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Facile synthesis of *N*-aryl phenothiazines and phenoxazines *via* Brønsted acid catalyzed C–H amination of arenes†

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***N*-Aryl phenothiazines and phenoxazines are of significant importance in various disciplines throughout academia and industry. The conventional synthetic strategy for the construction of these structures centers on the transition-metal-catalyzed cross-coupling of aryl halides with phenothiazines or phenoxazines. Here we present an organocatalytic approach to access *N*-naphthyl phenothiazine and phenoxazine scaffolds through a straightforward C–H amination of arenes as enabled by an azo group. This reaction features operational simplicity, adequate substrate generality and excellent functional group compatibility. Notably, the efficiency of the catalyst could be perfectly preserved after 5 catalytic cycles.**

Phenothiazines represent a class of nitrogen- and sulfur-based heterocyclic compounds with widespread utilization in the manufacture of dyes and pigments since the early days.[1] These butterfly shaped molecules exhibit diverse and remarkable pharmacological activities,[2] and hence constitute the core unit for numerous important drugs.[3] The extensive π-conjugated, electroactive and rigid frameworks uniquely present high molar absorption coefficients and intense luminescence to endow utilization potential in optoelectronics.[4] From a synthetic standpoint, *N*-aryl phenothiazines contain N–H bonds of low dissociation energy and could generate stable persistent *N*-centered radicals facilely upon oxidation,[5] all of which are favourable properties of photoredox catalysts.[6] The pronounced excited state reducibility of these catalysts has benefited the realization of various challenging transformations.[7] For instance, the reduction potentials of *N*-phenyl phenothiazine and derivatives rendered them as substitutes for expensive iridium photocatalysts in radical dehalogenation reactions of unactivated aryl halides.[8] Moreover, these appealing attributes could be modulated by tuning the electronic and steric properties of the substituents on phenothiazine and the nitrogen-tethered aryl ring.[9] Accordingly, the facile acquirement of structurally diverse *N*-aryl phenothiazines is of great significance in multiple research fields.

The transition-metal-catalyzed *N*-arylation of phenothiazines with aryl halides as Ullmann and Buchwald–Hartwig amination reactions represents the primary approach to synthesize *N*-aryl phenothiazines (Fig. 1a).[10] Generally, harsh conditions are required and halide substituents are hardly tolerated. As an alternative, the dehydrogenative cross-coupling reaction of phenothiazines and specific arenes featuring a high atom economy has been realized exploiting stoichiometric amounts of exogenous oxidants[11] or electrochemical tools (Fig. 1b).[12] The annulation reaction towards a heterocyclic core also provides an effective approach for these

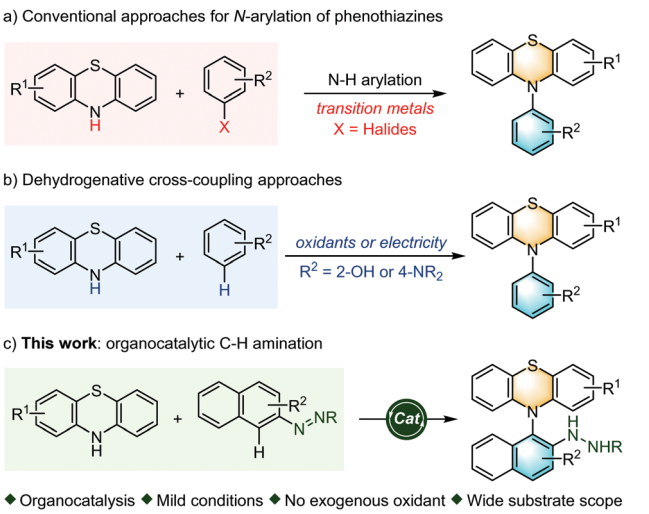

Fig. 1 Representative methods to forge *N*-aryl phenothiazines and our design.

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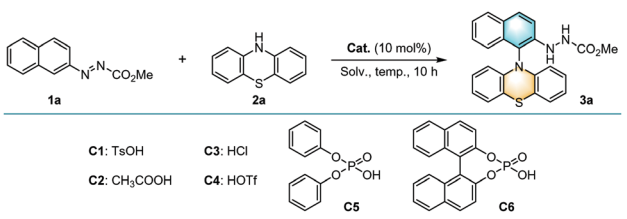
structures.[13] Inspired by these prior studies and our recent success on organocatalytic C–H/N–H cross-coupling enabled by an azo group,[14] we envisaged the applicability of phenothiazines as competent nucleophiles for azonaphthalenes to forge *N*-aryl phenothiazines (Fig. 1c). This chemistry could lift the requirement of an external oxidant and an expensive metal and, more importantly, accommodate halide substituents for follow-up functionalization. Herein, we present our results on this endeavour and preliminary efforts in an asymmetric variant to introduce the stereodefined *N*-aryl axis in these scaffolds.

Based on recent achievements[15] and our understanding[16] in hydrogen-bonding-assisted nucleophilic addition reactions of azonaphthalenes, the readily available *p*-toluenesulfonic acid (TsOH) **C1** was selected as the catalyst to promote the reaction of azonaphthalene **1a** and phenothiazine **2a** in CH_2Cl_2 at 40 °C. Pleasingly, an isolated yield of 16% was obtained for the desired product **3a** in 10 hours (Table 1, entry 1). Subsequently, a range of Brønsted acids of differing strengths (entries 2–6) were evaluated where the moderately acidic diphenyl hydrogen phosphate **C5** stood out as optimal to promote this amination reaction, boosting the chemical yield to 74% (entry 5). The subsequent survey revealed the superiority of chloroform ($CHCl_3$) within the scope of tested solvents (entries 8–15) to deliver *N*-naphthyl phenothiazine **3a** in 83% yield (entry 7). Variations in temperature, reaction duration and catalyst loading failed to further improve the reaction outcome (entries 16–18). Accordingly, the optimized conditions were concluded as follows: **1a** (1.0 equiv.), **2a** (1.5 equiv.), and **C5** (10 mol%) in $CHCl_3$ (1 mL) at 40 °C for 10 h.

Under the established optimal conditions, the substrate scope for this reaction was then probed. As summarized in Fig. 2, product **3a** was obtained in 84% yield when the reaction was conducted at 0.2 mmol scale. Varying the ester tethers of the azo group exerted a limited influence for this transformation and afforded the expected products **3b–3e** in 70–85% yields. The results for the formation of **3f–3l** suggested that the electronic nature and substitution patterns of the azonaphthalene counterparts exhibited a negligible effect. Similarly, differently substituted phenothiazines were found to be well suited to this set of conditions (**3m–3r**). It is worth noting the compatibility of halide substituents on both coupling partners in this case, which were uncommon in conventional transition-metal-catalyzed N–H amination reactions. Post-functionalization and divergent synthesis of *N*-naphthyl phenothiazines (**3j**, **3k**, **3o**, **3p** and **3r**) thus became viable.

After the accomplishment of C–H amination on phenothiazine substrates, we further investigated the applicability of phenoxazine type nucleophiles. As with phenothiazines, phenoxazine scaffolds are gaining recognition in various academic and industrial applications, such as pharmaceuticals and functional materials.[17] Extending the reaction scope to these coupling partners could further improve the utility of this transformation. Delightfully, the reaction of azonaphthalene **1a** and phenoxazine **4a** under standard conditions proceeded smoothly to afford the expected product **5a** in a near-quantitative yield (96%). The generality of phenoxazine substrates was then surveyed with the results summarized in Fig. 3. First, substituting the methyl ester entity on azonaphthalene **1a** with ethyl (**5b**) or isopropyl (**5c**) ester influenced the chemical

Table 1 Optimization of conditions with phenothiazine **2a**[a]



Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	**C1**	CH_2Cl_2	40	16
2	**C2**	CH_2Cl_2	40	9
3	**C3**	CH_2Cl_2	40	<5
4	**C4**	CH_2Cl_2	40	10
5	**C5**	CH_2Cl_2	40	74
6	**C6**	CH_2Cl_2	40	66
7	**C5**	$CHCl_3$	40	83
8	**C5**	CCl_4	40	48
9	**C5**	DCE	40	72
10	**C5**	Toluene	40	64
11	**C5**	CH_3CN	40	70
12	**C5**	THF	40	29
13	**C5**	EtOH	40	66
14	**C5**	EtOAc	40	27
15	**C5**	1,4-Dioxane	40	27
16[c]	**C5**	$CHCl_3$	25	79
17	**C5**	$CHCl_3$	50	77
18[cd]	**C5**	$CHCl_3$	40	78

[a] Unless otherwise specified, all the reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), and **Cat.** (10 mol%) in 1 mL of solvent at 40 °C for 10 h. [b] Isolated yields were provided. [c] 24 h reaction duration. [d] 5 mol% **C5** was used.

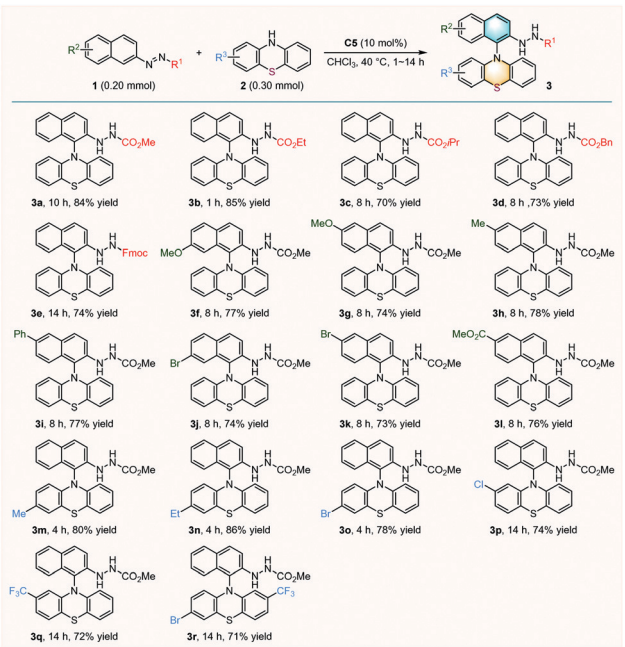


Fig. 2 Substrate generality for C–H amination with phenothiazines.

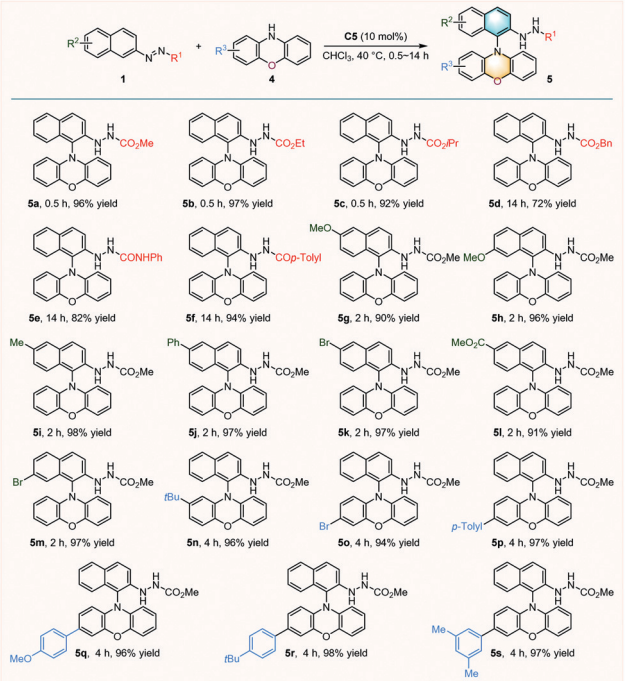


Fig. 3 Substrate scope for C–H amination with phenoxazines.

yield minimally, while a yield decrease was observed for the benzyl ester (**5d**) substrate. On interchange of ester with amide, the corresponding *N*-naphthyl phenoxazine was acquired in 82% yield (**5e**). Next, a series of substrates embedded with electron-donating and electron-withdrawing groups were smoothly converted to the target adducts in excellent efficiencies (**5g–5m**). To further enrich the structural diversity, a group of phenoxazines with modulated substitutions were investigated against azonaphthalene **1a**. Unsurprisingly, all substrates complied well under these conditions to deliver products (**5n–5s**) in 94–98% yields. Likewise, bromide handles were well preserved in the products under the developed conditions.

To investigate the practicality of this protocol, a gram-scale reaction of **1a** and **4a** was performed using the standard conditions. As displayed in Fig. 4a, product **5a** was furnished in 94% yield, slightly lower than that of the small-scale reaction (Fig. 3). Subsequently, compound **6a**, which has exhibited great potential in photochemical transformations as a photocatalyst, was synthesized in 76% yield by the cleavage of the N–N bond through hydrogenation with RANEY® Ni (Fig. 4b). Additionally, the recycling of the organocatalyst was attempted following this procedure: azonaphthalene **1g** (0.2 mmol, 1.0 equiv.), **C5** (0.02 mmol, 0.1 equiv.), phenoxazine **4a** (0.3 mmol, 1.5 equiv.) and $CHCl_3$ (2 mL) were added to a reaction tube. After reaction completion in 40 min at room temperature (monitored by TLC), product **5f** was precipitated because of the poor solubility in the reaction medium. Simple filtration and washing with $CHCl_3$ (2 mL) gave the pure product as a white solid. Meanwhile, **C5** and the excess **4a** were retained in the filtrate. The volume of the resulting mixture was evaporated to approximately 2 mL before a fresh batch of **1g** (0.2 mmol) and **4a** (0.22 mmol) was

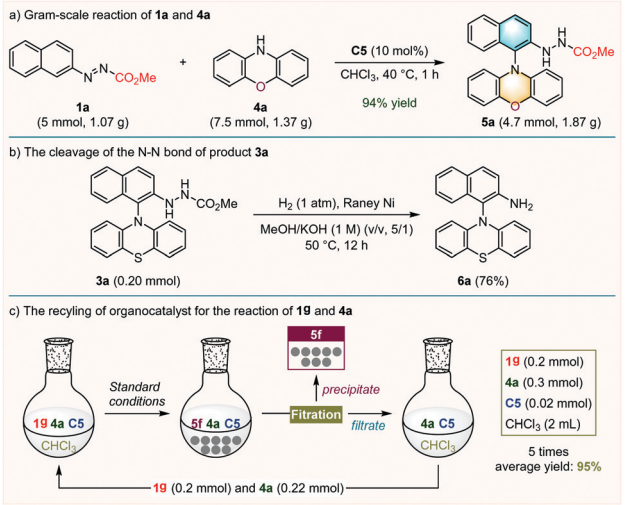


Fig. 4 Gram-scale reaction, transformation of the product and the recycling of the organocatalyst.

charged for the next round of the reaction. After a repetition of this procedure five times, an average yield of 95% was achieved, indicating the good recyclability of the organocatalyst in this transformation (Fig. 4c).

The asymmetric variant of this transformation was also attempted and the preliminary screening results of representative chiral phosphoric acids[18] (**CPA**s) are summarized in Fig. 5. Using azonaphthalene **1a** as the electrophile, phenothiazine **2g** and phenoxazine **4b** harbouring sterically hindered substituents were selected as the nucleophiles with the aim to render the then-forged *N*-aryl axis stereogenic. For better control of enantioselectivity, both reactions were conducted at room temperature with longer duration (3–5 d). Nonetheless, the best result for the reaction with **2g** was 71% yield with 16% enantiomeric excess (ee) when BINOL-derived **CPA1** possessing triphenylsilyl at the 3,3′-position was utilized. Similarly, the

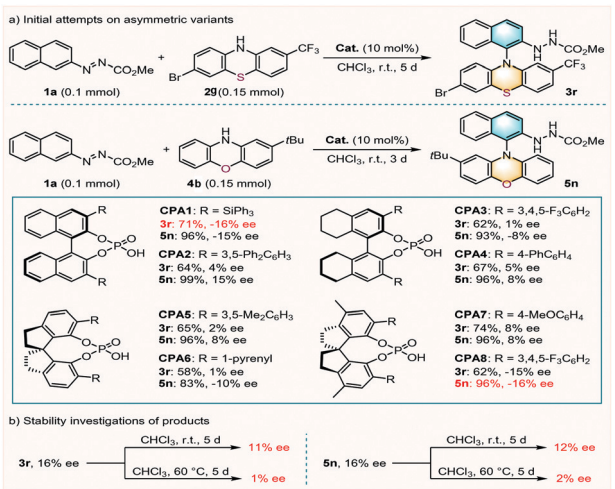


Fig. 5 Initial investigations on the atroposelective construction of *N*-aryl chiral axes and stability studies of the products.

optimal catalyst **CPA8** could only bring about 16% ee for the reaction with **4b**. The challenge in the enantiocontrol for this transformation probably originated from the distinct butterfly shape of phenothiazine and phenoxazine, as well as the attendant axial stability issue. For instance, the enantiomeric excess of **3r** and **5n** would decrease gradually at room temperature upon standing in $CHCl_3$ solution and almost complete racemization would result within a few days at 60 °C.

In conclusion, we have disclosed an efficient approach for forging *N*-naphthyl phenothiazine and phenoxazine structures through organocatalytic C–H amination of arenes without an oxidant. This approach accommodates wide substrate scope with up to 98% chemical yield. The mild reaction conditions have warranted excellent compatibility with functional groups including halides, thereby providing effective handles for downstream functionalization through orthogonal transition-metal-catalysis. The preserved efficiency of gram-scale experiments and recyclability of the organocatalyst enhanced the utility of this protocol. Further investigations on asymmetric variants of this transformation and applications of *N*-naphthyl phenothiazine and phenoxazine products are ongoing in our laboratory.

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Conflicts of interest

The authors declare no conflicts of interest.

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