Metal-Free Synthesis

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O_2-mediated dehydrogenative amination of phenols**

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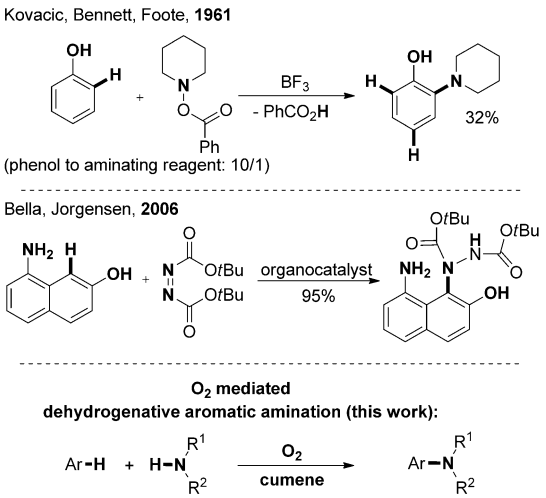
Abstract: *A method was developed for the direct dehydrogenative construction of C–N bonds between unprotected phenols and a series of cyclic anilines without resorting to any kind of metal activation of either substrate and without the use of halides. The resulting process relies on the exclusively organic activation of molecular oxygen and the subsequent oxidation of the aniline substrate. This allows the coupling of ubiquitous phenols, thus furnishing aminophenols through an atom-economical and most sustainable dehydrogenative amination method. This new reactivity, which relies on the intrinsic organic reactivity of cumene in what can be seen as a modified Hock activation process of oxygen, is expected to have a large impact on the formation of C–N bonds in organic synthesis.*

"L'acide nitrique attaque avec une violence extrême l'hydrate de phényle [phenol], chaque goutte que l'on y laisse tomber produit un bruissement, comme un fer rouge que l'on plonge dans l'eau, et par l'ébullition il se change entièrement en acide picrique [trinitrophenol]."[1] It was back in 1841 that Auguste Laurent expressed with these words the strong reactivity of phenol towards electrophilic amination. He was the first to isolate phenol in pure crystalline form and he used it to carry out simple nitration experiments.[1] One of the key advantages of the direct aromatic functionalization strategy, whether by electrophilic attack[2] or by the less common homolytic aromatic substitution (HAS),[3] is the absence of pre-activation steps for the aromatic C–H bonds. Molecular complexity can thus be achieved in a single chemical step. A great disadvantage, however, aside from the issue of C–H regioselectivity, resides in the necessity for pre-activation or pre-oxidation of the coupling partner such that it becomes sufficiently reactive for the condensation reaction to occur. To our knowledge, no dehydrogenative aromatic amination reaction has ever been proposed, whether by electrophilic attack (Scheme 1)[4,5] or homolytic substitution (HAS),[3] in which the oxidized aminating substrate would be generated in situ, thus avoiding pre-activation steps for both coupling partners, and moreover without metal[6] or halide additives. Such a reaction is desirable since it would be highly practical from a synthetic viewpoint and also sustainable, provided that O_2 can be utilized as sole terminal oxidant.[7]



Scheme 1. Selected metal-free amination reactions of phenols: no dehydrogenative examples.

In the course of our recent research efforts in the field of reactions for the formation of C–N bonds, a strategic connectivity in organic synthesis,[8–10] we have turned our attention to phenols, an important class of compounds in the food, material, and pharmaceutical industries.[11] Our original idea was to apply Ru-catalyzed C–H-activating amination techniques that we had previously developed.[12] We rapidly established that phenols indeed possess some dehydrogenative C–N coupling reactivity towards phenothiazines, also an important class of compounds in pharmaceutical and material sciences.[13] Phenothiazines are notably considered among the most important class of antipsychotic drugs. 2-chloro-phenothiazine (**1d**) and 2-trifluoromethyl-phenothiazine (**1e**), for example, are the direct precursors of Chlorpromazine and Fluphenazine, respectively, which are very important antipsychotic drugs and are on the latest list of essential medicines from the World Health Organization (WHO).[14]

It quickly transpired however, that this coupling also proceeds without any metal source.[15] Intrigued, we promptly optimized the reaction to give the following method: the phenothiazine (1 mmol), phenol (3 mmol), cumene (2.5 mL), and acetic acid (0.5 mL) are combined in a screw-cap reactor, flushed with O_2, and stirred at 150 °C for 24 h. Aminophenols **3a–q** were obtained in moderate to excellent yields (Scheme 2). It should be noted that as a result of the total absence of metals or any strong oxidants, a good number of functional groups that would otherwise be troublesome in metal-catalyzed transformations were tolerated in the reaction. These include ketones (**3k**), nitriles (**3l**), halides (**3d–j**),

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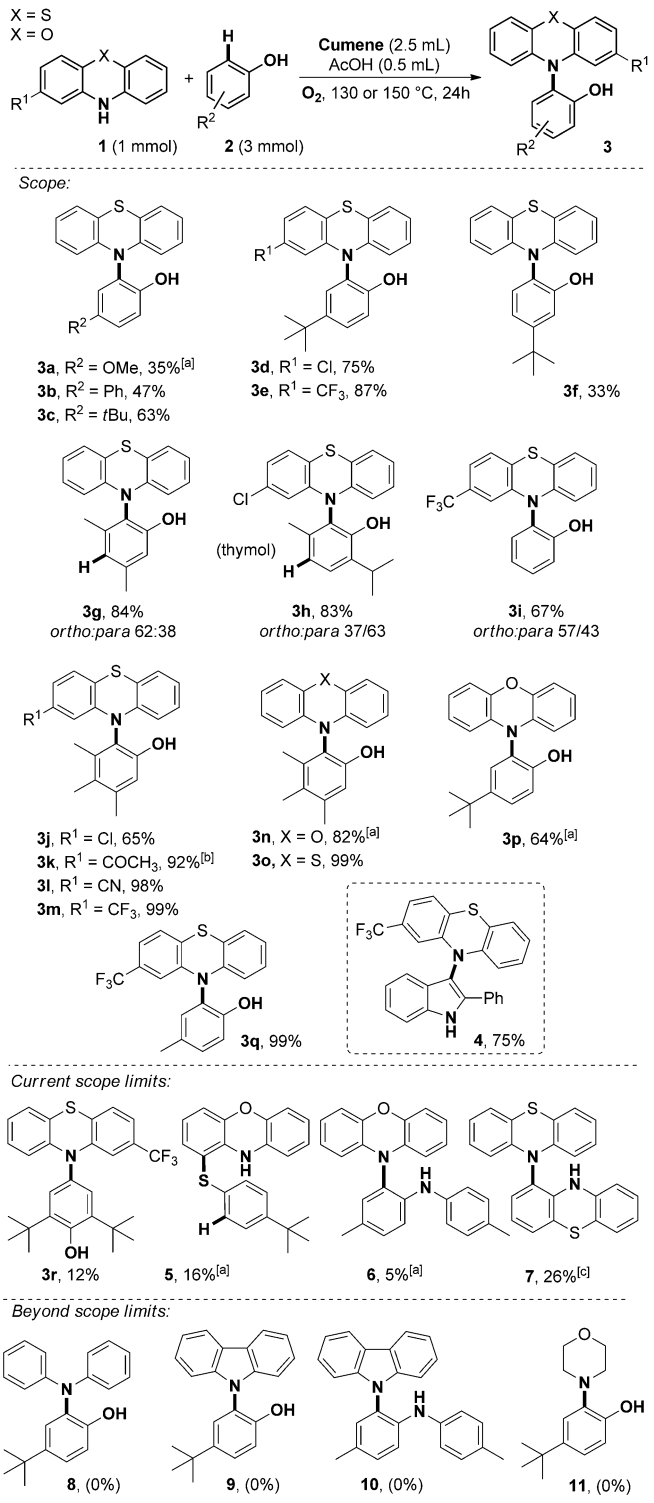


Scheme 2. Reaction conditions, yields of isolated product, and limits of the scope. [a] Reaction performed at 130 °C. [b] Reaction performed at 170 °C. [c] 2 mmol scale, 170 °C.

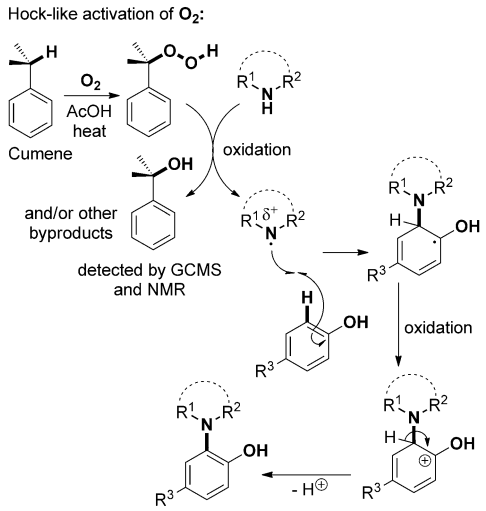
and thioethers. The reaction is most efficient when electron-rich phenols are combined with electron-poor phenothiazines, such as for products **3k**, **3l**, and **3m**, which were all isolated with yields above 90%. Several combinations even afforded quantitative yields (**3m**, **3o**, and **3q**).

This reaction is exceptional because: 1) it proceeds in an intermolecular fashion with two useful and general classes of substrates, namely phenols and phenothiazines, without any metals, ligands, or elaborated organocatalysts, 2) the system doesn't required protection, pre-activation, or pre-oxidation steps for either the C–H or N–H coupling partners, 3) all components in the reaction are cheap and easily available, and 4) most importantly, O_2 can be engaged as the sole terminal oxidant in spite of the absence of any metal activator, thus making this reaction one of the most sustainable processes among dehydrogenative amination reactions.

This new reactivity is particularly instructive through the nature of its limits. Anisole, for example, is completely unreactive, which indicates the importance of the free OH functional group.[16] In general, any overly reactive C–H substrates, which tend to yield competing C–C homocoupling products, are usually detrimental to the reaction. This is the case with entry **3r** (2,6-di-*t*Bu-phenol) and **5** (4-*t*Bu-thiophenol). Interestingly, biologically important and ubiquitous indoles constitute a more successful substrate class through their nucleophilic C3 position and C3-aminated product **4** was isolated in 75% yield, without the need to protect the indole N–H functional group (Scheme 2).[17] Thus our dehydrogenative amination reaction is reasonably general, as long as an appropriately nucleophilic C–H position is present in the substrate.

In terms of the N–H substrate, the strained cyclic geometry of phenothiazines and phenoxazine, sometimes referred to as a butterfly-shaped structure, seems important for the reaction. This geometry might lead to higher electrophilicity at nitrogen once it is oxidized, or a prior facilitated oxidation step, or both. Phenothiazines and phenoxazines are known to possess particularly low bond dissociation energies (BDE) compared to diphenylamine, which might point to differences in the oxidation rate.[18] Although this current metal-free method only tolerates phenothiazine derivatives as aminating partners, we are confident that future developments, in combination with metal-catalyzed N–H-activating/oxidizing techniques, will unlock other desired classes of aminating coupling partners in due time. The elaboration of such combined methods is currently ongoing in our laboratory.

Cumene, one of the cheapest and most readily available organic solvents on the market, plays an important role in this reaction. It outperforms by far any other solvents we tried, for example, chlorobenzene. We assume that cumene initiates the reaction by organically activating O_2, a step perhaps facilitated[19] by the acetic acid cosolvent (Scheme 3). Running the reaction under a strict N_2 atmosphere shuts down the reactivity, thus confirming the essential role of O_2 in this process. This O_2 activation mode seems plausible because it is also known to initiate the Hock rearrangement of cumene to give phenol and acetone, a very important industrial process.[20] In support of this, we could detect trace amounts of α-hydroxycumene in the crude reaction mixtures for several entries by means of GC–MS and NMR analysis. A subsequent amine oxidation followed by phenol coupling would then afford the dehydrogenative amination product. Given the relative stability of the N-centered radical form of pheno-



Scheme 3. Possible reaction mechanism.

thiazines, the final coupling step may occur through a classical homolytic aromatic substitution pathway (HAS, Scheme 3).[3] However, a classical electrophilic amination pathway cannot be completely excluded at this stage.

In summary, we have developed a dehydrogenative aromatic amination of phenols based on an exclusively organic O_2 activation. This reaction is expected to change the way that nitrogen reactivity is approached in C–N bond forming reactions, and thus to lead to new sustainable dehydrogenative amination methods.

Keywords: dehydrogenative amination · electrophilic amination · hock process · homolytic aromatic substitution · synthetic methods

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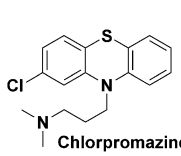

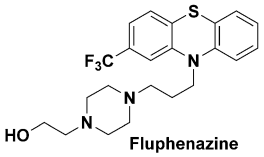

[15] Employing brand new magnetic bars, glass reactors, and screw caps did not change this reactivity, such that trace metal catalysis is in principle excluded.

[16] For all *ortho*-aminophenol products, a significant intramolecular O–H···N Hydrogen bond is observed in the neat IR characterizations (see the Supporting Information).

[17] While the N–H position remains free, the C2-position of the indole substrate must be functionalized, here with a phenyl group, in order to avoid undesired decomposition pathways.

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