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Mild, Periodate-Mediated, Dehydrogenative C−N Bond Formation with Phenothiazines and Phenols

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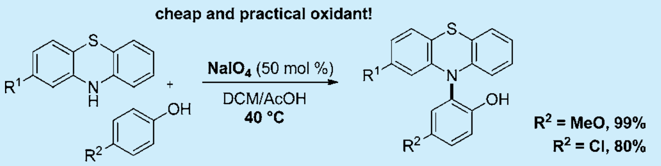
Ⓢ *Supporting Information*

ABSTRACT: The dehydrogenative amination of phenols with phenothiazines was achieved in transition-metal-free conditions, utilizing cheap sodium periodate as oxidant, at low temperature. A significantly larger scope of phenol substrates was tolerated compared to previous methods.

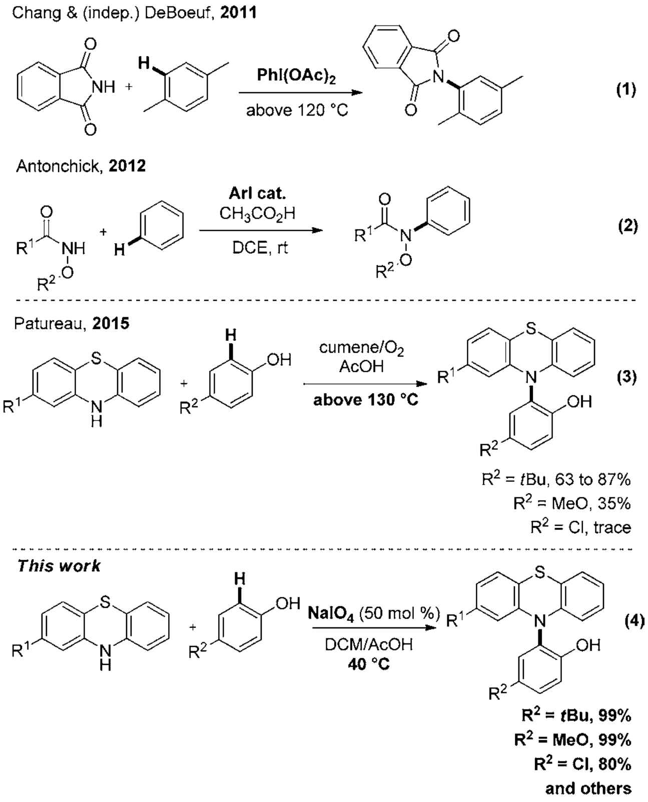


Cross-dehydrogenative couplings (CDCs) have emerged as a promising strategy for the direct construction of molecular complexity, as they typically avoid prefunctionalization steps.[1,2] In this field, high-valence iodine reagents constitute an exceptional class of tools for dehydrogenative amination methods.[3] The relatively benign character of iodine, its availability, its versatile redox activity, and its pronounced electrophilicity when in its higher oxidation states make it a convenient approach for mild dehydrogenative amination protocols. This has been exemplified recently in several hypervalent iodine mediated dehydrogenative C−N bond formation reactions by Chang,[3a] DeBoeuf,[3b] Antonchick,[3c] and others,[3] who have brought the C−N bond formation paradigm beyond classical Ullmann and Buchwald−Hartwig reactions[4] (Scheme 1, eqs 1 and 2). We recently reported a halide-free and metal-free dehydrogenative amination method of phenols, which operates under the sole action of an oxygen atmosphere in cumene and acetic acid.[5] This simple protocol (without iodine) requires, however, typically 150 °C of reaction temperature, which limits the scope and the functional group tolerance (Scheme 1, eq 3). With the goal of providing more useful synthetic methods, we decided to reconsider this dehydrogenative amination strategy and to bring it to a temperature range from originally 150 °C to lower than 50 °C while also enabling broader substrate classes, such as polyhalogenated phenols (which previously did not react), as well as electron-rich phenols like naphthol, which are typically subject to high versatility[6] or decomposition.

The term "amination" is utilized here for practical reasons. However, it should remain clear that the present method is only applicable to phenothiazines.[7] We first examined the reaction of 2-(trifluoromethyl)phenothiazine (**1a**) with 4-*tert*-butylphenol (**2a**) under a series of simple oxidizing reaction conditions (Table 1) at low temperatures.

Interestingly, utilizing a periodate oxidant[8] yielded the expected cross dehydrogenative amination product **3aa** in more than 91% isolated yield at 50 °C (entry 4). Periodate being a competent oxidant in this reaction is remarkable because it is traditionally used for oxidative bond cleavage, usually associated with a decrease of molecular complexity.[8] In contrast, periodate-mediated oxidative bond construction (increase of molecular complexity) is more rare.[8j] Moreover, periodate salts are significantly cheaper than most other hypervalent iodine reagents.

Scheme 1. A Selection of Metal-Free Cross-Dehydrogenative C−N Bond-Forming Reactions with Csp2−H Bonds



We then realized that in the presence of periodate cumene is no longer an essential solvent. Interestingly, dichloromethane is a

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Table 1. Optimization

entry[a]	oxidant (mol %)	solvent	cosolvent	atm (1 bar)	temp (°C)	yield[b] (%)
1	Ph-I (50)	cumene	AcOH	O_2	50	
2	CuI (50)	cumene	AcOH	O_2	50	trace
3[c]	TBAI (50)	cumene	AcOH	O_2	50	
4	KIO_4 (50)	cumene	AcOH	O_2	50	91
5	KIO_4 (50)	cumene	AcOH	O_2	rt	56
6[c]	KIO_4 (50)	DCM	AcOH	O_2	rt	78
7[c]	KIO_4 (50)	THF	AcOH	O_2	rt	trace
8	KIO_4 (50)	PhCl	AcOH	O_2	rt	trace
9	KIO_4 (50)	DCM		O_2	rt	
10	KIO_4 (5)	DCM	AcOH	O_2	rt	5
11	KIO_4 (50)	DCM	AcOH	air	rt	65
12	KIO_4 (50)	DCM	AcOH	air	40	95
13	**$NaIO_4$ (50)**	**DCM**	**AcOH**	**air**	**40**	**99**
14	$LiIO_4$ (50)	DCM	AcOH	air	40	10
15		DCM	AcOH	air	40	

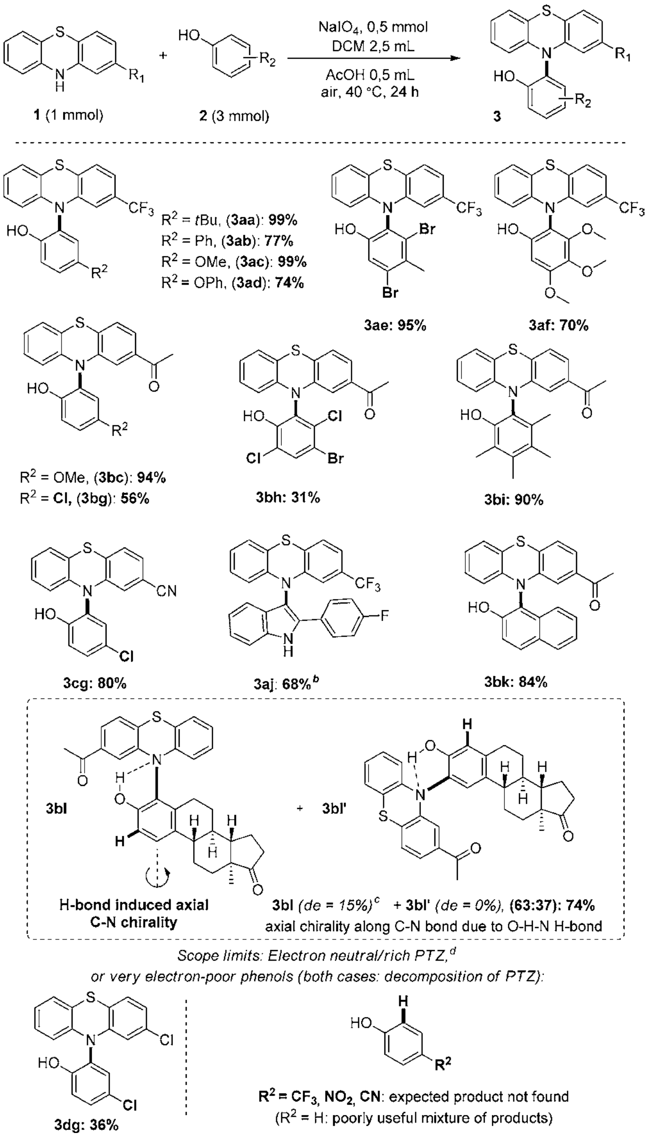
[a] Reaction conditions: **1a** (1.0 mmol) and **2a** (3.0 mmol) in solvent (2.5 mL) and cosolvent (0.5 mL) for 24 h under O_2 or air. [b] Yield of isolated product. [c] TBAI = tetrabutylammonium iodide, DCM = dichloromethane, THF = tetrahydrofuran.

good solvent for this reaction and is superior to chlorobenzene or THF (entry 6). It should be noted that there is no reactivity in the absence of acetic acid (entry 9). In addition, reducing the loading of periodate salt from 50 to 5 mol % decreases the yield of **3aa** to less than 5%, even under oxygen atmosphere. This indicates that periodate is the real terminal oxidant rather than just oxygen (entry 10). For operational convenience, we then switched to simple air atmosphere and performed a final screen on the periodate's counterion. Much to our surprise, the cation has a large effect on the efficiency of the reaction, with the sodium salt being significantly superior to the potassium analogue and lithium periodate being almost not effective (entry 14).

With these optimized conditions in hand (entry 13), we then explored a number of difficult to oxidize halogenated phenols and very electron-rich phenols with a reputed tendency to overoxidize and decompose (Scheme 2). The tolerance for both classes is remarkable. Chloro- and bromophenols are particularly well tolerated (**3ae**, **3bg**, and **3cg**). Very electron-rich phenols were also well tolerated, such as 4-methoxyphenol (**3ac**, 99%), tetramethylphenol (**3bi**, 90%), or 2-naphthol (**3bk**, 84%).

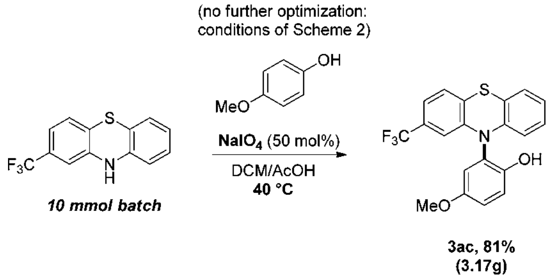
The female hormone estrone was also a competent phenol coupling partner, albeit with moderate regio- and diastereoselectivity.[9] Of note, the more sterically congested regioisomer **3bl** displays a probable OH−N H-bond stabilized axial chirality with a slight diastereomeric excess of 15% (±4%), a very low but encouraging diastereoselectivity which may serve as proof of concept for the development of future enantioselective versions of this reaction. In general, all products of Scheme 2 display a strong IR shift of the OH band, which is characteristic of an intramolecular OH−N H-bond, a documented interaction in *o*-aminophenols.[10] It should finally be noted that very electron-poor phenols (R^2 = CF_3, NO_2, or CN) are still completely unreactive with this new method. However, we were able to demonstrate the robustness of this new method with a multigram scale reaction, affording 3.17 g of **3ac** in one single batch (Scheme 3). This arguably constitutes an important advantage over the previous method with cumene and O_2 at 150 °C,[5] particularly in terms of safety and practicality.

Scheme 2. Substrate Scope and Isolated Yields[a]



[a] Conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), $NaIO_4$ (0.5 mmol) in DCM (2.5 mL) and cosolvent AcOH (0.5 mL) under air at 40 °C for 24 h. [b] At 50 °C. [c] **3bl**: de = 15% ± 4% depending on line broadening, phase correction and concentration with ^1H NMR integration. [d] PTZ: phenothiazine.

Scheme 3. Large-Scale Synthesis



Interestingly, TEMPO (1.5 equiv) is tolerated in the reaction and does not interfere with product formation, which is consistent with the finding of Xia in a related amination method.[11] Moreover, a competition experiment between phenol and phenol-d_5 indicates an equivalent reaction rate for both phenols (KIE = 1). No significant H/D scrambling was observed, whether in the remaining starting materials or in the products. Phenothiazines are documented to have a very low bond dissociation energy, and we thus assume, as previously proposed,[5] that the phenothiazine moiety must oxidize first.[12] The C−N bond-formation step with the phenol, or alternatively with an oxidized form of the phenol,[13] would occur thereafter. The electrophilic iodine center may play a significant coordinative role at the oxygen and/or nitrogen atoms of the substrates. However, the lack of direct evidence for those interactions forbids a detailed mechanism at this stage with periodate.

In summary, we developed a metal-free dehydrogenative amination method which operates at only 40 °C, with a significantly broader scope of ubiquitous phenols, whether polyhalogenated or electron-rich, than previously reported. Moreover, we established that cheap periodates, specifically $NaIO_4$, were competent oxidants for the direct elaboration of molecular complexity in the frame of cross-dehydrogenative couplings. This allowed the easy scale-up of the reaction on a multigram scale. Thus, we expect that periodates will impact the field of cross-dehydrogenative amination reactions in the coming years.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02223.

Experimental procedures and characterization of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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