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ARTICLE TYPE

Copper-catalyzed cyanoalkylarylation of activated alkenes with AIBN: a convenient and efficient approach to cyano-containing oxindoles†

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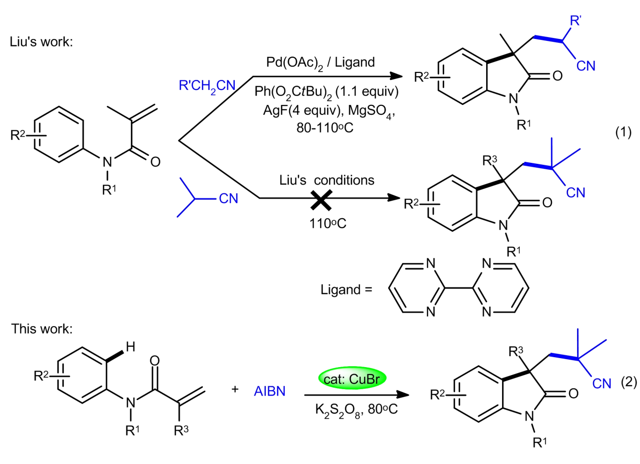
A novel, simple, and cost-effective copper-catalyzed direct cyanoalkylarylation of activated alkenes with AIBN has been developed with cheap $K_2S_2O_8$ as the oxidant. A series of cyano-containing oxindoles that are otherwise difficult to obtain through previous methods were efficiently synthesized using this protocol.

Transition metal-catalyzed direct oxidative difunctionalization of alkenes is one of the most fascinating and powerful tools for constructing various valuable organic compounds.[1] Over the past several years, remarkable progress has been made in this area, and some important and useful synthetic methodologies have been developed. In particular, the direct difunctionalization of alkenes, such as arylcarbonylation,[2] azidoarylation,[3] arylsulfonylation[4] aryltrifluoromethylation,[5] arylnitration,[6] arylphosphorylation[7] alkylarylation,[8] hydroxyalkylarylation,[9] arylalkoxycarbonylation,[10] has recently attracted considerable interests of chemists due to it could offer particularly appealing approaches to access various substituted oxindoles, an important class of heterocycles with unique pharmacological and biological activities.[11] Through this strategy, of note, some important functional groups such as carbonyl, phosphoryl, azidyl, trifluoromethyl, hydroxyl, nitro, and ester groups could be introduced into the oxindole framework. Moreover, cyano group as a key structural motif widely exists in many pharmaceuticals, agrochemicals, and materials.[12] Also, it can serve as versatile building block for various organic transformations. However, the introduction of cyano species into valuable heterocyclic compounds such as oxindoles via the direct oxidative difunctionalization of alkenes remains an extremely challenging but attractive task in current organic chemistry.[13]

In 2011, Liu et al reported an elegant work for palladium-catalyzed oxidative cyanoalkylarylation of alkenes with nitriles leading to cyano-containing oxindoles in the presence of stoichiometric amounts of $PhI(OPiv)_2/AgF/MgSO_4$ (eqn 1).[14] Nevertheless, when isobutyronitrile with significant steric effects was used as the substrate, the corresponding cyano-containing product was not obtained even at high temperature (eqn 1). This well developed method may suffer from some disadvantages of expensive transition metal catalysts, relatively complex reaction conditions, and limited substrate scope, which thereby can limit the applications of this transformation on a large scale. Therefore, there is a great demand for the development of simple, convenient, efficient and alternative strategy to access more diverse cyano-containing oxindoles via direct difunctionalization of alkenes.

With continuing interests on the development of new methods for difunctionalization of alkenes to obtain important organic compounds,[4b,5e,15] herein, we have proposed a novel, convenient, and cost-effective protocol for the construction of cyano-containing oxindoles by copper-catalyzed direct oxidative cyanoalkylarylation of activated alkenes with AIBN, with simple and cheap $K_2S_2O_8$ as the oxidant (eqn 2). The present methodology provides a highly attractive and complementary approach to a diverse range of cyano substituted oxindoles in moderate to high yields, together with excellent functional group tolerance through a radical process.



In an initial study, the reaction of N-methyl-N-arylacrylamide **1a** with AIBN was investigated by using a variety of transition metal complexes as catalysts, including Pd, Fe, Ag, Cu, Ni, Zn, and In salts, in the presence of $K_2S_2O_8$ (Table 1 and Supporting Information). Among the above metal salts examined, Cu salts especially CuBr was found to be the most effective one achieving the desired product **3a** in

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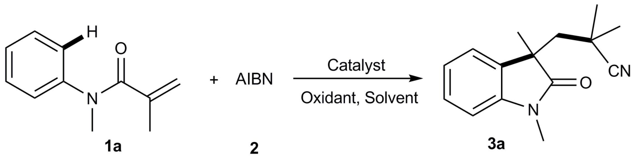
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant (1 equiv)	Solvent	Yield (%)[b]
1	CuI	$K_2S_2O_8$	DMF	66
2	$Cu(OAc)_2$	$K_2S_2O_8$	DMF	80
3	$Cu(OTf)_2$	$K_2S_2O_8$	DMF	63
4	$CuCl_2$	$K_2S_2O_8$	DMF	48
5	CuCN	$K_2S_2O_8$	DMF	78
6	**CuBr**	**$K_2S_2O_8$**	**DMF**	**83**
7	CuBr	$Na_2S_2O_8$	DMF	46
8	CuBr	$(NH_4)_2S_2O_8$	DMF	73
9	CuBr	TBHP	DMF	80
10	CuBr	DTBP	DMF	74
11	CuBr	Air(O_2)	DMF	56
12	CuBr	$PhI(OAc)_2$	DMF	72
13	CuBr	H_2O_2	DMF	70
14	CuBr	$K_2S_2O_8$	CH_3CN	47
15	CuBr	$K_2S_2O_8$	Toluene	62
16	CuBr	$K_2S_2O_8$	DME	58
17	CuBr	$K_2S_2O_8$	DMSO	46
18	CuBr	$K_2S_2O_8$	THF(reflux)	45
19	CuBr	$K_2S_2O_8$	1,4-dioxane	33
20	CuBr	$K_2S_2O_8$	DCE	77
21	CuBr	$K_2S_2O_8$	DMF	trace[c]
22	CuBr	$K_2S_2O_8$	DMF	55[d]
23	CuBr	$K_2S_2O_8$	DMF	75[e]
24	--	$K_2S_2O_8$	DMF	16
26	--	--	DMF	trace

[a] Reaction conditions: N-aryl acrylamide **1a** (0.25 mmol), AIBN **2** (1 mmol), catalyst (5 mol%), oxidant (2 equiv), solvent (1 mL), 80°C, 24 h. n.r. = no reaction. TBHP: tert-Butyl hydroperoxide, 70% solution in water; DTBP: Di-tert-butyl peroxide.[b] Isolated yields based on **1a**. [c] 25°C. [d] 60°C. [e] 100°C.

83% yield (Table 1, entry 6). The structure of **3a** was further unambiguously confirmed by single-crystal X-ray analysis (Figure 1). Further experiments of oxidant screening with CuBr as the catalyst revealed that $K_2S_2O_8$ was superior to the others such as $(NH_4)_2S_2O_8$, $Na_2S_2O_8$ TBHP, DTBP, $PhI(OAc)_2$

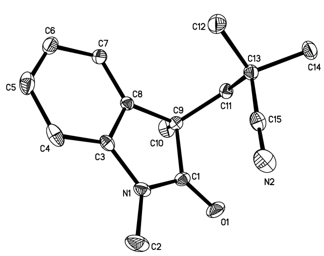
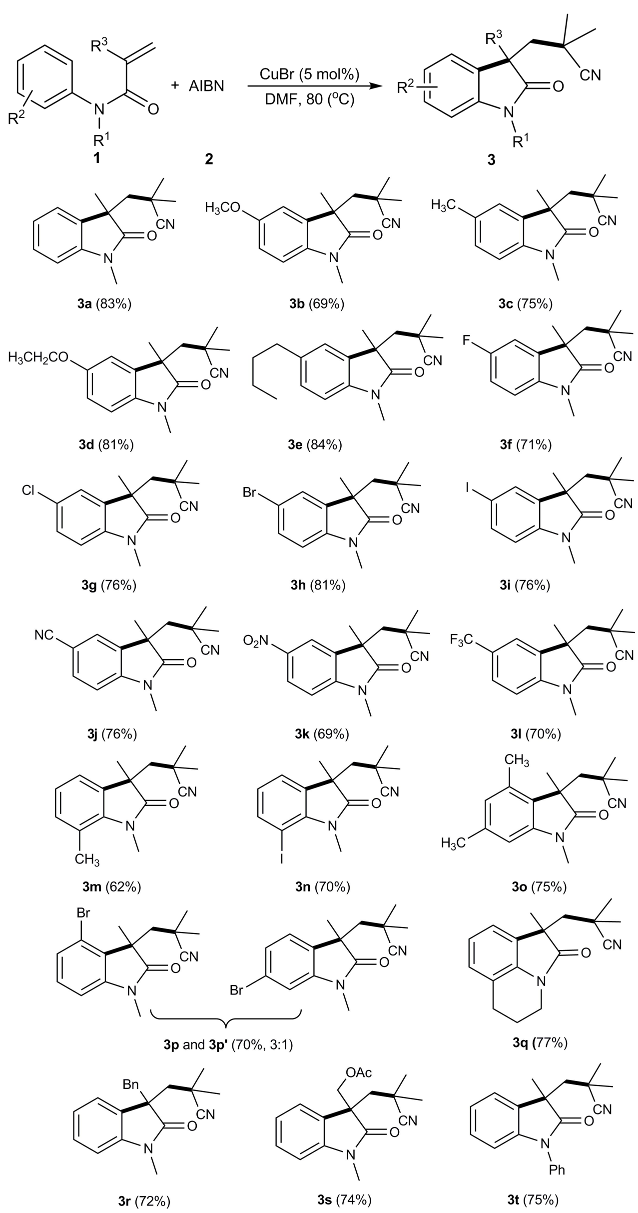


Figure 1. The crystal structure of **3a**. ORTEP drawing of $C_{15}H_{18}N_2O$ with 50% probability ellipsoids, showing the atomic numbering scheme.

Table 2 Cyanoalkylarylation of activated alkenes with AIBN.[ab,]

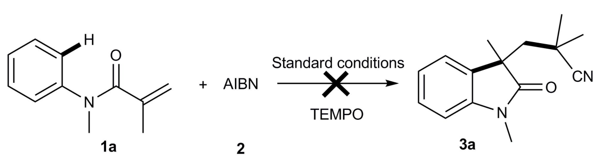


[a] Reaction conditions: N-aryl acrylamide **1** (0.25 mmol), AIBN **2** (1 mmol), CuBr (5 mol %), $K_2S_2O_8$ (2 equiv), DMF (1 mL), 80°C, 24-36 h. [b] Isolated yields based on **1**.

and H_2O_2 (Table 1, entries 6-12). The effects of different solvents on this reaction were also examined, and DMF was proved to be better than the others (Table 1, entries 13-19). Among the reaction temperatures were tested, it turned out that the reaction at 80°C gave the best results (Table 1, entries 6, 20–22). Furthermore, when the reaction was performed in the presence of $K_2S_2O_8$ or CuBr, the desired product was obtained in 53% and yield, respectively, nevertheless, only a trace amount of desired product **3a** was detected when the reaction was performed in the absence of catalyst and oxidant (Table 1, entry 24).

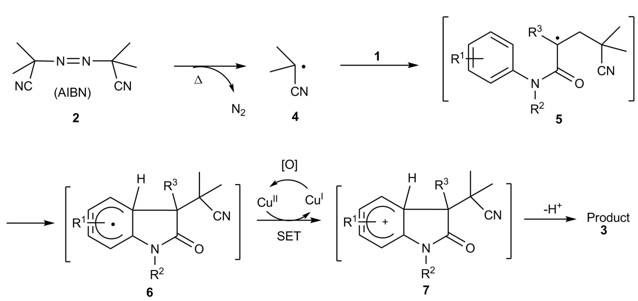
With the optimized conditions in hand, we next examined the reactions of various substituted N-arylacrylamides with AIBN to probe the scope and limitations of the reaction. As shown in Table 2, N-arylacrylamides with electron-donating or electron-deficient substitutents at aromatic ring moieties reacted smoothly to afford the desired products in moderate to good yields (**3a-3l**). Notably, diverse functional groups, including F, Cl, Br, I, cyano, and nitro groups could be tolerated, with corresponding products obtained in good yields (**3f-3k**). To our delight, the sterically congested *ortho* substituted substrates were compatible with this reaction to give products **3m** and **3n** in 61% and 70% yields, respectively. Furthermore, multisubstituted arylacrylamide was also well tolerated in this process, affording the cyano substituted oxindole **3o** in 75% yields. Here, meta-substituted substrate offered a mixture of two regioselective products (**3p** and **3p'**). It should be noted that the present catalytic reaction was also successfully applied to tetrahydroquinoline derivative of acrylamide; the corresponding tricyclic oxindole **3q** was obtained with good yield. The effects of substituents on alkenes were subsequently evaluated. In addition to methyl group, substrates bearing benzyl and ester protecting groups were well tolerated to this reaction to furnish the corresponding oxindoles (**3r** and **3s**) in good yields. Finally, the examination of different N-protection groups revealed that alkyl and aryl were appropriate for the reaction (**2a**–**2t**), in contrast, N-free and acetyl N-arylacrylamide failed to produce the corresponding product. Nevertheless, no desired products were obtained when other nitriles such as 2,2'-azobis(2,4-dimethyl)valeronitrile and 2,2'-azodi(2-methylbutyronitrile) were employed in the present reaction system.

It is well-known that 2-cyanoprop-2-yl radical would be generated from thermal decomposition of AIBN with the release of N_2,[16] which suggested that the reaction likely proceeded via a single-electron-transfer (SET) process triggered by free 2-cyanoprop-2-yl radical. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a well known radical-capturing species) was added into the present reaction system, the present cyanoalkylarylation reaction was completely suppressed (eqn 3). Accordingly, a radical pathway should be involved in this transformation.



(3)

Although the mechanism is not completely clear yet, based on the above experimental results and previous reports,[2-10,16] a postulated reaction pathway was thereby proposed as shown



Scheme 1. Postulated reaction pathway.

in Scheme 1. Initially, thermal decomposition of AIBN would lead to the generation of 2-cyanoprop-2-yl radical **4** with the release of N_2. Subsequently, the 2-cyanoprop-2-yl radical **4** selectively added to C–C double bond of N-aryl acrylamide **1** giving alkyl radical **5**, which underwent an intramolecular radical cyclization reaction leading to intermediate **6**. Next, single electron oxidation of intermediate **6** with Cu^{II} species to release the cationic intermediate **7**. Finally, the hydrogen abstraction of intermediate **7** by $K_2S_2O_8$ would produce the corresponding cyano-substituted oxindole **3**.

In summary, we have successfully employed copper-catalyzed oxidative cyanoalkylarylation of activated alkenes with AIBN for the synthesis of cyano-containing oxindoles. Such a protocol, which utilizes simple and cheap copper salts as catalyst and $K_2S_2O_8$ as the oxidant, provides a practical, convenient, and efficient approach to various cyano-containing oxindoles. It holds great promise of the potential applications of cyano-containing oxindoles in synthetic and pharmaceutical chemistry. The detailed scope, mechanism, and synthetic application of this reaction are under investigation.

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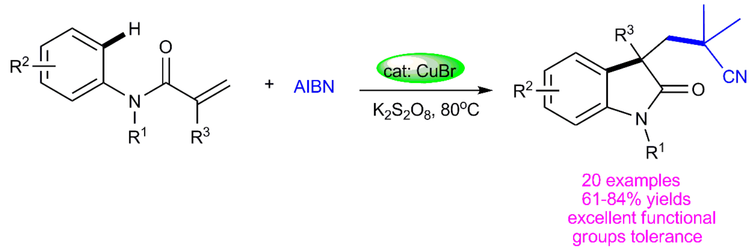

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