Cu-Catalyzed Cross-Dehydrogenative ortho-Aminomethylation of Phenols

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Abstract: A highly selective Cu(II)-catalyzed cross-dehydrogenative ortho-aminomethylation of phenols with aniline derivatives is described. The corresponding C(sp2)–C(sp3) coupling products were obtained in moderate to excellent yields under mild reaction conditions and with a broad substrate scope. A radical mechanism is proposed.

Carbon–carbon bond forming processes are at the heart of organic synthesis, since these typically allow the rapid construction of molecular complexity. In the past decade, direct transition-metal-catalyzed C–H bond functionalization has emerged as an important tool for the construction of various C–C bonds. The latter methods are increasingly popular due to atom- and step-economy considerations, which often lends them an inherently sustainable character. Therein, the field of cross-dehydrogenative couplings (CDCs) is particularly attractive because this concept avoids pre-activation steps for both coupling partners. The development of useful intermolecular CDCs, however, is associated with considerable challenges, such as regioselectivity or undesired homocoupling processes. In order to intercept the oxidation of the most electron-rich coupling partner into a true hetero-coupling process, one can resort to substrate bias (i.e., steric). Alternatively, one can utilize metal catalysis in order to control the various competing oxidation pathways, and thereby escape the narrow substrate specificity often imposed by metal-free systems. Herein, we propose such a strategy through the Cu(II)-catalyzed cross-dehydrogenative ortho-aminomethylation of phenols with aniline derivatives (Scheme 1 and Scheme 2).

The ortho-aminomethylation of phenols represents a useful retrosynthetic tool, because this particular motif is prevalent in natural products, medicines, and materials (Scheme 1). Thus, some synthetic methods have been reported to construct this strategic structural unit, such as the Mannich reaction (Scheme 2a).[7a,b] However, some drawbacks are usually associated with this synthetic approach. For instance, the substrate scope is usually limited to electron-rich and/or fused polycyclic phenols on the one hand, and often to aliphatic amines on the other. Moreover, the reaction conditions must accommodate very reactive formaldehyde, or a derivative of it, which typically leads to relatively poor chemoselectivity. Indeed, Mannich reactions are often associated with further cyclization and/or over-coupling events, which call for structural bias in the substrates (blocking/protecting undesired positions), as well as bias in the order, time, and speed of additions of the components, for example. In 2017, the Wang group reported a more concise way to achieve this process.[7c] However, this method requires pre-functionalization of the amine coupling partner (Scheme 2b). To the best of our knowledge, no CDC approach has ever been proposed (Scheme 2c).

We started our reactivity investigations with dichloro(1,10-phenanthroline)copper(II) (L¹CuCl²) as a prospective catalyst, since this species has been recently found to be successful in some inspiring radical coupling reactions.[8]
notably by the Stahl group\cite{Stahl2002} and independently by Liu group\cite{Liu2018}. We thus began our study by examining the reaction of 4-t-butylphenol (1a) and N,N-dimethylaniline (2a) in the presence of a catalytic amount of L’CuCl₂ (10 mol%) and di-tert-butyl peroxide (DTBP) as the oxidant to form coupling product 3a (Table 1, Entry 1). Importantly, it was found that

Moreover, unreacted phenol is usually detected at the end of the reaction, thus indicating that in spite of our best efforts at maximizing the yield of this reaction (Table 1, entry 4), full conversion is typically not reached. The reason for this became clearer when studying the regioselectivity of this reaction. Indeed, when testing unfunctionalized phenol substrate 1b under the optimized conditions, the ortho-selective product 3b was obtained in 47% yield of isolated product, as well as a small amount of double-functionalized byproduct 3b’ (Scheme 3).

To our delight, no para-functionalized product was detected. Interestingly, when the reaction temperature was raised to 90°C, 3b’ actually became the major product with a 41% yield of isolated product and still no para-functionalization detected (Scheme 3). This competing double-ortho-functionalization process explains why the temperature has to be kept at a moderate 80°C, and consequently why the reaction cannot be pushed to full conversion. The reaction scope was then investigated (Table 2 and Table 3, see the Supporting Information for a detailed description).

The N,N-dimethylaniline loading considerably affects the yield. Eventually, a loading of 0.6 mL of 2a (9.5 equiv) for 0.5 mmol of phenol 1a led to an improved 55% NMR yield (Table 1, entries 2, 3). When the amount of cumene solvent was reduced from 1.5 mL to 1.0 mL, the yield improved to 60% NMR yield (62% yield of isolated product, entries 4, 5). It should moreover be noted that no solvent performed better than cumene.\cite{EDA2000, Li2018} Conversely, benzene and tert-butylbenzene are both tolerated as solvents, albeit with lower yields (Entries 6 and 8), thus indicating that the benzylic C–H position is not essential. The higher performance of the cumene solvent may suggest the ability of persistent cumyl radicals to act as radical reservoirs in the reaction. However, cumene and [D₂]-cumene afford the same initial reaction rate (KIE = k_d/k_D ≈ 1, see the Supporting Information), such that this hypothesis cannot be confirmed at this stage.

It should be noted that in some cases, homocoupling byproducts derived from 2a as well as unidentified byproducts were detected. Importantly, no phenol homocoupling byproducts (so-called binols) could be detected under those reaction conditions by MS analysis of the crude mixture.

\begin{table}
\caption{Optimization of reaction conditions.}
\begin{tabular}{cccccc}
\hline
Entry & \(x\) & Catalyst & Oxidant & Solvent & Yield [\%]\tabularnewline
\hline
1 & 1.6 & L’CuCl₂ & DTBP & Cumene 1.5 mL & 20\tabularnewline
2 & 4.8 & L’CuCl₂ & DTBP & Cumene 1.5 mL & 38\tabularnewline
3 & 9.5 & L’CuCl₂ & DTBP & Cumene 1.5 mL & 55\tabularnewline
4 & 9.5 & L’CuCl₂ & DTBP & Cumene 1.0 mL & 60 (62)\tabularnewline
5 & 9.5 & L’CuCl₂ & DTBP & Toluene 1.0 mL & 58\tabularnewline
6 & 9.5 & L’CuCl₂ & DTBP & tBu-benzene 1.0 mL & 29\tabularnewline
7 & 9.5 & L’CuCl₂ & TBPB & Cumene 1.0 mL & trace\tabularnewline
8 & 9.5 & L’CuCl₂ & TBPB & Cumene 1.0 mL & trace\tabularnewline
9 & 9.5 & L’CuCl₂ & TBPB & Cumene 1.0 mL & 34\tabularnewline
10 & 9.5 & L’CuCl₂ & TBPB & Cumene 1.0 mL & 29\tabularnewline
11 & 9.5 & Cu(TC)\textsuperscript{[6]} & TBPB & Cumene 1.0 mL & 34\tabularnewline
12\textsuperscript{[a]} & 9.5 & CuF₂ + L’ & DTBP & Cumene 1.0 mL & 42\tabularnewline
13\textsuperscript{[a]} & 9.5 & CuCl₂ + L’ & DTBP & Cumene 1.0 mL & 12\tabularnewline
14\textsuperscript{[a]} & 9.5 & CuCl₂ + L’ & DTBP & Cumene 1.0 mL & 29\tabularnewline
15\textsuperscript{[a]} & 9.5 & CuCl₂ + L’ & DTBP & Cumene 1.0 mL & 12\tabularnewline
\hline
\end{tabular}
\textsuperscript{[a]} The yield was determined by \(^1\)H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. \textsuperscript{[b]} The amount of ligand was 15 mol%. \textsuperscript{[c]} thiophene-2-carboxylate.
\end{table}

\begin{table}
\caption{Phenol scope.}
\begin{tabular}{cccccc}
\hline
3a & R = tBu, 62% [22]\tabularnewline
3b & R = H, 47% [18]\tabularnewline
3c & R = Ad, 50% [18]\tabularnewline
3d & R = Ph(CH₂)₂C, 56% [24]\tabularnewline
3e & R = F, 45% [20]\tabularnewline
3f & R = MeO-CO, 70% [27]\tabularnewline
3h & R = PhO-CO, 61% [9]\tabularnewline
3i & R = MeO-CO, 82% [28]\tabularnewline
3j & R = Ac, 73% [38]\tabularnewline
3k & R = CN, 63% [37]\tabularnewline
3l & R = Me, 41% [8]\tabularnewline
3m & R = CN, 44% [9]\tabularnewline
3n & R = CN, 53% [37]\tabularnewline
3o & R = Me, 41% [8]\tabularnewline
\hline
\end{tabular}
\textsuperscript{[a]} Yields of isolated product. \textsuperscript{[b]} \(^1\)H NMR yields, 1,3,5-trimethoxybenzene as an internal standard, 80°C, 48 h. \textsuperscript{[c]} 90°C, 24 h.
\end{table}
In order to characterize the largest drawback of this method, which is arguably the excess of amine coupling partner, we also re-performed some of the most representative examples with only two equivalents of amine (yields in parentheses, Table 2 & Table 3). Clearly, this has a severe impact on the yields. Indeed, under those conditions, the highest yield does not exceed 43%, for product 4e. However, it was also found that a significant portion of the excess of amine coupling partner could be recovered. Out of five tested examples, 64%, 66%, 70%, and 72% of the initial amount of coupling partner 2a could be recovered from entries 3e, 3f, 3g, and 3o, respectively. Moreover, 67% of the initial coupling partner 2c could be recovered from entry 4c.

A series of mechanistic experiments were then performed. First, the addition of TEMPO completely suppresses product formation (Scheme 4a), thus suggesting a pronounced radical character to the reaction. Moreover, a normal KIE ($k_H/k_D$) of 1.7 was observed between phenol 1b and labelled phenol [D6]-1b in two parallel experiments ($t = 2$ h, Scheme 4b). Importantly, GCMS analysis shows complete preservation of the deuterium labels in the starting material ($t = 2$ h). Because the KIE lies significantly beneath 2, the phenolic $\text{C(sp^2)}$–$\text{H}$ bond cleavage may not be rate limiting.[10] In contrast, an inverse secondary KIE of circa 0.9 was observed upon comparing the initial rates of 2a and [D6]-2a (Scheme 4c). This modest secondary KIE may suggest a $\text{C(sp^2)}$-to-$\text{C(sp^3)}$ rate-determining step, which may thus correspond to the intermolecular $\text{C–C}$ bond formation step. Alternatively, it might also accommodate a sterically encumbered rate-determining Cu–N bond formation, prior to $\text{C–C}$ bond formation, which would be in good agreement with the required excess of amine.[11] Finally, we also tested phenol 1t, for which both ortho positions are blocked with methoxy groups (Scheme 4d), and which was chosen for its structural and electronic resemblance with successful phenol 1i (Table 2). Under standard conditions, the expected aminomethylation product could not be detected, thus confirming the exclusive ortho-selectivity of the reaction.

A proposed mechanism[12] is shown in Scheme 5. First, the low-valence copper species I would donate an electron to DTBP to generate copper species II and the tert-butoxy radical. The tert-butoxy radical would then abstract a hydrogen atom from either phenol 1, to form phenoxy radical intermediate III, and/or methylamine derivative 2 to generate the aminomethyl radical intermediate IV, a well-documented process.[13] The latter process is moreover expected to be a relatively facile and non-rate-limiting step considering the relatively low oxidative potentials of dimethylanilines.[13c] Copper phenolate intermediate V could otherwise form by proton exchange from phenol and the tert-butoxy-copper species II. The intermediacy of phenoxyl radicals III is moreover realistic in consideration of the relatively low and similar bond dissociation energies (BDEs) of phenols (88 kcal.

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**Table 3:** Methylamine scope.

| R^1 | R^2 | Product | Yield % | Reference |
|-----|-----|---------|---------|-----------|
| Me  | Me  | 1a      | 62%     | (3%)      |
| Ph  | Me  | 1b      | 77%     | (37%)     |
| Me  | Ph  | 1c      | 64%     | (96%)     |
| Me  | Ph  | 1d      | 68%     | (56%)     |
| Me  | OMe | 1e      | 49%     | (15%)     |
| Me  | Ph  | 1f      | 43%     | (23%)     |
| Me  | Ph  | 1g      | 73%     | (43%)     |
| Me  | Ph  | 1h      | 43%     | (23%)     |

**Scheme 4.** Mechanistic experiments, 1H NMR yields, 1,3,5-trimethoxybenzene as an internal standard.
The utility of this cross-dehydrogenative ortho-aminationmethylation reaction was then examined in the derivatization of a precious steroid natural product, Estrone 1u smoothly affording coupling product 3u (Scheme 6a). In addition, the reaction was found to be easily scalable (Scheme 6b). Indeed, 1.74 g of coupling product 31 could be obtained in a single batch (60% yield). Moreover, with a published method, a cyclization reaction was achieved from the aminomethylation product 31 to a 7-membered ring product 5 in excellent yield, thus increasing the scope of that method.

In summary, we have developed a CuI-catalyzed ortho-selective aminomethylation of phenols by direct intermolecular CDC reaction. Moreover, a relatively broad variety of functional groups were tolerated. This method represents a rare case of (sp2)–(sp2) CDC with phenols.[6] This unusual dehydrogenative process is anticipated to lead to the development of other general classes of C–C bond forming CDC reactions. Further mechanistic investigations may be necessary in order to rationally achieve those objectives.

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Conflict of interest

The authors declare no conflict of interest.

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