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Electrochemical phenothiazination of naphthylamines and its application in photocatalysis†

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***N*-Phenylphenothiazine as an inexpensive, highly reductive and oxygen tolerant organophotocatalyst has exhibited potential in various challenging photochemical transformations. Here we report a general and straightforward method to access structurally diverse *N*-phenylphenothiazine derivatives by means of a novel electrochemical tool. The introduction of a 2-naphthylamine moiety with an extended π-system and an amine group led to the variation of spectral characterization. Photochemical verification experiments demonstrated that the formed *N*-arylation products with good efficacy and chemo/site-control displayed competitive catalytic activity in challenging transformations.**

Photocatalysis has emerged as a powerful synthetic tool in organic synthesis because of its competency in the cleavage and reconstruction of chemical bonds under green and mild conditions. Over the past couple of decades, tremendous achievements have been acquired in the photochemical field and now it has become a significant branch in synthetic chemistry.[1–5] The photocatalyst (PC) as the switch to initiate the catalytic cycle has been widely recognized as one of the most crucial components in photochemical reactions and attempts to pursue green, inexpensive and efficient PCs have never stopped.[6–12] Undoubtedly, the utilization of rare metal-cored PCs has significantly promoted the evaluation of this field.[1–5,13–15] Now, the exploitation of inexpensive and readily accessible organophotocatalysts as the substitutes of metal-cored PCs has attracted extensive attention.[6–10,12] Phenothiazine contains a N–H bond of low dissociation energy and could generate stable persistent *N*-centered radicals upon oxidation.[16] These features render *N*-phenylphenothiazine (PTH) favourable for a photocatalyst. Various challenging transformations have been realized building upon the remarkable excited state reducibility of PTH and its derivatives.[17–21] Meanwhile, it has been verified that the modulation of PTH through the introduction/alternation of the heteroatom or extension of the π-conjugation system on PTH could not only affect the catalytic potency,[22–24] but also result in the variation of spectral characterization.[25–28] Accordingly, a universal and facile route to approach structurally diverse *N*-arylphenothiazines is of great significance to multiple research fields.[29,30]

N-Arylation of phenothiazines with aryl halides under transition-metal-catalysis is the most commonly used strategy to synthesize PTH and its derivatives.[31–33] However, classic Buchwald–Hartwig and Ullmann aminations are usually accompanied by novel metal catalysts and harsh conditions, and are incompatible with halide substituents which served as effective handles for downstream transformations. Alternatively, such structures are accessible through annulation towards heterocycles with preformed precursors.[34–36] Cross dehydrogenative coupling reactions between phenothiazines and aryl reagents appeal in terms of atom economy but are nonetheless associated with stoichiometric amounts of oxidant and confined substrate scope.[37–41] In this context, an elegant strategy for C–H/N–H dehydrogenative coupling of phenothiazines with anilines/phenols was disclosed by Lei[42,43] and Li[44] by means of emerging electrochemical oxidation. The site-selectivity was effectively controlled by the strong directing groups (Scheme 1a). Inspired by these pioneering achievements[45] as well as our continuous interest on *N*-arylation[46] and the chemistry with 2-naphthylamines,[47,48] we envisaged that 2-naphthylamines may be suitable arylation agents for this transformation. It is expected that the extended π-system and the free amine group could result in the variation of the spectral characterization and provide complementary potential to the reported PTH type photocatalysts (Scheme 1b). Since the aromatic amines have quite similar oxidation potentials to phenothiazines and the amine group has been revealed to be reactive under electrochemical conditions,[49,50] the control of chemoselectivity, particularly for the substrates with unmasked NH_2, is essential for this transformation.

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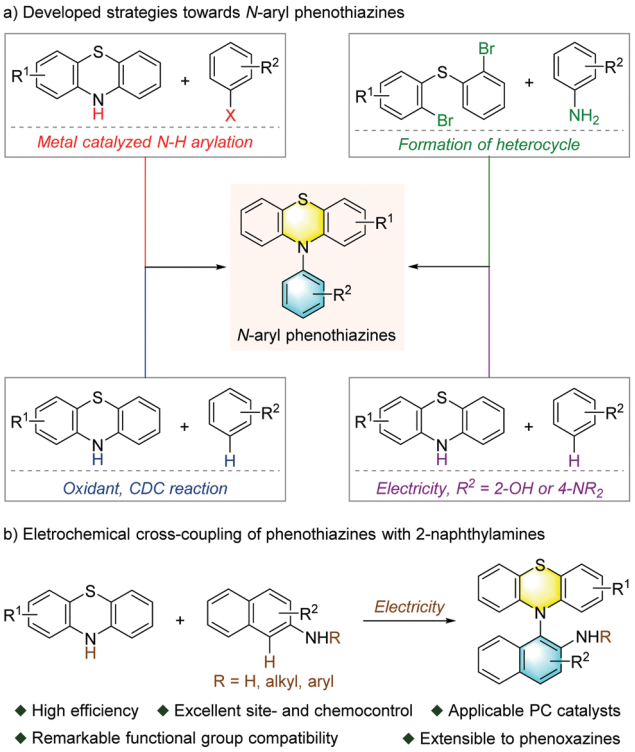
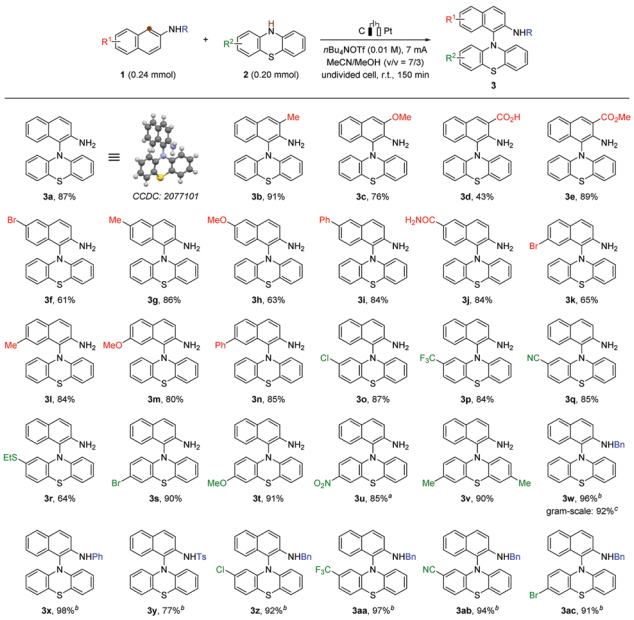


Scheme 1 Motivation and synthetic strategies towards *N*-aryl phenothiazines.

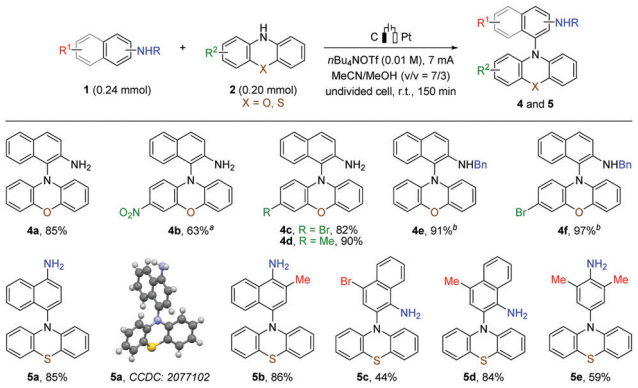


Scheme 2 Substrate scope with respect to 2-naphthylamines and phenothiazines. [a]CH_2Cl_2 (1 mL) was added to dissolve the substrate. [b]**1** (0.20 mmol) and **2** (0.20 mmol). [c]Graphite rod anode (ϕ 6 mm), platinum plate cathode (15 mm × 15 mm × 1 mm), constant current = 70.0 mA, **1o** (1.0 equiv., 5.0 mmol), **2a** (1.0 equiv., 5.0 mmol), nBu$_4$NOTf (0.1 equiv., 0.50 mmol), MeCN/MeOH (72 mL/18 mL).

The electrochemical cross-coupling of 2-naphthylamine (**1a**) and phenothiazine (**2a**) was commenced with nBu$_4$NBF$_4$ as the electrolyte (for details, see the ESI,† Table S1). The reaction proceeded smoothly in a mixed solvent of MeCN/MeOH under 7 mA constant current in an undivided cell, affording the desired product **3a** in 73% yield (Table S1, ESI,† entry 1). Subsequent screening on electrolytes found that nBu$_4$NPF$_6$, nBu$_4$NI, nBu$_4$NCl and Me$_3$PhNI brought about similar results (Table S1, ESI,† entries 2–5), while a slightly higher yield was obtained with nBu$_4$NOTf as the electrolyte (entry 6). Pleasingly, the yield was improved to 87% through the modulation of the solvent ratio (entry 9). Unsurprisingly, a single solvent failed to give satisfactory results for this transformation (entries 10 and 11). Subsequent optimizations including the alteration of the electric current and electrode material were ineffective (entries 12–16). Similar yield was procured when the reaction was conducted under an argon atmosphere (entry 17) and the reaction was completely inhibited without electric current (entry 18).

After the establishment of the optimized conditions, the substrate generality was then explored and the detailed results are summarized in Scheme 2. First, a wide range of 2-naphthylamines with different substituents and substituted patterns were evaluated and the desired products were obtained in moderate to excellent yields for most cases (**3a–3n**). It should be pointed out that the introduction of a carboxylic acid group on C3 of 2-naphthylamine resulted in sharp erosion of the yield (**3d**) and the good outcome was retained when the acid group was protected to an ester (**3e**). The amide group harbouring a free NH_2 was well tolerated for this set of conditions and the corresponding product **3j** was generated in 84% yield. Next, the substituent effect for phenothiazine was investigated and it was found that the substrates with electron-donating or electron-withdrawing groups could all give the expected PHT derivatives in quite high efficiency (**3o–3v**), except for **3r** with an ethylthio substituent. Meanwhile, a phenothiazine substrate with two methyl groups was applicable to give product **3v** in 90% yield. It is noteworthy that halides at both coupling partners could survive under this set of conditions, thus providing effective handles for the downstream derivatization through transition-metal-catalysis. Additionally, 2-naphthylamines with varied protecting groups were explored (**3w–3ac**). The reaction with benzyl or phenyl protected 2-naphthylamine proceeded smoothly to deliver the corresponding product in quantitative yield (**3w–3x**). The introduction of tosyl as the protecting group seriously affected the reactivity of 2-naphthylamine and provided product **3y** in only 77% yield. Utilizing benzyl protected 2-naphthylamine as a coupling partner, the electronic properties and substitution patterns of the phenothiazine counterparts exerted a negligible effect on the outcome (**3z–3ac**). The preparative-scale synthesis of compound **3w** was also performed under the standard conditions and no obvious deduction of yield was observed.

Subsequently, phenoxazines with similar chemical properties were also attempted for this transformation. As shown in Scheme 3, with unprotected 2-naphthylamine as the coupling partner, the reaction with phenoxazine furnished the desired product **4a** in 85% yield. When a strong electron-withdrawing group was installed on phenoxazine, only 63% yield was obtained. In contrast, the equipment of an electron-donating group slightly improved the efficiency. Unsurprisingly, excellent yields were obtained when benzyl protected 2-naphthylamine was used



Scheme 3 Evaluation of phenoxazines, 1-naphthylamines and aniline. [a]CH_2Cl_2 (1 mL) was added to dissolve the substrate. [b]**1** (0.20 mmol) and **2** (0.20 mmol).

(**4e** and **4f**). Besides 2-naphthylamines, 1-naphthylamines were also suitable coupling partners for this reaction. Interestingly, C4 was the favourable site for this case, which was unambiguously substantiated by the X-ray crystallographic analysis of **5a**. Similar yields were obtained for both **5a** and **5b** as compared to **3a**. When the C4 position was occupied, the active site moved to the C2 position of 1-naphthylamine (**5c** and **5d**). Apart from naphthylamines, 2,6-dimethylaniline was also amendable for this reaction to give the desired product **5e** in synthetically useful yield. However, other investigated anilines with varied substituents and substituted pattern could not give satisfactory results.

To gain more insights into the mechanism, cyclic voltammetry (CV) experiments were introduced to test the redox potential of both coupling partners. Phenothiazine **2a** (Black line, Fig. 1a) exhibited two oxidation and reduction peaks respectively, and the first oxidation peak was at 0.52 V. For 2-naphthylamine derivatives, the first oxidation peak of **1a** was at 0.66 V (Black line, Fig. 1b), and that of **1p** is more than 0.8 V (Green line, Fig. 1b). Other explored 2-naphthylamine derivatives displayed similar results to **1a**. Accordingly, **2a** with low oxidation potential was supposed to be oxidized first under standard conditions. After that, an electron paramagnetic resonance (EPR) experiment was performed under the given conditions and a radical signal was detected only for **2a** with a *g*-value of 2.0065 (Fig. 1c), indicating that **2a** was the only species oxidized to a radical in this transformation.

For comparison with the certified phenothiazine-centered PCs, the UV-vis absorption spectroscopy of PTH and representative products was then examined. As displayed in Fig. 1d, the introduction of an extended π-system and amine group enhanced the λ_{max} and intensity (**3a**). The λ_{max} could be further improved by the protection of amine with an electron-donating protecting group (**3w**, **3x** and **3aa**), while the product bearing an electron-withdrawing group generated no significant absorption peak (**3y**). With this information in hand, the potential of such products as PCs in a photochemical reaction was then attempted. First, the catalytic performance in dehalogenation of aryl halides **6** was evaluated and the results are summarized in Fig. 2a. For activated iodobenzene (**6a**) and bromobenzene

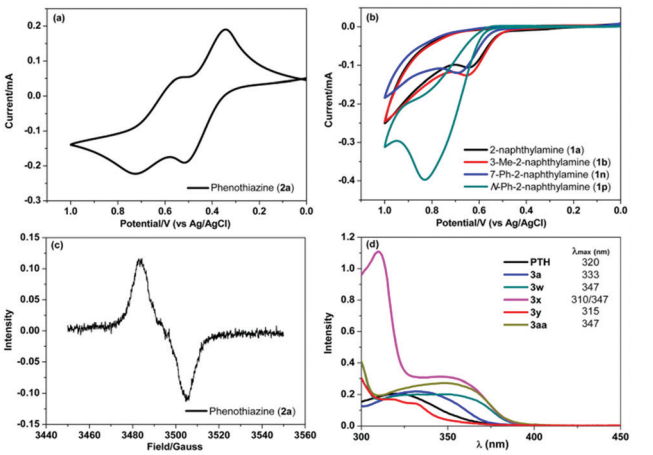


Fig. 1 Mechanistic investigations by CV/EPR experiments and UV-vis absorption spectroscopy of representative *N*-aryl phenothiazines. (a) Oxidation potential study of **2a**. (b) Oxidation potential studies of **1a** and its derivatives. (c) EPR spectrum of **2a**. (d) UV-Vis absorption spectroscopy of PTH and representative products.

(**6b**), all the tested PCs could achieve quite good efficiency. Nonetheless, the differentiation in the catalytic potency emerged when less active **6c** was used (78% for **3x** and 56% for PTH). Similar results were obtained for the dehalogenation reaction of C1 halide substituted 2-naphthols (**6d** and **6e**). These results demonstrated that it is effective to improve PC's potency through modifying its structure. The aryl radicals generated from dehalogenation could also be trapped by vinyl amine (**8**) to synthesize phenylethylamine **9** with complete regiocontrol (Fig. 2b).

In summary, we have established an efficient route for chemo/site-controlled cross dehydrogenative coupling between 2-naphthylamines and phenothiazines by virtue of an electrochemical tool to afford the PTH type photocatalysts with abundant structural diversity. CV and EPR experiments demonstrated that phenothiazine displaying lower oxidation potential relative to naphthylamine was oxidized to radical species during this process. UV-Vis absorption spectroscopy analysis revealed that the introduction of an extended π-system and

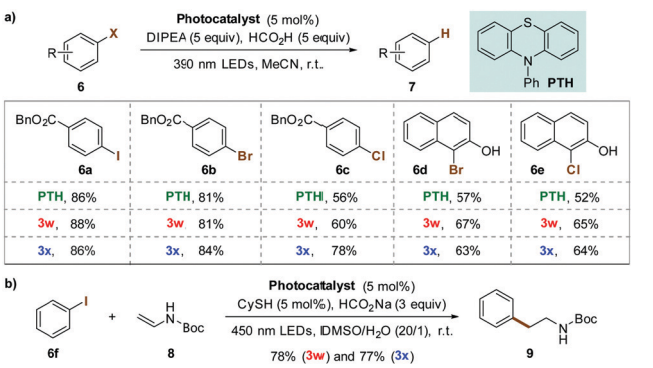


Fig. 2 Photocatalyst potential. (a) Application in photochemical dehalogenation. (b) Application in regioselective hydroarylation of vinyl amine with iodobenzene.

amine group enhanced the λ_{max} and intensity. The generated products outcompeted commonly used PTH photocatalysts in the dehalogenation reaction of less active aryl halides, substantiating the effectiveness of the modulation.

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Conflicts of interest

The authors declare no conflict of interest.

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