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

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Weiwei Gong,[a] Lei Xu,[a] Tao Ji,[a] Ping Xie,[b] Xueyong Qi,[a] Charles U. Pittman, Jr.[c] and Aihua Zhou[a]*

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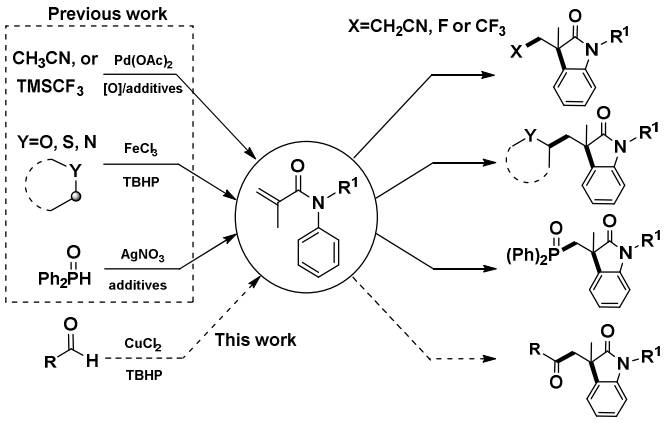
An oxidative cascade coupling reaction was developed between *N*-alkyl-*N*-phenylacrylamides and aryl aldehydes using $CuCl_2$/TBHP (*tert*-butyl hydroperoxide) as a catalyst and oxidant. The reaction involves oxidative cross coupling of the activated alkene Csp^2-H from the *N*-alkyl-*N*-phenylacrylamide with the aldehyde Csp^2-H bond (-CHO), followed by metal-mediated direct aryl Csp^2-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(sp^2)-H or alkyl C(sp^3)-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 (Csp^2-H) and an electron-rich aryl substrate (Csp^2-H) in one molecule, is a suitable synthetic substrate for planning this kind of cascade reaction. Reports exist of using *N*-alkyl-*N*-arylacrylamides as reactants for carrying out cascade reactions to synthesize oxindole derivatives, [4,8-11] but these transformations are still quite rare.

It is known that *N*-aryl amide substrates are suitable for C(sp^2)-H cyclization/functionalization.[5] Early work was reported by Hennsssey and Buchwald,[6] and later extended by Jia and Kündig.[7] Recently, more fascinating results were obtained when aryl C(sp^2)-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 difunctionalization (Scheme 1).[8] Li developed a novel $FeCl_3$-catalyzed oxidative coupling reaction of the alkene function substrate from *N*-arylacrylamide with either an aryl Csp^2-H bond or a Csp^3-H bond adjacent to a heteroatom to afford oxindole derivatives (Scheme 1).[9] Yang reported the preparation of various diphenylphosphoryl oxindoles by $AgNO_3$-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*-aryklacrylamide as one of reactants.

[a] *Pharmacy School, Jiangsu University, Xuefu Road 301, Zhenjiang, Jiangsu 212013, People's Republic of China, Email: ahz@ujs.edn.cn.*

[b] *Scientific Information Research Institute, Jiangsu University (Library), Xuefu Road 301, Zhenjiang, Jiangsu 212013, People's Republic of China.*

[c] *Mississippi State University, Mississippi State, MS 39762, USA.*

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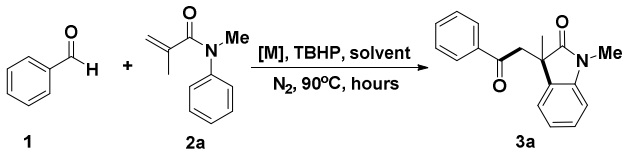
(Scheme 1).[10] Here, we report a copper-catalyzed oxidative cross coupling reaction of the double bonds' Csp^2-H of *N*-alkyl-*N*-phenylacrylamides with an aryl aldehyde Csp^2-H bond, followed by a Cu-mediated direct aryl Csp^2-H functionalization/cyclization to produce the ketone oxindole derivatives, 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.



1 2a 3a

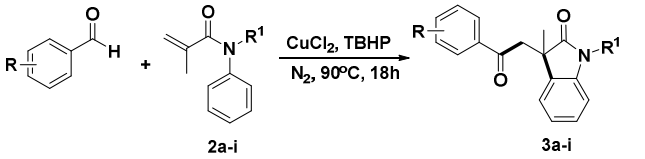
Entry	Cat. (mol%)	Solvent	Reaction time	Yield (%) [a]
1	$CuBr_2$ (20)	---	18	trace
2	CuO (20)	---	18	5%
3	CuI (20)	---	18	trace
4	CuBr (20)	---	18	trace
5	$CuCl_2$ (20)	DCE	18	---
6	$CuCl_2$ (20)	Toluene	18	trace
7	$CuCl_2$ (20)	CH_3CN	18	40
8	$CuCl_2$ (20)	DMF	18	trace
9[c]	$CuCl_2$ (10)	---	18	56
10	$CuCl_2$ (20)	---	18	70
11[d]	$CuCl_2$ (20)	---	10	50
12	---	---	18	52

[a] 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**. [b] Yield of isolated **3a**. [c] The reaction was run with 10 mol% catalyst $CuCl_2$. [d] The reaction was run for 10 hours.

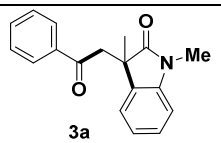
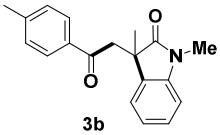
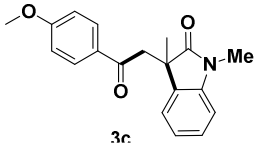
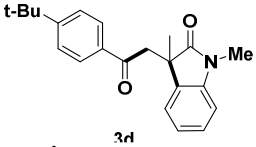
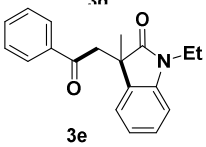
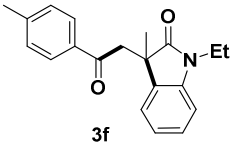
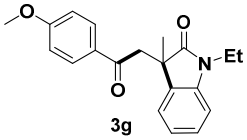
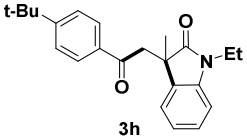
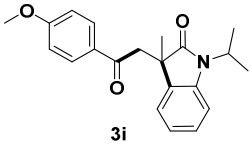
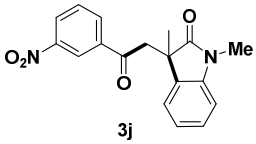
Very recently, Lei reported oxidative cross coupling reactions between phenyl-substituted alkenes with aldehydes.[11] We have extended this chemistry using the electron-deficient alkene functions from *N*-alkyl-*N*-phenylacrylamides in contrast to a phenyl-substituted alkene. By introducing an arylamide 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*-butylhydrogenperoxide (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,[12] 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.

Table 2 Oxidative cascade coupling reaction.



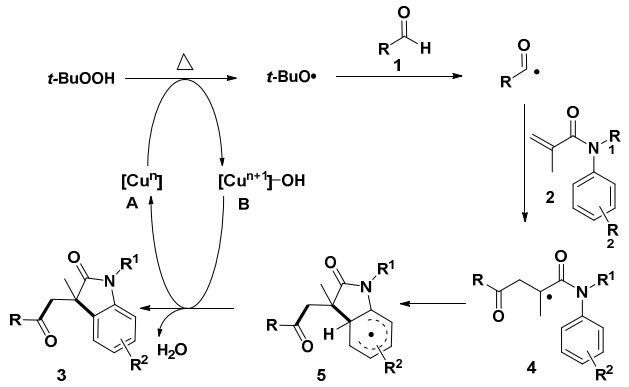
2a-i 3a-i

Entry	R	R^1	Product	Yield (%) [a]
1	H	Me	 3a	70
2	Me	Me	 3b	72
3	MeO	Me	 3c	62
4	*t*-Bu	Me	 3d	86
5	H	Et	 3e	70
6	Me	Et	 3f	69
7	MeO	Et	 3g	64
8	*t*-Bu	Et	 3h	84
9	MeO	*i*-Pr	 3i	80
10	*m*-NO_2	Me	 3j	trace

[a] Reaction conditions: aldehyde (3.5 equiv.), *N*-alkyl-*N*-phenylacrylamide (1 equiv.), aqueous TBHP (70 wt % in water, 2.5 equiv.), copper catalyst (20 mol% of **2a-i**), yield calculation is based on reactant **2a-i.** [b] Yield of isolated **3a-i.**

The synthesis starts with the reaction between benzaldehyde and *N*-methyl-*N*-phenyl-methacrylamide (Table 1). Excess benzaldehyde (3.5 equiv) and aqueous TBHP (70% in water, 2.5 equiv., added in two portions) as an oxidant were used to promote conversion. When $CuBr_2$, CuI, CuBr (20% mol) were used as catalysts in the absence of solvent (entries 1, 3, 4), none or only trace amounts of desired product **3a** was detected. Using CuO gave only about 5% of **3a**. Using solvents DCE, toluene or DMF (entries 5, 6, 8) with $CuCl_2$ as the catalyst afforded none or only trace amounts of **3a** in acetonitrile (entry 7), the reaction produced a moderate 40% yield of **3a**. Using $CuCl_2$ (10% mol) as the catalyst without solvent (entry 9) gave **3a** in 56% yield after 18 h. Increasing the amount of $CuCl_2$ to 20% mol (entry 10) also increased the rate and gave a good yield of 70%, after 18 h. More catalyst didn't increase the yield. When the reaction time was shortened to 10 h, a 50% yield (entry 11) was obtained. When no catalyst was used, the reaction proceeded but slowly. After 18 h, a 52% yield was observed. Based on the screening results, the optimized reaction conditions are: $CuCl_2$ (20 mol%), TBHP (2.5 equiv.), 90°C, 18h. ten reactions with different substituents were investigated (Table 2) at the optimized conditions. Besides electron-deficient *m*-nitrobenzaldehyde gave trace amount of reaction product **3j**. All other aromatic aldehydes underwent the oxidative cascade reactions well to give ketone oxindoles in good yields.

Based on previous reports[12] and these new results, a reaction mechanism is proposed in Scheme 3. First TBHP is reduced by one electron transfer from low valent copper species **A** to give the tBuO· radical and the ·OH radical, which coordinates to copper species B. The *tert*-butoxy radical abstracts a hydrogen atom from the aldehyde **1** to generate the acyl radical. This radical adds to the double bond of the *N*-alkyl-*N*-phenylacrylamide to give radical **4** which cyclizes to give product **3** via intermediate **5**.



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 $CuCl_2$/TBHP as catalyst and oxidant respectively. The reaction undergos oxidative cross coupling reactions of the activated alkenes Csp^2-H of the *N*-alkyl-*N*-phenylacrylamides with aldehyde Csp^2-H bonds, This is subsquently followed by metal-mediated direct aryl Csp^2-H functionalization/cyclization process to afford 3-(2-oxo-2-arylethyl)indolin-2-ones in good yields under mild reaction conditions.

Acknowledgments

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