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Editorial

Iron-catalyzed C–H activation: A sustainable approach to efficient organic synthesis

The activation of carbon-hydrogen (C–H) bonds is of great scientific importance and offers broad applications in modern organic chemistry [1]. In recent years, strategies for C–H bond activation have made notable advances, particularly in the efficient construction of complex molecular architectures. However, most existing C–H activation systems rely on expensive noble metal catalysts, including palladium, rhodium, ruthenium, and iridium. These metals not only come at a high cost but are also often associated with significant toxicity, which further limits their viability and sustainability in industrial applications. As a result, there has been a growing focus on developing catalytic systems based on more abundant, non-toxic, and affordable metals, with iron emerging as a promising candidate [2]. As the most abundant transition metal in the Earth's crust, iron has garnered increasing attention due to its environmental friendliness, cost-efficiency, and widespread availability. Compared with noble metal catalysts, iron offers distinct economic and environmental advantages, presenting new opportunities for sustainable organic synthesis. However, the advancement of iron-catalyzed C–H activation reactions continues to face significant challenges, including the requirement for high reaction temperatures and complex reaction conditions, which limit its broader application. Moreover, iron-catalyzed systems generally exhibit lower efficiency and selectivity. Thus, despite its potential, iron's progress in C–H activation remains slow, underscoring the need for breakthroughs to boost catalytic performance.

In recent years, the advent of photocatalysis has opened up new avenues for iron-catalyzed C–H activation. Photochemical methods enable researchers to achieve efficient C–H bond activation and transformation under mild conditions, greatly enhancing both reaction selectivity and efficiency. This light-mediated approach, which involves the generation of radical intermediates, minimizes the need for high temperatures and harsh reaction conditions, showcasing the significant potential of iron catalysis in organic synthesis. For instance, in 2024, Ackermann's group introduced a photoinduced iron-catalyzed cross-coupling reaction between aryl C(sp^2)-H bonds and alkynes [3]. Using *cis*-[Fe(H)$_2$(dppe)$_2$] as the catalyst and alkynes as alkenylation reagents, the C–H activation and alkenylation of aryl imines were successfully achieved under blue light irradiation at room temperature (Fig. 1). In this reaction, iron exists as iron(0) species and activates C–H bonds through oxidative addition, with light playing a crucial role in the process. The methodology is operationally simple, does not require Grignard reagents, and offers high atom economy alongside broad substrate scope, underscoring its practicality and effectiveness in organic synthesis.

The activation of C(sp^3)-H bonds is notably more difficult than that of C(sp^2)-H bonds due to the greater chemical inertness of hydrogen atoms on sp^3-hybridized carbons. With higher bond dissociation energy (BDE), C(sp^3)-H bonds require stronger activation to engage in reactions effectively. Photo-induced, radical-mediated hydrogen atom transfer (HAT) approaches have introduced a promising strategy to address this challenge. HAT directly activates C(sp^3)-H bonds without the need for pre-functionalization or directing group installation, thus offering significant potential for selective functionalization. Nevertheless, the high reactivity of HAT reagents, coupled with the minimal bond strength differences between various C(sp^3)-H bonds, has posed persistent challenges for achieving site selectivity in linear alkanes. Hu's group recently reported an iron-promoted photocatalytic HAT process that successfully enabled terminal C(sp^3)-H borylation of alkanes (Fig. 2) [4]. This system exhibited exceptional terminal regioselectivity across a wide range of substrates, underscoring its notable advantage in regioselectivity. To further illustrate the synthetic utility of the reaction, the authors applied the methodology to the functionalization of complex molecules, including D-galactose and several drug derivatives. Additionally, gram-scale reactions with cyclohexane and *n*-hexane were conducted in a flow reactor, demonstrating the method's scalability. Catalyst recycling experiments revealed that the iron catalyst remained active through six cycles, achieving a total turnover number (TON) of 33. The *in-situ* formation of boron-sulfoxide complexes was crucial to the high terminal regioselectivity of the reaction. This study offers an innovative ap-

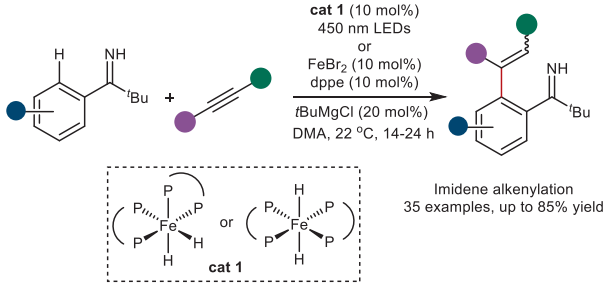

Fig. 1. Iron-catalysed C(sp^2)–H alkenylation of imines.

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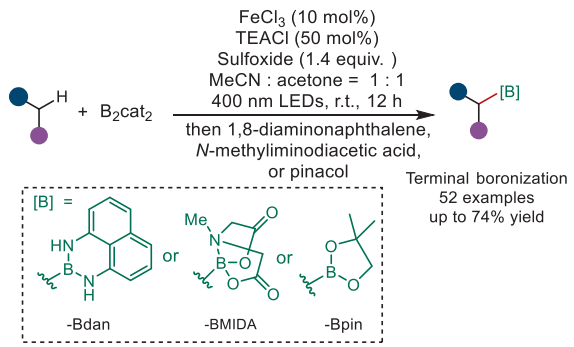

Fig. 2. Iron-catalysed terminal selective C(sp^3)–H borylation.

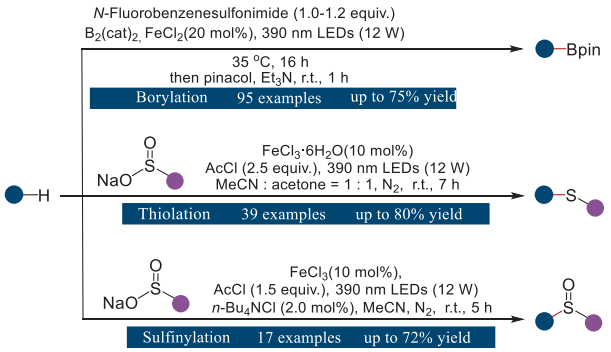

Fig. 3. Iron-catalysed C(sp^3)-H borylation, thiolation, and sulfinylation.

proach to the selective functionalization of C(sp^3)-H bonds, particularly excelling in the challenging terminal selective transformation of alkanes.

Alternatively, the photoinduced ligand-to-metal charge transfer (LMCT) process has emerged as an efficient tool for organic synthesis, offering a distinct approach from traditional redox reactions. By directly exciting high-valent metal-ligand complexes, reactive radical species can be generated, which trigger intermolecular HAT processes with hydrocarbons, thereby facilitating a wide range of C(sp^3)-H bond functionalization reactions. Xia and Guo's group successfully developed a ligand-free iron-catalyzed method for C(sp^3)-H borylation, thiolation, and sulfonylation through photoinduced LMCT (Fig. 3) [5]. This method exhibits an exceptionally broad substrate scope, encompassing over 150 examples ranging from simple alkanes to complex molecules containing C(sp^3)-H bonds, including ketones, nitriles, esters, ethers, amides, sulfonamides, halides, and silanes. Additionally, this strategy proved highly effective for the selective modification of pharmaceuticals and natural products, such as ibuprofen, celecoxib, and eucalyptol. To showcase the practical potential of the method, the team successfully carried out gram-scale synthesis of alkyl boron and alkyl sulfide compounds under continuous flow conditions, underscoring the scalability and synthetic utility of this approach. This approach effectively addresses key limitations of traditional catalytic systems, such as poor terminal regioselectivity and limited substrate applicability, and demonstrates the vast potential of the iron-catalyzed LMCT process in ligand-free C(sp^3)-H bond functionalization.

Despite the remarkable advancements in iron-catalyzed C–H activation, achieving highly efficient and selective reactions under mild conditions remains a challenge that requires further in-depth investigation and optimization. Future research should focus on expanding the substrate scope to increase the reaction's general applicability and versatility. Moreover, addressing the issue of catalyst stability during long-term cycles is critical for practical industrial applications. The integration of photocatalysis with iron catalysis offers promising avenues to overcome these challenges. In particular, fine-tuning the geometric configuration and electronic properties of iron catalysts could greatly enhance their selectivity and efficiency in complex molecule synthesis. This approach not only provides more robust strategies for precise organic synthesis but also introduces innovative methodologies and technological advancements to drive the progress of green chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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