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# Palladium-Catalyzed Aromatic C−H Halogenation with Hydrogen Halides by Means of Electrochemical Oxidation

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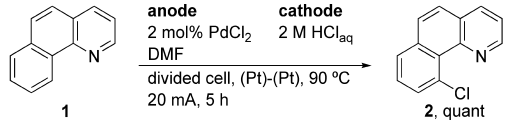
With the ever-increasing need for sustainable chemical processes, tremendous attention has been paid to efficient, atom-economical methods for production of organic molecules.[1] Direct, selective, catalytic functionalization of C−H bonds, which are ubiquitous in organic molecules, is one of the most recognized strategies for this purpose because it allows for the introduction of functional groups using all parts of the substrate except for one hydrogen atom.[2−9] A variety of functional groups have been directly introduced by cross-coupling with preactivated partners[2−6] or oxidative coupling with unactivated reagents using external oxidants.[7−9] We envisioned that transition-metal-catalyzed oxidative C−H functionalization without oxidants could be achieved by the application of techniques used in electroorganic synthesis, a promising candidate as a green-sustainable process.[10,11]

Recently, transition-metal-catalyzed regioselective halogenations of aromatic C−H bonds have been developed as a new synthetic tool using several halogenating agents.[5−7] However, separation of the remaining oxidants and the byproducts is unavoidable in the purification process. Therefore, we examined the halogenations using two of the simplest halogen sources, aqueous HCl and HBr, under electrochemical oxidation conditions, because they would enable direct C−H halogenation without generating organic byproducts.

Herein we report palladium-catalyzed halogenation of aromatic C−H bonds with hydrogen halides by means of electrochemical oxidation. The required reagents for this reaction are an arene and an aqueous hydrogen halide as substrates, a palladium salt as a catalyst, and an organic solvent. No further additives such as electrolytes, oxidants, or ligands are necessary to achieve effective catalytic activity. Several remarkable advantages of the use of the electrochemical method are also described.

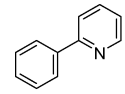
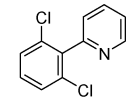
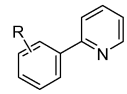
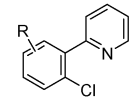
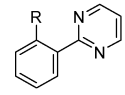
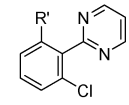
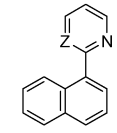
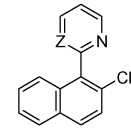
First, the chlorination was performed with benzo[*h*]quinoline (**1**) in DMF under ambient atmosphere using 2 mol % $PdCl_2$.[12] When the reaction was carried out for 5 h at 90 °C under constant-current electrolysis conditions at 20 mA, the 10-position of **1** was chlorinated regioselectively to afford **2** in a quantitative yield (eq 1): The reaction was complete within 2 h in the presence of 10




(1)

mol % catalyst. No reaction was observed in the absence of either the catalyst or the electric current. Our new chlorination protocol provided **2** with higher efficiency than the reported palladium-catalyzed chlorination of **1** with chlorinating agents (95% isolated yield in 3 days with NCS, 81% and 85% GC yields in ~12 h with $CuCl_2$ and Chloramine-T).[5] It is noteworthy that our reaction *proceeds without supporting electrolyte* because hydrogen halide can also act as the electrolyte, whereas the need for a large amount of supporting electrolyte is considered to be the major drawback of electroorganic synthesis.[13]

***Table 1.*** Palladium-Catalyzed Regioselective Chlorination of Arenes by Means of Electrochemical Oxidation[a]

| entry | arene | time (h) | product, yield |
|---|---|---|---|
| |  | |  |
| 1[b] | **3** | 3 | **4**, 94% |
| |  | |  |
| 2 | **5**, R = 2-$CH_3$ | 4 | **6**, 93% |
| 3 | **7**, R = 3-$CH_3$ | 3 | **8**, 87% |
| 4[b] | **9**, R = 3-$OCF_3$ | 3 | **10**, 92% |
| 5[c] | **11**, R = 3-$CF_3$ | 2.5 | **12**, 88% |
| 6 | **13**, R = 3-C(O)$OCH_3$ | 5 | **14**, 87% |
| |  | |  |
| 7[b,c] | **15**, R = H | 5 | **16**, R' = Cl, 91% |
| 8 | **17**, R = $CH_3$ | 2.5 | **18**, R' = $CH_3$, 94% |
| |  | |  |
| 9 | **19**, Z = CH | 5 | **20**, quant |
| 10 | **21**, Z = N | 6.5 | **22**, 95% |

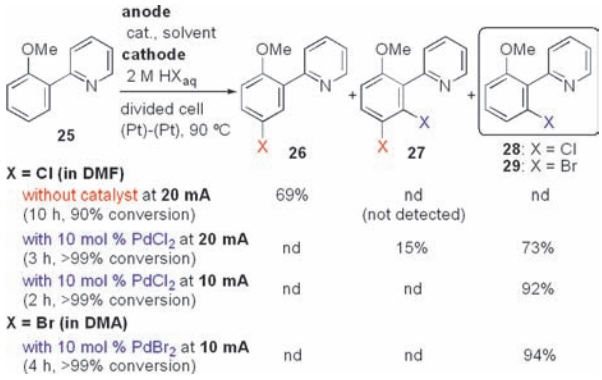
[a] Conditions: arene (0.25 mmol), $PdCl_2$ (10 mol %), DMF (10 mL) (anode), and 2 M HCl (10 mL) (cathode) in an H-type divided cell with two platinum electrodes and an anion-exchange membrane, 90 °C, 20 mA. [b] Performed at 100 °C. [c] Using 15 mol % $PdCl_2$.

The results for the chlorination of arenes are shown in Table 1. In all cases, the arenes were completely consumed, and excellent isolated yields were achieved. Predominant dichlorination was observed for 2-phenylpyridine (**3**) to afford **4** in 94% yield (entry 1), while 2-(2-methylphenyl)pyridine (**5**) provided monochlorination product **6** in 93% yield (entry 2). The chlorination of arylpyridines bearing meta substituents took place selectively at the less hindered ortho position, and both electron-donating and -withdrawing groups were tolerated (entries 3−6). Arylpyrimidines were also applicable for the chlorination. The use of 2-phenyl- and 2-(2-methylphenyl)pyrimidines (**15** and **17**) led to chlorination products **16** and **18** in excellent yields (entries 7 and 8). Naphthalene derivatives were also chlorinated regioselectively, and the reactions of naph-



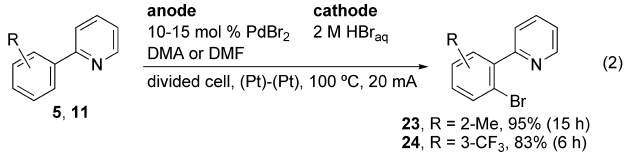
10.1021/ja9049228 CCC: $40.75 

***Scheme 1.*** Regioselective Halogenation by Controlling the Electric Current




thylpyridine **19** and naphthylpyrimidine **21** provided **20** and **22**, respectively, in >95% yield (entries 9 and 10).[14]

The bromination of C−H bonds was also successful. The reactions of **5** and **11** with hydrobromic acid using $PdBr_2$ as a catalyst afforded the corresponding products **23** and **24** in 94 and 83% isolated yields, respectively (eq 2):



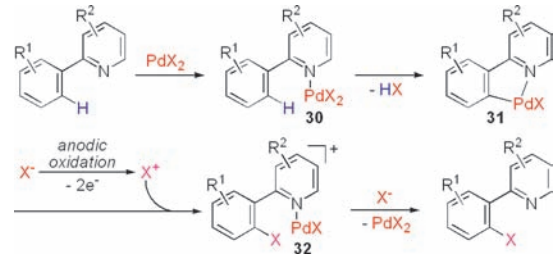

(2)

The regioselectivity in the halogenations of 2-(2-methoxylphenyl)pyridine (**25**) was controlled by tuning the electric current to an appropriate level (Scheme 1). The regioselective chlorination of **25** was problematic because chlorination at the para position of the methoxy group took place even in the absence of the palladium catalyst. In fact, partial chlorination at the para position was observed with a 20 mA electric current. However, simple reduction of the electric current to 10 mA led to exclusive formation of the desired product **28** in 92% yield. The electrochemical method allows for facile control over the rate of reactive chloronium ion generation to suppress the side reactions caused by an excess amount of chloronium ion. Similarly, the regioselectivity of the bromination was also controlled by tuning the electric current to 10 mA, and the bromination product was obtained in 94% yield.

One of the most appealing features of the present halogenation is that complete conversion to the product may significantly facilitate the purification process. Generation of the halonium ions can be stopped by turning off the electric current. The only organic materials present in the mixture are the product and the solvent. Therefore, a simple extraction process may afford the halogenation product in a pure form. In fact, product **2** was isolated in an analytically pure form (as determined by $^1H$ and $^{13}C$ NMR spectra and elemental analysis) simply by neutralization of the reaction mixture with aqueous $K_2CO_3$ followed by extraction with ether.

Our proposed reaction pathway for the present palladium-catalyzed C−H halogenation is shown in Scheme 2. Coordination of a nitrogen atom in the substrate to the palladium center yields complex **30**, and electrophilic palladation at the ortho C−H bond gives palladacycle **31**. Reaction of intermediate **31** with a halonium ion generated by electrochemical oxidation of a halide ion provides the C−X bond at the ortho position to form complex **32**. Dissociation of the product from the palladium center affords the product and regenerates the catalyst.

***Scheme 2.*** Proposed Reaction Pathway




We believe that our C−H functionalization protocol employing a combination of transition-metal-catalyzed C−H bond cleavage and electrochemical oxidation offers a new environmentally benign tool for introduction of functional groups on aromatic rings in an efficient, selective manner. Further investigation of catalytic C−H functionalization via dual activation by transition-metal catalysts and electrochemical oxidation is currently in progress.

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**Supporting Information Available:** Experimental procedures, spectroscopic data for new compounds, and X-ray crystallographic data for **20** and **22** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See the Supporting Information for the detailed experimental procedure.
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(14) The structures of **20** and **22** were confirmed by X-ray crystallography (see the Supporting Information).

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