Oxidative Coupling

International Edition: DOI: 10.1002/anie.201502638
German Edition: DOI: 10.1002/ange.201502638

Versatile Electrochemical C–H Amination via Zincke Intermediates

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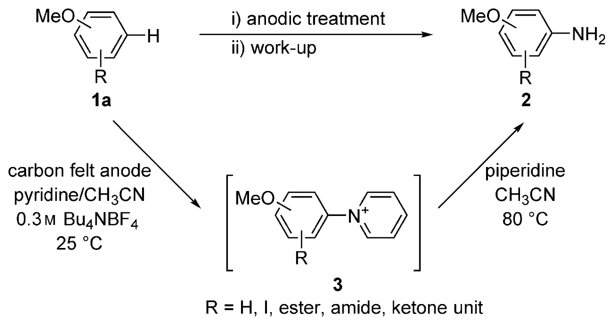
amination · electrochemistry · oxidative coupling · sustainable chemistry · synthetic methods

The sustainable installation of electron-releasing groups such as hydroxy or amino moieties is challenging and commonly considered to be the holy grail in C–H functionalization. Consequently, tremendous efforts have been made to perform this transformation in a catalytic manner.[1] In modern versions, this type of reaction does not require leaving groups[2] or is viable with ammonia as the NH_2 source.[3] However, these approaches require significant loadings of expensive catalysts based on copper or noble metals. Electroorganic synthesis is a highly attractive method for the preparation of organic compounds,[4] wherein the electric current provides a stoichiometric amount of the oxidizing or reducing agent. This approach avoids waste originating from the reagents and catalysts employed. The attractiveness of this method will increase in the future since it can be used for valorization of surplus electricity generated by renewable energy resources. Consequently, electrosynthetic processes are considered to be "green chemistry",[5] and have great technical significance.[6] However, the anodic installation of amino groups seems to be contradictory because upon modification the products become significantly more susceptible to oxidation.[7] Direct anodic amination of arenes with ammonia is considered to be unknown, although some irreproducible reports exist in the patent literature.[8] The anodic installation of a nitrogen functionality usually proceeds through initial oxidation of the organic substrate. The nucleophilic trapping of the radical cation represents the key step. Therefore, the nitrogen source has to provide sufficient nucleophilicity as well as stability towards anodic conditions. Reactions with acetonitrile generate acetanilides;[9] the pyridination of arenes was reported in a few cases but was mainly performed to construct the Zincke intermediates **3** (see Scheme 1).[10] In the past two years, the Yoshida group has systematically developed a reliable method for the electrochemical amination via pyridinium derivatives **3** and Zincke salts.[11]

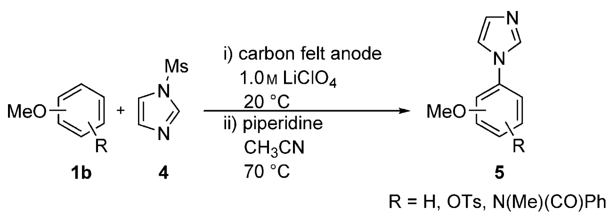
A broad variety of arenes **1a** was aminated in up to 99% yield (Scheme 1). Even sensitive moieties like iodo substituents were tolerated. However, only electron-rich and activated substrates could be successfully converted. Simple benzene or toluene seem to be unsuitable substrates. The application of a carbon felt (graphite) anode was chosen for operation at relative low current density. If regioisomers are possible, they will be formed.



Scheme 1. Electrochemical amination reaction of arenes.[11]

Similarly, *N*-mesyl-protected imidazoles **4** can be installed at aromatic substrates **1b** (Scheme 2).[12] This provides an alternative and elegant access to *N*-aryl imidazoles **5**, which have significant relevance as biologically active compounds. If a methyl group is present *para* to an electron-releasing group (**6**) the electrochemical C–H activation proceeds at the respective benzylic position (Scheme 3).

A significant breakthrough to convert less-activated substrates **8** and to circumvent the issue of regioisomers was achieved by an intramolecular version of the electrochemical amination reaction (Scheme 4).[13] It presents a promising way to easily obtain 2-aminobenzoxazoles and 2-aminobenzothiazoles **9** from phenols and thiophenols, respectively. After installation of a 2-pyrimidyl moiety at the hydroxy or thiol group (→**8**), benzoxazolopyrimidinium and benzothiazolopyridinium derivatives **10** are generated through intramolec-



Scheme 2. Anodic synthesis of *N*-arylimidazoles.[12]

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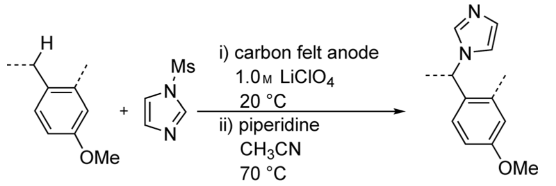
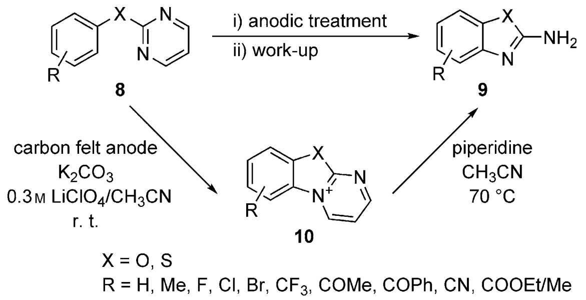


Scheme 3. Formation of *N*-benzylimidazoles.[12]



Scheme 4. Intramolecular anodic amination reaction.[13]

ular electrochemical amination reaction. These intermediates provide access to a broad variety of 2-aminobenzothiazoles or the corresponding benzoxazoles **9** after ring opening with piperidine. This class of compounds has been widely explored. A greatly expanded scope includes substrates with strong electron-withdrawing substituents, for example trifluoromethyl, cyano, and different types of carbonyl moieties. The yields are good to excellent. Because of the practicability and good tolerance of functional groups, this electrochemical amination process will be of interest for the construction of more-complex molecules. In this particular area, electro-organic synthesis is regaining significant attention.[14]

All conversions described are performed at graphite anodes. Therefore, the next steps will be the employment of anodes with a higher performance at more-positive potentials, for example, boron-doped diamond.[15] This might allow the electrolysis of less-activated substrates in the intermolecular approach. In addition, multiple conversions at large aromatic scaffolds might be viable. For further practicability, the liberating agent piperidine should be replaced by a simpler reagent. The regeneration of pyridine by, for example, ammonia would create a more sustainable process. When the above-mentioned points are solved, the Yoshida approach for the electrochemical amination will be an indispensable tool for organic synthesis—for small-scale as well as technical-scale transformations.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 6398–6399
Angew. Chem. **2015**, *127*, 6496–6497

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Received: March 22, 2015
Published online: May 12, 2015