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Chlorination Reaction of Aromatic Compounds and Unsaturated Carbon−Carbon Bonds with Chlorine on Demand

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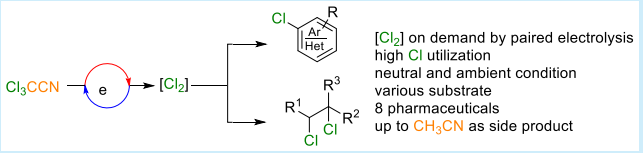
ABSTRACT: Chlorination with chlorine is straightforward, highly reactive, and versatile, but it has significant limitations. In this Letter, we introduce a protocol that could combine the efficiency of electrochemical transformation and the high reactivity of chlorine. By utilizing Cl_3CCN as the chloride source, donating up to all three chloride atom, the reaction could generate and consume the chlorine *in situ* on demand to achieve the chlorination of aromatic compounds and electrodeficient alkenes.



Chloride is presented in more than 200 FDA-approved pharmaceuticals[1] that play pivotal roles in treating respiratory, antiretroviral, cardiovascular, and other death-causing diseases (Scheme 1a). The introduction of chloride into molecules could regulate the properties of medicinal molecules by increasing the lipophilicity and polarity. It was suggested that the most important biological effect of nonreactive chlorine stems from substitution on the aromatic, heteroaromatic, or olefinic moiety.[2]

The chlorination reaction is one of the most straightforward approaches to introduce chloride into a molecule.[3] Although chlorine gas is a bulky chemical from the chloralkali industry, the direct chlorination using excess chlorine gas is limited by the demanding procedure during handling, the ratio of atom utilization, and the acidic HCl generated (Scheme 1b). Many protocols have been developed to achieve chlorination with control of the chemo-, regio-, and stereoselectivity.[3c] As the chlorination of aromatic compounds undergoes a dearomatized transition state with a high barrier, the chloride source needs preactivation by positive polarization in advance,[4] *in situ* activation by potent oxidants,[5] or anionic activation of the substrate.[6]

In addition to this chemistry, the photoredox protocol has inspired a new way to give reactive chloride species *in situ*. For example, the König group reported the photoredox chlorination of aromatic compounds with HCl[7] and N−Cl[8] reagents, respectively. The Hu group reported photoredox chlorination using NaCl as the chloride source in the presence of sodium persulfate.[9]

Recently, electricity-driven transformation has exhibited tremendous potential,[10] and electrochemical chlorination has achieved a breakthrough featuring the utilization of an inert and readily available chloride source.[11] By using Mn as a catalyst with metal chloride, the unprecedented radical dichlorination of alkenes was achieved by the Lin group with full control of the chemoselectivity.[12] The Lei group investigated the radical chlorination of heteroaromatic compounds and alkenes using NaCl[13] and CCl_4.[14] By using 1,2-dichloroethane in the electrocatalysis, the Jiao group established the chlorination of aromatic compounds including pharmaceutical compounds.[15] In 2019, Browne, Morrill, and coworkers applied electrochemical Mn catalysis in ring-opening chlorination.[16] An oxydichlorination of alkynes to α,α-dihaloketones was reported by the Huang group.[17] Most recently, an innovative chlorination of alkenes by merging shuttle catalysis and paired electrolysis was successfully applied to remediate a lindane-contaminated solid via a Mn-catalyzed pathway.[18] Despite this progress, chlorination utilizing *in-situ*-generated chlorine is still elusive. There were several features in this approach: First, the rate of generation of chlorine *in situ* could be regulated by electrochemical parameters, leading to the adequate involvement of chlorine with minimum escape from the reaction and facilitating reaction handling under ambient conditions. Second, the electrochemical generation of chlorine is independent of the chlorination reaction and is able to reach additional substrate scopes. Third, high usage of the chloride source could be feasible, avoiding the generation of HCl (Scheme 1c). Herein we report the first example of the electrochemical chlorination of aromatic compounds and electron-deficient alkenes with *in-situ*-generated chlorine in the on-demand manner.

At the onset of the study, compound **1a** was subjected to a variety of optimizations including the chloride sources, solvents, and supporting electrolytes (Table 1). When graphite felt was applied as both the anode and the cathode, Cl_3CCN was applied as the chloride source, and tetraethylammonium

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Scheme 1. Chloride in Drugs and Chlorination with Chlorine

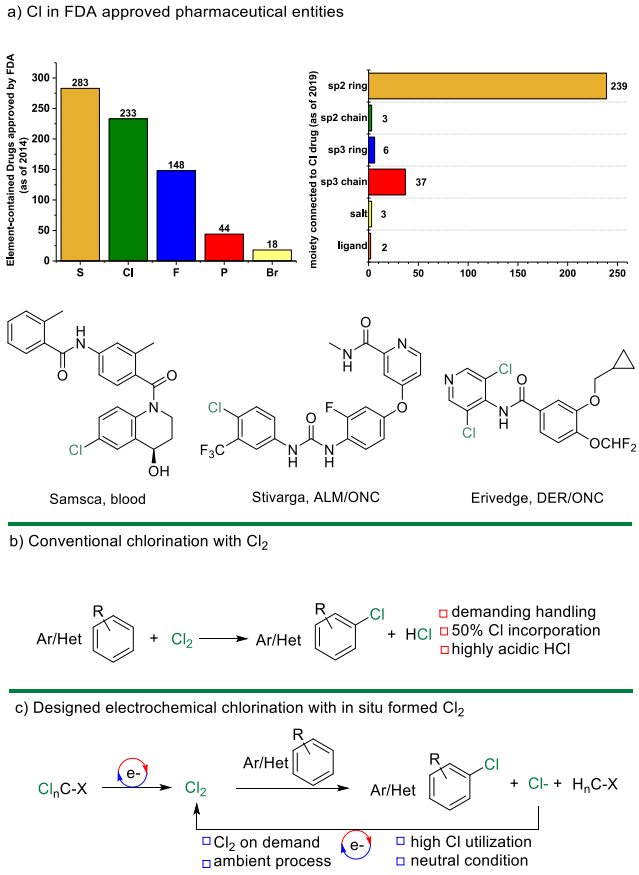
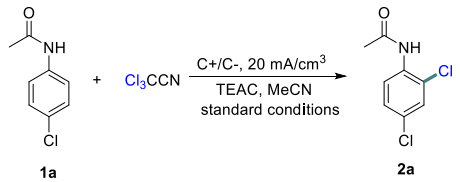


Table 1. Conditions Optimization Using Various Chemicals[a]



1a 2a

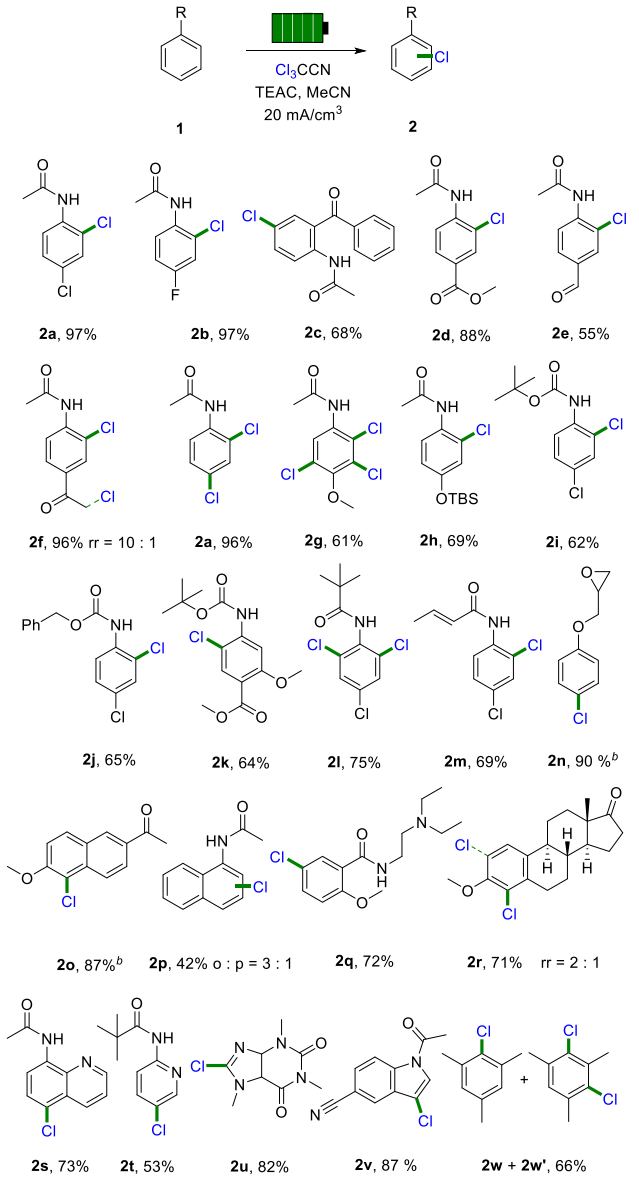
entry	deviation from standard conditions	yield (%)[b]
1	none	97
2	no electricity	ND[c]
3	CCl_4, $CHCl_3$, DCE, TCCA, DCDMH, $Ca(ClO)_2$ instead of CCl_3CN	trace
4	nBu_4NI, nBu_4NBr, nBu_4NOAc, instead of Et_4NCl	68−94
5	no Cl_3CCN	ND
6	EtOH, MeOH, DCM, THF, DMSO, DMF instead of MeCN	ND

[a]Reaction conditions: **1a** (0.2 mmol), Cl_3CCN (0.2 mmol, 1.0 equiv), Et_4NCl (0.5 equiv), CH_3CN (5 mL), graphite felt as anode and cathode, undivided cell, 20 mA/cm^3, 2 h, 23 °C. [b]Isolated yield. [c]ND = not detected.

chloride (TEAC) was applied as the supporting electrolyte, galvanostatic electrolysis gave product **2a** in 97% isolated yield. Other chlorinated reagents, such as CCl_4, $CHCl_3$, DCE, TCCA (trichloroisocyanuric acid), DCDMH (1,3-dichloro-5,5-dimethylhydantoin), and $Ca(ClO)_2$, gave only a trace amount of product. If tetrabutylammonium salts were used instead of TEAC, then the isolated yields of **2a** dropped to 68−94%. Next, solvent screening revealed that acetonitrile was the only solvent to deliver the desired product. If Cl3CCN was absent from the reaction containing TEAC, then no chlorination took place, suggesting that only a chloride anion was not adequate to affect the transformation.

With the optimized conditions, a variety of aromatic compounds were subjected to the chlorination reaction (Scheme 2). It was found the chlorination reaction proceeded

Scheme 2. Chlorination of Aromatic Compounds[a]



[a]**1** (0.2 mmol), Cl_3CCN (0.2 mmol), Et_4NCl (0.1 mmol), CH_3CN (5 mL), graphite felt as anode and cathode, undivided cell, 20 mA/cm^3, 2 h, 23 °C. [b]10 mA/cm^3.

smoothly when the aromatic compounds were substituted with both electron-donating and electron-withdrawing groups (**2b**−**2f**). We were glad to observe that the aldehyde group (**2e**) could be tolerated to the extent of 55% isolated yield. A ketone product **2f** was prepared along with an overchlorinated product in a 10:1 ratio. Next, the dichlorination gave product **2a** in 96% yield, suggesting the Cl_3CCN could provide the second chloride atom. Trichlorination took place to offer **2g** with two

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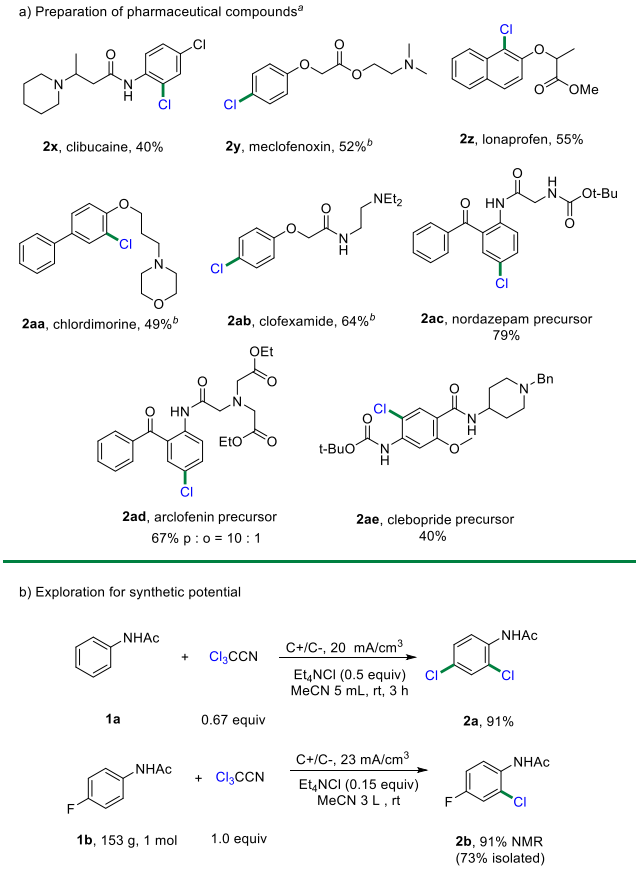
electron-donating groups in 61% yield. Product **2h** incorporating a silyl ether group that readily decomposed under acidic conditions could be prepared in 69% yield. Next, the anilines with other protecting groups were tested under the same conditions. We were glad to observe that the acid-labile groups, for example, Boc and Cbz in products **2i**–**2k**, could survive the electrolysis in ∼60% yields. In the case of product **2l**, dichlorination took place in 75% isolated yield. Product **2m** was obtained in 69% yield, suggesting that the electron-rich aromatic ring was favored over the α,β-unsaturated alkene. The phenyl ethers **2n** and **2o** were produced in good yields by applying a low current density. A regioselectivity of 3:1 was observed when naphthalene product **2p** was isolated from the reaction. Free amine could be well tolerated, and the corresponding product **2q** was achieved in 72% yield. Methyl oestrone was chlorinated to give two regioisomers **2r** in a 2:1 ratio. Heterocycles including quinolone, pyridine, caffeine, and indole underwent this electrochemical chlorination reaction to give monochlorinated products **2s**–**2v** in moderate to good yields. Mesitylene was chlorinated with this method, giving a mixture of mono (**2w**) and dichloro (**2w′**) products in 66% overall yield.

With these protocols, we could prepare a series of pharmaceutical compounds (Scheme 3a). For example, anesthetic clibucaine **2x**, nootropic meclofenoxin **2y**, anti-inflammatory lonaprofen **2z**, antifungal chlordimorine **2aa**, and antidepressant clofexamide **2ab** were synthesized. In the case of **2ab**, the chlorination was carried out with Cl_2 gas and gave a mixture of target product and dichlorinated byproduct (SI, section 5.2.2). The poor solubility of substrate sabotaged the yield of **2x** to some extent. Precursor **2ac** of anticonvulsant nordazepam, **2ad** of diagnostic aiding arclofenin, and **2ae** of prokinetic clebopride were prepared in moderate to good yields, respectively. Next, a reaction employing 0.67 equiv of Cl_3CCN was carried out with **1a** as the substrate for 3 h, and dichlorated product **2a** was isolated in 91% yield, suggesting all three chloride atoms in Cl_3CCN were utilized and MeCN was generated as the side product (Scheme 3b). In another experiment, the reaction to prepare **2b** was conducted on a 1 mol (153 g) scale, giving the product in 90% NMR yield and 73% isolated yield.

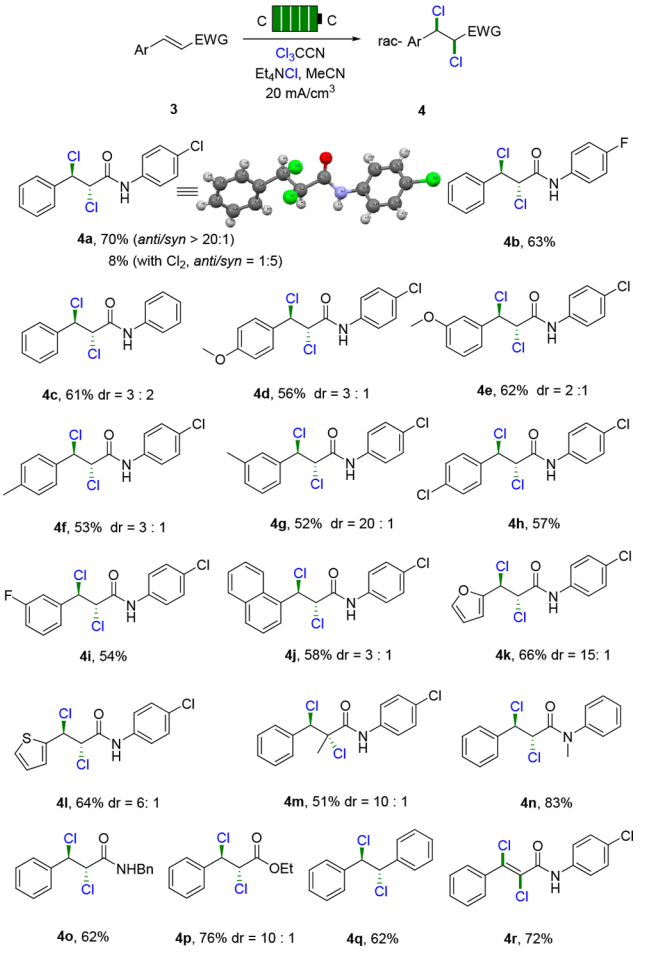
To further expand the scope of this method, we attempted the chlorination of α,β-unsaturated cinnamides **3**, which had not been explored by known protocols (Scheme 4). By using the standard conditions with 20 mA/cm^3 current density, the dichlorination of cinnamide **3a** was realized, giving **4a** in 70% yield as a predominant anti-diastereoisomer confirmed by X-ray analysis. It was unexpected that when the chlorination of **3a** was carried out with Cl_2 gas, **4a** was isolated in 8% yield with a

Scheme 3. Synthetic Applications of Electrochemical Chlorination Reactions[a]



[a]**1** (0.2 mmol), Cl_3CCN (1.0 equiv), Et_4NCl (0.5 equiv), MeCN (5 mL), graphite felt as anode and cathode, undivided cell, 20 mA/cm^3, 2 h, 23 °C. Isolated yield. [b]10 mA/cm^3

Scheme 4. Electrochemical Dichlorination of α,β-Unsaturated Compounds[a]



[a]Conditions: **3** (0.2 mmol), Cl_3CCN (1.2 equiv), Et_4NCl (1.0 equiv), MeCN (5 mL), graphite felt as anode and cathode, undivided cell, 20 mA/cm^3, 2 h, 23 °C, isolated yield.

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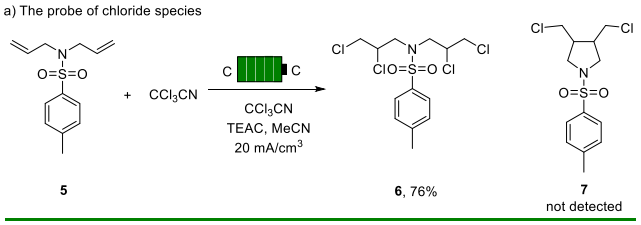
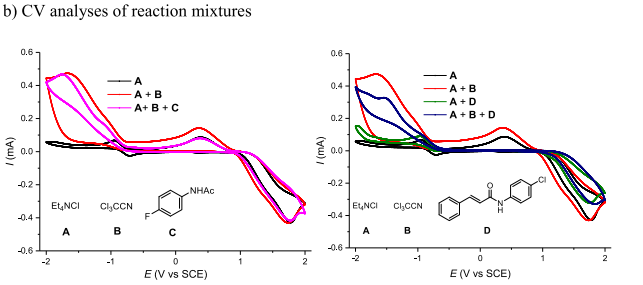
syn configuration as the major outcome (syn/anti 5:1; SI, section 5.2). Next, aniline-derived dichlorocinnamides **4b** and **4c** were generated in ∼60% yields. A dramatic contrast in diastereoselectivity between **4b** and **4c** was observed. We speculated that the formation of **4b** might undergo rigid intermediates and that the formation of **4c** would be more flexible due to the electronic effect. This electronic effect was also found in products **4d**−**4j**. Substrates bearing furan and thiophene moieties could be well tolerated, and corresponding products **4k** and **4l** were achieved in acceptable yields with moderate to good diastereoselectivities. *α*-Methyl cinnamide was also converted to the corresponding dichloro product **4m** in 51% yield with a 10:1 dr ratio. Subsequently, product **4n** without a N−H moiety was obtained in 83% yield. The benzylamine-derived product **4o** was prepared in 62% yield. Other *α*,*β*-unsaturated compounds, such as ethyl cinnamate, *trans*-stilbene, and ethyl 3-phenylpropiolate, were dichlorinated smoothly, giving products **4p**, **4q**, and **4r** in good yields.

Next, to gain more information on this reaction, we used the reported[12,19] probe **5** to identify the chloride species present in the reaction. By applying **5** as the substrate, we isolated the tetra-chlorinated product **6** in 76% yield, which supported the existence of chlorine; on the contrary, the cyclized product **7** as an indicator of the chloride radical was not detected (Scheme 5a). In addition, the reaction atmosphere on the 1 mol scale of

Scheme 5. Experiments to Explore the Reaction Mechanism

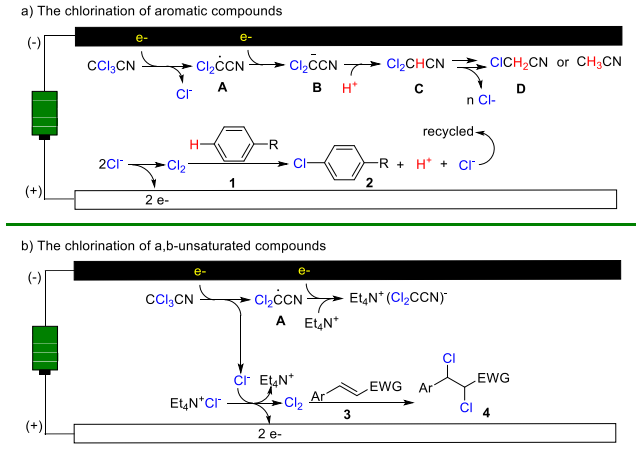




1b (Scheme 3b) showed a positive effect in the KI−starch experiment (SI, section 5), also confirming the presence of chlorine. Next, cyclic voltammetry (CV) analysis was performed to elucidate the electrode conditions for the generation of chlorine. Scan loops with a positive or a negative start both showed almost identical patterns, suggesting that a highly predominant pathway could exist (Scheme 5b). In two mixtures containing acetyl aniline **1b** and cinnamide **3a,** respectively, the CVs shared similar peaks at −1.7 V vs SCE and +1.8 V vs SCE, suggesting the reduction of CCl_3CN and the oxidation of the chloride anion in both cases.

With these results, a plausible reaction pathway is proposed in Scheme 6. For example, in the chlorination reaction of aromatic compound **1** (Scheme 6a), at first, the cathodic reduction of Cl_3CCN releases a chloride anion and a neutral radical **A**. A second electron transfer to **A** gives rise to dichloroacetonitrile anion **B**. At the anode, the oxidation of

Scheme 6. Plausible Reaction Pathways of Electrochemical Chlorination Using Cl_3CCN



two chloride anion produces chlorine, which in situ reacts with aromatic compounds and furnishes the final product **2**. The generated chloride anion can be recycled during the next cycle of anodic oxidation, and the proton can combine with anion **B** to give dichloroacetonitrile **C**. Intermediate **C** can release the remaining chloride anion at the cathode in a similar manner to give chloroacetonitrile **D**, and, in turn, acetonitrile. In comparison, the chlorination of *α*,*β*-unsaturated compounds **3** shares similarities and differences (Scheme 6b). In this transformation, the anodic reduction provides the chloride anion and dichloroacetonitrile anion **B**. At the anode, chlorine is produced from both the chloride anion generated at cathode and that from the supporting electrolyte TEAC. This anodic oxidation will release a tetraethylammonium cation, which forms a salt with anion **B**. The generated chlorine is independent of the electrochemical process and gives the final dichlorinated compounds **4** in the manner of electrophilic addition. Because a proton was not generated during the chlorination of cinnamide, 1 equiv of TEAC was required to supply the chloride anion and the ammonium cation. This chlorination process is independent of the electrochemical process and might also work in the electrochemical chlorination of an aromatic compound via the common chloride anion species.

In summary, we developed an electrochemical chlorination reaction using Cl_3CCN as the chloride source via paired electrolysis. The reaction proceeds under neutral conditions and tolerates a variety of functional groups labile under acidic conditions. This electrochemical reaction utilizes the *in-situ*-generated chlorine as a reactive species, making the electrochemical process independent of the chemical process in an on-demand manner. With this approach, both electron-rich aromatic compounds and electron-deficient *α*,*β*-unsaturated compounds could be efficiently chlorinated. The protocol was successfully applied in the preparation of commercialized pharmaceutical products and corresponding intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00704.

Experimental procedures, electrochemistry analytical data, and NMR spectra (PDF)

https://doi.org/10.1021/acs.orglett.1c00704
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Accession Codes

CCDC 2065525 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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