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Editorial

Divided or undivided? Electrolytic cells regulate site selectivity in C–H carboxylation of *N*-heteroarenes

The precise synthesis of molecules is of great significance to the fields of life science, material science, pharmaceutical chemistry and so on. The development of chemo-, regio- and stereo-selective reactions is therefore highly demanding in synthetic chemistry. Pyridines and related *N*-heteroarenes are core structures in various medicines, agricultural chemicals and bioactive molecules. The C–H functionalization of *N*-heteroarenes is becoming an important means to achieve the precise synthesis of many drugs and other functional molecules [1]. At present, the C–H arylation, alkylation and borylation of pyridine and its derivatives have been well reported, however, the C–H carboxylation of pyridine and other *N*-heteroarenes is rather underdeveloped. Carbon dioxide (CO_2) is an attractive renewable C1 source for both biological and chemical synthesis [2]. Along this line, it is of high values to provide accurate access to important *N*-heteroaromatic carboxyl acid derivatives through direct functionalization of C–H bonds in *N*-heteroarenes using CO_2 as an ideal carboxylation reagent. Despite impressive advances made in the above approach, great challenges still remain such as heavy substrate limitations and absence of precise selectivity control by means of other than electro- and stereo-structure of the feedstock itself.

Meanwhile, organic electrosynthesis, which uses electrons as redox reagents, is emerging as a unique and increasingly powerful method to prepare value-added compounds with electricity input instead of traditional redox chemicals. Among varied electrochemical reactions, electrocarboxylation with CO_2 proved to be a promising strategy for direct synthesis of carboxylic acids [3,4]. It is therefore of great interest whether electrosynthesis could meet the above-mentioned challenges in precise C–H carboxylation of *N*-heteroarenes. Very recently, Yu, Lin and co-workers reported a highly selective site-regulated C–H carboxylation of *N*-heteroarenes by changing the electrochemical reactors [5], where a divided cell gave rise to C5-carboxylation of pyridines and an undivided cell resulted in C4-carboxylation remarkably (Fig. 1).

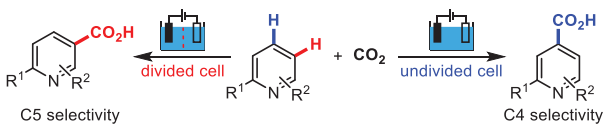

Fig. 1. Cell-regulated regiodivergent electrochemical C–H carboxylation of pyridines.

The authors first used 2-phenylpyridine as a model substrate to optimize the electrochemical reaction conditions and the C5-carboxylation product was selectively obtained (C5/C4 > 20:1) with a CO_2 balloon in a divided cell of $^nBu_4NI$/NMP electrolyte solution when iron and zinc were adopted as a cathode and sacrificial anode respectively with $Cu(OTf)_2$, KO^tBu, H_2O and O_2 as promoters (Fig. 2). In a sharp contrast, the C4-carboxylation product was favorably formed (C4/C5 > 20:1) using the iron cathode and platinum anode with KO^tBu in an undivided cell. This electrochemical protocol occurred under mild reaction conditions and proved to be of wide substrate applicability and good functional group compatibility on a series of substituted pyridine, quinoline and other *N*-heteroarenes. It's noteworthy that important nitrogenous aromatic carboxylic acids could be accessed from *N*-heteroarenes with CO_2 in moderate to good yields with precise and tunable control of site-selectivity.

Through mechanistic experiments and theoretical calculations, Yu, Lin and co-workers proposed the possible pathways for the site-divergent electrochemical C–H carboxylation reactions (Fig. 3). In divided cells, one-electron reduction of 2-phenylpyridine at the cathode generated radical anion **Int1**, the C5 position of which with higher electron density preferentially underwent nucleophile attack on CO_2 affording **Int2**. The second single electron reduction gave dianion **Int3**, which was then oxidized by O_2 to afford the C5 carboxylation product. DFT calculations confirmed that nucleophilic attack at the C5-position was preferred to that at the C4-position ($\Delta G^{\ddagger} = 13.7$ kcal/mol for C5 and 14.5 kcal/mol for C4). These thermodynamic data showed that the attack of radical anion **Int1** on CO_2 was reversible at both C5 and C4 positions. Moreover, DFT calculations indicated that the C4–H bond dissociation free energy in **Int4** was significantly lower than that of C5–H bond in **Int2**. In undivided cells, anodic oxidation of a large amount of I^- to I_2 compensated for non-productive reduction of I_2 at the cathode (Fig. 4). As a hydrogen acceptor, I_2 promoted the hydrogen atom transfer (HAT) or proton-coupled electron transfer (PCET) process of **Int4**, thereby altering the reaction selectivity by Curtin-Hammett principle [6] to deliver the C4-carboxylation products.

As further evidences for the above proposed mechanism, alternating current electrolysis was performed using a divided electrochemical cell, which mimicked an undivided cell by programmable changing the electrode. The radical anion **Int1** and I_2 were thus formed in the same chamber and the C4-carboxylation product was indeed detected as the major one. Meanwhile, the experiments on kinetic isotope effect showed that the k_H/k_D value was 2

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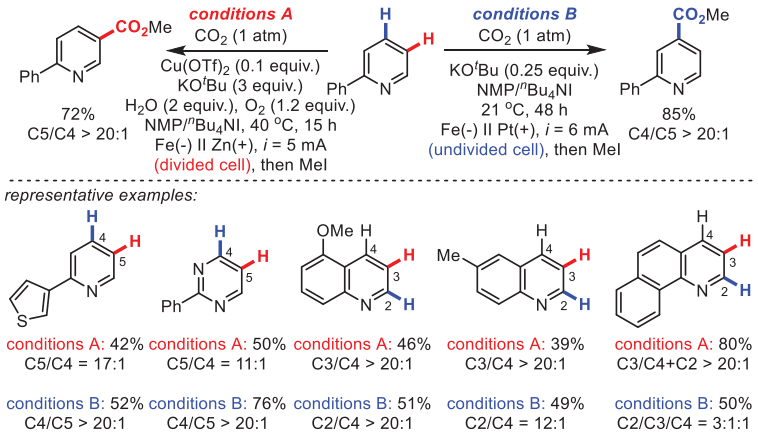

Fig. 2. Scope of electrochemical C–H carboxylation of pyridines.

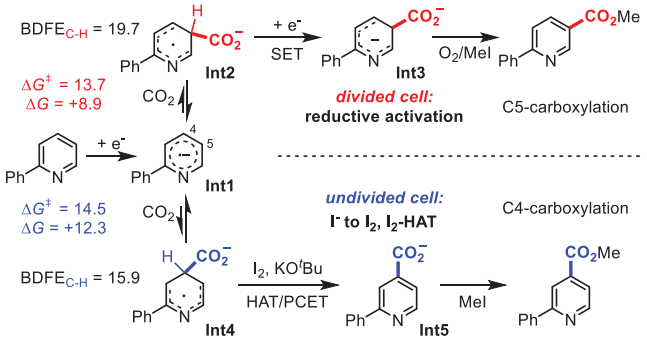

Fig. 3. Proposed mechanism for C5- and C4-carboxylation of pyridines.

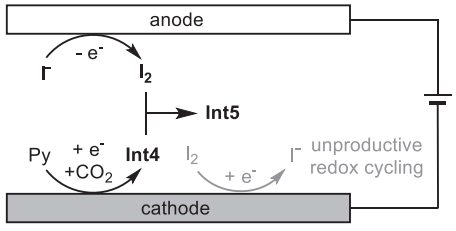

Fig. 4. Anionic oxidation of I^- to I_2 and its key role as a hydrogen acceptor for C4-carboxylation.

at C4 in the undivided cell, indicating that the C–H bond cleavage was rate-determining for C4-carboxylation, which was consistent with the proposed mechanism in Fig. 3.

In summary, Yu, Lin and coworkers developed an electrochemical strategy for highly site-selective C5–H and C4–H carboxylation of *N*-heteroarenes with CO_2 to achieve the precise synthesis of *N*-heteroaryl carboxylic acid molecules. Unlike the traditional tools to control the regio-selectivity in C–H functionalization including substrates' intrinsic electro- and stereo-structures, installation of directing groups, and catalyst/ligand design, this novel strategy realized the divergent site-selectivity by changing the electrochemical reactors, namely the undivided and divided cells, which provides inspiring hints for the selective regulation of various reactions beyond C–H activation. Also, this work demonstrates huge potentials and prospects of organic electrosynthesis and we believe that electrochemistry will greatly reshape the traditional synthesis of various functional molecules.

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