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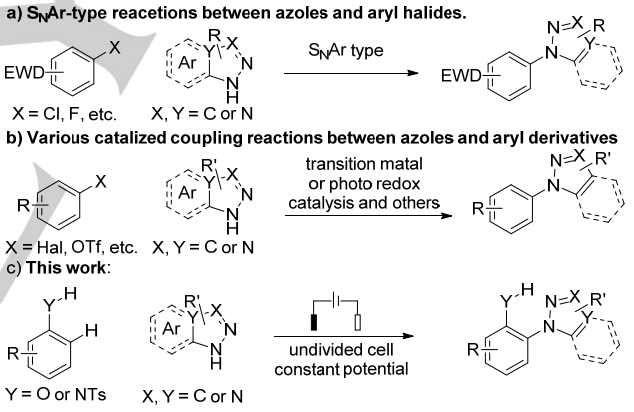
Electro-oxidative and Regioselective C-H Azolation of Phenol and Aniline Drivatives

Pengju Feng,*‡[a] Guojian Ma,‡[a] Xiaoguang Chen,[a] Xing Wu,[a] Ling Lin,[a] Peng Liu[b] and Tianfeng Chen*[a]

Abstract: *A general and practical protocol for regioselective C-H azolation of phenol and aniline derivatives via electro-oxidative cross coupling has been demonstrated. The reaction runs under metal, oxidant and reagent free condition, allowing access to a wide variety of synthetically useful hetero-arene derivatives. The reaction also tolerates a wide range of functional groups, and is amenable to gram scale synthesis. Finally, preliminary mechanistic study indicated a radical-radical combination pathway might be involved for the coupling reaction.*

Owing to their ubiquitous presence in natural products, pharmaceuticals, and functional materials, N-arylated heterocycle syntheses are of constant interest in organic synthesis.[1] The most known way to access these molecules is through S_NAr-type reactions between azoles and electron deficient halogenated arenes (Scheme 1, a).[2] During the last decade, the rapid development of transition metal-catalyzed amination reactions, such as Buchwald-Hartwig amination and the Ullmann-type coupling reaction, provided elegant azolation methods with constantly developing catalysts (Scheme 1, b).[3] Moreover, direct C-H activation enabled the opportunity for generation of complex molecules via a more straightforward and economical sequence. For example, visible-light-mediated photocatalysis provides attractive approach to generate azolated arene via direct C-H amination of aromatic compounds under mild conditions without the requirement of preactivation and/or preoxidation of the substrates.[4] Other methods, such as metal-catalyzed C-H azolation and hypervalent-iodine-mediated CH/NH cross-coupling are also useful options for the generation of azolated scaffold.[5] Undoubtedly, significant progress has been made for the synthesis of azolated arenes, while demand for more economical and environment friendly protocols to avoid tedious workup procedures, expensive catalyst or excess external oxidants still exists.

With the increasing environmental pressure, electrochemical synthesis, using electric current in place of chemical oxidants, has received unprecedented attention for the construction of C-X bonds via C-H functionalization.[6] In this field, the formation of $C(sp^2)$ –N bond under metal free condition is a main focus and several intramolecular C-N bond formation methods have been reported.[7] However, due to product over oxidation, synthetically useful examples of intermolecular aryl C-H amination,[8] especially the intermolecular azolation of arenes, are still rare.[9] Limited number of examples showed that imidazole derivatives as nucleophiles could react with aromatic and benzylic compounds intermolecularly to form mixture of C/N adducts of naphtha(1,2-a) pyrene,[10] tosyl-protected imidazolium ions[11] and pyren-1-ylazoliums.[12] Given the importance of N-arylated azoles, clean and practical protocols to derivatize structurally diverse azoles are highly desirable. Recent literatures revealed that both phenols and azoles could be electrochemically oxidized to form the corresponding radical intermediates under various conditions for versatile transformation, while combination of the two compounds under electrochemical condition are not achived.[13] Although the coupling of radicals can be useful for organic synthesis, it is not clear such transformation would be feasible due to high reactivities of the involved reaction intermediate and significant side reactions.[14] We report here that, under constant cell potential, the intermolecular combination between phenol/aniline derivatives and azoles to form N-arylated azoles in high yields (Scheme 1, c) and preliminary mechanism insights.



Scheme 1. Overview of Methodologies for the Synthesis of Azolation Arenes.

We chose 4-methoxyphenol (**1a**) as the model substrate to couple with simple pyrazole.[15] As outlined in table 1, the optimal condition was set by utilizing Bu_4NPF_6 (0.05 M) as supporting electrolyte, DCM/HFIP mixture as solvent, 0.60 mmol of 4-methoxyphenol (**1a**), and 0.50 mmol of pyrazole (**2a**). The reaction regioselectively furnished *o*-azolated phenol **3a** in 97% yield in an undivided cell equipped with Pt anode and cathode under 2.5 V constant cell potential and N_2 atmosphere (Table 1, entry 1). The solvent was crucial for achieving sufficient reactivity.[15] Decreased reaction yields were observed when using DCM or HFIP as the only solvent (entries 2-3). Other solvent mixture, such as MeOH/HFIP, gave lower reaction efficiency than HFIP alone. Another control experiment exhibited slightly lower yield with Bu_4NBF_4 as supporting electrolyte (entry 5). Both lower and higher potentials decreased the reaction

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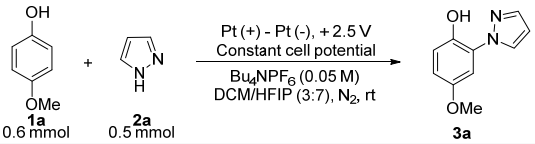
Table 1. Optimization of Reaction Conditions[a]



Entry	Variation from standard conditions[a]	Yield[b]
1	none	97%
2	DCM as the solvent	10%
3	HFIP as the solvent	84%
4	MeOH/HFIP (3:7) as the solvent	22%
5	Bu_4NBF_4 as the electrolyte	92%
6	2.0 V instead of 2.5 V	63%
7	3.0 V instead of 2.5 V	76%
8	under air	81%
9	without electricity	0%

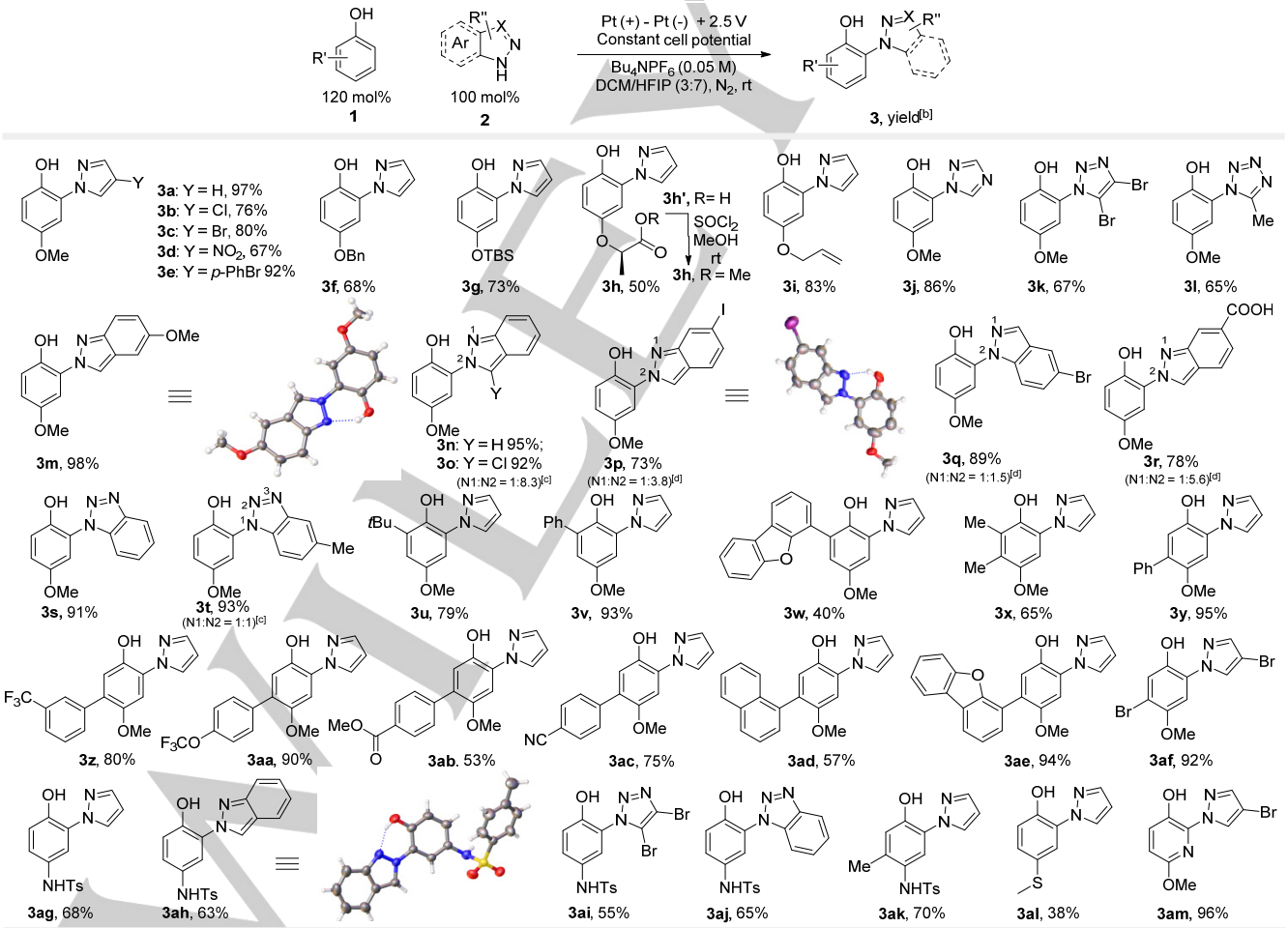
[a] Reaction condition: Platinum plate cathode and anode (10 mm × 10 mm × 0.1 mm), Constant cell potential, **1a** (1.2 equiv, 0.6 mmol), **2a** (1.0 equiv, 0.5 mmol), Bu_4NPF_6 (1.0 equiv, 0.5 mmol), DCM/HFIP (3.0 mL : 7.0 mL), rt, N_2, 10h. [b]isolated yield.

yields (entries 6-7). When the reaction was conducted in the air, the yield decreased to 81% (entries 8). No desired product was observed when the reaction was run without electricity.

Under the optimized condition with necessary adjustments, the substrate scope and generality of this electrochemical cross-coupling reaction were explored, and the results were tabulated in Scheme 2. Pyrazoles with different functional groups, such as Cl, Br, NO_2, *p*-PhBr, successfully reacted with 4-methoxyphenol (**1a**) to give desired products in good yields (**3b**-**3e**). Electron deficient pyrazole was relatively less reactive (**3d**). It was noteworthy that different protecting groups such as Bn, TBS, and allyl could be introduced without problem for hydroquinone to deliver corresponding coupling products (**3f**-**3g**, **3i**). The alkyl group with carboxylic acid is also compatible with the electron chemical coupling process (**3h**).

Various azoles (**3j**-**3t**) with a wide range of substituents were also tested for coupling with 4-methoxyphenol (**1a**). Notably, 1,2,4-triazole, 1,2,3-triazole, tetrazole, indazole and benzotriazole regioselectively gave single isomer of the C-N bond formation product in moderate to good yield (**3j**-**3n**, **3m**), while 5-methoxy-indazole delivered the single amination product (**3m**) whose structure was confirmed by X-ray diffraction study.

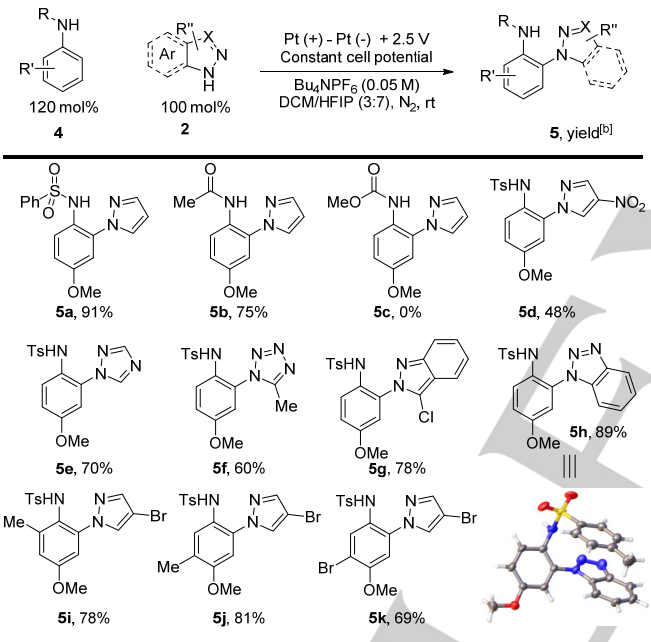
Table 2. Selected Examples of Electro-oxidative ortho C-H Azolation of Phenols[a]



[a]Reactions were run on a 0.6 mmol scale of **1** and 0.5 mmol scale of **2** in 10 mL mix-solvent under N_2 at rt by using both Platinum plate cathode and anode (10 mm × 10 mm × 0.1 mm) until the disappearance of **2**. [b]isolated yield. [c]the ratio of inseparable isomers. [d]the ratio of separable isomers.

Iodoindazole also underwent smooth electrochemical process, furnishing separable N1 and N2 isomers of **3p**. The structure of **3p** was further confirmed by X-ray study and NMR spectrum analysis. Bromoindazole, indazole carboxylic acid, chloroindazole and 5-methyl-benzotriazole furnished mixtures of separable isomers (**3q**-**3r**) and inseparable isomers (**3o**, **3t**) in high yields. Next, phenols with different functional groups were investigated. Several substituted 4-methoxyphenol were also proved to be good coupling partners for the electrochemical transformation (**3u**-**3af**). Remarkably, azoles always regioselectively attached to sterically less hindered ortho position of phenols (**3y**-**3af**, **3ak**). The substrate scope can be successfully extended to para-substituted phenols with a sulfonamide or methyl sulphide substituent (**3ag**-**3al**). Finally, high yield and good site selectivity has been achieved with 6-methoxypyridin-3-ol (**3am**).

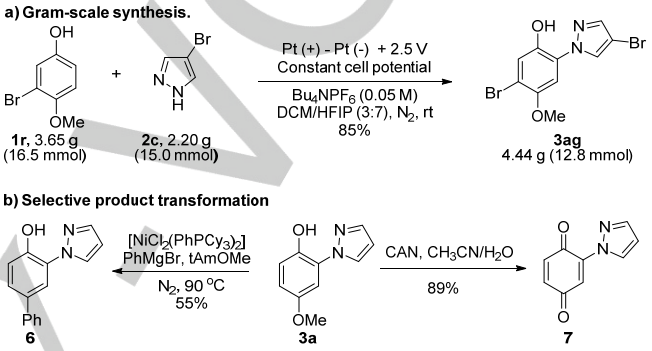
Table 3. Selected Examples Electro-oxidative ortho C-H Azolation of Anilines.[a]



[a]Reactions were run on a 0.5 mmol scale of **2** and 0.6 mmol scale of **4** in 10 mL mix-solvent under N_2 at rt by using both Platinum plate cathode and anode (10 mm × 10 mm × 0.1 mm) until the disappearance of **2.** [b]isolated yield.

Furthermore, the reaction was successfully conducted with para-methoxyl aniline derivatives under the same condition. Tosyl*p*-methoxylaniline (**4a**) coupled with pyrozole to afford **5a** in 91% yield. It was found the protecting group of amine was vital to the success of azolation. Replacement of Tosyl with Ac for **4a** would cause dramatic decrease in yield (**5b**, 75%). No product was observed when methyl (4-methoxyphenyl)carbamate (**5c**) was used in the azolation reaction. Coupling **4a** with different azoles, such as nitropyrazole, triazole, tetrazole, chloroindazole, benzotriazole, under standard electrochemical condition gave desired products in good yields (**5d**-**5k**). Notably, Tosylanilines show similar reaction activity with phenols, and the coupling reaction also exhibit high regioselectivity to deliver sterically less hindered ortho azolated anilines.

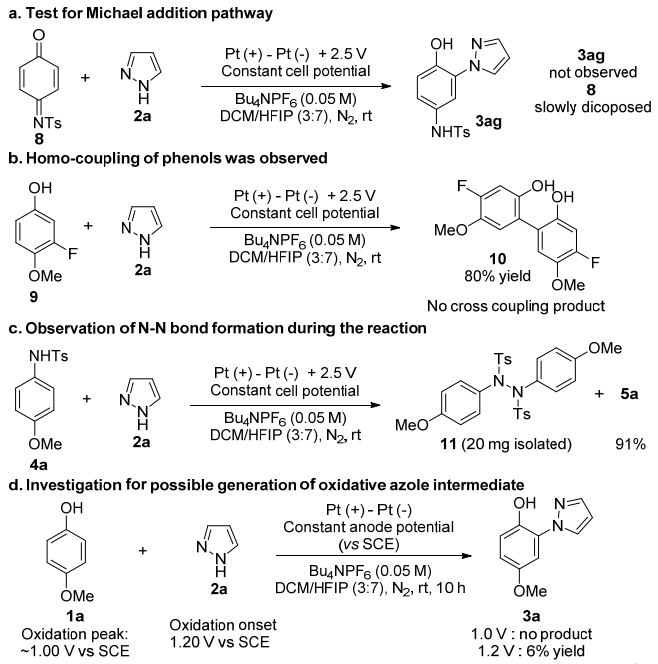
To demonstrate the practicality and scalability of current reaction, the coupling reaction was performed on gram scale with **1r** and **2c** under standard condition. Promisingly, the synthesis delivered 4.44 g of the desired product **3ag** in 85% yield, only marginally lower than the small scale reaction (Scheme 2, a). And the functional groups on products offer possibility for further manipulation. For example, the OMe group of **3a** delivered metal-catalyzed cross-coupling product **6** and oxidation product benzoquinone **7** which is viable for moreuseful transformations (Scheme 2, b).[17]



Scheme 2. Scalability Studies and Functional Group Manipulations

To gain insights into the reaction mechanism,**1t** was oxidized to compound **8** which was directly injected into the standard cross-coupling condition. It was found that **8** decomposed under the reaction condition rather than form the desired product **3aj**, which excluded the Michael addition pathway (Scheme 3, a).[18] During the study of electrochemical azolation, phenol **9** was found to form homo-coupling compound **10** as a major side product, which indicated that a radical intermediate of **9** may be generated during the reaction process (Scheme 3, b).[19] Additionally, both cross-coupling product **5g** and the homo-coupling product tosylbenzenesulfonohydrazide **11** possibly formed via N radical recombination, were obtained when **4a** was the starting material (Scheme 3, c).[20] Furthermore, Cyclicvoltammetry (CV) experiments on both reactants **1a** and **2a** were conducted (Figure S1). The results revealed that compound **2a** shows higher oxidation potential (oxidation onset of **2a**, 1.20 V vs SCE) than that of **1a** (oxidation peaks of **1a** (0.001M), around 1.0 V vs SCE). A control experiment was also conducted under corresponding anode potentials (1.00 V and 1.20 V vs SCE) for comparison (Scheme 3, d). Under constant anode potential of 1.00 V vs SCE, the desired product (**3a**) was not detected, excluding the possibility of nucleophilic addition of pyrozole to phenol cation radical.[9,10,11,12] In addition, compound **3a** could be formed in 6% yield under constant anode potential of 1.20 V vs SCE, which indicated that oxidation of **2a** was essential to facilitate the reaction(see Supporting Information for details).[12b,16] These observations, along with previous literatures,[22] suggested that radical recombination between N and C radicals during product formation may be involved. The

detailed mechanism is presented in the supporting information (Scheme S1).



Scheme 3. Evidences for the proposed reaction mechanism.

In summary, we presented in this paper a mild and general protocol for effective azolation of phenol and aniline derivatives under electrochemical condition. The reaction exhibits several useful advantages: (i) a wide range of azoles could react with structurally diverse phenol and aniline derivatives under constant potential at room temperature; (ii) functional groups including halogens, nitro groups, alkene, cyano, etc. which are synthetically useful handles for further manipulationare well tolerated; (iii) good regioselectivity was obtained; (iv) thetransformationis highly scalable (up to 15 mmol without decrease in productivity).

Experimental Section

Representative procedure: 4-Methoxy-2-(1*H*-pyrazol-1-yl)phenol (Table 2, **3a**) A solution of 4-methoxyphenol (**1a**) (0.6 mmol), pyrazole (**2a**) (0.5 mmol) and Bu_4NPF_6 (0.025 mmol) in HFIP/DCM = 7/3 (5.0 mL, 0.100 M of **2a**) was stirred at room temperature under N_2 atmosphere in a three-necked bottle which was equipped with platinum electrodes (1.0 cm×1.0 cm×0.1 mm) as both the anode and cathode. The reaction mixture was stirred and electrolyzed at a constant potential of 2.5 V until the completely consumption of **2a** around 20 h (detected by GC). The reaction mixture was directly concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate = 10 : 1 (v/v), to afford compound **3a** as a colourless oil (92 mg，97 % yield).

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Keywords: Electro-oxidation • C-H azolation • amidation • electrochemical synthesis • N-arylated heterocycle

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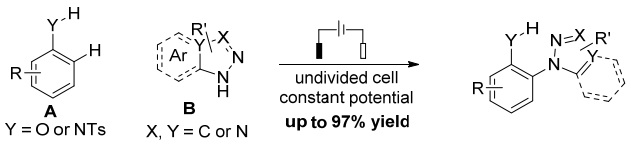

- 49 Examples
- FG compatibility and broad scope
- useful synthetic building blocks
- Metal free and mild conditoins
- Operationally simple
- Gram scale synthesis

What a move: Regioselective C-H azolation of phenol and aniline derivatives has been achieved through electro-oxidative cross coupling. The reaction runs under metal, oxidant and reagent free condition, allowing access to a wide variety of synthetically useful hetero-arene derivatives. The reaction alsotolerates a wide range of functional groups, and is amenable to gram scale synthesis.

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