

# A Copper-Catalyzed Synthesis of 3-Aroylindoles via a $sp^3$ C–H Bond Activation Followed by C–C and C–O Bond Formation

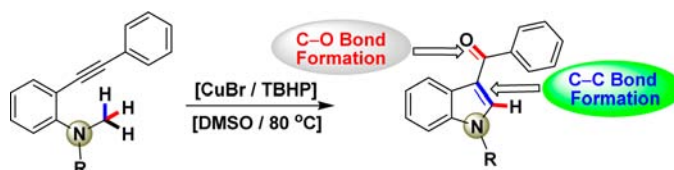
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## ABSTRACT



An efficient Cu(I)-catalyzed synthesis of 3-aryloxyindoles has been achieved from  $\alpha$ -alkynylated *N,N*-dimethylamines via a  $sp^3$  C–H bond activation  $\alpha$  to the nitrogen atom followed by an intramolecular nucleophilic attack with the alkyne using an aqueous solution of *tert*-butyl hydroperoxide (TBHP) as the oxidant. In this tandem catalytic synthesis of 3-aryloxyindoles both C–C and C–O bonds are installed at the expense of two  $sp^3$  C–H bond cleavages.

C–H bond functionalization processes have provided a great impetus to modern organic synthesis. Such functionalizations have led to the possibility of molecular diversities through the constructions of either C–C or C–X (X = heteroatom) bonds via the cleavage of ubiquitous C–H bonds.<sup>1</sup> The two strategies usually followed are directing-group-assisted C–H bond functionalization<sup>2</sup> and cross dehydrogenative coupling (CDC).<sup>3</sup> However, in recent times, the cross dehydrogenative coupling (CDC)

strategy has had an upsurge because it is step- and atom economic. The CDC approach has mostly been applied toward C–C bond-forming reactions which are important in creating several significant building blocks. Among the building blocks, the indolyl moiety, particularly the 3-acylindole, has immense importance because of its relevance in natural products and pharmaceutical entities;<sup>4</sup> thereby, considerable interest has been gained for their synthesis

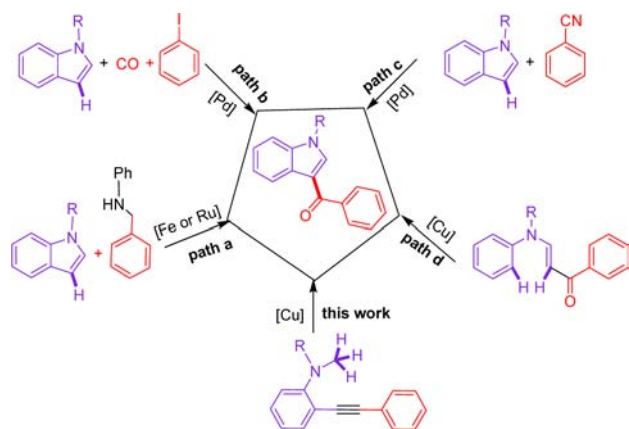
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**Scheme 1.** Existing Routes and Our Strategy to 3-Aroylindoles

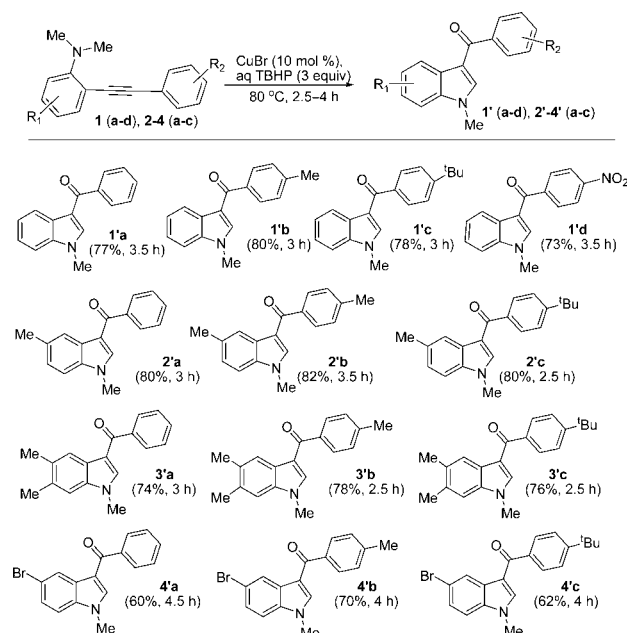


via C–H activation processes.<sup>5</sup> Apart from their bioactive nature they also serve as useful precursors to various other indole-based compounds through easy functional group transformations of its carbonyl group.<sup>4,6</sup> Along with the classical Friedel–Crafts<sup>7</sup> and Vilsmeier–Haack acylation reactions,<sup>8</sup> the 3-acylindoles have been synthesized via the C3–H activation of indoles involving various acyl group surrogates using Fe, Ru (Scheme 1, path a),<sup>9</sup> or Pd catalysts (Scheme 1, paths b and c).<sup>10</sup> Differing from these paths (Scheme 1, paths a–c) which use preformed indoles, the 3-acylindoles have also been achieved through a Cu-catalyzed direct C–C bond formation of *N*-aryl enaminones via a double C–H bond activation (Scheme 1, path d).<sup>11</sup> Despite the presence of several intriguing protocols in the

literature, the urge still remains as to “what next” could be improvised to achieve a practical route to 3-acyl/aroylindoles.

Tertiary amines possessing alkyl groups are useful precursors for the  $\text{sp}^3$  C–H bond functionalizations  $\alpha$  to the nitrogen atom.<sup>3b,d,e,h,12</sup> These functionalizations in most cases have been stimulated by various copper salts in combination with organic peroxides through a single electron transfer process.<sup>12</sup> However, a review of the literature reveals that these functionalizations occurred via an intermolecular attack of various C, N, or O nucleophiles at the iminium ion generated in situ. Following these reports, we reasoned that if the nucleophile attacks intramolecularly, they could be useful toward the synthesis of nitrogeneous heterocycles. As a prelude to this motivation, *N,N*-dimethyl-2-(2-phenylethynyl)benzenamine (**1a**) was chosen as the precursor, where the ethynyl group is expected to function as the internal nucleophile toward an intramolecular attack onto the iminium carbon. In a pursuit to the “what next”, an elegant protocol is reported for the direct synthesis of 3-acylindoles that proceeds via the  $\text{sp}^3$  C–H bond activation  $\alpha$  to the nitrogen atom of an *o*-alknylated amine with concomitant formation of C–C and C–O bonds.

**Scheme 2.** Substrate Scope for 3-Aroylindoles<sup>a</sup>



<sup>a</sup> Reaction conditions: **1(a–d)**, **2–4(a–c)** (0.5 mmol), CuBr (0.05 mmol), 70% aqueous TBHP (1.5 mmol) in DMSO (2 mL) at 80 °C. Reactions were monitored by TLC. Confirmed by spectroscopic analysis

We initiated our investigation by treating (**1a**) with CuBr (10 mol %) as the catalyst and TBHP (5–6 M in decane) (1 equiv) as the oxidant in toluene solvent at 80 °C, which

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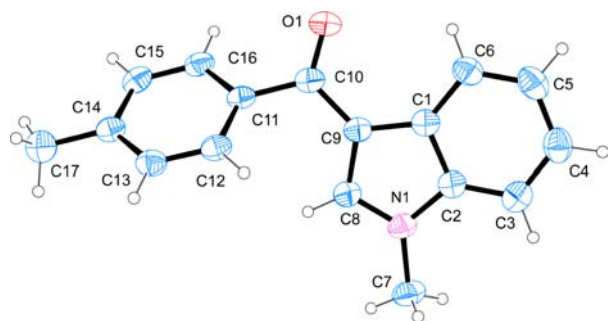
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yielded the aroylindole (**1'a**) in 45% isolated yield (entry 1, Table S1, see Supporting Information [SI]). Interestingly, the use of an aqueous TBHP (70 wt % in water) instead of TBHP in decane, gave a superior yield of 55% (entry 2, Table S1 [SI]). Further, increasing the amount of TBHP to 2 equiv and 3 equiv improved the yield to 62% and 70%, respectively (entries 3–4, Table S1 [SI]). Copper(I) bromide was found to be superior to the other copper (I and II) salts employed such as CuCl, CuI, Cu(OAc)<sub>2</sub>, CuCl<sub>2</sub>, and CuBr<sub>2</sub> (entries 5–9, Table S1 [SI]). Decreasing the catalyst loading to 5 mol %, significantly lowered the product yield (52%) (entry 10, Table S1 [SI]). Further, when the reaction was carried out in DMSO solvent instead of toluene, an improved yield of 77% was obtained (entry 11, Table S1 [SI]). The reaction in other solvents such as *o*-xylene, 1,4-dioxane, DMF, and THF did not give any satisfactory yields compared to that with DMSO (entries 12–15, Table S1 [SI]). Both increase (100 °C) and decrease (60 °C) in the reaction temperature had an adverse effect on the product yields (entries 16–17, Table S1 [SI]). The control experiments carried out with either the copper salt or TBHP alone did not give any trace of product (entries 18–19, Table S1 [SI]). The use of other catalysts such as Pd(OAc)<sub>2</sub>, CoCl<sub>2</sub>, and FeCl<sub>3</sub> in combination with aq TBHP gave inferior yields compared to CuBr (entries 20–22, Table S1 [SI]). During the optimization process, it was observed that copper(I) bromide as the catalyst and TBHP as the oxidant were sufficient to carry out the transformation without the requirement of any other additives. Thus, the nonrequirement of expensive Pd catalyst or the additives make the present protocol more economical and viable in comparison to the recently reported synthesis of 3-acylindoles by Liang et al.<sup>13</sup>

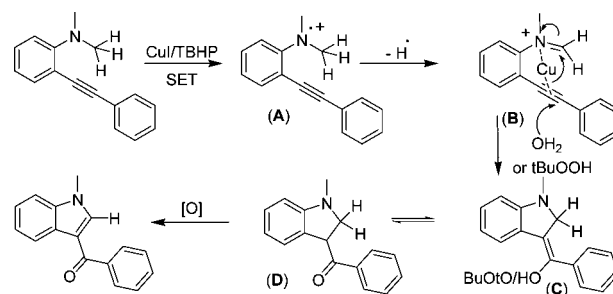


**Figure 1.** ORTEP View of **1'b**.

The scope of this novel methodology was next explored toward the synthesis of various 3-aroyleated indoles from their respective *o*-alkynylated *N,N*-dimethylamines under the optimized reaction conditions. As shown in Scheme 2, a variety of 2-alkynyl-*N,N*-dimethyl anilines could be

transformed to their corresponding 3-aroyleated indoles. Initially, the effects of various substituents on the aryl ring ( $R^2$ ) were examined. Irrespective of the nature of the substituents such as *p*-Me (**1b**), *p*-<sup>t</sup>Bu (**1c**), and *p*-NO<sub>2</sub> (**1d**), all gave their corresponding 3-aroyleated indoles (**1'b**), (**1'c**), and (**1'd**) with yields ranging from 73 to 80%. The structure of the 3-aroyleated indole (**1'b**) has been unequivocally confirmed by X-ray crystallography (Figure 1). When the *N,N*-dimethyl substituted aryl ring ( $R^1$ ) of 2-alkynyl-*N,N*-dimethyl aniline is substituted with an electron-donating group such as *p*-Me and the other aryl moiety ( $R^2$ ) without a substituent (**2a**) and with substituents such as *p*-Me (**2b**) and *p*-<sup>t</sup>Bu (**2c**), all yielded their 3-aroyleated products (**2'a**), (**2'b**), and (**2'c**), respectively, in excellent yields. Similarly, when the *N,N*-dimethyl substituted aryl ring ( $R^1$ ) of 2-alkynyl-*N,N*-dimethyl aniline is substituted with 3,4-dimethyl group and the other aryl moiety ( $R^2$ ) without a substituent (**3a**) and with substituents such as *p*-Me (**3b**) and *p*-<sup>t</sup>Bu (**3c**), all gave their expected aroylated products (**3'a**), (**3'b**), and (**3'c**), respectively, but in a slightly lesser yields. However, a significant drop in the yields were observed for substrates possessing a moderately electron-withdrawing group such as *p*-Br as has been demonstrated with substrates (**4a**), (**4b**), and (**4c**) all giving their expected products (**4'a**), (**4'b**), and (**4'c**) in the yields ranging from 60 to 70% as shown in Scheme 2.

**Scheme 3.** Proposed Mechanism for the Formation of 3-Aroylindole



As a probe to the mechanism, when the standard reaction was carried out in the presence of radical scavenger TEMPO (3 equiv), the reaction gave many other side products and only a trace of the desired product (< 10%), indicating the possibility of a radical mechanism. As a further support to the radical path of the mechanism, the reactions were carried out independently with Pd(OAc)<sub>2</sub> and CuBr without the use of aq TBHP. Both of these reactions failed to give any traces of the desired product, and the starting material was recovered completely. These control experiments suggest that neither Pd(II) nor Cu(I) alone is sufficient to form the iminium cation and the radical initiator TBHP is essential for this transformation. On the basis of literature reports<sup>12</sup> and observations of the control reactions and yield of the products obtained from substituted substrates, a mechanism analogous to the one recently proposed<sup>13</sup> can be envisaged for these reactions.

(13) While our manuscript was under preparation, a similar method was reported by Liang et al. for the synthesis of 3-acylindole. Xia, X.-F.; Zhang, L.-L.; Song, X.-R.; Niu, Y.-N.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, 49, 1410.

Copper salt in combination with peroxide serves as a single-electron oxidant.<sup>13</sup> This active oxidant accepts an electron from the nitrogen atom to form an aminyl radical cation species (**A**) (Scheme 3). Abstraction of a proton radical  $\alpha$  to the nitrogen atom gave an iminium intermediate (**B**). The intramolecular attack of the alkynyl group onto the iminium carbon in the intermediate (**B**) resulted in C–C bond formation with concurrent formation of a C–O bond by the attack of either water or TBHP onto the alkynyl moiety to give intermediate (**C**). Ketonization of the intermediate (**C**) provided 3-aroylindoline (**D**) which underwent further oxidation to give its 3-aroylindole (**1'a**). Although Liang et al. have proposed the nucleophilic attack of TBHP to the alkyne intermediate (**B**), in our case the attack of water as the nucleophile cannot be completely ruled out since the reaction proceeds better with aqueous TBHP. The proposed mechanism (Scheme 3) is supported by the fact that substrates containing an electron-withdrawing group such as bromo (**4a**, **4b**, and **4c**) in the *N,N*-dimethyl substituted aryl ring ( $R^1$ ) gave poor yields because of the instability of the aminyl radical cation (**A**). Further, when both the rings are substituted with electron-donating groups as in the case of **2a**, **2b**, and **2c**, the product yields were found to be better which is partly because of the enhanced stability of the intermediate (**B**).

In conclusion, irrespective of the nature of the mechanisms, we have developed an elegant method for the synthesis

of 3-aroylindoles through a copper-catalyzed oxidative process involving *o*-alkynylated *N,N*-dimethylamines in the presence of aqueous TBHP as the oxidant in DMSO solvent. This protocol simultaneously installs C–C and C–O bonds through an intramolecular oxidative path in the construction of 3-aroylindoles. This method uses an inexpensive Cu catalyst without the requirement of any cocatalyst and additives and proceeds at a relatively lower temperature. Besides being one-pot and atom economical, judging the practical utility makes the present method the best alternative synthesis for 3-aroylindoles.

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**Supporting Information Available.** General information, experimental procedures, spectral data and copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.