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Copper-Catalyzed Oxidative Cascade Coupling of N-Alkyl-N-phenylacrylamides with Aryl Aldehydes

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An oxidative cascade coupling reaction was developed between N-alkyl-N-phenylacrylamides and aryl aldehydes using CuCl2/TBHP (tert-butyl hydroperoxide) as a catalyst and oxidant. The reaction involves oxidative cross coupling of the activated alkene Csp2-H from the N-alkyl-N-phenylacrylamide with the aldehyde Csp2-H bond (-CHO), followed by metal-mediated direct aryl Csp2-H functionalization/cyclization to afford 3-(2-oxo-2-arylethyl)indolin-2-ones in good yields under mild reaction conditions without organic solvents involved.

Transition-metal-catalyzed oxidative cross coupling of activated alkenes has attracted a lot of attention,1 because these kinds of reactions are normally atom-economic, highly efficient and environment friendly.2 When these substrates are carefully designed, the reactions will not stop at the oxidative coupling stage. Instead, it will subsequently undergo metal-mediated functionalization/cyclization catalyzed by the same metal catalyst in one pot. For example, direct aryl C(sp2)-H or alkyl C(sp2)-H cyclization/functionalization can occur. In this way, the cascade reaction can generate a complex product skeleton in a highly efficient way.3 N-Alkyl-N-phenylacrylamides, which contain both an activated double bond (Csp2-H) and an electron-rich aryl substrate (Csp2-H) in one molecule, is a suitable synthetic substrate for planning this kind of cascade reaction. Reports exist of using N-arylacylamides as reactants for carrying out cascade reactions to synthesize oxindole derivatives,4,6,8–11 but these transformations are still quite rare.

It is known that N-aryl amide substrates are suitable for C(sp2)-H cyclization/functionalization.5 Early work was reported by Hensssey and Buchwald,6 and later extended by Jia and Kündig.7 Recently, more fascinating results were obtained when aryl C(sp2)-H cyclization/functionalization was combined with oxidative cross couplings of activated alkenes. Zhu and Liu independently used N-arylacrylamides as reactants for the oxindole syntheses by Pd(OAc)2-catalyzed oxidative bifunctionalization (Scheme 1).8 Li developed a novel FeCl3-catalyzed oxidative coupling reaction of the alkene function substrate from N-arylacrylamide with either an aryl Csp2-H bond or a Csp3-H bond adjacent to a heteroatom to afford oxindole derivatives (Scheme 1).9 Yang reported the preparation of various diphenylphosphoryl oxindoles by AgNO3-catalyzed difunctionalization of the alkene function on N-arylacrylamides through a carbon phosphorylation and C-H functionalization cascade.

Scheme 1 Transition-metal catalyzed cascade reactions of using N-arylacrylamide as one of reactants.

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Here, we report a copper-catalyzed oxidative cross coupling reaction of the double bonds' Csp²-H of N-alkyl-N-phenylacrylamides with an aryl aldehyde Csp²-H bond, followed by a Cu-mediated direct aryl Csp²-H functionalization/cyclization to produce the ketone oxindole derivatives, 3-(2-oxo-2-arylethyl)indolin-2-ones. This cascade reaction proceeded under mild, atom-economical and environmental friendly conditions. An inexpensive copper catalyst and aqueous tert-butylhydroperoxide (TBHP) were used without any organic solvents involved.

**Table 1** Optimization of reaction conditions.

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<th>Solvent</th>
<th>Reaction time</th>
<th>Yield (%)</th>
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<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>CuBr (20)</td>
<td>---</td>
<td>18</td>
<td>trace</td>
</tr>
<tr>
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<td>CuCl₂ (20)</td>
<td>DCE</td>
<td>18</td>
<td>---</td>
</tr>
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<td>18</td>
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</table>

*Reaction conditions: benzaldehyde (3.5 equiv.), N-methyl-N-phenyl-methacrylamide (1 equiv.), aqueous TBHP (70 wt % in water, 2.5 equiv.), copper catalyst (10 mol%, or 20 mol% of 2a); yield is based on reactant 2a. Yield of isolated 3a. The reaction was run with 10 mol% catalyst CuCl₂. The reaction was run for 10 hours.*

Very recently, Lei reported oxidative cross coupling reactions between phenyl-substituted alkenes with aldehydes. We have extended this chemistry using the electron-deficient alkene functions from N-alkyl-N-phenylacrylamides in contrast to a phenyl-substituted alkene. By introducing an arylamide substrate into the reactant structure, a one-pot cascade reaction generating ketone oxindoles in good yield was developed. An inexpensive copper catalyst and aqueous tert-butylhydroperoxide (TBHP) were used without any organic solvents involved.

Reaction conditions were screened to search for cascade promoting features. Benzaldehyde and N-methyl-N-phenyl-methacrylamide were selected and various catalysts, solvents, reaction times and yields were screened. Based on previous research, catalyst screening focused mainly on copper catalysts which are capable of promoting oxidative coupling of arylamide via single-electron transfer. There is no prior literature report of using a copper catalyst for this type of cascade reaction.
**Scheme 3** Proposed cascade coupling reaction mechanism.

In summary, we have developed a novel Cu-catalyzed oxidative cascade coupling reaction between N-alkyl-N-phenylacrylamides and aryl aldehydes using CuCl2/TBHP as catalyst and oxidant respectively. The reaction undergoes oxidative cross coupling reactions of the activated alkenes Csp2-H of the N-alkyl-N-phenylacrylamides with aldehyde Csp2-H bonds. This is subsequently followed by metal-mediated direct aryl Csp2-H functionalization/cyclization process to afford 3-(2-oxo-2-aryl)indolin-2-ones in good yields under mild reaction conditions.

**Acknowledgments**

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**Notes and references**


