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Research Highlight

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Regioselectivity of *N*-heteroarene electrocarboxylations: divided *vs.* undivided cell

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Site-selective C-H functionalized reactions of *N*-heteroarenes are effective approaches to the synthesis and modification of important molecules, thus providing great value for both academia and the pharmaceutical industry[1,2]. Among them, the CO_2-participated C-H carboxylation of *N*-heteroarenes attracts great attention for both economic and sustainable purposes because it can directly upgrade the greenhouse gas CO_2 to value-added molecule products[3,4]. Unfortunately, unlike the available transformation for arylation, alkylation, and borylation, the limited carboxylation synthetic methods so far still cannot break the intrinsic selectivity determined by the electro and steric structure of *N*-heteroarenes [Figure 1A and B][5-9]. How to realize the precise regioselective control of carboxylation remains a key challenge in this field.

Electrochemical organic synthesis has gained significant attention for its ability to activate molecules into unusual intermediates by providing electrons or protons under controllable potential, which has also been recently adopted in the challenging oxidative functionalization of C-H bonds[10]. Prof. Da-Gang Yu and his colleagues, at Sichuan University, in collaboration with Prof. Song Lin at Cornell University, have adopted

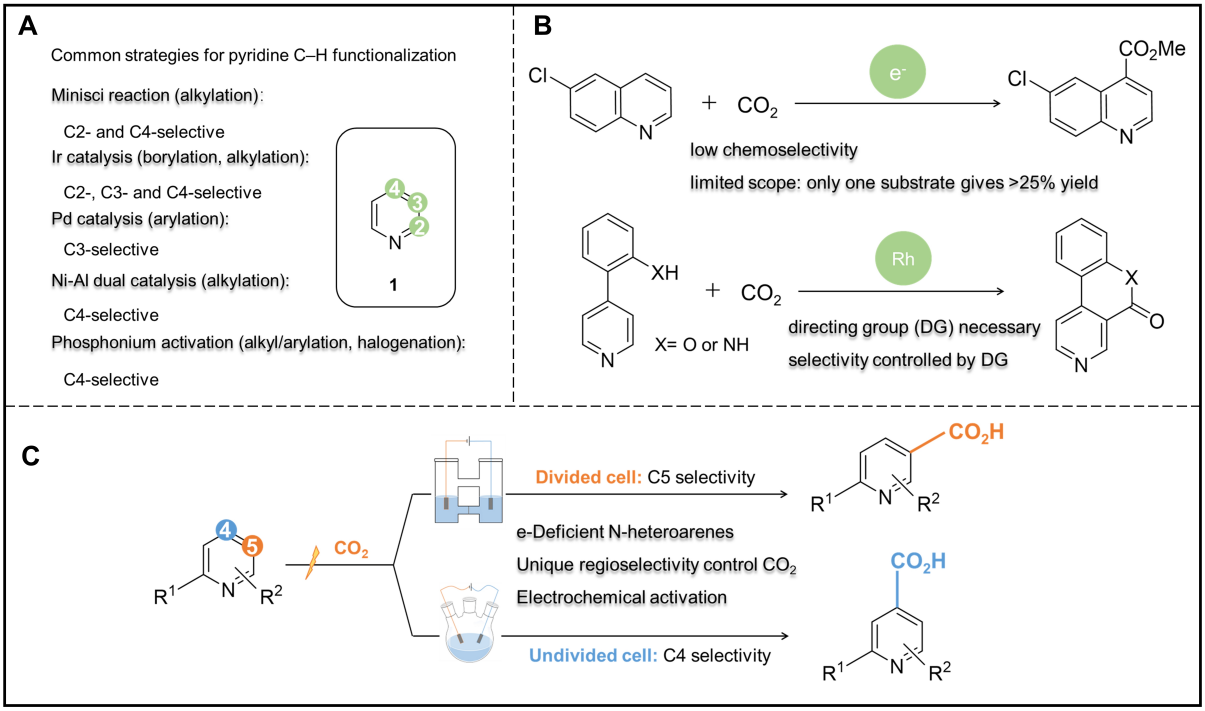

Figure 1. Strategies for pyridine C-H functionalization. (A) Common strategies on different sites with alkylation, arylation, borylation and halogenation. (B) Precedents for C-H carboxylation of pyridine and related *N*-heteroarenes with CO_2. (C) New concept of regiodivergent electrochemical C-H carboxylation of pyridines.

the electrochemical strategy to realize the direct carboxylation of *N*-heteroarenes using CO_2[11]. Impressively, they found that by changing the type of the electrolytic cell, the regioselectivity could be finely tuned between C5-carboxylation (in a divided cell) and C4-carboxylation (in an undivided cell), as shown in Figure 1C. Further mechanistic studies suggest that the C5-carboxylation in the divided cell starts with one electron reduction of the pyridine ring, forming radical anion **Int1** [Figure 2A]. Then, the nucleophilic addition of **Int1** to CO_2 takes place at the C5 position, which possesses the highest electron population among the pyridine ring carbon atoms. The resulting **Int2** would be further cathodically reduced to dianion **Int3**, followed by oxidative rearomatization by O_2 to C5-carboxylation product. However, DFT calculation depicts that the nucleophilic addition to CO_2 on **Int1** is reversible and endergonic on either C5 or C4 positions, allowing the carboxylation regioselectivity to be potentially altered if the follow-up reaction step favored an alternative pathway. Moreover, the calculation also reveals that if CO_2 is added to the C4 position, the resulting **Int4** may cost significantly lower energy during the following C-H dissociation step in the presence of a hydrogen-atom acceptor. Therefore, when the reaction takes place in an undivided cell, the anodically generated hydrogen acceptor I_2 from the electrolyte $^nBu_4NI$ promotes the more thermodynamically-favored conversion from **Int4** to **Int5** through either direct hydrogen-atom transfer (HAT) or proton-coupled electron transfer (PCET) process, and eventually diverts the reaction to C4-carboxylation pathway [Figure 2B].

More control experiments are conducted to verify their mechanism. By replacing $^nBu_4NI$ with other electrolytes, the C4-carboxylation is inhibited mainly due to the failure of generating hydrogen acceptor at the anodic side, while the reactivity of C5-carboxylation stays unaffected. The importance of pairing both electrodes in the C4-carboxylation is further highlighted by carrying an alternating current (AC) electrolysis in a divided cell and discovering C4-carboxylation as the major pathway. Moreover, it was later found that

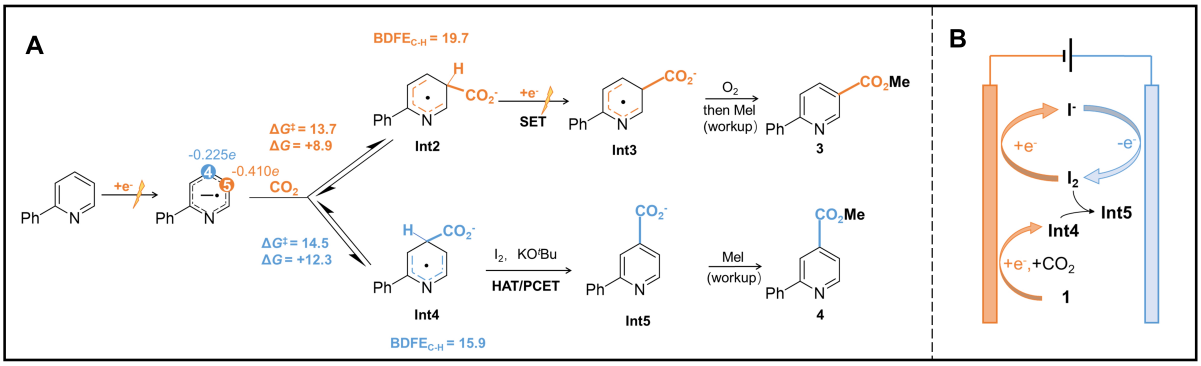

Figure 2. Possible mechanism diagram of the CO_2-participated C-H carboxylation of *N*-heteroarenes. (A) Reaction pathways determined by different mechanisms: C5-carboxylation via electro-reductive activation and C4-carboxylation via paired-electrolysis-enabled HAT. (B) Achievement of C4-carboxylation and regeneration of hydrogen acceptors in the undivided cell.

this method could be expanded to more substrates including bi- and terpyridines, pyrimidines, pyrazines and quinolines.

Meanwhile, Dr. Zhao *et al.* also observed the C4-carboxylation of pyridines during their work on C-H carboxylation of (hetero-)arenes under a similar condition using iodide-containing electrolytes in an undivided cell[12]. Interestingly, although the influence of the cell type was not explored, they discovered that the electrochemical carboxylation method could be expanded to substrates beyond pyridines. This included electron-deficient naphthalenes, simple phenyl derivatives, and substituted quinolines, all with high regioselectivity. This finding raises the question of whether the electrolyte cell type could similarly impact the electrocarboxylation regioselectivity of other arene-based substrates, and if so, whether this would result in differences in the underlying mechanism.

In summary, this work by Yu and Lin provides an effective strategy for the regioselective C-H functionalization of pyridines and related *N*-heteroarenes with CO_2 bringing advantages such as mild reaction conditions and wide substrate compatibility. Their discovery promotes the development of pharmacy and agronomy and facilitates biomolecular progress by not only enhancing the mechanistic understanding of the C-H carboxylation reaction but also contributing to the utilization of CO_2.

DECLARATIONS

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Authors' contributions

Wrote the draft manuscript: Zhong G

Revised and rewrote the manuscript: Huang Y, He L

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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