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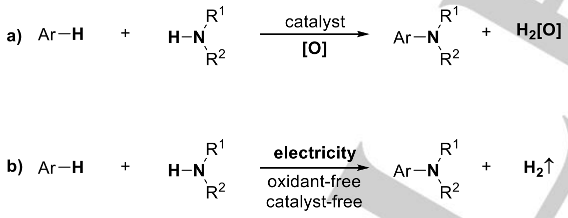
Electrochemical Oxidative C-H Amination of Phenols: Access to Triarylamine Derivatives

Shan Tang,+ Siyuan Wang,+ Yichang Liu, Hengjiang Cong, and Aiwen Lei*

Abstract: Dehydrogenative C-H/N-H cross-coupling serves as one of the most straightforward and atom-economical approaches for C-N bond formation. In this work, an electrochemical reaction protocol has been developed for the oxidative C-H amination of unprotected phenols under undivided electrolytic conditions. Neither metal catalysts nor chemical oxidants are needed to facilitate the dehydrogenation process. A series of triarylamine derivatives could be obtained with good functional group tolerance. The electrolysis is scalable and can be performed at ambient conditions.

Amination of aromatic compounds is of great importance in organic synthesis since C(sp^2)-N bonds widely exist in natural products, pharmaceuticals and fundamental materials.[1] Transition metal catalyzed amination of aryl halides or aryl boronic acids has been developed as reliable methods for the construction of C(sp^2)-N bonds.[2] Over the past few years, great attention has been paid to the direct aryl C-H amination since it has successfully skipped the pre-functionalization of arene substrates and broadened the substrate scope.[3] Among these transformations, dehydrogenative C(sp^2)-H/N-H cross-coupling serves as one of the most straightforward and atom-economical approaches for C(sp^2)-N bond formation.[4] However, these transformations usually require using stoichiometric amount of chemical oxidants (Scheme 1a). From the view of atom-economical and sustainable chemistry, developing chemical oxidant-free reaction protocols for the oxidative C-H amination of aromatic compounds would be much more appealing.[5]



Scheme 1. Intermolecular dehydrogenative amination of aromatic compounds.

As a versatile and environmentally friendly synthetic tool, electrochemistry has aroused continuous interest of synthetic chemists.[6] Electrochemical anodic oxidation serves as an ideal option for replacing chemical oxidants in oxidative C-H functionalization reactions.[7] In this field, great progress has been made in the dehydrogenative C-C cross-couplings.[8] In comparison, the construction of C-N bonds has achieved much less successful results.[9] In 2013, Yoshida and co-workers developed an oxidative aryl C-H amination of electron-rich arenes to access anilines with the combination of the electrochemical and chemical reactions.[10] Waldvogel applied a similar reaction approach to achieve the electrochemical aryl C-H amination of less activated, alkylated arenes by using boron-doped carbon electrodes.[11] As for the direct electrooxidative C-H/N-H cross-coupling, the group of Xu recently achieved the intramolecular dehydrogenative C(sp^2)-N bond formation for the synthesis of benzimidazoles.[12] Until now, there is still a lack of direct electrochemical intermolecular oxidative C(sp^2)-H amination methods. In this work, we would like to communicate our recent progress in an intermolecular electrooxidative C-H/N-H cross-coupling (Scheme 1b). *N*-aryl phenothiazines have been reported to be highly efficient photocatalysts in polymer synthesis.[13] Our method provides a simple and atom economical way for the synthesis of *N*-aryl phenothiazines from unprotected phenols and phenothiazine derivatives with up to 93% yield.[14]

By utilizing $^{n}Bu_4NBF_4$ as the electrolyte and CH_3CN/MeOH as co-solvents, the cross-coupling between *p*-methoxyphenol (**1a**) and phenothiazine (**2a**) could afford **3a** in a 93% yield under 7 mA constant current for 100 min in an undivided cell (Table 1, entry 1). Slightly decreased reaction yields were obtained either by decreasing or increasing the operating current (Table 1, entries 2 and 3). The effect of solvent was also explored. Good reaction reactivity could still be achieved by using acetonitrile or methanol as the only solvent (Table 1, entries 4 and 5). However, using water instead of methanol led to a lower reaction yield (Table 1, entry 6). As for the choices of supporting electrolyte, $LiClO_4$, $^{n}Bu_4NClO_4$ and $^{n}Bu_4NPF_6$ demonstrated similar reactivity with $^{n}Bu_4NBF_4$ (Table 1, entry 7). Notably, a good reaction yield could still be obtained by reducing the amount of supporting electrolyte (Table 1, entry 8). The effect of the electrode material was also demonstrated. Quite similar yields were obtained by replacing the carbon rod anode with carbon cloth or platinum plate anode (Table 1, entries 9 and 10). Platinum plate cathode showed a similar reactivity with nickel plate cathode (Table 1, entry 11) while graphite rod cathode was less effective than nickel plate cathode (Table 1, entry 12). A slightly decreased reaction yield could be obtained in open air (Table 1, entry 13) while no reaction took place without electric current (Table 1, entry 14). As was expected, large amount of hydrogen gas could be detected by GC analysis under standard conditions.

Table 1. Effects of reaction parameters.[a]

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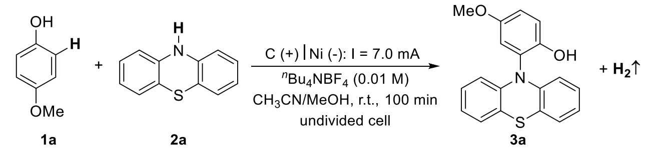
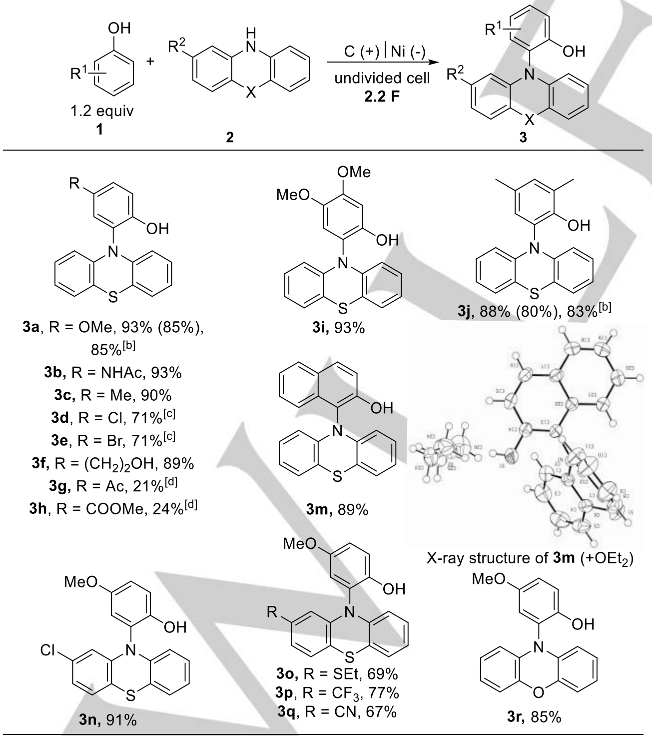


Entry	Variation from the standard conditions	Yield (%)
1	none	93
2	3.5 mA instead of 7 mA, 200 min	83
3	14 mA instead of 7 mA, 50 min	86
4	without MeOH	88
5	without MeCN	86
6	H_2O instead of MeOH	83
7	$LiClO_4$, $^{n}Bu_4NClO_4$ or $^{n}Bu_4NPF_6$ instead of $^{n}Bu_4NBF_4$	88-90
8	$^{n}Bu_4NBF_4$ (0.005 M)	85
9	carbon cloth anode	85
10	platinum plate anode	86
11	platinum plate cathode	95
12	graphite rod cathode	84
13	under air	88
14	without electric current, under air	n.r.

[a] Reaction conditions: graphite rod anode, nickel plate cathode, constant current = 7 mA, **1a** (1.2 equiv, 0.24 mmol), **2a** (1.0 equiv, 0.20 mmol), $^{n}Bu_4NBF_4$ (0.50 equiv, 0.10 mmol), MeCN/MeOH (8.0 mL/2.0 mL), room temperature, N_2, 100 min (Q = 42 C, 2.2 F). Isolated yields were shown. n.r. = no reaction.

Table 2. Electrooxidative *ortho* C-H amination of phenols with phenothiazine derivatives.[a]



3a, R = OMe, 93% (85%), 85%[b]
3b, R = NHAc, 93%
3c, R = Me, 90%
3d, R = Cl, 71%[c]
3e, R = Br, 71%[c]
3f, R = $(CH_2)_2OH$, 89%
3g, R = Ac, 21%[d]
3h, R = COOMe, 24%[d]

3i, 93%

3j, 88% (80%), 83%[b]

3m, 89%

X-ray structure of **3m** (+OEt_2)

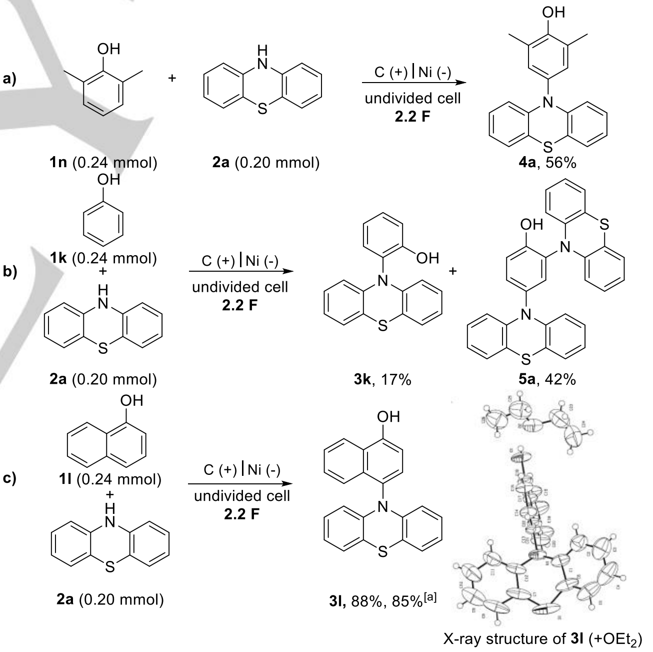
3n, 91%

3o, R = SEt, 69%
3p, R = CF_3, 77%
3q, R = CN, 67%

3r, 85%

[a] Reaction conditions: graphite rod anode (ϕ 6 mm), nickel plate cathode (15 mm×18 mm×1.0 mm), constant current = 7.0 mA (J_{anode} ≈ 6.5 mA/cm^2), **1** (0.24 mmol), **2** (0.20 mmol), $^{n}Bu_4NBF_4$ (0.10 mmol), MeCN/MeOH (8.0 mL/2.0 mL), room temperature, N_2, 100 min (Q = 42 C, 2.2 F). Isolated yields were shown. Yields shown in parentheses are of current efficiency. [b] The reaction was conducted at controlled potential (E = 0.70 V vs Ag/AgCl) and stopped until complete consumption of **2** (monitored by TLC). [c] 130 min. [d] The yield was determined by ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard.

The scope of this electrooxidative C(sp^2)-H/N-H cross-coupling was then explored. Firstly, different *para*-substituted phenols were applied as substrates in this amination reaction. Phenols bearing electron-donating or electron-neutral substituents at the *para* position could form the desired amination products in good to high yields (Table 2, **3a-3f**). Notably, chloro, bromo and free-hydroxyl group were well tolerated (Table 2, **3d-3f**). Phenols bearing electron-withdrawing acetyl or ester group at the *para* position could only give the C-N bond formation products in low yields (Table 2, **3g** and **3h**). Strong electron-rich 3,4-dimethoxyphenol was able to generate the amination product in 93% yield (Table 2, **3i**). 2,4-Dimethylphenol selectively furnished an *ortho* amination product in 88% isolated yield with 80% current efficiency (Table 2, **3j**). When 2,6-dimethylphenol was applied as the substrate, a *para* amination product could be obtained in 56% yield (Scheme 2a, **4a**).



a) **1n** (0.24 mmol) + **2a** (0.20 mmol) → **4a**, 56%

b) **1k** (0.24 mmol) + **2a** (0.20 mmol) → **3k**, 17% + **5a**, 42%

c) **1l** (0.24 mmol) + **2a** (0.20 mmol) → **3l,** 88%, 85%[a]

X-ray structure of **3l** (+OEt_2)

Scheme 2. Electrooxidative *para* C-H amination of phenols with phenothiazine. [a] The reaction was conducted at controlled potential (E = 0.70 V vs Ag/AgCl) and stopped until complete consumption of **1** (monitored by TLC).

Interestingly, the reaction with simple phenol only afforded the *ortho* amination product **3k** in 17% yield while a *para* and *ortho* double amination product **5a** could be isolated in 42% yield (Scheme 2b). By increasing the amount of phenothiazine and prolonging the reaction time, the double amination products of *ortho*-substituted phenols could be obtained in good to high yields (Scheme 3, **5b-5g**). As for other aromatic phenols, α-naphthol gave a C-4 amination product (Scheme 2c, **3l**) while β-naphthol could selectively furnish a C-1 amination product

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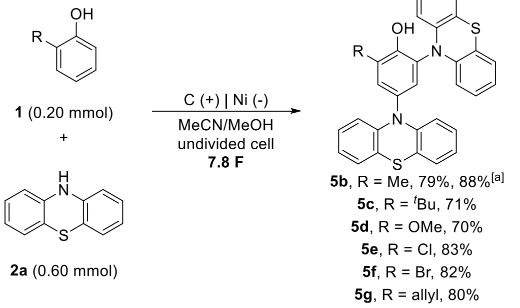
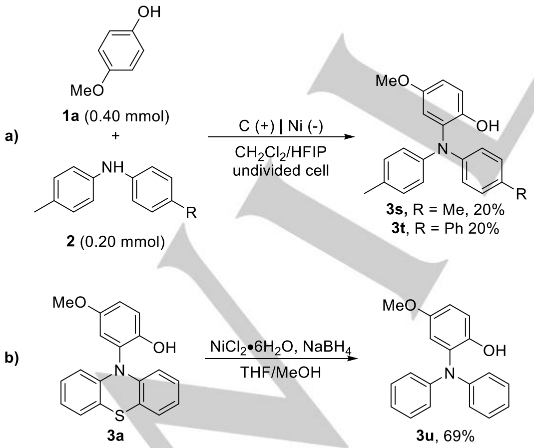
(Table 2, **3m**).[15] In addition, the scope of the amine moiety was also studied. Phenothiazines bearing chloride, electron-donating or electron-withdrawing substituents were all able to give the amination products in good to high yields (Table 2, **3n-3q**). Notably, phenoxazine was also suitable in this electrooxidative amination reaction, which furnished the C(sp^2)-N bond formation product in 85% yield (Table 2, **3r**).



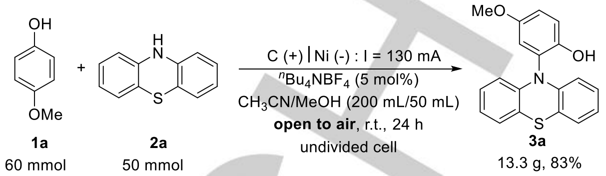
Scheme 3. Electrooxidative double C-H amination of *ortho* substituted phenols with phenothiazine. [a] The reaction was conducted at controlled potential (E = 0.70 V vs Ag/AgCl) and stopped until complete consumption of **1** (monitored by TLC).

Triphenylamines have been reported to serve as potential optoelectronic materials.[16] In order to access triphenylamines, efforts were taken to expand the scope of amine moiety from phenothiazine derivatives to diarylamines. By utilizing CH_2Cl_2/HFIP as co-solvents, the *ortho* C-H amination of *p*-methoxylphenol with electron-neutral diphenylamines could afford triphenylamines (Scheme 4a, **3s** and **3t**). Since the reaction with diarylamines suffered from low efficiency, another way to access triphenylamines was developed. By using a reduction system of $NiCl_2{\bullet}6H_2O$ and $NaBH_4$,[17] triphenylamine **3u** could also be obtained from the direct reduction of *N*-aryl phenothiazine **3a** in 69% yield (Scheme 4b). Thus, our electrochemical method was also able to access a series of functionalized triphenylamines.



Scheme 4. Synthesis of triphenylamines. HFIP = Hexafluoro-2-propanol.

The synthetic potential of this electrooxidative C-H amination was then evaluated by performing a 50 mmol scale reaction. By using 130 mA constant current, 13.3 g of **3a** could be synthesized with only 5 mol% of supporting electrolyte in the open air (Scheme 5).



Scheme 5. Gram scale synthesis.

Since the method has been established, attentions were then paid to understand the reaction mechanism. Cyclic voltammetry (CV) experiments were conducted to study the redox potential of the substrates (Figure 1). Two obvious oxidation peaks of phenothiazine **2a** in CH_3CN/CH_3OH were observed at 0.70 V and 0.91 V while two reduction peaks were observed on the reverse scan at 0.74 V and 0.61 V (Figure 1a). The first oxidation peak of **2a** was quasi-reversible and only one electon was transferred in the oxidation process (See Supporting Information for detailed data analysis). The oxidation potentials of phenols were also measured by conducting CV experiments. Even strong electron-rich *p*-methoxyphenol demonstrated higher oxidation potential than **2a** (Figure 1b). These results indicated that **2a** was likely to be first oxidized under electrolytic conditions. To confirm this assumption, the electrolysis was performed at the first peak oxidation potential of **2a** (0.70 V). The potential controlled electrolysis furnished the desired products in slightly decreased reaction yields for the mono C-H amination of *p*-methoxylphenol and 2,4-dimethylphenol and α-naphthol (Table 2, **3a, 3j** and **3l**). Meanwhile, a slightly increased reaction yield could be obtained for the double amination reaction of 2-methylphenol by utilizing potential controlled electrolysis instead of constant current electrolysis (Scheme 3, **5b**). Based on the above experimental results and previous reports,[14] a plausible mechanism for the electrooxidative C(sp^2)-H/N-H cross-coupling between **1a** and **2a** was proposed and described in *Supporting Information, Scheme S1*. The reaction is initiated by the anodic oxidation of **2a** to generate a radical cation.

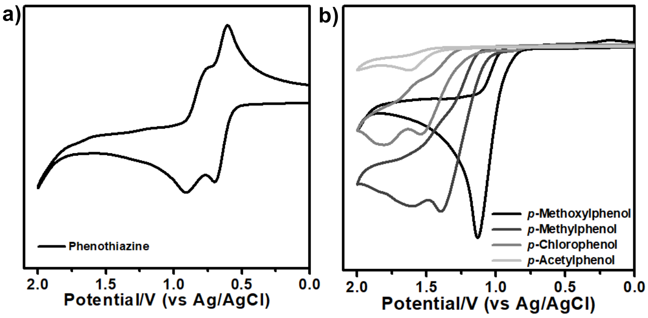


Figure 1. Cyclic voltammograms on a glassy carbon electrode (ϕ 3 mm) at 0.10 $V{\bullet}s^{-1}$ in CH_3CN/CH_3OH under nitrogen. a) Phenothiazine. b) Different phenols.

In conclusion, we have developed a novel method for the dehydrogenative C(sp^2)-H/N-H cross-coupling between phenols and phenothiazine derivatives under undivided electrolytic conditions. This reaction protocol avoids the use of external chemical oxidants, which provides a simple and atom-economical way for the synthesis of *N*-aryl phenothiazines. Triphenylamines can also be synthesized either from the direct electrooxidative aryl C-H amination of diphenylamines or from the reduction of *N*-aryl phenothiazines. Importantly, the reaction is scalable in the open air. Preliminary mechanistic study suggests that the amine substrates are firstly oxidized to generate radical cations during electrolysis.

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Keywords: C-N bond formation • electrochemistry • C-H functionalization • amination • hydrogen evolution

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[15] CCDC 1819981 (**3l**) and 1819982 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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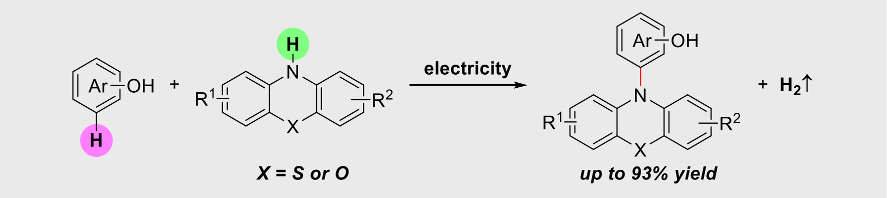

X = S or O

up to 93% yield

An atom economical oxidative C-H amination of unprotected phenols was achieved via an external oxidant-free electrochemical reaction protocol. Under undivided electrolytic conditions, triarylamines derivatives were produced in high functional group tolerance along with H_2 generation.

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