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Hydrogen atom transfer carbonylation for aliphatic carboxylic acid derivative synthesis

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Aliphatic C-H bonds are ubiquitous in industrial feedstocks and natural molecules, and their direct carbonylation represents a fundamentally important strategy to access aliphatic carboxylic acid derivatives. Conventional carbonylation approaches typically rely on prefunctionalized substrates such as alkyl halides or alkenes. In contrast, hydrogen atom transfer (HAT)-enabled strategies allow direct C-H bond activation, providing a more atom-economical and step-efficient route for molecular skeleton construction. This approach leverages differences in C-H bond dissociation energies as well as the intrinsic reactivity of open-shell intermediates, proceeding through a cascade sequence of HAT, CO capture, and acyl species formation to forge key C-C(O) bonds. As such, HAT-mediated carbonylation represents a powerful strategy for the construction of aliphatic carboxylic acids and their derivatives and has demonstrated broad potential in the selective functionalization of inert C-H bonds. This review summarizes the early developments and the latest advances in HAT-mediated C-H carbonylation reactions, with a particular focus on the construction of aliphatic carbonyl compounds, especially carboxylic acid derivatives.

Keywords: C-H bonds; Carbonylation; Carbon monoxide; Aliphatic carboxylic acid derivatives; Bulk chemicals.

1 Introduction

Aliphatic C-H bonds constitute attractive synthetic feedstocks for chemical transformation, owing to their ubiquitous presence in industrial chemicals, commodity feedstocks, and natural systems. Direct C-H carbonylation using carbon monoxide (CO) as a readily available and versatile C1 synthon provides an efficient approach to diverse carbonyl-containing compounds from simple C-H bonds, with broad applications in both academic and industrial contexts.[1-5] This approach enables rapid access to structural analogues within one or two steps, avoiding lengthy syntheses from simple precursors that require multiple prefunctionalization steps. Over the past few decades, C-H carbonylation reactions have generally been classified into two fundamental pathways: (1) transition-metal-catalyzed C-H carbonylation, which proceeds via an inner-sphere coordination mechanism to generate carbon-metal intermediates[6-8] and (2) HAT-mediated carbonylation, in which C-H bonds are activated via HAT.[9-10, 43] In recent years, transition-metal-catalyzed, coordination-assisted C-H activation enables site-selective transformations through the formation of metal-carbon intermediates,[11] whereas hydrogen atom transfer (HAT) has emerged as a versatile strategy for selective C-H bond activation based on the intrinsic properties of C-H bonds.[12] However, directing-group-based C-H carbonylation strategies often suffer from geometric constraints and the intrinsic requirement for proximal coordinating sites.[13-14] In contrast, HAT represents a fundamentally different and complementary mode of C-H carbonylation, in which selectivity arises from intrinsic C-H bond properties, particularly bond dissociation energy (BDE), rather than metal-carbon bond formation. More importantly, this mechanism enables the selective carbonylation of remote, high-BDE, and polar C-H bonds that are typically inaccessible to conventional directing-group strategies.

The efficiency and selectivity of HAT-mediated C-H carbonylation are controlled by a combination of thermodynamic and kinetic factors associated with C-H bond dissociation and subsequent C-C(O) bond formation. For the C-H activation step, thermodynamic parameters such as BDEs play a dominant role (detailed BDE values are shown in Scheme 2).[15-16] Weaker C-H bonds are preferentially cleaved due to the formation of more thermodynamically stable radical intermediates, consistent with the thermodynamic preference for stronger bond formation.[17] In the CO incorporation step, reversible addition of alkyl radicals to CO represents the key elementary process leading to acyl radical formation. It should be noted that acyl radical decarbonylation is governed by multiple factors, which can significantly influence the competition between productive carbonylation and CO

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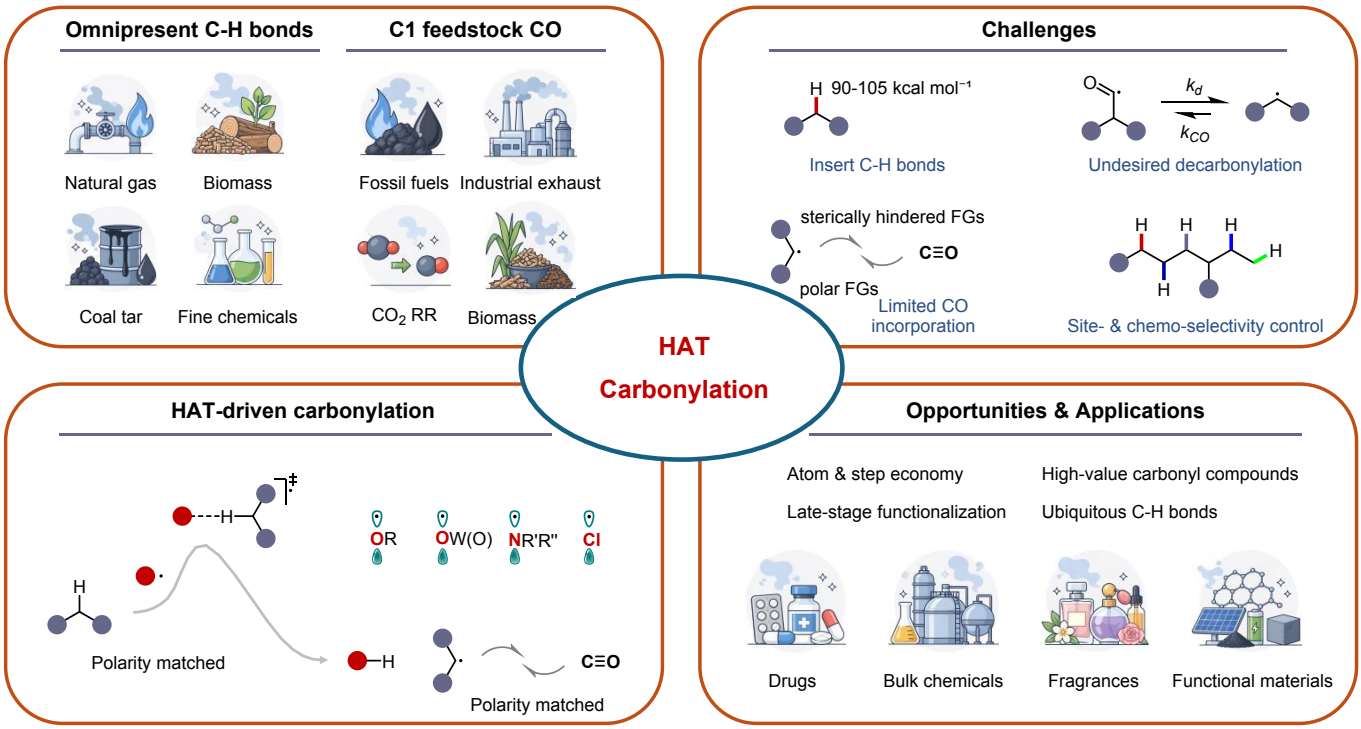
extrusion.[18-20] This step, together with the competing decarbonylation pathway, establishes a thermodynamically reversible equilibrium between alkyl and acyl radical species.[21-22] The position of this equilibrium is dictated by their relative thermodynamic stability. In general, acyl radical formation is an exergonic chain-extension process, whereas decarbonylation corresponds to an endergonic reverse transformation driven by radical stabilization.[23-24] Such reversibility is primarily modulated by differences in activation barriers and can be correlated with both radical stability and BDE considerations.[25-26] From a kinetic perspective, CO capture competes with a range of side reactions of alkyl radicals. Highly reactive and less stabilized alkyl radicals are prone to undergo non-selective termination processes, thereby diminishing CO incorporation efficiency.[27] In addition, the polarity of radical intermediates significantly influences the efficiency of CO insertion, as polar mismatches can destabilize the transition state and disfavor productive CO addition.[28] Steric hindrance further attenuates CO diffusion and binding, leading to reduced reaction efficiency in congested systems. For substrates bearing multiple C-H bonds in distinct chemical environments, site- and chemo-selectivity are ultimately dictated by the interplay between two key factors: the intrinsic BDE of the C-H bond, which determines the site of radical generation, and the subsequent kinetic competition during CO capture, which further refines both positional and product selectivity. Overall, the synergistic interplay among BDE, radical polarity, and steric constraints collectively govern the efficiency and selectivity of HAT carbonylation processes, thereby providing broad design opportunities for the development of highly selective C-H carbonylation strategies.



Scheme 1 Overview of HAT carbonylation: feedstocks, carbonyl, opportunities, challenges, and products.

From a transition-state perspective, polar effects are already operative at the early stage of the hydrogen atom transfer event in HAT-mediated C-H carbonylation. In general, electrophilic radicals preferentially abstract hydridic hydrogen atoms from electron-rich C-H bonds.[29-30] Notably, both the HAT event and the subsequent CO incorporation are governed by radical polarity matching, which enables a degree of predictable site selectivity based on the intrinsic electronic properties of C-H bonds. Importantly, polarity constraints associated with CO incorporation can feed back to influence the HAT step, thereby rendering the choice of hydrogen atom transfer reagents a key element in reaction design.[31] In established systems, commonly employed hydrogen atom abstractors include oxygen-centered, nitrogen-centered, and halogen radicals. The transformation can be conceptually described as follows: a hydrogen atom abstractor engages the substrate C-H bond through a polarity-matched transition state to generate alkyl radical intermediate, which subsequently undergoes CO capture under either metal-mediated or metal-free conditions. Overall, this sequential HAT-to-CO incorporation manifold provides a unifying mechanistic framework for HAT-mediated C-H carbonylation reactions.

In recent decades, significant progress has been achieved in transition-metal and photocatalytic C-H carbonylation, particularly for the efficient synthesis of aliphatic carboxylic acids from simple hydrocarbon feedstocks.[6, 9] These advances have substantially expanded the accessibility of carbonyl-containing frameworks from otherwise inert C-H precursors. The development of HAT-mediated carbonylation relies on a

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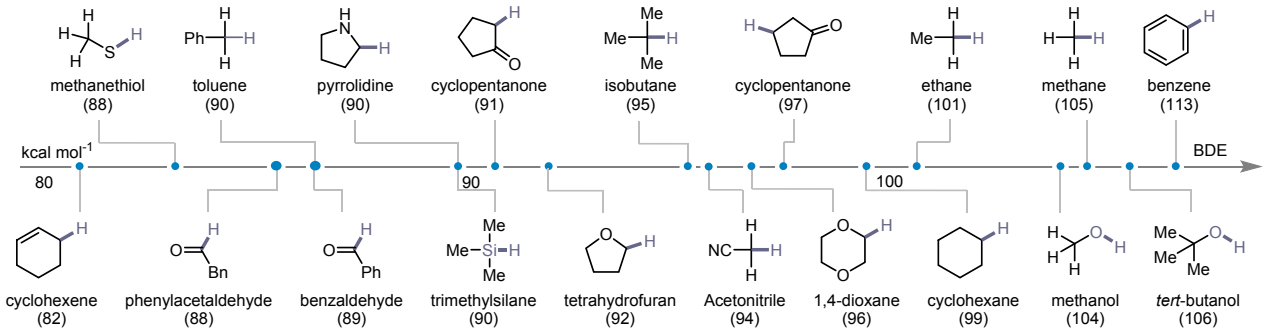
fundamental understanding of the interaction modes between radical intermediates and CO. However, the intrinsic inertness of C-H bonds, together with the high reactivity of both single-electron species and CO, renders a precise mechanistic delineation of reaction pathways and catalytic roles challenging. In general, HAT-mediated carbonylation can be categorized into two fundamental modes: direct C-H carbonylation leading to C+1 carboxylic acid frameworks, and radical relay or cascade processes enabling C+3 skeletal extension. These distinct manifolds reflect different modes of radical generation, migration, and CO incorporation, thereby underpinning the structural diversity accessible through HAT chemistry. Despite recent progress in specific catalytic systems, a comprehensive account of HAT-mediated aliphatic C-H carbonylation remains underdeveloped. This Review focuses on HAT-mediated C-H activation across transition-metal, photocatalytic, and metal-free systems, highlighting key advances, limitations, and emerging mechanistic paradigms. Overall, this strategy enables the direct and efficient conversion of inert C-H bonds into aliphatic carboxylic acid derivatives, enabling the formation of challenging C-C(O) bonds under non-prefunctionalized conditions with excellent atom and step economy.

As early as the 1980s and 1990s, Tanaka and co-workers pioneered the research on photoinduced C-H activation and regioselective carbonylation of alkanes. They established a classic catalytic system using $RhCl(CO)(PMe_3)_2$ as the catalyst. Under light irradiation at room temperature and atmospheric pressure of carbon monoxide, highly regioselective carbonylation occurred preferentially at the primary C-H bonds of hydrocarbons.[32, 33] This pioneering work laid the foundation for subsequent investigations and is regarded as an important origin of photoinduced alkane C-H carbonylation.



Scheme 2 Bond dissociation energies.

2 Iron catalysis

Methane, as the major component of natural gas, is one of the most abundant and inexpensive hydrocarbon resources on Earth and has long been recognized as an attractive C1 feedstock with significant synthetic potential.[34] However, its selective functionalization remains difficult because of the high bond dissociation energy and low polarizability of its C–H bonds.[35,36] Among the various methane upgrading strategies, catalytic carbonylation is particularly attractive because it enables the direct conversion of methane into acetic acid derivatives, providing a fundamental feedstock route to carbonyl-containing compounds.[37,38] A major obstacle arises from the dual inertness of methane and CO, while the generated reactive C1 intermediates are prone to overoxidation under oxidative conditions.[39,40] Consequently, achieving selective CO incorporation remains a long-standing challenge. Sen and co-workers first reported a rhodium-catalyzed system for the conversion of methane to acetic acid under high-temperature conditions.[41] More recently, this strategy has been extended to heterogeneous catalytic systems to improve catalyst stability and operational efficiency. Nevertheless, efficient and selective methane carbonylation remains rare.

To further address these limitations, Noël and co-workers recently developed a general and mild flow chemistry strategy in 2023 that integrates photocatalytic HAT with in-situ capture of gaseous CO, enabling the direct carbonylation of methane (Scheme 3a).[42] This flow-system significantly enhances gas–liquid mass transfer, accelerates reaction kinetics, suppresses competitive side reactions, and improves both scalability and operational safety. Mechanistically, the transformation is initiated via an iron-catalyzed ligand-to-metal charge transfer (LMCT) process.[43] Photoexcitation generates high-valent iron species **1e** that undergo electron transfer to produce highly reactive chlorine radicals,[44] which subsequently abstract hydrogen from methane via a HAT process. The resulting methyl radical is trapped by CO to form acyl radical **1h**, which is finally converted into ketone products in the presence of Michael acceptors. This study provides experimental validation for the feasibility of HAT-mediated carbonylation strategies in the functionalization of inert light alkanes. However, it should be emphasized that the efficiency of methane conversion in this system remains limited. The corresponding ketone product **1j** was obtained in only 33% yield, highlighting that the selective and high efficiency carbonylation of methane is still far from being fully realized and requires further methodological breakthroughs.

Subsequently, Zuo and co-workers developed an iron terpyridine catalytic system based on a LMCT process, in which the synergistic regulation of photocatalytic activation, methyl radical generation, and carbonylation enables excellent C2/C1 selectivity control (Scheme 3b).[45] In this system, the ligand

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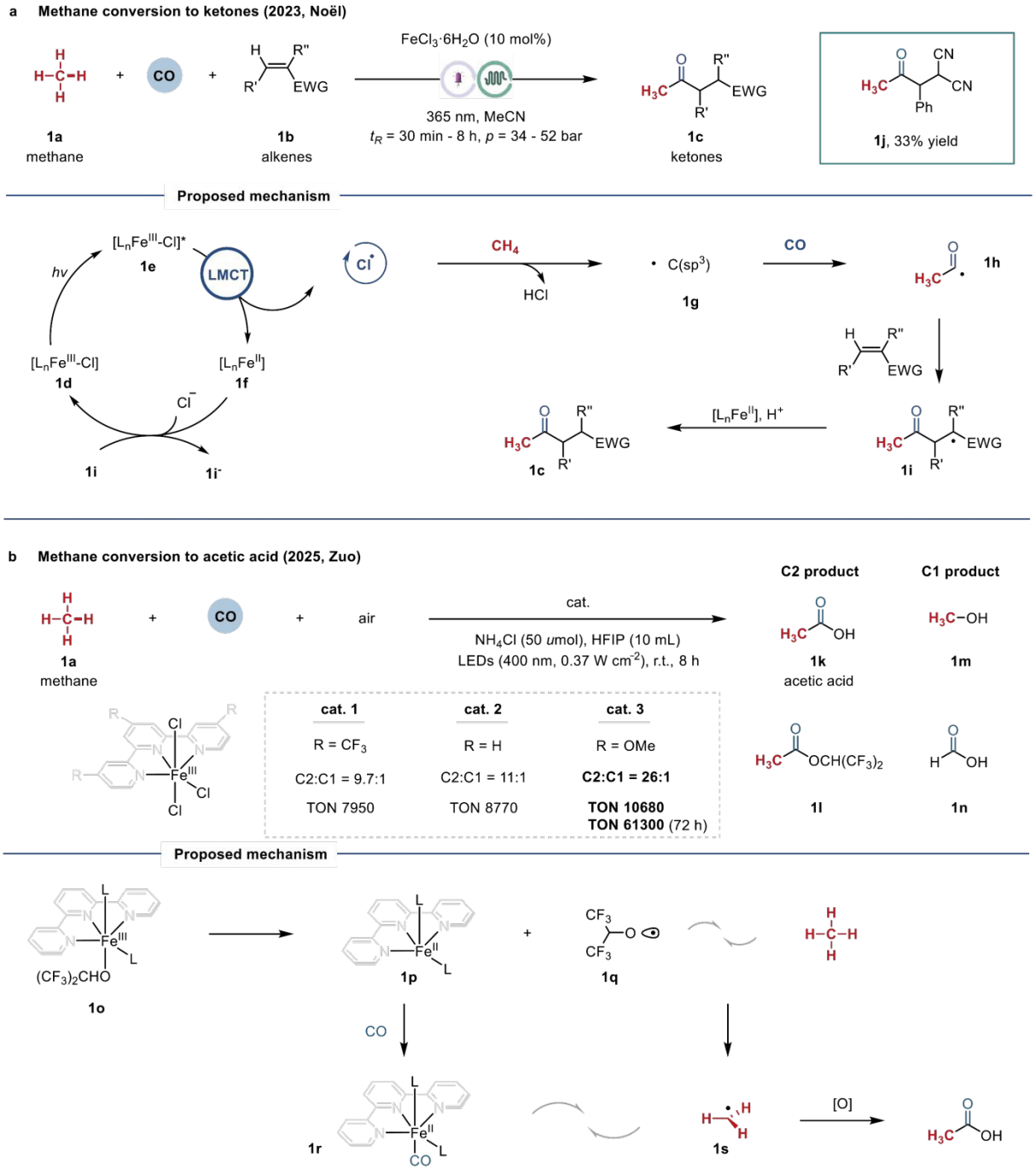
environment plays a decisive role in modulating the electronic structure of the iron center and, consequently, governs catalytic activity and selectivity. Catalysts bearing electron-withdrawing substituents such as trifluoromethyl groups (cat. 1) result in a marked reduction in both catalytic efficiency and selectivity toward acetic acid formation. In contrast, incorporation of electron-donating methoxy substituents (cat. 3) significantly improves chemo-selectivity, affording a selectivity ratio as high as 26:1, while simultaneously delivering substantially enhanced catalytic performance with a TON of 10680. Notably, under continuous operation without any external regeneration, the TON further increased to 61300 after three consecutive reaction cycles with 72 h total irradiation, highlighting the excellent catalytic robustness and sustained activity of the system. Mechanistic investigations suggest that Fe(II) species **1p** and the corresponding iron-carbonyl intermediates **1r** play a pivotal role in the catalytic cycle. These species facilitate a radical rebound-like pathway that effectively suppresses over-oxidation of methyl radicals, thereby enabling highly efficient and selective oxidative carbonylation of methane



Scheme 3 Iron-catalyzed carbonylation of methane. (a) Carbonylation of methane to ketones; (b) Carbonylation of methane to acetic acid.

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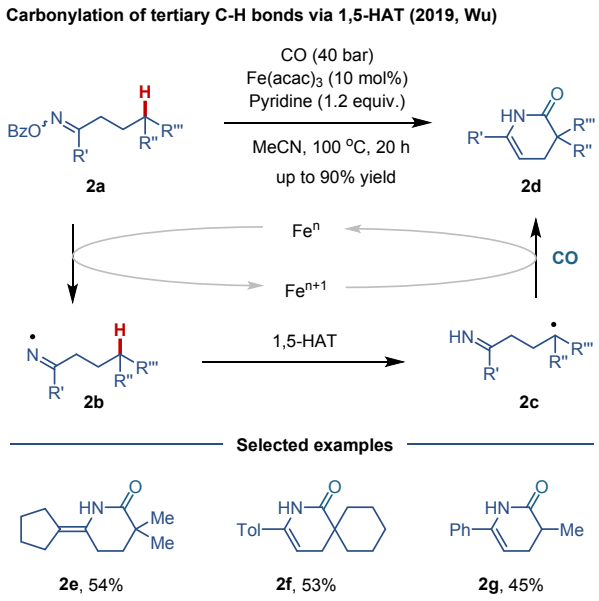
In HAT-mediated carbonylation of C-H bonds, geometric effects also play a decisive role in governing site-selectivity. For systems involving intramolecular hydrogen atom transfer, the reaction pathway is primarily dictated by the carbon chain length connecting the HAT site and the hydrogen donor, typically denoted as 1,n-HAT processes. The most favorable pathway generally corresponds to minimized conformational strain and a shorter spatial distance between the radical center and the abstractable hydrogen atom, which kinetically favors a 1,5-HAT event along the carbon backbone.[46-47] Building on this principle, Wu and co-workers in 2019 reported a controllable C-H carbonylation strategy enabled by a 1,5-HAT process (Scheme 4).[48] Mechanistic studies revealed that, under an iron-catalyzed system, the oxime ester **2a** undergoes single-electron transfer reduction to generate an iminyl radical intermediate **2b** along with an $Fe^{(n+1)}$ species. The resulting iminyl radical **2b** then undergoes intramolecular 1,5-hydrogen atom transfer to afford a new tertiary carbon-centered radical **2c**. This intermediate subsequently engages in CO trapping, followed by intramolecular cyclization to furnish the target products. This strategy enables the efficient construction of diverse six-membered lactam frameworks with good chemo-selectivity and moderate yields, as exemplified by products **2e-2g**.



Scheme 4 Carbonylation of tertiary C-H bonds via 1,5-HAT.

3 Cobalt catalysis

Ethers represent a fundamental class of organic structural motifs and occupy an indispensable position in industrial chemistry, being widely present in solvents, polymer monomers, and fine chemical production.[49-50] As such, they serve as key intermediates bridging bulk chemical feedstocks and high-value-added molecular architectures.[51-52] In 2022, Wu and co-workers reported a cobalt-catalyzed aminocarbonylation strategy that enables the selective carbonylation of otherwise inert C–H bonds in ethers, achieving the direct construction of α-oxyamide frameworks from ethers and amines in the presence of CO (Scheme 5a).[53] A central advance of this work lies in overcoming the long-standing inertness of ether substrates in carbonylation chemistry. Owing to the electron-donating effect of the adjacent oxygen atom and the propensity for competitive side reactions under radical conditions, ethers have historically been poorly reactive or even incompatible with conventional carbonylation systems.[54-55] This strategy addresses these limitations through a synergistic "radical initiation–metal trapping" design, which enables effective control over both reactivity and chemo-selectivity. From a mechanistic standpoint, the catalytic cycle highlights a distinctive cobalt-mediated carbonylation manifold. Initially, abstraction of the α-C-H bond in the ether via a HAT process generates an oxygen-stabilized carbon-centered radical **3d**. This radical is subsequently intercepted by a Co(II) species to form a Co(III) intermediate **3h**. After ligand exchange involving the amine component, CO insertion into the Co-C bond affords a key acyl-cobalt intermediate **3j**, thereby completing the formation of the α-carbonylated product. In an alternative pathway, the carbon-centered radical may directly undergo carbon monoxide capture to generate an acyl radical intermediate **3e**. Importantly, this methodology demonstrates clear potential for late-stage functionalization, as exemplified by its successful application in the efficient synthesis of Alfuzosin, underscoring its transition from methodological development to practical synthetic utility in complex molecule construction.

When various alcohols or phenols are employed as nucleophilic coupling partners, this cobalt-catalyzed direct C-H carbonylation of ethers also enables efficient construction of α-oxy ester motifs with generally high yields (Scheme 5b).[56] For instance, using phenolic **3o** as nucleophiles, the corresponding ester product **3p** can be obtained in 86% yield. Subsequent reduction of this product with $LiAlH_4$ affords tetrahydrofurfuryl alcohol (THFA) in 96% yield. Notably, THFA is an important biomass-derived alcohol that has been widely utilized as a green solvent in coatings, resins, agrochemicals, and fine chemical industries. In addition, Lei and co-workers in 2022 further extended cobalt-catalyzed C-H carbonylation to amine substrates, enabling the controlled carbonylative transformation of alkanes and delivering the corresponding

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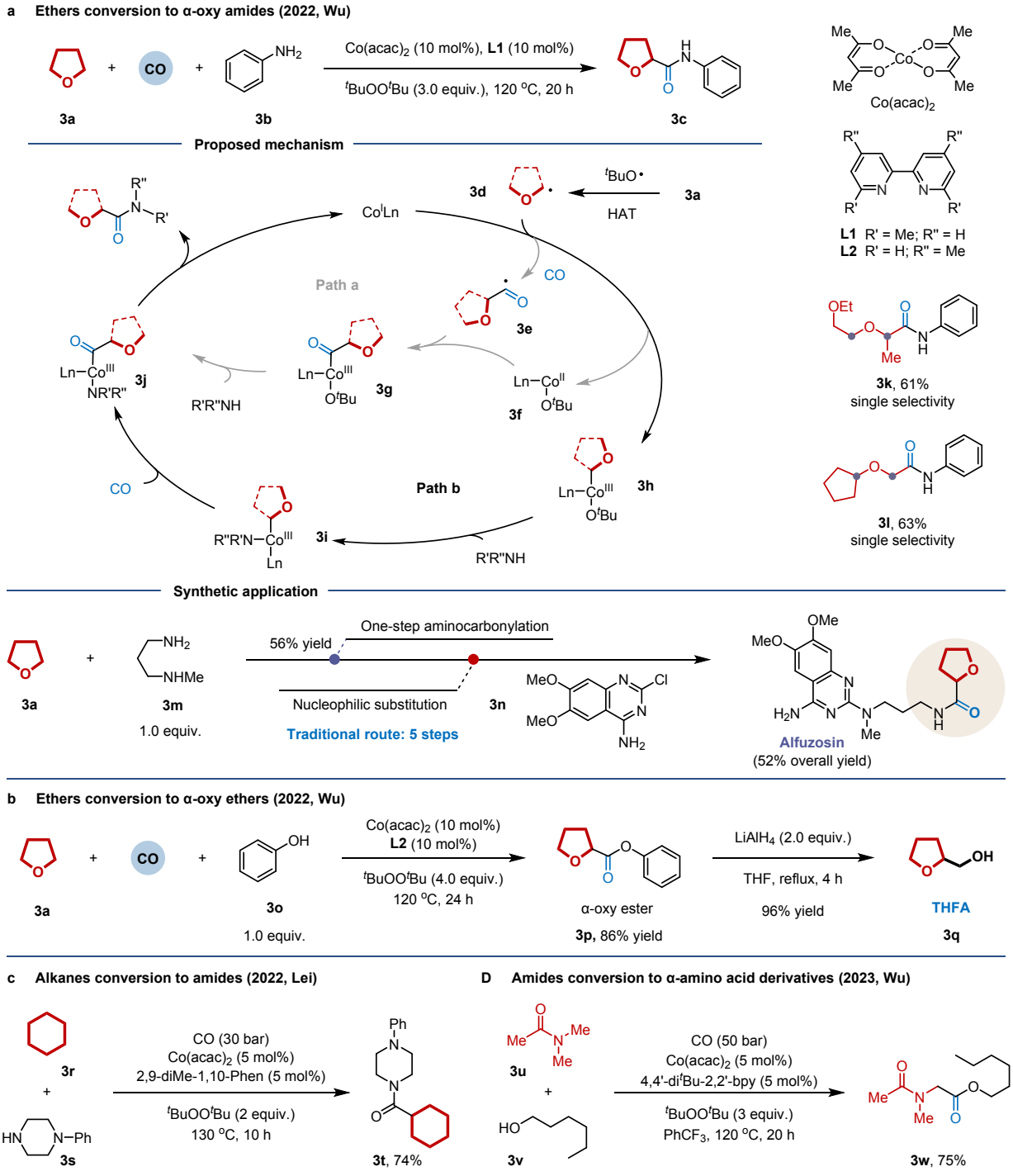
amide product **3t** in 74% yield (Scheme 5c).[57] Importantly, the Wu group systematically investigated the selective carbonylation of α-amino C-H bonds in a variety of nitrogen-containing substrates under cobalt catalysis, achieving efficient access to α-amino acid derivatives **3w**, and a representative example is illustrated in Scheme 5d.[58]



Scheme 5 Ethers conversion to α-oxy amides and esters.

In 2023, Wu and co-workers reported a cobalt-catalyzed radical relay carbonylation strategy that enables the one-step construction of structurally diverse γ-amino acid derivatives through a multicomponent coupling of amines, alkenes, and carbon monoxide (Scheme 6a).[59] γ-Amino acids are important bioactive motifs widely present in natural products and pharmaceuticals, and they also exhibit significant potential in peptide modification and drug delivery applications.[60-62] In this design, electron-withdrawing groups were introduced into the amine substrates to modulate the electronic properties of the

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resulting α-aminoalkyl radicals. This strategy reduces their nucleophilicity and suppresses undesired radical-polar crossover side reactions, thereby enabling efficient addition to simple alkenes. A variety of substrates bearing electron-withdrawing substituents were compatible with the reaction, affording the desired products in good yields, as illustrated by compounds **4e-4g**. Mechanistic studies suggest that peroxide decomposition generates *tert*-butoxy radical, which abstract the α-C-H bond of the amine via a hydrogen atom transfer process to form an α-aminoalkyl radical intermediate **4j**. This radical adds to the alkene to form a new carbon-centered radical **4k**, which subsequently undergoes carbonylation either through cobalt capture followed by CO insertion or through direct CO trapping to generate an acyl radical intermediate **4l**, ultimately affording the γ-amino acid derivative. Overall, this work addresses the challenge of selective addition of α-aminoalkyl radicals to simple alkenes and provides an efficient strategy for constructing γ-amino acid frameworks from readily available alkenes and CO.

Furthermore, the authors developed a cobalt-catalyzed multicomponent carbonylation system. Using inexpensive and readily available toluene, ethylene, and CO as feedstocks, the reaction enables the efficient construction of γ-aryl esters through the synergistic combination of C(sp^3)-H bond activation and ethylene insertion (Scheme 6b).[63] This strategy thus allows the direct transformation of simple bulk chemicals into higher-value phenylbutyrate derivatives such as **4p**. Building on this concept, the methodology was further extended to other simple feedstock combinations. Inspired by previous studies on formamide-derived HAT processes,[64] employing formamide, ethylene, and carbon monoxide as coupling partners enables the simultaneous installation of amide and ester functionalities through a tandem radical addition–carbonylation sequence, affording structurally complex difunctionalized products in a single step (Scheme 6c).[65] In addition, a cobalt-catalyzed four-component carbonylation of thioethers was developed. Through the cooperative coupling of thioethers, ethylene, CO, and nucleophiles such as amines or alcohols, this reaction provides efficient access to γ-carbonylated thioether derivatives such as **4u** (Scheme 6d).[66]

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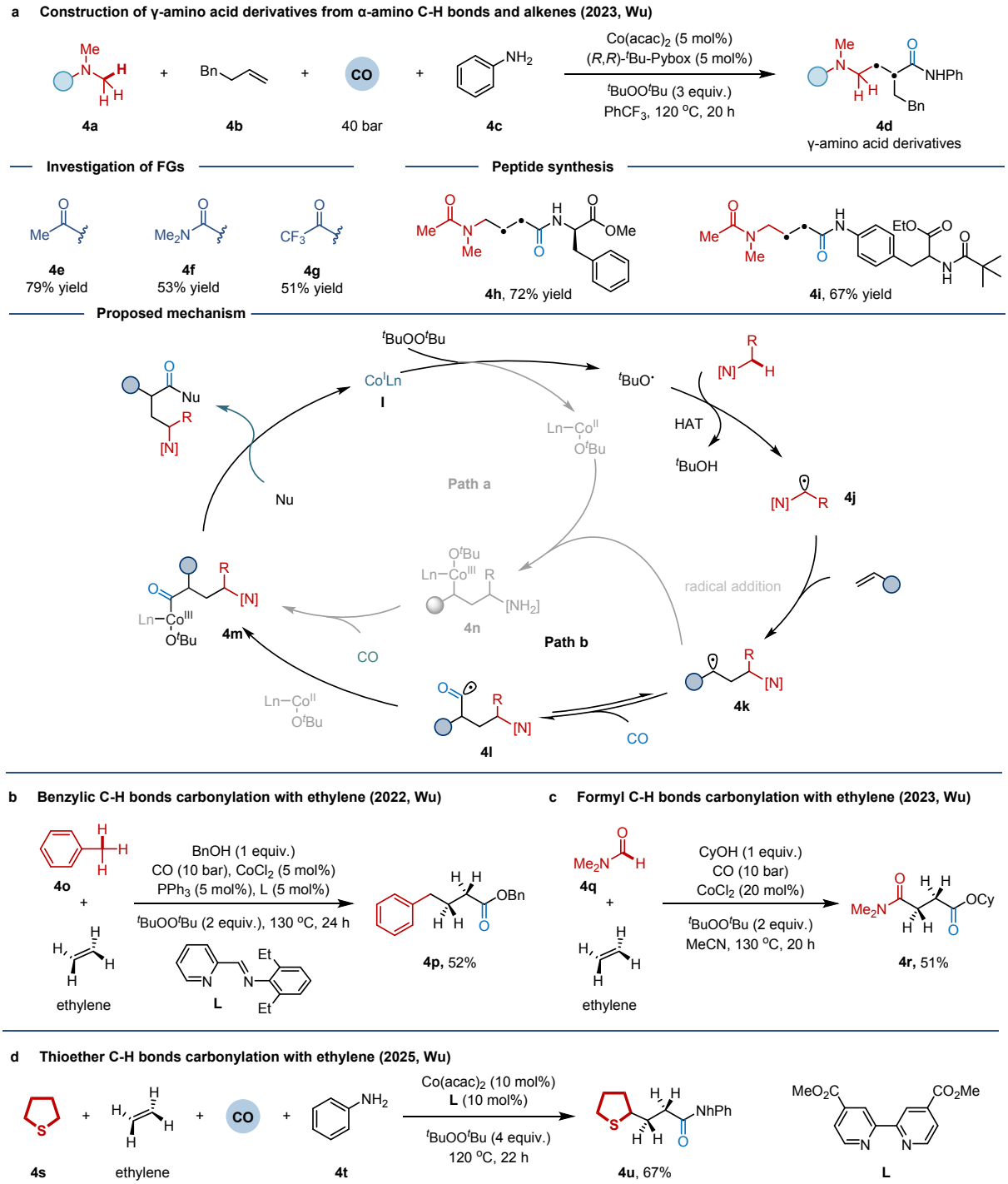

Scheme 6 Cobalt-catalyzed radical relay carbonylation of amine alkyl, benzylic, and aldehydic C-H bonds.

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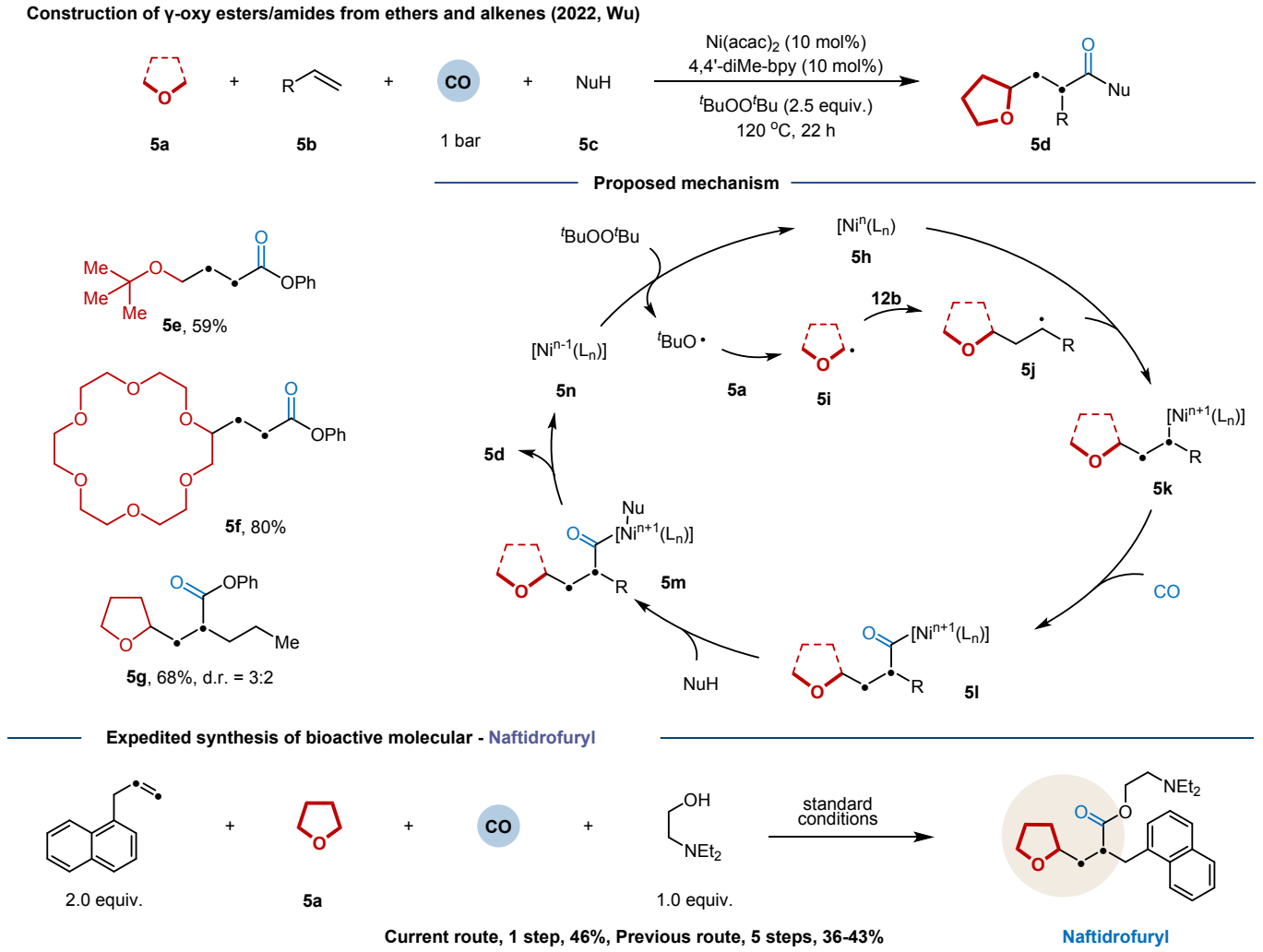
4 Nickel catalysis

As nickel catalysts are relatively inexpensive and highly active, nickel-catalyzed reactions in the field of carbonylation have recently attracted increasing attention. However, nickel readily coordinates with carbon monoxide to form nickel tetracarbonyl, which leads to catalyst deactivation during the reaction, thereby giving this area significant academic value. In 2022, Wu and co-workers reported an efficient nickel-catalyzed C-H functionalization reaction of ethers and their derivatives (Scheme 7).[67] This transformation has demonstrated significant synthetic utility, as can be further applied in the preparation of Naftidrofuryl, a highly effective pharmaceutical agent used for the treatment of cerebrovascular diseases (CVD). Moreover, this reaction exhibits excellent compatibility with a wide range of substrates. Nucleophiles such as amines, alcohols, and phenols, as well as olefins including ethylene and unactivated terminal alkenes, and various types of ether compounds, can all participate effectively in this transformation. The proposed reaction mechanism is illustrated in Scheme 7. Initially, the ether substrate is activated by DTBP to generate a new radical species **5i**. This radical then undergoes addition to an alkene, forming a new radical intermediate **5j**. Intermediate **5j** is subsequently captured by low-valent nickel to afford organonickel species **5k**. Next, migratory insertion of CO occurs to produce the acyl-nickel intermediate **5l**. Nucleophilic attack by the external nucleophile then leads to the formation of intermediate **5m**. Reductive elimination from **5m** furnishes the desired product along with a low-valent nickel species **5n**. Finally, oxidation by DTBP regenerates the active nickel catalyst **5h**, thereby completing the catalytic cycle.



Scheme 7 Nickel-catalyzed construction of γ-oxy esters/amides from ethers and alkenes.

In 2022, Huang group reported a nickel-catalyzed oxidative carbonylation that enables the efficient synthesis of functionalized arylacetic acids from inexpensive alkylarenes (Scheme 8a).[68] Substrates bearing both primary and secondary benzylic C–H bonds participate smoothly in this transformation. The practical utility of this strategy was further demonstrated through the synthesis of marketed drugs such as ibuprofen and diclofenac. As illustrated in Scheme 8, carbon monoxide,

together with a ligand, reduces $NiBr_2$ to generate the active Ni(0)L species **6c**. Subsequently, DTBP undergoes thermolysis to produce two tert-butoxy radicals. One of these radicals reacts with Ni(0) to form the Ni(I) species **6d**, while the other abstracts a hydrogen atom from the alkylarene to generate a benzyl radical. The Ni(I) species is then oxidized by the benzyl radical via a SET process to form the key benzylnickel complex **6e**. Due to the steric hindrance associated with the *tert*-butyl group in intermediate **6e**, it readily undergoes anion exchange to afford intermediate **6f**. This is followed by migratory insertion of CO to give the acyl-nickel species **6g**. Reductive elimination furnishes the desired arylacetic acid product while regenerating the active nickel catalyst **6c**, thus completing the catalytic cycle. In addition, an alternative pathway cannot be ruled out at present, which may involve the formation of acyl radical species **6h** and intermediates **6i**.

In 2023, Liang group developed a convenient and general nickel-catalyzed carbonylation protocol via remote C(sp^3)–H activation under 1 bar of CO.[69] In this system, a variety of substituted phenylboronic acids and *N*-fluorocarboxamides can be smoothly converted into the corresponding products in moderate yields. This method also features mild reaction conditions, broad functional group tolerance, and excellent chemical selectivity. As illustrated in Scheme 8b, the mechanism is proposed as follows. Initially, active catalyst undergoes transmetalation with phenylboronic acid to form species Ar-Ni, which then reacts with the *N*-fluorocarboxamide **6j** via a SET process to generate an amidyl radical **6o**. The amidyl radical **6o** then undergoes a 1,5-HAT to produce a benzyl radical **6p**. Finally, reductive elimination affords the desired product and regenerates the active catalyst (Scheme 8b).

Recently, Chu and co-workers reported a metallaphotoredox-catalyzed acceptorless dehydrogenative carbonylation of benzylic C-H bonds using CO and nucleophiles as coupling partners (Scheme 8c).[70] Enabled by a nickel/photoredox dual catalytic system, benzylic C(sp^3)-H bonds could be directly converted into esters and related carbonyl compounds under visible-light irradiation and atmospheric CO pressure. Notably, the reaction employs hydrocarbons as the limiting reagent and proceeds under oxidant-free conditions, releasing H_2 as the sole byproduct. A broad range of alkylarenes, alcohols, and structurally complex bioactive molecules were well tolerated, demonstrating excellent functional-group compatibility. Mechanistic studies suggested that bromine radical-mediated hydrogen atom transfer generates a benzylic radical, which subsequently undergoes nickel-catalyzed carbonylation. This strategy represents the first example of acceptorless dehydrogenative carbonylative coupling of benzylic C-H bonds and provides an atom-economical approach for the synthesis of carbonyl compounds from simple hydrocarbons.

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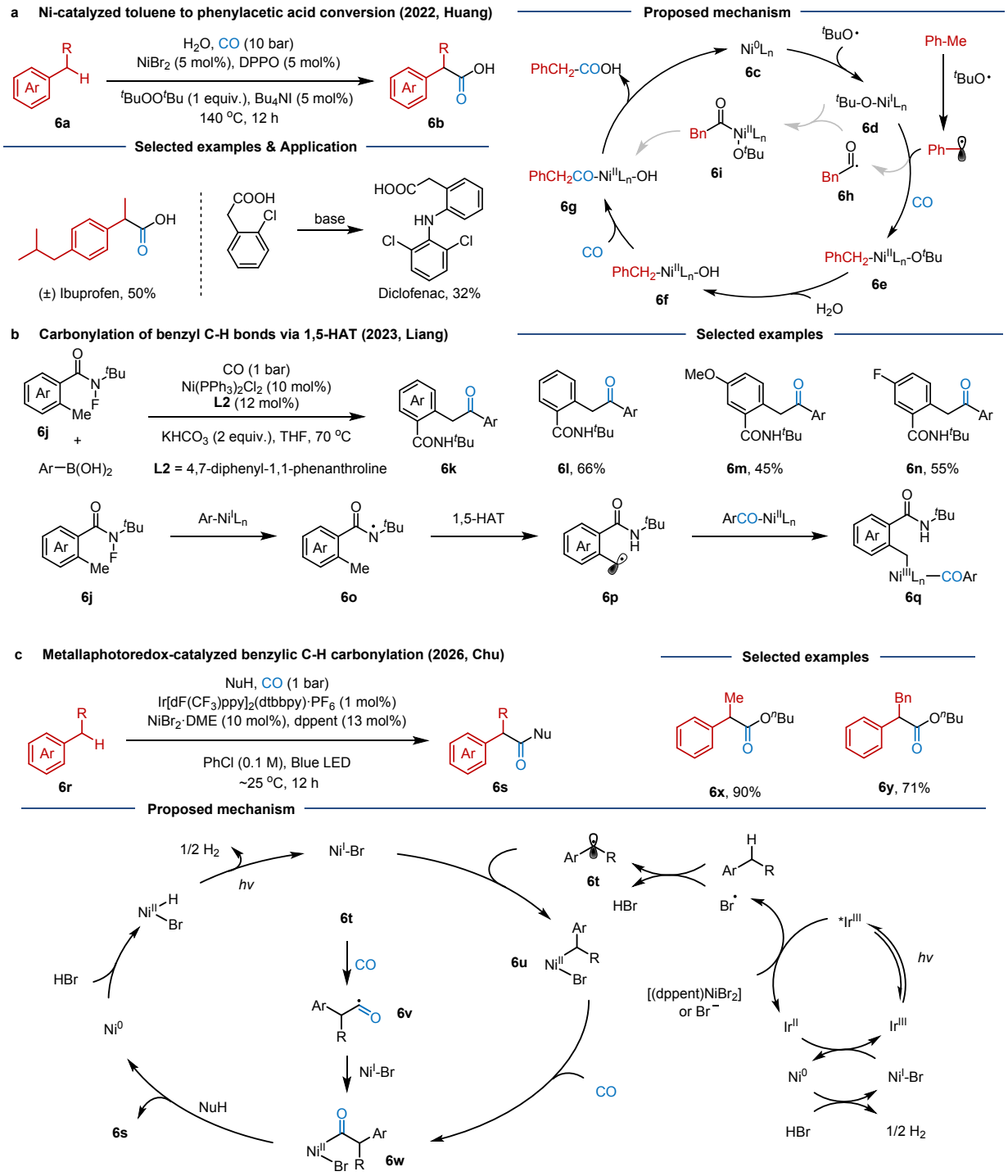

Scheme 8 Nickel-catalyzed benzylic C-H carbonylation.

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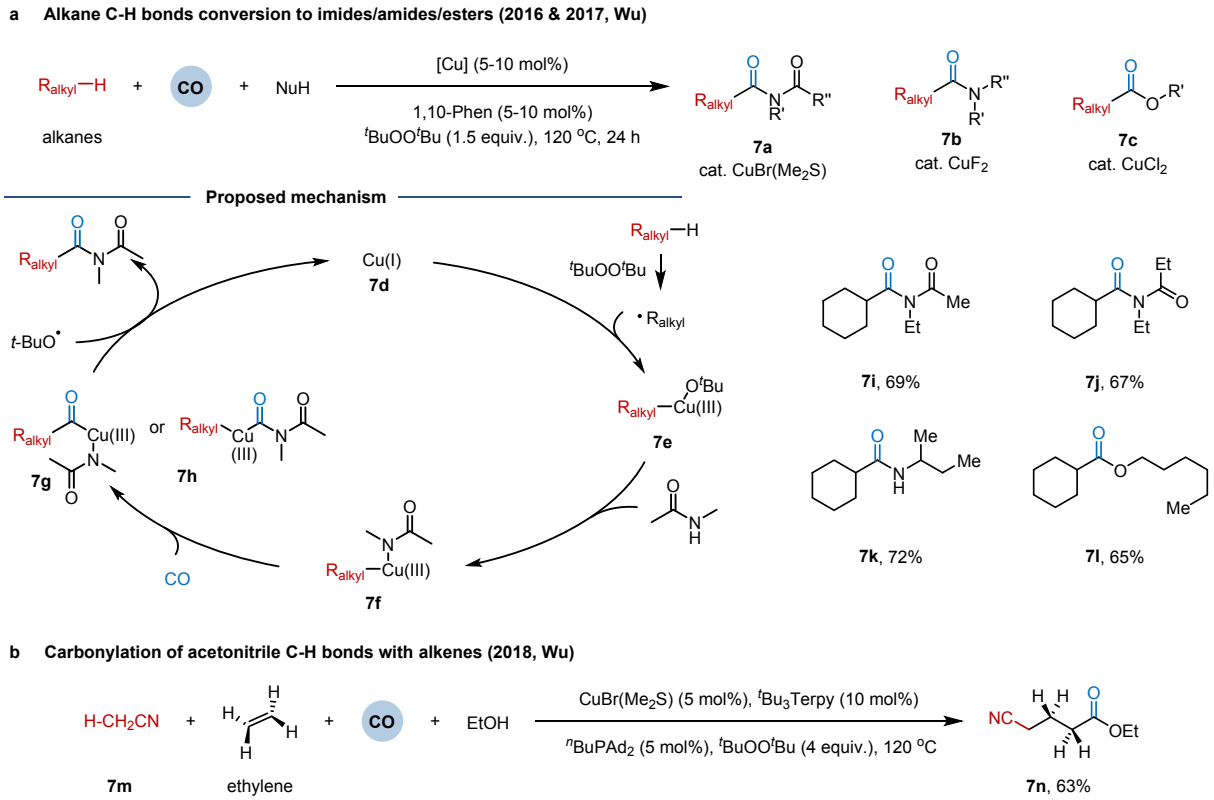
5 Copper catalysis

In addition to nickel catalysts, copper—being more abundant and inexpensive—has also emerged as an attractive alternative, and copper-catalyzed carbonylative transformations have witnessed rapid development over the past decade. For example, in 2018, Wu and co-workers reported a copper-catalyzed carbonylative reaction of alkanes. This transformation exhibits good functional group tolerance and affords the desired products in high yields. A variety of nucleophiles, including amines, alcohols, and amides, are compatible with this system. As illustrated in Scheme 9a, the reaction mechanism is proposed as follows. The process is initiated by copper(II)-catalyzed or thermally induced homolytic cleavage of peroxide to generate a tert-butoxy radical. This radical subsequently reacts with alkanes to form a carbon-centered radical. Meanwhile, the copper(I) catalyst **7d** captures this radical to generate a Cu(III)–alkyl intermediate **7e**. Next, intermediate **7e** reacts with a nucleophile to form Cu(III) intermediate **7f**. Subsequent CO insertion affords intermediate **7g** or **7h**, which then undergoes reductive elimination to deliver the desired carbonylation product, while regenerating the active Cu(I) catalyst **7d** for the next catalytic cycle.[71-73]

Acetonitrile is the simplest aliphatic nitrile compound. In organic synthesis, it is widely used as a polar aprotic solvent. Its industrial production is closely linked to the petrochemical industry, as it is one of the by-products in the manufacture of acrylonitrile, which is obtained from propylene and ammonia under oxidative conditions. It is also one of the inexpensive and readily available industrial solvents. In 2018, Wu and co-workers achieved a copper-catalyzed multicomponent carbonylation reaction involving acetonitrile (Scheme 9b).[74]



Scheme 9 Copper-catalyzed carbonylation. (A) Alkane C-H carbonylation to imides/amides/esters. (B) Radical relay carbonylation of acetonitrile and alkenes.

In 2019, Wu and co-workers reported a copper-catalyzed intramolecular and intermolecular carbonylative transformation of *N*-fluorosulfonamides via a 1,5-HAT process.[75] The proposed mechanism is illustrated in Scheme 10. First, Cu(I) induces a SET reduction of the *N*-fluorosulfonamide, generating an amidyl radical species **8c** along with a Cu(II) species. Subsequently, the amidyl radical undergoes an intramolecular 1,5-HAT to form a new carbon-centered radical **8d**. This radical intermediate **8d** is then trapped by CO together with the Cu(II) species, affording an acyl-copper intermediate **8e**. In the presence of a base, intermediate **8e** undergoes intra- or intermolecular ligand exchange and reductive elimination to produce the corresponding lactam or ester products (Scheme 10).

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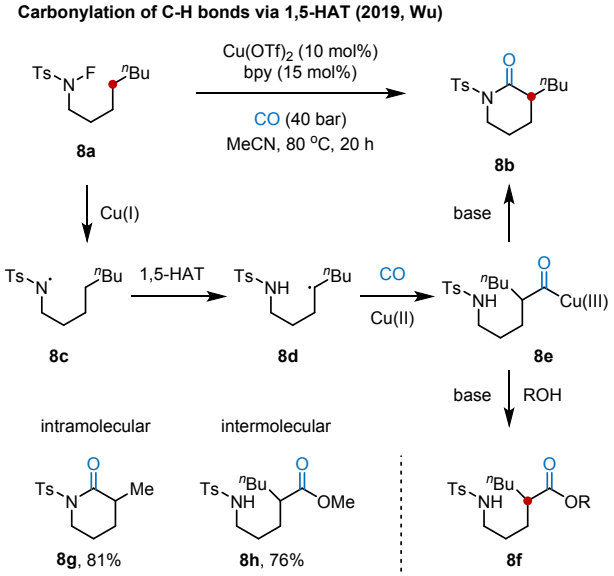
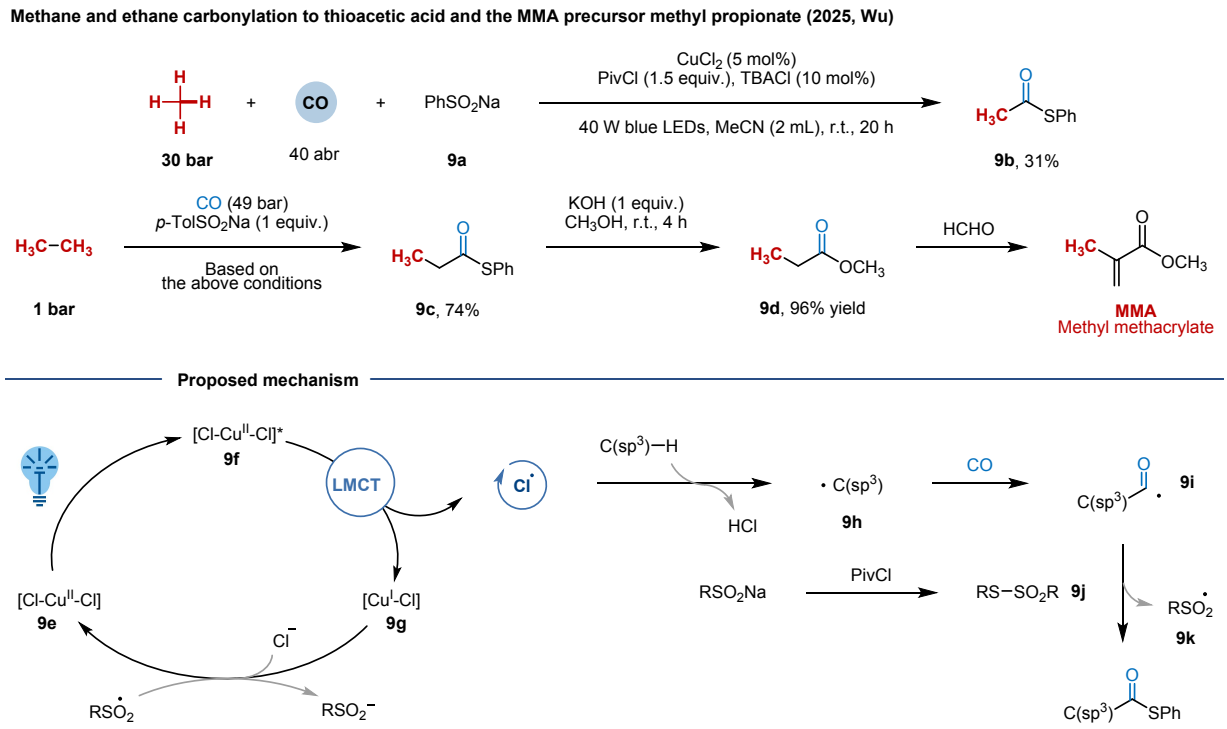


Scheme 10 Carbonylation of C-H bonds via 1,5-HAT.

Recently, Wu and co-workers reported a new synthetic route to MMA using cheaper and more readily available ethane as the feedstock.[76] As shown in Scheme 11, the reaction employs inexpensive copper(II) chloride **9e** as a catalyst. Under blue light irradiation, **9e** is converted to an excited state **9f**, which then generates chlorine radicals via a ligand-to-metal charge transfer (LMCT) process, forming chlorine radical. The chlorine radical acts as a key HAT agent, abstracting hydrogen from various alkanes to generate radical **9h**. In the presence of CO, **9h** is converted into an acyl radical **9i**. Reagent **9j** is an effective radical trapping agent, which can be prepared from sodium sulfinate and acyl chloride; it rapidly quenches the acyl radical to form thioester products while generating a sulfonyl radical **9k**. The sulfonyl radical can further act as an oxidant to promote the regeneration of intermediate **9e**. Notably, even methane, an inert gas, can be converted to the corresponding thioester in 31% yield (Scheme 13). In this copper-catalyzed photoinduced C-H carbonylation, both simple and functionalized alkanes are efficiently transformed. Notably, over ten classes of carbonyl compounds can be readily accessed, with representative examples **10g-10n** shown in Scheme 12.[77]



Scheme 11 Methane and ethane carbonylation to thioacetic acid and the MMA precursor methyl propionate.

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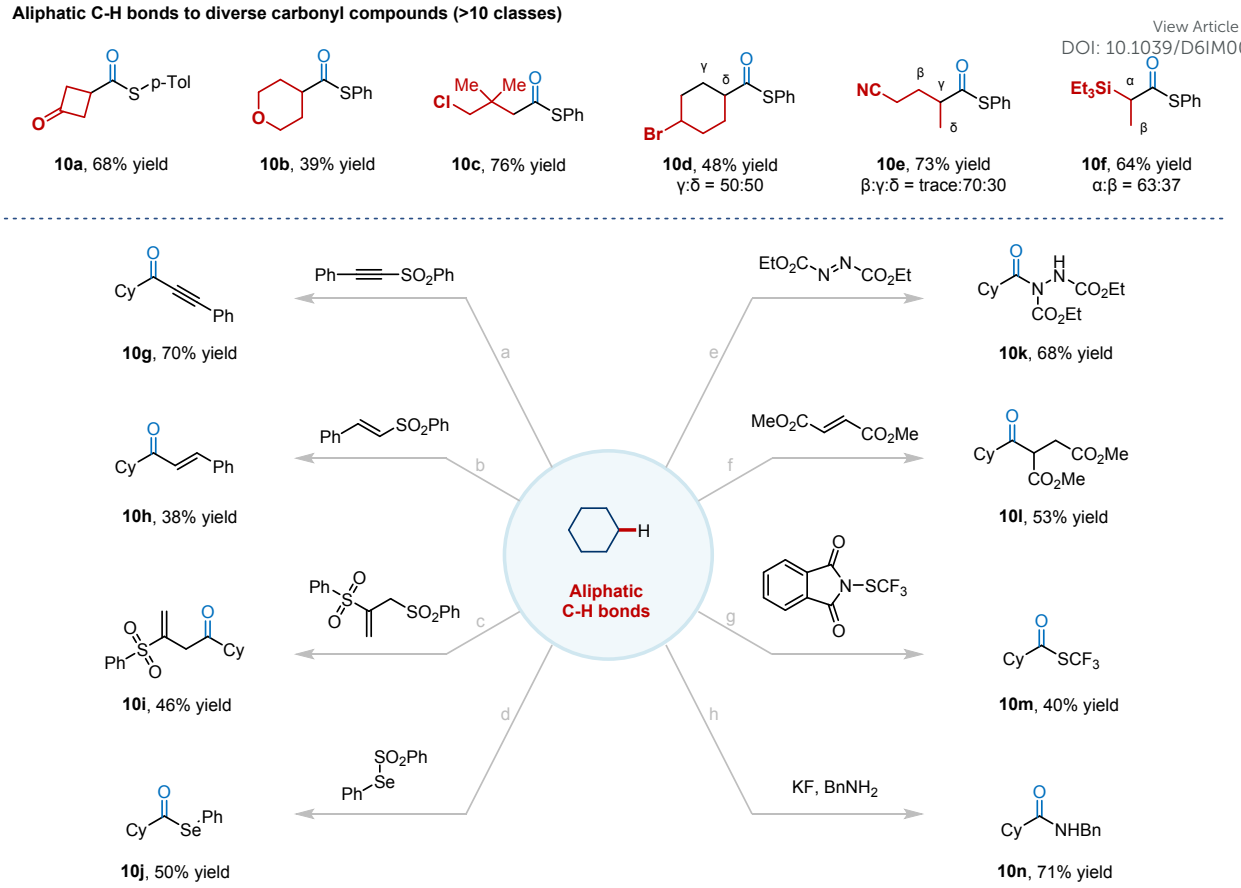

Scheme 12 Alkanes and functionalized alkanes toward diverse carbonyl compounds.

6 Palladium catalysis

Toluene is an inexpensive and readily available basic organic chemical raw material and solvent. It is mainly derived from petrochemical and coal chemical processes and is widely used in industrial production. Direct utilization of toluene for subsequent transformations to obtain valuable downstream products is highly meaningful. In 2012, Huang group developed a nondirected C(sp^3)-H carbonylation of toluene and its derivatives, and a series of phenylacetic acid derivatives were obtained in medium to good yield. The possible mechanism was described in Scheme 13. Initially, two alkoxyl radical intermediates were produced via homolytic cleavage of the DTBP, and benzyl radical was obtained by alkoxyl radical through hydrogen atom transfer process. Under the assistance of ligands, oxidation of palladium catalyst with the two radicals via the SET process provides the benzylpalladium complex **11c**. Due to the steric hindrance of intermediate **11c**, intermediate **11f** is given slowly by CO insertion, which leads to the less hindered intermediate **11d** via an anion-exchange process. Subsequent CO insertion forms complex **11e**, and then it undergoes reductive elimination to afford the final carbonylation product along with regeneration of palladium for the next catalytic cycle. The corresponding *tert*-butyl ester **11g** might also be produced as a minor byproduct. Nucleophiles include diverse alcohols and amines (Scheme 13a).[78-79] In 2016, Lei group reported an elegant radical oxidative alkoxycarbonylation of alkanes enabled by palladium catalysis, providing an efficient route to a diverse array of alkyl carboxylates. This protocol exhibits broad compatibility with various alkanes and alcohols, delivering the desired products in good to excellent yields. (Scheme 13b).[80]

In addition to alkanes, alkenes, toluene derivatives, and ether-type compounds, thioethers are also important structural motifs. They are widely found in natural products, pesticides, pharmaceuticals, and industrial materials. Therefore, using thioether in direct C-H functionalization reaction represents a valuable transformation. In 2026, Wu and co-workers developed a palladium-catalyzed direct aminocarbonylation of thioethers (Scheme 13c).[81] This reaction features a broad substrate scope and good functional group tolerance, enabling efficient C(sp^3)-H carbonylation of thioethers to give the corresponding sulfur-containing amides **11p** in good yields.

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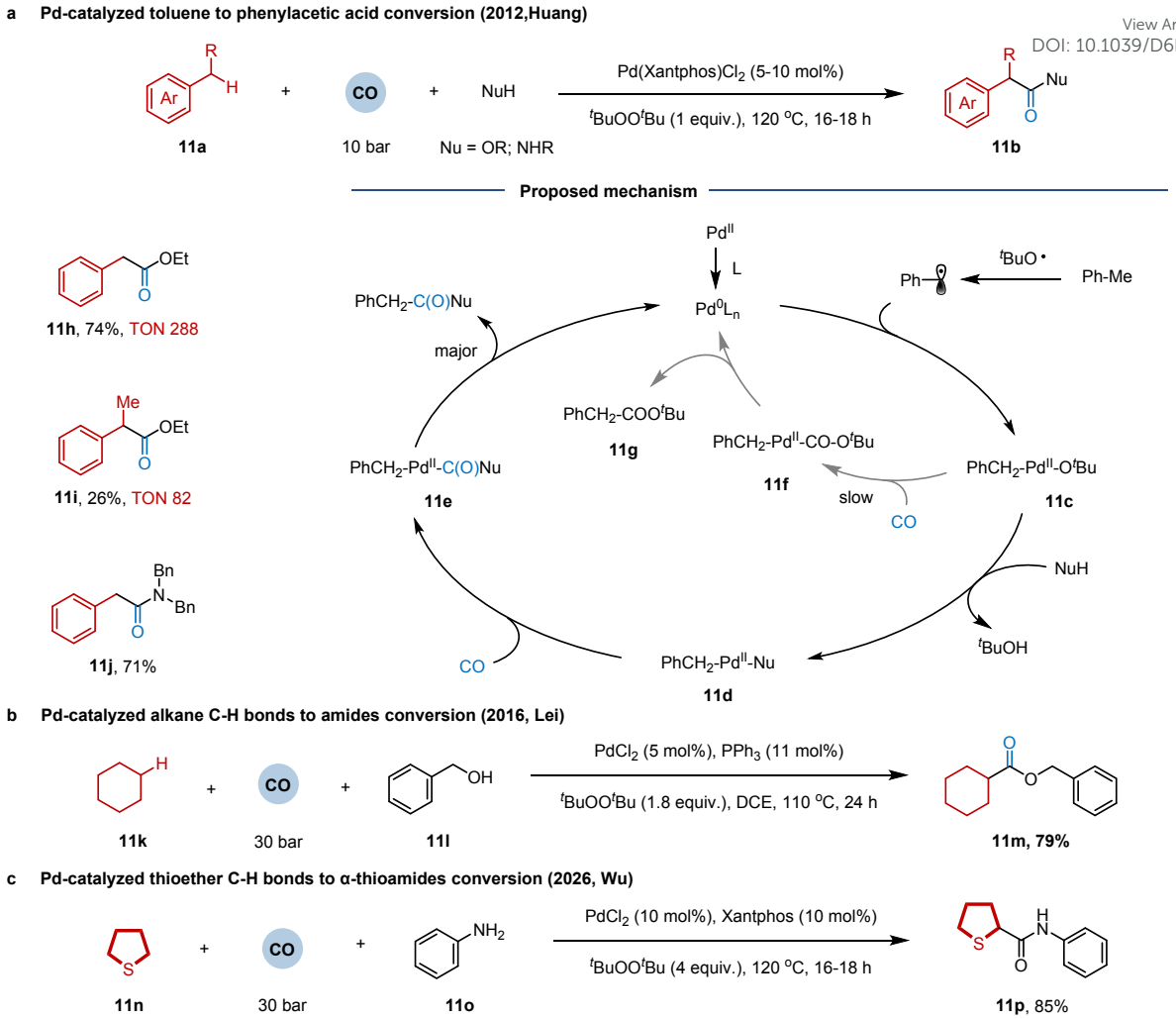

Scheme 13 Palladium-catalyzed carbonylation of arenes, alkanes, and thioethers.

In addition to realizing the direct carbonylation of toluene, Huang group has also developed more interesting carbonylative transformations of toluene. In 2023, they reported a carbonylative cycloaddition of toluene with imines to afford high-value β-lactam derivatives.[82] Mechanistically, this transformation is particularly innovative, as it involves the direct generation of a ketene intermediate from toluene. This reaction also shows good practical value. By using inexpensive starting materials such as toluene and imines, two types of bioactive molecules—antiproliferative agents and hypocholesterolemic agents—can be synthesized. As illustrated in Scheme 14, taking toluene as an example, the reaction begins with the formation of a benzyl radical **12e** from toluene under the action of DTBP. This radical is then captured by a palladium catalyst to form benzyl-palladium. Subsequently, under a CO atmosphere, migratory insertion takes place to give the acyl–palladium intermediate **12f**. Notably, intermediate **12f** undergoes β-hydride elimination to generate a ketene intermediate **12g**, which is highly reactive and undergoes cycloaddition with an imine to form the four-membered β-lactam ring. Overall, this reaction combines both practical utility and mechanistic innovation (Scheme 14a).

In 2024, the same group reported another interesting transformation.[83] This reaction employs an allylic position as the reactive site and likewise represents a C–H activation process, as illustrated in Scheme 14b. Distinct from previous examples, an allylic substrate undergoes hydrogen abstraction by DTBP to generate an allyl radical. To demonstrate the synthetic utility of this methodology, the authors further applied it to the synthesis of a biologically active antitumor agent.

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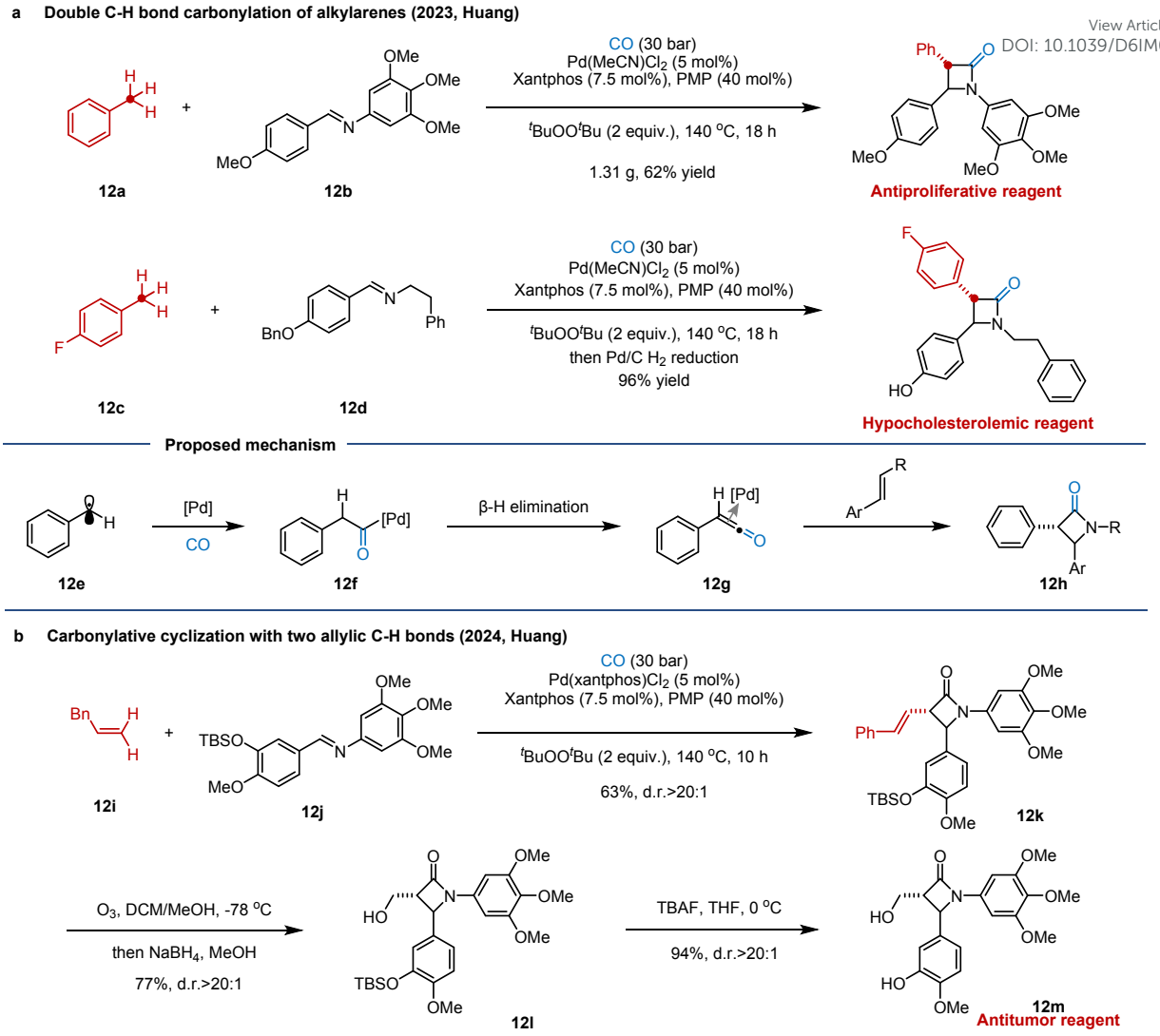

Scheme 14 Benzylic and allylic carbonylation. (a) Double C-H bond carbonylation of alkylarenes; (b) Carbonylative cyclization with two allylic C-H bonds.

7 Metal-free

In recent years, non-metal-mediated carbonylation reactions have rapidly emerged as an important complement to traditional transition-metal-catalyzed carbonylation strategies. These approaches typically rely on visible-light-driven organic photoredox catalysis or thermally induced radical processes, in which carbon-centered radicals are generated directly from inert C-H bonds via HAT or SET mechanisms. As a result, the need for pre-functionalization of substrates is avoided, significantly improving both step and atom economy. The resulting alkyl or aryl radicals can efficiently capture carbon monoxide to form acyl radical intermediates, which subsequently undergo addition, coupling, or migration processes, enabling the synthesis of a wide range of carbonyl compounds, including aldehydes, ketones, and α,β-unsaturated carbonyl derivatives. Nevertheless, due to the inherently high reactivity of radical intermediates, precise control over regio- and chemo-selectivity remains a significant challenge. In addition, further improvements are still required in terms of reaction efficiency, substrate scope, and scalability. Overall, non-metal carbonylation strategies integrate radical chemistry with CO insertion, offering a green and promising pathway for the efficient construction of value-added carbonyl compounds from simple feedstocks.

From the perspective of industrial chemical applications, the direct carbonylation of alkanes with CO, both of which are bulk commodity feedstocks, offers significant atom economy and strong industrial appeal for the synthesis of value-added carbonyl compounds. To achieve this goal, metal-free radical oxidative carbonylation strategies have demonstrated unique advantages. In 2017, the Lei group reported a metal-free protocol using DTBP as the oxidant to enable radical oxidative coupling of simple alkanes such as cycloalkanes with CO and alcohols or amides, successfully affording a series of esters and imides (Scheme 15a). This method avoids issues associated with transition-metal residues while showing broad substrate applicability and potential for gram-scale synthesis.[84] Building

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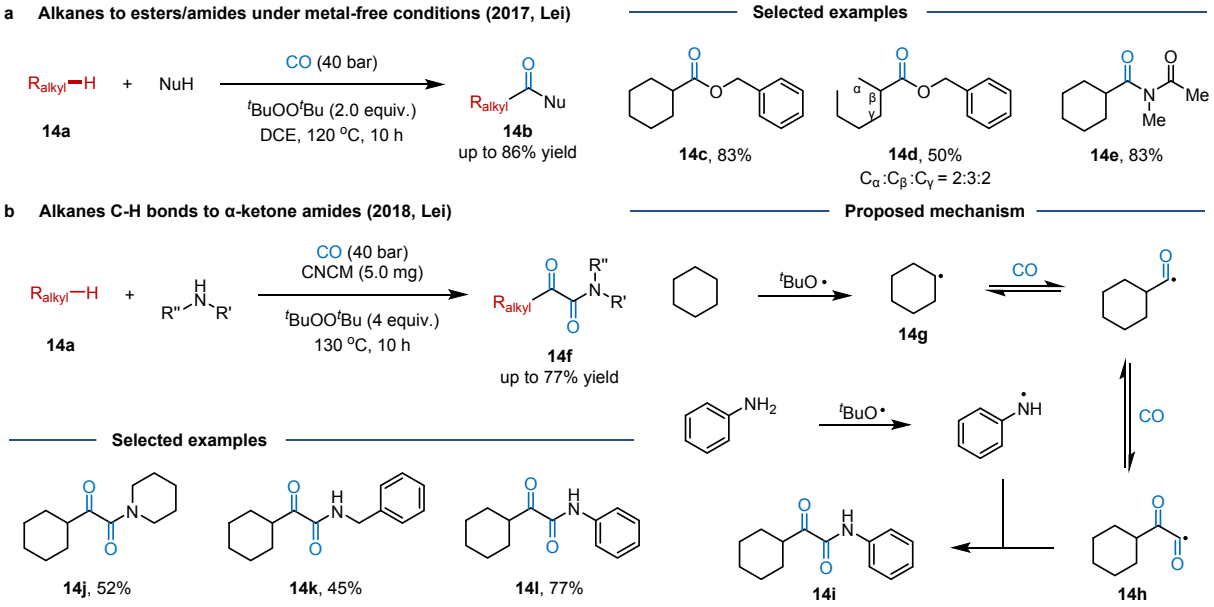
on this work, in 2018 the same group further extended the methodology to the more challenging double carbonylation reaction (Scheme 15b). The authors also proposed a plausible mechanism in which *tert*-butoxy radicals, generated by thermal homolysis of DTBP, activate alkanes to form alkyl radicals **14g**, which subsequently undergo sequential coupling with two molecules of CO to generate α-ketoacyl radicals **14h**, followed by coupling with aminyl radicals to furnish valuable α-ketoamide products. To address the key challenge of amine substrate decomposition under oxidative conditions, this study innovatively introduced chitin-derived nitrogen/oxygen co-doped carbon nanofiber microspheres (CNCM) as a promoter. Owing to their high surface area, hierarchical porous structure, and abundant oxygen/nitrogen-containing functional groups, CNCM can effectively adsorb amine substrates and suppress their oxidative degradation, significantly improving the double carbonylation yield to 77%, while also allowing catalyst recyclability.[85] The key advantage of these two studies lies in their shared strategy: both utilize tert-butoxy radicals generated from the thermal decomposition of DTBP to activate alkane C(sp^3)-H bonds via HAT, thereby forming alkyl radicals that subsequently undergo radical carbonylative coupling with CO, all without the need for metal catalysts. This approach directly employs inexpensive alkanes and CO as starting materials, featuring operational simplicity and the absence of metal contamination, thus providing a green and economically attractive pathway for upgrading bulk chemicals into high-value products.



Scheme 15 Metal-free radical oxidative carbonylation of alkanes via DTBP-enabled HAT process.

Light, as a clean and sustainable energy source, has long played a crucial role in promoting chemical transformations, and the integration of photochemistry with catalytic technologies has significantly advanced this field. In 2021, the Li group developed a three-component carbonylative coupling strategy based on the synergistic combination of organic photoredox catalysis and HAT, enabling the direct coupling of simple alkanes, alkenes, and CO for the efficient construction of α,β-unsaturated ketone frameworks (Scheme 16).[86] Specifically, the system employs 4CzIPN as the organic photocatalyst, while *N*-alkoxyazinium salt A serves both as the oxidant and as the precursor of oxygen-centered radicals under visible-light irradiation. Through a HAT process, hydrogen atoms are directly abstracted from inert alkanes to generate alkyl radicals **15g**, thereby avoiding the dependence on pre-functionalized substrates such as halides or amine salts required in traditional methods. The resulting alkyl radical **15g** subsequently combines with CO to form the acyl radical **15h**, which further undergoes addition to alkenes to generate intermediate **15i**. Subsequent single-electron oxidation and deprotonation then furnish the target α,β-unsaturated ketone product **15b**. This method proceeds under transition-metal-free conditions, exhibits broad substrate scope, including various diarylethylenes as well as cyclic and linear alkanes, and demonstrates potential for late-stage functionalization.

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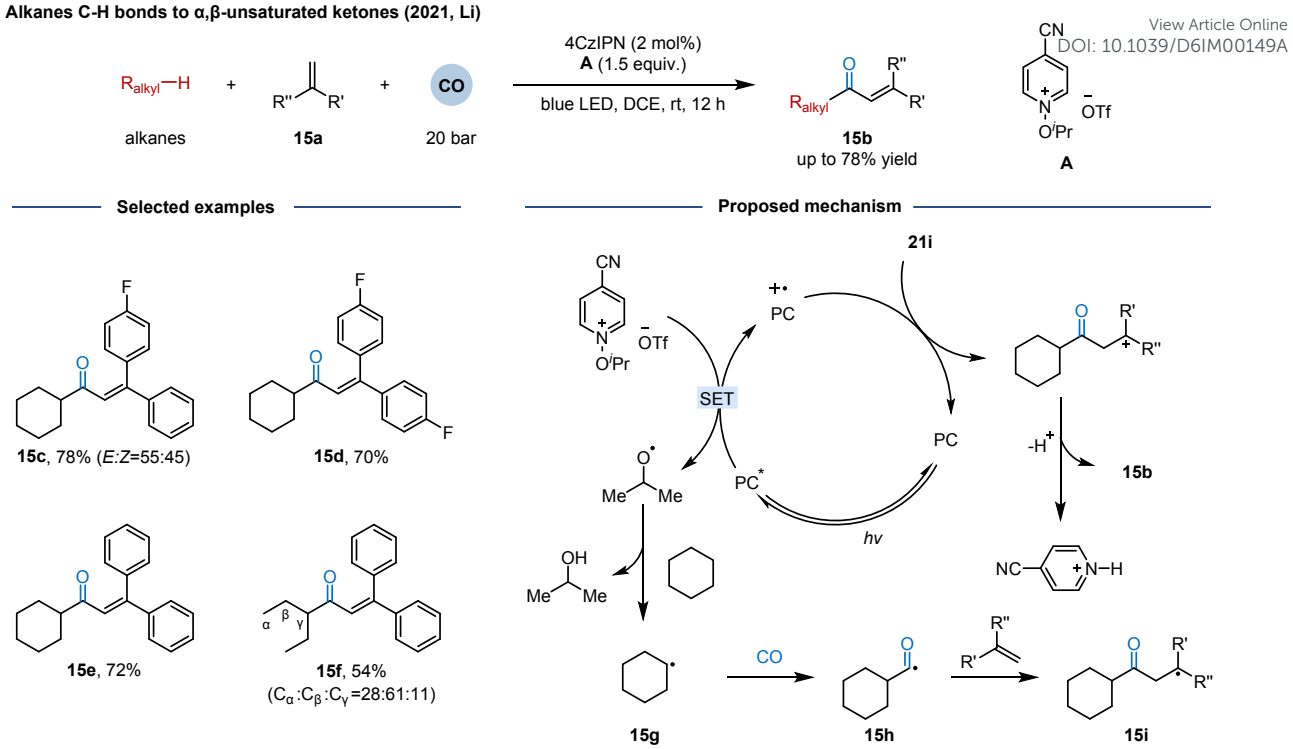

Scheme 16 Metal-free visible-light-driven carbonylation of alkanes with alkenes.

In radical carbonylation processes, the capture of CO is typically achieved by electron-rich carbon-centered radicals. Interestingly, silicon, which belongs to the same Group 14 as carbon, can also generate silyl radicals that trap CO through a similar pathway, thereby forming silyl acyl radical intermediates. In 2024, the Hou group reported for the first time a visible-light-mediated, metal-free strategy for the generation and transformation of silyl acyl radicals, enabling the efficient synthesis of acylsilanes (Scheme 17).[87] This method employs inexpensive and readily available hydrosilanes and CO as starting materials. Under the action of the organic photocatalyst 4CzIPN and a HAT catalyst, a silyl radical intermediate **16m** is generated in situ, which subsequently captures CO to form the silyl acyl radical intermediate **16n**. This intermediate is then trapped by electrophilic reagents such as alkenes or azo dicarboxylates to give intermediate **16o**, which ultimately undergoes single-electron reduction or radical hydrogenation to afford structurally diverse acylsilanes **16b** in a one-step process. The system operates under mild conditions with high atom economy, avoids the use of transition metals and sensitive reagents, and exhibits good functional group tolerance and broad substrate scope. Notably, the process can be scaled up to the gram level in a continuous flow photoreactor, delivering high conversions even under relatively low CO pressure and short residence times (15 minutes).

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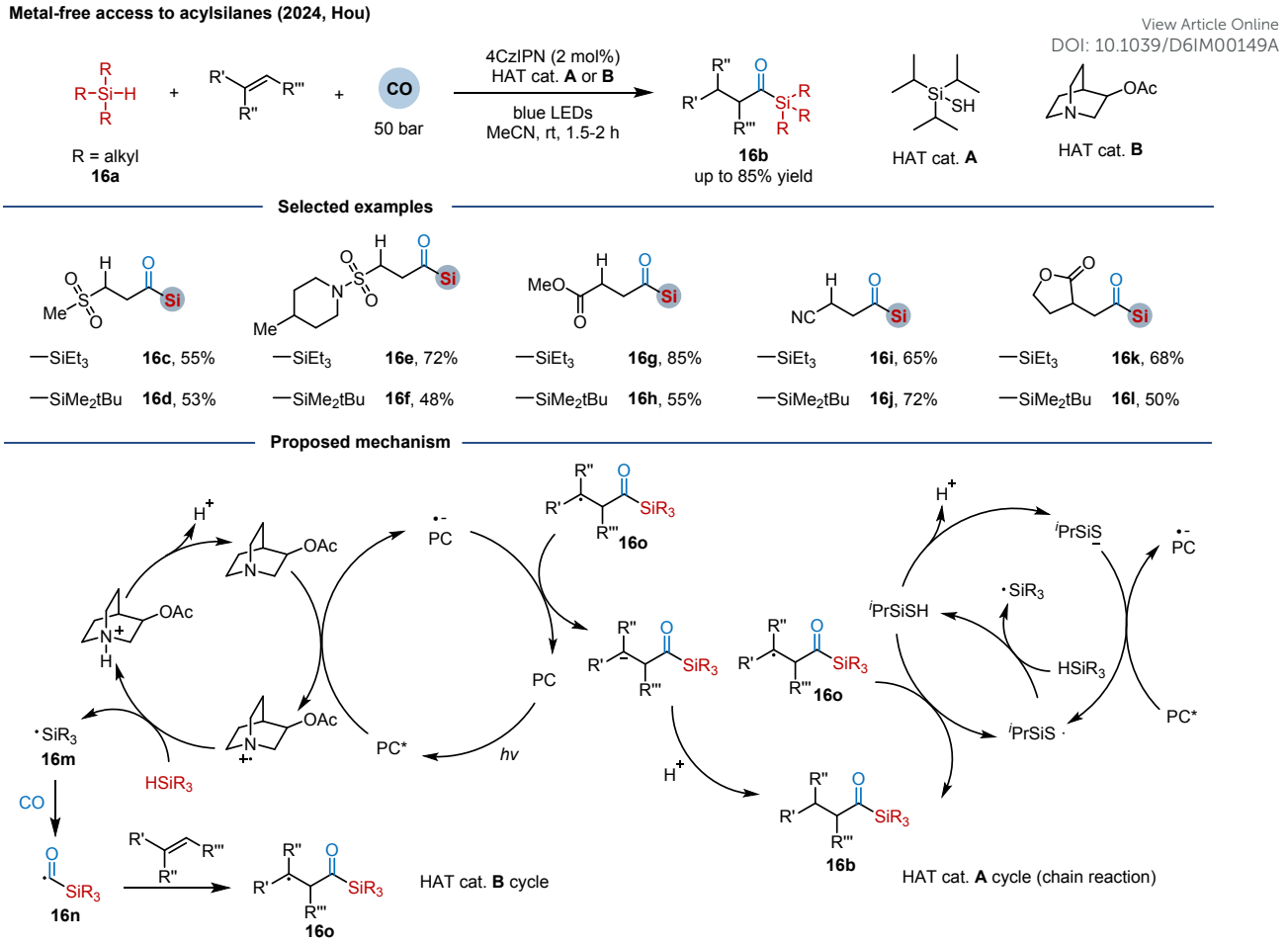
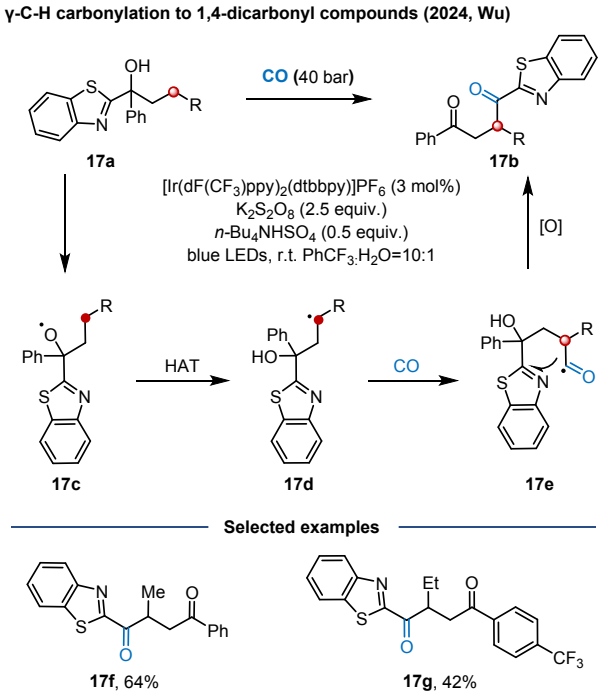


Scheme 17 Metal-free visible-light-driven carbonylation of hydrosilanes with alkenes.

The bond dissociation energy of O-H bonds is generally higher than that of C-H bonds, which enables oxygen-centered radicals to activate alkanes with broad generality. In 2024, the Wu group developed a remote γ-C(sp^3)-H heteroarylative carbonylation strategy based on CO insertion and photocatalytic HAT, successfully achieving the efficient conversion of tertiary alcohols into 1,4-dicarbonyl compounds (Scheme 18).[88] This method utilizes inexpensive and readily available CO as both a C1 source and a carbon-chain extension reagent. Under blue LED irradiation, a high-oxidation-potential Ir photocatalyst in combination with potassium persulfate generates the alkoxy radical **17c**, which initiates a 1,4-HAT process to form intermediate **17d**. Subsequent capture of CO affords intermediate **17e**, which promotes 1,4-migration of the heteroaryl group, thereby overriding the traditionally favored 1,5-HAT pathway and significantly improving the selectivity toward the target product **17b**. The reaction delivers the desired products in moderate to good yields and exhibits excellent tolerance toward a variety of substituents on the aromatic ring, including strongly electron-withdrawing groups such as the trifluoromethyl-substituted substrate **23g**. Notably, replacing the butyl group with a propyl group effectively suppresses side reactions, enabling precise functionalization at the remote γ position.



Scheme 18 HAT-enabled γ-C(sp^3)-H carbonylation of tertiary alcohols.

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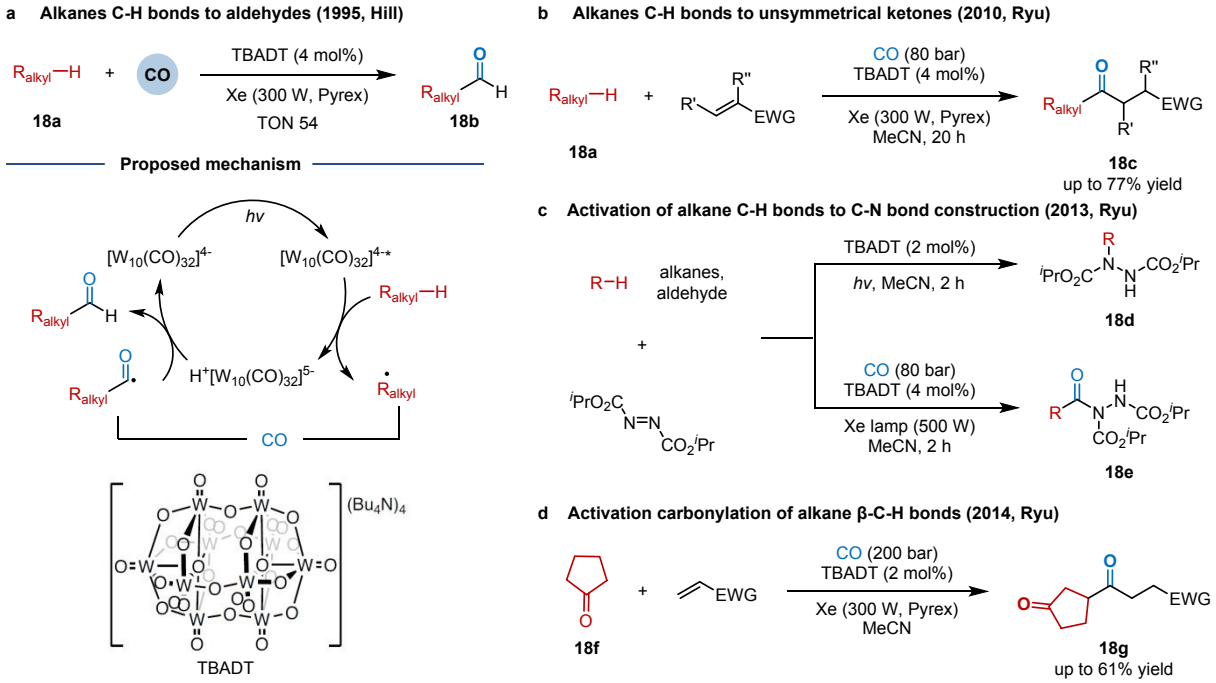
8 TBADT catalysis

Tetrabutylammonium decatungstate (TBADT) is a photosensitive species capable of activating alkane C-H bonds. Upon UV-light irradiation, the W=O bonds in decatungstate are excited to generate oxygen-centered radicals that can abstract hydrogen atoms, thereby enabling direct C-H bond activation. In 1995, the Hill group was the first to apply this type of catalyst to alkane C-H activation carbonylation reactions, successfully achieving the direct synthesis of aldehydes from alkanes (Scheme 19a).[89] This pioneering study established the feasibility of combining HAT-mediated C-H activation with CO incorporation and laid the foundation for the subsequent development of TBADT-catalyzed carbonylation chemistry. Under atmospheric pressure of carbon monoxide (1 bar) and UV irradiation, inexpensive and readily available alkanes such as cyclohexane, cyclooctane, and *n*-hexane were directly converted into the corresponding aldehydes. TBADT, as an efficient and recyclable polyoxometalate photocatalyst,[90] can directly activate inert C(sp³)-H bonds in a variety of substrates, including alkanes and cyclopentanone, under mild conditions.[91-92]



Scheme 19 TBADT-catalyzed C-H carbonylation to aldehydes, amides, and ketones.

Based on this strategy, Fagnoni and co-workers developed a series of radical carbonylation and functionalization reactions. In the presence of CO, TBADT photocatalyzes the three-component coupling of cycloalkanes or cyclopentanone with electron-deficient alkenes, enabling the highly selective construction of unsymmetrical ketones **18c** and β-acyl cyclopentanone derivatives **18g**. Under CO-free conditions, TBADT can also promote radical addition of C-H bonds from alkanes, aldehydes, or ethers to diisopropyl azodicarboxylate (DIAD), affording product **18d** and enabling efficient C-N bond formation; furthermore, by introducing CO, acyl hydrazide products **18e** can be obtained. Notably, this system exhibits excellent site selectivity. According to the polar transition-state theory, hydrogen atom transfer at the α-position of cyclopentanone is disfavored due to the formation of an unfavorable umpolung transition state, whereas β-C-H abstraction occurs preferentially, resulting in the exclusive formation of β-acylated product **27b**. These transformations require no transition-metal catalysts and proceed smoothly using only TBADT under simulated sunlight or natural sunlight irradiation, featuring operational simplicity and high atom economy. Moreover, they have been successfully extended to gram-scale synthesis and continuous-flow photoreactors, demonstrating strong potential for industrial-scale applications. These studies clearly demonstrate that TBADT-mediated photocatalytic C-H activation provides a highly promising green chemical strategy for the efficient synthesis of value-added carbonyl compounds, nitrogen-containing compounds, and other fine chemicals from inexpensive feedstocks such as alkanes, ketones, and nitriles.

In 2023, the Noël group developed a continuous-flow process based on HAT photocatalysis, achieving for the first time the direct C(sp³)-H carbonylation of a broad range of saturated hydrocarbons, from light alkanes (C1-C4) to heavier hydrocarbons and even natural product derivatives (Scheme 20).[42] Building on their pioneering studies on C(sp³)–H functionalizations of light hydrocarbons using decatungstate photocatalysis in flow,[93] the authors employed inexpensive and readily available TBADT as the photocatalyst. Under UV-LED irradiation, alkyl radicals were generated in situ from alkanes under mild conditions. These radicals subsequently undergo a three-component tandem coupling with carbon monoxide and

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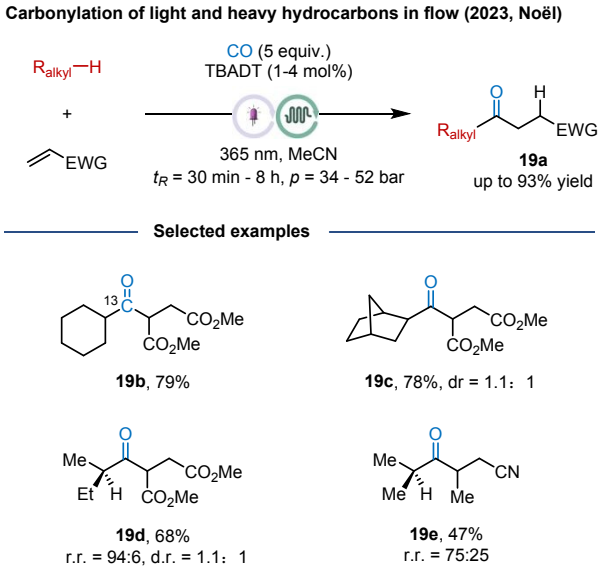
electron-deficient alkenes, efficiently constructing unsymmetrical ketones **19a**. The high surface-area-to-volume ratio and uniform light penetration of the flow reactor significantly improve gas-liquid mass transfer efficiency, reducing the residence time to less than 30 minutes. In addition, precise back-pressure control effectively suppresses the non-carbonylative Giese side reaction. This process not only demonstrates excellent substrate compatibility, ranging from cyclohexane and linear alkanes to light alkanes, but also enables gram-scale synthesis and ^{13}CO isotopic labeling to afford product **19b** through the continuous-flow platform, while significantly reducing the safety risks associated with handling high-pressure flammable gases.

In 2024, the Gong group proposed an "equilibrium utilization" strategy by coupling reversible photocatalytic alkane carbonylation with asymmetric tandem transformations, successfully enabling the efficient and enantioselective synthesis of β-amino ketones **20d** and α-amino ketones **20e** directly from simple bulk feedstocks such as alkanes, carbon monoxide, and anilines (Scheme 21).[94] Using TBADT as the HAT photocatalyst, the method generates aldehyde intermediate **20b** or acyl radical intermediate **20c** in situ under low CO pressure (2-3 bar) and mild 390 nm LED irradiation. These intermediates subsequently undergo relay transformations through either a chiral sodium phosphate-catalyzed asymmetric Mannich reaction or an asymmetric radical addition process, thereby overcoming the low conversion typically caused by the reversible equilibrium of alkane carbonylation. This protocol not only affords products such as **20f-20i** in good yields but also achieves gram-scale synthesis through the combination of continuous-flow and batch reactors, as demonstrated by the 4.6 g preparation of β-amino ketone **20f**.



Scheme 20 Carbonylation of light and heavy alkanes to ketones.

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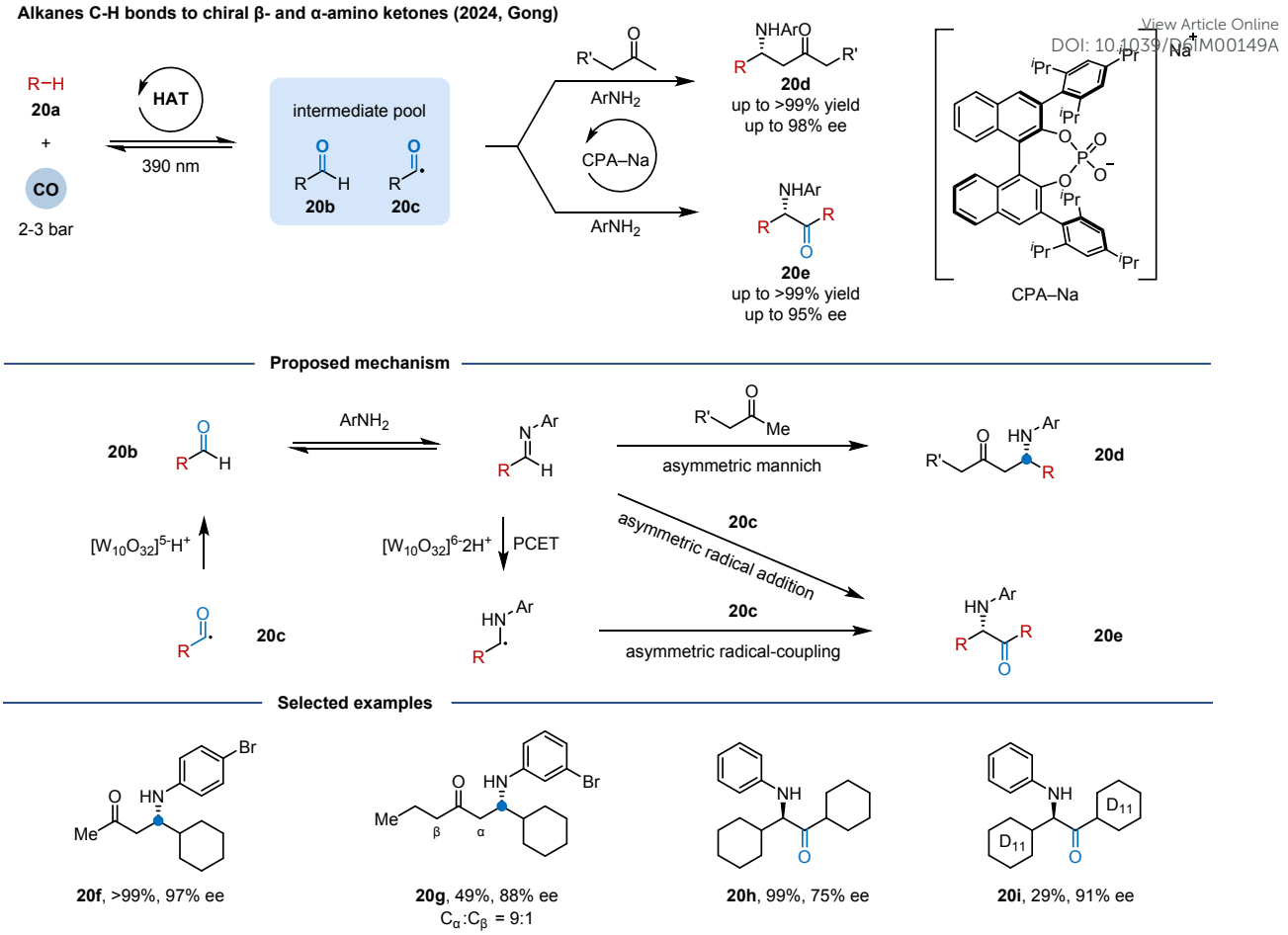

Scheme 21 Alkanes C-H bonds to chiral β- and α-amino ketones.

9 Summary and outlook

Aliphatic C-H bonds are ubiquitous in industrial feedstocks and natural molecules, and their direct carbonylation provides an efficient and atom-economical strategy for the construction of carboxylic acids and related derivatives. Carbon monoxide, as an ideal C1 synthon, enables direct conversion of inert C-H bonds into carbonyl functionalities without prefunctionalization. In recent years, HAT-based carbonylation strategies have emerged as an increasingly powerful approach in this field. Among them, HAT-based approaches enable selective activation of remote and otherwise inert C-H bonds by leveraging intrinsic differences in BDEs and the reactivity of open-shell intermediates, thereby overcoming the limitations of traditional directing-group strategies in terms of site selectivity and substrate scope. The reactivity of HAT-mediated carbonylation arises from the synergistic interplay of multiple factors, including BDE-driven radical generation, reversible CO capture equilibria, as well as combined effects of radical polarity matching and steric control. Overall, these transformations typically proceed through a cascade sequence involving hydrogen atom transfer, carbon monoxide capture, and acyl radical formation to construct key C-C(O) bonds. From the perspective of converting bulk chemicals into value-added products, this Review summarizes representative advances in this area, with a particular emphasis on homogeneous catalytic systems. Despite significant progress in reaction design and catalytic development, important challenges remain, particularly in scalability, control of CO insertion efficiency, and site-selectivity in structurally complex molecules. Future development of this field may proceed in three main directions: First, further improvements in reaction efficiency and CO utilization are necessary for practical applications in the production of fine chemicals and carboxylic acids. Second, the development of milder, safer, and more sustainable catalytic systems will be essential to enhance functional group compatibility and substrate generality. Third, achieving precise control over radical generation and reactivity, particularly through the coordinated regulation of HAT events and CO capture steps, will be crucial for enabling site-selective carbonylation of complex molecular scaffolds. Overall, with continued advances in these directions, HAT-mediated C-H carbonylation is expected to play an increasingly important role in chemical synthesis and industrial applications, representing a powerful platform for the sustainable construction of both commodity chemicals and high-value molecular intermediates.

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Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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