alkyl–copper(III) intermediate **13-C**, and it can also capture CO to give acyl radical **13-F**. Subsequent CO coordination affords the carbonylated Cu(III) complex **13-D**, which also can be formed from the acyl radical and **13-B**. Migratory insertion of CO yields intermediate **13-E**, which then undergoes reductive elimination in the presence of a nucleophile to deliver the final product, regenerating the Cu(I) catalyst. Notably, when the electronic nature of the radical precursor and alkene are mismatched, additives are often required. For example, activation of nitrogen-centered radical precursors may require the use of Lewis acids, which help modulate reactivity and enable the polarity-reversed addition of nucleophilic amino radicals to electron-rich alkenes.

In 2022, the Wu group developed a copper-catalyzed 1,2-dicarbonylative cyclization of alkenes *via* radical relay.[66] As illustrated in Fig. 14, this transformation represents a novel type of carbonylation reaction *via* a radical relay pathway. Initially, the alkyl bromide undergoes a single-electron transfer (SET) with a copper catalyst to generate an alkyl radical **14-A**. This radical is then captured by carbon monoxide to form an acyl radical **14-B**. Subsequently, **14-B** is added to an unactivated alkene, forming a new carbon-centered radical **14-C**. Then, a second CO molecule is incorporated by **14-C**, yielding another acyl radical intermediate **14-D**. This newly formed acyl radical undergoes electrophilic addition to an arene to **14-E**, followed by oxidation and rearomatization through deprotonation to deliver the final product. This transformation thus establishes a novel carbonylation strategy for the construction of 1,4-diketones *via* a radical cascade process.

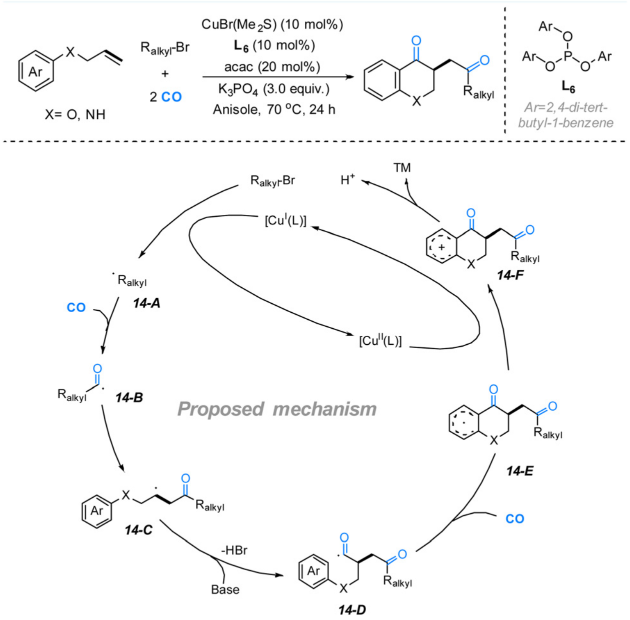

Fig. 14 Copper-catalyzed 1,2-dicarbonylative cyclization of alkenes *via* radical relay.

In summary, in the transformations of single electron reduction of organic halides, the reduction potential needs to be below −2 V compared to the saturated calomel electrode (SCE) for unactivated alkyl iodides; the reducing power of the copper catalyst can be enhanced by photoexcitation or by employing appropriate ligands. In addition, activated alkyl halides are more easily reduced than inactivated alkyl halides, and unactivated alkyl radicals tend to capture CO while activated alkyl radicals tend to add to alkenes. In our view, the active copper species-mediated single electron reduction of halides to acylsilane or R–CO–Bpin is a novel reaction mode compared to other metal catalysis in carbonylation chemistry.

3. Radical capture to form organocopper intermediates (HAT process and others)

The hydrogen atom transfer (HAT) process has found wide application in organic methodology. Common hydrogen abstractors include peroxides,[67] sodium decatungstate,[68] and specially designed nitrogen-centered radical precursors.[69] In recent years, the HAT tool has also emerged as a growing area of interest in carbonylation chemistry, with copper-, cobalt-, and nickel-catalyzed carbonylation reactions with the HAT process being actively explored.[11,70–73]

In 2016, Wu and co-workers developed a copper-catalyzed carbonylative coupling of cycloalkanes.[74,75] The proposed mechanism is illustrated in Fig. 15. The reaction begins with the thermal homolysis of di-*tert*-butyl peroxide (DTBP), generating *tert*-butoxy radicals. These radicals undergo hydrogen atom transfer (HAT) with alkanes to form carbon-centered radicals. The resulting radicals are then captured by **15-A** to generate Cu(III)–alkyl intermediates (**15-B**). Intermediate **15-B** subsequently reacts with an amine to form **15-C**, which undergoes CO insertion to give intermediates **15-D** or **15-E**.

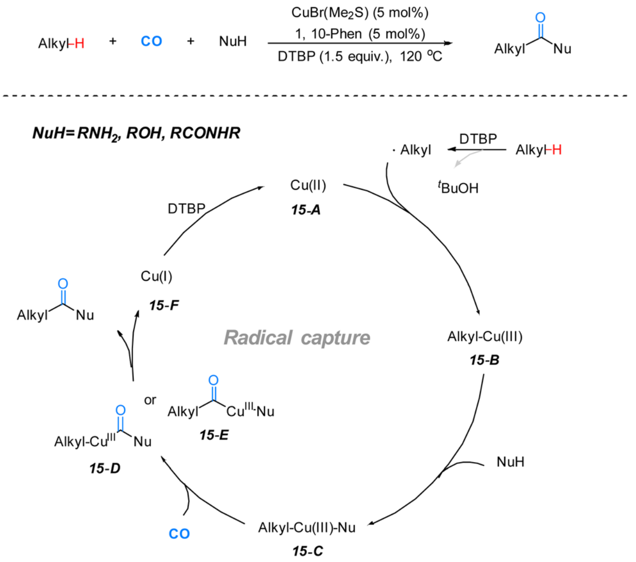

Fig. 15 Radical capture *via* HAT process towards esters or amides.

These species then undergo reductive elimination to produce the carbonylated product and regenerate Cu(I) **15-F**. Finally, Cu(I) is reoxidized to **15-A**, completing the catalytic cycle. Notably, this work represents the first report of copper-catalyzed carbonylation *via* C–H activation.

In the copper-catalyzed double carbonylation transformation (Fig. 16),[76] di-*tert*-butyl peroxide (DTBP) also undergoes thermal homolysis to generate *tert*-butoxy radicals. These radicals can abstract a hydrogen atom from either amines or alkanes *via* a hydrogen atom transfer (HAT) process, leading to the formation of carbon-centered or nitrogen-centered radicals. Upon capturing CO, these radicals are converted into the corresponding acyl or amide radicals. Based on control experiments, the authors proposed that in some cases, the acyl radical may further capture a second molecule of CO to generate an α-ketoacyl radical.

The proposed catalytic cycle proceeds as follows: the alkyl radical is first intercepted by Cu(I) to form intermediate **16-B**, which upon CO coordination yields the alkyl acyl–copper intermediate **16-C**. Alternatively, **16-C** may be formed by direct capture of an acyl radical by Cu(I). Subsequent capture of an acyl radical by **16-C** furnishes the intermediate **16-D**. An alternative pathway involves the α-ketoacyl radical being trapped by **16-B** to form the same intermediate **16-D**. Finally, it undergoes reductive elimination to deliver the double-carbonylated product and regenerate the active Cu(I) catalyst **16-A**.

In our group's first report on copper-catalyzed carbonylation *via* C–H activation, we serendipitously discovered a new reaction pathway involving β-scission of a radical intermediate to generate a methyl radical. The resulting methyl radical is then captured by the copper catalyst and CO to form an acyl–copper intermediate. Subsequent reductive elimination delivers the carbonylated product and regenerates the Cu(I) catalyst, as illustrated in Fig. 17.[77]

In this Cu-catalyzed carbonylation of acetonitrile *via* radical cascade process,[78] the reaction is initiated by the thermal homolysis of di-*tert*-butyl peroxide (DTBP), generating *tert*-butoxy radicals. These radicals abstract a hydrogen atom from acetonitrile *via* a hydrogen atom transfer (HAT) process to form a cyano-containing alkyl radical, which is subsequently added to an unactivated alkene to generate a new carbon-centered radical. This radical is then captured by **18-A** to form intermediate **18-B**. Following an anionic ligand exchange with a nucleophile, intermediate **18-C** is formed. Under a CO atmosphere, **18-C** undergoes CO insertion to give either intermediate **18-D** or **18-E**. Reductive elimination then affords the desired product along with a Cu(I) species (**18-F**), which is reoxidized by DTBP to regenerate **18-A**. This transformation exemplifies a copper-catalyzed strategy that merges the HAT process and radical relay pathways (Fig. 18).

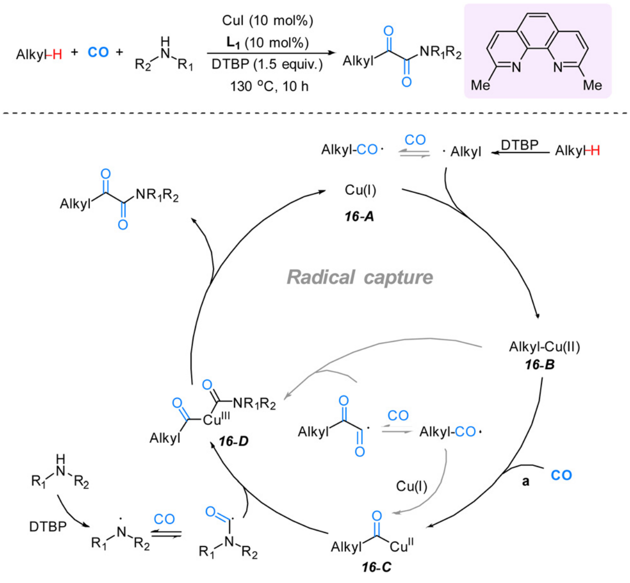

Fig. 16 Radical capture *via* HAT process toward dicarbonylated products.

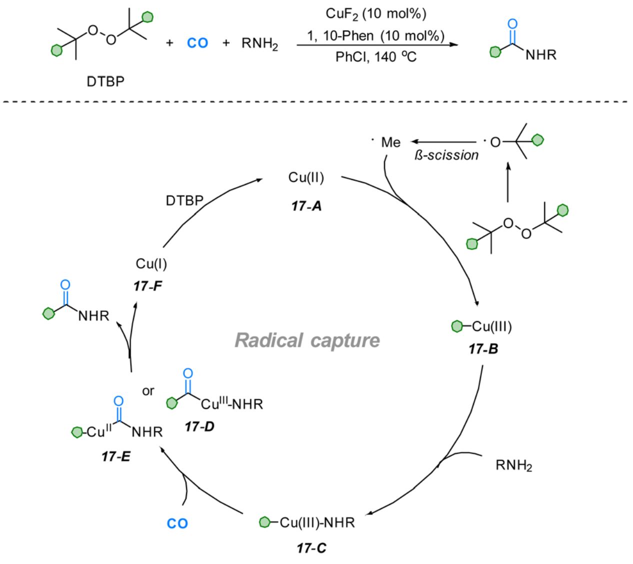

Fig. 17 Radical capture *via* β-scission toward acetamide derivatives.

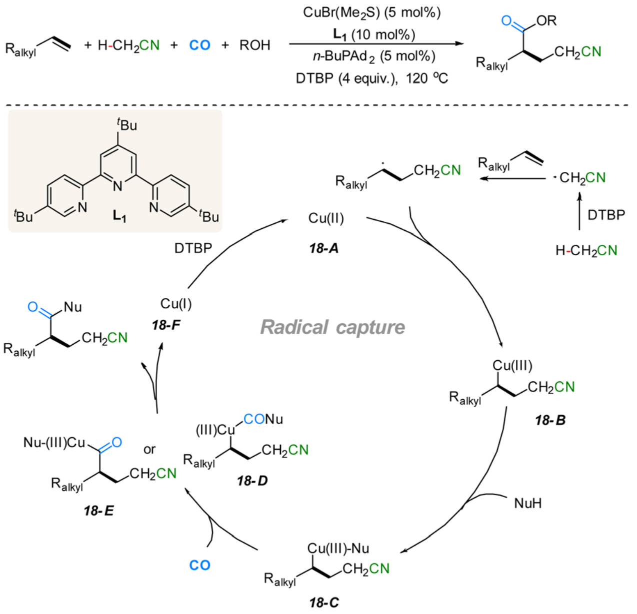

Fig. 18 Radical capture *via* radical cascade process.

4. Active copper species addition (except SET process)

4.1 Acyl copper intermediates isomerization to carbene species

In the past five years, Wu and co-workers have reported a series of copper-catalyzed carbonylation reactions involving carbene intermediates. These transformations enable the conversion of carbon monoxide into aldehydes, alcohols, methylene (–CH_2–), and –CH_2CO– motifs, offering new paradigms for carbonylation chemistry and significantly expanding the toolbox of copper catalysis. An overview of these reaction pathways is illustrated in Fig. 19.

Currently, two major classes of reactive copper intermediates have been identified: Cu–H and Cu–Bpin species. The LCu–H intermediate (**19-A**) is generated *via* transmetalation from copper catalysts, hydrogen gas, and base. This species captures CO to form an acyl copper intermediate **19-B**, which undergoes isomerization to generate an α-oxy carbene intermediate. The resulting carbene can then undergo either H_2 insertion *via* cleavage of the H–H bond or α-C–H insertion. The former leads to intermediate **19-E**, which upon protonation gives alcohol derivatives; the latter obtains intermediate **19-D**, which is further protonated and isomerized to afford aldehyde derivatives.[79]

The second pathway involves the Cu–Bpin intermediate **19-F**, formed *via* transmetalation from a copper catalyst, B_2Pin_2, and base. Upon trapping CO, **19-F** gives rise to the acyl-copper intermediate **19-G**, which can similarly isomerize into a carbene species **19-H**. This intermediate has been more extensively developed in carbonylation chemistry, enabling transformations such as β-C–H insertion (**19-I**),[80] further CO capture (**19-J**),[81,82] α-C–H insertion (**19-K**),[83] O–H insertion (**19-L**),[84] alkene capture (**19-M**),[85] and N–H insertion (**19-N**).[86] These transformations produce structurally diverse carbonyl- or CH_2-containing organoboron

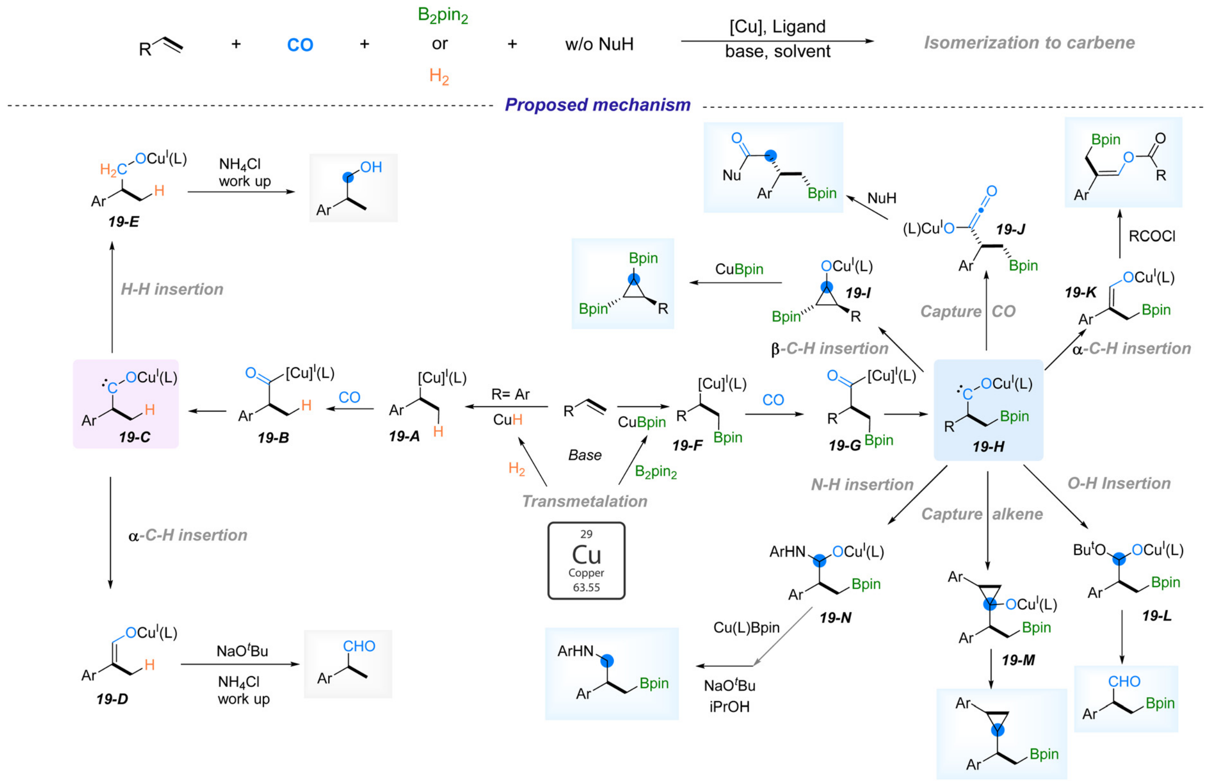

Fig. 19 Isomerization of organocopper intermediates to a carbene species in carbonylation chemistry.

compounds, which can be further diversified through downstream modifications such as vinylation, reduction, oxidation, halogenation, or Suzuki–Miyaura cross-coupling.

In summary, copper-catalyzed carbonylation reactions involving carbene intermediates operate through unique catalytic cycles based on low-valent copper species. Unlike conventional metal-catalyzed transformations, these reactions do not involve oxidative addition, reductive elimination, or single-electron transfer (SET) processes. While this approach offers novel reactivity, it still faces several limitations: for instance, the reaction typically requires alkene addition to initiate the catalytic cycle, limiting the initiation mode; CuH-based carbene transformations remain underdeveloped; and carbene routes involving Cu–[Si] species have not yet been realized. Moreover, mechanistic insights *via* DFT calculations could provide valuable validation and guidance for further development.

4.2 Organocopper intermediates coordinated with chiral ligands (Cu–Bpin and Cu–H species)

Chiral carbonyl-containing compounds play a vital role in medicinal chemistry, and carbonylation has emerged as an efficient and valuable strategy for their construction.[87] For example, BHC's industrial production of ibuprofen involves only three steps and achieves an atom economy of up to 77 percent. The final product is obtained as a racemate, and is widely used as an anti-inflammatory and analgesic agent. Although both enantiomers exhibit similar pharmacological properties, the (*S*)-enantiomer is 28 times more active than the (*R*)-enantiomer. This discrepancy has also prompted strong interest in the development of efficient asymmetric carbonylation technologies. Notable examples include asymmetric carbonylation reactions developed by the Liao and Shi groups, which predominantly rely on palladium catalysis.[88,89] However, due to the high cost of palladium, the development of asymmetric carbonylation methods based on earth-abundant metals such as copper is highly desirable. In 2020, the Wu group reported the first copper-catalyzed asymmetric carbonylation of aryl alkenes, affording chiral α-amides (**20-A**).[90] In 2023, they extended this methodology to alkyl alkenes, enabling the synthesis of chiral β-amides (**20-B**).[91] In 2024, they further developed an asymmetric reductive relay hydroaminocarbonylation strategy to access chiral γ-amides (**20-C**),[92] and in the same year, achieved asymmetric carbonylation of internal alkenes to furnish **20-D**.[93] In 2025, chiral α,β-unsaturated ketone derivatives were also synthesized *via* copper catalysis.[94] In addition to the CuH-mediated catalytic cycles, Cu–Bpin species have been employed in asymmetric carbonylation reactions.[95] The utilization of chiral ligands and specific reaction conditions are detailed in Fig. 20.

In summary, copper-catalyzed asymmetric carbonylation remains an emerging field, but recent advances have demonstrated excellent levels of chemo- and stereoselectivity. Our group is actively working on the development of new copper-catalyzed asymmetric carbonylation methodologies to

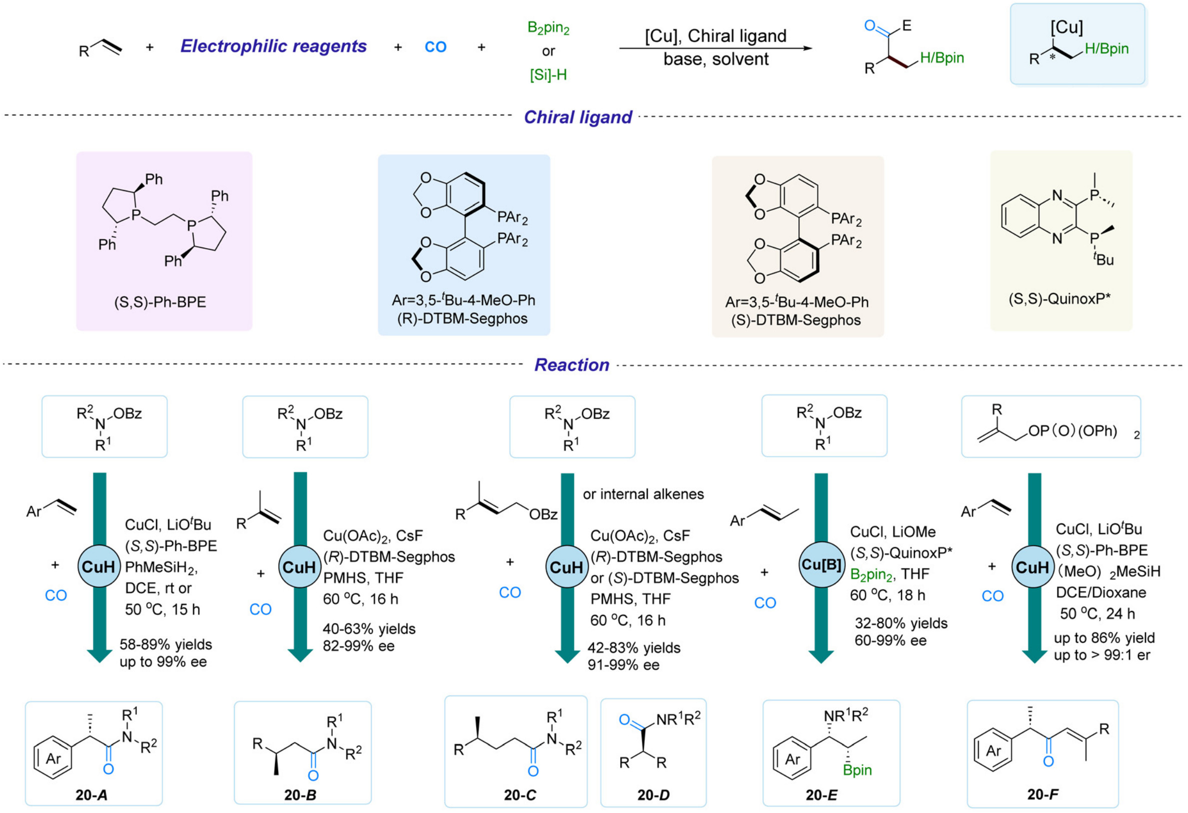

Fig. 20 Organocopper intermediates in the asymmetric carbonylative reaction (Cu–H and Cu–Bpin species addition to alkenes).

further expand the scope and applicability of this promising strategy.

5. Transmetalation

5.1 Transmetalation towards organocopper intermediates

Transmetalation is a fundamental step in organometallic catalysis and has been widely applied in numerous cross-coupling reactions, such as the Suzuki–Miyaura coupling (boron),[96] Stille coupling (tin),[97] Kumada coupling (magnesium),[98] and others. As early as 1996, Kang and co-workers reported a copper-catalyzed carbonylative Stille-type coupling reaction between organostannanes and hypervalent iodine salts.[99] In this transformation, transmetalation from tin to copper generated organocopper intermediates, which subsequently underwent carbonylation.[100] Since then, copper-catalyzed carbonylation reactions involving arylboronic acids with aryl iodides or alkyl halides have also been developed.[101,102] In these systems, aryl iodides tend to undergo carbonylation *via* a two-electron oxidative addition pathway, whereas alkyl halides tend to follow a single-electron transfer (SET) mechanism (Fig. 21).

5.2 Organocopper intermediates take transmetalation to diverse metal catalysts (Pd, Fe)

In the field of metal-catalyzed organic methodology, cooperative catalysis represents a form of multiple catalysis system that employs at least two distinct catalysts to enable reactions between two separately activated substrates. This approach has unlocked a plethora of previously unattainable transformations and novel chemical reactions. In carbonylation reactions involving organocopper intermediates, as summarized in Fig. 22, copper–palladium cooperative catalysis exemplifies this strategy-for instance, the transmetalation of alkynylcopper intermediates with acylpalladium species to afford alkynone derivatives **22-A.**[103] For example, after the addition of Cu–Bpin to unsaturated bonds, the resulting organocopper intermediate undergoes transmetalation with acylpalladium species, leading to the formation of boron-containing ketone compounds **22-B.**[104–107] In addition to copper-to-palladium transmetalation, copper-to-manganese transmetalation affords ketone compounds **22-C**,[101] while copper-to-iron transmetalation yields ester derivatives **22-D.**[108]

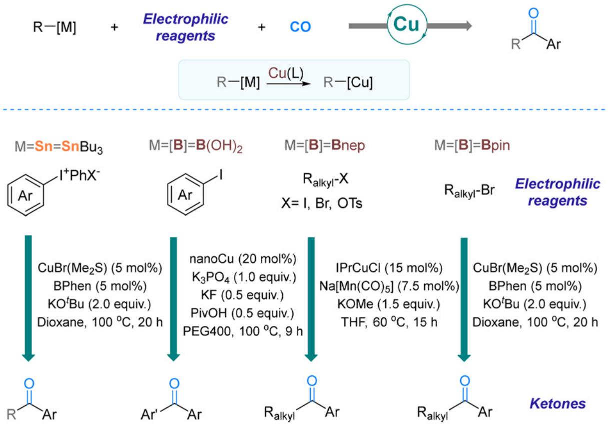

Fig. 21 Carbonylation initiated by transmetalation.

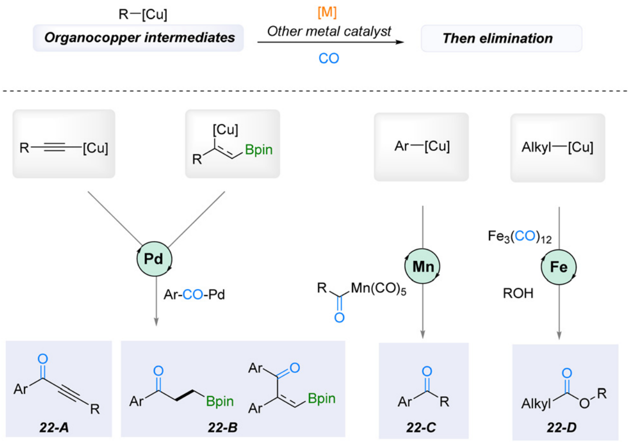

Fig. 22 Transmetalation of organocopper intermediates into other metal catalysts.

6. Others

In the developmental course of copper-catalyzed carbonylation reactions, there remain certain transformations that are still in their infancy and have not yet formed a unified reaction system, or reactions that require further development and exploration. This is entirely reasonable, so they are included in this section for contemplation and discussion.

As illustrated in Fig. 23, in 2009, the Xia group reported an intriguing example of the double carbonylation of aromatic iodides and amines. This conversion proceeded under mild conditions with good functional group tolerance. However, the reaction mechanism remains to be elucidated, and the reaction necessitates the addition of an excess of carbene ligand.[109]

In the developmental landscape of copper-catalyzed carbonylation reactions, the capture of carbene intermediates by copper catalysts represents a fascinating transformation. In 2023, Wu and co-workers reported a copper-catalyzed carbonylation of carbenes distinguished by exceptional functional group tolerance and chemoselectivity.[110] The proposed mechanistic pathway is delineated in Fig. 24. Initially, under a carbon monoxide atmosphere, the active copper catalyst **24-A** coordinates with CO to generate intermediate **24-B.** Subsequently, the

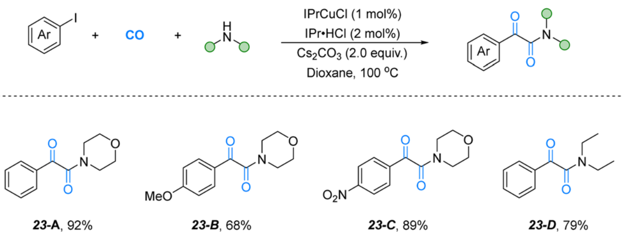

Fig. 23 Copper-catalyzed double carbonylation of aryl iodides and amines.

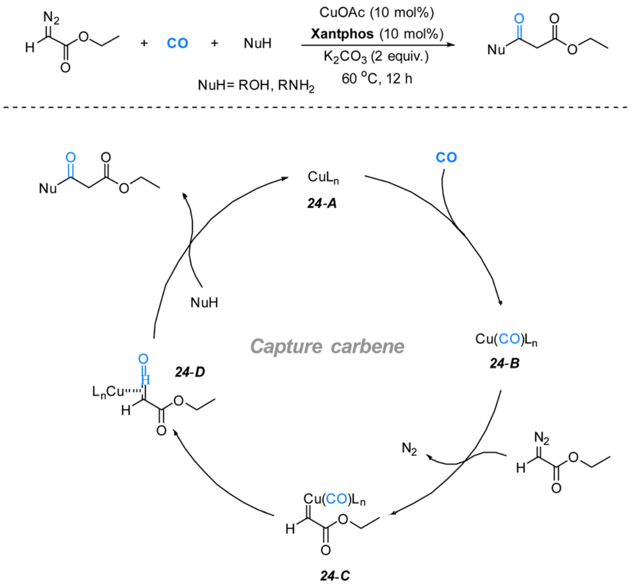

Fig. 24 Copper-catalyzed direct carbonylation of carbenes.

diazo compound engages in the reaction, yielding the copper–carbene intermediate **24-C** with the concomitant release of nitrogen. Through the insertion of CO, this intermediate is converted into the ketene intermediate **24-D**. Finally, nucleophilic attack, coupled with the liberation of the active copper complex **24-A** for subsequent catalytic cycles, furnishes the corresponding product.

In the realm of double carbonylation reactions, reports leveraging alcohols as nucleophiles to afford corresponding α-ketoester derivatives remain relatively scarce. In 2018, employing hexaketocyclohexane octahydrate as the carbonyl source, Wang and co-workers reported on a novel paradigm of copper-catalyzed double carbonylation of indoles with alcohols.[111] Noteworthily, while hexaketocyclohexane octahydrate generates CO gas under standard conditions, the product yield plummets to below 5% when using gaseous CO, rendering this transformation a distinctive case of oxidative carbonylation. Despite its synthetic potential, the mechanistic intricacies of this protocol warrant in-depth investigation, given the unique reactivity profile of the solid-state carbonyl source and the stark disparity in reaction efficiency compared to conventional CO gas systems (Fig. 25).

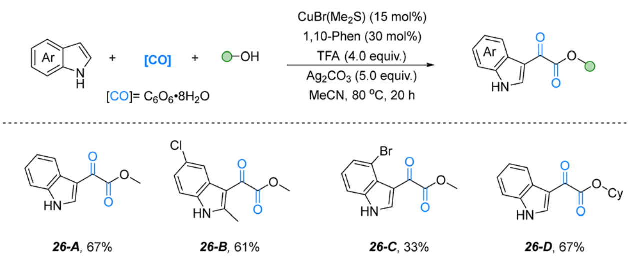

Fig. 25 Copper-catalyzed double carbonylation of indoles and alcohols.

7. Conclusion and outlook

Given the extensive applications of carbonyl-containing compounds in pharmaceuticals, agrochemicals, and materials science, the development of cost-effective catalytic systems for the rapid construction of such motifs is of paramount importance. Among contemporary carbonylation technologies, palladium-catalyzed methods and copper-catalyzed methodologies have emerged as two of the most prominent strategies. In the past decades, carbonylation reactions involving organocopper intermediates have witnessed rapid and vigorous development, paralleling advances in palladium catalysis and even surpassing it in terms of reaction diversity, owing to the burgeoning array of novel catalytic modes enabled by copper. These include single-electron reduction of organic halides, radical-trapping mechanisms, addition of reactive copper species to unsaturated bonds, asymmetric catalysis using chiral ligands, copper-mediated radical relay reactions, isomerization of acylcopper species to α-oxy carbene intermediates, and transmetalation processes, *etc.* Notably, certain reaction classes, such as the addition of reactive copper species to unsaturated bonds, not only exhibit chemoselectivity but also regioselectivity, allowing for the generation of diverse products through the meticulous modulation of organocopper intermediate formation using ligands, bases, solvents, and other reaction parameters.

In the investigation of these transformations, despite emphasizing the successful implementation of various catalytic modes, we have identified several unresolved challenges and ambiguous mechanisms in this field. For instance, the reaction mechanism of copper-catalyzed aryl halides remains unclear (whether it involves two-electron oxidative addition and what factors enable this process). Additionally, the addition of the active Cu–[Si] species to alkenes or alkynes and their isomerization to carbene in carbonylation reactions have not been realized. Although 1,4-copper migration and 1,3-copper migration have been achieved,[112–114] their application in carbonylation reactions remains unaccomplished. Furthermore, while palladium-catalyzed chain walking has matured,[115–119] copper-catalyzed remote carbonylation has not been realized. To address these challenges, innovative strategies are required, such as designing novel silicon-containing reagents or adopting synergistic catalysis combining photoredox and copper systems. Our research group is actively exploring these challenging reactions and investigating their mechanisms, with the aim of further expanding the potential of copper-catalyzed carbonylation reactions and contributing to the development of green, sustainable, and efficient catalytic systems.

Conflicts of interest

There are no conflicts to declare.

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.

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