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Synergy of Anodic Oxidation and Cathodic Reduction Leads to Electrochemical C-H Halogenation

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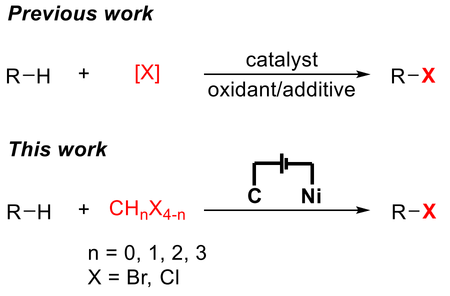
Summary of main observation and conclusion We herein uncovered an electrochemical C-H halogenation protocol that synergistically combines anodic oxidation and cathodic reduction for C-X bond formation. The reaction was demonstrated under exogenous-oxidant-free conditions. Moreover, this is the first example of activating CBr_4, $CHBr_3$, and CCl_3Br under electrochemical conditions.

Background and Originality Content

Electrochemical synthesis is a cost-effective, scalable and environmentally friendly method for C-H functionalization with the prospect of avoiding the use of stoichiometric oxidants or reductants.[1] In the past few years, extensive efforts have been made and great achievements have been accomplished.[2] In most cases, however, only one of the two electrochemical half-reaction leads to the product of interest, the chemistry that occurs at the counter electrode does not generate the target products. For example, the electrochemical anodic oxidation drived C-H functionalization, in which only anodic reaction yields expected products. Undoubtedly, synergy of anodic oxidation and cathodic reduction leads to C-H functionalization is a more ideal strategy. However, up to now, the strategic use of this concept in organic reaction design and discovery remains very rare and great challenge.[3]

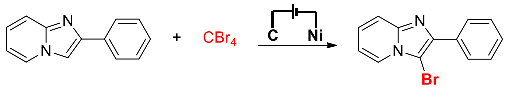
Organic halides, either aryl or alkyl halides are significant motifs frequently found in many biologically active compounds,[4] and serve as versatile building blocks for constructing various complex molecules.[5] Despite of remarkable progress in the field of synthesizing organic halides,[6] the reported methods frequently require stoichiometric oxidants/additives, metal catalysts, leaving groups/directing group, and/or toxic halogenating reagents (Scheme 1, top).

Scheme 1 Methods for C-H halogenation



Carbon tetrabromide is a readily available commercial reagent and has been widely used for organic synthesis.[7,8] Previous studies have revealed that carbon tetrabromide could take one electron from the electron donors and is reduced to bromine ion and tribromomethyl radical.[9] We recognized that above reductive transformation might also be achieved under the electrochemical conditions. Inspired by this idea and the fact that synergy of anodic oxidation and cathodic reduction forms the useful products is a more ideal strategy for C-H functionalization, we herein uncovered an electrochemical C-H halogenation protocol that tactfully makes anodic oxidation and cathodic reduction synergy for C-X bond formation (Scheme 1, bottom). It is worth noting that this is the first example of activating CBr_4, $CHBr_3$, and CCl_3Br under electrochemical conditions. Moreover, this reaction features broad substrate scope and can be easily scaled-up.

Table 1 Effect of reaction parameters[a]



1a **2a**

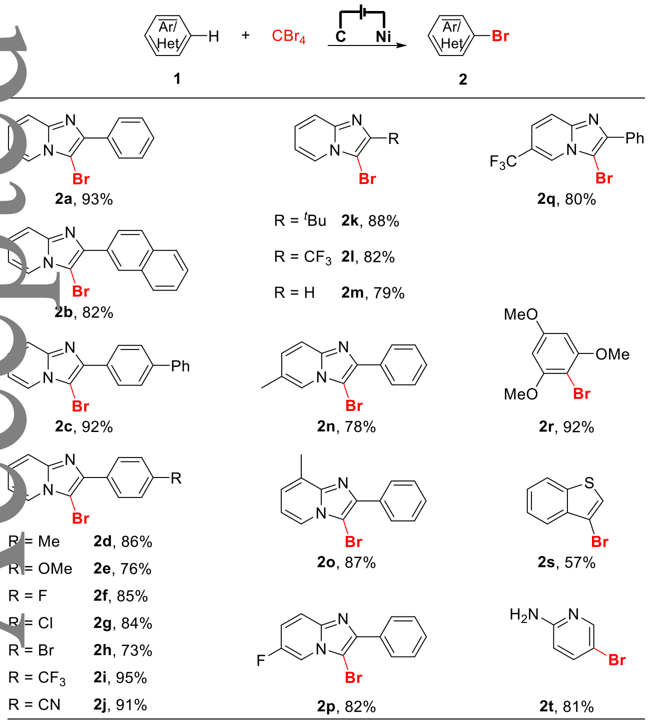
Entry	Variation from standard conditions	Yield (%)
1	none	93
2	C (+) | SS (-)	90
3	C (+) | Pt (-)	85
4	Pt (+) | Ni (-)	94
5	6 mA, 5,0 h	91
6	18 mA, 1.7 h	88
7	$^nBu_4NPF_6$	88
8	$^nBu_4NClO_4$	84
9	CH_3CN	82
10	CH_3CN/H_2O	89
11	$CH_3CN/MeOH = 10.5/0.5$	86
12	CH_3CN /MeOH = 9/2	88
13	no electric current	0
14	10 mmol scale	81 (2.21g)

[a] Reaction conditions: carbon rod anode, nickel plate cathode, constant current = 12 mA, **1a** (0.5 mmol), CBr_4 (0.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), MeCN (10 mL), MeOH (1 mL), 75 °C, N_2, 2.5 h, isolated yields, SS = stainless steel plate.

Results and Discussion

Our initial studies of the electrochemical C-H halogenation focused on the bromination of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) (Table 1). We were motivated to use this substrate because imidazopyridines represent one of the most prevalent structural units in many biologically active molecules, and the resultant products can be subsequently transformed into the other biologically active molecules. Gratifyingly, when CH_3CN and MeOH were employed as the co-solvent, the desired C-H bromination product **2a** was produced in 93% yield under a 12 mA constant current in an undivided cell (Table 1, entry 1). Both replacing the nickel plate cathode with stainless steel plate or platinum plate and replacing the carbon rod anode with platinum plate led to slightly decreased reaction yields (Table 1, entries 2-4). Either decreasing the operating current to 6 mA or increasing the operating current to 18 mA also led to slightly decreased reaction yields (Table 1, entries 5-6). Latter, different electrolytes were investigated. However, all had slightly lower effectiveness than $^nBu_4NBF_4$ (Table 1, entries 7-8). Next, some solvents were explored. Either using MeCN as the sole solvent or using CH_3CN and H_2O as the co-solvent showed similar reactivity with CH_3CN and MeOH (Table 1, entries 9-12). Control experiment confirmed that the reaction does not proceed without electric current (Table 1, entry 13). Notably, the bromination of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) could be easily conducted on a 10 mmol scale to afford **2a** in 81% yield (Table 1, entry 14, See ESI for details).

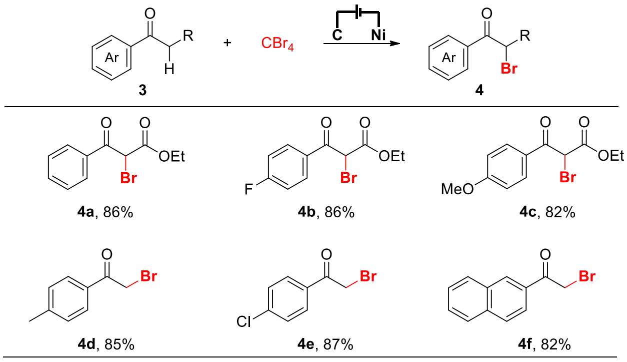
Table 2 Electrochemical C-H bromination of heteroarene/arenes[a]



[a] Reaction conditions: carbon rod anode, nickel plate cathode, constant current = 12 mA, **1** (0.5 mmol), CBr_4 (0.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), MeCN (10 mL), MeOH (1 mL), 75 °C, N_2, 2.5 h, isolated yields.

With the optimized conditions in hand, the substrate scope of the electrochemical C-H bromination was investigated by using various heteroarene/arenes (Table 2). Gratefully, our method was successfully amenable to a wide range of imidazo[1,2-a]pyridines. Imidazo[1,2-a]pyridines with either aryl or alkyl groups at the C-2 position were tolerated under the standard conditions, delivering the corresponding C-H bromination products in high to excellent yields (Table 2, **2a-2m**). Imidazo[1,2-a]pyridines bearing substituents such as methyl, fluorine, or trifluoromethyl groups at different positions of the pyridine ring also furnished the C-H bromination products in high yields (Table 2, **2n-2q**). Notably, the current electrochemical C-H bromination system was also compatible with other electron-rich heteroarene/arenes, such as 1,3,5-trimethoxybenzene, benzothiophene, and 2-aminopyridine (Table 2, **2r-2t**).

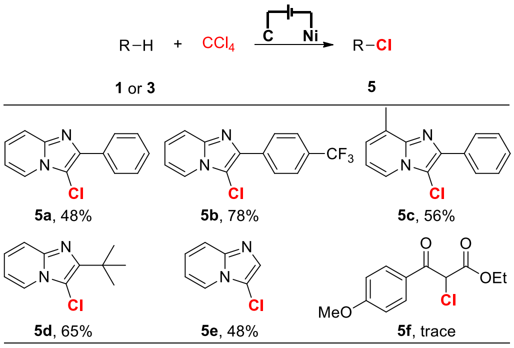
Table 3 Electrochemical C-H bromination of α-carbonyl compounds[a]



[a] Reaction conditions: carbon rod anode, nickel plate cathode, constant current = 12 mA, **3** (0.5 mmol), CBr_4 (0.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), MeCN (10 mL), MeOH (1 mL), 75 °C, N_2, 2.5 h, isolated yields.

Significantly, the scope of the electrochemical C-H bromination could be extended to α-carbonyl compounds (Table 3). It was observed that the desired C-H bromination products were obtained in 82-86% yields when ethyl benzoylacetate derivatives were used (Table 3, **4a-4c**). Notably, besides ethyl benzoylacetates, acetophenone derivatives were also suitable substrates in this electrochemical C-H bromination. For example, when the reaction was performed with 4-methylacetophenone, 4-chloroacetophenone, or 2-acetonaphthone, the reaction reacted smoothly and delivered the desired C-H bromination products in 82-87% yields (Table 3, **4d-4f**).

Table 4 Electrochemical C-H chlorination[a]



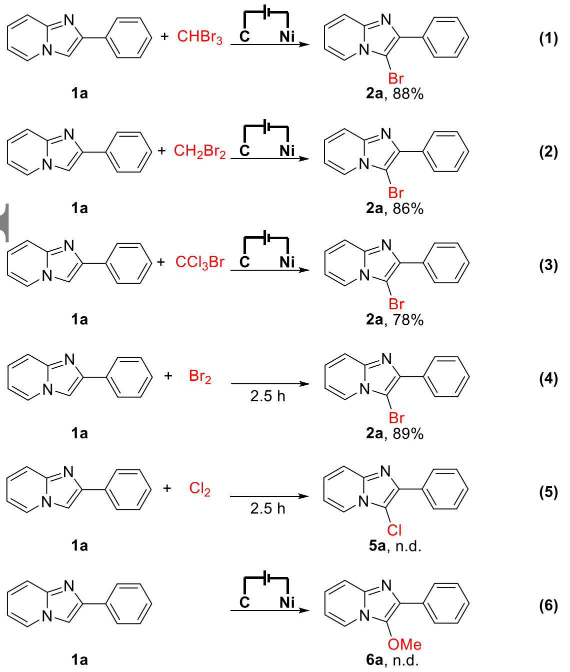
[a] Reaction conditions: carbon rod anode, nickel plate cathode, constant current = 12 mA, **1** or **3** (0.5 mmol), CCl_4 (0.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), MeCN (10 mL), MeOH (1 mL), 75 °C, N_2, 2.5 h, isolated yields.

It is worth noting that this versatile electrochemical C-H halogenation protocol was not limited to the bromination with carbon tetrabromide. Indeed, carbon tetrachloride was identified as amenable halogenating agents as well, delivering the desired C-H chlorination products in moderate to good yields (Table 4, **5a-5f**).

To gain some insights into the mechanism of this electrochemical C-H halogenation, some control experiments were conducted. First, cyclic voltammetry experiments were carried out (Figure S1-S3, See ESI for details). An oxidation peak of

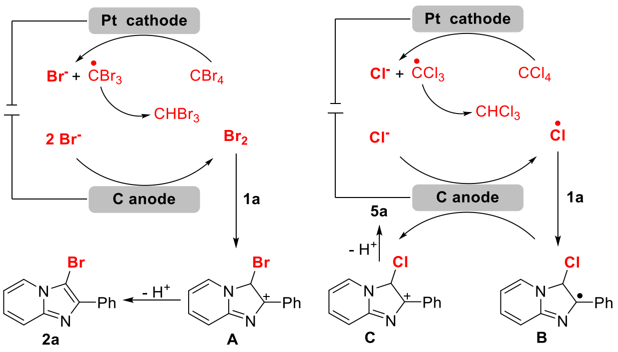
1a was observed at 1.55 V (vs Ag/AgCl), whereas the reduction pecks of CBr_4 and MeOH were observed at -0.67 V and -1.1 V (vs Ag/AgCl), respectively. This result indicates that CBr_4 is very easily reduced under electrochemical conditions. On the basis of this experimental result and literature reports,[9] we believe that this reaction should begin with the cathodic reduction of halogenating reagents. To further verify this conjecture, the other easily reduced substrates,[10] such as $CHBr_3$, CH_2Br_2, and CCl_3Br were also employed to this electrochemical C-H halogenation system (Scheme 2). To our delight, in the reaction of **1a** with $CHBr_3$, CH_2Br_2, or CCl_3Br, good to high yields of products were achieved under the standard reaction conditions, consistent with our hypothesis. Given that bromine ion and chlorine ion have a similar oxidation potential with **1a** (Figure S3, See ESI for details), the cathodic reduction generated bromine ion or chlorine ion may be subsequently oxidized to molecular Br_2 or Cl_2. To clarify whether this reaction involved a molecular Br_2 or Cl_2 intermediate, the reaction of **1a** with Br_2 and Cl_2 under the conditions of without current was carried out respectively and the C-H bromination product could be obtained in 89% yield, while no C-H chlorination product was detected (Scheme 2). This result indicates that molecular Br_2 might be the key intermediate of C-H bromination, while molecular Cl_2 might not be involved as the intermediate in C-H chlorination. In addition, when the reaction of **1a** was carried out in the absence of halogenating reagents, the capture product **6a** was not detected (Scheme 2). This result indicates that **1a** is first oxidized to the corresponding radical cation, followed by nucleophilic attack with bromine ion or chloride ion, can be ruled out.

Scheme 2 Control experiments



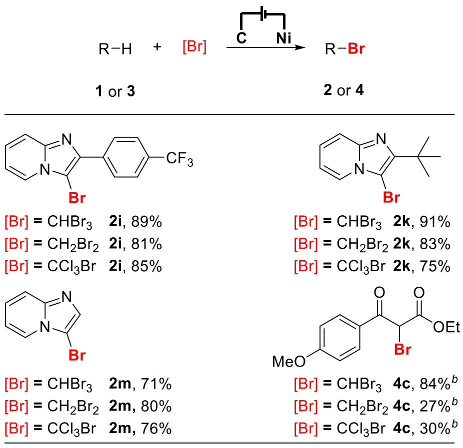
On the basis of the above experimental results and previous reports,[2q,9,10] a plausible mechanism for the electrochemical C-H C-H Halogenation is shown in Scheme 3. CBr_4 is first reduced at the cathode to generate bromine ion and tribromomethyl radical. Then, the generated tribromomethyl radical abstracts a hydrogen atom from solvent to afford tribromomethane. In the meanwhile, the generated bromine ion is oxidized at the anode to generate molecular Br_2. The reaction of **1a** with molecular Br_2 finally affords the corresponding C-H bromination product **2a**. It is worth noting that the generated tribromomethane intermediate could be detected by GC-MS in the reaction mixture, which verifies the possibility of this mechanism. In addition, according to the above experimental results, the generated tribromomethane would also be reduced at the cathode and finally access to desired product **2a**. Notably, the mechanism of C-H chlorination and C-H bromination might be different. In C-H chlorination, the generated chlorine ion might be oxidized at the anode to generate chlorine radical instead of molecular Cl_2.

Scheme 3 Proposed mechanism



Control experiments showed that $CHBr_3$, CH_2Br_2, and CCl_3Br were all suitable brominating reagents for the reaction. We subsequently investigated the substrate scope of the electrochemical C-H bromination using $CHBr_3$, CH_2Br_2, and CCl_3Br. It was found that imidazopyridines bearing aryl, alkyl, even -H groups at the C-2 position all delivered the corresponding C-H bromination products in good to excellent yields (Table 5). Moreover, α-carbonyl compounds, such as ethyl 3-(4-methoxyphenyl)-3-oxopropanoate, were also amendable to this procedure, although 3.0 equiv. of brominating reagents were used.

Table 5 Electrochemical C-H bromination with $CHBr_3$, CH_2Br_2, and CCl_3Br[a]



[Br] = $CHBr_3$ **2i**, 89%
[Br] = CH_2Br_2 **2i**, 81%
[Br] = CCl_3Br **2i**, 85%

[Br] = $CHBr_3$ **2k**, 91%
[Br] = CH_2Br_2 **2k**, 83%
[Br] = CCl_3Br **2k**, 75%

[Br] = $CHBr_3$ **2m**, 71%
[Br] = CH_2Br_2 **2m**, 80%
[Br] = CCl_3Br **2m**, 76%

[Br] = $CHBr_3$ **4c**, 84%[b]
[Br] = CH_2Br_2 **4c**, 27%[b]
[Br] = CCl_3Br **4c**, 30%[b]

[a] Reaction conditions: carbon rod anode, nickel plate cathode, constant current = 12 mA, **1** or **3** (0.5 mmol), [Br] (0.5 mmol), $^nBu_4NBF_4$ (0.1 mmol), MeCN (10 mL), MeOH (1 mL), 75 °C, N_2, 2.5 h, isolated yields. [b] [Br] (1.5 mmol).

Conclusions

In conclusion, we have developed an efficient electrochemical C-H halogenation protocol using CBr_4, $CHBr_3$, CH_2Br_2, CCl_3Br and CCl_4 as the halogenating agents. A series of significant aryl and alkyl halides were prepared under external-oxidant-free reaction conditions. It is worth noting that this is the first example of activating CBr_4, $CHBr_3$, and CCl_3Br under electrochemical conditions. Importantly, in this reaction, not only anodic oxidation but also cathodic reduction is reconciled to synergistically construct C-X bond. In addition, this reaction can be easily scaled-up.

Experimental

In an oven-dried undivided three-necked bottle (25 mL) equipped with a stir bar, 2-phenylimidazo[1,2-*a*]pyridine (**1a**, 0.5 mmol), carbon tetrabromide (0.5 mmol), and ^{n}Bu$_4$NBF$_4$ (0.1 mmol) were combined and added. The bottle was equipped with graphite rod (φ 6 mm, about 18 mm immersion depth in solution) as the anode and nickel plate (15 mm × 15 mm × 1 mm) as the cathode and was then charged with nitrogen. Under the protection of N$_2$, MeCN (10.0 mL) and MeOH (1.0 mL) were injected respectively into the tubes via syringes. The reaction mixture was stirred and electrolyzed at a constant current of 12 mA at 75 ^{o}C for 2.5 h. When the reaction was finished, the pure product was obtained by flash column chromatography on silica gel.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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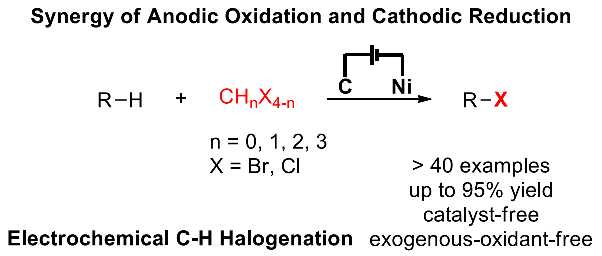

Zhilin Zhou, Yong Yuan, Yangmin Cao, Jin Qiao, Anjin Yao, Jing Zhao, Wanqing Zuo, Wenjie Chen, and Aiwen Lei,*

We herein uncovered an electrochemical C-H halogenation protocol that synergistically combines anodic oxidation and cathodic reduction for C-X bond formation.